General Synthesis of α-Acetoxy Ethers from Esters by DIBALH Reduction and Acetylation

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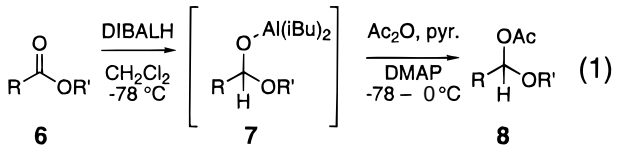
A long-standing interest in 4-(phenylthio)-1,3-dioxanes (**3**) as 1,3-diol synthons[1] led us to consider their preparation from 1,3-dioxan-4-ones **1** by the hypothetical route A illustrated in Figure 1. This route is untenable because of the instability of hemiacetal **2**, which spontaneously loses acetone to give a *β*-hydroxy aldehyde. A possible solution is illustrated in Figure 1, route B. Kiyooka[2] and Polt[3] independently showed that diisobutylaluminum alkoxides of hemiacetals, prepared by DIBALH reduction of esters, are much more stable than free hemiacetals and can be trapped *in situ* with TMSOTf−pyridine[2] or (trimethylsilyl)imidazole.[3] The mixed alkyl trimethylsilyl acetals that result react with nucleophiles in the presence of a Lewis acid to give alcohols or ethers depending upon whether the alkoxy or silyloxy substituent acts as the leaving group. In most cases the alkoxy group departs, and nucleophilic addition to the resulting aldehyde produces a secondary alcohol.[4] Indeed, ester reduction with DIBALH and *in situ* reaction with an organometallic reagent has been used to avoid the isolation of unstable or sensitive aldehydes.[5] One the other hand, activation of the (trimethylsilyl)oxy group in the presence of a nucleophile would lead to a branched ether. Several examples of this branched ether synthesis have been reported, but the regiochemistry of the alkyl trimethylsilyl acetal cleavage is substrate dependent.[3b,6] The mixed alkyl trimethylsilyl acetals do not appear to be reliable intermediates for the synthesis of branched ethers. Replacement of the TMS group with a more active leaving group would change the regioselectivity of the acetal cleavage and should provide an entry into the 4-(phenylthio)-1,3-dioxanes, and a possible synthesis of α-substituted ethers. The realization of this strategy using acetoxy leaving groups is outlined in Figure 1, route B, and is described below.



6 **7** **8** (1)

We have found that diisobutylaluminum alkoxides of hemiacetals, prepared by DIBALH reduction of esters, can be trapped *in situ* with acetic anhydride in the presence of pyridine and DMAP. The acetate group in the resulting α-acetoxy ether is a much better leaving group than the alkoxy group, and these mixed acetals react with nucleophiles regioselectively in the presence of a Lewis acid to give α-substituted ethers. The DIBALH reduction and acetylation of a variety of simple esters and cyclic esters is illustrated in Table 1 and eq 1. All of the reductions were carried out with 1.1 equiv of DIBALH at −78 °C for ca. 2 h in CH_2Cl_2 or toluene. The intermediate aluminum hemiacetal **7** was treated with pyridine (3 equiv), DMAP (1.1 equiv), and acetic anhydride (4 equiv) at −78 °C, and the mixture was allowed to warm slowly to ca. −20 °C. After an aqueous workup, the α-acetoxy ether **8** was isolated by chromatography on silica gel. The 1,3-dioxane-4-ones[7] in entries 1−3 (Table 1) each gave the equatorial acetate stereoselectively. Addition of hydride from the axial face of the carbonyl followed by stereoselective acetylation would account for the products. Large-ring lactone **15** gave the corresponding acetylated hemiacetal **16** in good yield (Table 1, entry 4). The cyclic malonate esters **17**[8] and **19**[9] in entries 5 and 6 (Table 1) produced the unusual 4,6-diacetoxy-1,3-dioxanes, which can be considered masked malonaldehyde equivalents. The meso diacetates **18** and **20** are intriguing synthons for the two-directional chain synthesis of polyols.[10] The examples in entries 7 and 8 (Table 1) show that the reaction works even with simple acyclic esters to give α-acetoxy ethers in good yields. The reaction does not always work well. Meldrum's acid, for example, gave none of the desired product, perhaps due to difficulties in the isolation, and dibenzyl malonate gave ca. 50% yield of the expected diacetate, but the product was contaminated with an inseparable impurity. Each of the hemiacetals derived from the esters listed in Table 1 is unstable, but in each

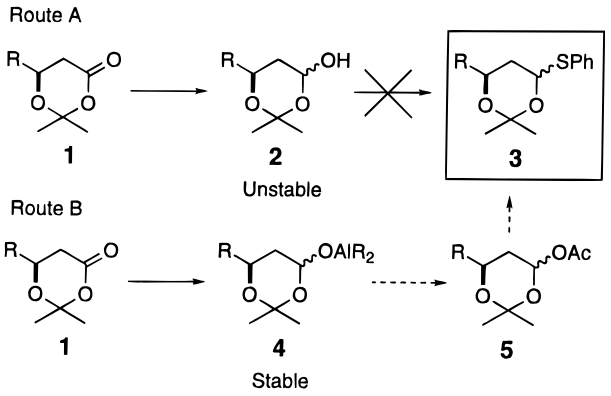


Figure 1. Possible synthesis of 4-(phenylthio)-1,3-dioxane **3** from 1,3-dioxan-4-one **1**.

(1) (a) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982−4984. (b) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336−4339.

(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.

(3) (a) Polt, R.; Peterson, M. A.; Deyoung, L. *J. Org. Chem.* **1992**, *57*, 5469−5480. (b) Sames, D.; Liu, Y. Q.; Deyoung, L.; Polt, R. *J. Org. Chem.* **1995**, *60*, 2153−2159.

(4) Polt has reported that selectivity in the addition of Grignard reagents to diisobutylaluminum hemiacetals varies depending on the identity of the starting ester alcohol and concludes that these reactions do not proceed by way of the free aldehyde.[3a]

(5) (a) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905−3906. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **1991**, *56*, 4370−4382. (c) Ishihara, T.; Hayashi, H.; Yamananka, H. *Tetrahedron Lett.* **1993**, *34*, 5777−5780.

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(7) Prepared by Noyori ketalization of the corresponding aldehyde or ketone with trimethysilyl 3-[(trimethylsilyl)oxy]butyrate. (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358. (b) Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945−2948. (c) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448−463.

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(10) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563.

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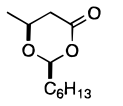
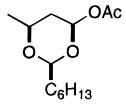
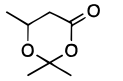
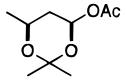
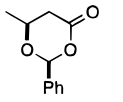
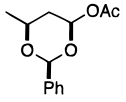
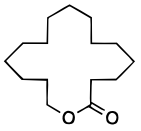
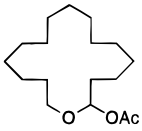
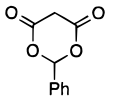
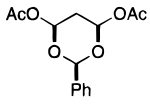
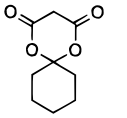
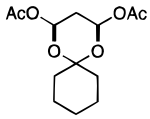
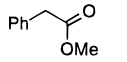
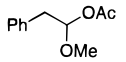
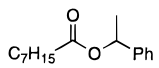
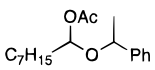
Table 1. DIBALH Reduction and in Situ Acetylation of Esters

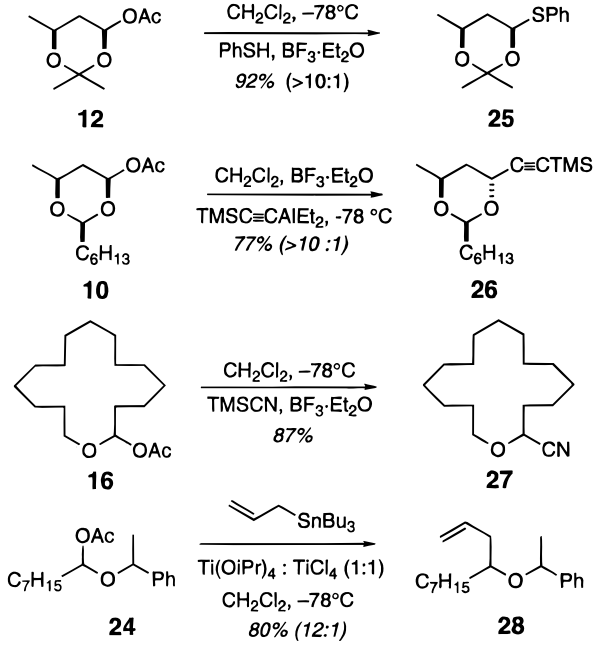
Entry	Starting Ester	Product	% Yield	Ratio[a]
1	 **9**	 **10**	91	>10:1
2	 **11**	 **12**	61	>10:1
3	 **13**	 **14**	79	>10:1
4[b]	 **15**	 **16**	71	—
5	 **17**	 **18**	75	4:1
6	 **19**	 **20**	68	>10:1
7	 **21**	 **22**	76	—
8[b]	 **23**	 **24**	82	2:1

[a] Ratios were determined by NMR analysis. Where assigned, the major isomer is illustrated. [b] Reaction run in toluene.

case the acetylated hemiacetal was isolated in good to excellent yield by way of the aluminum alkoxide. This reaction provides a direct and surprisingly general entry into α-acetoxy ethers from the corresponding esters.

We have previously reported that α-acetoxy ethers similar to **10** are versatile 1,3-diol synthons that can be induced to form carbon−carbon bonds by via cationic, radical, or anionic intermediates.[1,11] Lewis acid activation of α-acetoxy ethers generates an oxonium ion that will couple with carbon or heteroatom nucleophiles, Scheme 1. Reaction of the 4-acetoxy-1,3-dioxane **12** with thiophenol and $BF_3{\cdot}OEt_2$ gave the 4-(phenylthio)-1,3-dioxane **25** in nearly quantitative yield. The phenylthio acetal **25** is a precursor to the both the *cis*- and *trans*-α-alkoxy lithium reagents by reductive lithiation, and the present method is clearly superior to the original preparation of these phenylthio acetals.[1a] Radical intermediates are also accessible from α-acetoxy ethers. A 4-acetoxy-1,3-dioxane similar to **10** has been coupled with phenylselenol and the resulting α-phenylselenyl ether coupled with acrylonitrile under radical reduction conditions.[11] A variety of carbon nucleophiles will react with

Scheme 1



oxonium ions generated from α-acetoxy ethers. On treatment with diethylaluminum (trimethylsilyl)acetylide in the presence of $BF_3{\cdot}OEt_2$,[12] α-acetoxy ether **10** gave the *trans*-1,3-dioxane **26** in good yield with excellent stereoselectivity. Trans alkyne adduct **26** has the configuration expected from axial addition to a cyclic oxonium ion. The cis stereochemistry of **25** was unexpected and presumably arises by *in situ* equilibration to the thermodynamically more stable cis adduct. The large-ring cyanohydrin **27** was prepared by combining the lactol acetate **16** with TMSCN in the presence of $BF_3{\cdot}OEt_2$. The alkylation and reductive decyanation of medium and large-ring cyanohydrins is currently being investigated in our laboratory. Finally, acyclic α-acetoxy ether **24** was coupled with allyltributylstannane using a titanium-blend Lewis acid[13] to give the branched ether **28** as a 12:1 mixture of diastereomers. Seebach has reported the coupling of a similar oxonium ion with allyltrimethylsilane that led to a comparable diastereomeric ratio.[14] In each of these examples, the α-acetoxy ether was activated and coupled with nucleophiles at −78 °C with completely selective activation of the acetoxy group and formation of the branched ether.

Synthesis of α-acetoxy ethers by reduction and acetylation of esters is a surprisingly general route to these useful intermediates. The regioselective cleavage of these α-acetoxy ethers leads to α-substituted and α-heterosubstituted ethers that are otherwise difficult to prepare. Direct activation of α-acetoxy ethers with Lewis acids gives oxonium ions, and two-step transformations provide access to the corresponding radical or anionic intermediates. Selective activation of mixed acetals can be a powerful synthetic tool, and the new synthesis of α-acetoxy ethers by DIBALH reduction and acetylation of esters will be a powerful transformation for organic chemists.[15]

(11) Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555−556.

(12) Fotsch, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141−4147.

(13) Denmark's conditions were used in the coupling: Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458−6467.

(14) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 756−757.

Experimental Section[16]

Standard Procedure for the One-Pot DIBALH Reduction and Acetylation of an Ester. To 25 mL flame-dried, two-neck flask equipped with a low-temperature thermometer and an N_2 inlet was added a solution of the starting ester (1.0 mmol) in 5 mL of dry CH_2Cl_2. After the mixture was cooled to −78 °C, DIBALH (1.0 M in cyclohexane, 1.1 mL, 1.1 mmol, 1.1 equiv) was added dropwise (on a larger scale, a syringe pump was used for the slow addition). After being stirred for 2 h (TLC showed no ester) the reaction mixture was treated with pyridine (237 mg, 0.24 mL, 3.0 mmol, 3.0 equiv), and then a solution of DMAP (134 mg, 1.1 mmol, 1.1 equiv) in 2 mL of dry CH_2Cl_2 was slowly added by cannula. Finally, Ac_2O (408 mg, 0.38 mL, 4.0 mmol, 4.0 equiv) was added dropwise, the reaction vessel was packed in a Dewar flask containing dry ice, and the mixture was stirred under an N_2 atmosphere. After 12 h, the mixture was warmed to −20 °C and the reaction was quenched by adding saturated NH_4Cl (5 mL) solution. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, and then extracted with CH_2Cl_2 (×4). If the Al salts formed emulsions, they were disrupted by adding a saturated solution of Rochelle's salt with vigorous stirring. The combined CH_2Cl_2 extracts were washed with ice-cold 1 N $NaHSO_4$ (×2), saturated $NaHCO_3$ (×3), and brine (×1). After drying (anhydrous Na_2SO_4) and evaporation of CH_2Cl_2 extracts, the residue obtained was purified by flash chromatography on silica gel.

For malonates **17** and **19** the DIBALH reduction time was 4 h, and the quantities of the other reagents were doubled

(2*S,4*R**,6*S**)-4-Acetoxy-2-hexyl-6-methyl-1,3-dioxane (10).** Compound **9**[7b] (610 mg, 3.00 mmol) gave 670 mg (91.4%, 2.74 mmol) of **10** as a colorless oil after purification on silica gel (5% EtOAc/hexanes): IR (neat) 2955, 2930, 2860, 1762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dd, J = 2.7, 9.9 Hz, 1 H), 4.62 (t, J = 5.2 Hz, 1 H), 3.80−3.71 (m, 1 H), 2.08 (s, 3 H), 1.77−1.14 (m, 12 H), 1.23 (d, J = 6.1 Hz, 3 H), 0.83 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 169.2; *C*H 100.0, 93.0, 71.1; *C*H_2 37.4, 34.6, 31.7, 29.1, 23.9, 22.6; *C*H_3 21.3, 21.1, 14.1. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.73; H, 9.69.

(4*R,6*S**)-4-Acetoxy-2,2,6-trimethyl-1,3-dioxane (12).** Compound **11**[7c] (288 mg, 2.00 mmol) gave 228 mg (60.6%, 1.21 mmol) of **12** as a volatile colorless oil after purification on silica gel (10% EtOAc/hexanes, chromic acid stain used for visualization of the TLC plate): IR (neat) 2992, 2938, 2880, 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (dd, J = 3.0, 9.9 Hz, 1 H), 4.07−3.97 (m, 1 H), 2.06 (s, 3 H), 1.82−1.75 (m, 1 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.45−1.33 (m, 1 H), 1.19 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 169.4; *C*H 100.5, 89.4, 64.5, *C*H_2 37.5; *C*H_3 29.9, 21.8, 21.2, 20.8. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.18; H, 8.72.

(2*S,4*R**,6*S**)-4-Acetoxy-6-methyl-2-phenyl-1,3-dioxane (14).** Compound **13**[7c] (384 mg, 2.00 mmol) gave 372 mg (78.8%, 1.57 mmol) of **14** as a pale yellow oil after purification on silica gel (10% EtOAc/hexanes, chromic acid stain used for visualization of the TLC plate): IR (neat) 3067, 3037, 2976, 1761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2 H), 7.39−7.30 (m, 3 H), 6.09 (dd, J = 2.7, 9.0 Hz, 1 H), 5.65 (s, 1 H), 4.08−3.98 (m, 1 H) 2.11 (s, 3 H), 1.89−1.83 (m, 1 H), 1.77−1.62 (m, 1 H), 1.35 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 169.2, 137.4; *C*H 129.1, 128.3, 126.4, 99.3, 93.2, 71.8; *C*H_2 37.4; *C*H_3 21.4, 21.1. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.86; H, 6.72.

2-Acetoxy-1-oxacyclohexadecane (16). The reduction and acetylation of lactone **15** (962 mg, 4.00 mmol) was carried out in toluene to give 809 mg (71.1%, 2.84 mmol) of **16** as a colorless viscous oil after purification on silica gel (3% EtOAc/hexanes): IR (neat) 2928, 2858, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (dd, J = 3.3, 7.7 Hz, 2 H), 3.80−3.75 (m, 1 H), 3.46−3.39 (m, 1 H), 2.06 (s, 3 H), 1.72−.22 (m, 25 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 99.3, 69.5, 34.1, 29.0, 27.2 (2), 27.1, 27.0, 26.6, 26.1, 26.0 (2), 25.8, 25.0, 23.0, 21.3; MS (HRCI−isobutane) calcd for $C_{17}H_{33}O_3$ (M + H) 285.2429, found 285.2432. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 72.02; H, 11.27.

***cis,cis*-4,6-Diacetoxy-2-phenyl-1,3-dioxane (18).** Compound **17**[8] (770 mg, 4.00 mmol) gave 840 mg (75.5%, 3.02 mmol) of **18** as a yellow oil after chromatography on silica gel (20% EtOAc/hexanes): IR (neat) 3068, 3039, 2987, 1767, 1620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52−7.48 (m, 2 H), 7.39−7.35 (m, 3 H), 6.16 (dd J = 3.1, 10.1 Hz, 1 H), 5.75 (s, 1 H), 2.18 (s, 3 H), 2.03−1.96 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 135.7, 129.4, 128.3, 126.3, 96.2, 91.2, 89.5, 34.8, 21.0; MS (HRCI−isobutane) calcd for $C_{14}H_{15}O_6$ (M − H) 279.0869, found 279.0873. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 59.89; H, 5.70.

***cis*-2,4-Diacetoxy-1,5-dioxaspiro[5.5]undecane (20).** Compound **19**[9] (1.84 g, 10.00 mmol) gave 1.83 g (67.3%, 6.73 mmol) of **20** as a pale yellow oil after purification on silica gel (20% EtOAc/hexanes). The pale yellow oil solidified on standing: mp 48−51 °C; IR (neat) 2941, 2864, 1761, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, J = 4.0, 8.0 Hz, 2 H), 2.21−2.07 (m, 1 H), 2.11 (s, 6 H), 1.87−1.79 (m, 5 H), 1.62−1.53 (m, 4 H), 1.42−1.38 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 101.0, 87.4, 38.0, 33.7, 32.6, 25.1, 22.3, 22.1, 21.1; MS (HREI) calcd for $C_{13}H_{20}O_6$ (M^+) 272.1260, found 272.1260. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.52; H, 7.44.

1-Methoxy-2-phenethyl Acetate (22). Ester **21** (601 mg, 4.00 mmol) gave 590 mg (75.9%, 3.04 mmol) of **22** as a colorless oil after purification on silica gel (3% EtOAc/hexanes): IR (neat) 3065, 3031, 3002, 2938, 1740, 1684, 1653, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.21 (m, 5 H), 5.89 (t, J = 5.6 Hz, 1 H), 3.39 (s, 3 H), 3.01−2.94 (m, 2 H), 2.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 135.4, 129.7, 128.3, 126.7, 99.7, 56.9, 40.9, 21.1. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.00; H, 7.50.

1-(1-Phenylethoxy)-1-octyl Acetate (24). Ester **23** was prepared by the reaction of octanoic acid with 2-phenylethanol in presence of DCC and DMAP. Reduction and acetylation of compound **23** (1.99 g, 8.00 mmol) gave 1.92 g (82.0%, 6.56 mmol) of **24** as a colorless oil after chromatography on silica gel (3% EtOAc/hexanes, phosphomolybdic acid stain used for visualization of the TLC plate): IR (neat) 3032, 2956, 2928, 1739, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 7.37−7.22 (m, 10 H), 6.04 (t, J = 5.6 Hz, 1 H), 5.66 (t, J = 5.6 Hz, 1 H), 4.70−4.63 (m, 2 H), 2.09 (s, 3 H), 1.81−1.20 (m, 25 H), 1.59 (s, 3 H), 1.47 (d, J = 4.5 Hz, 3 H), 0.91−0.83 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of isomers) δ 170.8, 143.8, 142.7, 128.4, 128.1, 127.8, 127.2, 126.6, 126.0, 97.8, 96.7, 78.0, 76.0, 34.8, 34.6, 31.7, 29.2, 29.1, 28.6, 24.1, 24.0, 23.9, 23.6, 22.6, 21.3, 20.7, 14.0. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.80; H, 9.49.

(4*R,6*S**)-4-(Phenylthio)-2,2,6-trimethyl-1,3-dioxane (25).** Acetate **12** (94 mg, 0.50 mmol) was dissolved in 5 mL of dry CH_2Cl_2, and thiophenol (110 mg, 1.0 mmol, 2.0 equiv) was added. After being cooled to −78 °C, the reaction mixture was treated with $BF_3{\cdot}Et_2O$ (85 mg, 71 μL, 0.6 mmol, 1.2 equiv). After being stirred for 1 h, the reaction was quenched by adding 1 N NaOH (5 mL) at −78 °C. The mixture was warmed to room temperature and extracted with CH_2Cl_2 (×3). The combined CH_2Cl_2 extracts were washed with 1 N NaOH (×2), brine (×1) and dried over anhydrous Na_2SO_4. Evaporation of solvent followed by chromatography (SiO_2, 50% CH_2Cl_2/hexanes then 10% EtOAc/hexanes) gave 110 mg (0.46 mmol, 92.4%) of **25** as a colorless oil: IR (neat) 3075, 2990, 2913, 1584, 1457, 1440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52−7.44 (m, 2 H), 7.32−7.22 (m, 3 H), 5.26 (dd, J = 2.6, 12.1 Hz, 1 H), 4.05 (ddddd, J = 2.4, 6.1, 5.9, 5.9, 11.6 Hz, 1 H), 1.80 (td, J = 2.5 , 13.1 Hz , 1 H), 1.56−1.45 (m, 1 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.17 (d, J = 5.8 Hz, 3 H);

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(16) **General.** IR spectra were recorded on a Prospect IR. NMR spectra were recorded on a IBM NR-200 AF, an IBM NR-300AF, Varian VXR-500, or a GN Omega 500 MHz instrument. Chemical shifts of the ^1H NMR spectra were referenced to residual chloroform at 7.26 ppm. Chemical shifts of the ^{13}C spectra were referenced to $CDCl_3$ at 77.0 ppm. Carbon multiplicities were determined by use of the DEPT pulse sequence. Capillary GC analysis was performed on a Hewlett Packard Model 5890 A instrument with a 30 m PhMe-Silicon column, a flame ionization detector and a Hewlett Packard 3390 A integrator. Combustion analysis were performed by M-H-W Laboratories, Phoenix, AZ. Mass spectra were determined on an AE2-MS 30 instrument or a PG 7070E-HF instrument. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230−400 mesh). Moisture sensitive reactions were carried out under atmosphere of N_2 using oven dried glassware and standard syringe/septa techniques. DIBALH (1.0 M in cyclohexane), compounds **15** and **21** were purchased from Aldrich Chemical Co.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 134.2, 100.1; *C*H 131.2, 128.8, 127.1, 77.5, 65.6; *C*H_2 38.2; *C*H_3 30.2, 21.9, 19.8. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.77; H, 7.39.

(2*S,4*R**,6*S**)-2-Hexyl-6-methyl-4-[(trimethylsilyl)ethynyl]-1,3-dioxane (26).** (Trimethylsilyl)acetylene (134 mg, 0.19 mL, 1.36 mmol, 2.2 equiv) was dissolved in 5 mL of dry Et_2O and cooled to −78 °C. A 2.4 M solution of *n*-BuLi in hexanes (0.52 mL, 1.24 mmol, 2.0 equiv) was added dropwise. The solution was stirred at 0 °C for 30 min and then Et_2AlCl (1.8 M, in toluene, 0.69 mL, 1.24 mmol, 2.0 equiv) was added slowly. The white suspension was stirred at 0 °C for 30 min and then cooled to −78 °C. $BF_3{\cdot}Et_2O$ (132 mg, 0.10 mL, 1.5 equiv) was added, and the mixture was stirred for 15 min. Finally, a solution of acetate **10** (152 mg, 0.62 mmol, 1.0 equiv) in 5 mL of dry CH_2Cl_2 was added by cannula. The suspension was allowed to warm to 0 °C over 14 h, and the reaction was quenched with saturated $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (×3), and the combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation gave a yellow oil which was purified by chromatography (SiO_2, 3% EtOAc/hexanes) to afford 136 mg (77.3%, 0.481 mmol) of **26** as a volatile colorless oil: IR (neat) 2957, 2929, 2861, 2170, 1460, 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (t, J = 5.2 Hz, 1 H), 4.81 (d, J = 5.0 Hz, 1 H), 4.10−4.03 (m, 1 H), 1.82−1.76 (m, 1 H), 1.63−1.53 (m, 3 H), 1.44−1.23 (m, 8H), 1.21 (d, J = 6.2 Hz, 3 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.3, 96.4, 92.3, 68.6, 64.3, 37.3, 34.8, 31.7, 29.0, 23.9, 22.6, 21.5, 14.1, −0.11 (3); MS (HRCI−isobutane) calcd for $C_{16}H_{29}O_2Si$ (M−H) 281.1937, found 281.1948. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.90; H, 10.75.

2-Cyano-1-oxacyclohexadecane (27). Compound **16** (285 mg, 1.00 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (5 mL), cooled to −78 °C. Trimethylsilyl cyanide (198 mg, 2.00 mmol, 2.0 equiv) was added by syringe. After 5 min, $BF_3{\cdot}Et_2O$ (212 mg, 1.50 mmol, 1.5 equiv) was added dropwise to the reaction mixture. The mixture was stirred for 2 h and then carefully diluted with 5 mL of saturated $NaHCO_3$ at −78 °C. The two-phase mixture was warmed to room temperature, stirred for 1 h, and extracted the with CH_2Cl_2 (×3). The combined organic layers were washed with brine (×1), dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (SiO_2, 2% EtOAc/hexanes) to afford 219 mg (87.2%, 0.87 mmol) of **27** as a pale yellow oil: IR (neat) 2929, 2858, 1460 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (dd, J = 4.0, 8.0 Hz, 1 H), 3.88−3.82 (m, 1 H), 3.42−3.35 (m, 1 H), 1.90−1.79 (m, 2 H), 1.62−1.24 (m, 23 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.7, 70.3, 68.1, 33.1, 28.6, 27.2, 27.0, 26.9, 26.6 (2), 26.0, 25.9, 25.8, 25.7, 24.9, 23.4; MS (HREI) calcd for $C_{16}H_{29}NO$ (M^+) 251.2249, found 251.2260. Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.43; H, 11.39; N, 5.43.

4-Undecenyl 2-Phenylethyl Ether (28). To 10 mL of dry CH_2Cl_2 under Ar was added $TiCl_4$ (1.0 M in CH_2Cl_2, 2.0 mL, 2.0 mmol, 2.0 equiv), and then $Ti(O^iPr)_4$ (569 mg, 0.60 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The clear solution was stirred at room temperature for 1 h. Acetate **24** (292 mg, 1.00 mmol, 1.0 equiv) was dissolved in 10 mL of dry CH_2Cl_2 along with allyltributyltin (662 mg, 0.62 mL, 2.00 mmol, 2.0 equiv), and the mixture was cooled to −78 °C. The Ti-blend solution prepared above was then added to the reaction mixture over 2 h using a syringe pump. The mixture was stirred at −78 °C for 3 h and then the reaction was quenched with a solution of 1 N NaOH in 5 mL of MeOH. The mixture was warmed to room temperature and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with brine (×1), dried (Na_2SO_4) and evaporated to give a colorless oil. Purification by flash chromatography (SiO_2, 3% Et_2O−pentane) gave 219 mg (79.9%, 0.79 mmol) of **28** as a colorless oil: IR (neat) 3076, 3066, 3029, 2973, 2957, 1641, 1493 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5 H), 5.74−5.66 (m, 1 H), 4.98−4.49 (m, 2 H), 4.51 (q, J = 6.4 Hz, 1 H), 3.33 (p, J = 5.8 Hz, 1 H), 2.20−2.12 (m, 2 H), 1.54−1.22 (m, 1 4 H), 1.42 (d, J = 6.4 Hz, 3 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 135.5, 128.2, 127.2, 126.4, 116.4, 76.5, 75.7, 39.2, 33.2, 31.8, 29.8, 25.0, 24.1, 22.7, 14.1. Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.19; H, 10.86.

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