Anti-1,3-diols by Addition of Dialkylzinc Reagents to 4-Acetoxy-1,3-dioxanes

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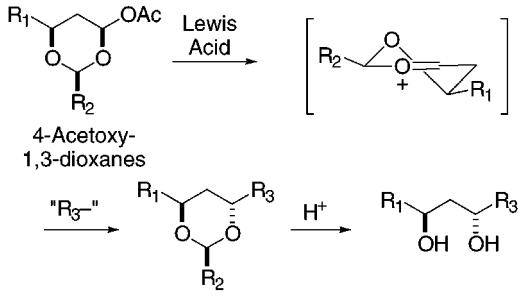
Dialkylzincs couple with 4-acetoxy-6-alkyl-1,3-dioxanes in the presence of trimethylsilyl triflate (TMSOTf) to form *trans*-4,6-dialkyl-1,3-dioxanes with excellent diastereoselectivities. These dioxanes could be deprotected to yield *anti*-1,3-diols. A variety of functional groups are tolerated in the dialkylzinc, although silyl and benzyl ethers led to diminished diastereoselectivities. Substituents at the C5-position of the dioxane ring have little effect on the selectivity, while small C2 (acetal) substituents led to slightly reduced diastereoselectivity. These couplings work best with cyclic acetals, which can be difficult to hydrolyze. The 4-(benzyloxy)butanal (BOB) acetal has been developed as a new cyclic acetal protecting group that is compatible with dialkylzinc coupling reactions. BOB protecting groups are easily removed by catalytic hydrogenation followed by mild acid hydrolysis.

Introduction

Skipped polyols and 1,3-diols are common segments in a wide variety of natural products. We have synthesized several polyene macrolide antibiotics,[1] such as roflamycoin[2] and roxaticin,[3] which contain skipped polyol chains. As part of this program, we have been interested in new methods for the stereoselective syntheses of both *syn*- and *anti*-1,3-diols.[4,5] *Syn*-1,3-diols are readily prepared by alkylation and reductive decyanation of cyanohydrin acetonides.[6] It appeared that 4-acetoxy-1,3-dioxanes could be useful intermediates for the preparation of *anti*-1,3-diols, and we had recently developed a general route to these compounds.[7] We were intrigued by 4-acetoxy-1,3-dioxanes because Lewis acid-mediated solvolysis of the acetate would lead to the formation of an oxacarbenium ion at the 4-position of the 6-substituted 1,3-dioxane ring, Scheme 1. This position is analogous to the 2-position of a tetrahydropyran in that anisotropic stabilization by the adjacent oxygen dominates the nucleophile addition selectivity. Irreversible addition of nucleophiles from the axial direction[8] would lead to *trans*-4,6-disubstituted 1,3-dioxanes, which would give *anti*-1,3-diols upon removal

Scheme 1



of the acetal protecting group.[9] Coupling of heteroatom nucleophiles (PhSH, $TMSN_3$, and TMSCN)[10] verified this assumption, although the addition of allyltrimethylsilane was plagued by the epimerization of the acetal center after the coupling event.[11] It was later found that proper choice of reaction conditions suppressed the acetal epimerization.[12] Subsequent investigations have revealed that allylsilanes,[11] enol silanes,[12] crotyl organometallics,[13] alkynyl alanes and stannanes,[14] and dialkylzinc reagents[15] couple readily with 4-acetoxy-1,3-dioxanes to give acetal protected *anti*-1,3-diols in very high diastereoselectivities. Described herein is a full account of the coupling of dialkylzinc reagents with 4-acetoxy-1,3-dioxanes.

We have developed two methods for the preparation of 4-acetoxy-1,3-dioxanes, Scheme 2. Our original route utilized β-hydroxy aldehydes.[10] The neat aldehydes exist preferentially as a dimer in equilibrium with the free

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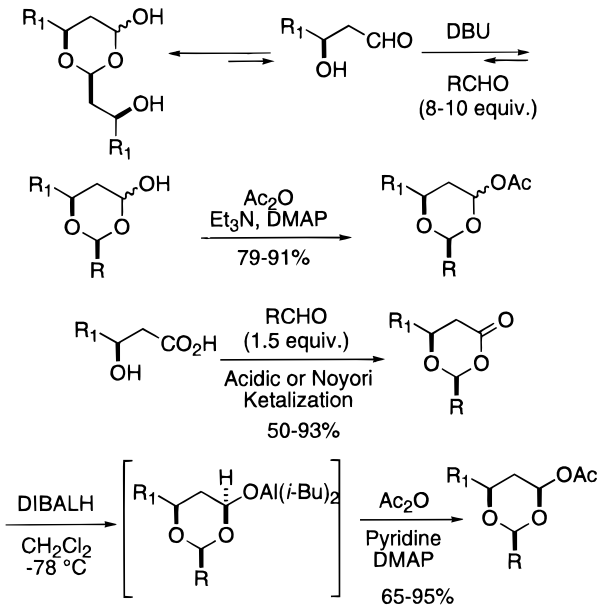
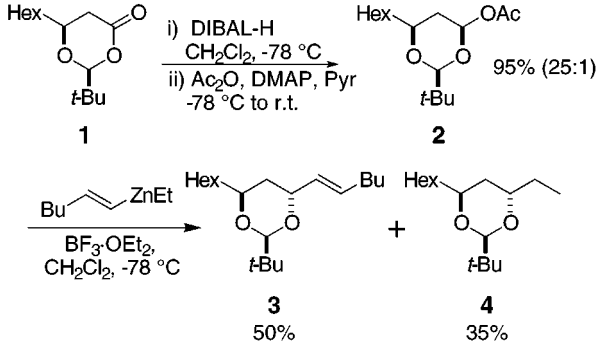
Scheme 2



Scheme 3



β-hydroxy aldehydes. Treatment with 0.5 equiv of DBU in the presence of a large excess of an inexpensive aldehyde led to an exchange reaction that gave an intermediate cyclic hemiacetal. The cyclic hemiacetals are prone to reversion to the dimer upon standing, but can be isolated after acetylation with Ac_2O to give the 4-acetoxy-1,3-dioxanes. Although this reaction has been performed on a 1.4 mole scale, it is limited by the 8−10 equiv of aldehyde that must be used to achieve good conversion. When applied to α-substituted β-hydroxy aldehydes, however, significant α-epimerization was observed.[16]

To avoid this scrambling, a more general route was developed from β-hydroxy carboxylic acids, which are easily prepared in enantiopure form.[17] Conversion to the corresponding 1,3-dioxan-4-one with a slight excess of aldehyde under acidic[18] or Noyori[19] acetalization conditions proceeds in high yields with a wide variety of aldehydes. Low-temperature DIBALH reduction gives the diisobutylaluminum alkoxide hemiacetal, which undergoes acetylation with Ac_2O in the presence of pyridine and DMAP.[7] This method has allowed for the formation of a much wider variety of 4-acetoxy-1,3-dioxanes and prevents scrambling of any α-stereocenters.

Dialkylzinc reagents are versatile synthetic reagents that have been used widely in palladium- and copper-catalyzed coupling reactions,[20] as well as the asymmetric addition to aldehydes catalyzed by 1,2-amino alcohols and 1,2-diamines.[21] Dialkylzincs are noted for the compatibility of the C−Zn bond with a wide variety of functional groups. The lower dialkylzinc reagents (R ≤ Bu) are most easily prepared by the direct insertion of zinc metal into an alkyl iodide, followed by distillation of the dialkylzinc.[22] Highly functionalized dialkylzincs[20,23] can be prepared by the transmetalation of alkyllithium or Grignard reagents,[24] the CuI-catalyzed[25] or light-initiated[26] iodide−Zn exchange of an alkyl iodide, the Et_2BH hydroboration of an alkene and transmetalation with Et_2Zn,[27] or the Ni-catalyzed Et_2Zn hydrozincation of olefins.[28] Complex zinc reagents have great potential in fragment coupling reactions for natural product synthesis. However, they are relatively poor nucleophiles and do not react with the most useful electrophiles, aldehydes and ketones, without added catalysts or high temperatures.[20]

We became interested in the coupling of dialkylzinc reagents while attempting to couple vinyl organometallic reagents with 4-acetoxy-1,3-dioxane **2**, Scheme 3. The $BF_3{\cdot}OEt_2$-mediated coupling of **2** with the vinyl zirconocene generated by hydrozirconation of 1-hexyne gave the desired allylic *anti*-1,3-dioxane **3** in a modest 23% yield. To increase the nucleophilicity of the vinyl organometallic, the vinyl zirconocene was transmetalated with Et_2Zn to form 1-hexenyl ethyl zinc.[29] Coupling with **2** in the presence of $BF_3{\cdot}OEt_2$ gave the desired product **3** in 50% yield along with 35% of the unexpected ethyl adduct **4**. A variety of additional Lewis acids (TMSOTf, $TiCl_4$, $ZnCl_2$) resulted in the almost exclusive transfer of the ethyl ligand. In addition, both the vinyl and ethyl adducts were isolated as single isomers by GC analysis. The *anti*-1,3-dioxane geometry of **3** and **4** was readily apparent in NOE experiments. We were surpised that the ethyl group transferred competively with the vinyl group, as addition of vinyl alkyl zinc complexes to

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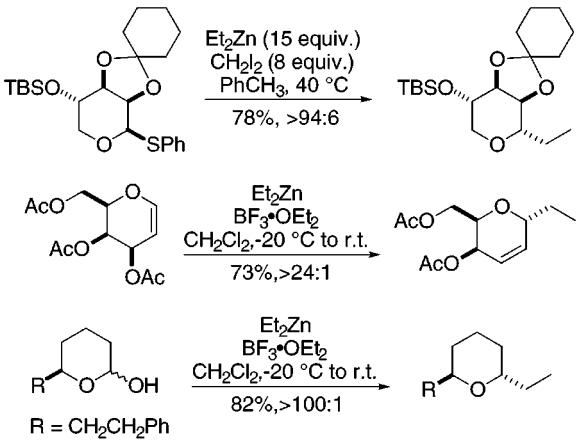


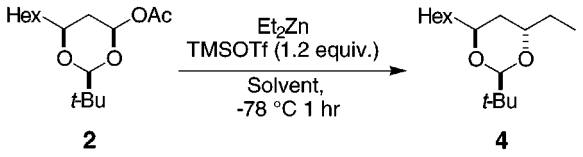
Figure 1. Literature examples of *C*-glycoside syntheses using dialkylzinc reagents.

aldehydes results in exclusive transfer of the vinyl group to give allylic alcohols.[29a] Saturated alkylzinc reagents are known to couple with a variety of glycosides, glycals, and pyranosyl lactols to give the corresponding *C*-glycosidation products in good yields and high diastereoselectivities, Figure 1.[30] However, the coupling diastereoselectivity in glycals depends greatly upon the substitution pattern around the glycal ring, ranging from >24:1 to only 1.5:1 α:*β*. Intrigued by the apparent high diastereoselectivity of the coupling of the vinyl alkyl zincs, and by the possibility of using functionalized alkylzinc reagents in convergent chain synthesis, we decided to investigate the scope and selectivity of the alkylzinc coupling with 4-acetoxy-1,3-dioxanes.

Results and Discussion

Our initial couplings of Et_2Zn with **2** in the presence of $BF_3{\cdot}OEt_2$ were somewhat discouraging. The coupling proved to be quite sluggish, proceeding to completion only upon warming the reaction mixture from −78 °C to 23 °C over 5 h and gave **4** in 75% yield as a 6:1 mixture of acetal epimers. This result is at odds with the more effective coupling observed in Scheme 3. Turning to trimethylsilyl trifluoromethansulfonate (TMSOTf) as the Lewis acid led to a tremendous rate acceleration, Table 1. When the coupling of Et_2Zn and **2** was performed in the presence of 1.2 equiv of TMSOTf at −78 °C, the expected adduct **4** was isolated in 91% yield as a 51:1 mixture of acetal epimers (entry a). TLC monitoring indicated that the reaction was complete at −78 °C after 10−15 min. Typically, we allowed the reaction to stir at −78 °C for 1 h to ensure completion. The reaction has been performed on scales of 0.1−0.2 mmol with yields of 80−98%. The acetal epimer ratio is dependent upon the method used to quench the reaction. Acidic quenches (saturated aqueous NH_4Cl) resulted in 1:1 mixtures of acetal epimers, while basic quenches (Et_3N/MeOH or saturated aqueous $NaHCO_3$) limited the epimerization, although the reaction mixture must be vigorously stirred while the aqueous solution is added at −78 °C to prevent the immediate freezing of the aqueous layer.

Table 1. Coupling of Et_2Zn with 2



2 **4**

Entry	Equiv. Et_2Zn	Solvent	Yield	Acetal Epimer Ratio
a	2	CH_2Cl_2	91%	51:1
b	0.6	CH_2Cl_2	90%	100:0
c	2	Et_2O	100%	100:0
d	2	THF	83%	21:1
e	2	$PhCH_3$	91%	15:1

One of the most intriguing discovers was that *both* of the ethyl groups in Et_2Zn are available for transfer to the intermediate oxacarbenium ion. When 0.6 equiv of Et_2Zn was coupled with **2**, the product **4** was isolated in 90% yield as a single diastereomer (entry b). This was surprising as dialkylzincs are known to transfer only one alkyl group in the asymmetric addition to aldehydes in the presence of chiral ligands.[21] However, dialkylcadmiums are known to transfer both alkyl groups to quinones.[31] The ability to transfer both ligands efficiently is an advantage when using complex dialkylzinc reagents and suggests that this method would be useful in natural product synthesis.

The coupling was also found to work in a number of different solvents. Under the standard conditions, the use of Et_2O as the reaction solvent gave a quantitative yield of **4** as a single diastereomer (entry c), while the more Lewis basic THF solvent gave a slightly lower 83% yield as a 21:1 mixture of acetal epimers (entry d). The reaction also proceeded in the more nonpolar solvent toluene, which gave **4** in 91% yield (entry e). However, the nonpolar solvent resulted in significant acetal epimerization (15:1), perhaps due to the insolubility of the aqueous $NaHCO_3$ used to quench the reaction.

The purity of the TMSOTf was found to be critical for the success of the coupling. None of the desired product was formed with the use of commercial TMSOTf that had been stored in a desiccator at 5 °C for several weeks. The reported yields were obtained with TMSOTf prepared in our lab. The most practical method for the large scale preparation of TMSOTf was the reaction of triflic acid with excess tetramethylsilane at −20 °C.[32] Distillation under reduced pressure gave TMSOTf in very high purity that could be stored under Ar at room temperature over poly(4-vinyl)pyridine for 6−7 months without loss of activity.

To correctly identify the presence of minor dioxane diastereomers in the GC traces of the crude product, the *syn*- and *anti*-1,3-dioxane diastereomers were synthesized, Scheme 4. This allowed us to unambiguously confirm the identity of the observed minor diastereomer as the acetal epimer **5**. Analysis of the crude product by

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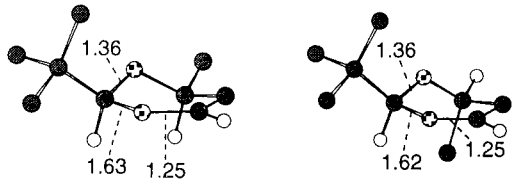
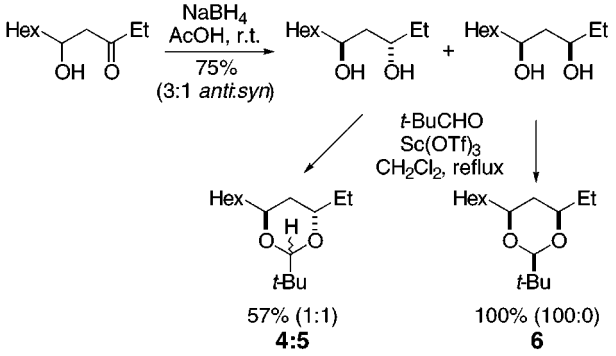


8 0.0 kcal/mole **9** 1.45 kcal/mole

Figure 2. Ab initio calculations of oxacarbenium ion intermediates in the dialkylzinc coupling reactions (HF/3-21G). Bond lengths are reported in angstroms, and selected hydrogen atoms have been omitted for clarity.

Scheme 4



GC (on-column injection) and doping with an authentic sample of **6** to correctly identify the peaks of interest revealed that the *syn*-1,3-dioxane **6** was present in the crude product in only 0.34%, correlating to an *anti*:*syn* diastereoselectivity of >290:1 (eq 1). The 4-acetoxy-1,3-dioxane **2** used in these experiments was a 24:1 mixture of acetal diastereomers, which implies that the acetal stereocenter underwent isomerization prior to reaction with Et_2Zn.[33] This was conclusively shown by submitting the acetal epimer **7**, isolated by careful chromatography of **2**, to the reaction conditions with Et_2Zn to give a 180:1 mixture of *anti*- and *syn*-1,3-dioxanes (eq 2). Isolation of **4** as the major anti acetal diastereomer clearly indicates that the acetal isomerizes under the reaction conditions. Ab inito calculations (HF/3-21G) of the two oxacarbenium ion intermediates indicate that the equatorial isomer **8** is 1.45 kcal/mol lower in energy than the axial epimer **9** (Figure 2). If the equilibrium between the oxacarbenium ion epimers **8** and **9** controls the stereoselectivity of the coupling reaction, then one would expect a diastereoselectivity of <100:1 *anti*:*syn*. The observed >290:1 *anti*:*syn* diastereoselectivity suggests a Curtin−Hammett situation, with Et_2Zn reacting preferentially with the more sterically accessible oxacarbenium ion **8**.

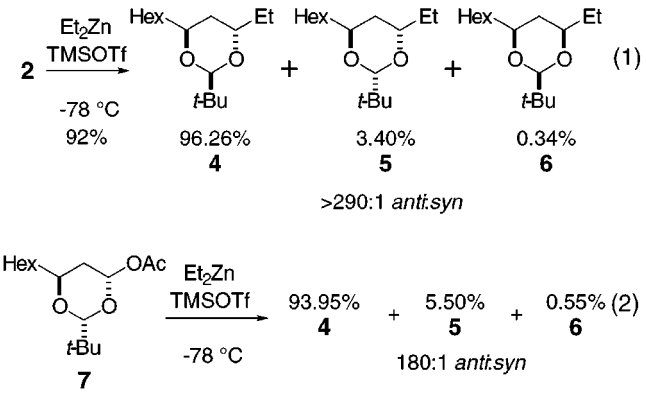
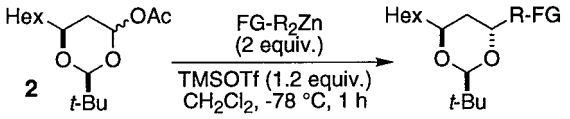
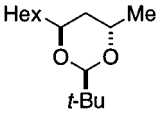
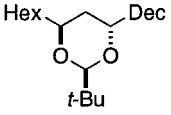
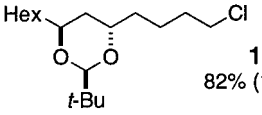
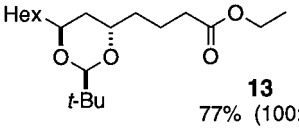
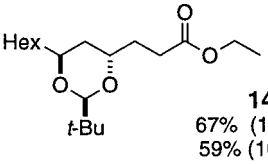
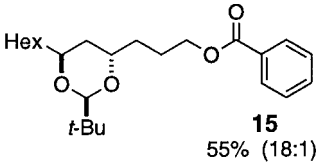
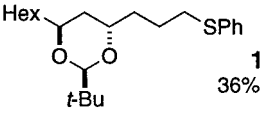


Table 2. Coupling of Functionalized Dialkylzinc Reagents



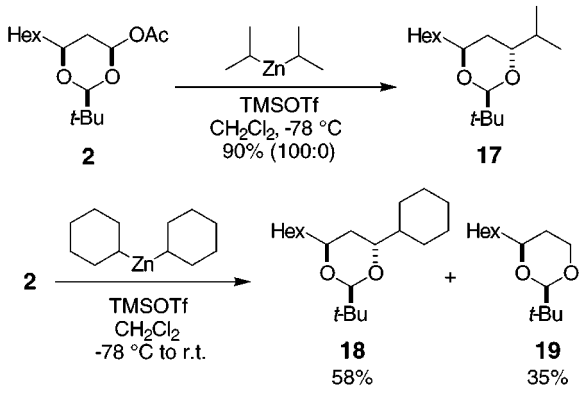
Entry	FG-R	Product	Yield (Epimeric Ratio)
a	Me		**10** 90% (100:0)
b	Dec[a]		**11** 69% (100:0)
c	$Cl(CH_2)_4$[b]		**12** 82% (100:0)
d	$EtO_2C(CH_2)_3$[b]		**13** 77% (100:0)
e	$EtO_2C(CH_2)_2$		**14** 67% (100:0)[b] 59% (100:0)[c]
f	$PhCO_2(CH_2)_3$[a]		**15** 55% (18:1)
g	$PhS(CH_2)_3$[a]		**16** 36% (8:1)

[a]Prepared by B-Zn transmetalation from olefin. [b]Prepared by CuI-catalyzed iodide-Zn exchange from primary iodide. [c]Prepared by light-initiated iodide-Zn exchange from primary iodide.

Encouraged by the extremely high diastereoselectivity observed in the coupling of Et_2Zn with **2**, we examined the coupling of other dialkylzinc reagents, Table 2. Commercially available Me_2Zn coupled with **2** under the standard reaction conditions to give the methyl adduct **10** in 90% yield as a single diasteromer (entry a). Didecylzinc also coupled to give **11** in 69% yield as a single diastereomer (entry b). We were particularly interested

(33) An alternative pathway was suggested by one of the referees, namely that the reaction of **7** could give **5** initially, followed by subsequent isomerization to **4**. Two arguments detract from this possibility. First, it would require very selective *equatorial* addition of diethylzinc to **9**, which appears unlikely considering the high axial selectivity observed throughout this work. Second, the isomerization of **5** to **4** would need to account for the observed 5:94 ratio, where the expected equilibrium ratio is 50:50. The alternative pathway thus requires a contra-thermodynamic equilibration and cannot account for the bulk of the product.

Scheme 5

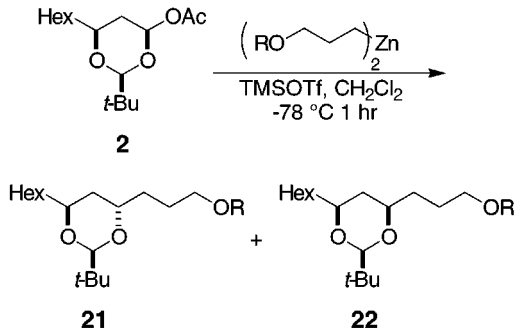


in more functionalized dialkylzincs. Di(4-chlorobutyl)zinc coupled readily with **2** to give the 4-chlorobutyl adduct **12** in 87% as a single diastereomer (entry c). Esters are also compatible with the coupling conditions as di(3-carboethoxypropyl)zinc and di(2-carboethoxyethyl)zinc coupled to give **13** and **14** in 77% and 67% yields, respectively, as single diastereomers (entry d and e). In both cases, the dialkylzinc was prepared by Knochel's CuI-catalyzed iodide−Zn exchange of the primary iodide.[25] Di(2-carboethoxyethyl)zinc prepared by Charette's light-initiated iodide−Zn exchange procedure[26] coupled as well to give **14** in a slightly lower 59% yield as a single diastereomer (entry e). Benzoate-protected alcohols are also compatible. Di(3-benzoyloxypropyl)zinc coupled with **2** to give **15** in 55% yield as an 18:1 mixture of acetal epimers (entry f). Sulfides are less successful in this coupling as di(3-thiophenylpropyl)zinc reacted sluggishly with **2** to give the desired adduct **16** in only 36% yield as an 8:1 mixture of acetal epimers (entry g).

We were especially interested in the coupling of secondary dialkylzincs with **2**, Scheme 5. Diisopropylzinc[34] coupled with **2** under the standard reaction conditions to give the hindered *anti*-1,3-dioxane **17** in an excellent 90% yield as a single diastereomer. It is worth mentioning that none of the corresponding *syn*-1,3-dioxane diastereomer was observed by 500 MHz ^{1}H NMR. The more hindered dicyclohexylzinc[27b] also coupled with **2** upon warming to 23 °C to give the desired cyclohexyl adduct **18** in 58% yield. In addition, the hydride transfer product **19** was isolated in 35% yield. Apparently, the more sterically hindered dicyclohexylzinc undergoes competitive β-hydride transfer to the oxacarbenium ion. The coupling of secondary dialkylzincs opens up the intriguing possibility that configurationally stable secondary dialkylzinc reagents[35] may couple stereoselectively with 4-acetoxy-1,3-dioxanes. This idea is currently under investigation.

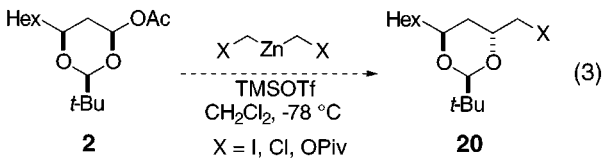
We were also interested in the coupling of di(halomethyl)zincs with 4-acetoxy-1,3-dioxanes, as these reagents would convert the electrophilic 4-acetoxy-1,3-dioxanes into a nucleophilic halide that could be used in the synthesis of polyol chains.[6] However, all attempts have been unsuccessful, eq 3. Both di(iodomethyl)zinc and di(chloromethyl)zinc[36] or their more soluble DME complexes[37] failed to give any of the desired *anti*-1,3-dioxane **20**, instead giving complex mixtures of products. Believing that the problem may lie in the degradation of the product under the reaction conditions, we attempted to couple di(pivaloxymethyl)zinc as a means of transferring a one-carbon nucleophile. Unfortunately, this also led to a complex mixture of products.

Table 3. Coupling of Di(3-alkoxypropyl)zincs



Entry	R	Yield	*Anti*:*Syn* Ratio (**21**:**22**)
a	TBS[a]	98%	6.3:1
	TBS[b]	100%	5.6:1
b	TIPS[a]	60%	9.5:1
c	Bn[a]	83%	17:1
	Bn[b]	93%	33:1
d	Piv[a]	36%	100:0

[a] Prepared by hydroboration/transmetalation from olefin
[b] Prepared by CuI-catalyzed iodide-Zn exchange from iodide



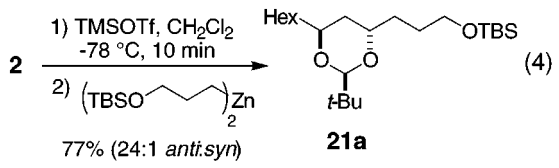
A surprising result was obtained in the coupling of di(3-alkoxypropyl)zincs with **2**, Table 3. When di(3-*tert*-butyldimethylsilyoxypropyl)zinc was coupled with **2** under the standard reaction conditions, the desired *anti*-1,3-dioxane **21a** was obtained in 85% yield. However, the *syn*-1,3-dioxane diastereomer **22a** was also isolated in 13% yield (entry a). We had initially assumed that the minor diastereomer was simply the acetal epimer that we had observed in the other couplings since the C4 and C6 dioxane ring methine protons overlapped in **22a**.[15] The C4 and C6 methine protons could be differentiated in the corresponding primary alcohol (**22**, R = H), and the *syn*-1,3-dioxane ring geometry was determined by NOE analysis. The geometry of **22a** was unequivocably confirmed by an independent synthesis. We were disturbed to find that the diastereoselectivity had eroded to 6.3:1 with the use of di(3-*tert*-butyldimethylsilyoxypropyl)zinc. Since the dialkylzinc had been prepared by the

(34) Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732−1734.
(35) (a) Micouin, L.; Oestreich, M.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 245−246. (b) Micouin, L.; Knochel, P. *Synlett* **1997**, 327−328. (c) Darcel, C.; Flachsmann, F.; Knochel, P. *Chem. Commun.* **1998**, 205−206.
(36) (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651−2652. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081−1083.
(37) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592−2602.

hydroboration−transmetalation route, we were concerned that the lower diastereoselectivity might result from direct coupling of the trialkylboron with 4-acetoxy-1,3-dioxane **2**. This possibility was ruled out when both Et_3B and tris(3-*tert*-butyldimethylsiloxypropyl)boron failed to couple with **2** under extended reaction times and elevated temperatures. In addition, when the dialkylzinc was prepared by the iodide−Zn exchange procedure and coupled with **2**, the *anti*- and *syn*-1,3-dioxanes **21a** and **22a** were isolated in 100% combined yield and a 5.6:1 ratio. Since the same *anti*:*syn* ratio was obtained when the dialkylzinc was prepared by two different methods, we concluded the lower diastereoselectivity was a result of the silyl ether functionality.

Examination of other protecting groups in the dialkylzinc revealed an interesting pattern of diastereoselectivity. Increasing the steric bulk of the silyl group with di(3-triisopropylsilyloxypropyl)zinc gave an improved 9.5:1 *anti*:*syn* ratio in 60% combined yield of **21b** and **22b** (entry b). Di(3-benzyloxypropyl)zinc coupled with **2** to give a 17:1 *anti*:*syn* ratio in 83% yield of **21c** and **22c** when prepared by the hydroboration/transmetalation route, entry c. The same dialkylzinc prepared from the alkyl iodide gave a 33:1 *anti*:*syn* ratio in 93% combined yield of **21c** and **22c**. In contrast, di(3-pivaloxypropyl)-zinc coupled with **2** to give only the *anti*-1,3-dioxane diastereomer, but the yield was modest (entry d). In all cases, the identity of the minor *syn*-1,3-dioxane diastereomer was confirmed by independent synthesis and GC doping experiments.[38]

One possible explanation for the formation of the *syn*-1,3-dioxane diastereomers is S_N2 displacement of an anomeric triflate.[39] However, pretreatment of **2** with TMSOTf for 10 min. at −78 °C prior to the addition of di(3-*tert*-butyldimethylsiloxypropyl)zinc led to an improved 24:1 *anti*:*syn* ratio in 77% yield of **21a** and **22a**, eq 4. We concluded that anomeric triflates are not intermediates in the coupling reaction. Instead, pretreatment merely led to increased isomerization to the thermodynamically more stable oxacarbenium ion intermediate prior to the coupling with the dialkylzinc.



We believe that the lower diastereoselectivity observed in the di(3-alkoxypropyl)zincs is a result of an equilibrium between the open-chain form **23** and the intramolecular chelated form **24** of the dialkylzinc which increases the steric environment about the C−Zn bond.[27b,40] As the steric hinderence increases, the dialkylzinc is less likely to add to the oxacarbenium ion **8** from the more sterically hindered axial direction (Figure 3). Instead, competitive addition from the less-hindered equatorial direction to give the all equatorially substituted 1,3-dioxane conformer **22** is observed. The benzyl-protected di(3-benzloxypropyl)zinc presumably exists largely as the chelated structure; however, the smaller steric enviroment of the benzyl group allows the kinetic axial addition to dominate and leads to the observed 17−33:1 *anti*:*syn* ratios. Di(3-*tert*-butyldimethylsiloxypropyl)zinc adds competitively from the less-hindered equatorial direction due to the increased steric bulk of the TBS group to give a 6:1 *anti*:*syn* ratio. Surprisingly, the triisopropylsilyl (TIPS)-protected dialkylzinc reagents are slightly more selective and lead to a 9.5:1 *anti*:*syn* ratio. Steric hindrence of the TIPS group may reduce chelation in di(3-triisopropylsilyloxypropyl)zinc, but the steric bulk of the TIPS group still exerts an effect in the open form and could account for the small amount of equatorial addition. In contrast to ether substitution, the *syn*-1,3-dioxane diastereomer was not observed in the couplings with ester substituents (entry d). These dialkylzincs would form relatively unhindered seven-membered ring chelates or open-chain forms rather than five-membered ring chelates, and only the *anti*-1,3-dioxanes were observed.

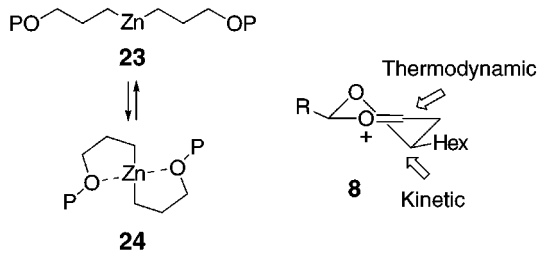
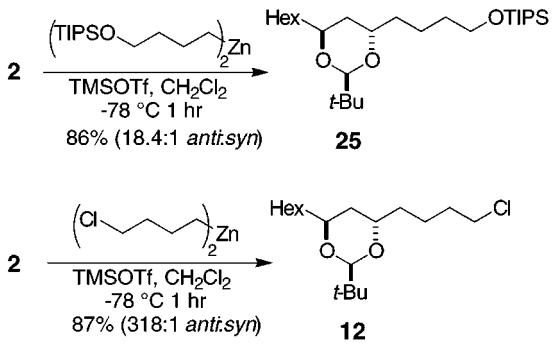


Figure 3. Conformation of dialkylzinc and oxacarbenium ion **8**.

Scheme 6



The lower diastereoselectivity seen in the three-carbon ethereal dialkylzincs was also observed in the coupling of four-carbon ethereal dialkylzincs, Scheme 6. Di(4-triisopropylsilyloxybutyl)zinc coupled with **2** under the standard reaction conditions to give **25** in 86% yield as an 18.4:1 mixture of *anti*:*syn* diastereomers. The formation of the *syn*-1,3-dioxane diastereomer may result from intramolecular six-membered ring coordination to form a very hindered dialkylzinc. Substitution of the TIPS ether for a nonchelating chloride in di(4-chlorobutyl)zinc gave an 87% of **12** as a 318:1 *anti*:*syn* mixture! This dramatic reversal reflects the effect of silyloxy substitution on coupling diastereoselectivity. These results clearly must be taken into account when planning a polyol chain synthesis.

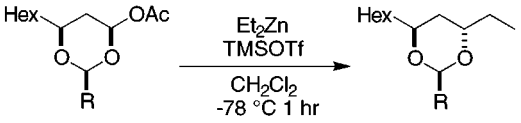
What role does the sterically demanding *tert*-butyl acetal play in these reactions? One incentive to investigate other acetals was our concern about the deprotection of *tert*-butyl acetals. A number of 4-acetoxy-1,3-dioxanes containing isopropyl **26**, methyl **28**, and methylene acetals **30** were prepared by the DIBALH reduction/

(38) Details for the synthesis and characterization of **22a**−**c** are given in the Supporting Information

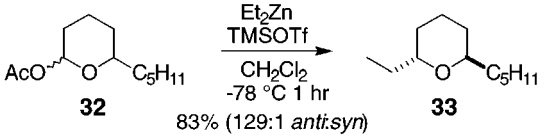
(39) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(40) Berninger, J.; Koert, U.; Eisenberg-Höhl, C.; Knochel, P. *Chem. Ber.* **1995**, *128*, 1021−1028.

Table 4. Affect of Acetal Group on Coupling



SM	R	Yield	Prodct	*Anti*:*Syn* ratio
2	$C(CH_3)_3$	91%	**4**	290:1
26	$CH(CH_3)_2$	86%	**27**	287:1
28	CH_3	63%	**29**	200:1
30	H	66%	**31**	120:1

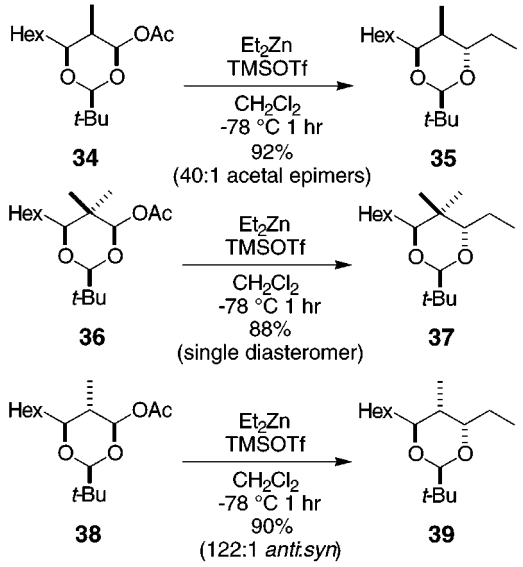


acetylation method. Coupling with Et_2Zn under the standard conditions revealed an interesting diastereoselectivity pattern, Table 4. The *tert*-butyl acetal **2** gave **4** with >290:1 *anti*:*syn* diastereoselectivity in 91% yield (entry a). The slightly smaller isopropyl acetal **26** coupled with Et_2Zn to give **27** in 86% yield as a 287:1 *anti*:*syn* mixture. The even smaller methyl acetal **28** gave **29** in a lower 66% yield as a 200:1 *anti*:*syn* mixture. Although smaller acetal groups did result in slightly lower *anti*:*syn* ratios, the selectivities were still synthetically useful. To determine the real effect of the acetal substituent, the methylene acetal **30** was submitted to the coupling reaction to give **31** in 66% yield as a 120:1 *anti*:*syn* mixture. This is analagous to the diastereoselectivity seen in the coupling of decanolactone acetate **32** with Et_2Zn to give the *anti*-tetrahydropyran **33** in 83% yield as a 129:1 *anti*:*syn* mixture. The identities of the *syn*-1,3-dioxane diastereomers were confirmed by independent synthesis and GC doping experiments.

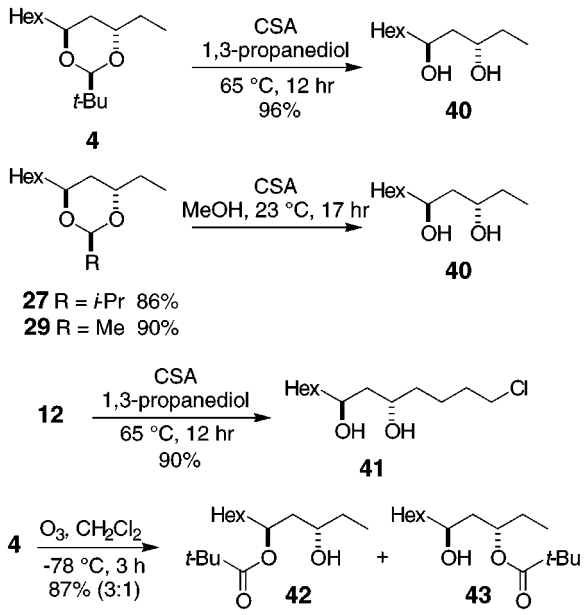
We were also interested in the synthesis of polypropionates. The reactions of Et_2Zn with a series of C5-substituted 4-acetoxy-1,3-dioxanes were investigated, Scheme 7.[41] Coupling of Et_2Zn with the C5 axial methyl dioxane **34** under the standard conditions gave **35** in 92% yield as a 40:1 mixture of acetal epimers. The slight epimerization of the acetal **35** is understandable considering the presence of two axial substituents. The C5 *gem*-dimethyl-substituted **36** also coupled readily with Et_2Zn to give **37** in a comparable 88% yield as a single diastereomer. The coupling of Et_2Zn and the C5 equatorial methyl-substituted **38** proceeded in a slightly lower diastereoselectivity to give **39** in 90% yield as a 122:1 *anti*:*syn* mixture. The lower diastereoselectivity results from increased steric hindrance on the α-face of the oxacarbenium ion, attributable to the equatorial C5 methyl group. In each case, the *trans*-1,3-dioxane geometry of **35**, **37**, and **39** was apparent from NOE analysis.

A last requirement for the successful implementation of this methodology is the deprotection of the 1,3-dioxanes

Scheme 7



Scheme 8



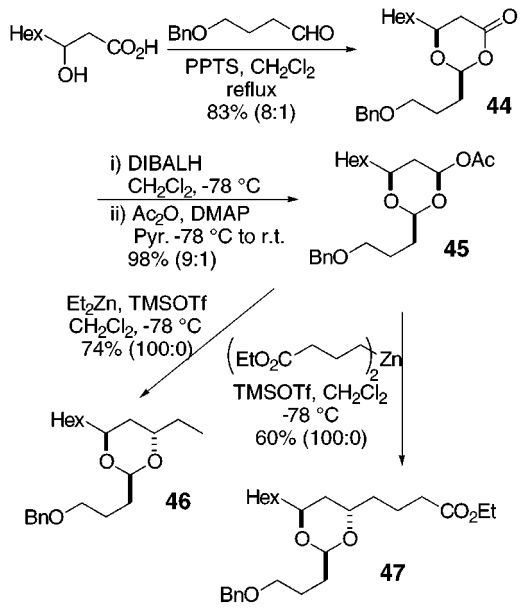
to give *anti*-1,3-diols. Unfortunately, cyclic acetals are relatively difficult to hydrolyze.[42] For simple adducts, treatment of the acetal **4** with catalytic CSA in 1,3-propanediol at 65 °C led to isolation of the *anti*-1,3-diol **40** in 96% yield, Scheme 8. Refluxing in MeOH with CSA also led to **40**, albeit in only 76% yield. The functionalized acetals **12** also could be deprotected to give **41** in 90% yield. The less-hindered acetals proved easier to hydrolyze. Simple stirring of **27** and **29** with catalytic CSA in MeOH at 23 °C overnight resulted in the isolation of **40** in 86% and 90% yield, respectively. A less obvious strategy was treatment of **4** with ozone[43] at −78 °C to oxidize the *tert*-butyl acetal to a mixture of monopivalate esters **42** and **43** in 87% yield as a 3:1 mixture of pivalate regioisomers. Although not applicable to unsaturated

(41) Syntheses of **34**−**36** are described in Powell, N. A., Ph.D. Thesis, University of California, Irvine, 1998. The preparation of these compounds will be discussed in a forthcoming paper by S. D. Rychnovsky, V. H. Dahanukar, A. J. Buckmelter, and D. S. Skalitzky.

(42) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 118−135.

(43) (a) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565−1567. (b) Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465−2467. (c) Deslongchamps, P.; Atlani, P.; Fréhel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651−3664.

Scheme 9



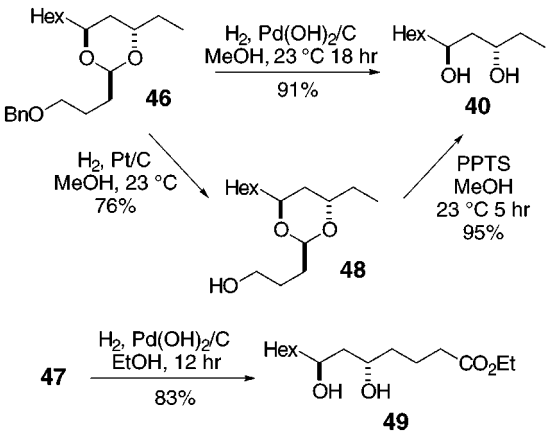
substrates, this deprotection strategy should be compatible with highly oxygenated compounds.

A New Acetal Protecting Group: BOB. An intramolecular transketalization strategy was envisioned to facilitate very mild deprotections. An acetal like **48**, Scheme 10, would equilibrate to a diol monoprotected with a tetrahydrofuranyl (THF) group by intramolecular acetal exchange. Both the acetal exchange and the deprotection of the THF group should take place under very mild acid catalysis. Related cyclic acetals have been isolated as side products in the THP protection of 1,2- and 1,3-diols,[44] but have not been used as diol protecting groups.[45] Protection of the primary alcohol in **48** with almost any silyl or ether protecting group would stabilize the acetal. The resulting diol protecting group would be removed in a two-step sequence: primary alcohol deprotection followed by mild acid hydrolysis.

We tested this strategy by preparing 4-acetoxy-1,3-dioxane **45** containing a 3-(benzyloxy)propyl acetal side chain, Scheme 9. The PPTS-catalyzed acetalization[46] of 3-hydroxynonanoic acid with 4-(benzyloxy)butanal gave 1,3-dioxan-4-one **44** in 83% as a 8:1 mixture of acetal epimers. DIBALH reduction/acetylation of **44** gave **45** in an excellent yield as a 9:1 mixture of diastereomers. Coupling of **45** and Et_2Zn under the standard conditions gave **46** in 74% yield as a single diastereomer. Functionalized dialkylzincs, such as di(3-carboethoxypropyl)zinc, also coupled with **45** to give **47** in 60% yield as a single diastereomer.

Deprotection of these acetals was easily achieved. Prolonged hydrogenation of **46** over $Pd(OH)_2/C$ in MeOH resulted in debenzylation and deprotection of the acetal to give the *anti*-1,3-diol **40** in 91% yield, Scheme 10. Apparently, the Pd catalyst is acidic enough to promote the intramolecular transketalization of the intermediate primary alcohol **48**. The deprotection can also be accomplished through a two-step procedure. The primary alcohol **48** could be isolated in reasonable yield by the use of Pt/C or by brief exposure to $Pd(OH)_2/C$ as the hydrogenation catalyst. On treatment with catalytic PPTS in MeOH at 23 °C, the acetal was smoothly deprotected to give **40** in 95% yield. The two-step deprotection may be advantegous for sensitive substrates. Functional groups such as esters are compatible with these deprotection conditions, as hydrogenation of **47** over $Pd(OH)_2/C$ gave the *anti*-1,3-diol **49** in 83% yield.

Scheme 10



The 4-**b**enzyl**o**xy**b**utanal (BOB) acetal protecting group used in Schemes 9 and 10 is just one member of a new class of diol protecting groups. Use of almost any simple alcohol protecting group would produce an acetal protecting group that could be removed in two steps: primary alcohol deprotection followed by mild acid hydrolysis. Deprotection of a 4-hydroxybutanal acetal takes place under much milder conditions than normal acetals, and a judicious selection of the alcohol protecting group would produce a set of orthogonally 1,3-diol protecting groups.

Conclusions

We have shown that dialkylzinc reagents couple readily with 4-acetoxy-1,3-dioxanes in excellent yields and with outstanding diastereoselectivities. A variety of functionalized dialkylzincs containing chlorides and esters are compatible with the reaction. Secondary dialkylzincs also couple, although increasing the steric bulk of the secondary dialkylzinc leads to competative hydride transfer. The coupling of di(3-alkoxypropyl)zincs proceeds in good yields, but the diastereoselectivities are a function of the oxygen protecting group. The modest diastereoselectivities observed with ether protecting groups appear to correlate with intramolecular chelation in the dialkylzinc reagents. Equatorial substitution at the C5 position of the dioxane ring results in slightly lower diastereoselectivity. The stereoselectivities also drop slightly with small substituents at the C2 position. The *anti*-1,3-dioxanes formed in this methodology are deprotected under acidic or oxidative conditions, and the smaller acetal groups can be deprotected under milder conditions. A very mild intramolecular transacetalization strategy for acetal deprotection has been demonstrated by the development of the BOB protecting group. The application of this chemistry to the convergent synthesis of highly oxygenated natural products is under investigation.

Experimental Section[47]

General Procedure for the Coupling of Dialkylzincs with 4-Acetoxy-1,3-dioxanes. (2*R,4*S**,6*S**)-2-*tert*-Butyl-**

(44) Nouguier, R. *Tetrahedron Lett*. **1982**, *23*, 2951−2. Pegg, N. A.; Paquette, L. A. *J. Org. Chem*. **1991**, *56*, 2461−8.

(45) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994.

(46) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839−841.

4-ethyl-6-hexyl-1,3-dioxane (4). A flame-dried 10 mL flask was charged with 0.216 g (0.753 mmol) of **2** and 3 mL of CH_2Cl_2 and cooled to −78 °C in a dry ice/acetone bath. Et_2Zn (1.51 mL, 1.51 mmol, 1 M in hexane) was added via syringe, followed by 205 μL (1.13 mmol) of TMSOTf. The reaction was stirred at −78 °C for 1 h and then quenched with Et_3N and satd $NaHCO_3$ and warmed to 23 °C. The organic layer was washed with ice-cold 1 N $NaHSO_4$ and satd $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residual oil was purified by flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes) to give 0.176 g (91%) of a clear oil as a 51:1 mixture of diastereomers: FT-IR (neat) 1218, 1136, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (s, 1 H), 3.91 (ddd, J = 10.7, 5.8, 5.8 Hz, 1 H), 3.67 (m, 1 H), 1.99 (m, 1 H), 1.74 (ddd, J = 12.5, 12.5, 6.1 Hz, 1 H), 1.45 (m, 4 H), 1.29 (m, 8 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.85 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.0; *C*H 99.4, 73.2, 71.6; *C*H_2 36.0, 31.6, 28.9, 24.8, 24.5, 23.4, 22.3; *C*H_3 24.4 (3), 13.8, 10.1; HRMS (CI/isobutane) calcd for $[C_{16}H_{32}O_2 + H]^+$ 257.2480, found 257.2470. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 75.27; H, 12.39.

(2*R,4*R**,6*S**)-2-*tert*-Butyl-4-ethyl-6-hexyl-1,3-dioxane (6).** A 10 mL round-bottomed flask fitted with a Soxhlett extractor containing 4 Å MS and a reflux condensor was charged with 0.10 g (0.531 mmol) of (3*R**,5*S**)-3,5-dihydroxyundecane, 6 mL of CH_2Cl_2, and 9 mg (0.019 mmol) of $Sc(OTf)_3$. The mixture was heated to reflux for 4 h and then washed with water, dried over $MgSO_4$, and concentrated. The residual oil was purified by flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes) to give 0.141 g (100%) of a clear oil as a single diastereomer: FT-IR (neat) 1217, 1121, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 1 H), 3.47 (m, 1 H), 3.39 (m, 1 H), 1.53 (m, 2 H), 1.41 (m, 4 H), 1.28 (m, 8 H), 0.93 (t, J = 7.6 Hz, 3 H), 0.90 (s, 9 H), 0.89 (*t*, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.9; *C*H 106.7, 77.4, 76.1; *C*H_2 36.9, 36.0, 31.9, 29.3, 29.0, 25.1, 22.6; *C*H_3 24.8 (3), 14.1, 9.5; HRMS (CI/isobutane) calcd for $[C_{16}H_{32}O_2 + H]^+$ 257.2480, found 257.2471. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 75.33; H, 12.70.

(2*R,4*S**,6*S**)-2-*tert*-Butyl-6-hexyl-4-methyl-1,3-dioxane (10).** Reaction of 0.156 g (0.544 mmol) of **2**, 0.55 mL (1.09 mmol, 2 M in toluene) of dimethylzinc, and 148 μL (0.818 mmol) of TMSOTf according to the general protocol yielded 0.119 g (90%) of a clear oil as a single diastereomer after purification by flash chromatography (30% CH_2Cl_2/hexanes): FT-IR (neat) 1378, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (s, 1 H), 5.27 (dq, J = 6.7, 6.7 Hz, 1 H), 3.71 (m, 1 H), 1.75 (ddd, J = 12.1, 6.1 Hz, 1 H), 1.53−1.24 (m, 11 H), 1.31 (d, J = 6.9 Hz, 3 H), 0.88 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 34.7; *C*H 99.6, 71.3, 67.7; *C*H_2 36.2, 35.4, 31.9, 29.3, 25.1, 22.6; *C*H_3 24.7 (3), 17.3, 14.1; HRMS (CI/isobutane) calcd for $[C_{15}H_{30}O_2 + H]^+$ 243.2324, found 243.2323. Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47. Found: C, 74.49; H, 12.43.

(2*R,4*S**,6*S**)-2-*tert*-Butyl-4-decyl-6-hexyl-1,3-dioxane (11).** A 100 mL Schlenk flask was charged with 2.02 mL (10.69 mmol) of 1-decene and 15 mL of THF under Ar. BH_3·SMe_2 (0.35 mL, 3.56 mmol) was added via syringe, and the resulting clear solution was stirred at 23 °C for 16 h. The volatiles were distilled under vacumn (0.2 mmHg, 0 °C to 23 °C, 6 h). The resulting clear oil was dissolved in 10 mL of dry hexanes and cooled in an ice bath. Et_2Zn (0.73 mL, 7.13 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The volatiles were removed under vacumn and the excess Et_2Zn was removed by distillation (0.2 mmHg, 25 °C, 3 h). The resulting brown oil was diluted with 3 mL dry hexanes to make a 1.8 M solution.

Treatment of **2** (0.100 g, 0.349 mmol) with 0.58 mL of Dec_2Zn (1.05 mmol, 1.8 M in hexanes) and 95 μL (0.524 mmol) of TMSOTf according to the general protocol yielded 88.3 mg (69%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2, 15% CH_2Cl_2/hexanes then 20%): FT-IR (neat) 1217, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 4.01 (m, 1 H), 3.68 (m, 1 H), 1.97 (m, 1 H), 1.73 (ddd, J = 12.5, 12.5, 6.2 Hz, 1 H), 1.56−1.20 (m, 28 H), 0.88 (s, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.8; *C*H 99.7, 71.9, 71.8; *C*H_2 36.3, 34.5, 31.9, 31.8, 30.7, 29.6 (3), 29.5, 29.3, 29.2, 25.8, 25.1, 22.7, 22.6; *C*H_3 24.7 (3), 14.1 (2); HRMS (CI/isobutane) calcd for $[C_{24}H_{48}O_2 + H]^+$ 369.3732, found 369.3731.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(4-chlorobutyl)-6-hexyl-1,3-dioxane (12).** A flame-dried 25 mL Schlenk flask was purged with Ar and charged with ca. 4 mg of CuI (1 mol %) and 0.32 mL (2.62 mmol) of 4-chloro-1-iodobutane. Et_2Zn (0.40 mL, 3.93 mmol) was added via syringe, and the resulting gray slurry was stirred at 50 °C for 18 h. The Schlenk flask was then evacuated (0.1 mmHg) and heated at 50 °C for 2 h to distill off excess Et_2Zn. The residual reddish gray oil was dissolved in 3 mL of CH_2Cl_2 and reacted with 0.150 g (0.524 mmol) of **2** and 115 μL (0.628 mmol) of TMSOTf according to the general protocol to yield 0.137 g (82%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes then 30%): FT-IR (neat) 1216, 1123 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (s, 1 H), 4.01 (dddd, J = 5.4, 5.4, 5.4, 5.4 Hz, 1 H), 3.67 (m, 1 H), 3.55 (t, J = 6.7 Hz, 2H), 2.05 (m, 1 H), 1.80 (m, 3 H), 1.60−1.28 (m, 13 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.9; *C*H 99.8, 71.8, 71.5; *C*H_2 45.0, 36.3, 34.4, 32.3, 31.8, 29.9, 29.2, 25.1, 23.1, 22.6; *C*H_3 24.7 (3), 14.1; HRMS (CI/isobutane) calcd for $[C_{18}H_{35}ClO_2 - H]^+$ 317.2247, found 317.2251. Anal. Calcd for $C_{18}H_{35}ClO_2$: C, 67.79; H, 11.06. Found: C, 68.25; H, 11.06.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(3-carbethoxypropyl)-6-hexyl-1,3-dioxane (13):** A 25 mL Schlenk flask was charged with 0.507 g (2.10 mmol) of ethyl 4-iodobutyrate and 2 mg (0.011 mmol) of CuI. Et_2Zn (0.32 mL, 3.1 mmol) was added via syringe, and the resulting slurry was stirred at 50 °C for 18 h. Excess Et_2Zn was distilled off under vacuum (0.1 mmHg, 50 °C, 3 h). The resulting black oil was treated with 0.150 g (0.524 mmol) of **2** and 115 μL (0.628 mmol) of TMSOTf according to the general procedure to yield 0.139 g (77%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2, 50% CH_2Cl_2/hexanes then 5% EtOAc/hexanes): FTIR- (neat) 1738, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (s, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.02 (dddd, J = 5.4, 5.4, 5.4, 5.4 Hz, 1 H), 3.66 (m, 1 H), 2.34 (m, 2H), 2.05 (dddd, J = 14.0, 10.0, 10.0, 4.5 Hz, 1 H), 1.80 (m, 1 H), 1.77 (ddd, J = 12.8, 12.8, 6.1 Hz, 1 H), 1.63 (m, 1 H), 1.49 (m, 1 H), 1.28 (m, 11 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 173.6, 34.8; *C*H 99.7, 71.8, 71.4; *C*H_2 60.2, 36.2, 34.4, 33.9, 31.8, 30.0, 29.2, 25.0, 22.6, 21.3; *C*H_3 24.7 (3), 14.2, 14.1; HRMS (CI/isobutane) calcd for $[C_{20}H_{38}O_4 + H]^+$ 343.2848, found 343.2843. Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 69.67; H, 11.03.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(2-carbethoxyethyl)-6-hexyl-1,3-dioxane (14).** A 25 mL Schlenk flask was charged with 308 mg (1.40 mmol) ethyl 3-iodopropionate and 2 mg (0.011 mmol) of CuI. Et_2Zn (0.21 mL, 2.09 mmol) was added via syringe, and the resulting slurry was stirred at 50 °C for 18 h. Excess Et_2Zn was distilled off under vacuum (0.1 mmHg, 50 °C, 3 h). The resulting reddish brown oil was treated with 105.7 mg (0.0.369 mmol) **2** and 83 μL (0.443 mmol) TMSOTf according to the general procedure to yield 80.7 mg (67%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2, 40% CH_2Cl_2/hexanes then 50%): FT-

(47) General experimental: Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using oven or flame-dried glassware and standard syringe/septa techniques. CAUTION: Et_2Zn is an extremely pyrophoric compound. Great care should be taken to exclude water or air from any reactions where Et_2Zn is present. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. Et_2Zn was purchased in neat form from Strem Chemicals. Tetrahydrofuran, diethyl ether, and methylene chloride were dried by filtration through alumina according to the procedure described by Grubbs. (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518-1520.) Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on E. Merck reagent silica gel 60 (230−400 mesh). NMR data for ^{13}C DEPT experiments are reported as quaternary (C), tertiary (CH), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals, the number of carbon atoms is given in parentheses. Combustion analyses were performed by M-H-W laboratories, Phoenix, AZ.

IR (neat) 1738, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 1 H), 4.13 (q, J = 6.8 Hz, 2 H), 4.02 (m, 1 H), 3.68 (m, 1 H), 2.34 (m, 2H), 2.05 (m, 3 H), 1.79 (ddd, J = 12.8, 12.8, 6.1 Hz, 1 H), 1.66 (m, 1 H), 1.50 (m, 1 H), 1.28 (m, 10 H), 1.26 (t, J = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) *C* 173.6, 34.5; *C*H 99.7, 71.8, 71.0; *C*H_2 60.4, 36.2, 34.4, 31.8, 30.6, 29.2, 25.9, 25.0, 24.6, 22.6; *C*H_3 24.6 (3), 14.2, 14.1; HRMS (CI/isobutane) calcd for $[C_{19}H_{36}O_4 - H]^+$327.2535, found 327.2533. Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.39; H, 10.88.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(3-(benzoyloxy)propyl)-6-hexyl-1,3-dioxane (15).** A 50 mL Schlenk flask was charged with 0.226 g (1.40 mmol) of allyl benzoate and 3 mL of Et_2O and cooled in an ice bath. Et_2BH (0.14 mL, 98 mg, 1.4 mmol) was added via syringe, and the solution was stirred at 23 °C for 3 h. The volatiles were removed under reduced pressure (0.1 mmHg, 0 °C, 30 min). After cooling in an ice bath, Et_2Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 30 min. Excess Et_2Zn was distilled off under vacuum (0.1 mmHg, 0 °C to 23 °C, 3 h). The oil was treated with 0.100 g (0.349 mmol) of **2** and 76 μL (0.093 mmol) of TMSOTf according to the general procedure to yield 0.0748 g (55%) of a clear oil as a 18:1 ratio of acetal epimers after purification by flash chromatography (SiO_2, 50% CH_2Cl_2/hexanes then 5% EtOAc/hexanes): FT-IR (neat) 3065, 1721, 1603, 1274 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.4, 1.2 Hz, 2 H), 7.56 (tt, J = 7.6, 1.2 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 4.38 (m, 2 H), 4.32 (s, 1 H), 4.09 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.69 (m, 1 H), 2.19 (dddd, J = 15.1, 10.3, 10.3, 4.8 Hz, 1 H), 1.93 (m, 1 H), 1.80 (m, 2 H), 1.50 (m, 2 H), 1.42−1.28 (m, 10 H), 0.89 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 166.6, 130.4, 34.8; *C*H 132.8, 129.5, 128.3, 99.7, 71.8, 71.2; *C*H_2 64.8, 36.2, 34.5, 31.8, 29.2, 27.2, 25.2, 25.0, 22.6; *C*H_3 24.6 (3), 14.0; HRMS (CI/isobutane) calcd for $[C_{24}H_{38}O_4 + H]^+$ 391.2848, found 391.2840. Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.65; H, 10.11.

(2*R,4*R**,6*S**)-2-*tert*-Butyl-4-isopropyl-6-hexyl-1,3-dioxane (17).** Reaction of 99.2 mg (0.346 mmol) of **2** with 0.10 mL (0.70 mmol) of *i*-Pr_2Zn[34] and 76 μL (0.419 mmol) of TMSOTf according to the general protocol yielded 0.103 g (90%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes): FT-IR (neat) 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (s, 1 H), 3.63 (m, 1 H), 3.45 (ddd, J = 10.4, 5.2, 1.6 Hz, 1 H), 2.26 (m, 1H), 1.64 (ddd, J = 13.6, 11.2, 6.0 Hz, 1 H), 1.55 (m, 1 H), 1.50−1.34 (m, 10H), 0.96 (d, J = 6.4 Hz, 3 H), 0.89 (s, 12 H), 0.84 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) *C* 43.5; *C*H 95.7, 78.0, 72.8, 36.8; *C*H_2 44.5, 40.9, 40.9, 38.8, 35.5, 33.5; *C*H_3 35.2 (3), 31.2, 30.8, 26.7; HRMS (CI/isobutane) calcd for $[C_{17}H_{34}O_2 + H]^+$ 271.2637, found 271.2636. Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67. Found: C, 75.61; H, 12.56.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(3-(*t*-butyldimethylsilyloxy)propyl)-6-hexyl-1,3-dioxane (21a).** A 25 mL Schlenk flask was charged with 0.242 g (1.40 mmol) 1-(*tert*-butyldimethylsilyloxy)-2-propene under Ar. Et_2BH (0.20 mL, 2.1 mmol) was added via syringe, and the solution was stirred at 23 °C for 18 h. The volatiles were removed under reduced pressure (0.2 mmHg, 25 °C, 2 h). After cooling in an ice bath, Et_2Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 45 min. Excess Et_2Zn was distilled off under vacuum (0.2 mmHg, 50 °C, 5 h). The residual black oil was treated with 100.4 mg, (0.349 mmol) of **2** and 77 μL (0.421 mmol) of TMSOTf according to the general procedure to yield 119.3 mg (83%) of **21a** as a clear oil as a single diastereomer and 18.9 mg (13%) of **22a** after purification by flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes then 30%). **Data for 21a**: FT-IR (neat) 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 4.02 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.69 (m, 1 H), 3.65 (m, 2 H), 2.05 (m, 1 H), 1.76 (ddd, J = 13.1, 13.1, 6.2 Hz, 1 H), 1.63 (m, 1 H), 1.55−1.28 (m, 13 H), 0.88 (s, 12 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.8, 18.3; *C*H 99.7, 71.8, 71.7; *C*H_2 62.9, 36.3, 34.6, 31.9, 29.2, 29.1, 27.0, 25.0, 22.62; *C*H_3 26.0 (3), 24.70 (3), 14.0, −5.3 (2); HRMS (CI/isobutane) calcd for $[C_{23}H_{48}O_3Si + H]^+$ 401.3451, found 401.3454. Anal. Calcd for $C_{23}H_{48}O_3Si$: C, 68.94; H, 12.07. Found: C, 69.09; H, 12.10.

Data for 22a: FT-IR (neat) 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.04 (s, 1 H), 3.62 (m, 2 H), 3.48 (m, 2 H), 1.67 (m, 1 H), 1.56 (m, 1 H), 1.51 (m, 3 H), 1.41 (ddd, J = 10.5, 2.3, 2.3 Hz, 1 H), 1.39 (m, 2 H), 1.28 (m, 7 H), 1.14 (ddd, J = 12.8, 11.2, 11.2 Hz, 1 H), 0.89 (s, 18 H), 0.88 (t, J = 7.2 Hz, 3 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.9, 18.1; *C*H 106.7, 76.1, 75.9; *C*H_2 63.3, 37.4, 36.0, 32.4, 31.9, 29.2, 28.4, 25.1, 22.6; *C*H_3 26.0 (3), 24.8 (3), 14.1, −5.3 (2); HRMS (CI/NH_3) calcd for $[C_{23}H_{48}O_3Si + H]^+$ 401.3451, found 401.3450. Anal. Calcd for $C_{23}H_{48}O_3Si$: C, 68.94; H, 12.07. Found: C, 68.90; H, 11.95.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(3-(triisopropylsilyloxy)-propyl)-6-hexyl-1,3-dioxane (21b).** A 25 mL Schlenk flask was charged with 299 mg (1.40 mmol) of 1-(triisopropylsilyloxy)-2-propene under Ar. Et_2BH (0.20 mL, 2.1 mmol) was added via syringe, and the solution was stirred at 23 °C for 18 h. The volatiles were removed under reduced pressure (0.2 mmHg, 0 °C, 2 h). After cooling in an ice bath, Et_2Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 45 min. Excess Et_2Zn was distilled off under vacuum (0.2 mmHg, 50 °C, 3 h). The residual black oil was treated with 103.5 mg (0.361 mmol) of **2** and 78 μL (0.433 mmol) of TMSOTf according to the general procedure to yield 96.2 mg (60%) of a clear oil as a single diastereomer (GC of the crude product indicated a 9.5:1 *anti*:*syn* ratio) after purification by flash chromatography (SiO_2, 30% CH_2Cl_2/hexanes then 50%): FT-IR (neat) 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 1 H), 4.03 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.72 (td, J = 7.1, 1.2 Hz, 2 H), 3.68 (m, 1 H), 2.08 (m, 1 H), 1.76 (ddd, J = 13.2, 11.8, 6.3 Hz, 1 H), 1.68 (m, 1 H), 1.52 (m, 3 H), 1.41 (m, 2 H), 1.29 (m, 8 H), 1.07 (m, 21 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.8; *C*H 99.7, 71.8, 71.7, 12.0 (3); *C*H_2 36.3, 24.6, 21.9, 29.3, 29.2, 27.0, 25.4, 22.6; *C*H_3 24.7 (3), 18.0 (6), 14.1; HRMS (CI/isobutane) calcd for $[C_{26}H_{54}O_3Si - H]^+$ 441.3764, found 441.3773. Anal. Calcd for $C_{26}H_{54}O_3Si$: C, 70.53; H, 12.29. Found: C, 70.42; H, 12.16.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(3-(benzyloxy)propyl)-6-hexyl-1,3-dioxane (21c).** A 25 mL Schlenk flask was charged with 387 mg (1.40 mmol) 1-(benzyloxy)-3-iodopropane and 5 mg of CuI under Ar. Et_2Zn (0.22 mL, 2.1 mmol) was added via syringe, and the mixture was stirred at 50 °C for 48 h. Excess Et_2Zn was distilled under vacuum (0.2 mmHg, 50 °C, 43 h). The residual black oil was treated with 100.9 mg (0.352 mmol) of **2** and 77 μL (0.423 mmol) of TMSOTf according to the general protocol to yield 123.7 mg (93%) of a clear oil as a single diastereomer (GC of the crude product indicated a 33:1 *anti*:*syn* ratio) after purification by flash chromatography (SiO_2, 30% CH_2Cl_2/hexanes then 60%): FT-IR (neat) 3087, 3064, 3031, 1808, 1730, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 4 H), 7.28 (m, 1 H), 4.52 (s, 2 H), 4.31 (s, 1 H), 4.03 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.68 (m, 1 H), 3.52 (m, 2 H), 2.08 (m, 1 H), 1.77 (m, 2 H), 1.65 (m, 1 H), 1.50 (m, 2 H), 1.29 (m, 10 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 138.6, 34.5; *C*H 128.3 (2), 127.6 (2), 127.5, 99.7, 71.8, 71.6; *C*H_2 36.3, 34.5, 31.8, 29.2, 27.4, 26.1, 25.0, 22.6; *C*H_3 24.7 (3), 14.1; HRMS (CI/isobutane) calcd for $[C_{24}H_{40}O_3 + H]^+$ 377.3055, found 377.3057. Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.65; H, 10.58.

(2*S,4*S**,6*S**)-2-*tert*-Butyl-4-(4-(triisopropylsilyloxy)-butyl)-6-hexyl-1,3-dioxane (25).** A 25 mL Schlenk flask was charged with 319 mg (1.40 mmol) 4-(triisopropylsilyloxy)-1-butene under Ar. Et_2BH (0.20 mL, 2.1 mmol) was added via syringe, and the solution was stirred at 23 °C for 18 h. The volatiles were removed under reduced pressure (0.2 mmHg, 0 °C, 2 h). After cooling in an ice bath, Et_2Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 45 min. Excess Et_2Zn was distilled off under vacuum (0.2 mmHg, 50 °C, 3 h). The residual black oil was treated with 103.0 mg (0.360 mmol) of **2** and 78 μL (0.430 mmol) of TMSOTf according to the general procedure to yield 140.5 mg (86%) of a clear oil as a single diastereomer (GC of the crude product indicated 18.4:1 *anti*:*syn* ratio) after purification by

flash chromatography (SiO_2, 20% CH_2Cl_2/hexanes then 30%): FT-IR (neat) 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 4.01 (m, 1 H), 3.69 (td, J = 6.4, 1.7 Hz, 2 H), 3.68 (m, 1 H), 2.04 (m, 1 H), 1.75 (ddd, J = 13.0, 11.9, 6.3 Hz, 1 H), 1.58 (m, 2 H), 1.50 (m, 1 H), 1.40 (m, 3 H), 1.28 (m, 10 H), 1.06 (m, 21 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.5; *C*H 99.8, 71.9, 71.8, 12.0 (3); *C*H_2 63.4, 36.3, 34.4, 32.9, 31.9, 30.6, 29.2, 25.1, 22.6, 22.3; *C*H_3 24.7 (3), 18.0 (6), 14.1; HRMS (CI/isobutane) calcd for $[C_{27}H_{56}O_3Si - H]^+$ 455.3920, found 455.3916. Anal. Calcd for $C_{27}H_{56}O_3Si$: C, 70.99; H, 12.36. Found: C, 70.70; H, 11.97.

(2*R,4*S**,6*S**)-4-Ethyl-6-hexyl-2-isopropyl-1,3-dioxane (29).** Treatment of 150.1 mg (0.551 mmol) **26** with 0.09 mL (0.83 mmol) Et_2Zn and 120 μL (0.661 mmol) TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 5% EtOAc/hexanes) gave 114.5 mg (86%) of a clear oil as a 96:1 mixture of acetal epimers (GC of crude product indicates 287:1 *anti*:*syn* ratio): FT-IR (neat) 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 (d, J = 6.0 Hz, 1 H), 3.92 (ddd, J = 10.1, 5.6, 5.6 Hz, 1 H), 3.69 (m, 1 H), 1.99 (m, 1 H), 1.78 (ddd, J = 13.3, 11.8, 6.3 Hz, 1 H), 1.73 (doublet of sextets, J = 6.6, 6.6 Hz, 1 H), 1.54 (m, 1 H), 1.47 (m, 1 H), 1.39 (m, 1 H), 1.35 (dd, J = 13.4, 1.5 Hz, 1 H), 1.28 (m, 7 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 6 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C*H 98.4, 73.5, 71.9, 33.0; *C*H_2 36.3, 34.2, 31.8, 29.2, 25.1, 23.6, 22.6; *C*H_3 17.4, 17.4, 14.1, 10.3; HRMS (EI) calcd for $[C_{15}H_{30}O_2 - H]^+$ 241.2168, found 241.2177. Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47. Found: C, 74.69; H, 12.53.

(2*R,4*S**,6*S**)-4-Ethyl-6-hexyl-2-methyl-1,3-dioxane (30).** Treatment of 150.4 mg (0.616 mmol) **27** with 0.10 mL (0.92 mmol) of Et_2Zn and 134 μL (0.739 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 5% EtOAc/hexanes) gave 83.0 mg (63%) of a clear oil as a single diastereomer (GC of crude product indicates 200:1 *anti*:*syn* ratio): FT-IR (neat) 1248, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (q, J = 5.1 Hz, 1 H), 3.92 (ddd, J = 8.9, 6.4, 6.4 Hz, 1 H), 3.73 (m, 1 H), 1.96 (doublet of sextets, J = 8.9, 7.4 Hz, 1 H), 1.79 (ddd, J = 13.3, 11.8, 6.3 Hz, 1 H), 1.53 (m, 2 H), 1.39 (m, 3 H), 1.28 (m, 7 H), 1.28 (d, J = 5.1 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C*H 91.5, 73.8, 71.9; *C*H_2 36.3, 33.5, 31.8, 29.3, 25.0, 23.6, 22.6; *C*H_3 21.5, 14.1, 10.4; HRMS (EI) calcd for $[C_{13}H_{26}O_2 - H]^+$ 213.1855, found 213.1856. Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 72.89; H, 12.45.

(4*S,6*S**)-4-Ethyl-6-hexyl-1,3-dioxane (31).** Treatment of 151.0 mg (0.656 mmol) of **28** with 0.10 mL (0.98 mmol) of Et_2Zn and 142 μL (0.787 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 5% EtOAc/hexanes) gave 86.4 mg (66%) of a clear oil as a single diastereomer (GC of crude product indicates 117:1 *anti*:*syn* ratio): FT-IR (neat) 1739, 1242, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.86 (s, 2 H),3.85 (m, 1 H), 3.78 (m, 1 H), 1.76 (m, 2 H), 1.65 (t, J = 5.4 Hz, 2 H), 1.49 (m, 2 H), 1.40 (m, 2 H), 1.28 (m, 6 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C*H 73.1, 71.7; *C*H_2 87.0, 34.4, 33.0, 31.8, 29.2, 26.0, 25.4, 22.6; *C*H_3 14.1, 9.9; HRMS (EI) calcd for $[C_{12}H_{24}O_2 - H]^+$199.1698, found 199.1691.

(2*R,6*R**)-6-Ethyl-2-hexyltetrahydropyran (33).** Treatment of 107.0 mg (0.499 mmol) of **32** with 0.10 mL (1.0 mmol) of Et_2Zn and 110 μL (0.599 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 5% EtOAc/hexanes) gave 76.2 mg (83%) of a clear oil as a single diastereomer (GC of crude product indicates 129:1 *anti*:*syn* ratio): FT-IR (neat) 1264, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.65 (m, 1 H), 3.56 (m, 1 H), 1.62 (m, 7 H), 1.29 (m, 9 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C*H 72.3, 70.7; *C*H_2 33.4, 31.9, 30.3, 29.8, 26.2, 25.5, 22.7,18.7; *C*H_3 14.1, 10.3; HRMS (EI) calcd for $[C_{12}H_{24}O_2]^+$ 184.1827, found 184.1819. Anal. Calcd for $C_{12}H_{24}O$: C, 78.2; H, 13.12. Found: C, 78.13; H, 13.28.

(2*R*,4*S*,5*S*,6*S*)-2-*tert*-Butyl-4-ethyl-6-hexyl-5-methyl-1,3-dioxane (35). Treatment of 100.1 mg (0.333 mmol) of **34** with 0.07 mL (0.66 mmol) of Et_2Zn and 90 μL (0.500 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 30% CH_2Cl_2/hexanes) gave 82.8 mg (92%) of a clear oil as a 40:1 mixture of diastereomers: $[\alpha]^{23}_D$ −35.0° (*c* 0.99, EtOH); FT-IR (neat) 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 3.76 (m, 1 H), 3.59 (dd, J = 10.0, 5.3 Hz, 1 H), 2.05 (m, 1 H), 1.53 (m, 1 H), 1.43 (m, 2 H), 1.28 (m, 9 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.9; *C*H 100.0, 81.0, 74.2, 34.4; *C*H_2 32.8, 31.9, 29.3, 25.6, 23.2, 22.6; *C*H_3 24.6 (3), 14.1, 13.2, 10.4; HRMS (CI/isobutane) calcd for $[C_{17}H_{34}O_2 + H]^+$ 271.2637, found 271.2637. Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67. Found: C, 75.36; H, 12.59.

(2*R,4*S**,6*S**)-2-*tert*-Butyl-5,5-dimethyl-4-ethyl-6-hexyl-1,3-dioxane (37).** Treatment of 115.2 mg (0.366 mmol) of **36** with 0.08 mL (0.73 mmol) of Et_2Zn and 100 μL (0.550 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 20% CH_2Cl_2/hexanes) gave 91.5 mg (88%) of a clear oil as a single diastereomer: FT-IR (neat) 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (s, 1 H), 3.48 (dd, J = 8.4, 3.8 Hz, 1 H), 3.34 (dd, J = 12.0, 3.6 Hz, 1 H), 1.98 (m, 1 H), 1.50 (m, 1 H), 1.32 (m, 10 H), 1.09 (s, 3 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.91 (s, 9 H), 0.90 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) *C* 35.0, 34.9; *C*H 99.5, 84.1, 78.9; *C*H_2 31.9, 29.2, 28.9, 26.4, 22.6, 18.3; *C*H_3 24.5 (3), 21.9, 21.8, 14.1, 10.1; HRMS (CI/isobutane) calcd for $[C_{18}H_{36}O_2 + H]^+$ 285.2793, found 285.2794. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 76.19; H, 12.81.

(2*R,4*S**,5*R**,6*S**)-2-*tert*-Butyl-4-ethyl-6-hexyl-5-methyl-1,3-dioxane (39).** Treatment of 115.2 mg (0.366 mmol) **38** with 0.08 mL (0.73 mmol) of Et_2Zn and 100 μL (0.550 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 20% CH_2Cl_2/hexanes) gave 91.5 mg (88%) of a clear oil as a single diastereomer (GC of crude product indicates 122:1 *anti*:*syn* ratio): FT-IR (neat) 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (s, 1 H), 3.73 (ddd, J = 12.0, 4.5, 4.5 Hz, 1 H), 3.38 (ddd, J = 8.7, 8.7, 2.3 Hz, 1 H), 1.91 (m, 2 H), 1.52 (m, 2 H), 1.30 (m, 9 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.90 (s, 9 H), 0.88 (t, J = 6.8 Hz, 3 H), 0.71 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 34.9; *C*H 99.2, 77.6, 76.7, 37.4; *C*H_2 33.1, 31.9, 29.3, 24.8, 22.7, 17.8; *C*H_3 24.7 (3), 14.1, 12.8, 10.1; HRMS (CI/isobutane) calcd for $[C_{17}H_{34}O_2 - H]^+$ 269.2481, found 269.2474. Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67. Found: C, 75.71; H, 12.47.

General Procedure for the Transketalization Deprotection of *Anti*-1,3-Dioxanes. (3*S,5*S**)-3,5-Dihydroxyundecane (40).** A 1 dram screw-cap vial was charged with 21.8 mg (0.085 mmol) of **4**, 1 mL of 1,3-propanediol, and a spatula tip of CSA. The vial was sealed and heated to 65 °C overnight. After dilution with 15 mL of H_2O, the product was extracted with 3× EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 30% EtOAc/hexanes) gave 15.3 mg (96%) of a white solid: mp = 47−50 °C; FT-IR (KBr) 3305 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.75 (m, 1 H), 3.66 (m, 1 H), 2.05 (bs, 1 H), 2.02 (bs, 1 H), 1.37 (m, 5 H), 1.22 (m, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.83 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) 70.5, 69.2, 42.6, 37.9, 32.24, 20.7, 29.8, 26.2, 23.0, 14.3, 10.3. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 69.88; H, 12.69.

(2*S,6*S**)-2-(3-(Benzyloxy)propyl)-6-hexyl-1,3-dioxan-4-one (44).** A 50 mL flask equipped with a Soxhlett extractor containing 4 Å MS and a reflux condensor was charged with 0.887 g (5.09 mmol) of 3-hydroxynonanoic acid, 20 mL of CH_2Cl_2, 1.18 g (6.62 mmol) of 4-(benzyloxy)propanal, and 128 mg (0.509 mmol) of PPTS. The solution was heated to reflux overnight. After cooling to 23 °C, the organics were washed with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 15% EtOAc/hexanes then 20%) gave 1.42 g (83%) of a clear oil as a 8:1 mixture of diastereoemers: FT-IR (neat) 3087, 3063, 3031, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.32 (t, J = 5.0 Hz, 1 H), 4.50 (s, 2 H), 3.81 (m, 1 H), 3.51 (t, J =

6.3 Hz, 1 H), 2.62 (dd, J = 17.7, 4.4 Hz, 1 H), 2.39 (dd, J = 17.7, 10.8 Hz, 1 H), 1.89 (m, 2 H), 1.79 (m, 2 H), 1.64 (m, 1 H), 1.47 (m, 2 H), 1.29 (m, 7 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 168.0, 138.4; *C*H 128.4 (2), 127.6 (2), 127.5, 103.3, 74.4; *C*H_2 72.8, 69.5, 36.3, 35.4, 31.6, 31.6, 29.0, 24.7, 23.4, 22.5; *C*H_3 14.0; HRMS (CI/isobutane) calcd for $[C_{20}H_{30}O_4 + H]^+$ 335.2222, found 335.2230.

(2*S,4*R**,6*S**)-4-Acetoxy-2-(3-(benzyloxy)propyl)-6-hexyl-1,3-dioxane (45).** Treatment of 0.470 g (1.40 mmol) of **44** with 1.9 mL (1.82 mmol, 1 M in hexanes) of DIBALH according to the general reduction/acylation procedure and purification by flash chromatography (SiO_2, 10% EtOAc/hexanes) gave 0.519 g (98%) of a clear oil as a 9:1 mixture of diastereomers: FT-IR (neat) 3061, 3030, 1760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.86 (dd, J = 9.9, 2.5 Hz, 1 H), 4.67 (t, J = 5.0 Hz, 1 H), 4.50 (s, 2 H), 3.60 (m, 1 H), 3.48 (t, J = 6.1 Hz, 2 H), 2.11 (s, 3 H), 1.76 (m, 4 H), 1.60 (m, 1 H), 1.46 (m, 3 H), 1.30 (m, 8 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 169.2, 138.6; *C*H 128.3 (2), 127.6 (2), 127.4, 99.7, 93.1; *C*H_2 74.7, 69.9, 35.8, 35.5, 31.7, 31.2, 29.1, 24.9, 24.2, 22.6; *C*H_3 21.1, 14.0; HRMS (CI/isobutane) calcd for $[C_{22}H_{34}O_5 - H]^+$ 377.2328, found 377.2321.

(2*R,4*S**,6*S**)-2-(3-(Benzyloxy)propyl)-4-ethyl-6-hexyl-1,3-dioxane (46).** Treatment of 203.7 mg (0.538 mmol) of **45** with 0.09 mL (0.81 mmol) of Et_2Zn and 117 μL (0.646 mmol) of TMSOTf according to the general procedure and purification by flash chromatography (SiO_2 5% EtOAc/hexanes) gave 137.9 mg (74%) of a clear oil as a single diastereomer: FT-IR (neat) 3088, 3064, 3030, 1146 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 4.4 Hz, 3 H), 7.27 (m, 2 H), 4.75 (t, J = 5.1 Hz, 1 H), 4.50 (s, 2 H), 3.92 (ddd, J = 9.2, 6.1, 6.1 Hz, 1 H), 3.69 (m, 1 H), 3.49 (t, J = 6.4 Hz, 2 H), 1.95 (doublet of sextets, J = 9.1, 7.4 Hz, 1 H), 1.80 (ddd, J = 13.3, 11.9, 6.3 Hz, 1 H), 1.72 (m, 2 H), 1.66 (m, 2 H), 1.50 (m, 2 H), 1.38 (m, 2 H), 1.38 (m, 8 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 138.7; *C*H 128.3 (2), 127.6 (2), 127.4, 94.4, 76.7, 72.0; *C*H_2 72.8, 70.2, 32.3, 34.0, 32.0, 31.8, 29.3, 25.1, 24.6, 23.5, 22.6; *C*H_3 14.1, 10.4; HRMS (CI/isobutane) calcd for $[C_{22}H_{36}O_3 + H]^+$ 349.2742, found 349.2741. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.63; H, 10.52.

(2*S,4*S**,6*S**)-2-(3-(Benzyloxy)propyl)-4-(3-carbethoxypropyl)-6-hexyl-1,3-dioxane (47).** A 25 mL Schlenk flask was charged with 5 mg of CuI and 250.0 mg (1.03 mmol) of ethyl 4-iodobutyrate under Ar. Et_2Zn (0.16 mL, 1.55 mmol) was added, and the resulting gray slurry was stirred at 50 °C for 21 h. The excess Et_2Zn was removed under reduced pressure (0.1 mmHg, 50 °C, 3 h). The residual black oil was dissolved in 4 mL of CH_2Cl_2 and reacted with 127.0 mg (0.336 mmol) of **45** and 117 μL (0.646 mmol) of TMSOTf according to the general procedure. Purification by flash chromatography (SiO_2 10% EtOAc/hexanes) gave 87.5 mg (60%) of a clear oil as a single diastereomer: FT-IR (neat) 3088, 3064, 3030, 1735, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 4.4 Hz, 3 H), 7.26 (m, 2 H), 4.75 (t, J = 5.1 Hz, 1 H), 4.50 (s, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.03 (ddd, J = 9.8, 5.7, 5.7 Hz, 1 H), 3.69 (m, 1 H), 3.48 (t, J = 6.4 Hz, 2 H), 2.34 (t, J = 7.3 Hz, 2 H), 2.01 (m, 1 H), 1.81 (ddd, J = 13.3, 11.9, 6.3 Hz, 1 H), 1.72 (m, 2 H), 1.66 (m, 2 H), 1.52 (m, 1 H), 1.40 (m, 2 H), 1.34 (m, 1 H), 1.27 (m, 8 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) *C* 173.4, 138.6; *C*H 128.3 (2), 127.6 (2), 127.4, 94.5, 71.9, 71.6; *C*H_2 72.8, 70.1, 60.3, 36.2, 34.3, 33.9, 32.0, 31.8, 29.9, 29.2, 25.0, 24.5, 22.6, 21.4; *C*H_3 14.3, 14.1; HRMS (CI/isobutane) calcd for $[C_{26}H_{42}O_5 + H]^+$ 435.3110, found 435.3109. Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.00; H, 9.60.

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Supporting Information Available: Experimental details for the synthesis and characterization of the *syn*-1,3-diol acetals **22**−**22c** as authentic samples. This material is available free of charge via the Internet at http://pubs.acs.org.

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