Stereochemistry of 1,2-elimination reactions at the E2–E1cB interface—*tert*-butyl 3-tosyloxybutanoate and its thioester†

Jerry R. Mohrig,* David G. Alberg, Craig H. Cartwright, Mary Kay H. Pflum, Jeffrey S. Aldrich, J. Kyle Anderson, Shelby R. Anderson, Ryan L. Fimmen and Amy K. Snover

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Experimental data on the stereoselectivity of base-catalyzed 1,2-elimination reactions that produce conjugated carbonyl compounds are scarce in spite of the importance of these reactions in organic and biochemistry. As part of a comprehensive study in this area, we have synthesized stereospecifically-deuterated β-tosyloxybutanoate esters and thioesters and studied the stereoselectivity of their elimination reactions under non-ion pairing conditions. With the availability of both the (2*R**,3*R**) and (2*R**,3*S**) diastereomers the innate stereoselectivity could be determined unambiguously. ^{1}H and ^{2}H NMR data show that these substrates produce 5–6% *syn* elimination, the usual amount for acyclic substrates undergoing E2 reactions. Contrary to earlier suggestions, activation by a carbonyl group has virtually no influence upon the stereoselectivity. Elimination of the (2*R**,3*R**) diastereomer of the β-tosyloxyester and thioester produces 21–25% of the (*Z*)-alkene, much more than observed with a poorer β-nucleofuge. A relatively large amount of (*Z*)-alkene product seems to be a good marker for an E2 pathway, in which the transition state is E1cB-like, rather than an $E1cB_{irrev}$ mechanism. *Syn* KIE values were higher than those for *anti* elimination for the esters as well as the thioesters. Experimental challenges to the synthesis of stereospecifically-deuterated β-tosyloxyesters are discussed.

Introduction

There has been substantial interest in the stereochemistry of base-catalyzed E2 and E1cB-like 1,2-elimination reactions over the past 40 years. It is generally recognized that *anti* elimination will dominate over *syn* elimination under normal conditions, where ion pairing or the complex conformational factors of cyclic compounds do not play a major role.[1–2] In *anti* eliminations orbital overlap is maximized and torsional strain is minimized. However, it has been suggested that E1cB-transition states, such as those expected for relatively acidic thioesters, may favor *syn* stereochemistry.[1,3–4] If the E2 transition state becomes more E1cB-like, in the More O'Ferrall–Jencks notation, the normal conformational, electronic and orbital symmetry factors favoring *anti* elimination could become less important, allowing *syn* elimination to compete more effectively; however, the experimental base on which this proposal depends is quite small.

The activating influence of a carbonyl group on the stereochemistry of 1,2-elimination reactions is an important piece of the puzzle. Before our research began, very little was known about how the pK_a of a carbonyl substrate affects the stereochemistry of a base-catalyzed 1,2-elimination reaction to form a conjugated alkene. Our research has focused on simple, acyclic β-substituted butanoate esters and thioesters, using conditions where the effects of aggregation phenomena do not dominate.[5] This system was chosen because it provides an appropriate model for the substrate of enoyl-CoA hydratase (EC 4.2.1.17), which catalyzes the *syn* elimination–addition of water in the *S*-β-hydroxybutyryl CoA/*S*-crotonyl CoA reaction.[6]

In addition to the acidity of the proton, the nature of the leaving group may also play an important role in the stereochemistry of 1,2-elimination reactions.[1–2,4] This paper reports the reaction stereoselectivity where the *p*-toluenesulfonyloxy or tosyloxy group is the nucleofuge. Tosylate is an excellent leaving group and is a common reference nucleofuge for stereochemical studies of 1,2-elimination reactions.[2,4,7] The two substrates that form our data set are stereospecifically-labelled *tert*-butyl (2*R**,3*R**)-3-tosyloxy-2,3-$^{2}H_2$-butanoate (**1**) and its (2*R**,3*S**) diastereomer (**2**) and *S*-*tert*-butyl (2*R**,3*R**)-3-tosyloxy-2,3-$^{2}H_2$-butanethioate (**3**) and its (2*R**,3*S**) diastereomer (**4**). In every case these substrates were converted cleanly into *tert*-butyl (*E*)-2-butenoate (**5**) and *S*-*tert*-butyl (*E*)-2-butenethioate (**6**), respectively, plus a small percentage of the (*Z*)-isomers.

Results and discussion

The synthesis of stereospecifically-labelled **1** and **2** presented a challenge. We had expected to model the synthesis on that of *tert*-butyl (2*R**,3*R**)-3-acetoxy-2,3-$^{2}H_2$-butanoate (**7**) and its (2*R**,3*S**) diastereomer (**8**),[5] which involved the rigorous *syn* deuterogenation of the (*E*)- and (*Z*)-isomers of *tert*-butyl 3-acetoxy-2-butenoate by Wilkinson's catalyst,[8] Fig. 1.

Using this kind of methodology for the synthesis of **1** and **2** depended on the successful synthesis of the (*E*)- and (*Z*)-enol tosylates and their stereoselective deuterogenation. Reaction of the

Department of Chemistry, Carleton College, Northfield, MN 55057, USA. E-mail: jmohrig@carleton.edu

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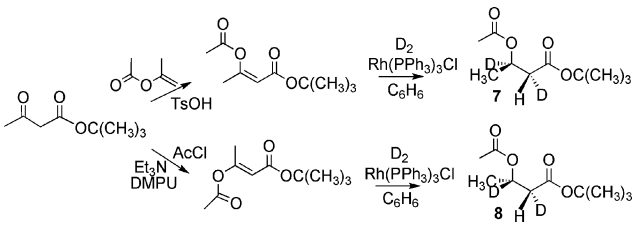


Fig. 1 Preparation of acetoxy esters **7** and **8**.

enolate of *tert*-butyl acetoacetate with *p*-toluenesulfonyl fluoride led to a 3 : 1 mixture of *tert*-butyl (*E*)- and (*Z*)-3-tosyloxy-2-butenoate (**9a** and **9b**), which could readily be separated by flash chromatography on SiO_2. However, exhaustive efforts to find conditions under which **9a** could be deuterogenated to **2** were unsuccessful. In fact, deuterogenation of **9a** led solely to cleavage of the *tert*-butyl ester, producing (*E*)-3-tosyloxy-2-butenoic acid (**10**), Fig. 2.

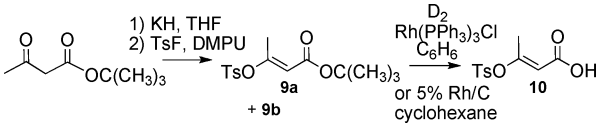


Fig. 2 Synthesis and attempted deuterogenation of **9a**.

Hydrogenation of **9a** with 5% Rh/C under more vigorous conditions in 1 : 1 v/v EtOD–C_6H_6 produced *tert*-butyl ethyl ether, *p*-toluenesulfonic acid (TsOH), butanoic acid, and ethyl butanoate. This experiment suggests that **10** results from acid-catalyzed cleavage of the *tert*-butyl ester through an S_N1 pathway, presumably because a small amount of TsOH is produced under the hydrogenation conditions. No addition of H_2 to the C=C was observed in the presence of 5% Pt/C, 5% Rh/Al_2O_3, or 5% $Pd/BaSO_4$. **9a** is remarkably resistant to simple hydrogenation.

Another possible approach for the synthesis of stereospecifically-labelled **1** and **2**, which was ultimately unsuccessful, was the deuterogenation of *tert*-butyl (*E*)- and (*Z*)-3-trimethylsilyloxy-2-butenoate, followed by cleavage of the silyl ether and subsequent tosylation of the β-hydroxy esters. Deuterogenation of the silyl enol ether with Wilkinson's catalyst under the usual conditions was successful and stereospecific. Since the trimethylsilyl enol ether was unstable on SiO_2, even in the presence of Et_3N, chromatography was attempted using Florisil®. However, separation of the (*E*)- and (*Z*)-isomers was poor and recovered yields were small. Chromatography of the *tert*-butyldimethylsilyl enol ether on Florisil® was successful in producing pure *tert*-butyl (*E*)-3-(*tert*-butyldimethylsilyloxy)-2-butenoate, but only vanishingly small amounts of pure (*Z*)-isomer could be isolated. Since the success of our elimination studies required the availability of both **1** and **2** to obtain the necessary kinetic isotope effects (KIEs), we abandoned the silyl enol ether synthetic methodology.

We ultimately resorted to the synthesis of **1** and **2** by hydrolysis of the acetoxy esters **7** and **8** followed by tosylation of the resulting β-hydroxy esters, even though a fair amount of the stereospecifically-deuterated acetoxy ester was lost to competing base-catalyzed elimination reactions, Fig. 3. Use of a more polar solvent mixture produced a lower elimination/hydrolysis ratio, making the loss due to elimination (~30%) acceptable.[5] Isotopic exchange at C-2 of the β-hydroxy esters was minimized (<2%) by carefully monitoring the hydrolysis reactions. Substrates **1** and **2** contained 5–9% of the C-2 diprotonated esters.

The thioesters **3** and **4** were synthesized by deblocking the *tert*-butyl esters **1** and **2** with TFA and esterification with 2-methyl-2-propanethiol,[9] Fig. 3. As long as excess TFA was not present, no H/D exchange or rearrangement was observed in the transesterification reaction.

In our elimination reactions of ester **1** with KOH in 3 : 1 v/v EtOH–H_2O a deuteron is removed by *anti* elimination in the formation of the deuterated (*E*)-alkene **5**, whereas a proton is removed from ester **2**. Reactions of **1** produced 79% of **5** plus 21% of its deuterated isomer, *tert*-butyl (*Z*)-2-butenoate. With ester **2** only 2.2% of the deuterated (*Z*)-alkene was produced. Elimination of TsOH from nondeuterated *tert*-butyl 3-tosyloxybutanoate **11** produced 6–7% *tert*-butyl (*Z*)-2-butenoate.

(*E*)-Alkenes **5** and **6** from the base-catalyzed elimination of TsOH from substrates **1–4** were purified by preparative GC before multiple ^2H NMR integrations were used to determine the amount of *anti* and *syn* elimination from the isotopically-labeled diastereomers, as shown in Table 1. 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.

The elimination of TsOH from thioesters **3** and **4** with KOH in 3 : 1 EtOH–H_2O produced mainly deuterated *S*-*tert*-butyl (*E*)-2-butenethioate (**6**) plus a smaller amount of deuterated *S*-*tert*-butyl (*Z*)-2-butenethioate.[5] Thioester **3** produced 25% of the (*Z*)-isomer whereas **4** produced 1–2%. Elimination of TsOH from nondeuterated **12** gave 7% *S*-*tert*-butyl (*Z*)-2-butenethioate. Our kinetic studies show that thioester **12** reacts 18 times faster than ester **11** at 30.0 °C with KOH in 3 : 1 EtOH–H_2O, reflecting the greater activating influence of the thioester group.[10]

In order to ensure the validity of the results shown in Table 1, we have carried out three sets of control experiments on **1** and **11**. Virtually no isomerization of *tert*-butyl (*Z*)-2-butenoate[11] to its (*E*)-isomer **5** was observed under the reaction conditions. GC analysis showed that only 0.33% ± 0.01% of the (*Z*)-isomer rearranged to **5** under elimination conditions; such a small amount of isomerization would have no effect on our results or conclusions. When the reaction was carried out with only 50% of the KOH

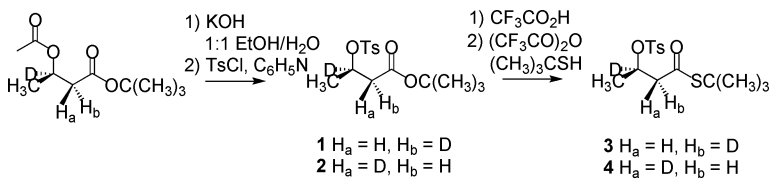
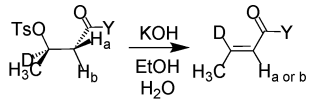


Fig. 3 Synthesis of tosyloxyesters **1** and **2** and thioesters **3** and **4**.

Table 1 Stereoselectivity data and KIEs for esters **1** and **2** and thioesters **3** and **4**



(R*R*) **1** and **3**, H_a=H, H_b=D
(R*S*) **2** and **4**, H_a=D, H_b=H

5, Y=$OC(CH_3)_3$
6, Y=$SC(CH_3)_3$

	$\%syn_{R^*R^*}$	$\%syn_{R^*S^*}$	$k_{R^*S^*}/k_{R^*R^*}$	$(k_H/k_D)_{syn}$[a]	$(k_H/k_D)_{anti}$[b]
1,**2**: Y = $OC(CH_3)_3$	13.6 ± 0.2	1.0 ± 0.2	2.31 ± 0.07	5.9	2.6
3,**4**: Y = $SC(CH_3)_3$	12.3 ± 0.2	1.0 ± 0.2	1.98 ± 0.06	6.2	2.2

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

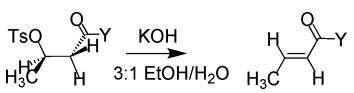
necessary for complete elimination of **1**, the deuterium content of **5** was virtually identical to that observed at complete reaction; in addition, the recovered **1** showed no loss of stereochemical integrity. Finally, carrying out the elimination reaction using nondeuterated **11** with KOD and EtOD–D_2O showed <1% H/D exchange in the recovered **5**.

The k_H/k_D KIEs in Table 1 are consistent with the KIE values for other thioester and ester substrates,[1,5,12] and for KIE values in the elimination reactions of β-tosyloxyethyl phenyl sulfone.[13] In all cases the KIEs for *syn* elimination were higher than those for *anti* elimination.

Using the data in Table 1, 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 2. Although $(k_H/k_D)_{syn}$ is subject to a substantial error, this error is not propagated to the innate stereoselectivities shown in Table 2. Any error in $(k_H/k_D)_{syn}$ is offset by the compensating error in the percentage of *syn* elimination from the (2*R**,3*S**) diastereomer by which it must be multiplied to obtain the innate stereoselectivity. As an additional check, the calculated stereoselectivity percentages shown in Table 2 were the same when calculated from both the (2*R**,3*R**) and (2*R**,3*S**) diastereomers. Secondary deuterium KIEs are unlikely to be greater than 1.03 and would have a negligible effect on the results.[12]

The stereochemical results from our β-tosyloxy substrates show the usual amount of *syn* elimination for acyclic substrates undergoing E2 reactions; 4–6% is common under non-ion pairing conditions.[2] Table 2 shows that the carbonyl group has virtually no influence upon the stereoselectivity of these elimination reactions; this was also the case that we found with β-trimethylacetoxy esters and thioesters.[5] Our experimental results indicate that base-catalyzed 1,2-elimination reactions that produce conjugated esters and thioesters follow the same stereochemical pattern as those found with unactivated substrates. This pattern suggests that

Table 2 Innate stereoselectivity of base-catalyzed *p*-toluenesulfonic acid elimination



Y	%*syn* elimination
$OC(CH_3)_3$	5.6 ± 1.2
$SC(CH_3)_3$	5.9 ± 1.2

contrary to earlier suggestions electronic factors do not induce a preference for *syn* elimination in esters or thioesters with good or modest leaving groups. We will report our results on systems with a poor leaving group, which clearly react by the $E1cB_{irrev}$ mechanism, in the near future.[14]

Thibblin has pointed out that there can be a hyperconjugative interaction between the β-leaving group and the proton being abstracted. This suggests that proton transfer and cleavage of the leaving group are to some extent coupled both in the E2 and E1cB pathways. Accordingly, a periplanar positioning between the base and the tosyloxy group is associated with some double-bond character of the C_α–C_β bond.[15] Calculations have corroborated this idea.[16]

A classic problem in diagnosing reaction mechanisms has been using kinetic studies to distinguish between the $E1cB_{irrev}$ mechanism and the E2 mechanism in which the transition state is E1cB-like.[1] Perhaps the surest sign that **11** and **12** undergo elimination by the E2 mechanism is the relative percentages of their (*E*)- and (*Z*)-alkene products. Base-catalyzed elimination of TsOH from simple secondary alkyl tosylates under non-ion pairing conditions normally produces 15–35% (*Z*)-alkene by the E2 pathway, with the range reflecting steric effects as well as product stability.[17,18]

Steric effects have been implicated because other excellent leaving groups in E2 reactions, in particular iodide and bromide, produce only 67% as much of the (*Z*)-alkene as found with tosylate substrates.[17] This differential is less pronounced in aprotic solvents (80%) than in protic solvents (56%), due to H-bonding of the tosyloxy group, which effectively increases its size. The data include the 2-pentyl, 2-hexyl, 3-hexyl, 2-decyl, and 5-decyl systems, all studied under non-ion pairing conditions. On average, the secondary alkyl iodides and bromides produce 17–18% ± 3% (*Z*)-alkene, whereas in protic solvents the tosylates produce 31% ± 5% (*Z*)-alkene. Nevertheless, all of these secondary acyclic iodides, bromides, and tosylates produce fairly large amounts of (*Z*)-alkene products, making this phenomenon a hallmark of the E2 pathway.

Whereas simple acyclic (*E*)-alkenes are only about 4.2 kJ mol^{-1} lower in energy than the (*Z*)-isomers, calculations have indicated that the (*E*)-isomers of *tert*-butyl 2-butenoate and *S*-*tert*-butyl 2-butenethioate are 8.8 kJ mol^{-1} more stable than their (*Z*)-isomers.[5] Nonetheless, 7% of the (*Z*)-isomers are formed in the KOH-catalyzed eliminations of TsOH from **11** and **12** in EtOH–H_2O. This is a 4–5-fold increase in the percentage of (*Z*)-alkene compared to the elimination reactions of β-trimethylacetoxybutanoate esters and thioesters, which likely

proceed through $E1cB_{irrev}$ pathways.[5] Furthermore, the alkene products from the stereospecifically-deuterated substrates **1** and **3** contained 21% and 25% of the deuterated (*Z*)-alkene, where an *anti* elimination leading to the (*E*)-alkene involves removal of a deuteron. By contrast, the analogous stereospecifically-deuterated β-trimethylacetoxybutanoate esters and thioesters produced 1.3–1.5% of the deuterated (*Z*)-alkene. In addition, we have observed very small amounts of (*Z*)-alkene products in the elimination of β-(*m*-trifluoromethylphenoxy)butanoate esters and thioesters, which are definitely at the E1cB interface.[14]

A relatively large amount of (*Z*)-alkene from elimination reactions producing conjugated carbonyl compounds seems to be a good marker for an E2 pathway, in which the transition state is E1cB-like, rather than an $E1cB_{irrev}$ mechanism. It is not unlikely that it may also be an additional mechanistic marker for E2 pathways in elimination reactions of substrates with β-activating groups such as cyano, nitro or sulfonyl, which produce 1,2-disubstituted alkenes, especially when the energy difference between (*E*)- and (*Z*)-alkene products is reasonably large.

Experimental

General methods

^{1}H NMR spectra were run on a 200 MHz Bruker/IBM or 300 MHz Nicollet FT NMR spectrometer. The solvent for 76 MHz ^{2}H NMR spectroscopy was C_6H_6 with a small amount of C_6D_6 as an internal reference (δ_D 7.15). Multiple ^{1}H and ^{2}H NMR integrations were used to determine the isotopic purities of deuterated substrates, and elimination and competition results were corrected for the presence of C-2 diprotonated substrates and diastereomeric impurities. Capillary GC was run with a 5% phenylmethyl silicone (SPB-5) column. Preparatory GC was done on a modified Varian Aerograph Model 90 with an 8 ft × 3/8 in 5% Carbowax 20 M or 15% methylsilicone column. Flash chromatography was carried out using silica gel (Aldrich, 7–230 mesh, 60 Å). For elimination reactions of deuterated substrates, all glassware was soaked in $NaHCO_3$ solution, rinsed with distilled water and oven-dried. Melting points were calibrated against a benzoic acid standard.

tert-Butyl (*E*)- and (*Z*)-3-tosyloxy-2-butenoate 9a and 9b

tert-Butyl acetoacetate (36 g, 0.22 mol) was added dropwise to a stirred slurry of KH (0.23 mol) in THF (250 mL, N_2). After 1 h a solution of tosyl fluoride (38 g, 0.22 mol) in *N*,*N*′-dimethylpropyleneurea (DMPU, 60 mL) was added over a 20 min period and the reaction was stirred for 84 h. Aqueous workup, with acidification to pH 7, and Et_2O extractions gave a 3 : 1 mixture of **9a** and **9b**. Flash chromatography (15 : 1 SiO_2 : crude product, Et_2O–hexane) gave **9a** (20.6 g, 30%), mp 35.5–37 °C (from hexane), **9b** (6.9 g, 10%), mp 64.5–65.5 °C (from hexane), and *tert*-butyl (*E*)- and (*Z*)-3-fluoro-2-butenoate (5%). **9a**: found: C, 57.5; H, 6.6. Calc. for $C_{15}H_{20}O_5S$: C, 57.7; H, 6.45%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, Me), 2.3 (3 H, d, Me), 2.46 (3 H, s, Me), 5.64 (1 H, q, =CH), 7.4 (2 H, d), 7.8 (2 H, d). **9b**: found: C, 57.7; H, 6.4; S, 10.55. Calc. for $C_{15}H_{20}O_5S$: C, 57.7; H, 6.45; S, 10.3%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.41 (9 H, s, Me), 2.0 (3 H, d, Me), 2.43 (3 H, s, Me), 5.42 (1 H, q, =CH), 7.33 (2 H, d), 7.87 (2 H, d).

Attempted reduction of 9a with $^2H_2$

Reaction of **9a** (3.0 g, 9.5 mmol) for 4 days at 40 °C with $^2H_2$ (150 psi) and $Rh(PPh_3)_3Cl$ (0.30 g, 0.32 mmol) in C_6H_6 or 5% Rh/C in cyclohexane led to (*E*)-3-tosyloxy-2-butenoic acid **10** (0.81 g, 34%), mp 123.5–124.5 °C (from EtOH–H_2O). **10**: found: C, 51.1; H, 5.0; S, 12.8. Calc. for $C_{11}H_{12}O_5S$: C, 51.5; H, 4.7; S, 12.5%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.31 (3 H, d), 2.47 (3 H, s), 5.70 (1 H, q), 7.37 (2 H, d), 7.82 (2 H, d). Reaction of **9a** with H_2 and 5% Rh/C in 1 : 1 v/v EtOD–C_6H_6 produced *p*-toluenesulfonic acid, ethyl butanoate, butanoic acid, and *tert*-butyl ethyl ether.

tert-Butyl 3-tosyloxybutanoate 11

Reaction of *tert*-butyl 3-hydroxybutanoate with *p*-tosyl chloride in the presence of DMAP in CH_2Cl_2 produced **11**: found: C, 57.3; H, 6.75; S, 10.3. Calc. for $C_{15}H_{22}O_5S$: C, 57.3; H, 7.05; S, 10.2%; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 (3 H, d), 1.40 (9 H, s), 2.42 (3 H, s), 2.46 (2 H, d), 4.97 (1 H, m), 7.33 (2 H, d), 7.79 (2 H, d).

S-tert-Butyl 3-tosyloxybutanethioate 12

Reaction of **11** with TFA, TFAA and $(CH_3)_3CSH$ gave **12**, mp 42–43.5 °C (from hexane). **12**: found: C, 54.7; H, 6.7. Calc. for $C_{15}H_{22}O_4S_2$: C, 54.5; H, 6.7%; δ_H (60 MHz; $CDCl_3$; Me_4Si) 1.3 (3 H, d), 1.4 (9 H, s), 2.4 (3 H, s), 2.7 (2 H, d), 4.9 (1 H, m), 7.3 (2 H, d), 7.8 (2 H, d); *m*/*z* (ESIMS) 353.0858 (M^+; calc. for $C_{15}H_{22}O_4S_2Na$: 353.0852).

tert-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-hydroxy-2,3-$^2H_2$-butanoate

Hydrolyses of *tert*-butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-acetoxy-2,3-$^2H_2$-butanoate[5] were carried out in stirred solutions of 1 : 1 v/v EtOH–H_2O at 22 °C for 45–60 min, using 2.0 mL solvent per 1.0 g substrate and 10% molar excess KOH. Reactions were quenched with 1–2 drops of acetic acid and after standard workup the crude product mixtures were used in the syntheses of **1** and **2**.

tert-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-tosyloxy-2,3-$^2H_2$-butanoate 1 and 2

A solution of tosyl chloride (17.6 g, 90.5 mmol) in pyridine (68 mL) was added dropwise to *tert*-butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-hydroxy-2,3-$^2H_2$-butanoate (3.0 g, 18.5 mmol) over 30 min while stirring, and the reaction was continued for 14 h. After filtration, a few mL of ice were added and the mixture was stirred for 10 min. Addition of hexane, washing with H_2O, HCl and $NaHCO_3$, and purification by flash chromatography (60 : 1 SiO_2 : compd, 10–20% Et_2O–hexane) produced **1** (4.7 g, 77%) and **2** (3.7 g, 63%). **1**: δ_D (76 MHz; C_6H_6; C_6D_6) 2.07 (s, 2CD), 5.06 (s, 3CD); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.31 (3 H, s), 1.44 (9 H, s), 2.44 (3 H, s), 2.63 (1 H, br s), 7.31 (2 H, d), 7.81 (2 H, d). **2**: δ_D (76 MHz; C_6H_6; C_6D_6) 2.45 (s, 2CD), 5.06 (s, 3CD); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.31 (3 H, s), 1.44 (9 H, s), 2.44 (3 H, s), 2.40 (1 H, br s), 7.31 (2 H, d), 7.81 (2 H, d).

S-tert-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-tosyloxy-2,3-$^2H_2$-butanethioate 3 and 4

To 3.0 g (9.5 mmol) of esters **1** and **2** at 0 °C (N_2, stirring) were added 3.0 molar equiv. TFA, and the mixture was allowed to return to rt. After 13 h 1.2 molar equiv. of TFAA were added at 0 °C. After 1 hr 1.2 molar equiv. of 2-methyl-2-propanethiol were added and the reaction was continued for 22 h, followed by an aqueous workup (Et_2O, H_2O, $NaHCO_3$, evaporation). Recrystallization from hexane produced **3** (2.05 g, 65%), mp 46–47 °C and **4** (2.4 g, 76%), mp 46–48 °C. **3**: δ_D (76 MHz; C_6H_6; C_6D_6) 2.19 (s, 2CD), 5.00 (s, 3CD); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, s), 1.40 (9 H, s), 2.44 (3 H, s), 2.85 (1 H, br s), 7.31 (2 H, d), 7.81 (2 H, d). **4**: δ_D (76 MHz; C_6H_6; C_6D_6) 2.61 (s, 2CD), 5.00 (s, 3CD); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.29 (3 H, s), 1.40 (9 H, s), 2.44 (3 H, s), 2.59 (1 H, br s), 7.31 (2 H, d), 7.81 (2 H, d).

General method for elimination reactions of deuterated substrates

Stereospecifically deuterated tosyloxyester and thioester substrates (250–800 mg) were stirred in 3 : 1 v/v EtOH–H_2O in a 22–25 °C water bath with 10% molar excess KOH. Concentrations were 1.6 M for **1** and **2** and 1.13 M for **3** and **4**. Reaction times for esters **1** and **2** were 7–8 min and for thioesters **3** and **4** were 30 s. Reactions were quenched with 2–4 drops of acetic acid and then neutralized with $NaHCO_3$. Flash chromatography (SiO_2/hexane–Et_2O), careful evaporation at rt or short path distillation, analysis by capillary GC, and separation by preparatory GC led to the recovery of deuterated **5** from ester substrates and **6** from thioester substrates. The (*Z*)-alkene product from **3** was also recovered in one experiment and was ~99% deuterated at C-2. Alkenes **5** and **6** were analyzed by multiple ^2H NMR integrations (C_6H_6) of samples from two or more separate experiments. **5**: δ_D (76 MHz; C_6H_6; C_6D_6) 5.73 (s, 2CD), 6.82 (s, 3CD); δ_H (200 MHz; C_6D_6; C_6H_6) 1.34 (3 H, s), 1.41 (9 H, s), 5.75 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s), 1.85 (3 H, s), 5.75 (s). **6**: δ_D (76 MHz; C_6H_6; C_6D_6) 5.91 (s, 2CD), 6.69 (s, 3CD); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.46 (9 H, s), 1.81 (3 H, s), 5.95 (s).

k_H/k_D kinetic isotope effects

KIEs were determined from the percentages of *syn* and *anti* elimination from substrates **1–4** and the 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. The relative rates were corrected for the percentages of (*Z*)-alkenes from the two diastereomers in the calculation of $k_{R^*S^*}/k_{R^*R^*}$. For each pair of substrates 2–3 competition reactions were run. After SiO_2/hexane–ether flash chromatography and careful rotary evaporation at <30 °C, the extent of the reactions of **3** and **4** was ascertained by 200 MHz ^1H NMR integrations of the tosyloxy CH_3 peak, as well as the allyl CH_3 peaks of **6** and its (*Z*)-isomer, using carefully determined sensitivity factors ($CDCl_3$, 2.0 s delay). The extent of the reactions of **1** and **2** and the diastereomeric composition in reactions of **1**/**2** and **3**/**4** were determined directly by multiple 76 MHz ^2H integrations (C_6H_6) 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.

Values for $(k_H/k_D)_{syn}$ are subject to much greater relative error than $(k_H/k_D)_{anti}$, because the values of the *syn* KIE depend directly upon the very small percentage of *syn* elimination from the (2*R**,3*S**) diastereomers. A worst-case analysis showed that whereas $(k_H/k_D)_{anti}$ could have as much as ±5% relative error, the relative error for $(k_H/k_D)_{syn}$ could be as high as ±25%.

Conclusion

In conclusion, we have shown that contrary to earlier suggestions, activation by a carbonyl group has virtually no influence upon the stereoselectivity of base-catalyzed, 1,2-elimination reactions of β-tosyloxybutanoate esters and thioesters, even though these reactions take place at the E2–E1cB interface. Under conditions in which aggregation phenomena and the complex conformational effects of cyclic compounds play no role, electronic effects by themselves do not seem to be a major determining factor leading to *syn* elimination.

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