Unsaturated Oxo−Nitriles: Stereoselective, Chelation-Controlled Conjugate Additions

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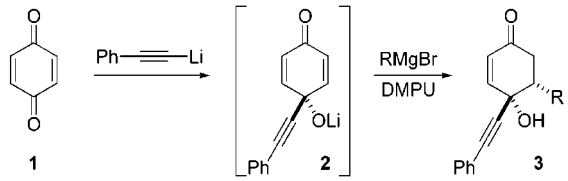
Received June 17, 1999

Addition of Grignard reagents to the unsaturated oxo−nitrile **10** (4-hydroxy-4-methyl-6-oxocyclohex-1-enecarbonitrile) provides conjugate addition products with virtually complete stereocontrol. Mechanistic evidence supports a chelation-controlled conjugate addition via alkylmagnesium alkoxide intermediates. Diverse Grignard reagents having sp^3-, sp^2-, and sp-hybridized carbons react with comparable efficiency, with even sterically demanding nucleophiles adding with complete stereocontrol. Unsaturated oxo−nitriles that are incapable of chelation afford diastereomeric conjugate addition products through an unusual boatlike transition state. Collectively, these reactions illustrate the complementary stereoselectivity of chelation-controlled conjugate additions to hydroxylated, unsaturated oxo−nitriles and stereoelectronically controlled conjugate additions to enones.

Introduction

Conjugate addition reactions are one of the most important carbon−carbon bond-forming reactions in organic synthesis.[3] The central importance of conjugate addition reactions results from the efficient, stereoselective, formation of a new bond two or more carbons removed from an electron-withdrawing group. High stereoselectivity is routinely achieved in conjugate additions either through stereoelectronic control[4] or by using inherent structural features to bias the approach of the nucleophile.[5]

Complementary stereoselectivity to the more hindered face of a Michael acceptor is a significant synthetic challenge. Excellent success in this area has been achieved by chelating the nucleophile[6] with an alcohol-derived alkoxide[7] or an ether oxygen,[8] prior to the conjugate addition reaction. Chelation-controlled addition reactions have been most extensively investigated with quinol alkoxides (**2**) that react with Grignard reagents to afford conjugate addition products (**3**).[9] Chelation between the alkoxide and the Grignard reagent results in a transient complex[10] that delivers the nucleophile from the same face and establishes the syn stereochemistry between the alkyl and the hydroxyl groups.



1 2 3

The mechanism of chelation-controlled conjugate additions is succinctly illustrated in a key step performed during the synthesis of (±)-euonyminol.[11] Deprotonation of **4** affords a lithium alkoxide that was sequentially treated with 15-crown-5 and isopropenylmagnesium bromide to ensure first a lithium−magnesium exchange, followed by displacement of the Schlenk equilibrium from the binary complex **5** toward the more reactive ternary ate complex[10] **6**. Nucleophilic addition from the ate complex **6** is more favorable than from **5**[10] and provides the conjugate adduct **7** as the sole diastereomer. The conversion of **4** → **7** underscores the complementary stereoselectivity of chelation-controlled additions since **4** reacts with $(CH_2{=}CHMe)_2CuCNLi_2$ to give the diastereomeric conjugate addition product.[11]

The chelation-controlled conjugate additions of **1** and **4** are typical in employing alcohols where dehydration is not possible (**1** → **3** and **4** → **7**) or effectively prevented

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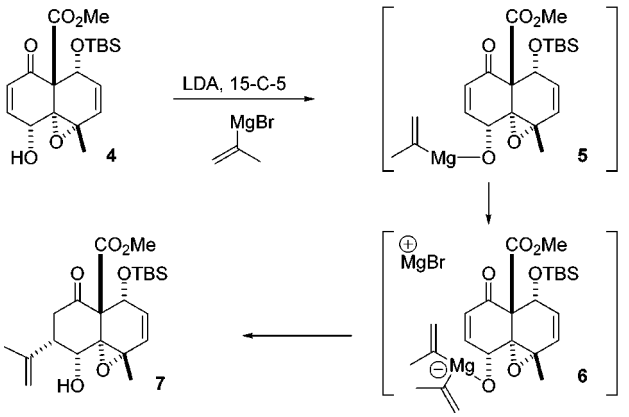
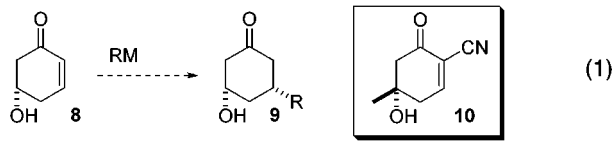
(3) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992.
(4) For cyclic systems see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Exeter, U.K., 1983; pp 221−242. For a leading reference to stereocontrol in acyclic systems, see: (b) Yamamoto, K.; Ogura, H.; Jukuta, J.-i.; Inoue, H.; Hamada, K.; Sugiyama, Y.; Yamada, S. *J. Org. Chem.* **1998**, *63*, 4449.
(5) Reference 3, pp 162−163.
(6) For a compilation of several examples see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(7) (a) Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152. (b) Pappo, R.; Collins, P. W. *Tetrahedron Lett.*, **1972**, 2627. (c) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.*, **1975**, 4217. (d) Metz, P.; Meiners, U.; Frohlich, R.; Grehl, M. *J. Org. Chem.* **1994**, *59*, 3687. (e) Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1978**, 5079. (f) Sato, T.; Nakakita, M.; Kimura, S.; Fujisawa, T. *Tetrahedron Lett.* **1989**, *30*, 977. (g) Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430. (h) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739. (i) Carreno, M. C.; Gonzalez, M. P.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687.
(8) (a) Raczko, J. Tetrahedron Asymm. **1997**, *8*, 3821. (b) Klemeyer, H. J.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 7924. (c) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678. (d) Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413. (e) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525. (f) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 4727.
(9) (a) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127. (b) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.
(10) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.
(11) (a) White, J. D. *Pure Appl. Chem.* **1994**, *66*, 2183. (b) White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404.

10.1021/jo9909709 CCC: $18.00
Published on Web 10/26/1999



because of geometrical constraints.[12] We hoped to extend this methodology to conjugate additions with unsaturated aldols (**8** → **9**) since, although prone to dehydration, chiral aldols are readily prepared in high optical purity[13] and the conjugate adducts **9** are potentially amenable to further dehydration−conjugate addition reactions. We envisaged minimizing the potential dehydration by using an extremely reactive Michael acceptor to promote the conjugate addition reaction (eq 1). We were specifically

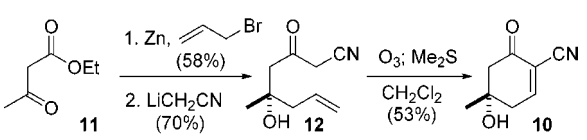


(1)

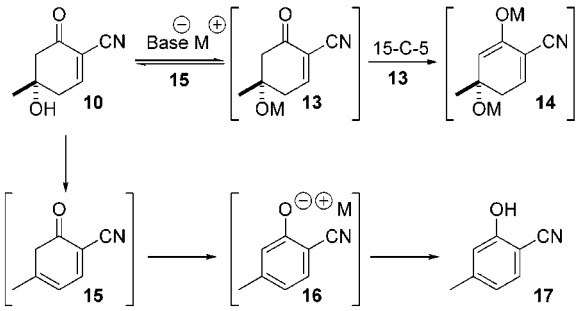
interested in using α,β-unsaturated oxo−nitriles since these are readily prepared[14] and react conjugately even with sterically hindered Grignard reagents.[15] This account describes the successful chelation-controlled conjugate additions to the unsaturated oxo−nitrile **10**, diastereomeric conjugate additions to the corresponding silyl ether, and a mechanistic discussion of the complementary stereoselectivity exhibited in these Michael reactions.

Results and Discussion

The prototype unsaturated oxo−nitrile **10** is readily prepared using our domino ozonolysis−aldol cyclization method[14] (**12** → **10**). Addition of allylzinc bromide to **11** provides a tertiary alcohol that is treated with excess lithioacetonitrile (3.5 equiv) to provide the desired nitrile **12** with essentially no dehydration being observed. Applying our domino ozonolysis-aldol methodology to **12** unmasks an aldehyde and triggers an intramolecular aldol cyclization-dehydration sequence that affords **10** in a single synthetic operation.



Scheme 1



The synthesis of **10** efficiently provides a prototype oxo−nitrile for probing chelation-controlled conjugate addition reactions. Deprotonation of **10** under conventional conditions[10] (LDA[16]), followed by the addition of 15-crown-5 and MeMgCl, afforded none of the desired conjugate addition product but resulted in exclusive dehydration to give the aromatic nitrile **17** (Scheme 1). We reasoned that the facile aromatization might result from a competitive deprotonation of the more acidic γ-protons of **10**, in preference to the more accessible hydroxyl proton. The resulting dehydration of **10** generates the relatively acidic dienone **15** allowing protonation of the coformed alkoxide **13**. Protonation of **13** regenerates **10** and allows a series of proton transfers to equilibrate the desired alkoxide **13** to the more stable aromatic nitrile **17**.

We reasoned that aromatization might be avoided by using an excess of base to preferentially deprotonate any coformed dienone **15**. Even with this precaution aromatization is still conceivable since the subsequent metal−alkoxide exchange of **13** (M = Li to M = Mg) generates a relatively basic alkoxide. Self-deprotonation of **13** would generate **10** and the alkoxide **14**, providing another equilibration route to the aromatic nitrile **17**. We therefore chose to avoid formation of a "free" alkoxide by directly generating the desired magnesium alkoxide with an excess of methylmagnesium chloride.

We were pleased to find that simply adding an excess of methylmagnesium chloride (2.5 equiv) to **10** provides the desired conjugate addition product **19** in 51% yield (Scheme 2). Characterization of **19** was particularly difficult since oxo−nitriles readily enolize[17] providing, in this case, two equilibrating diastereomers. The stereochemistry of the epimers was determined by silylating the intermediate enolate with excess TBDMSCl (3 equiv), resulting in two conjugate addition products (42% yield, **20a**:**21**, 6.8:1 ratio) and the aromatic nitrile **22** (11% yield). The diastereomers were separated by radial chromatography, providing pure samples of the major and minor isomers resulting from chelation-controlled and uncomplexed[18] conjugate addition reactions, respectively (vide infra).

Determining the stereochemistry of the conjugate addition products **20a** and **21** proved particularly chal-

(12) (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett*. **1979**, 3465. (b) Ichikawa, Y.; Goto, T.; Bai, D.-L.; Isobe, M. *Tetrahedron* **1987**, *43*, 4737. (c) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863.

(13) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, pp 181−238.

(14) Fleming, F. F.; Huang, A.; Sharief, V. Q.; Pu, Y. *J. Org. Chem*. **1999**, *64*, 2830.

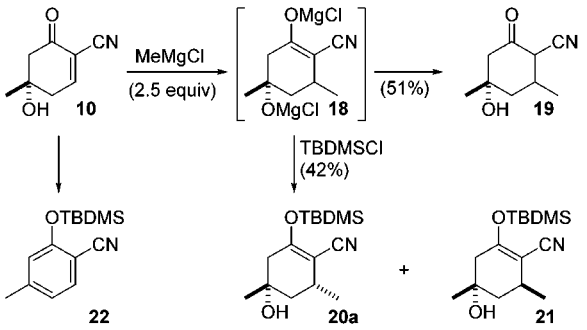
(15) Fleming, F. F.; Tercek, F.; Pu, Y. *J. Org. Chem*. **1997**, *62*, 4883.

(16) Use of LiH, *n*-BuLi, or KH afforded only the aromatic nitrile **17**.

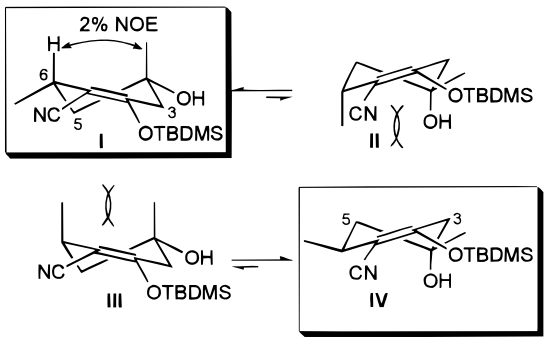
(17) Elnagdi, M.; Elmoghayar, M.; Elgemeie, G. *Synthesis* **1984**, 1.

(18) In a somewhat related system the conjugate addition of prenylmagnesium bromide occurs without chelation control: Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *J. Org. Chem*. **1999**, *64*, 1086.

Scheme 2

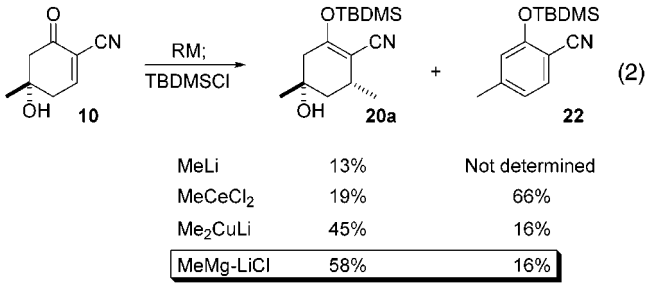


lenging. A conformational analysis of the two diastereomers reveals that these isomers will preferentially adopt different half-chair conformations. The major isomer, tentatively assigned with the hydroxyl and secondary methyl groups on the same side, will prefer conformation **I** to avoid the 1,3 diaxial interaction between the methyl and hydroxyl groups that exists in conformation **II**.[19] The minor isomer will prefer the alternative half-chair conformation **IV** to avoid the severe 1,3-diaxial interaction that is present in conformation **III**. Initial support for these complementary conformational preferences came from the significant ^{1}H NMR chemical shift differences of the C-6 methine protons in **20a** (m, δ = 2.36−2.46) and **21** (br s, δ = 2.62), and was later substantiated from an analysis of coupling constants and NOE experiments.



The complete ^{1}H NMR assignment of the two diastereomers was facilitated by distinctive W-couplings between the equatorial protons at C-3 and C-5.[20] Furthermore, in the major isomer the axial proton at C-5 appeared as a well-resolved dd with a large diaxial coupling (J = 11 Hz) to the C-6 proton, establishing **I**, with the equatorially oriented methyl group, as the preferred conformation. Determining the conformation of the major isomer allowed the relative configurations at C-4 and C-6 to be assigned through NOE experiments. NOESY spectra of **20a** were not well resolved, and therefore, selective NOE experiments were performed in benzene-d_6, where the two methyl signals exhibit significantly greater chemical shift differences than in $CDCl_3$. Irradiation of the quaternary methyl group in **20a** provided a small, but clear, enhancement of the proton at C-6, confirming that the major isomer has the methyl and hydroxyl groups on the same face, as expected for a chelation-controlled conjugate addition. The minor isomer **21** is therefore epimeric at C-6 and presumably arises by a competitive uncomplexed conjugate addition.

Formation of **20a** as the major product represents a rewarding proof-of-principle for the chelation-controlled addition to labile aldols. Initially the reaction was optimized with more nucleophilic and less basic organometallic reagents, having the potential to circumvent formation of the aromatic nitrile **22**. Screening a variety of organometallic nucleophiles indicated that methylmagnesium chloride was the most effective reagent with Me_2Mg, MeCu, MeZnI (from Zn and MeI), and MeZnCl (from $ZnCl_2$ and MeMgCl) providing only the aromatic nitrile **22** (eq 2). Of the organometallic reagents surveyed



MeLi	13%	Not determined
$MeCeCl_2$	19%	66%
Me_2CuLi	45%	16%
MeMg-LiCl	58%	16%

only MeLi, $MeCeCl_2$, and $LiCuMe_2$ provided conjugate addition products, with a combination of MeMgCl and LiCl being the most effective in terms of both yield and stereoselectivity. Optimization therefore focused on the use of Grignard reagents with lithium chloride, particularly since this results in the exclusive isolation of diastereomer **20a**.

The role of lithium chloride in the conjugate addition reaction is intriguing. The marked change in reactivity suggests a shift in the solution composition of the Grignard reagent—a speculation that is somewhat supported by our observation that LiCl is considerably more soluble in THF solutions of MeMgCl than in THF alone. Lithium chloride may associate with the Grignard reagent to form an ate complex $[RMgXCl]^{-}{}^{+}Li$[21] in which the increased charge density facilitates the subsequent alkyl transfer to the magnesium alkoxide intermediate. An accelerated alkyl transfer explains the formation of one diastereomer, assuming that the alkyl transfer from the ate complex for the subsequent chelation-controlled reaction is faster than the uncomplexed conjugate addition. Similar alkyl transfers have been promoted with DMPU[9a] although in the present case the efficiency with DMPU is essentially the same as that obtained when lithium chloride is omitted (Table 1, entries 2 and 3). Further evidence for the role of the chloride ion is seen in the lower yields obtained when lithium perchlorate is substituted for lithium chloride (Table 1, entries 1 and 4, respectively), with 3 equiv of lithium chloride being optimal (compare Table 1, entries 1 and 5).

The chelation-controlled conjugate addition is extremely fast, being complete within 5 min at −78 °C. The anion (**18**) resulting from the conjugate addition is best silylated immediately with TBDMSCl and warmed to room temperature, since this rather delicate silylation[22]

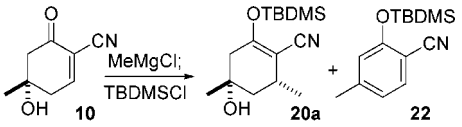
(19) The extremely small size of the nitrile group means that the A[12] interaction in **I**, between the methyl and nitrile groups, is significantly less than 1,3-diaxial interaction in **II**. See: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7.

(20) The proton assignments were fully corroborated by COSY and selective proton decoupling experiments.

(21) Reike, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775.

(22) For example, anions of oxo−nitriles react efficiently with *t*-$BuMe_2SiCl$ but not with *t*-$BuPh_2SiCl$: Gonzalez, B.; Gonzalez, A. M.; Pulido, F. J. *Synth. Commun.* **1995**, *25*, 1005.

Table 1. Addition of MeMgCl to 10



entry	solvent	additive (equiv)	yield (%) 20a	22
1	THF	LiCl (3)	58	16
2	THF	DMPU (5)	44	19
3	THF		42	11
4	THF	$LiClO_4$ (5)	15	12
5	THF	LiCl (5)	58	*a*
6	THF	*b*	31	22
7	THF	LiCl (5)[c]	45	18
8	THF	LiCl (5)[d]	55	10
9	Et_2O	LiCl (3)	43	19
10	DME	LiCl (3)	52	12

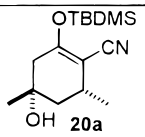
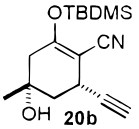
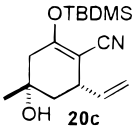
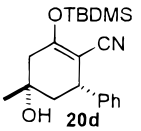
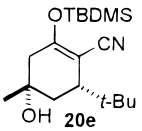
[a] The yield was not determined. [b] TBDMSCl was added at −78 °C, 3 h after the addition of MeMgCl. [c] The reaction mixture temperature was kept at −78 °C for 6 h after the addition of TBSCl and then allowed to warm to room temperature overnight. [d] Inverse addition.

is adversely affected by a delay in the addition of TBDMSCl (Table 1, compare entry 3 with 6 and entry 1 with 7). Reversing the order of addition, with **10** being added to the Grignard reagent, has essentially no effect on the reaction (Table 1, entry 8). DME and THF are the most suitable solvents with diethyl ether affording less of the conjugate adduct (Table 1, entries 9 and 10).

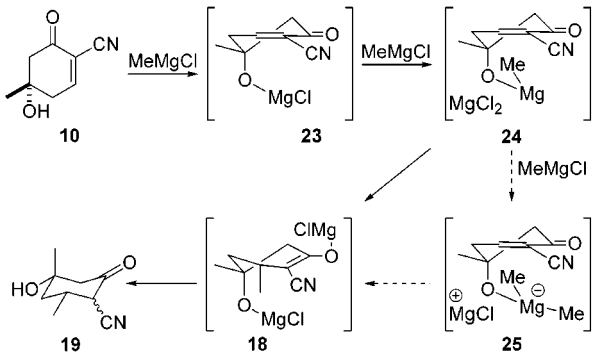
With the chelation-controlled conjugate addition with MeMgCl having been optimized, the generality of the reaction was probed with several different Grignard reagents. Diverse nucleophiles with sp, sp^2, and sp^3 hybridization react with comparable efficiency, providing only one diastereomer and no detectable[23] addition to the ketone group (Table 2). Even sterically demanding nucleophiles such as *t*-BuMgCl add relatively efficiently. The modest yields result from the competitive formation of the aromatic nitrile **22** and the formation of an uncharacterized polymeric material.[24] These modest yields are partially offset by an excellent stereoselectivity, with only one diastereomer being detected in each of these reactions.

Two diverging mechanisms can be envisaged for these chelation-controlled conjugate addition reactions (Scheme 3). The alkoxide **23**, resulting from the deprotonation of **10**, is thought to exchange with the Grignard reagent to give the methylmagnesium alkoxide **24**. On the basis of the fact that Mg−O bonds are relatively strong,[25] we speculate that the Grignard reagents react with the alkoxide **23** by a halogen−alkyl ligand exchange, rather than a metal exchange (MgCl → MgR), although we currently have no definitive information that allows differentiation between these two sequences. Once formed, the alkylmagnesium alkoxide **24** can react either with an additional 1 equiv of the Grignard reagent to generate the ate complex **25** or directly trigger the conjugate addition reaction (**24** → **18**). Differentiating between these mechanisms was possible by the incremental addition of MeMgCl to **10**.[26] Sampling the reaction

Table 2. Chelation-Controlled Additions to 10

Entry	RMgX	Product	Yield (%) 20	22
1	MeMgCl		58	16
2	HCCMgCl		47	9
3	$CH_2CHMgBr$		49	15
4	PhMgCl		58	9
5	*t*-BuMgCl		43	15

Scheme 3



mixture after the addition of 1 equiv of MeMgCl provided mainly unreacted starting material, approximately 10% of the aromatic nitrile **17**, and a trace of the conjugate addition product **19**. Addition of a further 1 equiv of MeMgCl generates the conjugate adduct **19** with no change occurring with additional MeMgCl. This experiment suggests an initial competitive proton abstraction from the alcohol group affording primarily the alkoxide **23**, with smaller amounts of γ-deprotonation leading ultimately to the aromatic nitrile **17**. Once formed, the alkoxide **23** requires only one additional 1 equiv of MeMgCl for the conjugate addition, implying that the reactive species is the alkylmagnesium alkoxide **24** and not the ate complex **25**. Presumably the high reactivity of unsaturated oxo−nitriles facilitates the chelation-controlled addition with an alkylmagnesium alkoxide **24**

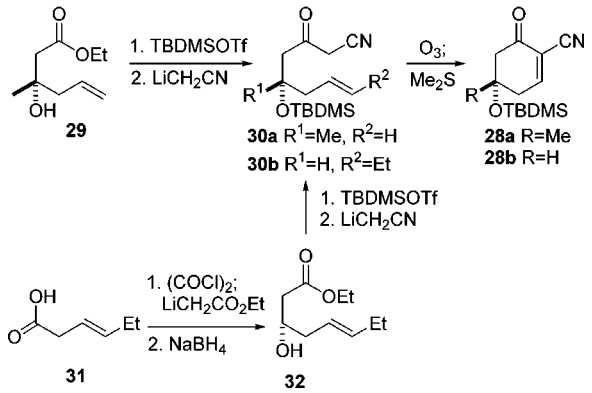
(23) Based on ^1H NMR spectra of the crude reaction mixture.

(24) Self-condensation of oxo−nitriles leads to trimers and higher oligomers: Andresen, S.; Margaretha, P. J. *Chem. Res., Synop.* **1995**, 455.

(25) Mader, M. M.; Edel, J. C. *J. Org. Chem.* **1998**, *63*, 2761.

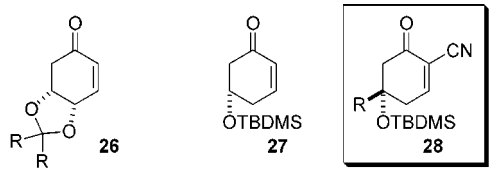
(26) Performed in the absence of LiCl to avoid potential complications through formation of additional ate complexes.

Scheme 4



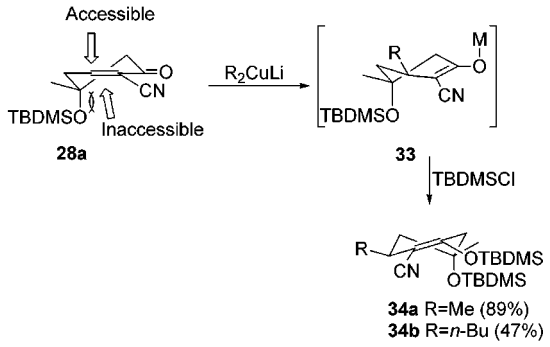
whereas less reactive enones (**24**, CN = R) require the more reactive ate complex for the conjugate addition.[10] Further support for the addition proceeding through an alkylmagnesium alkoxide (**24**) is implied from reactions with DMPU. The addition of DMPU to ate complexes is known[10] to promote the reactions with enones, but DMPU has essentially no effect with unsaturated oxo−nitriles, implying that the reactive species is not the ate complex but an alkylmagnesium alkoxide.

The diastereoselectivity of the chelation-controlled conjugate additions to **10** complements most organocopper-based additions to C-5 substituted enones.[27] Stereoselective additions to C-5 oxygenated enones have most often employed cyclic acetals[28] (**26**) in which the nucleophilic attack is sterically biased to one face of the enone, although highly selective conjugate additions of organocopper reagents were recently achieved with the C-5 TBDMSO-substituted enone **27**.[29] We reasoned that organocopper additions to silylated oxo−nitriles (**28**) would provide conjugate adducts diastereomeric to those obtained by chelation control, since the silyl group would effectively bias the nucleophilic addition through the combined influence of steric and stereoelectronic constraints. We therefore prepared two C-5 TBDMSO−oxo−nitriles and evaluated the stereoselectivity of their conjugate addition reactions.



The preparation of **28a**,**b** uses our one-pot, domino ozonolysis−aldol synthesis[14] of oxo−nitriles (Scheme 4).[30] In each case the ozonolysis precursor **30** is obtained by reacting lithioacetonitrile with the corresponding ester **29** or **32**. Interestingly, the synthesis of **32** proceeds without isomerization of the double bond and potentially

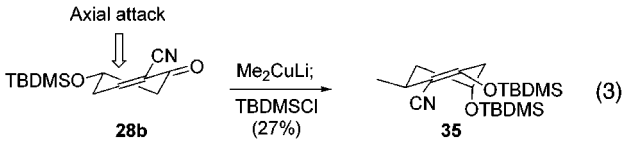
Scheme 5



allows for a chiral oxo−nitrile synthesis by reducing the intermediate β-keto ester[31] with a chiral reagent.[32] As expected, the oxo−nitriles **30a**,**b** cyclize smoothly upon ozonolysis, providing the unsaturated oxo−nitriles **28a**,**b** in 57% and 85% yield, respectively.

Cuprate additions to the unsaturated oxo−nitrile **28a** were both efficient and stereoselective. Addition of Me_2-CuLi provides an excellent yield (89%) of a single nitrile diastereomer[33] **34a** following silylation of the intermediate enolate **33** (Scheme 5). Formation of **34a** is unusual in proceeding through a boatlike transition state[4a] leading to the enolate **33**, and is presumably a consequence of the severe 1,3-diaxial interaction that would otherwise occur in an attack cis to the TBDMS ether.[34] The *n*-butylcuprate reacts similarly, to provide the analogous conjugate adduct **34b**.

We anticipated extending this stereoelectronically controlled conjugate addition to the less-substituted oxo−nitrile **28b**.[35] The TBDMS ether anchors the cyclohexane ring[36] so that nucleophilic attack is predisposed toward an axial addition with stereoelectronic control (eq 3).



(3)

Addition of Me_2CuLi occurs stereoselectively from the axial direction (18:1)[37] but the yield was unacceptably low, presumably resulting from oligomerization of the

(27) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(28) (a) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387. (b) Marino, J. P.; Emonds, M. V. M.; Stengel, P. J.; Oliveira, A. R. M.; Simonelli, F.; Ferreira, J. T. B. *Tetrahedron Lett.* **1992**, *33*, 49. (c) Bhatt, R. K.; Ye, J.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 3811. For related systems see: (d) Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745. (e) Deruyttere, X.; Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 51.

(29) Hareau-Vittini, G.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2099.

(30) Direct treatment of **10** with various silylating reagents causes dehydration to the aromatic nitrile **22**.

(31) Prepared using the procedure developed by Taber and Ruckle: Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.

(32) For leading references see: (a) Blanc, D.; Henry, J.-C.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Tetrahedron Lett.* **1997**, *38*, 6603. (b) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (c) Medson, C.; Smallridge, A. J.; Trewhella, M. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1049.

(33) The stereochemistry was determined by spectral comparison of **34a** with the hydroxyl analogue **21**. Furthermore, the diastereomeric silyl ether derived from **20a** exhibits distinctly different spectral data than that of **34a** (see the Experimental Section for details).

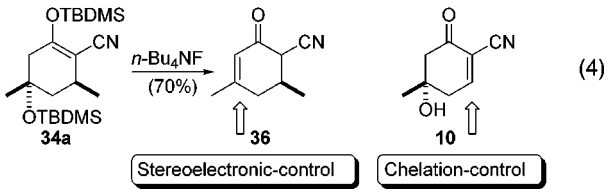
(34) The discussion of facial selectivity assumes that the preferred conformation has the smaller TBDMS ether in the axial orientation as shown: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7.

(35) Our aim was to access both conjugate addition diastereomers through a stereoelectronically controlled conjugate addition to **28b** and a stereocomplementary chelation-controlled addition to the hydroxyl analogue (**28b**, TBDMS = H). The synthesis of the desired alcohol (**28b**, TBDMS = H) directly parallels Scheme 4 and provides the desired oxo−nitrile (**28b**, TBDMS = H) in good yield. Unfortunately this oxo−nitrile decomposes readily on purification, preventing our efforts toward implementing this stereochemical strategy.

(36) The conformational preference shown is based on the large axial couplings of the methine proton (J = 13 Hz for the peak width at half-height).

intermediate enolate.[24] The high stereoselectivity of this conjugate addition is one of the few examples where a C-5-TBDMS enone controls the facial selectivity and suggests that this strategy may be particularly useful with less reactive enones.

In contrast to the sparse use of C-5 ether-substituted enones,[28,29] alkyl substituents are routinely employed in stereoelectronically controlled conjugate additions.[27] We demonstrated the use of aldols in sequential conjugate additions by eliminating **34a** with *n*-Bu_4NF, to provide the C-5-substituted enone **36** (eq 4). Collectively, these transformations illustrate the complementary stereoselectivity of conjugate additions to enones (stereoelectronic control) and hydroxylated oxo−nitriles (chelation control).



(4)

Conclusion

Alkoxide-directed conjugate addition reactions provide a highly stereoselective method of generating carbon−carbon bonds. The alkoxide-directed additions to oxo−nitrile **10** proceed with diverse Grignard reagents having sp^3-, sp^2-, and sp-hybridized carbons, with even sterically demanding nucleophiles adding with complete stereocontrol. The use of aldol-type enones demonstrates the complementary stereoselectivity of chelation and stereoelectronically controlled conjugate additions. Insights into the mechanism of the chelation-controlled conjugate addition, and the role of lithium chloride, provide the understanding required for further chelation-controlled reactions, particularly with aldol-type Michael acceptors.

Experimental Section[38]

General Conjugate Addition Procedure. A THF solution of the Grignard reagent (2.5 equiv) was added, by syringe, to a THF solution of LiCl (3 equiv) at room temperature. The resultant solution was stirred for 5 min and was then added to a cold (−78 °C), stirred, THF solution (0.12 M) of **10** (1 equiv). The resultant solution was stirred for 5 min, and then solid TBDMSCl (2.5 equiv) was added. The −78 °C bath was removed, and the solution was allowed to warm to room temperature, with stirring, overnight. Saturated, aqueous ammonium chloride was then added to the reaction mixture, the aqueous phase was extracted with EtOAc (3 × 2 mL), and the extracts were combined and then dried over anhydrous $MgSO_4$. The crude material was concentrated under reduced pressure and was then purified by radial chromatography.

(±)-(4*R*,6*R*)-4-Hydroxy-4,6-dimethyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (19). The general procedure was employed with MeMgCl (2.9 M, 1.09 mmol) and **10** (66 mg, 0.44 mmol) (without the addition of LiCl) and was quenched by the addition of saturated, aqueous NH_4Cl (2 mL). Chromatography (1 mm plate, 1:3 EtOAc/hexanes) provided 11 mg (19%) of **17** and 37 mg (51%) of **19** as an oily mixture of predominantly one diastereomer: IR (film) 3427, 2970, 2251, 2204, 1728 cm^{-1}; ^1H NMR δ 1.26 (s, 3H), 1.32 (d, J = 6.3 Hz, 3H), 1.72 (br t, J = 13.2 Hz, 1H), 1.83−2.16 (m, 3H), 2.56 (br d, J = 13.2 Hz, 1H), 2.65 (dd, J = 13.3, 1.9 Hz, 1H), 3.21 (d, J = 11.8 Hz, 1H); ^{13}C NMR δ 20.7, 27.3, 33.1, 46.6, 50.1, 54.3, 71.9, 115.7, 198.0; MS *m/e* 168 (MH).

(±)-(4*S*,6*R*)-4-Hydroxy-4,6-dimethyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (20a). The general procedure was employed with **10** (160 mg, 1.06 mmol in 6 mL THF), methylmagnesium chloride (2.9 M, 2.65 mmol), LiCl (137 mg, 3.23 mmol in 3 mL THF), and TBDMSCl (400 mg, 2.65 mmol). Radial chromatography (1:3 EtOAc/hexanes) of the crude product, followed by concentration of the appropriate fractions, provided 42 mg of **22** (16%) and 172 mg (58%) of **20a** as an oil: IR (film) 3425, 2931, 2214, 1625 cm^{-1}; ^1H NMR δ 0.24 (s, 3H), 0.25 (s, 3H), 0.98 (s, 9H), 1.23 (d, J = 6.7 Hz, 3H), 1.27 (s, 3H), 1.34 (dd, J = 13,11 Hz, 1H), 1.60 (s, 1H), 1.80 (ddd, J = 13, 6, 2 Hz, 1H), 2.23 (dt, J = 17, 2 Hz, 1H), 2.36 (dd, J = 17, 2 Hz, 1H), 2.36−2.46 (m, 1H); ^{13}C NMR δ −3.8, 18.1, 20.7, 25.5, 26.8, 29.0, 44.6, 45.5, 69.3, 95.0, 117.6, 163.0; MS *m/e* 282 (M + H).

(±)-(4*S*,6*S*)-4-Hydroxy-4,6-dimethyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (21). The general procedure was employed with MeMgCl (2.9 M, 2.02 mmol), **10** (122 mg, 0.81 mmol), and TBDMSCl (207 mg, 1.37 mmol, but without the addition of LiCl. Chromatography (1 mm plate, 1:3 EtOAc/hexanes) provided 89 mg (37%) of **20a** and 12 mg (5%) of **21** as an oil: IR (film) 3444, 2932, 2211, 1624 cm^{-1}; ^1H NMR δ 0.24 (s, 6H), 0.98 (s, 9H), 1.21 (d, J = 6.8 Hz, 3H), 1.25−1.39 (m, 1H), 1.32 (s, 3H), 1.41−1.61 (m, 2H), 1.84 (ddd, J = 13.7, 5.3, 3 Hz, 1H), 2.15 (d, J = 18.2 Hz, 1H), 2.26 (dd, J = 18.2, 3 Hz, 1H), 2.62 (br s, 1H); ^{13}C NMR δ −3.7, 18.1, 20.3, 25.5, 27.0, 30.1, 43.4, 44.5, 69.0, 95.8, 117.6, 162.4; MS *m/e* 281 (M).

(±)-(4*S*,6*S*)-6-Ethynyl-4-hydroxy-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (20b). The general procedure was employed with **10** (43 mg, 0.28 mmol in 3 mL of THF), ethynylmagnesium chloride (0.5 M, 0.71 mmol), LiCl (37 mg, 0.87 mmol in 2 mL of THF), and TBDMSCl (108 mg, 0.72 mmol). Radial chromatography (1:4 EtOAc/hexanes) of the crude product, followed by concentration of the appropriate fractions, provided 6 mg of **22** (9%) and 39 mg (47%) of **20b** as an oil: IR (film) 3425, 3301, 2932, 2214, 1625 cm^{-1}; ^1H NMR δ 0.25 (s, 3H), 0.26 (s, 3H), 0.98 (s, 9H), 1.29 (s, 3H), 1.90−1.95 (m, 2H), 2.22 (d, J = 18 Hz, 1H), 2.32 (d, J = 2.6 Hz, 1H), 2.37 (d, J = 18 Hz, 1H), 2.17−2.36 (br s, 1H), 3.38−3.49 (m, 1H); ^{13}C NMR δ −3.7, 18.1, 25.4, 26.5, 28.2, 40.1, 44.7, 69.2, 71.5, 83.2, 90.2, 117.1, 164.0; MS *m/e* 292 (M + H).

(±)-(4*S*,6*S*)-4-Hydroxy-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)-6-vinylcyclohex-1-enecarbonitrile (20c). The general procedure was employed with **10** (80 mg, 0.53 mmol in 4 mL THF), vinylmagnesium bromide (1 M, 1.32 mmol), LiCl (114 mg, 2.69 mmol in 2 mL of THF), and TBDMSCl (200 mg, 1.33 mmol). Radial chromatography (1:3 EtOAc/hexanes) of the crude product, followed by concentration of the appropriate fractions, provided 19 mg of **22** (15%) and 76 mg (49%) of 20c as an oil: IR (film): 3425, 3082, 2931, 2212, 1623 cm^{-1}; ^1H NMR δ 0.25 (s, 3H), 0.26 (s, 3H), 0.98 (s, 9H), 1.29 (s, 3H), 1.55−1.86 (br s, 1H), 1.61 (dd, J = 13, 8.3 Hz, 1H), 1.81 (ddd, J = 13, 6, 1 Hz, 1H), 2.25 (dt, J = 17.7, 1.6 Hz, 1H), 2.36 (dd, J = 17.7, 2.4 Hz, 1H), 3.02 (br dd, J = 14, 7 Hz, 1H), 5.18 (d, J = 10 Hz, 1H), 5.23 (d, J = 17 Hz, 1H), 5.74−5.89 (ddd, J = 17, 10, 7 Hz, 1H); ^{13}C NMR δ −3.7, 18.1, 25.5, 27.7, 39.2, 41.6, 45.3, 69.6, 92.3, 116.8, 117.7, 139.1, 163.8; MS *m/e* 294 (M + H).

(±)-(4*S*,6*S*)-4-Hydroxy-4-methyl-6-phenyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (20d). The general procedure was employed with **10** (117 mg, 0.77 mmol in 6 mL THF), phenylmagnesium chloride (2 M, 1.94 mmol), LiCl (100 mg, 2.36 mmol in 3 mL of THF), and TBDMSCl (292 mg, 1.94 mmol). Radial chromatography (1:4 EtOAc/hexanes) of the crude product, followed by concentration of the appropriate fractions, provided 17 mg of **22** (9%) and 155 mg (58%) of **20d** as an oil: IR (film) 3420, 3028, 2931, 2212, 1624 cm^{-1}; ^1H NMR δ 0.20 (s, 3H), 0.22 (s, 3H), 0.92 (s,

(37) The inseparable diastereomers were assigned by spectral comparison of the major diastereomer with **21** since **35** and **21** adopt a common conformation and have identical spectral signatures.

(38) For general experimental procedures, see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.

9H), 1.25 (s, 3H), 1.62 (dd, J = 12.9, 10.5 Hz, 1H), 1.69 (br s, 1H), 1.88 (ddd, J = 12.9, 6.0, 2 Hz, 1H), 2.23 (dt, J = 17.6, 2 Hz, 1H), 2.40 (dd, J = 17.6, 3 Hz, 1H), 3.42−3.52 (m, 1H), 7.08−7.31 (m, 5H); ^{13}C NMR δ −3.7, 18.1, 25.5, 26.8, 41.7, 45.5, 46.0, 69.6, 93.5, 117.4, 127.2, 127.6, 128.8, 142.1, 164.4; MS *m/e* 344 (M + H).

(±)-(4S,6S)-6-(*tert*-Butyl)-4-hydroxy-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (20e). The general procedure was employed with **10** (53 mg, 0.35 mmol in 3 mL of THF), *tert*-butylmagnesium chloride (1 M, 0.88 mmol), LiCl (73 mg, 1.72 mmol in 2 mL of THF), and TBDMSCl (133 mg, 0.88 mmol). Radial chromatography (1:3 EtOAc/hexanes) of the crude product, followed by concentration of the appropriate fractions, provided 13 mg of **22** (15%) and 49 mg (43%) of **20e** as an oil: IR (film) 3418, 2960, 2208, 1606 cm^{-1}; ^{1}H NMR δ 0.22 (s, 3H), 0.25 (s, 3H), 0.98 (s, 9H), 1.05 (s, 9H), 1.23 (s, 3H), 1.30−1.45 (m, 1H), 1.72 (ddd, J = 12.7, 6, 3 Hz, 1H), 1.72 (br s, 1H), 2.14−2.25 (m, 2H), 2.35 (dd, J = 16.9, 3.1 Hz, 1H); ^{13}C NMR δ −3.7, 18.2, 25.6, 26.0, 28.0, 34.2, 39.1, 44.1, 45.8, 70.0, 92.3, 119.7, 166.1; MS *m/e* 324 (M + H).

4-Methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)benzenecarbonitrile (22). In the conjugate addition reactions of MeMgCl with **10**, varying amounts of **22** were obtained as an oil: IR (film) 2930, 2226, 1608 cm^{-1}; ^{1}H NMR δ 0.27 (s, 6H), 1.04 (s, 9H), 2.35 (s, 3H), 6.69 (s, 1H), 6.81 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ −4.4, 18.1, 21.9, 25.5, 102.3, 117.3, 120.5, 122.5, 133.1, 145.3, 157.9; MS *m/e* 248 (M + H).

(±)-(5*S*)-5-Methyl-3-oxo-5-(1,1,2,2-tetramethyl-1-silapropoxy)oct-7-enenitrile (30a). Pyridine (2.37 mL, 29 mmol) and TBDMSOTf (4.14 mL, 18 mmol) were added, sequentially, to a stirred, cold (0 °C) CH_2Cl_2 solution (50 mL) of **29**[14] (2.072 g, 12 mmol). The resultant solution was stirred for 5 min, and then the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into a separatory funnel, washed with saturated $NaHCO_3$ solution, and extracted with EtOAc (3 × 3 mL) and was then dried over $MgSO_4$. The crude material was concentrated under reduced pressure and purified by radial chromatography (4 mm plate, 1:6 EtOAc/hexane) to afford 2.53 g (73%) of ethyl (±)-(3*S*)-3-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy)hex-5-enoate as an oil: IR (film) 3078, 2957, 1732, 1640 cm^{-1}; ^{1}H NMR δ 0.09 (s, 6H), 0.85 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.35 (s, 3H), 2.28−2.48 (m, 4H), 4.09 (q, J = 7.1 Hz, 2H), 5.03−5.10 (m, 2H), 5.78−5.93 (m, 1H); ^{13}C NMR δ −2.1, −2.0, 14.2, 18.1, 25.7, 27.7, 46.7, 47.4, 60.1, 74.4, 118.0, 134.5, 171.0; MS *m/e* 286 (M). Neat CH_3CN (60 mL, 1.15 mmol) was added dropwise to a cold (−78 °C), stirred, THF solution (1.5 mL) of *n*-BuLi (1.15 mmol). The resultant solution was stirred for 5 min, and then a THF solution (2 mL) of ethyl (±)-(3*S*)-3-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy)hex-5-enoate (133 mg, 0.47 mmol) was added. The resultant solution was stirred for 30 min at −78 °C and then allowed to warm to room temperature overnight. Aqueous HCl (2% v/v) was added until the reaction mixture was acidic to litmus, and then the aqueous phase was extracted with EtOAc (3 × 8 mL). The extracts were combined, washed successively with saturated $NaHCO_3$ solution and brine, and then dried ($MgSO_4$). The crude materials was concentrated and then purified by radial chromatography (1 mm plate, 1:19 EtOAc/hexanes) to afford 124 mg (95%) of **30a** as an oil: IR (film) 3079, 2930, 2259, 1732, 1636 cm^{-1}; ^{1}H NMR δ 0.12 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.35 (s, 3H), 2.28 (dd, J = 13.6, 7.9 Hz, 1H), 2.41 (dd, J = 13.6, 6.7 Hz, 1H), 2.50 (d, J = 14 Hz, 1H), 2.71 (d, J = 14 Hz, 1H), 3.53 (d, J = 19.5 Hz, 1H), 3.62 (d, J = 19.5 Hz, 1H), 5.05−5.13 (m, 2H), 5.70−5.87 (m, 1H); ^{13}C NMR δ −1.9, 18.1, 25.9, 27.7, 34.4, 47.5, 52.7, 75.6, 113.7, 119.0, 133.6, 196.6; MS *m/e* 266 (M − CH3).

(±)-(4*S*)-4-Methyl-6-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (28a). A stream of ozone was passed through a cold (−78 °C), dichloromethane solution (3 mL) of **30a** (69 mg, 0.25 mmol) until the distinctive blue color of ozone was clearly observed. Ozonolysis was then terminated, the excess ozone was displaced by passing a stream of nitrogen through the solution, and then neat Me_2S (1 mL) was added dropwise at −78 °C. The resultant solution was allowed to warm to room temperature over 6 h. The reaction mixture was then concentrated and purified by radial chromatography (1 mm plate, 1:9 EtOAc/hexane) to afford 37 mg (57%) of **28a** as a white waxy solid: mp 100.3−103.2 °C; IR 2928, 2234, 1694, 1615 cm^{-1}; ^{1}H NMR δ 0.06 (s, 3H), 0.08 (s, 3H), 0.77 (s, 9H), 1.42 (s, 3H), 2.50−2.78 (m, 4H), 7.55−7.59 (m, 1H); ^{13}C NMR δ −2.5, −2.4, 17.8, 25.4, 29.2, 41.8, 52.0, 74.0, 113.9, 117.4, 158.5, 191.2; MS *m/e* 266 (M + H).

(±)-Ethyl (5*E*)-3-Hydroxyoct-5-enoate (32). A hexanes solution (4 mL) of *trans*-3-hexenoic acid (0.48 mL, 4.0 mmol), containing 1 drop of dry DMF, was cooled to 0 °C, and then neat oxalyl chloride (0.35 mL, 4.0 mmol) was slowly added. The cooling bath was then removed, and after 1.5 h the solvent was evaporated to provide *trans*-3-hexenoyl chloride as a relatively pure oil. A THF solution (2 mL) of *trans*-3-hexenoyl chloride was added to a cold (−78 °C), THF solution (15 mL) of ethyl lithioacetate,[39] prepared by the addition of neat ethyl acetate (1.2 mL, 12.0 mmol) to a cold (−78 °C), THF solution of LiHMDS (hexamethyldisilazane, 2.5 mL, 12.0 mmol; MeLi, 8.7 mL, 11.6 mmol) followed by stirring for 10 min. Following the addition of *trans*-3-hexenoyl chloride, the solution was allowed to stir at −78 °C for 5 min and then the cooling bath was removed. After 1 h aqueous HCl (10% v/v, mL) was added and the crude reaction mixture was extracted with EtOAc. Purification of the crude material by radial chromatography (4 mm plate, 1:19 EtOAc/hexane) provided 379.9 mg (52%) of ethyl (5*E*)-3-oxooct-5-enoate as an oil: IR 2969, 1745, 1708, 1649 cm^{-1}; ^{1}H NMR δ 0.93 (t, J = 7 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.96−2.05 (m, 2H), 3.17 (d, J = 6.5 Hz, 2H), 3.41 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 5.38−5.48 (m, 1H), 5.58 (ddd, J = 15.3, 6.3, 6.0 Hz); ^{13}C NMR δ 13.2, 13.9, 25.4, 46.6, 48.4, 61.1, 119.8, 137.5, 167.0, 201.3; MS *m/e* 184 (M). A cold (0 °C), ethanol solution (1.5 mL) of ethyl (5*E*)-3-oxooct-5-enoate (556.0 mg, 3.0 mmol) was reduced by the slow addition of solid $NaBH_4$ (56.7 mg, 1.5 mmol). After the vigorous reaction subsided, the cooling bath was removed and the solution was then stirred for a further 10 min. Aqueous HCl (3% v/v, mL) was added, and the crude reaction mixture was then extracted with EtOAc. Purification of the crude material by radial chromatography (4 mm plate, 1:19 EtOAc/hexane) provided 495.5 mg (88%) of **32** as an oil: IR 3509, 1731 cm^{-1}; ^{1}H NMR δ 0.97 (dd, J = 7.4, 6.2 Hz, 3H), 1.26 (td, J = 7.1 Hz, 1.4 Hz, 3H), 2.02 (br quintet, J = 7 Hz, 2H), 2.13−2.26 (m 2H), 2.50 (dd, J = 16, 4 Hz, 1H), 2.89 (s, 1H), 4.02 (br s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 5.34−5.44 (m, 1H), 5.56 (dt, J = 15.3, 6 Hz, 1H); ^{13}C NMR δ 13.7, 14.1, 25.6, 39.8, 40.7, 60.6, 67.8, 124.0, 136.2, 172.8; MS *m/e* 187 (M + H).

(±)-(7*E*)−(5R)-3-Oxo-5-(1,1,2,2-tetramethyl-1-silapropoxy)dec-7-enenitrile (30b). Treatment of **32** with pyridine (0.62 mL, 7.4 mmol) and TBDMSOTf (1.1 mL, 4.5 mmol) as described for **30a** provided 844.1 mg (92%) of ethyl (7*E*)-3-(1,1,2,2-tetramethyl-1-silapropoxy)dec-7-enoate as an oil: IR 2932, 1734 cm^{-1}; ^{1}H NMR δ 0.02 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.95 (dd, J = 7.6, 7.4 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 2.00 (br quintet, J = 7 Hz, 2H), 2.17 (br t, J = 6 Hz, 2H), 2.37 (dd, J = 15, 7 Hz, 1H), 2.43 (dd, J = 15, 5 Hz, 1H), 4.05−4.18 (m, 3H), 5.31−5.41 (m, 1H), 5.50 (dt, J = 15.3, 6 Hz, 1H); ^{13}C NMR δ −4.9, −4.5, 13.7, 14.2, 18.0, 25.6, 25.7, 41.0, 42.3, 60.2, 69.5, 124.4, 135.3, 171.9; MS *m/e* 300 (M + H). Addition of a THF solution of ethyl (7*E*)-3-(1,1,2,2-tetramethyl-1-silapropoxy)dec-7-enoate to lithioacetonitrile [from BuLi (1.19 mL, 1.57 mmol) and acetonitrile (82.1 mL, 1.57 mmol)], as described for **30a**, provided 226.8 mg (98%) of 30b as an oil: IR 2257, 1725 cm^{-1}; ^{1}H NMR δ 0.04 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H), 2.02 (br quintet, J = 7 Hz, 2H), 2.11−2.27 (m, 2H), 2.60 (dd, J = 14.7, 4.6 Hz, 1H), 2.68 (dd, J = 14.7, 7.3 Hz, 1H), 3.15 (s, 2H), 4.17 (tt, J = 7.2, 4.8 Hz, 1H), 5.32 (dtt, J = 15.4, 7.0, 1 Hz, 1H), 5.52 (dt, J = 15.4, 6 Hz); ^{13}C NMR δ −4.9, −4.5, 13.6, 18.0, 25.6, 25.8, 33.9, 40.9, 48.5, 69.5, 113.5, 123.5, 136.3, 197.0; MS *m/e* 296 (M + H).

(4*R*)-6-Oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (28b). Ozonolysis of a dichloromethane

(39) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

solution (30 mL) of **30b** (1.5 g, 5.1 mmol) using the same procedure as described for **28a**, provided, after reduction with Me_2S (60 mL), 1.09 g (85%) of **28b** as an oil: IR 3025, 1684, 1608 cm^{-1}; ^1H NMR δ 0.07 (s, 6H), 0.86 (s, 9H), 2.56−2.84 (m, 4H), 4.35 (dddd, J = 10, 4, 3.6 Hz), 7.60 (t, J = 4 Hz, 1H); ^{13}C NMR δ −5.0, −4.9, 17.9, 25.6, 36.0, 46.8, 66.3, 113.8, 118.1, 158.4, 190.7; MS *m/e* 252 (M + H).

(±)−(4*R*,6*R*)-2,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-4,6-dimethylcyclohex-1-enecarbonitrile (34a). A THF solution of Me_2CuLi [1 mL, prepared from Me_2S·CuBr (58 mg, 0.28 mmol) and MeLi (0.28 mmol)] was added, by syringe, to a cold (−78 °C), stirred THF solution (1 mL) of **28a** (49 mg, 0.18 mmol). After 30 min, TBDMSCl (55 mg, 0.36 mmol) was added and then the resultant solution was allowed to warm to room temperature overnight. Saturated, aqueous NH_4Cl (2 mL, pH = 8) was then added, the aqueous phase was extracted with EtOAc (3 × 3 mL), and the extracts were combined and then dried with anhydrous magnesium sulfate. The crude material was concentrated under reduced pressure and purified by radial chromatography (1 mm plate, 1:99 EtOAc/hexanes) to afford 65 mg (89%) of **34a** as an oil: IR (film) 2931, 2210, 1634 cm^{-1}; ^1H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.23 (s, 6H), 0.83 (s, 9H), 0.97 (s, 9H), 1.16−1.24 (m, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.31 (s, 3H), 1.82 (dd, J = 13.2, 5.0 Hz, 1H), 2.15 (br s, 2H), 2.54−2.71 (m, 1H); ^{13}C NMR δ −3.8, −3.7, −2.3, 18.0, 20.1, 25.4, 25.7, 27.3, 30.1, 44.7, 45.3, 71.4, 95.5, 117.9, 162.7; MS *m/e* 396 (M + H).

(6*S*,4*R*)-2,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-4,6-dimethylcyclohex-1-enecarbonitrile. Pyridine (20 mL, 0.25 mmol) and TBDMSOTf (45 mL, 0.20 mmol) were added, sequentially, to a stirred, CH_2Cl_2 solution (1.5 mL) of **20a** (37 mg, 0.13 mmol), and the resultant solution was stirred for 14 days at room temperature. Saturated aqueous $NaHCO_3$ was added, and the organic phase was then dried over $MgSO_4$. The crude material was concentrated under reduced pressure and was then purified by radial chromatography (1 mm plate, 1:66 EtOAc/hexanes) to afford 5.5 mg (15%) of recovered **20a** and 29 mg (56%) of (6*S*,4*R*)-2,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-4,6-dimethylcyclohex-1-enecarbonitrile as an oil: IR (film): 2958, 2215, 1631 cm^{-1}; ^1H NMR δ 0.09 (s, 6H), 0.23 (s, 3H), 0.24 (s, 3H), 0.85 (s, 9H), 0.98 (s, 9H), 1.18−1.33 (m, 4H), 1.22 (s, 9H), 1.80 (br dd, J = 11, 5 Hz, 1H), 2.17 (br d, J = 17.9 Hz, 1H), 2.28−2.36 (m, 2H); ^{13}C NMR δ −3.8, −1.9, 17.8, 18.1, 20.7, 25.5, 25.7, 26.8, 28.9, 45.5, 46.8, 71.7, 95.1, 117.7, 163.1; MS *m/e* 396 (M + H).

(±)-(4*R*,6*R*)-2,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-6-butyl-4-methylcyclohex-1-enecarbonitrile (34b). The procedure for **34a** was employed using *n*-Bu_2CuLi [1 mL, prepared from Me_2S·CuBr (115 mg, 0.56 mmol) and *n*-BuLi (0.56 mmol)], **28a** (99 mg, 0.37 mmol), and TBDMSCl (112.5 mg, 0.75 mmol). The crude material was concentrated under reduced pressure and purified by radial chromatography (1 mm plate, 1:99 EtOAc/hexane) to afford 76 mg (47%) of **34b** as an oil: IR (film) 2930, 2209, 1622 cm^{-1}; ^1H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.22 (s, 3H), 0.23 (s, 3H), 0.83 (s, 9H), 0.91 (t, J = 7.0 Hz, 3H), 0.96−1.08 (m, 4H), 0.97 (s, 9H), 1.18−1.30 (m, 2H), 1.32 (s, 3H), 1.75−1.85 (m, 1H), 1.85 (dd, J = 13, 5.2 Hz, 1H), 2.15 (d, J = 2.1 Hz, 2H), 2.46−2.61 (m, 1H); ^{13}C NMR δ −3.7, −3.6, −2.2, 14.1, 18.1, 22.8, 25.5, 25.7, 28.3, 30.4, 32.2, 33.7, 41.5, 45.5, 71.4, 95.2, 118.1, 163.0; MS *m/e* 438 (M + H).

(4*R*,6*R*)-2,4-Bis(1,1,2,2-tetramethyl-1-silapropoxy)-6-methylcyclohex-1-enecarbonitrile (35). A THF solution of Me_2CuLi [1 mL, prepared from Me_2S·CuBr (138.8 mg, 0.68 mmol) and MeLi (0.95 mL, 1.35 mmol)] was added to a THF solution (1 mL) of **28b** (111.0 mg, 0.50 mmol) followed by TBDMSCl (136.0 mg, 0.90 mmol) as described for the synthesis of **34a**. The crude product was purified by radial chromatography (1 mm plate, 1:19 EtOAc/hexanes) to afford 50.9 mg (27%) of **35** as an oil: IR 2947, 2212, 1631 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.23 (s, 3H), 0.24 (s, 3H), 0.87 (s, 9H), 0.98 (s, 9H), 1.18 (d, J = 7.1 Hz, 3H), 1.34 (dtt, J = 13.2, 7.9, 2.3 Hz, 1H), 1.75 (ddd, J = 13.2, 6.6, 1.0 Hz, 1 H), 2.10 (br ddt, J = 19, 4, 1 Hz, 1H), 2.35 (br ddd, J = 19, 4, 2 Hz, 1H), 2.63 (br quintet, J = 7 Hz, 1H); ^{13}C NMR δ −4.9, −4.7, −3.9, −3.8, 18.0, 18.1, 20.5, 20.9, 25.5, 25.7, 26.7, 38.0, 64.3, 96.1, 118.1, 162.2; MS *m/e* 382 (M + H).

(±)-(6*R*)-4,6-Dimethyl-2-oxocyclohex-3-enecarbonitrile (36). A THF solution of tetrabutylammonium fluoride (1 M, 0.39 mmol) was added to a THF solution of **34a** (61 mg, 0.15 mmol). The resultant solution was refluxed for 2 h, diluted with EtOAc (8 mL), and washed with saturated, aqueous $NaHCO_3$ and was then dried over $MgSO_4$. The crude material was concentrated under reduced pressure and was then purified by radial chromatography (1 mm plate, 1:19 EtOAc/hexanes) to afford 16 mg (70%) of **36** as an oil consisting of two diastereomers (2:1 ratio): IR (film) 2932, 2248, 1682, 1634 cm^{-1}; ^1H NMR for major δ 1.32 (d, J = 6.5 Hz, 3H), 2.01 (s, 3H), 2.32−2.52 (m, 3H), 3.18 (d, J = 12.2 Hz, 1H), 5.98 (br s, 1H); ^1H NMR for minor δ 1.23 (d, J = 6.7 Hz, 3H), 2.02 (s, 3H), 2.09−2.24 (m, 3H), 3.44 (d, J = 4.3 Hz, 1H), 5.94−5.97 (m, 1H); ^{13}C NMR for major δ 20.0, 24.3, 33.7, 38.6, 47.2, 116.2, 124.6, 162.7, 188.2; ^{13}C NMR for minor δ 17.5, 24.5, 32.0, 36.5, 44.7, 115.1, 124.2, 163.3, 188.2; MS *m/e* 150 (M + H).

Acknowledgment. We gratefully acknowledge financial support from the NIH (Grant CA/GM 74355-01) and helpful discussions with Drs. Peter Wipf and Dennis Liotta.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9909709