Improved Procedure for the Reductive Acetylation of Acyclic Esters and a New Synthesis of Ethers

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An optimized protocol for the DIBALH 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.[1] The general strategy involved trapping of the aluminum hemiacetal intermediate found in the reduction of an ester to an aldehyde by diisobutylaluminum hydride (DIBALH). Other groups had previously trapped the same type of intermediate with a trimethylsilyl group.[2] 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.[1] 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.[3] 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 DIBALH is shown in Figure 1.[1] Treatment of an ester of general structure **1** with a slight excess (1.1 equiv) of DIBALH in dichloromethane at −78 °C for 2 h generated the proposed aluminum hemiacetal intermediate **2**, which then underwent acylation 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 DIBALH 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 (**3**). 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

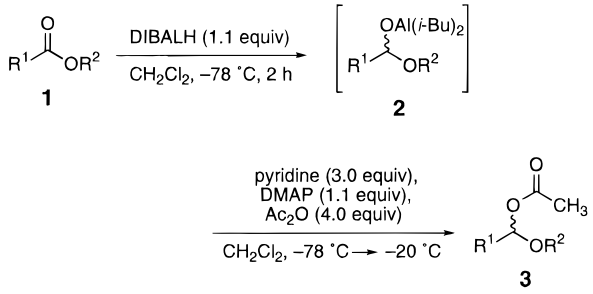
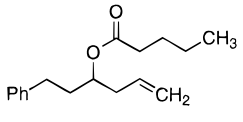


Figure 1. Original DIBALH reductive acetylation conditions for lactones and some acyclic esters.



4

(1) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320.

(2) (a) Kiyooka, S.; Shirouchi, M.; Kaneko, Y. *Tetrahedron Lett.* **1993**, *34*, 1491−1494. (b) Kiyooka, S.; Suzuki, K.; Shirouchi, M.; Kaneko, Y.; Tanimori, S. *Tetrahedron Lett.* **1993**, *34*, 5729−5732. (c) Kiyooka, S.; Shirouchi, M. *J. Org. Chem.* **1992**, *57*, 1−2. (d) Polt, R.; Peterson, M. A.; Deyoung, L. *J. Org. Chem.* **1992**, *57*, 5469−5480. (e) Sames, D.; Liu, Y. Q.; Deyoung, L.; Polt, R. *J. Org. Chem.* **1995**, *60*, 2153-2159.

(3) Rychnovsky, S. D.; Hu, Y. Q.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274.

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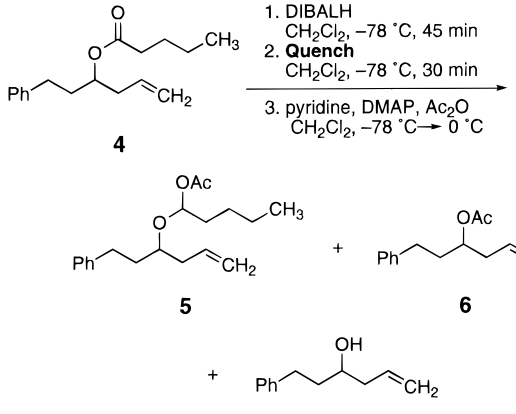
Table 1. Effect of DIBALH Quench on the Reductive Acetylation of Valerate Ester 4



		yield[b] (%)			
entry[a]	quench (equiv)	**5**	**6**	**7**	recovered **4**
1		52	38		2
2	HCO_2Et (3)	47	41		4
3	AcOH (1.5)	44	55		1
4	MeOH (1.5)	10	36	52	2
5	H_2O (1.5)	63	24		2

[a] For all entries, 2.0 equiv of DIBALH, 3.0 equiv of pyridine, 1.1 equiv of DMAP, and 4.0 equiv of Ac_2O were used. [b] The products were not cleanly separable by chromatography. Yields were determined by ^1H NMR and gas chromatographic analysis of partially purified mixtures.

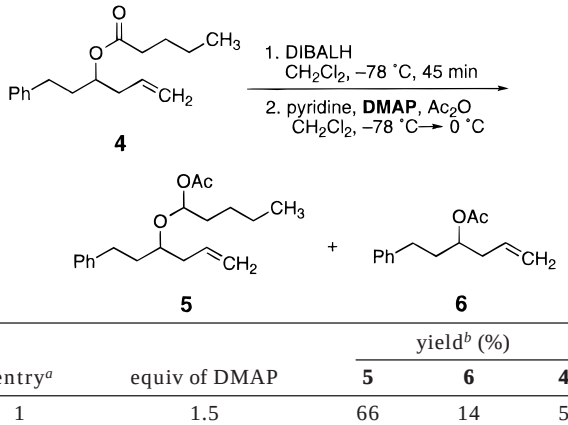
DIBALH reductive acetylation of valerate ester **4**. We chose ester **4** as a test substrate since it possesses moderate complexity and is an acyclic precursor for a Lewis acid-mediated Prins cyclization.[3] Preliminary studies suggested that increasing the amount of reducing agent and reducing the reaction time before the in situ acetylation 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 equivalent 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 acetylated 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 dichloromethane 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 competing reaction rates: since DMAP catalyzes the acetylation reaction, the presence of greater amounts of DMAP in

(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.

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



		yield[b] (%)		
entry[a]	equiv of DMAP	**5**	**6**	**4**
1	1.5	66	14	5
2	2.0	79	17	1
3[c]	2.0	73	10	3
4	3.0	81	19	0

[a] For all entries, 2.0 equiv of DIBALH, 3.0 equiv of pyridine, and 6.0 equiv of Ac_2O were used. [b] The products were not cleanly separable by chromatography. Yields were determined by ^1H NMR and gas chromatographic analysis of partially purified mixtures. [c] Toluene was used as the solvent.

the reaction leads to a heightened rate of aluminum hemiacetal acylation versus aluminum hemiacetal breakdown. 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 acetylation 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 effective 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 acetylation of **4** in these solvents led to significantly diminished 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 investigated. 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 acetylation procedure was deemed unnecessary.

The optimization studies described above for valerate ester **4** have established the need for several key modifications 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).

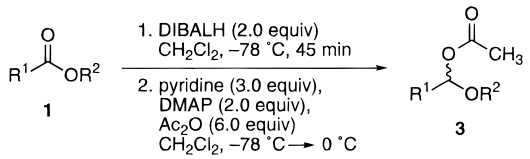
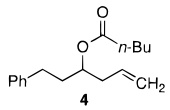
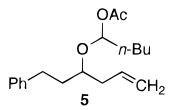
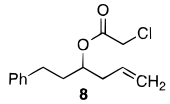
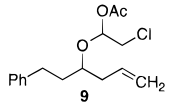
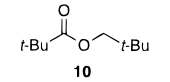
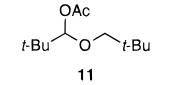
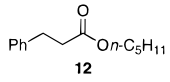
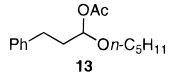
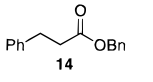
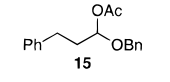
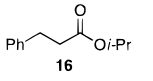
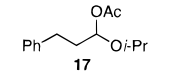
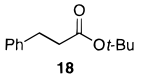
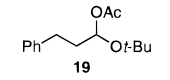
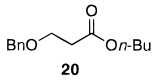
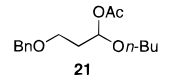
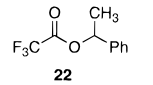
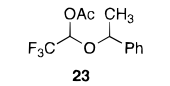
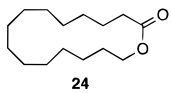
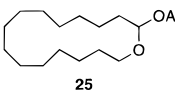


Figure 2. Optimized DIBALH reductive acetylation conditions for acyclic esters.

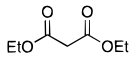
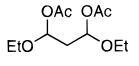
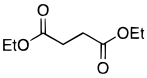
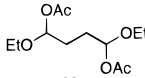
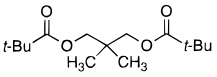
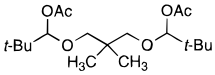
Table 3. DIBALH Reductive Acetylation of Acyclic Esters and Lactones

Entry[a]	Starting Ester	Product	Yield (%)[b]	Ratio[c]
1	 **4**	 **5**	79[d]	1.1:1
2	 **8**	 **9**	92	1.1:1
3	 **10**	 **11**	87	–
4	 **12**	 **13**	78	–
5	 **14**	 **15**	78	–
6	 **16**	 **17**	89	–
7	 **18**	 **19**	90	–
8	 **20**	 **21**	81	–
9	 **22**	 **23**	93	2.2:1
10	 **24**	 **25**	84[e]	–

[a] All entries were run in CH_2Cl_2 using 2.0 equiv of DIBALH, 3.0 equiv of pyridine, 2.0 equiv of DMAP, and 6.0 equiv of Ac_2O (reduction time = 45 min). [b] Except for entry 1, all product yields are after chromatography. [c] Diastereomeric ratios were determined by ^1H NMR analysis. [d] Acetal **5** was contaminated with the corresponding overreduction product **6** (additional 17% yield). [e] A modified workup procedure was employed.

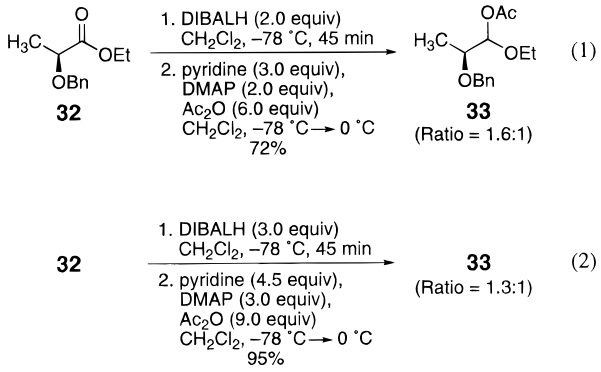
Reductive Acetylation of Acyclic Esters. The applicability of these optimized DIBALH reductive acetylation conditions to a series of acyclic substrates was investigated (Table 3). In all cases, the α-acetoxy ether products were isolated in good to excellent yields (78−93%). The facile generation of hindered 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 macrolactone **24** under the optimized reductive acetylation conditions (84%, Table 3, entry 10) relative to the original protocol (72% yield)[1] illustrates the utility of the optimized conditions for the reductive acetylation of lactones.

Table 4. DIBALH Reductive Acetylation of Acyclic Esters

Entry[a]	Starting Diester	Product	Yield (%)[b]	Ratio[c]
1	 **26**	 **27**	75[d]	1.9:1
2	 **28**	 **29**	60	1.1:1
3	 **30**	 **31**	66	1.9:1

[a] All entries were run in CH_2Cl_2 using 4.0 equiv of DIBALH, 6.0 equiv of pyridine, 4.0 equiv of DMAP, and 12.0 equiv of Ac_2O (reduction time = 45 min). [b] Reported yields are for chromatographed products. [c] Diastereomeric ratios were determined by ^1H NMR analysis. [d] Bis-acetal **27** was contaminated with a minor amount of the corresponding monoacetal. The yield of **27** (75%) and the yield of the corresponding monoacetal (3%) were determined by ^1H NMR analysis of the product.

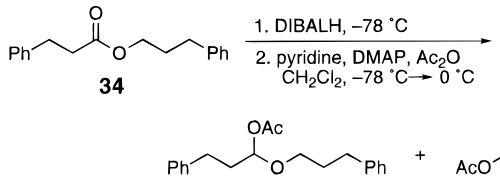
Scheme 1



Several acyclic esters were problematic substrates. A larger excess of DIBALH was required for the complete conversion of benzyl-protected (*S*)-ethyl lactate[5] (**32**) into α-acetoxy ether **33** (Scheme 1). Competing aluminum coordination by the benzyloxy group of **32** may account

(5) (a) Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229−4232. (b) Stojanovic, A.; Renaud, P. *Helv. Chim. Acta* **1998**, *81*, 268−283. (c) The enantiomeric excess of ester **32** was determined to be 71% by optical rotation.

Table 5. DIBALH Reductive Acetylation of 3-Phenylpropyl Ester 34



entry	DIBALH (equiv)	reduction time	acetylation conditions[a]	yield[b] (%) 35	36
1	1.1	2 h	A	19	68
2	2.0	45 min	B	47	49
3	1.7	45 min	B	56	42

[a] Conditions A: 3.0 equiv of pyridine, 1.1 equiv of DMAP, and 4.0 equiv of Ac_2O. Conditions B: 3.0 equiv of pyridine, 2.0 equiv of DMAP, and 6.0 equiv of Ac_2O. Conditions B: 3.0 equiv of pyridine, 2.0 equiv of DMAP, and 6.0 equiv of Ac_2O. [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 ^1H NMR).

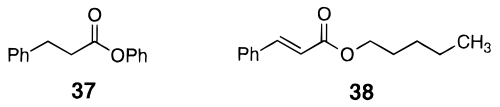


Figure 3. Unsucessful acyclic ester substrates for the DIBALH reductive acetylation reaction.

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 a variety of conditions examined (Table 5). A slight modification of the optimized protocol was required to obtain a moderate yield (56%) of desired α-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 1). 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 α-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 by reductive desulfurization with either Raney nickel[9] or organotin hydrides[10] has been reported. Our procedure entails treatment of an α-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 °C for <30 min to generate ether **40**. The reaction is proposed to proceed via oxacarbenium ion intermediate **39** (Scheme 2).

Scheme 2

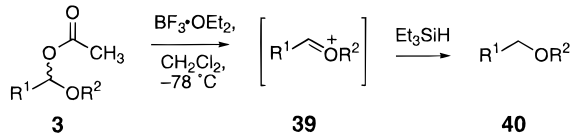
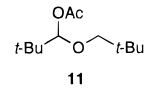
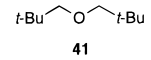
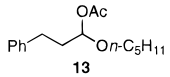
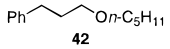
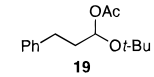
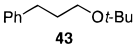
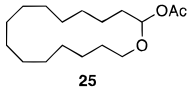
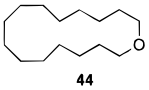
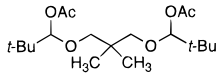
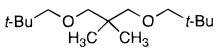
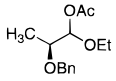
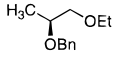


Table 6. BF_3·OEt_2/Et_3SiH-Mediated Reduction of α-Acetoxy Ethers to the Corresponding Ethers

Entry[a]	Starting Acetal	Product	Yield (%)[b]
1	 **11**	 **41**	99
2	 **13**	 **42**	95
3	 **19**	 **43**	83
4	 **25**	 **44**	98
5[c]	 **31**	 **45**	96
6[d]	 **33**	 **46**	100

[a] General reaction conditions: 2.5 equiv of boron trifluoride etherate and 2.5 equiv of triethylsilane were added to the acetal in CH_2Cl_2 at −78 °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 °C.

The reduction of a number of α-acetoxy ethers to the corresponding ethers 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

(6) For a brief summary of the Williamson reaction, see: Feuer, H.; Hooz, J. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; John Wiley & Sons: New York, 1967; pp 446−448.

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(8) Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 10139−10140.

(9) (a) Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831−832. (b) Bradshaw, J. S.; Jones, B. A.; Gebhard, J. S. *J. Org. Chem.* **1983**, *48*, 1127−1128.

(10) (a) Nicolaou, K. C.; Sato, M.; Theodorakis, E. A.; Miller, N. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1583−1585. (b) Jang, D. O.; Song, S. H.; Cho, D. H. *Tetrahedron* **1999**, *55*, 3479−3488. (c) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504−2506.

(11) (a) Gash, V. W. *J. Org. Chem.* **1972**, *37*, 2197−2201. (b) Davies, R.; Hudec, J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1395−1400. (c) Masada, H.; Murotani, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1213−1214.

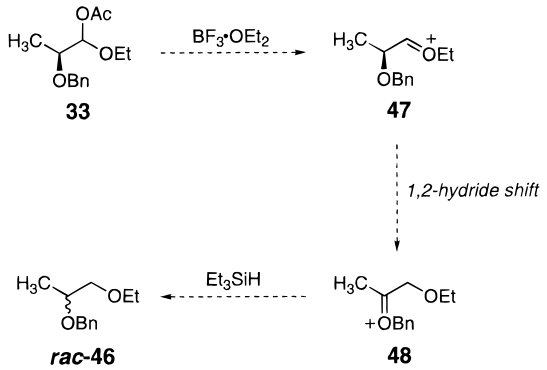

Figure 4. Possible oxacarbenium ion isomerization pathway for the reduction of α-acetoxy ether **33**.

metal and neopentyl alcohol at reflux, followed by prolonged heating at 120 °C with neopentyl tosylate in DMSO.[11c] 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.[12] 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.[5] The optical purity of benzyl ether **46** was determined to be 68% ee by hydrogenolysis and Mosher's ester analysis.[13] 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[14]

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 sodium potassium tartrate (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%, 0.106 mmol) of **5** and 4.9 mg (17%, 0.022 mmol) of acetate **6** as a light yellow oil. ^{1}H NMR analysis indicated that **5** was isolated as a 1.1:1 mixture of diastereomers. Data for pure **5**: IR (mixture of isomers, neat) 1734, 1242 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 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 (s, 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); ^{13}C NMR (125 MHz, $CDCl_3$, 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 $C_{16}H_{23}O_3$ (M − C_3H_5) 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. ^{1}H NMR analysis indicated that **9** was isolated as a 1.1:1 mixture of diastereomers: IR (mixture of isomers, neat) 1744, 1229 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 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), 2.53−2.82 (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); ^{13}C NMR (125 MHz, $CDCl_3$, 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,

(12) For a review of crown ether synthesis, see: Laidler, D. A.; Stoddart, J. F. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulfur Analogues*; Patai, S., Ed.; John Wiley & Sons: New York, 1980; pp 1−57.

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543−2549.

(14) The general experimental procedure is included in the Supporting Information.

44.0, 39.1, 38.6, 35.9, 35.7, 31.6, 31.2, 21.2, 21.1; MS (HRCI-isobutane) calcd for $C_{13}H_{16}O_3Cl$ (M − C_3H_5) 255.0788, found 255.0782. Anal. Calcd for $C_{16}H_{21}O_3Cl$: C, 64.75; H, 7.13. Found: C, 64.97; H, 7.21.

1-(2,2-Dimethylpropoxy)-2,2-dimethylpropyl Acetate (11). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **10** (850 mg, 4.93 mmol) gave a light yellow oil that was purified by chromatography on deactivated silica gel (8% ethyl ether/hexanes) to give 930 mg (87%, 4.30 mmol) of **11** as a volatile light yellow oil: IR (neat) 1740, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (s, 1 H), 3.29 (d, J = 8.7 Hz, 1 H), 3.08 (d, J = 8.7 Hz, 1 H), 2.09 (s, 3 H), 0.93 (s, 9 H), 0.90 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 103.0, 79.9, 35.7, 32.0, 26.5, 24.5, 21.0; MS (HRCI-isobutane) calcd for $C_{12}H_{24}O_3$ (M^+) 216.1725, found 216.1732.

1-Pentoxy-3-phenylpropyl Acetate (13). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **12** (250 mg, 1.13 mmol) gave a light yellow oil that was purified by chromatography on silica gel (8% ethyl ether/hexanes) to give 232 mg (78%, 0.88 mmol) of **13** as a colorless oil: IR (neat) 1738, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.31 (m, 2 H), 7.16−7.21 (m, 3 H), 5.83 (t, J = 5.5 Hz, 1 H), 3.63−3.71 (m, 1 H), 3.43−3.51 (m, 1 H), 2.63−2.81 (m, 2 H), 2.06 (s, 3 H), 1.99−2.06 (m, 2 H), 1.55−1.63 (m, 2 H), 1.30−1.37 (m, 4 H), 0.92 (t, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 141.1, 128.4, 128.3, 126.0, 98.2, 69.6, 36.0, 30.3, 29.3, 28.2, 22.4, 21.2, 14.0. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.68; H, 9.16. Found: C, 72.64; H, 8.91.

1-Benzyloxy-3-phenylpropyl Acetate (15). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **14** (34.9 mg, 0.145 mmol) gave a yellow oil that was purified by chromatography on silica gel (2% *tert*-butylmethyl ether/hexanes grading to 5% *tert*-butylmethyl ether/hexanes) to give 32.0 mg (78%, 0.113 mmol) of **15** as a yellow oil: IR (neat) 1736, 1237 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.38 (m, 7 H), 7.14−7.22 (m, 2 H), 5.96 (dd, J = 5.9 Hz, 5.0 Hz, 1 H), 4.73 (d, J = 11.9 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 2.63−2.79 (m, 2 H), 2.04 (s, 3 H), 2.00−2.13 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 141.1, 137.4, 128.5, 128.4, 127.9, 127.8, 126.0, 97.7, 71.4, 67.4, 36.0, 30.4, 21.2. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.00; H, 6.97.

1-(1-Methylethoxy)-3-phenylpropyl Acetate (17). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **16** (500 mg, 2.60 mmol) gave a light yellow oil that was purified by chromatography on deactivated silica gel (10% ethyl ether/hexanes) to give 547 mg (89%, 2.32 mmol) of **17** as a light yellow oil: IR (neat) 1736, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.31 (m, 2 H), 7.15−7.22 (m, 3 H), 5.93 (t, J = 5.5 Hz, 1 H), 3.97 (septet, J = 6.2 Hz, 1 H), 2.60−2.80 (m, 2 H), 2.06 (s, 3 H), 1.97−2.05 (m, 2 H), 1.18 (t, J = 6.3 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 141.1, 128.4, 128.3, 126.0, 96.7, 71.2, 36.3, 30.4, 23.2, 21.9, 21.4. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.07; H, 8.30.

1-(1,1-Dimethylethoxy)-3-phenylpropyl Acetate (19). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **18** (500 mg, 2.42 mmol) gave a light yellow oil that was purified by chromatography on deactivated silica gel (10% ethyl ether/hexanes) to give 543 mg (90%, 2.17 mmol) of **19** as a light yellow oil: IR (neat) 1731, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.32 (m, 2 H), 7.15−7.22 (m, 3 H), 6.09 (dd, J = 6.5 Hz, 4.4 Hz, 1 H), 2.57−2.78 (m, 2 H), 2.02 (s, 3 H), 1.91−2.05 (m, 2 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.2, 128.3, 128.3, 125.9, 93.8, 75.7, 37.0, 30.3, 28.3, 21.6. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.06; H, 8.69.

1-Butoxy-3-benzyloxypropyl Acetate (21). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **20** (34.6 mg, 0.146 mmol) gave a yellow oil that was purified by chromatography on silica gel (8% ethyl acetate/hexanes) to give 33.1 mg (81%, 0.118 mmol) of **21** as a yellow oil: IR (neat) 1738, 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.36 (m, 5 H), 6.00 (t, J = 5.6 Hz, 1 H), 4.50 (d, J = 12.1 Hz, 1 H), 4.47 (d, J = 12.1 Hz, 1 H), 3.65−3.71 (m, 1 H), 3.45−3.61 (m, 3 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 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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) calcd for $C_{14}H_{21}O_3$ (M − C_2H_3O) 237.1491, found 237.1493. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.95.

1-(1-Phenylethoxy)-2,2,2-trifluoroethyl Acetate (23). According to the general procedure for the preparation of α-acetoxy ethers described above, ester **22** (300 mg, 1.38 mmol) gave a light yellow oil that was purified by chromatography on silica gel (8% ethyl ether/hexanes) to give 336 mg (93%, 1.28 mmol) of **23** as a light yellow oil. ^1H NMR analysis indicated that **23** was isolated as a 2.2:1 mixture of diastereomers: IR (mixture of isomers, neat) 1762, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ 7.26−7.42 (m, 2 H), 6.22 (q, J_{HF} = 3.9 Hz, 1 H, major isomer), 5.88 (q, J_{HF} = 3.9 Hz, 1 H, minor isomer), 4.83 (q, J = 6.5 Hz, 1 H, major isomer), 4.82 (q, J = 6.5 Hz, 1 H, minor isomer), 2.19 (s, 3 H, minor isomer), 1.72 (s, 3 H, major isomer), 1.55 (d, J = 6.5 Hz, 3 H, major isomer), 1.53 (d, J = 6.5 Hz, 3 H, minor isomer); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers) δ 169.7, 169.2, 141.9, 140.6, 128.7, 128.6, 128.4, 128.0, 126.9, 126.2, 120.9 (q, J_{CF} = 282 Hz), 89.7 (q, J_{CF} = 36 Hz), 88.3 (q, J_{CF} = 36 Hz), 80.7, 78.1, 23.7, 23.5, 20.6, 20.1. Anal. Calcd for $C_{12}H_{13}O_3F_3$: C, 54.96; H, 5.00. Found: C, 54.77; H, 5.20.

2-Acetoxy-1-oxacyclohexdecane (25). The general procedure for the preparation of α-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 (×4), the combined organic 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 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, $CDCl_3$) δ 5.78 (dd, J = 7.8 Hz, 3.1 Hz, 1 H), 3.75−3.81 (m, 1 H), 3.39−3.47 (m, 1 H), 2.07 (s, 3 H), 1.24−1.76 (m, 26 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 99.2, 69.5, 34.1, 29.0, 27.2, 27.2, 27.1, 27.0, 26.6, 26.0, 26.0, 26.0, 25.7, 24.9, 23.0, 21.3; MS (HRCI-isobutane) calcd for $C_{17}H_{32}O_3$ (M^+) 284.2351, found 284.2349. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.57; H, 11.16.

***(2S)*-1-Ethoxy-2-benzyloxypropyl Acetate (33).** Ester **32**[5] (100 mg, 0.48 mmol) was dissolved in dichloromethane (4 mL). Upon cooling to −78 °C, DIBALH (1 M in hexanes, 1.44 mL, 1.44 mmol, 3.0 equiv) was added dropwise via syringe. After 45 min, the solution was treated sequentially with pyridine (175 μL, 2.16 mmol, 4.5 equiv) dropwise via syringe, a solution of DMAP (176 mg, 1.44 mmol, 3.0 equiv) in dichloromethane (2.1 mL) dropwise via cannula, and acetic anhydride (408 μL, 4.32 mmol, 9.0 equiv) dropwise via syringe. The mixture was stirred at −78 °C for 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 (7.5 mL) and saturated aqueous sodium potassium tartrate (6 mL). The resultant mixture was warmed to room temperature and stirred vigorously for 30 min. After extraction with dichloromethane (×4), and 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 resultant yellow oil was purified by flash column chromatography on silica gel (10% ethyl ether/hexanes) to give 115 mg (95%, 0.46 mmol) of **33** as a light yellow oil. ^1H NMR analysis indicated that **33** was isolated as a 1.3:1 mixture of diastereomers: IR (mixture of isomers, neat)

1738, 1238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 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); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers) δ 170.9, 138.5, 128.4, 127.8, 127.6, 127.6, 98.4, 97.5, 75.2, 75.0, 71.8, 71.7, 65.7, 21.2, 15.1, 14.7; MS (HRCI-isobutane) calcd for $C_{12}H_{17}O_2$ (M − $C_2H_3O_2$) 192.1150, found 192.1158. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 67.02; H, 7.68.

General Procedure for the DIBALH Reductive Acetylation of Diesters. The diester (1.0 mmol) was dissolved in dichloromethane (12 mL). Upon cooling to −78 °C, DIBALH (1 M in hexanes, 4.0 mL, 4.0 mmol, 4.0 equiv) was added dropwise via syringe. After 45 min, the reaction was treated sequentially with pyridine (486 μL, 6.0 mmol, 6.0 equiv) dropwise via syringe, a solution of DMAP (488 mg, 4.0 mmol, 4.0 equiv) in dichloromethane (6 mL) dropwise via cannula, and acetic anhydride (1.13 mL, 12.0 mmol, 12.0 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 (20 mL) and saturated aqueous sodium potassium tartrate (15 mL). The resulting 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 previously deactivated with 2% triethylamine/hexanes.

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 187 mg (75%, 0.75 mmol) of **27** and 7 mg (3%, 0.03 mmol) of the corresponding mono-α-acetoxy ether as a yellow oil. ^1H NMR analysis indicated that **27** was isolated as a 1.9:1 mixture of diastereomers. Data for pure **27**: IR (mixture of isomers, neat) 1739, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ 5.94 (t, J = 5.9 Hz, 2 H, minor isomer), 5.90 (t, J = 5.8 Hz, 2 H, major isomer), 3.67−3.77 (m, 2 H), 3.49−3.59 (m, 2 H), 2.09 (s, 6 H, major isomer), 2.07 (s, 6 H, minor isomer), 2.04−2.18 (m, 2 H), 1.20 (t, J = 7.0 Hz, 6 H, minor isomer), 1.18 (t, J = 7.0 Hz, 6 H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 170.6, 94.8, 94.7, 65.2, 65.0, 39.7, 39.3, 21.1, 15.0, 14.9. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.25; H, 7.93.

1,4-Diacetoxy-1,4-diethoxybutane (29). According to the general procedure for the preparation of bis-α-acetoxy ethers described above, diester **28** (49.4 mg, 0.284 mmol) gave a yellow oil that was purified by chromatography on deactivated silica gel (10% ethyl acetate/hexanes) to give 44.3 mg (60%, 0.169 mmol) of **29** as a yellow oil. ^1H NMR analysis indicated that **29** was isolated as a 1.1:1 mixture of diastereomers: IR (mixture of isomers, neat) 1738, 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of isomers) δ 5.85 (br m, 2 H), 3.66−3.76 (m, 2 H), 3.50−3.58 (m, 2 H), 2.08 (s, 6 H, minor isomer), 2.07 (s, 6 H, major isomer), 1.72−1.83 (m, 4 H), 1.95 (t, J = 7.0 Hz, 6 H, minor isomer), 1.95 (t, J = 7.0 Hz, 6 H, major isomer); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers) δ 170.9, 97.8, 97.7, 65.0, 29.1, 29.1, 21.2, 15.0; MS (HRCI-isobutane) calcd for $C_{10}H_{19}O_4$ (M − $C_2H_3O_2$) 203.1283, found 203.1282. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.82; H, 8.30.

1-(1-Acetoxy-2,2-dimethylpropyloxy)-3-(1-acetoxy-2,2-dimethylpropyloxy)-2,2-dimethylpropane (31). According to the general procedure for the preparation of bis-α-acetoxy ethers described above, diester **30** (300 mg, 1.10 mmol) gave a light yellow oil that was purified by chromatography on deactivated silica gel (7% ethyl acetate/hexanes) to give 261 mg (66%, 0.72 mmol) of **31** as a colorless oil. ^1H NMR analysis indicated that **31** was isolated as a 1.9:1 mixture of diastereomers: IR (mixture of isomers, neat) 1737, 1242; ^1H NMR (400 MHz, $CDCl_3$, 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); ^{13}C NMR (100 MHz, CDCl3, mixture of isomers) δ 171.3, 102.8, 102.6, 74.9, 74.8, 36.1, 36.0, 35.7, 24.5, 24.5, 22.1, 22.0, 21.9, 21.0; MS (HRFAB) calcd for $C_{19}H_{36}NaO_6$ (M + Na) 383.2410, found 383.2426. Anal. Calcd for $C_{19}H_{34}O_6$: C, 63.66; H, 9.56. Found: C, 63.51; 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, triethylsilane (400 μL, 2.5 mmol, 2.5 equiv) was added via syringe. Boron trifluoride etherate (317 μL, 2.5 mmol, 2.5 equiv) was then added dropwise via syringe. 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.[11c]

1-(3-Phenylpropyl)-1-pentyl Ether (42). According to the general procedure for the preparation of ethers described above, α-acetoxy ether **13** (30.1 mg, 0.114 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) 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 128.5, 128.3, 125.7, 71.0, 69.9, 32.4, 31.3, 29.5, 28.4, 22.5, 14.0; MS (HRCI-isobutane) calcd for $C_{14}H_{23}O$ (M + H) 207.1749, found 207.1741. Anal. Calcd for $C_{14}H_{22}O$: 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) 1197, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 128.5, 128.3, 125.7, 72.6, 60.8, 32.6, 32.2, 27.7; MS (HRCI-isobutane) calcd for $C_{13}H_{20}O$ (M^+) 192.1514, found 192.1519. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.33; H, 10.49.

Oxacyclohexadecane (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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 29.4, 27.3, 27.1, 26.5, 26.2, 26.2, 25.3; MS (HRCI-isobutane) calcd for $C_{15}H_{31}O$ (M + H) 227.2375, found 227.2365. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.73; H, 13.12.

1-(2,2-Dimethylpropyloxy)-3-(2,2-dimethylpropyloxy)-2,2-dimethylpropane (45). Bis-α-acetoxy ether **31** (95 mg, 0.26 mmol) was dissolved in dichloromethane (8 mL). Upon cooling to −78 °C, triethylsilane (211 μL, 1.32 mmol, 5.0 equiv) was added via syringe. Boron trifluoride etherate (167 μL, 1.32 mmol, 5.0 equiv) was then added dropwise via syringe. The

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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 81.7, 77.3, 36.8, 32.3, 26.8, 22.2; MS (HRCI-isobutane) calcd for $C_{15}H_{33}O_2$ (M + H) 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-(2*S*)-(2-Benzyloxypropyl)-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 (×1). 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 ^1H 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}; ^1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 139.0, 128.3, 127.6, 127.4, 74.7, 74.0, 71.1, 66.7, 17.4, 15.3; MS (HRCI-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, 74.19; H, 9.34. Found: C, 74.03; H, 9.14.

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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.

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