An optimized protocol for the Dibal-H reductive acetylation of acyclic esters and diesters is described. This reductive acetylation procedure allows a wide variety of esters to be converted into the corresponding α-acetoxy ethers in good to excellent yields. It was found that, under mild acidic conditions, many α-acetoxy ethers can be further reduced to the corresponding ethers. This net two-step ester deoxygenation is an attractive alternative to the classical Williamson synthesis for certain ethers.

Introduction

The reduction and in situ acetylation of esters was developed in our laboratory several years ago to provide access to unusual cyclic acetal structures. The general strategy involved trapping the aluminum hemiacetal intermediate found in the reduction of an ester to an aldehyde by disobutylaluminum hydride (Dibal-H). Other groups had previously trapped the same type of intermediate with a trimethylsilyl group. After some exploration, we found that acetic anhydride, Dmap, and pyridine led to efficient trapping to give α-acetoxy ethers from the cyclic esters we had been studying. We were surprised to find that the same conditions gave satisfactory yields of the α-acetoxy ethers from acyclic esters. The α-acetoxy ethers can be activated with a variety of Lewis acids to give oxacarbenium ions. Thus, the synthesis of α-acetoxy ethers from acyclic esters is a potentially general route to new oxacarbenium ions. We have used this strategy in a new entry to Prins cyclization reactions. The reductive acetylation conditions were initially developed for cyclic esters and did not work well with some acyclic substrates. We have now optimized the reaction for the reduction of acyclic esters, and the results are reported below.

Results and Discussion

Optimization Studies. The original protocol for the reductive acetylation of lactones and some acyclic esters with Dibal-H is shown in Figure 1.1 Treatment of an ester of general structure 1 with a slight excess (1.1 equiv) of Dibal-H in dichloromethane at −78 °C for 2 h generated the proposed aluminum hemiacetal intermediate 2, which then underwent acetylation at low temperature by the combined action of acetic anhydride, pyridine, and a slight excess (1.1 equiv) of 4-(dimethylamino)pyridine (Dmap). After gradual warming to −20 °C over a 12 h period, an α-acetoxy ether of the general structure 3 was isolated. The reaction conditions described above were found to be effective for the reductive acetylation of cyclic esters and several acyclic esters, but further studies in our laboratory have demonstrated that a number of acyclic esters do not undergo efficient reductive acetylation under these conditions. In some cases, incomplete conversion and/or overreduction predominate. Clearly, there is a need for more versatile and structurally tolerant Dibal-H reductive acetylation conditions. Several key reaction parameters were examined at the outset. The exclusion of either Dmap or pyridine from the acetylation step was shown to preclude the formation of any α-acetoxy ether product. Also, the gradual warming of the reaction mixture to 0 °C instead of −20 °C during the acetylation step had no effect upon the reaction outcome. Thus, the reductive acetylation reactions described below were all warmed to a final temperature of 0 °C for the sake of convenience. It is critical that the acetylation step be conducted at low temperature (−78 °C) for an extended period of time (12–14 h) before forcing the reaction to completion by warming to 0 °C. If the acetylation is warmed to 0 °C too quickly, decomposition of the aluminum hemiacetal intermediate (2) predominates. Early optimization studies focused upon the...
of desired
of the quenching agents tested led to diminished yields
DIBALH for 30 min prior to acetylation (Table 1). Most
the slow acylation step. A series of experiments examined
entries 2
addition of a larger excess of DMAP (2.0 equiv, Table 2,
yield. This study (Table 2) clearly suggested that the
was the impact of DMAP stoichiometry upon product
formations of the corresponding hemiacetal intermediate
was determined that the reduction of ester
acetylation of the aluminum hemiacetal intermediate.

1.1 equiv of DMAP, and 4.0 equiv of Ac₂O were used.
were determined by 1H NMR and gas chromatographic analysis
of partially purified mixtures.
DIBALH reductive acetylation of valerate ester 4. We
chose ester 4 as a test substrate since it possesses
moderate complexity and is an acyclic precursor for a
Lewis acid-mediated Prins cyclization.3 Preliminary stud-
ies suggested that increasing the amount of reducing agent and reducing the reaction time before the in situ
acylation step minimized overreduction. Specifically, it
was determined that the reduction of ester 4 with a 2-fold excess of DIBALH for 45 min at low temperature prior
to acetylation was optimal.

When 2.0 equiv of DIBALH was utilized, a full equiva-
Ient of DIBALH was present in solution after complete
formation of the corresponding hemiacetal intermediate
of 4. This excess reagent may lead to complications in
the slow acylation step. A series of experiments examined
the effectiveness of in situ quenching of the excess
DIBALH for 30 min prior to acetylation (Table 1). Most
of the quenching agents tested led to diminished yields
of desired α-acetoxy ether 5 and increased yields of
acylated overreduction product 6 (Table 1, entries 2–4).
Water was the sole quenching agent that partially
suppressed overreduction (entry 5), suggesting that the
presence of a small amount of ice in the –78 °C dichlo-
romethane solution before acetylation may be beneficial.

Another key variable that was independently examined
was the impact of DMAP stoichiometry upon product yield. This study (Table 2) clearly suggested that the
addition of a larger excess of DMAP (2.0 equiv, Table 2,
entries 2–3) to the reaction increased product formation.4
This trend can be rationalized by considering the compet-
ing reaction rates: since DMAP catalyzes the acetylation
reaction, the presence of greater amounts of DMAP in
the reaction leads to a heightened rate of aluminum
hemiacetal acylation versus aluminum hemiacetal break-
don. The use of >2 equiv of DMAP provided no
additional benefit to the reaction outcome (Table 2, entry 4). The effect of solvent choice upon the reductive
acylation of 4 was also explored. For compound 4, as
well as a number of other acyclic esters examined,
toluene and dichloromethane proved to be equally effec-
tive reaction mediums, although overall yields tend to
be slightly lower in toluene solvent in most cases (for
example, see Table 2, entry 3). Other solvents such as
ether, tetrahydrofuran (THF), and mixtures of hexanes
and toluene were not as effective. The reductive acety-
ation of 4 in these solvents led to significantly dimin-
ished yields (30–62%) of 5 under conditions identical to
those described in Table 2.

At this point, the efficacy of incorporating a DIBALH
quenching step prior to in situ acetylation was investi-
gated. Recall that water was effective in earlier studies
(Table 1), so in situ quenching with water was examined.
The effectiveness of an ethyl formate quench was also
explored. These quenching experiments establish that,
for both dichloromethane and toluene solvent, the in situ
quenching of excess DIBALH with either quenching
agent for 30 min prior to acetylation generates yields
(75–82%) of α-acetoxy ether 5 comparable to that of the
normal two-step protocol (79%, see Table 2, entry 2). The
inclusion of a DIBALH quenching step in the reductive
acylation procedure was deemed unnecessary.

The optimization studies described above for valerate
ester 4 have established the need for several key modi-
fications of the original DIBALH reductive acetylation
conditions (Figure 1) when the starting ester substrate
is acyclic. These changes include increasing the DIBALH
stoichiometry (2.0 equiv) and reducing the duration of
the reduction before acetylation (45 min). Moreover, the
amounts of DMAP and acetic anhydride employed in
the acetylation step should be increased to 2.0 and 6.0 equiv,
respectively, and a gradual warming of the reaction to a
final temperature of 0 °C is preferred (Figure 2).

---

Table 1. Effect of DIBALH Quench on the Reductive Acetylation of Valerate Ester 4

<table>
<thead>
<tr>
<th>entry</th>
<th>quench (equiv)</th>
<th>5 yield (%)</th>
<th>6 yield (%)</th>
<th>7 recovered 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCO₂Et (3)</td>
<td>52</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (1.5)</td>
<td>44</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (1.5)</td>
<td>10</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>H₂O (1.5)</td>
<td>63</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>52</td>
<td>38</td>
<td>2</td>
</tr>
</tbody>
</table>

* For all entries, 2.0 equiv of DIBALH, 3.0 equiv of pyridine, and 1.1 equiv of DMAP, and 4.0 equiv of Ac₂O were used. The products were not cleanly separable by chromatography. Yields were determined by 1H NMR and gas chromatographic analysis of partially purified mixtures.

---

Table 2. Effect of DMAP on the Reductive Acetylation of Valerate Ester 4

<table>
<thead>
<tr>
<th>entry</th>
<th>equiv of DMAP</th>
<th>5 yield (%)</th>
<th>6 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>66</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>79</td>
<td>17</td>
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<tr>
<td>3</td>
<td>2.0</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>81</td>
<td>19</td>
</tr>
</tbody>
</table>

* For all entries, 2.0 equiv of DIBALH, 3.0 equiv of pyridine, and 6.0 equiv of Ac₂O were used. The products were not cleanly separable by chromatography. Yields were determined by 1H NMR and gas chromatographic analysis of partially purified mixtures. Toluene was used as the solvent.

---

(4) It was necessary to increase the amount of acetic anhydride employed when larger excesses of DMAP were used to ensure complete acylation of the aluminum hemiacetal intermediate.
Reductive Acetylation of Acyclic Esters. The applicability of these optimized DIBALH reductive acetylation conditions to a series of acyclic substrates was investigated (Table 3). In all cases, the α-acetoxy ether products were isolated in good to excellent yields (78–93%). The facile generation of hindered α-acetoxy ethers such as neopentyl acetal 11 and tert-butyl acetal 19 is remarkable (Table 3, entries 3 and 7), and the suppression of β-elimination in the formation of n-butyl acetal 21 is noteworthy (Table 3, entry 8). A substantial increase in the yield of cyclic acetal 25 from macroactone 24 under the optimized reductive acetylation conditions (84%, Table 3, entry 10) relative to the original protocol (72% yield) illustrates the utility of the optimized conditions for the reductive acetylation of lactones.

The improved DIBALH reductive acetylation protocol also elicited facile conversion of acyclic diesters into the corresponding bis-acetals (Table 4). The amounts of all reagents used were doubled for diester substrates relative to the standard reductive acetylation conditions for esters, but the reduction time was not altered. Diethyl malonate (26) and diethyl succinate (28) were transformed into bis-acetals 27 and 29, respectively, in good yields (60–75%, Table 4, entries 1–2). A minimal amount of the mono-acetal byproduct was detected in the reduction of 26. Bis-reductive acetylation of neopentyl glycol-derived diester 30 generated bis-acetal 31 in 66% yield (Table 4, entry 3) along with a low yield (19%) of the corresponding monoacetal. Several acyclic esters were problematic substrates. A larger excess of DIBALH was required for the complete conversion of benzyl-protected (S)-ethyl lactate 32 into α-acetoxy ether 33 (Scheme 1). Competing aluminum coordination by the benzylxoy group of 32 may account for the lower yield of the α-acetoxy ether product.

![Figure 2. Optimized DIBALH reductive acetylation conditions for acyclic esters.](image)

Table 3. DIBALH Reductive Acetylation of Acyclic Esters and Lactones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Ester</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>92</td>
<td>1:1:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>92</td>
<td>1:1:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph-CH₂-Cl</td>
<td>OAc</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>BnO-CH₂-Cl</td>
<td>OAc</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F₂C-CH₂-Cl</td>
<td>OAc</td>
<td>93</td>
<td>2:2:1</td>
</tr>
<tr>
<td>10</td>
<td>F₂C-CH₂-Cl</td>
<td>OAc</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. DIBALH Reductive Acetylation of Acyclic Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Diester</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO-CH₂-Cl</td>
<td>OAc</td>
<td>75</td>
<td>1.9:1</td>
</tr>
<tr>
<td>2</td>
<td>EtO-CH₂-Cl</td>
<td>OAc</td>
<td>60</td>
<td>1:1:1</td>
</tr>
<tr>
<td>3</td>
<td>H₂C-CH₂-Cl</td>
<td>OAc</td>
<td>84</td>
<td>1:1:1</td>
</tr>
</tbody>
</table>

**Scheme 1**

Reductive Acetylation of Acyclic Esters.

![Scheme 1. DIBALH reductive acetylation of acyclic esters.](image)

(c) The enantiomeric excess of ester 32 was determined to be 71% by optical rotation.
The Chemistry of the Ether Linkage

Hooz, J. In Ether Synthesis. Wiley & Sons: New York, 1967; pp 446-

The reduction of a number of \( \alpha \)-acetoxy ethers to the corresponding ester, with equiproportional amounts of boron trifluoride etherate and triethylsilane in dichloromethane at \(-78^\circ C\) for \( <30 \) min to generate ethers. The reaction is proposed to proceed via oxacarbenium ion intermediate 39 (Scheme 2).

The reduction of a number of \( \alpha \)-acetoxy ethers to the corresponding esters proceeded in excellent yields (83-100%, Table 6). The synthesis of dineopentyl ether (41) by our method (Table 6, entry 1) compares favorably to a Williamson ether synthesis of the same material.\(^{11}\) Masada synthesizes 41 in 62% yield by combining sodium

by reductive desulfurization with either Raney nickel\(^9\) or organotin hydrides\(^10\) has been reported. Our procedure entails treatment of an \( \alpha \)-acetoxy ether 3, obtained by DIBALH reductive acetylation of the corresponding ester, with equimolar amounts of boron trifluoride etherate and triethylsilane in dichloromethane at \(-78^\circ C\) for \( <30 \) min to generate ether 40. The reaction is proposed to proceed via oxacarbenium ion intermediate 39 (Scheme 2).

The reduction of a number of \( \alpha \)-acetoxy ethers to the corresponding esters proceeded in excellent yields (83–100%, Table 6). The synthesis of dineopentyl ether (41) by our method (Table 6, entry 1) compares favorably to a Williamson ether synthesis of the same material.\(^{11}\) Masada synthesizes 41 in 62% yield by combining sodium

for the slow consumption of starting material in the presence of only 2 equiv of DIBALH. 3-Phenylpropyl ester 34 was a poor substrate for the reductive acetylation reaction under any conditions examined (Table 5). A slight modification of the optimized protocol was required to obtain a moderate yield (56%) of desired \( \alpha \)-acetoxy ether 35 (Table 5, entry 3). The original reductive acetylation conditions were unable to suppress the overreduction of ester 34 to any useful extent (Table 5, entry 4). The propensity of ester 34 to undergo facile overreduction is surprising and cannot be easily rationalized since it possesses a structure similar to those of a number of highly successful reductive acetylation substrates described above (see Table 3, entries 4–7). Phenyl ester 37 and (E)-cinnamate ester 38 failed to undergo reductive acetylation under any conditions (Figure 3). Exclusive overreduction occurred in both cases, presumably due to the instability of the corresponding aluminum hemiacetal intermediates.

**Ether Synthesis.** As an extension of the DIBALH reductive acetylation methodology, a one-step transformation of \( \alpha \)-acetoxy ethers into the corresponding ethers has been developed. This new method is an alternative to the popular Williamson reaction\(^6\) and provides easy access to sterically congested ethers. The net deoxygenation of acyclic esters has been achieved previously in low to moderate yields by treatment of an ester with a mixture of boron trifluoride etherate and either lithium aluminum hydride or sodium borohydride.\(^7\) This transformation has also been accomplished with manganese acetyl complexes in the presence of triphenylsilane.\(^8\) Moreover, the conversion of acyclic thionoesters to ethers

\( \text{Table 5. DIBALH Reductive Acetylation of 3-Phenylpropyl Ester 34} \)

<table>
<thead>
<tr>
<th>entry</th>
<th>DIBALH (equiv)</th>
<th>reduction time</th>
<th>acetylation conditions</th>
<th>( % )</th>
<th>( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>2 h</td>
<td>A</td>
<td>19</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>45 min</td>
<td>B</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>45 min</td>
<td>C</td>
<td>56</td>
<td>42</td>
</tr>
</tbody>
</table>

\(^a\) Conditions A: 3.0 equiv of pyridine, 1.1 equiv of DMAP, and 4.0 equiv of AcO. Conditions B: 3.0 equiv of pyridine, 2.0 equiv of DMAP, and 6.0 equiv of AcO. Conditions C: 3.0 equiv of pyridine, 2.0 equiv of DMAP, and 6.0 equiv of AcO. \(^b\) Compounds 35 and 36 were only partially separable by flash column chromatography, thus product yields were calculated from both pure and mixed fractions (ratios of products in mixed fractions determined by \(^1\)H NMR).

Figure 3. Unsuccessful acyclic ester substrates for the DIBALH reductive acetylation reaction.

\( \text{Table 6. BF}_3\text{OEt}_2/\text{Et}_3\text{SiH-Mediated Reduction of} \ \alpha\text{-Acetoxy Ethers to the Corresponding Ethers} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Acetal</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{H} ) ( \text{Bu} ) ( \text{O} )( \text{O} ) ( \text{H} ) ( \text{Bu} )</td>
<td>( \text{O} )( \text{O} ) ( \text{H} ) ( \text{Bu} ) ( \text{O} )( \text{O} ) ( \text{Bu} )</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Ph} ) ( \text{O} )( \text{O} ) ( \text{O} ) ( \text{O} ) ( \text{C} )( \text{H} )<em>( \text{H} )</em>( \text{C} )</td>
<td>( \text{Ph} ) ( \text{O} )( \text{O} ) ( \text{O} ) ( \text{O} ) ( \text{C} )( \text{H} )<em>( \text{H} )</em>( \text{C} )</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Ph} ) ( \text{O} )( \text{O} ) ( \text{O} ) ( \text{O} ) ( \text{Bu} )</td>
<td>( \text{Ph} ) ( \text{O} )( \text{O} ) ( \text{O} ) ( \text{O} ) ( \text{Bu} )</td>
<td>19</td>
</tr>
</tbody>
</table>
| 4     | \( \text{Ph} \) \( \text{O} \)\( \text{O} \) \( \text{O} \) \( \text{O} \) \( \text{H} \) \( \text{Bu} \) | \( \text{Ph} \) \( \text{O} \)\( \text{O} \) \( \text{O} \) \( \text{O} \) \( \text{O} \) \( \text{H} \) \( \text{Bu} \) | 5
| 5     | \( \text{Ph} \) \( \text{O} \)\( \text{O} \) \( \text{O} \) \( \text{O} \) \( \text{Bu} \) | \( \text{Ph} \) \( \text{O} \)\( \text{O} \) \( \text{O} \) \( \text{O} \) \( \text{Bu} \) | 43 |
| 6     | \( \text{H} \)\( \text{S} \) \( \text{H} \) \( \text{C} \)\( \text{H} \)_\( \text{H} \)_\( \text{O} \)\( \text{O} \) \( \text{O} \) | \( \text{H} \)\( \text{S} \) \( \text{H} \) \( \text{C} \)\( \text{H} \)_\( \text{H} \)_\( \text{O} \)\( \text{O} \) \( \text{O} \) | 100 |

\(^a\) General reaction conditions: 2.5 equiv of boron trifluoride etherate and 2.5 equiv of triethylsilane were added to the acetal in \( \text{CH}_2\text{Cl}_2 \) at \(-78^\circ C\). \(^b\) All product yields are after chromatography or distillation. \(^c\) 5 equiv each of boron trifluoride etherate and triethylsilane were used. \(^d\) The reduction was performed at \( 0^\circ C \).

metal and neopentyl alcohol at reflux, followed by prolonged heating at 120 °C with neopentyl tosylate in DMSO. By comparison, our two-step protocol for the reduction of esters to ethers is mild and relatively efficient. Our method was also excellent for the synthesis of other hindered ethers, namely tert-butyl ether 43 and novel diether 45 (Table 6, entries 3 and 5). Moreover, this method provides an excellent route to macrocyclic ethers such as 44 (Table 6, entry 4). Macrocycles containing one or more ether linkages (crown ethers) are difficult to access efficiently from acyclic precursors by a classical Williamson approach. Not surprisingly, the reduction failed for trifluoromethyl acetal 23 (Table 3), even at elevated reaction temperatures. Stereoelectronic factors play a role in this result; the α-trifluoromethyl group strongly destabilizes oxacarbenium ion formation by an inductive effect. This same effect is less pronounced in the reduction of ethyl acetal 33, where the α-benzyloxy substituent prevents facile oxacarbenium ion formation at −78 °C but does not hinder reduction at 0 °C (Table 6, entry 6).

It is worth noting that the reduction of 33 to 46 is expected to proceed through an oxacarbenium ion, and a 1,2-hydride shift from the initially formed primary oxacarbenium ion 47 can be envisioned that would generate a more stable secondary oxacarbenium ion 48 (Figure 4). This pathway has been ruled out by examining the optical purity of the starting material and product. The optical purity of ester 32, precursor to α-acetoxy ether 33, was found to be 71% ee by optical rotation. The optical purity of benzyl ether 46 was determined to be 68% ee by hydrogenolysis and Mosher’s ester analysis. The lack of significant epimerization upon conversion of 33 to 46 is inconsistent with a 1,2-hydride shift of the initial oxacarbenium ion to the achiral secondary oxacarbenium ion. In this case reduction is faster than cationic rearrangement, which is a useful feature in oxacarbenium ion reactions.

Conclusions

By the systematic variation of key reaction parameters, an improved procedure for the reductive acetylation of acyclic esters with DIBALH has been developed. This protocol has been shown to convert most of the examined acyclic esters and diesters into the corresponding α-acetoxy ethers in good to excellent yields. These α-acetoxy ethers can be further reduced to the corresponding ethers under mild acidic conditions. This two-step ester deoxygenation protocol is an alternative to the classical Williamson ether synthesis and is particularly useful for the synthesis of hindered ethers or polyethers.

Experimental Section

Preparation of α-Acetoxy Ethers. General Procedure for the DIBALH Reductive Acetylation of Monoesters. The ester (1.0 mmol) was dissolved in dichloromethane (6 mL). Upon cooling to −78 °C, DIBALH (1 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 equiv) was added dropwise via syringe. After 45 min, the reaction was treated sequentially with pyridine (243 µL, 3.0 mmol, 3.0 equiv) dropwise via syringe, a solution of DMAP (244 mg, 2.0 mmol, 2.0 equiv) in dichloromethane (3 mL) dropwise via cannula, and acetic anhydride (566 µL, 6.0 mmol, 6.0 equiv) dropwise via syringe. The mixture was stirred at −78 °C for 12–14 h, warmed to 0 °C, and stirred for an additional 30 min, and then the reaction was quenched at 0 °C with saturated aqueous ammonium chloride (10 mL) and saturated aqueous potassium carbonate (7.5 mL). The resultant mixture was warmed to room temperature and stirred vigorously for 30 min or until layer separation was complete. After extraction with dichloromethane (×4), the combined dichloromethane extracts were washed with ice-cooled 1 M sodium bisulfate (×2), saturated aqueous sodium bicarbonate (×3), and brine (×1). After drying (anhydrous sodium sulfate) and evaporation of dichloromethane, the residue was purified by flash column chromatography on silica gel or on silica gel previously deactivated with 2% triethylamine/hexanes unless otherwise noted.

1-Butyl-2-oxo-3-(2-phenylpropyl)-5-hexenyl Acetate 5)

According to the general procedure for the preparation of α-acetoxy ethers described above, ester 4 (34.8 mg, 0.134 mmol) gave a crude mixture of 32.3 mg (79%, 0.160 mmol) of 5 and 4.9 mg (17%, 0.022 mmol) of acetate 6 as a light yellow oil. 1H NMR analysis indicated that 5 was isolated as a 1:1 mixture of diastereomers. Data for pure 5: IR (mixed with isomers, neat) 1734, 1242 cm⁻¹; 1H NMR (500 MHz, CDCl₃, mixture of isomers) δ 7.25–7.32 (m, 2 H), 7.15–7.21 (m, 3 H), 5.89–5.97 (m, 1 H), 5.72–5.87 (m, 1 H), 5.04–5.11 (m, 2 H), 3.60–3.71 (m, 1 H), 2.54–2.83 (m, 2 H), 2.26–2.36 (m, 2 H), 2.07–2.12 (m, 3 H, major isomer), 2.03 (s, 3 H, minor isomer), 1.73–1.85 (m, 2 H), 1.64–1.74 (m, 2 H), 1.29–1.42 (m, 4 H), 0.91 (t, J = 6.7 Hz, 3 H); 13C NMR (125 MHz, CDCl₃, mixture of isomers) δ 171.1, 171.0, 142.2, 142.0, 134.6, 133.9, 128.4, 128.4, 128.3, 128.3, 125.9, 125.8, 117.8, 117.0, 98.5, 97.4, 78.6, 76.9, 39.3, 38.7, 36.1, 35.9, 34.7, 34.5, 31.7, 31.3, 29.7, 26.4, 26.3, 22.4, 21.5, 21.4, 14.0; MS (HREI-isobutane) calcd for C₂₁H₃₀O₂ (M – C₆H₅CH₃) 263.1647, found 263.1646.

1-Chloromethyl-2-oxo-3-(2-phenylpropyl)-5-hexenyl Acetate 9)

According to the general procedure for the preparation of α-acetoxy ethers described above, ester 8 (36.2 mg, 0.143 mmol) gave a light yellow oil that was purified by chromatography on silica gel (8% ethyl ether/hexanes) to give 39.0 mg (92%, 0.131 mmol) of 9 as a light yellow oil. 1H NMR analysis indicated that 9 was isolated as a 1:1 mixture of diastereomers: IR (mixture of isomers, neat) 1744, 1229 cm⁻¹; 1H NMR (500 MHz, CDCl₃, mixture of isomers) δ 7.25–7.32 (m, 2 H), 7.16–7.22 (m, 3 H), 6.02 (dt, J = 19.5 Hz, 5.2 Hz, 1 H), 5.76–5.87 (m, 1 H), 5.05–5.15 (m, 2 H), 3.71–3.79 (m, 1 H), 3.54–3.62 (m, 2 H), 2.82 (m, 2 H), 2.30–2.40 (m, 2 H), 2.10 (s, 3 H, minor isomer), 2.08 (s, 3 H, major isomer), 1.77–1.91 (m, 2 H); 13C NMR (125 MHz, CDCl₃, mixture of isomers) δ 170.7, 170.4, 141.9, 141.8, 134.1, 133.6, 128.5, 128.4, 128.3, 125.9, 125.9, 118.2, 117.4, 95.9, 94.8, 79.7, 78.1, 44.1, 39.0 mg (92%, 0.131 mmol) of 9 was isolated as a 1:1 mixture of diastereomers: IR (mixture of isomers, neat) 1744, 1229 cm⁻¹; 1H NMR analysis indicated that 9 was isolated as a 1:1 mixture of diastereomers: IR (mixture of isomers, neat) 1744, 1229 cm⁻¹; 1H NMR (500 MHz, CDCl₃, mixture of isomers) δ 7.25–7.32 (m, 2 H), 7.16–7.22 (m, 3 H), 6.02 (dt, J = 19.5 Hz, 5.2 Hz, 1 H), 5.76–5.87 (m, 1 H), 5.05–5.15 (m, 2 H), 3.71–3.79 (m, 1 H), 3.54–3.62 (m, 2 H), 2.82 (m, 2 H), 2.30–2.40 (m, 2 H), 2.10 (s, 3 H, minor isomer), 2.08 (s, 3 H, major isomer), 1.77–1.91 (m, 2 H); 13C NMR (125 MHz, CDCl₃, mixture of isomers) δ 170.7, 170.4, 141.9, 141.8, 134.1, 133.6, 128.5, 128.4, 128.3, 125.9, 125.9, 118.2, 117.4, 95.9, 94.8, 79.7, 78.1, 44.1,

Figure 4. Possible oxacarbenium ion isomerization pathway for the reduction of α-acetoxy ether 33.
According to the general procedure for the preparation of \( \alpha \)-acetoxy ethers described above, ester 20 (346 mg, 1.46 mmol) gave a yellow oil that was purified by chromatography on silica gel (8% ethyl ether/hexanes) to give 331 mg (81%, 1.18 mmol) of 21 as a light yellow oil. 1H NMR analysis indicated that 21 was isolated as a 2:1 mixture of diastereomers: 1H NMR (isomers, neat) 7.13 (m, 3 H), 4.47 (d, \( J = 121.7 \) Hertz, 1 H), 3.65–3.71 (m, 1 H), 3.45–3.61 (m, 2 H), 2.05 (s, 3 H), 1.96–2.03 (m, 2 H), 1.47–1.56 (m, 2 H), 1.30–1.39 (m, 2 H), 0.90 (s, \( J = 7.3 \) Hertz, 3 H); 13C NMR (125 MHz, CDC\(_3\)) \( \delta \) 170.8, 138.3, 128.4, 127.7, 127.6, 96.5, 73.0, 69.5, 65.6, 34.9, 31.6, 21.2, 19.2, 13.8; MS (HRCI-isobutane) calcld for C\(_{23}\)H\(_{33}\)O\(_5\) \( \times \) 437.1493. Anal. Calcd for C\(_{23}\)H\(_{33}\)O\(_5\): C, 54.96; H, 5.00. Found: C, 54.77; H, 5.20.

2-Ethoxy-1-oxacyclohexdecane (25). The general procedure for the preparation of \( \alpha \)-acetoxy ethers described above was carried out for lactone 24 (500 mg, 2.04 mmol) except that a modified workup was performed: The reaction was quenched at 0 °C with saturated aqueous ammonium chloride (21.5 mL) and saturated aqueous sodium potassium tartrate (16.5 mL). The resulting mixture was warmed to room temperature, stirred vigorously for 4 h, and then saturated with sodium chloride. After extraction with ethyl ether (3 × 200 mL), the combined organic extracts were washed with ice-cooled 1 M sodium bisulfate (2 ×), saturated aqueous sodium bicarbonate (2 ×), and brine (1 ×). After drying (anhydrous sodium sulfate) and evaporation of solvent, the resultant light yellow oil was purified by flash column chromatography on silica gel (7% ethyl ether/hexanes) to give 490 mg (84%, 1.72 mmol) of 25 as a viscous colorless oil that partially solidified upon standing: IR (neat) 1738, 1244 cm\(^{-1}\); 1H NMR (400 MHz, CDC\(_3\)) \( \delta \) 7.35–7.38 (m, 2 H, major isomer), 5.84 (d, \( J = 5.9 \) Hertz, 1 H), 4.74 (d, \( J = 11.9 \) Hertz, 1 H), 4.50 (d, \( J = 11.8 \) Hertz, 1 H), 2.63–2.79 (m, 3 H, minor isomer); 13C NMR (125 MHz, CDC\(_3\)) \( \delta \) 159.6, 141.1, 132.9, 128.5, 124.6, 127.9, 127.8, 126.0, 97.7, 71.4, 67.4, 36.0, 30.4, 21.2. Anal. Calcd for C\(_{25}\)H\(_{39}\)O\(_5\): C, 76.03; H, 7.92. Found: C, 76.00; H, 6.97.
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1738, 1238 cm⁻¹; 1H NMR (500 MHz, CDCl₃, mixture of isomers) δ 7.25–7.36 (m, 5 H), 5.89 (d, J = 4.2 Hz, 1 H, minor isomer), 5.80 (d, J = 5.1 Hz, 1 H, major isomer), 4.55–4.70 (m, 2 H), 3.72–3.81 (m, 1 H), 3.53–3.66 (m, 2 H), 2.11 (s, 3 H, minor isomer), 2.09 (s, 3 H, major isomer), 1.23 (d, J = 6.5 Hz, 3 H), 1.21 (t, J = 6.4 Hz, 3 H); 13C NMR (125 MHz, CDCl₃, mixture of isomers) δ 170.9, 138.5, 128.4, 127.8, 127.6, 126.7, 108.5, 75.3, 75.0, 71.8, 71.7, 65.7, 65.6, 21.2, 19.1, 18.1; [HRCI-isobutane] calcld for C₁₂H₂₀O₆: M + Na = 219.1220, found 219.1158. Anal. Calcld for C₁₂H₂₀O₆: C, 66.6%; H, 10.06. Found: C, 65.4%; H, 10.31.

1,3-Diacetoxy-1,3-diethoxypropane (27). According to the general procedure for the preparation of bis-α-acetoxy ethers described above, diester 26 (160 mg, 1.00 mmol) gave a yellow oil that was purified by chromatography on deactivated silica gel (15% ethyl ether/hexanes) to give a mixture of isomers (neat) 1738, 1239 cm⁻¹, 30 mg (66%, 0.72 mmol) of 27 as a colorless oil. 1H NMR analysis indicated that 31 was isolated as a 1.9:1 mixture of diastereomers: 1R (mixture of isomers, neat) 1737, 1242; 1H NMR (400 MHz, CDCl₃, mixture of isomers) δ 5.51 (d, J = 1.8 Hz, 2 H), 3.34 (dd, J = 26.5 Hz, 8.7 Hz, 2 H), 3.19 (dd, J = 20.1 Hz, 8.7 Hz, 2 H), 2.08 (s, 6 H, minor isomer), 2.07 (s, 6 H, major isomer), 0.91 (s, 18 H), 0.87 (s, 6 H, major isomer), 0.87 (s, 6 H, minor isomer); 13C NMR (100 MHz, CDCl₃, mixture of isomers) δ 171.3, 102.9, 72.9, 74.9, 74.7, 74.6, 36.1, 36.0, 35.7, 24.5, 24.5, 22.1, 22.0, 21.9, 21.0; MS (HRFAB) calcld for C₂₁H₄₂O₁₂: M + Na = 383.2410, found 383.2426. Anal. Calcld for C₂₁H₄₂O₁₂: C, 66.6%; H, 9.56. Found: C, 65.31%; H, 10.00.

Preparation of Ethers. General Procedure for the Synthesis of Ethers from α-Acetoxy Ethers. The α-acetoxy ether (1.0 mmol) was dissolved in dichloromethane (20 mL). Upon cooling to −78 °C, tributylsilane (400 µL, 2.5 mmol, 2.5 equiv) was added via syringe. Boron trifluoride etherate (317 µL, 2.5 mmol, 2.5 equiv) was added dropwise, respectively. The reaction was stirred at −78 °C until complete by TLC analysis (<~30 min) and then was partitioned between pentane (60 mL) and saturated aqueous sodium bicarbonate (60 mL). The aqueous layer was extracted with additional pentane (×1). The combined pentane extracts were dried (anhydrous sodium sulfate). After evaporation of solvent, the residue was purified by flash column chromatography on silica gel or by Kugelrohr distillation.

1-(2,2-Dimethylpropyl)-1-(2,2-dimethylpropyl) ether (41). According to the general procedure for the preparation of ethers described above, α-acetoxy ether 11 (890 mg, 4.11 mmol) gave a light yellow oil that was purified by Kugelrohr distillation (760 mmHg) to give 645 mg (99%, 4.07 mmol) of 41 as a clear oil: bp 135–137 °C. All spectral data for compound 41 were identical to data reported previously.¹²

1-(3-Phenylpropyl)-1-phenyl Ether (42). According to the general procedure for the preparation of ethers described above, α-acetoxy ether 13 (136 mg, 0.54 mmol) gave a light yellow oil that was purified by chromatography (2% ethyl ether/hexanes) to give 22.2 mg (95%, 0.108 mmol) of 42 as a light yellow oil: IR (neat) 1141 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.25–7.31 (m, 2 H), 7.15–7.22 (m, 3 H), 3.42 (t, J = 6.4 Hz, 2 H), 3.40 (t, J = 6.6 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 1.85–1.94 (m, 2 H), 1.53–1.64 (m, 2 H), 1.29–1.39 (m, 4 H), 0.91 (t, J = 7.0 Hz, 3 H); 13C NMR (100 MHz, CDCl₃) δ 142.1, 128.5, 128.3, 125.7, 71.0, 69.9, 32.4, 33.3, 29.5, 28.4, 22.5, 14.0; [HRCI-isobutane] calcld for C₂₁H₂₄O₂: M + H⁺ = 277.1789, found 277.1741. Anal. Calcld for C₂₁H₂₄O₂: C, 81.49; H, 10.75. Found: C, 81.69; H, 10.88.

1-(3-Phenylpropyl)-1-(1,1-dimethylethyl) Ether (43). According to the general procedure for the preparation of ethers described above, α-acetoxy ether 19 (136 mg, 0.54 mmol) gave a light yellow oil that was purified by chromatography (2% ethyl ether/hexanes) to give 86 mg (83%, 0.45 mmol) of 43 as a colorless oil: IR (neat) 1120 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.29–7.36 (m, 2 H), 7.19–7.28 (m, 3 H), 3.41 (t, J = 6.4 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 1.87–1.95 (m, 2 H), 1.25 (s, 9 H); 13C NMR (125 MHz, CDCl₃) δ 142.4, 128.5, 128.3, 125.7, 72.5, 60.8, 32.6, 32.2, 27.7; MS (HRCI-isobutane) calcld for C₁₉H₂₆O₂: M + H⁺ = 292.1514, found 292.1519. Anal. Calcld for C₁₉H₂₆O₂: C, 81.20; H, 10.48. Found: C, 81.33; H, 10.49.

Octacyclohexadecane (44). According to the general procedure for the preparation of ethers described above, α-acetoxy ether 25 (136 mg, 0.54 mmol) gave a light yellow oil that was purified by chromatography (2% ethyl ether/hexanes) to give 86 mg (83%, 0.45 mmol) of 44 as a colorless oil: IR (neat) 1120 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 3.42 (t, J = 5.5 Hz, 4 H), 1.50–1.60 (m, 4 H), 1.39–1.49 (m, 4 H), 1.29–1.38 (m, 18 H); 13C NMR (100 MHz, CDCl₃) δ 69.9, 29.4, 27.3, 27.1, 26.5, 26.2, 25.3; MS (HRCI-isobutane) calcld for C₂₁H₃₀O₂: M + H⁺ = 227.2375, found 227.2365. Anal. Calcld for C₂₁H₃₀O₂: C, 79.58; H, 13.36. Found: C, 79.73; H, 13.12.
mixture was stirred at −78 °C for 25 min, and then was partitioned between pentane (35 mL) and saturated aqueous sodium bicarbonate (35 mL). The aqueous layer was extracted with additional pentane (x1). The combined pentane extracts were dried (anhydrous sodium sulfate). Evaporation of solvent gave a colorless oil which was purified by flash column chromatography on silica gel (1% ethyl ether/pentane) to give 62 mg (96%, 0.25 mmol) of 45 as a colorless oil: IR (neat) 1116 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.15 (s, 4 H), 3.01 (s, 4 H), 0.89 (s, 18 H), 0.89 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 81.7, 77.3, 36.8, 32.3, 26.8, 22.2; MS (HRCl-isobutane) calcd for C$_{15}$H$_{33}$O$_2$ (M$^+$) 245.2480, found 245.2486. Anal. Calcd for C$_{15}$H$_{32}$O$_2$: C, 73.71; H, 13.20. Found: C, 73.85; H, 12.97.

1-(25)-(2-Benzylxypropyl)-1-ethyl Ether (46). α-Acetoxy ether 33 (104 mg, 0.41 mmol) was dissolved in dichloromethane (11.5 mL). Upon cooling to −78 °C, triethylsilane (164 µL, 1.03 mmol, 2.5 equiv) was added via syringe. Boron trifluoride etherate (130 µL, 1.03 mmol, 2.5 equiv) was then added dropwise via syringe. The mixture was warmed to 0 °C and stirred for 20 min, and then was partitioned between pentane (60 mL) and saturated aqueous sodium bicarbonate (60 mL). The aqueous layer was extracted with additional pentane (x1). The combined pentane extracts were dried (anhydrous sodium sulfate). Evaporation of solvent gave a light yellow oil that was purified by flash column chromatography on silica gel (15% ethyl ether/hexanes) to give 80 mg (100%, 0.41 mmol) of 46 as a light yellow oil. Hydrogenolysis of 46 (H$_2$, 10% Pd/C, MeOH, room temperature) followed by comparative $^1$H NMR analysis of the (R)- and (S)-Mosher esters$^{13}$ of the resultant alcohol indicated that 46 was isolated with an enantiomeric excess of 68%. Data for 46: IR (neat) 1116 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.24–7.39 (m, 5 H), 4.63 (s, 2 H), 3.68–3.76 (m, 1 H), 3.49–3.56 (m, 3 H), 3.40 (dd, $J$ = 10.1 Hz, 4.7 Hz, 1 H), 1.22 (t, $J$ = 7.0 Hz, 3 H), 1.21 (d, $J$ = 6.3 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.0, 128.3, 127.6, 127.4, 74.7, 74.0, 71.1, 66.7, 17.4, 15.3; MS (HRCl-isobutane) calcd for C$_{12}$H$_{18}$O$_2$ (M$^+$) 194.1307, found 194.1299. Anal. Calcd for C$_{12}$H$_{18}$O$_2$: C, 73.71; H, 9.34. Found: C, 74.03; H, 9.14.

Acknowledgment. Support has been provided by the National Cancer Institute (CA-81635) and the University of California, Irvine. We are grateful to Alexandre J. Buckmelter for early work on the reductive acetylation of compound 34.

Supporting Information Available: General experimental details and procedures for the preparation of the ester substrates are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9914521