Alkylation and Reductive Decyanation of 4-Cyano-2,2-dimethyl-1,3-dioxanes (Cyanohydrin Acetonides)

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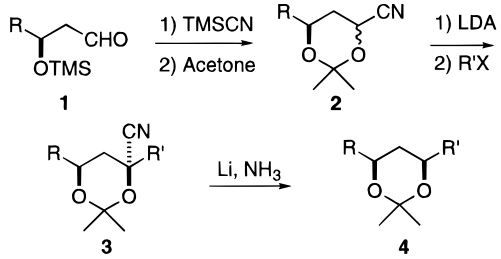
Cyanohydrin acetonide couplings are a very effective methodology for the synthesis of polyol chains. We report a detailed investigation of the alkylation and reductive decyanation of 4-cyano-2,2-dimethyl-1,3-dioxanes (cyanohydrin acetonides). The various parameters influencing the reaction were investigated, including the choice of base, electrophile, time, and temperature. It was found that LHMDS was greatly superior to LDA in the alkylation of allylic and propargylic halides, but no such difference was found with saturated alkylating agents. The minor side products obtained from these reactions were identified, and methods for their minimization were developed. These studies led to a greater understanding of these alkylation reactions which were key steps in the convergent synthesis of polyene macrolide antibiotics like roxaticin and roflamycoin.

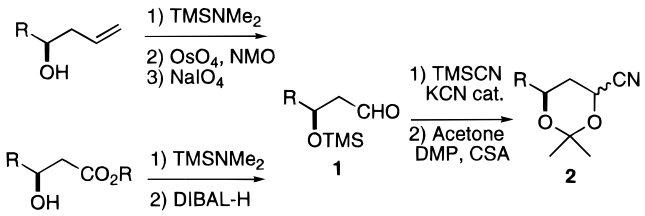
Polyol chains are found in many natural products, including the polyene macrolide antibiotics.[1] The most common polyol chains are made up of repeating acetate or propionate subunits. Many synthetic strategies such as two-directional chain synthesis,[2] convergent synthetic methods,[3,4] and iterative synthetic methods[5] have capitalized on this repeating structure. We have developed 4-cyano-2,2-dimethyl-1,3-dioxanes (cyanohydrin acetonides) as key synthons for the convergent synthesis of polyol chains[6] and have employed these as intermediates in the synthesis of roxaticin and roflamycoin.[7,8] Presented in this paper is a complete account of cyanohydrin acetonide coupling methodology.

An overview of the preparation, alkylation, and reductive decyanation of cyanohydrin acetonides is shown in Scheme 1. Cyanohydrin acetonide **2** is prepared from β-trimethylsilyloxy aldehyde **1**. Deprotonation followed by alkylation with an electrophile gives the alkylated product **3**. Reductive decyanation replaces the nitrile group selectively with an axial hydrogen to give **4**.[9] This sequence is related to the alkylation and reduction of anomeric sulfones developed by Sinay.[10] Many different

Scheme 1



Scheme 2



substituents are compatible with this coupling sequence including alkyl, aryl, cyclic alkyl, alkenyl, TBS ethers, TIPS ethers, and acetals. Easily reduced functional groups like benzyl ethers and alkynes are normally reduced in the decyanation reaction. The configuration at the newly formed center is ultimately set in the decyanation step, although the alkylation step is generally highly selective for the axial nitrile isomer. The alkylation step is the most complex in the sequence and will be discussed in detail. Overall, this series of reactions leads to an acetonide protected *syn*-1,3-diol and is a very powerful synthetic method for the convergent synthesis of polyol chains.

Preparation of Cyanohydrin Acetonides. Cyanohydrin acetonides were prepared from β-trimethylsilyloxy aldehydes **1** as shown in Scheme 2. Optically pure β-hydroxy aldehydes are readily available by way of enantioselective allylation of aldehydes[11] or enantioselective hydrogenation of β-keto esters.[12,13] Silylation[14] of the alcohol followed by oxidative cleavage[15] or DIBAL-H reduction, respectively, produces the β-trimethylsilyloxy aldehyde **1**. Cyanohydrin formation was effected by

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(1) (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040. (b) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351−404.

(2) (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563. (b) Poss, C.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (c) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090−1091.

(3) (a) Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423−6. (b) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4387−4388. (c) Mori, Y.; Kohchi, Y.; Suzuki, M.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1991**, *56*, 631−637. (d) Mori, Y.; Kohchi, Y.; Suzuki, M.; Furukawa, H. *Chem. Pharm. Bull.* **1992**, *40*, 1934−1936.

(4) (a) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525−8. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645.

(5) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559−1563.

(6) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550−5551.

(7) (a) Rychnovsky, S. D.; Rodriguez, C. *J. Org. Chem.* **1992**, *57*, 4793−4795. (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753−1765.

(8) (a) Rychnovsky, S. D.; Griesgraber, G.; Kim, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 2621−2622. (b) Rychnovsky, S. D.; Khire, U.; Yang, G. *J. Am. Chem. Soc.*, in press.

(9) Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.

(10) Lancelin, J.-M.; Morrin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355−356.

(11) For example, see (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092−3. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.

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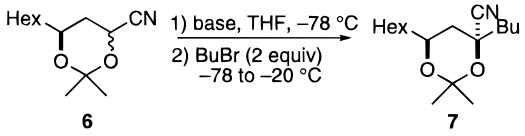
Table 1. Effect of Base on Alkylation of Cyanohydrin Acetonide 6

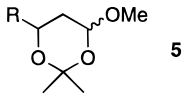


6 **7**

entry	base	equiv	% yield
1	LTMP	1.2	73
2	$LiNEt_2$	1.2	58
3	Li pyrrolidide	1.2	55
4	KHMDS	1.2	60
5	LHMDS	1.2	55
5	LDA	1.2	67
7	LDA	1.2	85[a]
8	LDA	1.2	30[b]
9	LDA	2.4	82

[a] Two equiv of DMPU was added prior to addition of the electrophile. [b] Two equiv of HMPA was added prior to addition of the electrophile.

treatment with 1.05 equiv of TMSCN and catalytic KCN/18-crown-6 complex.[16] This addition was usually run neat, but on a multigram scale the mixture was diluted with CH_2Cl_2 and/or cooled to 0 °C to moderate the exothermic reaction. It was important to confirm that the cyanohydrin formation had gone to completion to avoid formation of byproducts such as **5**.



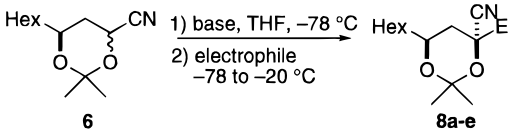
5

A sufficient amount of camphorsulfonic acid (CSA) was added to neutralize the KCN catalyst, and the mixture was diluted with a 3:1 mixture of acetone and 2,2-dimethoxypropane (DMP). When acetonide formation was complete, the reaction was quenched with Et_3N, concentrated, and purified by chromatography. An alternative cyanide source, acetone cyanohydrin, has some advantages for large-scale preparations, but this procedure has not been used extensively and is not as reliable as the TMSCN procedure.[17] The TMSCN route has been successfully applied to many different β-trimethylsilyloxy aldehydes and is the method of choice for a new substrate.

Alkylation of Cyanohydrin Acetonides. The alkylation step is the most challenging one in the sequence and provides the largest variations in yield and reproducibility. The reaction has a large number of variables, the most important of which are discussed below.

The choice of base was examined, and the results are listed in Table 1. Most amide bases such as $LiNEt_2$, LDA, and lithium tetramethylpiperidide (LTMP) worked well in a sample alkylation with *n*-butyl bromide. The yield was higher with 2.4 equiv of the LDA rather than the standard 1.2 equiv. Addition of DMPU improves the alkylation by stabilizing the anion and increasing the nucleophilicity.[18] HMPA should have provided a similar effect, but did not improve the yield in this case.[19] Both LHMDS and KHMDS were effective without being superior to the other amide bases. Except in unusually hindered cases, LDA or LTMP are the bases of choice for these alkylation reactions.

Table 2. Alkylation of the Anion of Cyanohydrin 6 with Electrophiles



6 **8a-e**

entry	base	equiv	electrophile	% yield (**8**)
1	LHMDS	1.2	Cl–OBn	70 (**8a**)
2	LDA	1.2	TBSO–Br	71 (**8b**)
3	LHMDS	2.4	"	28 (**8b**)
4	LHMDS	2.4		8 (**8c**)
5	$LiNEt_2$	2.4	"	42 (**8c**)
6	LDA	1.2	"	44[a] (**8c**)
7	$LiNEt_2$	1.0	I–Cl	72 (**8d**)
8	LDA	1.2	Br	43[a] (**8e**)
9	$LiNEt_2$	1.2	"	62[a] (**8e**)

[a]Two equiv of DMPU was added prior to addition of the electrophile.

Cyanohydrin acetonide anions can be alkylated with a variety of electrophiles, and several examples are listed in Table 2. In all entries, the cyanohydrin acetonide was the limiting reagent. It is sometimes more desirable to use the electrophile as the limiting reagent, and the yields are generally higher in these cases. The standard conditions involved a 2 h deprotonation at −78 °C, followed by addition of 2.0 equiv of the electrophile. The reactions were run at −78 °C for 2 h, warmed to −20 °C for 1 h, and then quenched. Small amounts of starting cyanohydrin acetonides were recovered in most cases. Reactive electrophiles like benzyl chloromethyl ether alkylate well using LHMDS as the base. Homoallylic bromides and alkyl dihalides, which are prone to elimination, gave reasonable yields of products (entries 7−9). Even relatively unreactive alkyl halides like the β-silyloxy bromide in entry 2 were effective. Epoxides could be used, but the yields were lower and *in situ* cyclization of the resulting nitrile alkoxides generates lactones as side products.[20] Additions to aldehydes and ketones generally gave modest yields, even in dilute solution (**13** in eq 1).[21]

Allyl halides show substantially different alkylation behavior, as illustrated in Table 3. The most startling

(12) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−31.

(13) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424.

(14) For an alternative to the *N*-(trimethylsilyl)dimethylamine conditions see: Bruynes, C. A.; Jurriens, T. K. *J. Org. Chem.* **1982**, *47*, 3966−3969.

(15) The two-step procedure for cleavage of the olefin is more reliable than ozonolysis for these substrates.

(16) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55−56.

(17) For example, see the synthesis of cyanohydrin **7** in reference 7a.

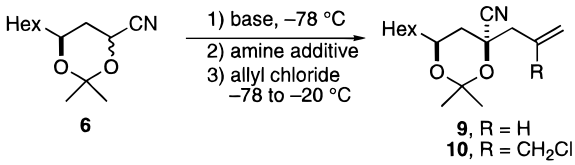
(18) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 3, pp 2123−2127.

(19) The surprisingly poor performance of HMPA as an additive may have been due to impurities in the HMPA. Given the health concerns associated with the use of HMPA, we chose to focus on the use of DMPU as an additive.

(20) Wovkulich, P. M.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R.; Mayer, E.; Norman, A. W. *J. Org. Chem.* **1983**, *48*, 4433−4436.

(21) Carlier, P. R.; Lo, K. M. *J. Org. Chem.* **1994**, *59*, 4053−4054.

Table 3. Alkylations Using Allyl Chlorides and LDA or LHMDS

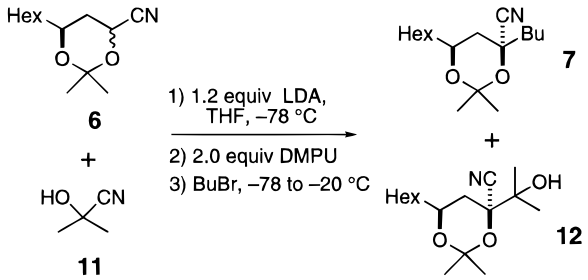


entry	base (equiv)	R	amine (equiv)	% yield
1	LDA (1.2)	H	–	5
2	LDA (2.4)	H	–	23
3	KHMDS (2.4)	H	–	73
4	LHMDS (2.4)	H	–	82
5	LDA (1.2)	H	HMDS (1)	34
6	LHMDS (2.4)	H	*i*-Pr_2NH (1)	65
7	LHMDS (1.0)	CH_2Cl	–	64
8	LDA (1.1)	CH_2Cl	–	13

observation was that LDA gave essentially none of the allylated product (entry 1) whereas KHMDS gave excellent yields (entry 3). Initially it was assumed that the potassium counterion was essential, but the excellent yields observed with LHMDS (entry 4) disproved this hypothesis. The dramatic change on using LDA versus LHMDS implicates the spectator amine in the alkylation of the nitrile anion. The role of the amine was probed by preparing the nitrile anion with LDA and adding 1 equiv of hexamethyldisilazane (HMDS). Alkylation with allyl chloride gave 34% yield (entry 5), a significant improvement over the 5% yield with LDA alone. To further bracket the reactivity, the nitrile anion was prepared with LHMDS, doped with 1 equiv of *i*-Pr_2NH, and then alkylated with allyl chloride. In this case the 82% yield with LHMDS was reduced to 65% (entry 6). It is known that nitrile anions form mixed aggregates with LDA[22] and LHMDS[23] under some conditions. In this case the amine additive seems to be changing the reactivity of the aggregates in solution, but Collum has shown that amines are poor ligands compared with THF which makes the amine effect very surprising.[24] However, the amine is not the only factor influencing the reactivity of this system. The striking reactivity difference between LDA and LHMDS does not exist for the alkylation with butyl bromide (entries 5 and 6, Table 1), implying that the electrophile is also strongly influencing the outcome. One possibility is that the LiCl generated in the reaction affects the outcome. Collum has shown that LDA[25] forms mixed aggregates with LiCl while LHMDS[26] resists the formation of such aggregates. The difference in reactivity between the anions generated from LDA and LHMDS is difficult to understand but very reproducible. The same effect was also observed in the alkylation of substituted allyl halides (entries 7 and 8) and propargyl halides.[27] For alkylation of allyl and propargyl halides, LHMDS or KHMDS is the base of choice.

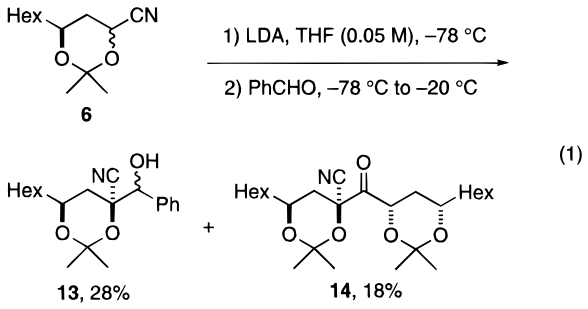
Cyanohydrin acetonide alkylations generate a number of characteristic side-products. One recurring side-product was the acetone adduct **12**. The formation of this

Scheme 3



11 (equiv)	% yield 7	% yield 12
0.0	84	<1
0.1	49	10
0.5	38	52

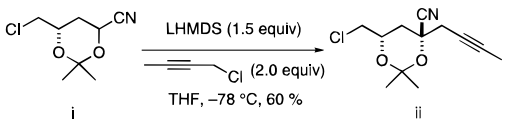
product requires a source of acetone, that was initially believed to arise from decomposition of the cyanohydrin acetonide anion.[28] The most likely culprit is acetone cyanohydrin, which can be formed as a byproduct in the cyanohydrin acetonide synthesis.[29] Acetone cyanohydrin **11** can be detected as an impurity by ^1H NMR analysis carried out in benzene-d_6 where the methyl peak shows up at 1.21 ppm, versus residual H_2O at 0.4 ppm.[29] Using this NMR analysis, some cyanohydrin acetonide samples prepared by the standard method were found to be contaminated with acetone cyanohydrin. To determine the effect of acetone cyanohydrin impurities in alkylation reactions, cyanohydrin **6** was doped with varying amounts of acetone cyanohydrin **11**. The results shown in Scheme 3 demonstrate a definite correlation between the amount of **11** added and the amount of acetone adduct **12** obtained. Another side-product observed on occasion is the Thorpe–Ziegler coupling product **14**, eq 1. Formation of this side-product can be minimized by using a slight excess of base to insure complete deprotonation. Taking care to remove any acetone cyanohydrin in the starting material will suppress the formation of the acetone adduct and improve the yield of the desired alkylated product.



(1)

How stable are the nitrile anions? A series of experiments were carried out to address this question and are illustrated in Figure 1 and Table 4. For each alkylation

(22) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1392–1394.
(23) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602–11603.
(24) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5100–5110.
(25) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053-5054.
(26) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198–9202.
(27) For an example see: Richardson, T. I.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 4219–4231.



(28) The cyanohydrin acetonides used in these studies showed <2% acetone by ^1H NMR, yet the acetone adduct was often obtained in 10–20%, so acetone itself could not account for the formation of **12**.
(29) Acetone cyanohydrin can often go unnoticed in normal NMR analysis as the methyl peak occurs at 1.64 ppm in $CDCl_3$, which can easily be mistaken for the residual H_2O peak at 1.62 ppm.

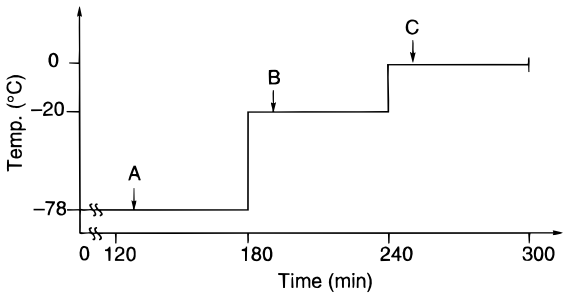


Figure 1. Temperature profile study for alkylation of **6**. Anion formation took place from 0 to 120 min at −78 °C, followed by electrophile addition at the specified times: reaction A (130 min), reaction B (195 min), and reaction C (255 min). The results are shown in Table 4.

Table 4. Stability of Anion of 6

reaction	% yield **7**[a]	% yield **9**[b]
A	69	79
B	67	80
C	55	41

[a] Deprotonation using 1.2 equiv of LDA and addition of 2 equiv of DMPU 5 min prior to addition of butyl bromide. [b] Deprotonation using 2.4 equiv of KHMDS with allyl chloride used as the electrophile.

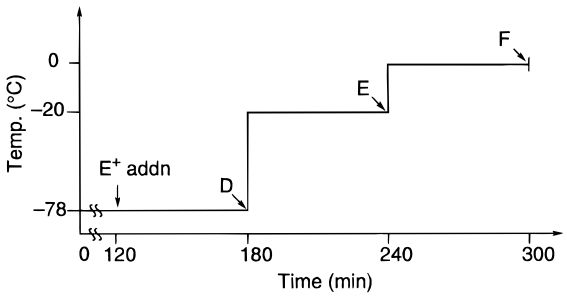


Figure 2. Temperature profile study for the alkylation of **6**. Anion formation took place from 0 to 120 min at −78 °C. Electrophile addition was at 120 min in all reactions which were quenched at the following times: reaction D (180 min), reaction E (240 min), and reaction F (300 min). Results are shown in Table 5.

the deprotonation was run for 120 min and then submitted to the following temperature profile: −78 °C for 60 min, −20 °C for 60 min, and 0 °C for 60 min. Each reaction was then quenched, and the product was isolated using the normal protocol. The only variable was the time at which the electrophile was added. Under conditions A the electrophile (butyl bromide or allyl chloride) was added at 130 min during the −78 °C stage. Conditions B and C involved adding the electrophile at 195 or 255 min, 15 min after the temperature had been increased to −20 °C or 0 °C, respectively. All of the alkylations gave reasonable yields of the isolated product, but the yields for conditions A and B were higher than for conditions C. These experiments show that the nitrile anions are stable at −20 °C but begin to decompose around 0 °C. For difficult alkylations the preferred procedure is to add the electrophile at −78 °C, transfer to −20 °C bath and then allow the temperature to increase very slowly.

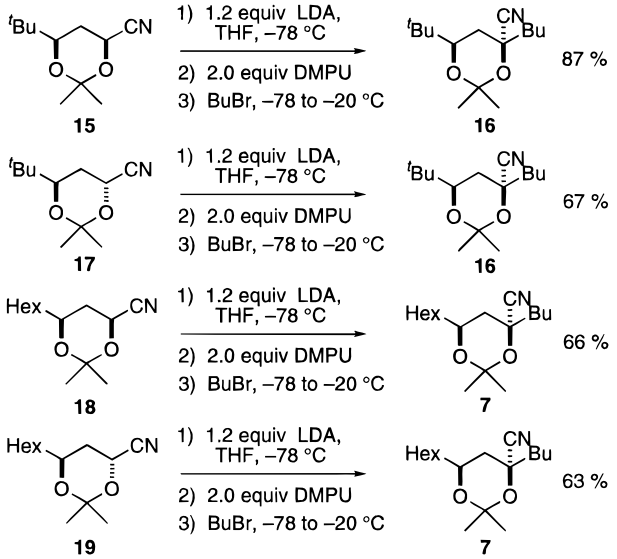
A second series of experiments was designed to determine the rate of alkylation for simple electrophiles like butyl bromide or allyl chloride. The experiments are outlined in Figure 2 and Table 5, and follow the same temperature profile as the experiments in Figure 1. The difference here is that the electrophile was added at 120

Table 5. Rate of Alkylation of 6

reaction	% yield **7**[a]	% yield **9**[b]
D	69	73
E	85	73
F	66	79

[a] Deprotonation using 1.2 equiv of LDA and addition of 2 equiv of DMPU 5 min prior to addition of butyl bromide. [b] Deprotonation using 2.4 equiv of KHMDS with allyl chloride used as the electrophile.

Scheme 4

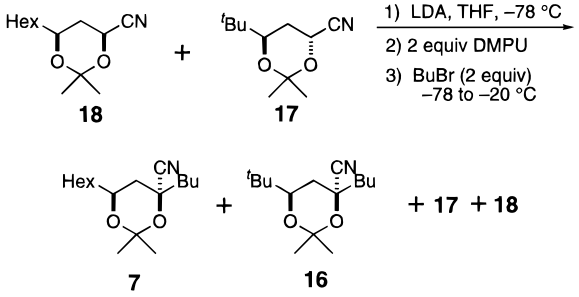


min in each case and then quenched at the end of the −78 °C phase (D), the −20 °C phase (E), or the 0 °C phase (F). The alkylation reactions were nearly complete after 60 min at −78 °C, and further warming to −20 °C only increased the yield by a small amount. Warming to 0 °C is unnecessary and may even decrease the yield, but the range of yields for the whole series does not fall far outside the normal scatter. For these reactive alkylating agents, the reactions were essentially complete at −78 °C but could certainly be warmed to −20 °C without harm. Less reactive alkylating agents such as β-alkoxy bromides do not alkylate effectively at −78 °C and must be warmed to −20 °C for complete reaction.[30]

Small amounts of unreacted cyanohydrin acetonide were often recovered from the alkylation reactions, usually as the cis isomer rather than the trans isomer. Does this material arise from incomplete deprotonation or reprotonation of the nitrile anion? The cis and trans isomers of hexyl and *tert*-butyl cyanohydrin acetonides were each alkylated separately; results are shown in Scheme 4. The cis and trans isomers showed similar results, demonstrating that the practice of using a mixture of isomers is justified. The question of relative deprotonation rates is addressed in Table 6. A 1:1 mixture of the *cis*-hexyl cyanohydrin **18** and *trans*-*t*-butyl cyanohydrin **17** were deprotonated and alkylated with butyl bromide. In no case was any of the *trans*-hexyl cyanohydrin **19** or *cis*-*t*-butyl cyanohydrin **15** observed, demonstrating that essentially none of the recovered

(30) Not unexpectedly, direct competition between butyl bromide and 2-(*t*-butyldimethylsilyloxy)-1-bromoethane in the alkylation reaction with **6** gave only the butyl adduct. A β-silyloxy activating effect has been invoked by Smith based on the acceleration caused by *remote* electron-withdrawing substituents in S_N2 reactions. We have found no β-silyloxy activating effect in our studies. (a) Smith, A. B. III.; Chen, K.; Robinson, D. J.; Laasko, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271−4274. (b) Holtz, H. D.; Stock, L. M. *J. Am. Chem . Soc.* **1965**, *87*, 2404−2409.

Table 6. Crossover Study of Compounds 17 and 18 As Shown in Scheme 2. The Ratios of Starting Materials and Alkylated Products Are Compared[a]

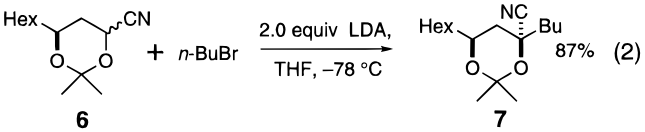


entry	equiv base	deprotonation time	ratio 18	7	17	16
1	0.5	2 h	10.8	0	6.7	1
2	1.0	2 h	1	1.3	0	1.7
3	2.0	2 h	0	1.4	0	1
4	1.0	15 min	1	2.5	0	2.7
5	1.2	5 min	1	25.3	0	20.9
6	1.2	0	1	5.1	0	5.1

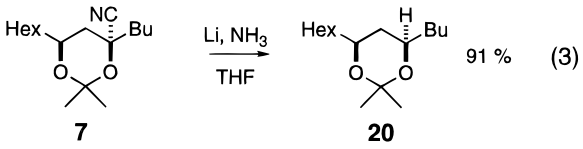
[a] Ratios determined by GC analysis.

starting material arose from reprotonation of the anion. In entries 1−3 the amount of base was increased from 0.5 to 1.0 and 2.0 equiv. Deprotonation of the trans cyanohydrin **17** was faster than the cis isomer **18** as judged by the extent of conversion in each case, but with 2.0 equiv of base both cis and trans nitrile alkylations go to completion. An unexpected observation was made when the time allowed for deprotonation was decreased from the normal 2 h to 15 min, 5 min, and 0 min in entries 4−6. In each case the trans cyanohydrin was completely consumed, while the cis cyanohydrin alkylation proceeded nearly to completion. Apparently electrophiles like butyl bromide are compatible with LDA, and the cyanohydrin acetonides can be deprotonated in the presence of the alkyl halide.

The possibility of deprotonation in the presence of electrophile proved intriguing. A preparative reaction was carried out by adding a mixture of cyanohydrin acetonide **6** and butyl bromide to LDA at −78 °C. The reaction gave an excellent yield of the alkylated product **7**, eq 2. Addition of a mixture of electrophile and alkyl halide to base, or *vice versa*, has practical advantage in small-scale coupling reactions. It also opens up the possibility of using intramolecular alkylations to form macrocycles.

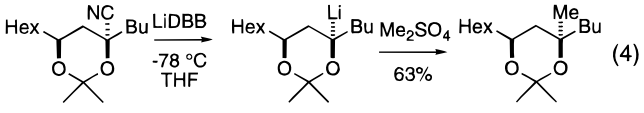


Preferred Alkylation Conditions. The proper pairing of base and electrophile was very important to the outcome of the alkylation reaction. For simple alkyl halides, LDA or LTMP were the bases of choice. In very complex systems better results have been occasionally observed with $LiNEt_2$.[7,8] Oxygenated substrates were much less reactive than simple alkyl halides, requiring longer reaction times and higher temperatures. Dihalogenated alkanes or homoallylic halides gave the best results when only a slight excess of base was employed. Presumably these conditions avoid the base-induced decomposition of the alkyl halides prior to alkylation. Aldehydes and ketones gave only modest yields of coupled products, regardless of base employed. Allyl and propargyl systems require the use of LHMDS for efficient alkylation. General protocols for the various alkylation reactions can be found in the Experimental Section.



Reductive Decyanations. The reductive decyanation of cyanohydrin acetonides is a simple and robust process, eq 3.[6,31] The standard procedure involves reduction of the alkylated cyanohydrin with lithium metal in a mixture of ammonia and THF at −78 °C. Where the other functional groups are compatible, the reduction can be warmed to −33 °C to ensure complete reduction. Yields are typically >90%, and the selectivity is usually >99:1.[6] Sufficient THF should be present in the solution to prevent precipitation of nonpolar substrates, and negatively charged substrates may require longer reaction times for complete reduction. The cyanohydrin functional group is decyanated very rapidly and can be reduced at −78 °C in the presence of allyl ethers[32] (**21**) and isolated phenyl rings[33] (**23**), Scheme 5. Benzyl ethers[8b] (**25**) and alkynes[27] (**27**) are reduced under the same reaction conditions (Scheme 5). Other powerful reducing conditions like lithium/diethylamine or almost any alkali metal in liquid ammonia also decyanate cyanohydrin acetonides.

Reductive decyanation reactions formally proceed by way of an alkyllithium intermediate that is protonated by ammonia *in situ*. Reductive lithiation of alkylated cyanohydrin **7** with lithium di-*tert*-butylbiphenylide (LiDBB) *in the absence of a proton source* generates 4-lithio-1,3-dioxane **29**, eq 4. The alkyllithium **29** reacts with Me_2SO_4 to give the axial methylated product **30** in 63% yield.[34] The preparation and alkylation of 4-lithio-1,3-dioxanes generated from alkylated cyanohydrins is an interesting approach to the synthesis of tertiary alcohols in polyol chains, but the modest overall yield limits its potential. Secondary cyanohydrin acetonides (e.g. **6**) are not useful precursors to 4-lithio-1,3-dioxanes, and even the normally reliable reductive decyanation works poorly with these substrates.



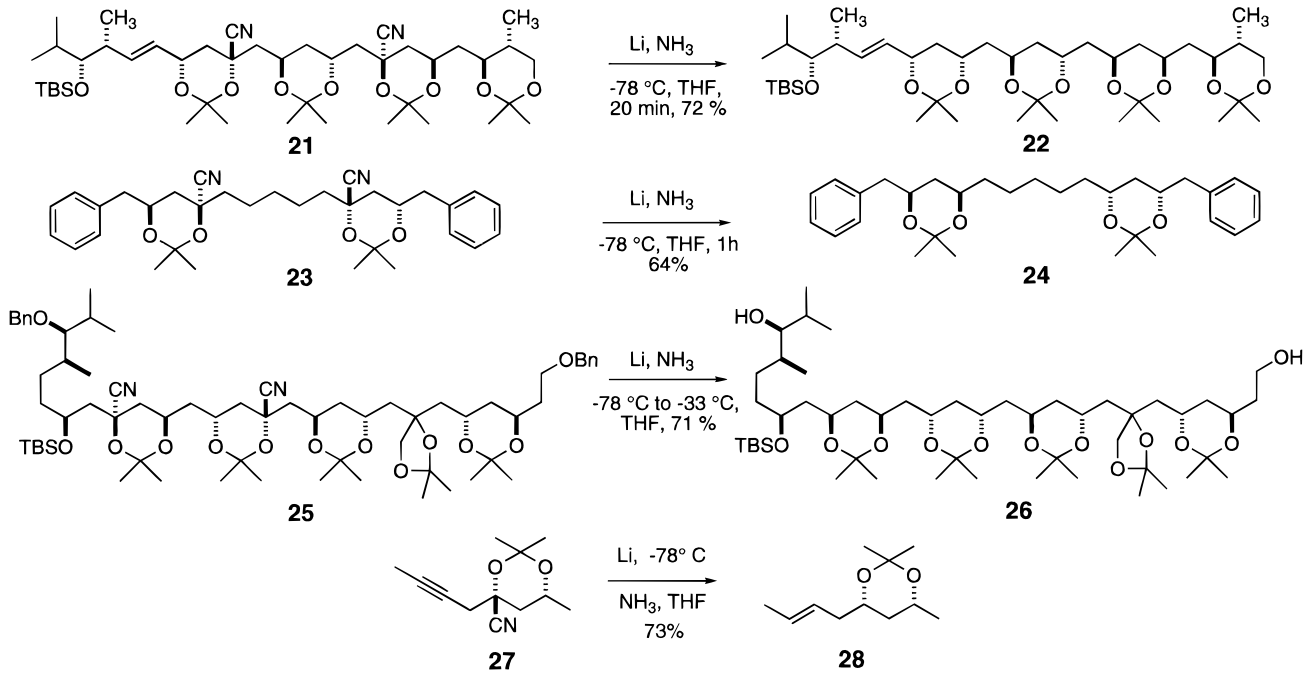
The alkylated cyanohydrins are usually isolated as a single isomer with the cyano group in the axial position, and reductive decyanation also leads to a single isomer with proton in the axial position. The configuration of the product is determined in the decyanation step.[6,9] Although the stereoselectivity of the alkylation reaction is of no consequence to stereoselectivity of the overall sequence, it does facilitate the purification and handling of alkylated cyanohydrin intermediates.

Conclusion

Cyanohydrin acetonides are very useful intermediates for the convergent synthesis of polyol chains. They are

(31) Skalitzky, D. J.; Ph.D. Thesis, University of Minnesota, 1992.
(32) We thank Dr. R. C. Hoye for conducting this experiment.
(33) Choo, C.; Ph.D. Thesis, University of Minnesota, 1995.
(34) We thank D. J. Skalitzky for conducting this experiment.

Scheme 5



easily prepared from β-hydroxy esters or homoallylic alcohols and can be alkylated with a variety of alkylating agents. Reductive decyanation generates acetonide-protected *syn*-1,3-diols with exceptionally high stereoselectivity. Cyanohydrin acetonides were key intermediates in the synthesis of roflamycoin and roxaticin.[7,8]

Experimental Section[35]

General Procedure for the Synthesis of Cyanohydrin Acetonide (6). Ethyl 3-hydroxynonanoate (5.03 g, 24.9 mmol, 1.0 equiv) and 5 mg of saccharin (0.1 mol %) were dissolved in 30 mL of dichloromethane and heated to reflux. A 5.51 mL sample of hexamethyldisilazane (HMDS) (26.1 mmol, 1.05 equiv) was added under a stream of nitrogen to expel the ammonia generated. The mixture was refluxed for an additional 16 h, cooled to room temperature, and concentrated under reduced pressure. Removal of residual HMDS (high-vacuum) provided 7.11 g of a pale yellow oil. This was dissolved in 100 mL of dry ether and cooled to −78 °C. A 1.0 M solution of DIBAL-H (28.6 mmol, 1.1 equiv) was added dropwise and stirred for 1 h at −78 °C. The excess DIBAL-H was quenched by addition of 0.77 mL of ethyl acetate (7.79 mmol, 0.3 equiv) and then 75 mL of a 30% aqueous solution of sodium potassium tartrate. The mixture was allowed to warm to room temperature, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers were extracted (3 × Et_2O). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was chromatographed (SiO_2, 10% ethyl acetate/hexanes), providing 5.24 g of a pale yellow oil. The compound was cooled to 0 °C under nitrogen atmosphere, and 3.17 mL of trimethylsilyl cyanide (23.8 mmol, 1.05 equiv) was added, followed by a catalytic amount of KCN/[18-c-6] complex. The ice bath was removed, and the mixture was stirred overnight. A 3:2 solution of acetone/2,2-dimethoxypropane (50 mL) was added along with 527 mg of CSA (0.1 equiv). After stirring for 2 h, the reaction was quenched with 2.0 mL of triethylamine. The mixture was concentrated and chromatographed (SiO_2, 7% ethyl acetate/hexanes), providing 4.58 g (20.4 mmol, 82% overall yield) of the product (1:1 cis/trans isomers) as a pale yellow oil. The isomers were separated for characterization by careful silica gel chromatography.

Cis isomer: IR (neat) 2995, 2933, 2862, 1465, 1382, 1261, 1204, 1164, 1137, 1110, 1002, 876, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, J = 4.4, 10.5 Hz, 1 H), 3.80 (m, 1 H), 1.83−1.77 (m, 2 H), 1.55−1.27 (m, 8 H), 1.42 (s, 6 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 117.8, 99.8; *C*H 67.8, 59.0; CH_2 35.6, 34.4, 31.4, 24.2, 22.4; CH_3 29.5, 19.0, 13.8. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 68.11; H, 9.99.

Trans isomer: IR (neat) 2996, 2934, 2861, 1646, 1383, 1267, 1237, 1204, 1162, 1128, 1079, 1056, 985, 878, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (dd, J = 3.1, 5.8 Hz, 1 H), 4.10 (m, 1 H) 1.90−1.79 (m, 2 H), 1.66 (s, 3 H), 1.62−1.29 (m, 8 H), 1.37 (s, 3 H), 0.89 (t, J = 6.6 Hz, 3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 120.1, 100.9; *C*H 65.6, 59.0; CH_2 35.6, 33.5, 31.6, 24.4, 22.5; CH_3 29.8, 21.8, 14.0. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 68.02; H, 9.91.

General Procedure for Alkylations with Butyl Bromide. (4*R,6*S**)-4-Butyl-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (7).** A solution containing 154.7 mg (0.69 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 2.0 mL of THF was added via cannula to a solution of LDA (0.83 mmol, 1.2 equiv) in 3.0 mL of THF at −78 °C. After 2 h at −78 °C, 167 μL (1.38 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 148 μL (1.38 mmol, 2.0 equiv) of 1-bromobutane. The solution was stirred at −78 °C for 2 h and then transferred to a methanol/ice bath at −20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 2% ethyl acetate/hexanes) gave 165 mg (0.59 mmol, 85%) of the product as a clear, colorless oil: IR (neat) 2957, 2931, 2861, 1461, 1382, 1256, 1205, 1135, 877 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 1.68 (s, 3 H), 1.37 (s, 3 H), 1.8−1.2 (complex, 18 H), 0.92 (t, J = 7.2 Hz,

(35) Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230−400 mesh). [Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925]. THF and ether were distilled from potassium/benzophenone ketyl. CH_2Cl_2, diisopropylamine, and toluene were distilled from CaH_2. Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals, the number of carbon atoms is given in parentheses. Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument with a 30 m PhMe-Silicon column, a flame ionization detector, and a Hewlett Packard computer-interfaced integrator. Combustion analysis were performed by M-H-W Laboratories, Phoenix, AZ. Mass spectra were determined on an AE2-MS 30, a PG 7070E-HF, a CG Analytical 7070E, or a Fisions autospec spectrometer.

3 H), 0.88 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 122.2, 100.9, 70.1; *C*H 66.3; *C*H_2 42.4, 39.6, 35.8, 31.8, 29.1, 25.2, 24.8, 22.7, 22.5; *C*H_3 31.0, 21.5, 14.1, 13.9. Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10. Found: C, 72.55; H, 11.25.

General Procedure for Alkylations with Allyl chloride. (4*R,6*S**)-4-Cyano-2,2-dimethyl-6-hexyl-4-(2-propenyl)-1,3-dioxane (9).** A 96 mg sample of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (0.42 mmol, 1.0 equiv) was dissolved in 1.5 mL of THF and cooled to −78 °C. To this solution was added 1.46 mL (1.02 mmol, 2.4 equiv) of lithium bis(trimethylsilyl)amide (0.7 M in hexanes). After stirring for 1.5 h, 209 μL of allyl chloride (2.56 mmol, 6.1 equiv) was added. The solution was stirred at −78 °C for 2 h, and then the mixture was warmed to −20 °C. After 1 h, the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 91 mg (0.34 mmol, 82%) of the product as a clear, colorless oil: IR (neat) 2995, 2929, 2859, 1642, 1383, 1265, 1206, 1171, 1116, 996 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.24 (s, 1 H), 5.20 (d, J = 7.9 Hz, 1 H), 4.07 (m, 1 H), 2.54 (dd, J = 6.9, 13.8 Hz, 1 H), 2.44 (dd, J = 7.5, 13.8 Hz, 1 H), 1.76 (dd, J = 1.8, 13.5 Hz, 1 H), 1.67 (s, 3 H), 1.37 (s, 3 H), 1.6−1.2 (complex, 11 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 121.6, 100.9, 69.5; *C*H 129.9, 66.1; *C*H_2 120.6, 46.5, 38.7, 35.6, 31.6, 28.9, 24.6, 22.4; *C*H_3 30.7, 21.3, 13.9. Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25. Found: C, 72.40; H, 10.03.

(5*R,7*R**,9*S**)-7-Cyano-3,5-*O*-isopropylidene-5,7,9-pentadecanetriol and (5*S**,7*R**,9*S**)-7-Cyano-3,5-*O*-isopropylidene-5,7,9-pentadecanetriol (8c).** A solution containing 237.7 mg (1.06 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 1.5 mL of THF was added via cannula to a solution of LDA (1.27 mmol, 1.2 equiv) in 3.0 mL of THF at −78 °C. After 2 h at −78 °C, 123 μL (1.02 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 123 μL (1.02 mmol, 2.0 equiv) of 1,2-epoxyhexane. The reaction was stirred at −78 °C for 2 h and then gradually warmed to 25 °C and quenched with a saturated NH_4Cl solution. The mixture was extracted (3 × CH_2Cl_2), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 73.8 mg (0.23 mmol, 44%) of a 2:3 mixture of isomers as a colorless oil: IR (neat) 3520, 2994, 2931, 2860, 1464, 1381, 1261, 1209, 1163, 1127, 1049, 879, 727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (m, 1.6 H), 3.99 (m, 0.4 H), 3.10 (s, 0.6 H), 2.55 (s, 0.4 H), 2.04 (dd, J = 8.5, 14.5, 0.4 H), 1.87−1.82 (m, 2.6 H), 1.71−1.69 (2 s, 3 H), 1.58−1.27 (complex, 20 H), 0.88 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 122.1, 121.4, 101.8, 101.6, 71.5, 69.5; *C*H 69.1, 67.4, 66.3; *C*H_2 49.2, 48.5, 40.3, 39.1, 37.5, 36.9, 35.7, 35.6, 29.1 (2), 27.5, 27.4, 24.8, 24.7, 22.7, 22.6; *C*H_3 31.0, 21.5, 14.1 (2). HRMS (EI) Calcd for $C_{18}H_{32}NO_3$ 310.2382 (M-CH_3), found 310.2384 (M-CH_3). Anal. Calcd for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84. Found: C, 70.08: H, 10.68.

(4*R,6*S**)-4-(3-Butenyl)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (8e).** A solution containing 229 mg (1.01 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 2.0 mL of THF was added via cannula to a solution of lithium diisopropylamide (LDA) (1.22 mmol, 1.2 equiv) in 5.0 mL of THF at −78 °C. After 2 h at −78 °C, 245 μL (2.03 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 206 μL (2.03 mmol, 2.0 equiv) of 4-bromo-1-butene. The solution was stirred at −78 °C for 2 h and then transferred to a methanol/ice bath at −20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 175 mg (0.63 mmol, 62%) of the product as a clear, colorless oil: IR(neat) 3078, 1996, 2930, 2860, 1642, 1460, 1379, 1260, 1206, 1163, 1119, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 5.01 (m, 2 H), 4.20 (m, 1 H), 2.41 (m, 2 H), 1.67 (s, 3 H), 1.36 (s, 3 H), 1.8−1.2 (complex, 14 H), 0.88 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 121.9, 100.9, 69.6; *C*H 136.8, 66.3; *C*H_2 115.4, 41.6, 39.5, 35.7, 31.7, 29.1, 27.4, 24.7, 22.6; *C*H_3 30.9, 21.4, 14.0. Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46. Found: C, 73.27; H, 10.21.

General Protocol for the Anion Stability Study in Figure 1. A solution containing 196 mg (0.87 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 1.5 mL of THF was added via cannula to a solution of LDA (1.04 mmol, 1.2 equiv) in 3.0 mL of THF at −78 °C. After 3 h at −78 °C, the solution was warmed to −20 °C. After 10 min, 210 μL (1.74 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 187 μL (1.74 mmol, 2.0 equiv) of 1-bromobutane. The solution was stirred at −20 °C for 45 min and then transferred to an ice bath at 0 °C and stirred for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 164 mg (0.58 mmol, 67%) of the product **7** as a clear, colorless oil.

General Protocol for the Rate of Alkylation Study in Figure 2. A 86 mg sample of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (0.38 mmol, 1.0 equiv) was dissolved in 1.5 mL of THF and cooled to −78 °C. To this solution was added 1.01 mL (0.92 mmol, 2.4 equiv) of potassium bis(trimethylsilyl)amide (0.91 M in toluene). After stirring for 1.5 h, 191 μL of allyl chloride (2.34 mmol, 6.1 equiv) was added. The solution was stirred at −78 °C for 1.5 h and then the mixture was warmed to −20 °C. After 1 h, the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 74 mg (0.28 mmol, 73%) of the product **9** as a clear, colorless oil.

General Procedure for the Crossover Study from Table 6. A solution containing 86 mg (0.38 mmol, 0.5 equiv) of (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane and 75 mg (0.38 mmol, 0.5 equiv) of (4*R**,6*S**)-4-cyano-2,2-dimethyl-6-*tert*-butyl-1,3-dioxane in 1.5 mL of THF was added via cannula to a solution of LDA (1.51 mmol, 2.0 equiv) in 4.0 mL of THF at −78 °C. After 2 h at −78 °C, 183 μL (1.51 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 162 μL (1.51 mmol, 2.0 equiv) of 1-bromobutane. The solution was stirred at −78 °C for 2 h and then transferred to a methanol/ice bath at −20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. The GC trace showed the complete disappearance of both starting materials and the presence of both the corresponding alkylated products.

General Protocol for the Alkylation Where Nitrile and Electrophile Are Premixed As Shown in Eq 2. A solution containing 161 mg (0.71 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane and 77 μL (0.71 mmol, 1.0 equiv) of 1-bromobutane in 1.5 mL of THF was added via cannula to a solution of LDA (1.43 mmol, 2.0 equiv) and 173 μL (1.43 mmol, 2.0 equiv) of DMPU in 3.0 mL of THF at −78 °C. After 2 h at −78 °C, the flask was transferred to a methanol/ice bath at −20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 3% ethyl acetate/hexanes) gave 175 mg (0.62 mmol, 87%) of the product **7** as a pale yellow oil.

General Protocol for Acetone Cyanohydrin Doping from Scheme 3. A solution containing 217 mg (0.96 mmol, 1.0 equiv) of (4*R**,6*S**)- and (4*S**,6*S**)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane and 44 μL (0.48 mmol, 0.5 equiv) of acetone cyanohydrin in 1.5 mL of THF was added via cannula to a solution of LDA (1.72 mmol, 1.8 equiv) in 4.0 mL of THF at −78 °C. After 2 h at −78 °C, 232 μL (1.92 mmol, 2.0 equiv) of DMPU was added. The mixture was stirred for 5 min, followed by addition of 206 μL (1.92 mmol, 2.0 equiv) of 1-bromobutane. After 2 h at −78 °C, the flask was transferred to a methanol/ice bath at −20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purifica-

tion by column chromatography (SiO_2, 5 to 10% ethyl acetate/hexanes) gave 103 mg (0.37 mmol, 38%) of **7** as a clear, colorless oil and 143 mg (0.50 mmol, 52%) of **12** as a clear, colorless oil: IR (neat) 3494, 2991, 2932, 2860, 1464, 1381, 1208, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (m, 1 H), 2.26 (s, 1 H), 1.72 (s, 3 H), 1.69 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.8−1.2 (complex, 12 H), 0.88 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.3, 101.4, 76.6, 75.6; *C*H 66.1; *C*H_2 35.7, 33.1, 31.7, 29.0, 24.7, 22.5; *C*H_3 30.7, 24.3, 22.7, 21.5, 14.0. Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31. Found: C, 67.58; H, 10.43.

Reductive Decyanation Reactions. (4*R,6*S**)-4-Butyl-2,2-dimethyl-6-hexyl-1,3-dioxane (20).** A solution containing 419.5 mg (1.49 mmol, 1.0 equiv) of (4*R**,6*S**)-4-butyl-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 5 mL of THF was added via cannula to a bright blue solution of lithium (15 equiv) in 50 mL of NH_3 at −78 °C. After 1 h at −78 °C, the reaction was quenched with solid NH_4Cl, and the NH_3 was allowed to evaporate. Water was added, and the residue was extracted (3× CH_2Cl_2). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 2 to 5% ethyl acetate/hexanes) gave 348.4 mg (1.36 mmol, 91%) of the product as a clear, colorless oil: IR (neat) 2991, 2931, 2858, 1466, 1377, 1263, 1199, 1171, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85−3.70 (m, 2 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.6−1.0 (complex, 18 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 1.00−0.81 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 97.9; *C*H 68.8; *C*H_2 36.8, 36.3, 36.0, 31.5, 29.0, 26.7, 24.7, 22.4, 22.3; *C*H_3 30.1, 19.5, 13.7; HRMS (EI) calcd for $C_{15}H_{29}O_2$ (M − CH_3) 241.2167; found 241.2160. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.83; H, 12.62.

(4*R,6*S**)-4-Butyl-2,2-dimethyl-6-hexyl-4-methyl-1,3-dioxane (30).** A 0.4 M solution of LiDBB in THF was prepared by addition of Li wire to a solution of 4,4′-di-*tert*-butylbiphenyl (1.07 g, 4 mmol) in 10 mL of THF at 0 °C. This solution was transferred to a new flask by cannula and cooled to −78 °C, and then a solution containing 397.4 mg (1.41 mmol, 1.0 equiv) of (4*R**,6*S**)-4-butyl-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane in 5 mL of THF was added via cannula, rinsing with 2 mL of THF. After 15 min at −78 °C, 530 μL of dimethyl sulfate (5.60 mmol, 4.0 equiv) was added turning the green solution orange. The solution was stirred at −78 °C for 3 h and slowly warmed to room temperature overnight. The reaction was quenched with a 10% solution of NH_4OH/NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 30% CH_2Cl_2/hexanes to 2% to 4% *tert*-butyl methyl ether/hexanes) gave 240.6 mg (0.89 mmol, 63%) of the product as a pale yellow oil: IR (neat) 2932, 2860, 1560, 1542, 1466, 1377, 1255, 1197, 1094, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (m, 1 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.6−1.0 (complex, 18 H), 1.28 (s, 3 H), 0.9−0.8 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 98.1, 72.8; *C*H 65.5; *C*H_2 45.4, 39.5, 36.4, 31.8, 29.2, 25.4, 25.0, 23.1, 22.5; *C*H_3 31.8, 26.3, 25.0, 14.1, 14.0.

Polyacetonide 22. To 20 mL of liquid NH_3 was added 11 mg of Li wire (0.6 mmol, 7.7 equiv) at −78 °C. A 63.4 mg sample of **21** (0.078 mmol, 1 equiv) in 8 mL of THF was added. After 10 min at −78 °C, the reaction was quenched with solid NH_4Cl and warmed, allowing the NH_3 to evaporate. The residue was taken up with 10 mL each of H_2O and CH_2Cl_2. The layers were separated, and the aqueous was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 42.2 mg (0.056 mmol, 72%) of the product as a colorless oil: $[\alpha]^{24}_D = -14.3°$ (*c* = 1.36, CH_2Cl_2); IR (neat) 2989, 2949, 2856, 1462, 1379, 1251, 1224, 1200, 1170, 1127, 1059, 939 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (dd, *J* = 7.9, 15.5 Hz, 1 H), 5.35 (dd, *J* = 6.4, 15.5 Hz, 1 H), 4.26 (m, 1 H), 4.03 (m, 5 H), 3.63 (dd, *J* = 5.2, 11.7 Hz, 1 H), 3.48 (m, 1 H), 3.44 (t, *J* = 11.5 Hz, 1 H), 3.21 (t, *J* = 4.8 Hz, 1 H), 2.27 (sextet, *J* = 6.2 Hz, 1 H), 1.9−1.0 (m, 14 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 6 H), 1.33 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 6 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.86 (s, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.69 (d, *J* = 6.6 Hz, 3 H), −0.01 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 100.6, 98.6, 98.5, 98.0, 18.5; *C*H 136.2, 129.5, 80.9, 71.4, 70.4, 65.6, 64.8, 64.7, 62.4 (2), 40.6, 34.3, 31.6; *C*H_2 66.1, 42.4, 42.2, 39.6, 39.0, 37.6, 36.7; *C*H_3 30.3 (2), 29.8, 26.2 (3), 24.4 (2), 20.5, 20.0, 19.8, 19.0, 17.8, 15.7, 12.6, −3.5, −3.7; HRMS (FAB) calcd for $C_{42}H_{78}O_9SiNa$ (M + Na) 777.5315; found 777.5303. Anal. Calcd for $C_{42}H_{78}O_9Si$: C, 66.80; H, 10.41. Found: C, 66.85; H, 10.36.

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