Stereospecific Synthesis of 2-Deuterio-3-hydroxybutanoate Esters. Regiochemistry and Stereochemistry of Homogeneous Hydrogenation with Wilkinson's Catalyst

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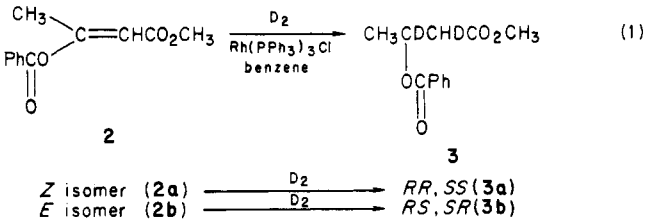
Hydrogenation of the methyl esters of (*Z*)- and (*E*)-3-(benzoyloxy)-2-butenoate produces reduced products in good yield with highly stereoselective syn addition. Reaction of the alkenes with deuterium is preferable to reaction of the 2-deuterioalkenes with hydrogen. NMR measurements indicated 99.8% or greater syn addition of D_2 with the *Z* alkene. Addition of HD to the *E* alkene produced no regioselectivity, indicating that either the alkylrhodium intermediate forms without kinetic isotope effects or without regioselectivity.

Hundreds of papers on the use of Rh(I)–phosphine catalysis in the hydrogenation of alkenes have appeared in the past few years and extensive studies of the reaction mechanisms have been carried out.[1,2] Much less work has been done to exploit the usefulness of Rh(I) catalysis in the synthesis of isotopically labeled molecules of known relative configuration.[2c] The stereochemical ambiguities and isomerizations that can accompany heterogeneous catalysis are well-known.[3] It is not uncommon for deuterium scrambling to accompany the addition of D_2 to alkenes, reflecting adsorption–desorption equilibria on the catalyst surface. Naturally, the value of any measurement of reaction stereochemistry rests upon unequivocal assignment of the configurations of reactant and product. Configurational determinations can be more difficult in acyclic, conformationally mobile molecules than with cyclic systems. Yet, for stereochemical investigations it is vital that the configurational purity of isotopically labeled acyclic substrates be accurately known.

Hydrogenations with Wilkinson's catalyst, $Rh(PPh_3)_3Cl$ (**1**), have consistently shown syn stereoselectivity, with NMR coupling constants usually being used to distinguish relative configurations.[4] Of course, it is difficult to assess configurational purity with accuracy by this method. More recent work has focused upon asymmetric hydrogenation of (*N*-acylamino)alkenes usually with Rh(I) ligated to chiral bis(phosphines); addition of D_2 has been shown to proceed with highly stereoselective syn addition.[5] It is not clear if chelation of the *N*-acylamino group to rhodium influences the stereoselectivity of the addition.

Derivatives of β-hydroxybutyric acid are important biochemical metabolites. In fact, polymers of this acid are the dominant carbon and energy storage form for many bacteria. Many bioorganic studies of this system demand the availability of 2-deuterio- or 2-tritio-3-hydroxybutanoic acid or their esters, in which the relative configurations of the chiral centers are unambiguous. In conjunction with our studies on the stereochemistry of base-catalyzed elimination reactions which produce carbon–carbon double bonds conjugated to carbonyl groups,[6] we set out to determine the stereoselectivity of homogeneous hydrogenation using **1** with methyl (*Z*)- and (*E*)-3-(benzoyloxy)-2-butenoate (**2**).



Our earlier work on the stereospecific synthesis of 2-deuterio-3-hydroxybutanoic acid depended upon the S_N2 opening of an epoxide with borodeuteride.[7] NMR analysis indicated complete stereoselectivity and product yields were acceptable. It was an efficient synthetic method for isotopically labeled 3-hydroxybutanoic acid, but unfortunately only the *RR*, *SS* mixture was available by this route. Homogeneous hydrogenation of **2** seemed an attractive alternate for the synthesis of both **3a** and **3b**.

Results

The synthesis of β-(acyloxy)-α,β-unsaturated esters can be accomplished in good yield by the method of Casey and Marten.[8] Clean separation of the *Z* and *E* isomers was possible on a silica gel column. The stereochemical assignments in **2a** and **2b** rest upon NMR shift correlations.[8,9] Protons that are cis to oxygen and carbalkoxy groups are shifted downfield.

In our initial work we expected to use **2**, substituted with deuterium at C-2, as the hydrogenation substrate. Methyl acetoacetate-2-$^2H_2$ (4-$^2H_2$) was synthesized in two cycles from methyl acetoacetate (**4**) by reaction with NaH in diethyl ether, followed by addition of D_2O/D_2SO_4. One deuteration cycle produced **4** with 17% H at C-2; two cycles gave 4-$^2H_2$ with only 3% H at C-2 (multiple NMR integrations). There was also some H/D exchange at C-4

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(~8% D). Reaction of 4-$^2H_2$ with isopropenyl acetate and *p*-toluenesulfonic acid[8] gave a great deal of H/D exchange and low isotopic yields of **2a**-$^2H_1$. Exchange was not a major problem with triethylamine catalysis and product yields were high (80–90%). Since with amine catalysis benzoyl chloride gives higher yields of enol esters than does acetyl chloride,[8] we chose the former. Our few reactions with acetyl chloride confirmed the lower yields, although this route has been used recently to produce deuterated β-(acyloxy)crotonates.[10] Since H/D exchange during the reaction always decreased the deuterium content of **2**-$^2H_1$ (93–96% D was normal) and since prevention of H/D exchange during the purification of 4-$^2H_2$ was troublesome, our later work delayed the incorporation of deuterium until the hydrogenation step.

The best-known method of homogeneous hydrogenation with unambiguous stereochemistry uses diimide as the reductant. Unfortunately, diimide adds slowly to trisubstituted double bonds and those with electron-withdrawing substituents. We found its use for the reduction of **2** completely impractical, due to the extremely slow hydrogenation rate and competing pathways for the decomposition of diimide under reduction conditions.

Reduction of **2** in the presence of $Rh(PPh_3)_3Cl$/benzene led to 85–95% yields of recovered **3**. As expected, the *Z* isomer was reduced substantially faster than the *E* isomer and addition of D_2 was faster than addition of H_2 under comparable conditions.[1,5b,c,11,12] At 50 °C and 10.2 atm D_2 the *Z* isomer (**2a**) was reduced completely in 24 h and **2b** in 5 days. A benzene–ethanol solvent is known to produce faster reduction rates with Wilkinson's catalyst but could not be used because of substantial H/D exchange with the solvent. There was no indication of *E*/*Z* isomerization as has sometimes been observed.[5b,13] Irregular induction periods were not noticed and the reductions were quite reproducible. Slow, irregular reductions of β-(acyloxy)-crotonates and the darkening of the reaction mixtures, along with the facile reduction of these substrates with 5% Rh/C, have led to the suggestion that Rh(0) is in fact the active catalyst.[10] This seems unlikely since addition of D_2 to **2** with Rh/C catalysis is accompanied by substantial deuterium incorporation at C-4 of **3**; no H/D exchange at C-4 accompanies the homogeneous catalysis.[14] In addition, substantial scrambling of tritium has been observed when H_2/HT was added to α,β-unsaturated carbonyl compounds in the presence of 5% Rh/C but not with $Rh(PPh_3)_3Cl$/benzene.[15]

The addition of D_2 to **2a** and **2b** (reaction 1) gives a clear demonstration of the stereoselectivity of hydrogenation with Wilkinson's catalyst. Figure 1 shows the complementary spectra. As expected, the nondeuterated analogue of **3**, methyl 3-(benzoyloxy)butanoate (**5**), exhibits an ABX pattern in the peaks associated with the C-2 protons; J_{AX} = 7.36 Hz, J_{BX} = 5.74 Hz, and J_{AB} = −15.46 Hz. Syn addition of deuterium to the *Z* alkene produced the racemic mixture **3a**, methyl (*R*,*R*)- and (*S*,*S*)-3-(benzoyloxy)[2,3-$^2H_2$]butanoate, whose principal peak is downfield (Figure 1a). The converse is the case with **3b**; here, syn addition of deuterium to the *E* alkene produced the (*R*,*S*) and (*S*,*R*) mixture (Figure 1b).

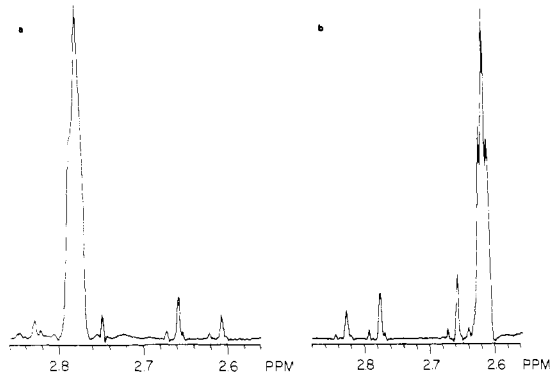

Figure 1. (a) The AB portion (protons at C-2) of the 300-MHz NMR spectrum of **3a**. (b) The AB portion of **3b**.

The assignment of relative configurations in **3a** and **3b** rests upon the comparison of their NMR spectra with those of compounds whose configurations have been determined unambiguously. The NMR spectrum of the known racemic mixture, (*R*,*R*)- and (*S*,*S*)-*S*-*tert*-butyl 3-acetoxy[2-$^2H_1$]butanethioate, revealed the C-2 proton in the downfield portion of the AB pattern. Its configurational assignment rests upon the known stereochemistry of the S_N2 reaction, as well as upon confirming values of NMR coupling constants.[7] That the C-2 proton of **3a** is also in the downfield portion of the AB pattern suggests that it has the same configuration as the thioester. Thus, **3a** is a racemic mixture with the *R*,*R* and *S*,*S* configurations. This can be formed in reaction 1 only by a syn addition of D_2 to **2a**. In the same way, **2b** reacted by syn addition to give the *R*,*S* and *S*,*R* mixture **3b**.

Confirming evidence for these assignments comes from the work of Rozzell,[10] who related the hydrogenation products from β-(acyloxy)crotonates to (2*R*),(3*S*)-3-hydroxy[2-$^2H_1$]butanoic acid; the configurational assignments depended upon the syn addition of tritiated diborane to ethyl crotonate.[16] In every known example of 3-hydroxy[2-$^2H_1$]butanoic acid and its esters, the *R*,*R* and *S*,*S* mixture has the C-2 proton in the downfield part of the AB pattern and the *R*,*S* and *S*,*R* mixture has the C-2 proton in the upfield part when $CDCl_3$ is the solvent. This may prove to be a useful correlation for the configurations of other isotopically labeled esters of 3-hydroxybutanoic acid.

A quantitative value for the stereoselectivity with **1** comes from examination of Figure 1a. In this case the geminal deuterium isotope effect[17] should shift the C-2 proton resonance of any **3b** to δ 2.615, where it appears in Figure 1b. There is a barely distinguishable peak at this position in Figure 1a. By analysis of peak heights one can calculate that the stereoselectivity of the deuterium addition to **2a** was 99.8% or greater. Homogeneous catalysis with $Rh(PPh_3)_3Cl$ provides a stereospecific route to **3a** and **3b**.

Preliminary results also indicate that *tert*-butyl (*E*)-3-acetoxy-2-butenoate reacts with D_2 in the presence of **1** to give the racemic mixture, (*R*,*S*)- and (*S*,*R*)-*tert*-butyl 3-acetoxy[2,3-$^2H_2$]butanoate, by a stereospecific syn addition.

The minor peaks of Figure 1 result from the presence of small amounts of monodeuterated and nondeuterated products. For example, the two major peaks in the upfield portion of Figure 1a come from addition of HD to **2a** to give methyl 3-(benzoyloxy)[3-$^2H_1$]butanoate (**6**). Vicinal

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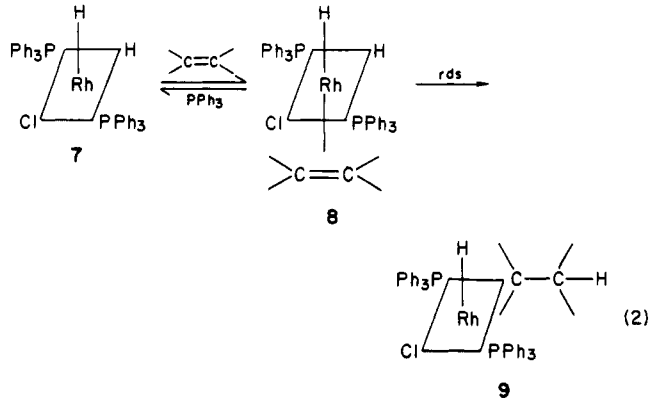
H–D coupling constants are small and the two protons at C-2 effectively reduce to an AB system, somewhat shifted upfield by the deuterium at C-3. Four tiny peaks in the upfield portion of Figure 1a indicate the presence of nondeuterated **5**. A similar pattern can be seen in the downfield portion of Figure 1b. The magnitude of the geminal H–D coupling constant (2.0 Hz in **3b**) is within the expected range.[17]

Discussion

Although details of the mechanism may vary for different alkenes and reaction conditions, Halpern's mechanism for catalysis by **1** provides the best starting point.[2c,18] In part of this pathway, the alkene is seen to coordinate with rhodium to form **8**, after oxidative addition of hydrogen has formed the dihydride species **7** (reaction 2). The syn addition of rhodium and hydrogen to the coordinated alkene is the rate-determining step under ordinary conditions. This is followed by cleavage of the carbon–rhodium bond in **9** and formation of the second C–H bond with retention of configuration.

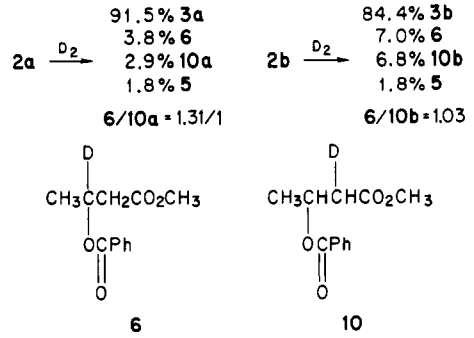


(*N*-acylamino)alkenes, carboxylates, and carboxamides have been shown to chelate with rhodium in cationic complexes involving chelating bis(phosphine) ligands.[19] It is difficult to know if such chelation through alkene carbon and ester oxygen would come into play when **2a** or **2b** are present in **8** and **9**. Formation of **9** has been shown to be regiospecific.[19a,b]

Addition of HD to C-2 and C-3 of **2a** and **2b** has interesting regiochemical aspects. One might expect to see regioselectivity if a deuterium isotope effect influences the rate of the product-determining step. In one instance, the kinetic isotope effect (k_H/k_D) for the conversion of **8** to **9** was 1.15.[18a] However, on several occasions a complete lack of regioselectivity has been observed in the addition of HD.[5b,20] The alkenes varied from propene and styrene to (*Z*)-α-acetamidocinnamic acid and *N*-vinylacetamide. In the later study, (*Z*)-α-acetamidocinnamic acid showed modest regioselectivity (1.35/1).[20b]

It was possible to analyze the spectra in Figure 1 to estimate the regioselectivity in the addition of HD to **2a** and **2b**. The two major peaks in the upfield portion of Figure 1a result from the addition of HD to **2a**, giving **6**. A small multiplet at δ 5.5 in the spectrum of **3a** is due to the presence of nondeuterated **5**, as well as monodeuterated **10a**. Careful integrations of the spectra of **3a** and **3b**, each from two separate hydrogenations, showed the compositions in Chart I.

Chart I. Product Distribution and Regiochemistry of HD Additions



An attractive hypothesis for the lack of regioselectivity in the addition of HD to **2b** is that there is a prior commitment as to which hydrogen adds in the formation of **9**. Since it is clear that formation of the Rh–C and H–C bonds in **9** has syn stereochemistry, only the hydrogen in the plane is able to add. The *trans*-hydrogen cannot add, along with rhodium, in a syn process. Whether deuterium is a trans or cis ligand to the alkene is determined in the oxidative addition step. One expects that there would be an equal equilibrium distribution of H and D in the two ligand positions. Lack of overall regioselectivity would result no matter which carbon is bound to rhodium in **9**. The small regioselectivity seen in addition of HD to the *Z* isomer **2a**, which is reduced over five times faster than **2b**, may reflect lesser equilibration of **7** and **8**.

Conclusion

The addition of hydrogen or deuterium to β-(acyloxy)-crotonates in the presence of $Rh(PPh_3)_3Cl$ is a syn process and the stereoselectivity is very high. The reaction provides an efficient synthetic route for 2-deuterio-3-hydroxybutanoate esters of unambiguous relative configuration, which will be useful in bioorganic studies. Lack of regioselectivity in the addition of HD to alkenes with Wilkinson's catalyst may simply result from the lack of discrimination between H and D for the axial and equatorial positions of the oxidative addition reaction intermediate.

Experimental Section

General Methods. Proton NMR spectra were run on a 60-MHz Perkin Elmer R-24B spectrometer and a 300-MHz Nicollet NT-300 spectrometer with $CDCl_3$ solutions and Me_4Si as the internal standard. For GC analyses, 6-ft columns of 8% Carbowax 1540 and 8% SF-96 on Anakrom ABS were used on a Carle GC-8700. Glassware was oven dried and cooled in a desiccator where appropriate. All reactions of deuterated compounds were carried out under a N_2 atmosphere. Benzoyl chloride was distilled under N_2; hexane and triethylamine were distilled from Na under N_2 before use.

Synthesis of Methyl Acetoacetate-*2*-$^2H_2$ (4-$^2H_2$). Methyl acetoacetate (0.487 mol, Aldrich, 99+%) was added dropwise to a stirred slurry of NaH (0.583 mol) in Et_2O (200 mL) over a 45-min period. Et_2O was added as necessary for efficient stirring. After H_2 evolution ceased (1.5 h), 10 mL of D_2O (99.8% D) was added and the stirring continued for 40 min. A solution of D_2SO_4 (98%, 12 mL) in D_2O (20 mL) was added dropwise over a 1-h period; additional D_2SO_4 was used to bring the pH to 7. The ether solution was decanted and evaporated under vacuum. Vacuum distillation at 2.6 kPa gave a 60–80% yield of 4-$^2H_2$. NMR integration showed 80–90% deuteration at C-2. The 4-$^2H_2$ product after a second exchange reaction had 97% deuterium at C-2.

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Synthesis of Methyl (*Z*)- and (*E*)-3-(Benzoyloxy)-2-butenoate (2).[8] A solution of **4** (11.0 g, 0.095 mol), triethylamine (12.3 g, 0.12 mol, Aldrich, 99%), and 50 mL hexane (Mallincrodt, AR) was cooled to 0 °C. Benzoyl chloride (16.9 g, 0.12 mol, Aldrich, 99+%) was added dropwise over a 40-min period to the stirred solution. After 1.5 h, the reaction was stirred at 25 °C for an additional 3 h. Water (50 mL) and Et_2O (50 mL) were added and two layers formed. The separated water layer was extracted again with 50 mL of Et_2O. After washing the combined Et_2O solutions (H_2O, 0.05 M Na_2CO_3, 0.05 M Na_2CO_3/NaCl, saturated NaCl), the Et_2O was filtered, dried ($MgSO_4$), and removed by evaporation. The crude product was distilled through a Vigreaux column at 3.3 Pa giving a 70% yield of **2**; yields ranged over 70–90%. NMR integrations showed that the product was 70% *E* isomer (**2b**) and 30% *Z* isomer (**2a**).

Separation of **2a** and **2b** was carried out on silicic acid (100 mesh, Mallincrodt) with N_2 pressure with 20 g of silicic acid per gram of alkene. Columns were packed by using hexane and eluted with hexane–Et_2O (95:5). The **2b** isomer eluted first and could be followed down the column by using a UV lamp. When **2b** reached the bottom of the column, the eluent was changed to 9:1 hexane–Et_2O. Elution of **2a** was done with 7:3 hexane–Et_2O. **2a** was a white solid, mp 54 °C. For separation of 5 g of **2**, 85% recovery of pure **2a** and **2b** was usual. NMR analysis of **2a** showed peaks at δ 2.1 (s, 3 H), 3.5 (s, 3 H), 5.65 (s, 1 H) and 7.5 and 8.0 (m, 5 H); **2b** had peaks at δ 2.45 (s, 3 H), 3.65 (s, 3 H), 5.8 (s, 1 H) and 7.5 and 8.0 (m, 5 H).

Synthesis of 2-$^2H_1$. The usual procedure for synthesis of **2** was employed. Yields of 80–90% were obtained from **4**-$^2H_2$. Even with great care to exclude proton sources, **2**-$^2H_1$ had 10% ^1H at C-2 when starting with **4**-$^2H_2$ having 3% ^1H. Addition of 3 mL of D_2O to the reaction mixture gave **2**-$^2H_1$ with 4% ^1H at C-2. Vacuum distillation of this product caused an additional loss of deuterium content.

Attempted Reduction of 2 with N_2H_2. Potassium azodicarboxylate was synthesized from azodicarbonamide (Aldrich) by using a 40% KOH solution at 0 °C.[21] It was stored under N_2 at 0 °C. Reaction of a 3-fold excess of potassium azodicarboxylate with **2b** in dry dioxane, with acetic acid/dioxane added dropwise in the usual manner,[21] gave no formation of **3** (NMR analysis) after 71 h, at which time the brilliant yellow color of potassium azodicarboxylate was gone.

Reduction of 2a with D_2/Rh(PPh$_3$)$_3$Cl (1). Nitrogen (Airco, 99.999%) was bubbled through 50 mL of benzene (Mallincrodt, thiophene free) for 20 minutes. Under a N_2 atmosphere the deoxygenated benzene, along with **2a** (3.0 g, 0.014 mol) and **1** (0.4 g, 8.6×10^{-4} mol, Aldrich), was sealed into a 300-mL Parr 452 HC high-pressure reaction vessel. The reaction vessel was charged with D_2 (3.4 atm, MG Scientific Gases, 99.5% D), the gas vented, and the vessel recharged with D_2 (10.2 atm). The reaction was run for 24 h at 40 °C. The crude reaction mixture was a clear, golden liquid. After evaporation of the solvent, petroleum ether (60 mL, bp 30–60 °C, Baker, AR) was added; **1** was removed by suction filtration and the petroleum ether by evaporation. NMR analysis of the crude product showed that the reduction was complete and indicated 5.6% ^1H at C-2 and no deuterium at C-4.

The crude product (2.7 g) was chromatographed on silicic acid (40 g, Mallincrodt, 100 mesh) in the usual way with hexane–Et_2O (95:5). A 1.97-g yield (73%) of methyl (*R*,*R*)- and (*S*,*S*)-3-(benzoyloxy)[2,3-$^2H_2$]butanoate (**3a**) was recovered as a faintly yellow liquid. NMR analysis of **3a** showed peaks at δ 1.4 (s, 3 H), 2.77 (s, 1 H), 3.65 (s, 3 H) and 7.4 and 8.0 (m, 5 H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.82; H, 6.39.

Reduction of 2b with D_2/1. The same procedure was followed as above except that complete reduction occurred only after 5 days. The methyl (*R*,*S*)- and (*S*,*R*)-3-(benzoyloxy)[2,3-$^2H_2$]butanoate (**3b**) product had 7.8% ^1H at C-2 and no deuterium at C-4. The proton decoupled ^2H NMR spectrum of **3b** at 46 MHz showed only two signals (δ 2.77 and 5.50) of approximately equal area, corresponding to deuterium at C-2 and C-3. The NMR spectrum of **3b** was the same as that of **3a** except the C-2 proton was at δ 2.62.

Reduction of 2-$^2H_1$ with H_2/1. The same procedures were used as above except that H_2 (3.9 atm) was the reductant and benzene–ethanol (1:1) was the solvent. The reaction was run at 50 °C in a Parr 3910 hydrogenation apparatus and produced a deep rust-colored liquid. **2a**-$^2H_1$ was reduced in 2 days, whereas reduction of **2b**-$^2H_1$ was complete only after 15 days. Yields of crude products were 90% or greater.

Synthesis and Reduction of *tert*-Butyl (*Z*)- and (*E*)-3-Acetoxy-2-butenoate (11). The same general procedures used in the synthesis of **2** were employed. Acetyl chloride (15.0 g, 0.19 mol) was added dropwise over 60 min to the hexane solution of *tert*-butyl acetoacetate (15.0 g, 0.095 mol, Aldrich, vacuum distilled under N_2) and triethylamine. Only 60% reaction had occurred within the usual reaction time. Distillation of the crude product gave 6.8 g (60% yield) of **11**, bp 60 °C (5.3 Pa). NMR analysis indicated 55% of the *E* isomer and 45% *Z* isomer.

Chromatography of 4.5 g of **11** with silicic acid (100 g) and elution with hexane, replaced later with hexane–Et_2O (95:5, 9:1), gave 3.4 g of pure alkenes. NMR analysis showed the following peaks. *E* isomer: δ 1.45 (s, 9 H), 2.1 (s, 3 H), 2.25 (s, 3 H) and 5.5 (s, 1 H). *Z* isomer: δ 1.4 (s, 9 H), 1.9 (s, 3 H), 2.15 (s, 3 H) and 5.4 (s, 1 H).

Reduction of (*E*)-**11** (1.98 g) with D_2/1 under the usual conditions gave (*R*,*S*)- and (*S*,*R*)-*tert*-butyl 3-acetoxy[2,3-$^2H_2$]butanoate (1.62 g, 81% yield). NMR analysis showed peaks at δ 1.28 (s, 3 H), 1.44 (s, 9 H), 2.0 (s, 3 H) and 2.39 (t, 1 H). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.56; H, 8.86.

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