Novel Approach to Remote Asymmetric Induction in Carbonyl Addition and Related Reactions

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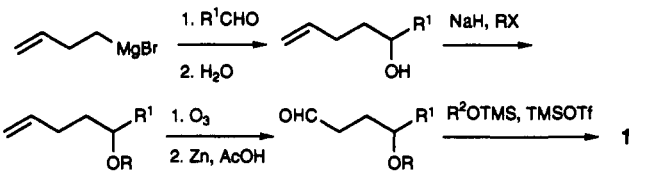
Abstract: Neighboring group participation is postulated to be responsible for high asymmetric induction in the addition of various nucleophiles (e.g., Me_3SiCN, allylsilanes, and allylstannanes) to chiral alkoxy acetals and aldehydes. Thus, oxocarbenium ions generated by treatment of these substrates with various Lewis acids suffer intramolecular solvation by a neighboring alkoxy group. This establishes a conformationally defined, cyclic oxonium ion intermediate which can be attacked by the nucleophile, providing high diastereoselectivity in the process. The strategy employed is particularly effective for 1,4-asymmetric induction, and it has been extended to 1,2- and 1,3-asymmetric induction as well. The scope of the reaction with regard to the nature of the acetal and participating group was revealed through a series of reactions of appropriate γ-alkoxy acetals with various nucleophiles under Lewis acid catalysis.

Introduction

The diastereoselective addition of nucleophiles to chiral aldehydes is an area of interest which continues to receive great attention from synthetic organic chemists. Virtually all effective strategies for remote acyclic stereocontrol rely upon some means to limit the number of degrees of freedom available to the substrate and subsequently allow facial selectivity in the addition of nucleophiles to this conformationally restricted electrophile. Many of the most successful methods for acyclic stereocontrol employ the concept of chelation control of stereochemistry.[2] In this approach, a metal ion complexes simultaneously with the aldehyde and a Lewis basic group located at a stereogenic center within the molecule. Face-selective attack of the nucleophile at the aldehyde ensues, relaying stereochemical information from the preexisting stereocenter to the newly created asymmetric carbon.

Although extraordinarily successful in many instances, some of the limitations of chelation control are readily apparent. Both the prostereogenic center (carbonyl unit in this case) and the stereodirecting group must be Lewis basic. Additionally, both centers must be reasonably close to one another. Aldehydes possessing remote alkoxy groups may never chelate the metal ion or alternatively may not provide a structure which is conformationally restrictive enough to relay stereochemical information. As an example, 1,4-asymmetric induction via chelation control requires the formation of a seven-membered-ring chelate. Even though seven-membered-ring chelates have been isolated and fully characterized,[3] their stability and conformational rigidity are certainly less than those of corresponding five- and six-membered-ring systems, and examples wherein high degrees of diastereoselectivities are achieved are rare.[2a-e] Even in less demanding examples of stereochemical control (e.g., 1,2- and 1,3-asymmetric induction) the organized chelate may not lower the activation energy of the addition reactions relative to that of nonchelated substrates. In these instances, reaction through the nonchelated pathway may compete with reaction via the chelated intermediate. Alternatively, the rate of formation of the chelates may be competitive with the rate of nucleophilic addition to the carbonyl.[4] Again, this permits addition through a nonchelated pathway leading to diminished stereoselectivity.

Scheme I



In order to circumvent limitations of this type, we have developed an approach to diastereoselective carbonyl addition reactions based on classical solvolysis chemistry. Neighboring group participation is thus postulated as an effective strategy for remote asymmetric induction.[5] By alleviating the necessity for a metal ion to restrict conformation by chelation, thereby allowing a basic site to interact directly with an electrophilic center, two atoms (the metal ion and the carbonyl oxygen) are removed from potential cyclic intermediates. As reported earlier,[6] we have made use of this strategy by employing γ-alkoxy substituents as stereodirecting groups for 1,4-asymmetric induction in carbonyl and acetal substrates. These electrophiles undergo Lewis acid-promoted reaction with a variety of nucleophiles to provide diastereomerically enriched ethers. We now report a more detailed study of the factors involved in achieving remote stereochemical control and the extension of this method to 1,2- and 1,3-asymmetric induction.

(1) Alfred P. Sloan Foundation Fellow, 1987-1991. American Cyanamid Academic Awardee, 1991.

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(5) (a) Lemieux, R. U. *Adv. Carbohydr. Chem.* **1954**, *9*, 1. (b) Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1. (c) Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45. (d) Goodman, L. *Adv. Carbohydr. Chem.* **1967**, *22*, 109. (e) Paulsen, H. *Adv. Carbohydr. Chem.* **1971**, *26*, 127. (f) Reetz, M. T.; Sauerwald, M.; Walz, P. *Tetrahedron Lett.* **1981**, *22*, 1101. (g) Utimoto, K.; Horiie, T. *Tetrahedron Lett.* **1982**, *23*, 237. (h) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (i) Reetz, M. T.; Chatziiosifidis, I.; Künzer, H.; Müller-Starke, H. *Tetrahedron* **1983**, *39*, 961. (j) Utimoto, K.; Wakabayashi, Y.; Horlie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967. (k) Narasaka, K.; Ichikawa, Y.; Kubota, H. *Chem. Lett.* **1987**, 2139. (l) Broka, C. A.; Gertlis, J. F. *J. Org. Chem.* **1988**, *53*, 2144. (m) Chatani, N.; Ikeda, T.; Sano, T.; Sonoda, N.; Kurosawa, H.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1988**, *53*, 3387. (n) Brückner, C.; Holzinger, H.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2450. (o) Saigo, K.; Kudo, K.; Hashimoto, Y.; Kimoto, H.; Hasegawa, M. *Chem. Lett.* **1990**, 941. (p) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1991**, *56*, 2617.

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Table I. 1,4-Relative Asymmetric Induction: Protocol A

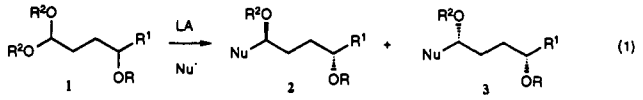
product	R	R^1	R^2	nucleophile	Lewis acid	diastereomeric ratio[a] (2:3)	% isoltd yield (2 + 3)
2a	Me	Me	*i*-Pr	TMSCN	TMSOTf	5:1	96
2b	Me	*n*-Bu	*i*-Pr	TMSCN	TMSOTf	5:1	95
2c	Me	*t*-Bu	*i*-Pr	TMSCN	TMSOTf	6:1	95
2d	Me	Ph	*i*-Pr	TMSCN	TMSOTf	6:1	93
2e	Me	*i*-Pr	*i*-Pr	TMSCN	TMSOTf	15:1	97
2f	Me	cyclohexyl	*i*-Pr	TMSCN	TMSOTf	10:1	100
2g	Me	*i*-Pr	$(ClCH_2)_2CH$	TMSCN	$SnCl_4$	11:1	89
2h	Me	*i*-Pr	$(ClCH_2)_2CH$	allyltrimethylsilane	$SnCl_4$	6:1	92
2i	Me	Me	Bn	TMSCN	$SnCl_4$	4:1	97
2j	Me	*n*-Bu	Bn	TMSCN	$SnCl_4$	4:1	94
2k	Me	Ph	Bn	TMSCN	$SnCl_4$	3.5:1	82
2l	Me	*i*-Pr	Bn	TMSCN	$SnCl_4$	8:1	94
2m	Me	*t*-Bu	Bn	TMSCN	$SnCl_4$	6.5:1	91
2n	Me	cyclohexyl	Bn	TMSCN	$SnCl_4$	6.5:1	75
2o	Me	Ph	Bn	allyltributylstannane	TMSOTf	8:1	71
2p	Me	*t*-Bu	Bn	allyltributylstannane	TMSOTf	8:1	60
2q	Me	cyclohexyl	Bn	allyltributylstannane	TMSOTf	7:1	77
2r	Me	*i*-Pr	Bn	allyltributylstannane	TMSOTf	9:1	73
2s	Me	*i*-Pr	4-BrBn	TMSCN	$SnCl_4$	5:1	87
2t	Me	*i*-Pr	4-NO_2Bn	TMSCN	$SnCl_4$	5:1	54
2u	Me	*i*-Pr	2-MeBn	TMSCN	$SnCl_4$	8:1	85
2v	Bn	*n*-Pr	Bn	allyltributylstannane	TMSOTf	8:1	86
2w	Bn	*i*-Pr	Bn	TMSCN	$SnCl_4$	6:1	95

[a] Determined by GC analysis on the crude reaction mixture using fused-silica GC capillary columns.

Results and Discussion

Lewis acid-promoted additions of nucleophiles to acetals were chosen as a starting point for our studies because in these reactions substantial positive charge develops at the electrophilic center prior to nucleophilic addition. The electron demand that is created during this process provides the opportunity for neighboring group participation and subsequent stereochemical control. However, further consideration of the limiting mechanisms involved in Lewis acid-promoted substitution reactions of acetals is required. As in chelation-controlled processes, nonproductive reaction pathways create the potential for diminished diastereoselectivity. The nucleophile in Lewis acid-mediated reactions of acetals can either substitute in an S_N2 fashion by displacing an alkoxy/Lewis acid complex or in an S_N1 mode via an oxocarbenium ion.[7] For substrates with stereogenic centers far removed from the electrophilic site, neither of these reaction pathways is expected to elicit high asymmetric induction in the absence of other factors (Figure 1). Perhaps only intramolecular solvation of the developing oxocarbenium ion in such reactions can provide organization, thereby establishing a more or less rigid intermediate with enhanced opportunities for stereochemical control in the key carbon–carbon bond-forming reaction.

1,4-Asymmetric Induction. In order to examine the feasibility of this protocol for remote asymmetric induction, a survey was undertaken to examine the effects of the acetal, the participating group, and alkyl substituents on 1,4-asymmetric induction (eq 1).



(1)

The acetals required for the initial study were prepared via the route depicted in Scheme I. First, 3-butenyl-1-magnesium bromide was added to appropriate aldehydes. The alcohol generated was subjected to Williamson etherification utilizing NaH and desired organic halides in DMF. Finally the alkoxy olefin

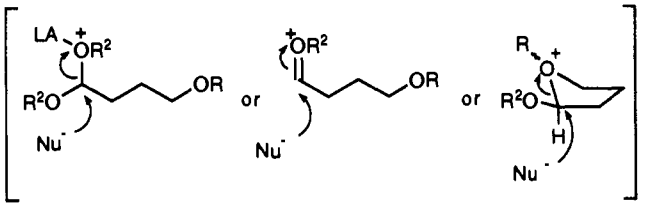
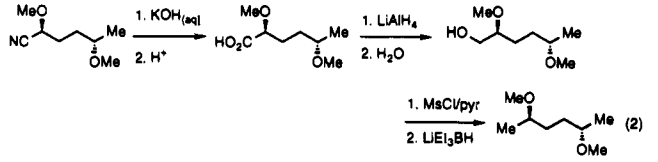


Figure 1. Possible reaction pathways for Lewis acid-promoted additions to acetals.

was ozonolyzed to provide the aldehyde, and the latter was further transformed to the desired acetal by treatment with R^2OTMS and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 at −78 °C.[8] Several acetals were treated with trimethylsilyl cyanide (TMSCN) or allyltributylstannane in the presence of nonchelating Lewis acids in CH_2Cl_2 at −78 °C. The diastereomeric ratios and chemical yields are provided in Table I.

When 1,1,4-trimethoxypentane was treated with 1 equiv of TMSCN and catalytic TMSOTf,[9] 2,5-dimethoxyhexanenitrile was formed as a 3:2 ratio of diastereomers. However, when 1,1-diisopropoxy-4-methoxypentane (**1a**) was treated with TMSCN and TMSOTf, the resulting nitrile was isolated as a 5:1 ratio of diastereomers. In fact, among the acetals investigated, the isopropyl acetals provided among the highest de's.

The stereochemical assignment of the products was based upon two different structure proofs. In the first, one of the dimethoxy nitriles generated was converted to a product of known stereochemistry (eq 2). Thus 1,2-dimethoxyhexanenitrile (3:2 mixture



(2)

of diastereomers) was hydrolyzed to the carboxylic acid with KOH_{aq} (96% yield).[10] This acid was reduced to the alcohol by

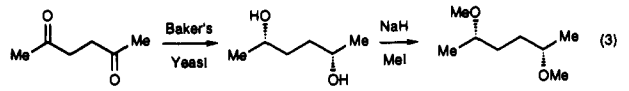
(7) (a) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (b) Ishihara, K.; Yamamoto, H.; Heathcock, C. H. *Tetrahedron Lett.* **1989**, *30*, 1825. (c) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. (d) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. (e) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (f) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (g) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (h) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (i) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997.

(8) Noyori, R.; Tsunoda, T.; Suzuki, M. *Tetrahedron Lett.* **1980**, 1357.

(9) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Osterele, T.; Steppen, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

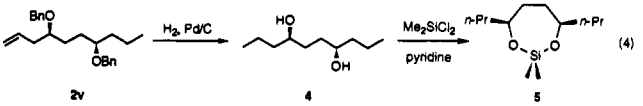
(10) Tarbell, D. S.; Willson, J. W.; Fanta, P. E. *Organic Syntheses*; Wiley: Collect. Vol. 3, 267.

$LiAlH_4$ in ether (81% yield). Treatment of the dimethoxy alcohol with MsCl in pyridine provided the mesylate (100% yield), which was reduced to the dimethoxyalkane by $LiEt_3BH$.[11] The resulting 3:2 mixture of diastereomeric 2,5-dimethoxyhexanes was then compared to authentic (2*S*,5*S*)-2,5-dimethoxyhexane prepared by an unambiguous route as outlined in eq 3. Thus, the diether



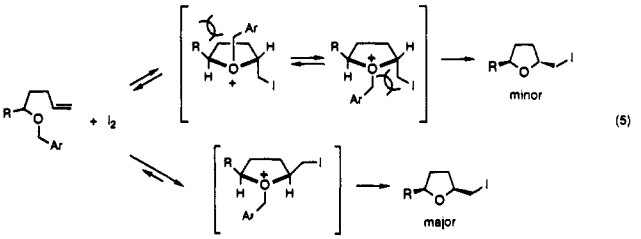
required for comparison was generated from the corresponding diol by a Williamson ether synthesis utilizing MeI and NaH in DMF. The diol itself was synthesized via the baker's yeast reduction of 2,5-hexanedione.[12] With the diether derived from the yeast reduction in hand, its ^{13}C NMR spectrum was compared to the ^{13}C NMR spectrum of the material obtained ultimately from 1,2-dimethoxyhexanenitrile. The spectrum of the syn diastereomer generated from the yeast reduction was identical to the spectrum of the minor diastereomer generated via the procedure outlined above. Consequently, the major diastereomer generated in the initial nucleophilic addition process possesses the anti configuration.

In a second confirmation of stereochemistry, **2v** was exhaustively hydrogenated to provide **4**. The latter was treated with Me_2SiCl_2 in pyridine, generating **5** (eq 4).[13] The ^1H NMR of this material displayed two distinct methyl singlets, indicating that the methyl



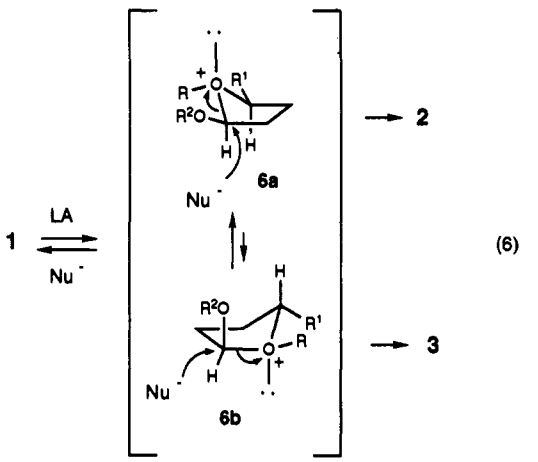
groups attached to the silicon were diastereotopic. Consequently, the propyl groups must be oriented cis on the heterocyclic ring of **5**, and **2v** must possess the anti configuration. The stereochemistry of the remainder of the entries in Table I was assigned anti by analogy.

That more hindered acetals provide higher diastereoselectivities in these reactions is perhaps not surprising. Denmark and Willson have established that more highly hindered acetals react with nucleophiles by an S_N1 mechanism which is attributable to relief of steric strain upon ionization of these bulky moieties.[7c,d] Although rapid ionization may contribute in some way to the high diastereoselectivities observed (e.g., by enhancing intramolecular solvation of the oxocarbenium ion relative to intermolecular S_N2 displacement of a Lewis acid-complexed alkoxy group by the nucleophile), perhaps a more cogent argument can be based upon the studies of electrophile-promoted cyclization of γ-hydroxyalkenes (eq 5).[14] In these reactions a tetrahydrofuranonium ion



intermediate is generated. Thermodynamic equilibration of this ion has been postulated to serve a vital role in achieving high diastereoselectivity in the synthesis of 2,5-disubstituted tetrahydrofurans. Thus a bulky substituent on the heteroatom of the newly formed ring interacts sterically with substituents on C-2 and C-5. The most stable configuration of the tetrahydrofuranonium ion is the trans,trans-trisubstituted intermediate, leading to generation of cis-2,5-disubstituted tetrahydrofurans.

A similar argument can be proposed in the present case. If the cyclic oxocarbenium ions generated are thermodynamically equilibrated, then some rationale for the observed diastereoselectivity of the reactions can be proposed on the basis of the ground-state energies of these intermediates. The fluxional nature of five-membered rings, combined with uncertainties concerning the pyramidalization about the oxonium ion oxygen,[15] prevent wholly accurate and reliable assessment of the factors leading to high diastereoselection. However, one can analyze limiting conformations of likely intermediates which provide some insights into the reaction process.[16] Two such diastereomeric intermediates are depicted in eq 6. According to Macromodel MM2 molecular



mechanics calculations on isoelectronic model systems (*N*-methyl-2-methoxypyrrolidines), the trans–trans set of conformational intermediates analogous to those first proposed by Barrtlett and co-workers (**6a**) is estimated to be the thermodynamically most prevalent structure, comprising 85% of the equilibrium mixture at −78 °C. These intermediates place all of the substituents in pseudoequatorial orientations about the ring. Subsequent S_N2-type displacement of the oxonium ion oxygen leads to the observed diastereomer (**2**). An isoelectronic model of intermediate **6b** is the next highest in energy, reaction of which would lead to the minor diastereomer **3**. All other model structures were calculated to lie >0.85-kcal/mol above the model for **6b**.

The cyanohydrin ethers generated from isopropyl acetals lead to diethers in a highly diastereoselective fashion; however, the products contain both an isopropyl ether and a methyl ether. There is little hope of differentiation between the two ethers if further elaboration of the molecule is desired. Although a few methods exist for the cleavage of alkyl ethers, they are harsh and not suitable for polyethers.[17] The sensitivity of the cyanohydrin ether and cyanohydrin to acidic conditions makes these cleavage procedures even more unattractive. To remedy the situation, the possibility of generating the acetals from moieties which might be more easily cleaved was explored.

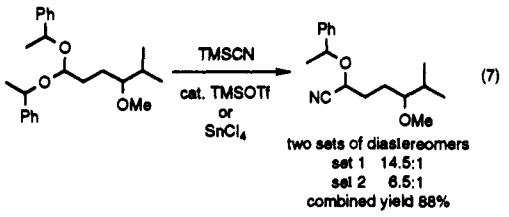
Consequently dibenzyl acetals were the next class of acetals examined. Benzyl groups are versatile alcohol protecting groups,[18]

(11) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669.
(12) (a) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765. (b) Short, P. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.
(13) Cragg, R. H.; Lane, R. D. *J. Organomet. Chem.* **1985**, *289*, 23.
(14) (a) Novak, E. R.; Tarbell, D. S. *J. Am. Chem. Soc.* **1967**, *89*, 73. (b) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 4008. (c) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 4012. (d) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (e) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III. *J. Org. Chem.* **1987**, *52*, 4191. (f) Marek, I.; Lefrancois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* **1992**, *33*, 1747.

(15) Schleyer and Kos have performed MNDO calculations indicating that the methyl group of the *O*-methyltetrahydrofuran cation lies out of the C_2–O–C_5 plane by only 8.5° and the inversion barrier is of the order of 0.1 kcal/mol.[14d]
(16) Adequate force fields for oxonium ions of the type postulated herein have not been incorporated into molecular modeling programs. Consequently, we have used molecular mechanics calculations on methyl-substituted, isoelectronic *N*-methyl-2-methoxypyrrolidines to select appropriate ground-state conformations for the intermediates described in this paper. Clearly, only crude estimates of the relative energies of intermediates can be derived from such an approach.
(17) For a review of ether cleavages see: Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; p 501.

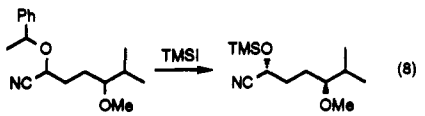
and the use of benzyl acetals would of course create a stereocenter possessing a benzyloxy group as one of the substituents. This protecting group could subsequently be cleaved by hydrogenation or selective ether-cleaving agents. The results achieved in synthesizing compounds **2i–2p** as displayed in Table I attest to the success of this protocol for remote asymmetric induction. Although the diastereoselectivities were lower than those of the isopropyl acetals, the products obtained were more useful because elaboration of the new alkoxy group could be achieved. It is important to point out that although dealkylation was a concern at the outset of these studies,[14d,e] the worry proved unnecessary. No dealkylation was observed under the reaction conditions described herein.

The *sec*-phenethyl alcohol acetal in eq 7 represents an attempt to design an acetal which would mimic the diastereoselectivity of the isopropyl group yet allow selective cleavage of the benzyl ether moiety of the final product. Reaction of this acetal with



(7)

TMSCN and catalytic TMSOTf or $SnCl_4$ (the reaction works equally well with either Lewis acid catalyst) provided the expected products. However, employing racemic *sec*-phenethyl alcohol for the overall transformation led to complications in product analysis. Because *sec*-phenethyl alcohol is chiral, the addition products possessed three stereocenters. Consequently, a total of four diastereomers were now generated. Furthermore, in the TLC analysis of the crude reaction mixture, the products eluted as two spots. These two groups of products were isolated separately and characterized. Gas chromatographic analysis of the products of higher R_f gave a 14.5:1 ratio of diastereomers, while GC analysis of the products of lower R_f indicated a 6.5:1 ratio of diastereomers. Both sets of diastereomers were isolated in roughly equal amounts. With only these data, no determination could be made concerning the overall diastereoselectivity of the process or, in fact, which diastereomer was eluting at any given R_f. Consequently, both sets of diastereomers were subjected to reaction with TMSI[19] in order to cleave the *sec*-phenethyl group and provide the trimethylsilyl cyanoethers (eq 8). The major diastereomer in each

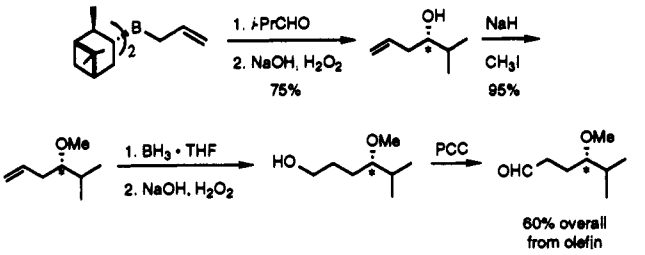


(8)

case proved to be the anti diastereomer. The overall picture was still not clear, however, because the ultimate source of asymmetric induction had not been identified. The possibility existed that the *sec*-phenethyl alcohol stereocenter on the acetal was the origin of the diastereoselectivity[20] or that this stereocenter worked in concert with the alkoxy center to produce the products with high diastereoselectivity.

In order to ascertain whether the *sec*-phenethyl group was contributing to the observed diastereoselectivity by double asymmetric induction,[21] enantiomerically enriched diastereomeric starting materials had to be synthesized and utilized for the transformation in separate reactions. Using such acetals, one could determine if the (*R*)-*sec*-phenethyl alcohol derived acetal yielded the same ratio of diastereomers or a different ratio of diastereomers

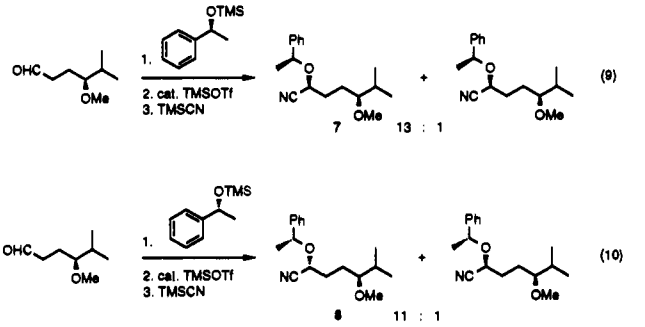
Scheme II



than the (*S*)-*sec*-phenethyl alcohol derived acetal using a stereochemically identical alkoxy aldehyde starting material in each experiment. The observation of different ratios would constitute definitive evidence for double asymmetric induction.

The preparation of the enantiomerically enriched methoxy aldehyde is described in Scheme II. The Brown asymmetric allylboration procedure[22] was utilized to provide the homoallylic alcohol in 91% enantiomeric excess (ee). This alcohol was then converted to the methyl ether by reaction with NaH and CH_3I in DMF. Hydroboration/oxidation of the olefin provided the primary alcohol, which was further oxidized to the aldehyde by pyridinium chlorochromate. This aldehyde was used in a one-pot reaction (vide infra, Protocol B) to probe for double asymmetric induction. Fortunately, both enantiomers of *sec*-phenethyl alcohol are commercially available in greater than 98% ee. Utilizing these enantiomers as their trimethylsilyl ethers in a one-pot procedure satisfied the need for enantiomerically enriched R^2OTMS components.

Equations 9 and 10 display the results of our probe for double asymmetric induction. Somewhat surprisingly, when the (*S*)-*sec*-phenethyl trimethylsilyl ether was employed (eq 9), nearly the same ratio of diastereomers was formed as for the (*R*)-*sec*-phenethyl trimethylsilyl ether (eq 10). These results affirm that



(9)

(10)

no double asymmetric induction occurs in reactions shown in eqs 7, 9, or 10; i.e., *all of the asymmetric induction is derived from the remote stereogenic center*. Additionally, the observance of two sets of spots in the TLC analysis of the reaction displayed in eq 7 is a result of (SS or RR) and (RS or SR) combinations of configurations at the newly created stereocenter and the *sec*-phenethyl stereocenter, respectively.

It proved useful at this point to examine the reaction conditions more closely, seeking experimental efficiencies that might be brought to bear on the overall process. Typically, a 0.1 M solution of an acetal in CH_2Cl_2 was cooled to −78 °C, and the nucleophile was added. Following the addition of the nucleophile, the Lewis acid was added and the reaction was stirred until TLC analysis indicated that the reaction was complete. This procedure shall be called Protocol A. A variation of this protocol (Protocol B) produced the same products with the same diastereomeric ratios as Protocol A but eliminated the need for isolating the acetal from which the products were derived. Protocol B took advantage of the fact that an intermediate oxocarbenium ion could be generated in situ from an aldehyde without first isolating an acetal.[23] To illustrate, the Noyori method for formation of an acetal from an

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(22) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1991**, *56*, 401.
(23) Mekhalfia, A.; Marko, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779.

Table II. 1,4-Relative Asymmetric Induction: Protocol B

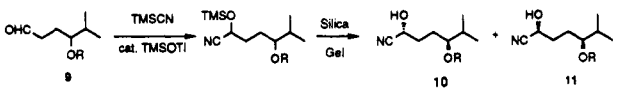
product	R	R^1	R^2	nucleophile	Lewis acid	diastereomeric ratio[a] (2:3)	% isoltd yield (2 + 3)
2j	Me	*n*-Bu	Bn	TMSCN	$SnCl_4$	6:1	92
2q	Me	cyclohexyl	Bn	allyltributylstannane	TMSOTf	7:1	55

[a] Determined by GC analysis on the crude reaction mixture using fused-silica GC capillary columns.

Table III. 1,4-Relative Asymmetric Induction: Protocol C

entry	R	diastereomeric ratio (10:11)	% isoltd yield (10 + 11)
10a	Ac	1:1	80
10b	*t*-Bu(Me)$_2$Si	1:1	80
10c	allyl	7:1	70
10d	Bn	7:1	50
10e	Me	10:1	92

aldehyde requires R^2OTMS and catalytic TMSOTf in CH_2Cl_2 at −78 °C[8] and involves the same oxocarbenium ion generated by treating an acetal with TMSOTf. If indeed the ionization of the acetal to the intermediate oxocarbenium ion is the first step in the addition of a nucleophile to an acetal under Lewis acid catalysis, then it would seem unnecessary to isolate the acetal at all. A simple modification of the nucleophilic addition procedure is described. An appropriate γ-alkoxy aldehyde and R^2OTMS in CH_2Cl_2 was cooled to −78 °C, and the nucleophile was added. Following the addition of the nucleophile, TMSOTf was added. From this point the procedure was exactly the same as Protocol A. Without the necessity to isolate an acetal (with a tedious purification), the versatility of the newly developed method for 1,4-asymmetric induction via neighboring group participation increases. Table II displays results obtained using Protocol B. Ready comparison of these products to those prepared via Protocol A illustrates Protocol B's utility. Moreover, if the next step in a synthesis involving the chemistry discussed here is cleavage of the protected alcohol, then even this step can be eliminated, further simplifying the synthetic route to the target. This modification is identified as Protocol C. γ-Alkoxy aldehydes are sufficiently electrophilic that participation occurs when they are treated with TMSOTf. This participation generates an oxonium ion resembling a trimethylsilyl-protected hemiacetal. This intermediate reacts with TMSCN to provide trimethylsilyl-protected cyanohydrins. A simple aqueous workup yields the parent cyanohydrin (eq 11). The advantage is that Protocol C enables the direct isolation of the parent alkoxy cyanohydrin and avoids a deprotection step. Table III lists the cyanohydrins prepared via Protocol C.



(11)

Protocol C was employed to provide evidence that neighboring group participation was responsible for the observed 1,4-asymmetric induction. Three of the aldehydes in Table III have alkyl ethers as participating groups (specifically, allyl, methyl, and benzyl ethers). In each of these cases the resultant diastereoselectivities were on the order of the previously discussed levels. However, the two aldehydes containing either the acetate or the *tert*-butyldimethylsiloxy group provided a 1:1 ratio of diastereomers when treated with TMSCN and TMSOTf. In the case of the *tert*-butyldimethylsiloxy participating group, both steric and electronic arguments surface for the lack of its participation. Jorgensen and co-workers have performed calculations modeling silyl ethers.[24] One of the conclusions from this study was that silicon may reduce the Lewis basicity of the bound oxygen. If these calculations accurately describe the Lewis basicity of silyl ethers, then one might expect that participation of the *tert*-butyldimethylsilyl group would be diminished in the intramolecular solvation processes described as compared to that of alkyl ethers.

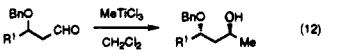
The second argument against participation is based purely on steric hindrance. Eliel and co-workers maintain that silyl ethers are just as basic as alkyl ethers but that their inability to complex is owed entirely to steric hindrance.[4] In either case, the *tert*-butyldimethylsiloxy group was not anticipated to solvate the oxocarbenium ion, and this expectation was born out in the lack of diastereoselectivity observed.

In the case of the acetate group, low diastereoselectivity was expected because intramolecular solvation would have to take place via an entropically disfavored seven-membered ring. Because neither acetate nor *tert*-butyldimethylsiloxy groups were selective, these results provide further evidence that neighboring group participation is the means by which high asymmetric induction is achieved in these nucleophilic addition reactions.

Besides the nature of the acetal, another factor influencing the degree of asymmetric induction is the size of the alkyl substituent on the directing stereocenter (R^1). If the acetals of a homologous series where R^1 is varied are subjected to identical reaction conditions, the steric effect of R^1 can be seen. Alkyl substituents having α branching usually lead to greater diastereoselectivity (Table I, Series **2a–2f** and **2i–2n**), although the effect is certainly not dramatic.

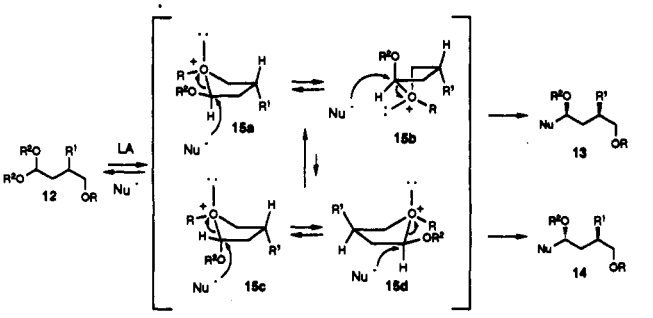
An assessment of the role of the nucleophile and the Lewis acid in these reactions is less straightforward, and indeed a systematic, thorough investigation was not carried out along these lines. In general, however, the combination of allylstannane/TMSOTf appeared comparable to that of TMSCN/$SnCl_4$ (Table I, **2k** and **2o**, **2n** and **2q**). Although only limited investigations were performed, these indicated that allyltrimethylsilane/$SnCl_4$ was decidedly inferior to TMSCN/$SnCl_4$ in terms of diastereoselectivity (Table I, **2g**, **2h**), and thus further studies with allylsilanes were not carried out. In promoting reactions of TMSCN, TMSOTf and $SnCl_4$ appeared to be equally effective Lewis acid promoters (eq 7).

1,3-Asymmetric Induction. After exploring 1,4-asymmetric induction, an examination of 1,3-asymmetric induction was undertaken. In cases of chelation control, the products of 1,3-asymmetric induction are substituted as shown in eq 12.[2b,n,25] If



(12)

the substitution pattern of these products is compared to that of the products obtained by 1,3-asymmetric induction via neighboring group participation (eq 13), one recognizes that the Lewis basic



(13)

group OR is placed one carbon further removed from the stereocenter in the latter operation. This particular substitution pattern is very difficult to access in a highly diastereoselective

(24) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

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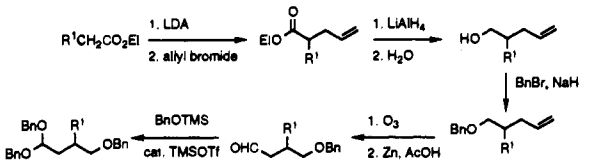
Table IV. 1,3-Relative Asymmetric Induction: Protocol A

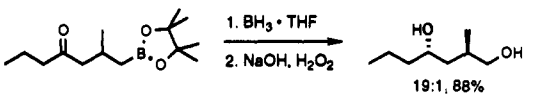
product	R	R^1	R^2	nucleophile	Lewis acid	diastereomeric ratio[a] (13:14)	% isoltd yield (13 + 14)
13a	Bn	Me	Bn	allyltributylstannane	TMSOTf	11:1	92
13b	Bn	*i*-Pr	Bn	allyltributylstannane	TMSOTf	19:1	86
13c	Bn	Me	Bn	TMSCN	$SnCl_4$	6:1	90
13d	Bn	Ph	Bn	TMSCN	$SnCl_4$	4:1	87
13e	Bn	*i*-Pr	Bn	TMSCN	$SnCl_4$	10:1	89

[a] Determined by GC analysis on the crude reaction mixture using fused-silica GC capillary columns.

Scheme III

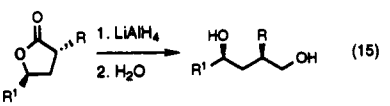


fashion.[26] Recently, Bobbitt, Murray, and Molander reported an anti selective procedure which afforded compounds possessing the same substitution pattern as the products in eq 13.[27] In that study, keto boronates were reduced with borane and the reaction mixture was subsequently oxidized with NaOH and H_2O_2 to provide the diol (eq 14). By the keto boronate reduction protocol



(14)

the desired diols were obtained in very good yields (71–92%) with diastereoselectivities ranging from 19:1 to 60:1, thus providing diols of anti stereochemistry in a very straightforward fashion. A stereochemically complementary alternative to this procedure is outlined in eq 15. Alkylation of 5-substituted butyrolactones



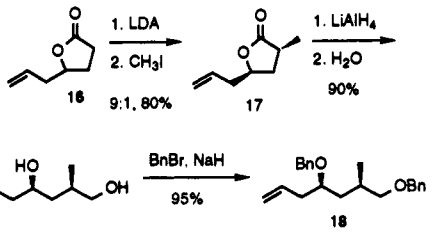
(15)

provides predominantly trans-3,5-disubstituted lactones.[28] Reduction of these lactones provides 1,4-diols in 70% to 90% yields, with diastereoselectivities ranging from 5:1 to 15:1 in favor of the syn diastereomer.

The protocol for 1,3-asymmetric induction by neighboring group participation followed that developed previously for 1,4-asymmetric induction. The acetals were prepared via the route shown in Scheme III. Alkylation of an appropriate ester with LDA and allyl bromide provided an unsaturated ester.[29] This ester was reduced by $LiAlH_4$ to the alcohol, which was transformed into the participating group. Subsequent ozonolysis of the olefin to the aldehyde and conversion to the acetal as described above[8] yielded the requisite β-alkyl-γ-alkoxy acetal.

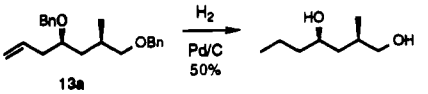
The use of an appropriately substituted acetal under the standard reaction conditions (Protocol A) formed products in which the syn diastereomer predominated (eq 13). Table IV displays the yields and ratios of compounds generated by 1,3-asymmetric induction via neighboring group participation. As in the 1,4-asymmetric induction case, utilization of sterically bulky R^1 groups led to higher diastereoselectivities.

Scheme IV



The stereochemistry of the major diastereomer was determined to be syn by two different means. In the first, **13a** was compared to the syn diastereomer **18** prepared by the butyrolactone protocol mentioned previously (Scheme IV). Lactone **16** was alkylated to provide the trans-3,5-disubstituted lactone **17** in 80% yield as a 9:1 mixture of diastereomers.[28] This lactone was then reduced with $LiAlH_4$ to provide the corresponding diol in 90% yield. Treatment of this diol with NaH and benzyl bromide in DMF afforded **18** as the major diastereomer. Analysis of **18** by ^{13}C NMR confirmed that it was identical in every respect to **13a**.

In addition to the structure proof discussed above for the products of 1,3-asymmetric induction, another exercise was carried out which further supported the stereochemical assignment of the major diastereomer. As mentioned previously, the keto boronate reduction method provided a means to prepare the anti diastereomeric series of compounds otherwise analogous to those synthesized by the present procedure.[27] The synthesis of the requisite diol for comparison to **13a** is outlined in eq 14. Compound **13a** itself was prepared by the procedure described herein utilizing the concept of neighboring group participation as a stereochemical control element. Allyltributylstannane addition to the acetal in eq 13 (R^1 = Me, R = R^2 = Bn) yielded the bis(benzyloxy) olefin in 92% yield as an 11:1 mixture of diastereomers (**13a** predominating). The syn diol was produced by exhaustive hydrogenation of **13a** (eq 16). Spectroscopic analysis clearly showed that the product generated by this process and that utilizing the keto boronate reduction protocol were diastereomeric, thereby confirming the structural assignments and further establishing that the two procedures were indeed stereochemically complementary.



(16)

Molecular modeling studies were again performed to elucidate these results, with the recognition that such explanations would be highly speculative because of the inadequacy of our model system, not to mention the fact that they model ground-state intermediates and not transition states. Nevertheless, these calculations revealed that the lowest energy conformation of the isoelectronic pyrrolidine model of **15a** would constitute 77% of the equilibrium mixture at −78 °C, leading to the observed major (syn) diastereomer upon S_N2-type displacement of the oxonium ion oxygen by the nucleophile (eq 13). The next set of intermediates (pyrrolidine analogues of **15b–d**) are clustered at energies >0.61-kcal/mol higher in energy. One member of this latter set (**15b**) would lead to the major diastereomer by the same S_N2-type process, while reaction of the other two (**15c** and **15d**) would provide the minor (anti) diastereomer.

As with 1,4-asymmetric induction, Protocol B can be applied to 1,3-asymmetric induction. The results are outlined in Table

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(28) (a) Nishida, Y.; Konno, M.; Ohrui, H.; Meguro, H. *Agric. Biol. Chem.* **1986**, *50*, 187. (b) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. (c) Maier, M. E.; Schoffling, B. *Tetrahedron Lett.* **1991**, *32*, 53.

(29) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.

Table V. 1,3-Relative Asymmetric Induction: Protocol B

product	R	R^1	R^2	nucleophile	Lewis acid	diastereomeric ratio[a] (13:14)	% isoltd yield (13 + 14)
13b	Bn	*i*-Pr	Bn	allyltributylstannane	TMSOTf	22:1	91
13e	Bn	*i*-Pr	Bn	TMSCN	$SnCl_4$	12:1	90
13a	Bn	Me	Bn	allyltributylstannane	TMSOTf	11:1	68
13c	Bn	Me	Bn	TMSCN	$SnCl_4$	6:1	61

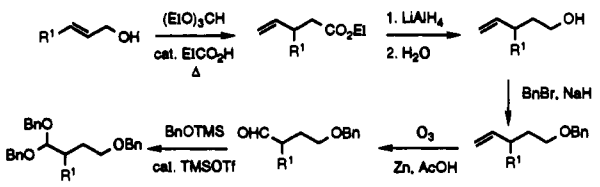
[a] Determined by GC analysis on the crude reaction mixture using fused-silica GC capillary columns.

Table VI. 1,2-Relative Asymmetric Induction: Protocol A

product	R	R^1	R^2	nucleophile	Lewis acid	diastereomeric ratio[a] (20:21)	% isoltd yield (20 + 21)
20a	Bn	Me	Bn	allyltributylstannane	TMSOTf	1:1	81
20b	Bn	*i*-Pr	Bn	allyltributylstannane	TMSOTf	4:1	70
20c	Bn	Me	Bn	TMSCN	$SnCl_4$	3:1	74
20d	Bn	*i*-Pr	Bn	TMSCN	$SnCl_4$	12:1	72

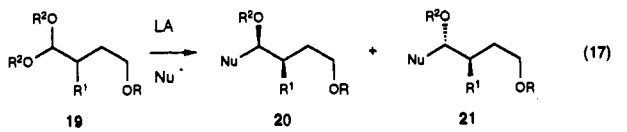
[a] Determined by GC analysis on the crude reaction mixture using fused-silica GC capillary columns.

Scheme V



V. If a comparison of Tables IV and V is made, one finds the ratio of diastereomers to be nearly identical. It was gratifying to learn that Protocol B was extendable to 1,3-asymmetric induction, because the formation of the required benzyl acetals was plagued with a tedious chromatographic resolution. Consequently, one can simply avoid this step by utilizing Protocol B.

1,2-Asymmetric Induction. The next logical step in the study was to determine whether or not we could take advantage of the cyclic oxonium ion to control 1,2-asymmetric induction (eq 17).

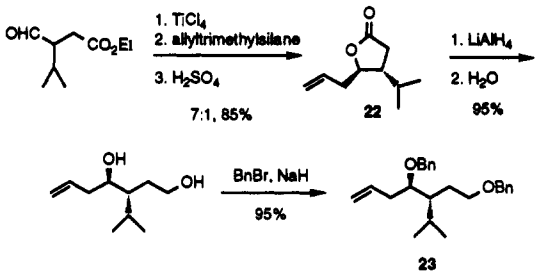


Accordingly, substrates were prepared having an alkyl group α to the acetal via the route described in Scheme V. Appropriate allylic alcohols were warmed in triethyl orthoformate using propionic acid as a catalyst. During the course of the reaction, ethanol was distilled from the reaction mixture. The resulting Claisen[30] rearrangement product was reduced by $LiAlH_4$ to the primary alcohol. Benzyl bromide and NaH were used to convert the alcohol to the benzyl ether. The resulting benzyloxy olefin was oxidized to the corresponding aldehyde by ozone, and this material was carried on to make the acetal as described previously. Treatment of these acetals with either TMSCN and $SnCl_4$ or allyltributylstannane and TMSOTf provided the expected products. The results are summarized in Table VI.

The major diastereomer was determined to be syn by the following analysis (Scheme VI). Lactone **22** was generated by the addition of allyltrimethylsilane to the chelated formyl ester[31] with subsequent acidic workup. This predominantly trans-4,5-disubstituted lactone was reduced by $LiAlH_4$ to the diol. Treatment of the diol with NaH and benzyl bromide yielded **23**. Spectroscopic examination of **23** in comparison to that of **20b** revealed that they were diastereomers. Consequently **20b** was assigned the syn configuration, and major products from other selective reactions (**20c** and **20d**) were assigned syn by analogy.

The results in Table VI indicate that reactions generating **20b** and **20c** exhibit only slightly better stereoselectivity than Cram or Felkin–Ahn selectivity for the addition of nucleophiles to α-substituted aldehydes.[32] In addition, **20a** shows no selectivity and **20d** is far outside the range of the other entries in Table VI. Calculations on an isoelectronic pyrrolidine model were far less useful in this case than in the case of the previous substrates. Although one set of intermediates was calculated to predominate (80:20 equilibrium mixture at −78 °C), a complication in modeling the transition states in this series derives from a consideration of the approach trajectory of the nucleophile. Because the nucleophile must pass along a trajectory more or less parallel to the substituent adjacent to the alkoxy group (R^1) for reaction to take place via a cyclic oxonium ion intermediate, a steric interaction on the order of an eclipsed butane interaction is created. Thus the transition-state energies would be expected to rise or fall substantially depending on the critical approach angle of the nucleophile. The many uncertainties involved in the model systems combined with the extremely low diastereoselectivities generates little confidence in any postulations concerning viable intermediates in these cases. In fact, because the nucleophile must approach along such a highly hindered trajectory in the cyclic oxonium ion intermediates, reactions proceeding via acyclic intermediates may intercede, leading to the low diastereoselectivities observed.

Scheme VI



Conclusions

Prior to this study, the process of chelation control for predictable 1,4-asymmetric induction was of singular importance. As demonstrated here, γ-alkoxy acetals and aldehydes undergo diastereoselective addition reactions when catalyzed by the nonchelating Lewis acid TMSOTf. The magnitude of remote asymmetric induction developed in this study compares well with the handful of chelation control methods reported in the literature. Neighboring group participation thus provides a viable route to 1,3- and 1,4-asymmetric induction for carbon–carbon bond-forming reactions, while 1,2-asymmetric induction is minimal. Diastereomeric ratios of up to 15:1 have been obtained for 1,4-asymmetric induction. Similarly, outstanding diastereoselectivity for 1,3-asymmetric induction has been realized utilizing neighboring group participation. Freed from the constraint of metal ion chelation, this method provides an inroad to diastereomerically enriched substituted 1,4-diol derivatives.

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Experimental Section

IR spectra were recorded on an FT-IR spectrophotometer. ^1H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, unless indicated otherwise. $CDCl_3$ was employed as the solvent for both ^1H and ^{13}C NMR, with $CHCl_3$ as the reference for ^1H NMR and $CDCl_3$ as the reference for ^{13}C NMR. Capillary GC analyses were performed on a 25 m × 320 μm 5% phenyl SE-54 fused-silica column. Low-resolution and exact mass spectra were recorded with perfluorokerosene as the internal standard. Standard flash chromatography procedures were followed with silica gel.[33] Standard bench-top techniques were employed for handling air-sensitive reagents, and all reactions were carried out under Ar.[34]

General Procedure for Addition of Nucleophiles to Acetals. Protocol A: A 10-mL round-bottomed flask containing a magnetic stirring bar was charged with an acetal (0.5 mmol) and CH_2Cl_2 (5 mL). Under a stream of Ar, this solution was cooled to −78 °C and the nucleophile (0.55 mmol) was added followed by the Lewis acid (0.05 mmol). The reaction was quenched with 1 N KOH when judged complete by TLC. The crude product was eluted from silica gel by a mixture of hexanes/EtOAc (10:1) and Kugelrohr distilled to provide the product as a mixture of diastereomers. Protocol B: A 10-mL round-bottom flask containing a magnetic stir bar was charged with an aldehyde (0.5 mmol), R^2OTMS (1.0 mmol), and CH_2Cl_2 (5 mL). Under a stream of Ar, this solution was cooled to −78 °C and TMSOTf (0.50 mmol) was added followed by the nucleophile (0.55 mmol). The reaction was quenched with 1 N KOH when judged complete by TLC. The crude product was eluted from silica gel by a mixture of hexanes/EtOAc (10:1) and Kugelrohr distilled to provide the product as a mixture of diastereomers. Protocol C: A 10-mL round-bottom flask containing a magnetic stir bar was charged with an aldehyde (0.5 mmol) and CH_2Cl_2 (5 mL). Under a stream of Ar, this solution was cooled to −78 °C and the nucleophile (0.55 mmol) was added followed by the Lewis acid (0.05 mmol). The reaction was quenched with silica gel (1 g) when judged complete by TLC. The crude product was eluted from silica gel by a mixture of hexanes/EtOAc (10:1) and Kugelrohr distilled to provide the product as a mixture of diastereomers.

Compounds **2t** and **10a–e** were too unstable to obtain either combustion analysis or suitable high-resolution (exact mass) spectra.

(2*R,5*R**)-2-Isopropoxy-5-methoxyhexanenitrile (2a).** Isolated by flash chromatography in 96% yield as a 5.2:1 mixture of diastereomers; estimated purity ≥95% by ^{13}C NMR. ^1H NMR: δ 4.19 (t, *J* = 6.4 Hz, 1 H), 3.83 (sept, *J* = 8 Hz, 1 H), 3.28 (m, 1 H), 3.25 (s, 3 H), 2.00–1.75 (m, 2 H), 1.69–1.56 (m, 2 H), 1.33 (d, *J* = 8 Hz, 3 H), 1.15 (d, *J* = 8 Hz, 3 H), 1.13 (d, *J* = 8 Hz, 3 H). ^{13}C NMR: δ 119.0, 76.2, 72.3, 66.3, 55.9, 31.4, 30.1, 22.6, 20.9, 18.8. IR ($CDCl_3$): 2963, 2915, 2805, 1451, 1360, 1323, 1079, 951 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.81; H, 10.34. Found: C, 64.11; H, 10.41.

(2*R,5*R**)-2-Isopropoxy-5-methoxynonanenitrile (2b).** Isolated by flash chromatography in 95% yield as a 5:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 4.19 (t, *J* = 6.1 Hz, 1 H), 3.84 (sept, *J* = 6.1 Hz, 1 H), 3.30 (s, 3 H), 3.17 (m, 1 H), 1.96–1.25 (m, 10 H), 1.23 (d, *J* = 6.1 Hz, 3 H), 1.14 (d, *J* = 6.1 Hz, 3 H), 0.88 (t, *J* = 6.88 Hz, 3 H). ^{13}C NMR: δ 119.0, 80.1, 72.2, 66.2, 56.4, 32.8, 29.8, 28.4, 27.3, 22.8, 22.6, 20.9, 14.0. IR ($CDCl_3$): 2975, 2924, 2831, 2479, 1449, 1085, 975 cm^{-1}. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.67; H, 11.09. Found: C, 68.42; H, 11.09.

(2*R,5*S**)-6,6-Dimethyl-2-isopropoxy-5-methoxyheptanenitrile (2c).** Isolated by flash chromatography in 95% yield as a 6:1 mixture of diastereomers; estimated purity ≥95% by ^{13}C NMR. ^1H NMR: δ 4.15 (t, *J* = 5.37 Hz, 1 H), 3.82 (sept, *J* = 6.10 Hz, 1 H), 3.42 (s, 3 H), 2.69 (dd, *J* = 2.44, 9.77 Hz, 1 H), 2.08–1.41 (m, 4 H), 1.23 (d, *J* = 6.10 Hz, 3 H), 1.14 (d, *J* = 6.10 Hz, 3 H), 0.86 (s, 9 H). ^{13}C NMR: δ 119.0, 89.9, 72.3, 66.4, 61.4, 36.0, 31.8, 26.5, 26.1, 22.6, 20.9. IR ($CDCl_3$): 2972, 2874, 2828, 2644, 2255, 1481, 1107, 914 cm^{-1}. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.67; H, 11.09. Found: C, 67.86; H, 11.04.

(2*R,5*S**)-2-Isopropoxy-5-methoxy-5-phenylpentanenitrile (2d).** Isolated by flash chromatography in 93% yield as a 6:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 7.24 (m, 5 H), 4.15 (m, 2 H), 3.78 (sept, *J* = 6.25 Hz, 1 H), 3.18 (s, 3 H), 2.00–1.65 (m, 4 H), 1.19 (d, *J* = 6.25 Hz, 3 H), 1.08 (d, *J* = 6.25 Hz, 3 H). ^{13}C NMR: δ 141.0, 128.0, 127.0, 126.0, 119.0, 83.2, 72.1, 65.9, 56.7, 33.3, 31.5, 30.6, 22.6, 20.8, 14.1. IR ($CDCl_3$): 3074, 3034, 2983, 2942, 2831, 1456, 1388, 1331, 1112 cm^{-1}. HRMS Calcd for $C_{15}H_{21}NO_2$: 247.1567. Found: 247.1572.

(2*R,5*S**)-2-Isopropoxy-5-methoxy-6-methylheptanenitrile (2e).** Isolated by flash chromatography in 97% yield as a 15:1 mixture of diastereomers. ^1H NMR: δ 4.16 (t, *J* = 5.86 Hz, 0.91 H), 4.05 (t, *J* = 5.86 Hz, 0.09 H), 3.83 (sept, *J* = 5.86 Hz, 1 H), 3.45 (s, 0.18 H), 3.30 (s, 2.82 H), 2.87 (m, 1 H), 1.97–1.47 (m, 5 H), 1.21 (d, *J* = 6.35 Hz, 3 H), 1.12 (d, *J* = 5.86 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR: δ 119.0, 85.5, 72.2, 66.3, 57.5, 30.2, 25.1, 22.6, 20.9, 18.4, 17.4, 15.2. IR ($CDCl_3$): 2951, 2230, 1429, 1358, 1059, 871, 692, 636 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.55; H, 10.87. Found: C, 67.16; H, 10.77.

(2*R,5*S**)-2-Isopropoxy-5-cyclohexyl-5-methoxypentanenitrile (2f).** Isolated by flash chromatography in 100% yield as a 10:1 mixture of diastereomers. ^1H NMR: δ 4.19 (t, *J* = 6.11 Hz, 1 H), 3.82 (sept, *J* = 6.11 Hz, 1 H), 3.30 (s, 3 H), 2.90 (m, 1 H), 2.00–1.30 (m, 11 H), 1.10 (d, *J* = 6.10 Hz, 3 H), 1.21 (d, *J* = 5.86 Hz, 5 H), 0.95 (m, 2 H). ^{13}C NMR: δ 119.0, 84.9, 72.2, 66.4, 57.7, 40.5, 30.1, 29.0, 28.2, 26.5, 26.3, 25.5, 22.6, 20.9. IR ($CDCl_3$): 2975, 2925, 2850, 2238, 1444, 1381, 1325, 1091, 988 cm^{-1}. Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.09; H, 10.75. Found: C, 70.70; H, 10.65.

(2*R,5*S**)-2-(1,3-Dichloroisopropoxy)-5-methoxy-6-methylheptanenitrile (2g).** Isolated by flash chromatography in 89% yield as an 11:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 4.4 (dd, *J* = 5.86, 12.5 Hz, 1 H), 3.97 (m, 1 H), 3.69 (m, 4 H), 3.32 (s, 3 H), 2.91 (m, 1 H), 1.99–1.56 (m, 5 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR: δ 118.17, 85.47, 78.84, 68.77, 57.45, 42.78, 42.74, 30.15, 29.81, 24.66, 18.47, 17.16. IR (thin film): 2962.3, 2825.1, 1442.7, 1386.8, 1367.9, 1328.1, 1290.3, 1261.1, 1190.2, 1147.8, 1093.3, 983.1, 956.5, 889.4, 830.8, 761.8, 705.6, 608.0 cm^{-1}. Anal. Calcd for $C_{12}H_{21}Cl_2NO_2$: C, 51.05; H, 7.50. Found: C, 51.02; H, 7.79.

(4*R,7*S**)-4-(1,3-Dichloroisopropoxy)-7-methoxy-8-methylnon-1-ene (2h).** Isolated by flash chromatography in 92% yield as a 6:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 5.79 (m, 1 H), 5.07 (d, *J* = 17 Hz, 1 H), 5.06 (d, *J* = 10 Hz, 1 H), 3.75 (m, 1 H), 3.61 (m, 4 H), 3.45 (m, 1 H), 3.32 (s, 3 H), 2.85 (m, 1 H), 2.27 (t, *J* = 7.1 Hz, 2 H), 1.86–1.33 (m, 5 H), 0.86 (dd, *J* = 7.1, 7.1 Hz, 6 H). ^{13}C NMR: δ 134.37, 117.51, 86.30, 79.69, 77.05, 57.56, 43.69, 43.54, 38.95, 30.38, 30.13, 25.71, 18.27, 17.59. IR (thin film): 3076.6, 2958.8, 2821.1, 1385.3, 1287.7, 1148.8, 1641.0, 1366.5, 1254.2, 1094.3, 1463.2, 1441.1, 1346.4, 1329.0, 1209.2, 1188.8, 992.5, 916.7, 859.8, 744.5, 702.0, 651.7 cm^{-1}. Anal. Calcd for $C_{14}H_{26}Cl_2O_2$: C, 56.54; H, 8.82. Found: C, 56.83; H, 8.84.

(2*R,5*R**)-2-(Benzyloxy)-5-methoxyhexanenitrile (2i).** Isolated by flash chromatography in 97% yield as a 4:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 7.34 (b s, 5 H), 4.83 (d, *J* = 11.6 Hz, 1 H), 4.51 (d, *J* = 11.6 Hz, 1 H), 4.17 (t, *J* = 6.4 Hz, 1 H), 3.27 (b s, 4 H), 1.97–1.55 (m, 4 H), 1.11 (d, *J* = 6.1 Hz, 3 H). ^{13}C NMR: δ 135.95, 128.54, 128.31, 128.10, 118.23, 75.67, 72.09, 67.52, 55.86, 31.19, 29.36, 18.71. IR (thin film): 2971.0, 2930.4, 2822.9, 1456.0, 1086.5, 741.2, 698.8 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21. Found: C, 71.88; H, 8.24.

(2*R,5*R**)-2-(Benzyloxy)-5-methoxynonanenitrile (2j).** Isolated by flash chromatography in 94% yield as a 4:1 mixture of diastereomers. ^1H NMR (250 MHz, $CDCl_3$): δ 7.34 (m, 5 H), 4.83 (d, *J* = 11.6 Hz, 1 H), 4.50 (d, *J* = 11.6 Hz, 1 H), 4.18 (t, *J* = 6.4 Hz, 1 H), 3.28 (s, 3 H), 3.15 (m, 1 H), 2.05–1.20 (m, 10 H), 0.88 (t, *J* = 0.65 Hz, 3 H). ^{13}C NMR: δ 135.96, 128.53, 128.29, 128.09, 118.21, 79.83, 72.08, 67.62, 56.28, 32.70, 29.13, 28.22, 27.21, 22.67, 13.88. IR (thin film): 3032.9, 2935.4, 1497.1, 1455.6, 1378.1, 1336.2, 1207.6, 1090.2, 1028.0, 738.5, 698.8 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 73.87; H, 9.16.

(2*R,5*S**)-2-(Benzyloxy)-5-methoxy-5-phenylpentanenitrile (2k).** Isolated by flash chromatography in 82% yield as a 3.5:1 mixture of diastereomers. ^1H NMR: δ 7.33 (m, 10 H), 4.80 (d, *J* = 11.6 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 4.16–4.07 (m, 2 H), 3.17 (s, 3 H), 2.00–1.82 (m, 4 H). ^{13}C NMR: δ 141.30, 135.85, 128.54, 128.51, 128.42, 128.17, 128.14, 126.39, 118.14, 82.82, 72.04, 67.25, 56.48, 32.97, 29.79. IR (thin film): 3063.3, 3030.6, 2930.7, 2871.1, 2823.0, 1494.9, 1454.0, 1355.9, 1336.0, 1310.9, 1208.4, 1098.1, 1027.4, 950.5, 915.4, 742.2, 700.1 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17. Found: C, 77.08; H, 7.31.

(2*R,5*S**)-2-(Benzyloxy)-5-methoxy-6-methylheptanenitrile (2l).** Isolated by flash chromatography in 94% yield as an 8:1 mixture of diastereomers. ^1H NMR: δ 7.73 (m, 5 H), 4.82 (d, *J* = 12 Hz, 1 H), 4.50 (d, *J* = 12 Hz, 1 H), 4.17 (t, *J* = 6.8 Hz, 1 H), 3.30 (s, 3 H), 2.87 (m, 1 H), 1.99–1.50 (m, 5 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR: δ 135.99, 128.58, 128.34, 128.15, 128.20, 118.29, 85.29, 72.13, 67.70, 57.42, 29.90, 29.65, 24.92, 18.36, 17.34. IR (thin film): 2960.8, 2932.7, 2873.3, 2823.1, 1497.5, 1456.1, 1387.3, 1367.4, 1334.6, 1244.0, 1206.8, 1094.2, 1027.8, 938.1, 739.2, 698.5, 611.9, 551.8 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.51; H, 8.88. Found: C, 73.24; H, 9.11.

(2*R,5*S**)-2-(Benzyloxy)-6,6-dimethyl-5-methoxyheptanenitrile (2m).** Isolated by flash chromatography in 91% yield as a 6.5:1 mixture of

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diastereomers. ^{1}H NMR: δ 7.34 (b s, 5 H), 4.84 (d, J = 11.7 Hz, 1 H), 4.51 (d, J = 11.7 Hz, 1 H), 4.13 (dd, J = 5.6, 7.3 Hz, 1 H), 3.40 (s, 3 H), 2.66 (dd, J = 2.7, 9.7 Hz, 1 H), 2.05 (m, 1 H), 1.87 (m, 1 H), 1.71 (m, 1 H), 1.46 (m, 1 H), 0.86 (s, 9 H). ^{13}C NMR: δ 135.93, 128.60, 128.39, 128.22, 118.25, 89.71, 72.16, 67.68, 61.36, 35.93, 31.12, 26.43, 26.12. IR (thin film): 3033.0, 2960.1, 2826.6, 1497.1, 1480.6, 1455.4, 1393.8, 1362.7, 1336.8, 1244.0, 1208.3, 1181.7, 1106.3, 1027.6, 944.7, 740.4, 699.0 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 74.23; H, 9.03.

(2*R,5*S**)-2-(Benzyloxy)-5-cyclohexyl-5-methoxypentanenitrile (2n).** Isolated by flash chromatography in 75% yield as a 6.5:1 mixture of diastereomers. ^{1}H NMR: δ 7.34 (b s, 5 H), 4.83 (d, J = 11.5 Hz, 1 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.17 (t, J = 6.3 Hz, 1 H), 3.29 (s, 3 H), 2.87 (m, 1 H), 1.97–0.92 (m, 15 H). ^{13}C NMR: δ 135.99, 128.58, 128.34, 128.15, 118.29, 84.71, 72.14, 67.75, 57.55, 40.35, 29.46, 28.95, 28.10, 26.46, 26.18, 25.29. IR (thin film): 3064.8, 3032.4, 2925.1, 2850.4, 1496.9, 1453.6, 1392.7, 1369.7, 1336.1, 1260.4, 1208.2, 1179.1, 1145.9, 1095.3, 1028.0, 962.0, 912.4, 891.3, 843.6, 740.4, 698.7 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.70; H, 9.03. Found: C, 75.84; H, 8.95.

(4*R,7*S**)-4-(Benzyloxy)-7-methoxy-7-phenylhept-1-ene (2o).** ^{1}H NMR: δ 7.30 (m, 10 H), 5.82 (m, 1 H), 5.06 (d, J = 14 Hz, 1 H), 5.04 (d, J ≈ 6.6 Hz, 1 H), 4.52 (d, J = 11.5 Hz, 1 H), 4.43 (d, J = 11.5 Hz, 1 H), 4.05 (t, J = 6.3 Hz, 1 H), 3.43 (m, 1 H), 3.19 (s, 3 H), 2.32 (m, 2 H), 1.85–1.40 (m, 4 H). ^{13}C NMR: δ 142.24, 138.74, 134.81, 128.36, 128.30, 127.77, 127.50, 127.46, 126.67, 116.99, 84.08, 78.36, 70.82, 56.57, 38.22, 33.87, 29.99. IR (thin film): 3060.3, 3025.0, 2919.2, 2848.7, 1495.9, 1454.8, 1349.0, 1090.5, 908.3, 732.1, 696.8 cm^{-1}. HRMS Calcd for $C_{21}H_{26}O_2$: 310.1911. Found: 310.1915.

(4*R,7*S**)-4-(Benzyloxy)-7-methoxy-8,8-dimethyl-1-nonene (2p).** Isolated by flash chromatography in 60% yield as an 8:1 mixture of diastereomers. Major isomer ^{1}H NMR: δ 7.35 (m, 5 H), 5.84 (m, 1 H), 5.11 (d, J = 12.5 Hz, 1 H), 5.07 (d, J = 10 Hz, 1 H), 4.59 (d, J = 11.5 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 3.43 (b s, 4 H), 2.66 (dd, J = 2.44, 9.8 Hz, 1 H), 2.35 (t, J = 6.1 Hz, 2 H), 1.90–1.20 (m, 4 H), 0.87 (s, 9 H). ^{13}C NMR: δ 138.82, 134.89, 128.27, 127.46, 116.93, 90.76, 78.94, 70.98, 61.26, 38.39, 35.91, 31.64, 27.17, 26.20. IR (thin film): 2953.0, 2866.9, 1453.5, 1360.3, 1346.8, 1098.8, 1027.8, 993.5, 911.1, 734.8, 695.9 cm^{-1}. HRMS Calcd for $C_{19}H_{31}O_2$ (M + 1): 291.2324. Found: 291.2335.

(4*R,7*S**)-4-(Benzyloxy)-7-cyclohexyl-7-methoxy-1-heptene (2q).** Isolated by flash chromatography in 77% yield as a 7:1 mixture of diastereomers. ^{1}H NMR: δ 7.35 (m, 5 H), 5.86 (m, 1 H), 5.13 (dd, J = 15.1, 1.2 Hz, 1 H), 5.07 (dd, J = 10, 0.9 Hz, 1 H), 4.85 (d, J = 11.5 Hz, 1 H), 4.50 (d, J = 11.5 Hz, 1 H), 3.44 (m, 1 H), 3.33 (s, 3 H), 2.86 (m, 1 H), 2.34 (m, 2 H), 2.80–0.95 (m, 15 H). ^{13}C NMR: δ 138.92, 135.01, 128.31, 127.78, 127.46, 116.92, 85.81, 78.87, 70.93, 57.67, 40.75, 38.36, 29.66, 28.77, 28.54, 26.63, 26.36, 26.11. IR (thin film): 3062.1, 3022.9, 2915.1, 2846.5, 1448.1, 1345.2, 1247.2, 1203.1, 1095.3, 1070.8, 869.8, 840.4, 727.7, 698.3 cm^{-1}. HRMS Calcd for $C_{21}H_{33}O_2$ (M + 1): 317.2480. Found: 317.2473.

(4*R,7*S**)-4-(Benzyloxy)-7-methoxy-8-methyl-1-nonene (2r).** Isolated by flash chromatography in 73% yield as a 9:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34 (m, 5 H), 5.85 (m, 1 H), 5.10 (d, J = 12.5 Hz, 1 H), 5.06 (d, J = 7.5 Hz, 1 H), 4.58 (d, J = 11.6 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 3.44 (m, 1 H), 3.33 (s, 3 H), 2.85 (m, 1 H), 2.34 (m, 2 H), 1.84–1.38 (m, 5 H), 0.87 (t, J = 17 Hz, 6 H). ^{13}C NMR: δ 138.87, 134.95, 128.28, 127.76, 127.44, 116.90, 86.31, 78.79, 70.88, 57.54, 38.34, 30.18, 29.80, 25.77, 18.18, 17.80. IR (thin film): 3029.8, 2930.9, 1496.1, 1385.0, 1095.8, 912.8, 734.3, 696.9 cm^{-1}. HRMS Calcd for $C_{18}H_{29}O_2$ (M + 1): 277.2167. Found: 277.2173.

(2*R,5*S**)-2-((4-Bromobenzyl)oxy)-5-methoxy-6-methylheptanenitrile (2s).** Estimated purity ≥95% by ^{13}C NMR. ^{1}H NMR: δ 7.51 (d, J = 8.5 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 4.79 (d, J = 11.7 Hz, 1 H), 4.48 (d, J = 11.7 Hz, 1 H), 4.20 (t, J = 6.4 Hz, 1 H), 3.33 (s, 3 H), 2.91 (m, 1 H), 2.10–1.45 (m, 5 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 135.09, 131.76, 129.73, 122.35, 118.13, 85.35, 71.41, 68.00, 57.45, 29.90, 29.69, 24.86, 18.43, 17.33. IR (thin film): 2960.9, 2872.6, 2822.7, 1593.4, 1488.2, 1462.9, 1407.8, 1244.8, 1144.7, 1093.2, 1011.9, 898.6, 836.4 cm^{-1}. Anal. Calcd for $C_{16}H_{22}NO_2Br$: C, 56.45; H, 6.52. Found: C, 57.00; H, 6.32.

(2*R,5*S**)-2-((4-Nitrobenzyl)oxy)-5-methoxy-6-methylheptanenitrile (2t).** ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 4.91 (d, J = 12.5 Hz, 1 H), 4.57 (d, J = 12.5 Hz, 1 H), 4.28 (t, J = 6.5 Hz, 1 H), 3.32 (s, 3 H), 2.90 (m, 1 H), 2.23–1.60 (m, 5 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 147.69, 143.57, 128.07, 123.70, 117.86, 85.31, 70.85, 68.78, 57.39, 29.79, 29.68, 24.69, 18.40, 17.22. IR (thin film): 3646.1, 3112.1, 3080.8, 2960.7, 2874.0, 2824.8, 1723.6, 1681.8, 1607.1, 1519.2, 1495.0, 1462.3, 1386.5, 1347.2, 1296.5, 1246.6, 1204.6, 1178.0, 1090.5, 1015.5 cm^{-1}.

(2*R,5*S**)-5-Methoxy-6-methyl-2-((2-methylbenzyl)oxy)heptanenitrile (2u).** Isolated by flash chromatography in 85% yield as an 8:1 mixture of diastereomers. ^{1}H NMR: δ 7.24 (m, 4 H), 4.88 (d, J = 11 Hz, 1 H), 4.54 (d, J = 11 Hz, 1 H), 4.21 (t, J = 7 Hz, 1 H), 3.34 (s, 3 H), 2.91 (m, 1 H), 2.39 (s, 3 H), 2.03–1.55 (m, 5 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 137.25, 133.92, 130.51, 129.37, 128.68, 125.93, 118.35, 85.35, 70.75, 67.77, 57.44, 29.91, 29.76, 24.97, 18.71, 18.39, 17.33. IR (thin film): 3023.4, 2962.2, 2824.6, 2252.9, 1493.2, 1463.9, 1386.6, 1367.8, 1333.9, 1188.0, 1094.2, 911.9, 734.6, 648.3 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 74.35; H, 9.12.

(4*R,7*R**)-4,7-Bis(benzyloxy)-1-decene (2v).** Isolated by flash chromatography in 86% yield as an 8:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31 (m, 10 H), 5.82 (m, 1 H), 5.08 (d, J = 9 Hz, 1 H), 5.03 (d, J = 10 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 1 H), 4.47 (s, 2 H), 4.46 (d, J = 11.6 Hz, 1 H), 3.40 (m, 2 H), 2.31 (m, 2 H), 1.75–1.25 (m, 8 H), 0.89 (t, J = 7.1 Hz, 3 H). ^{13}C NMR: δ 139.02, 138.82, 134.86, 128.21, 128.19, 127.63, 127.36, 127.30, 116.86, 78.76, 78.57, 70.77, 70.63, 38.22, 36.03, 29.27, 29.25, 18.48, 14.16. IR (thin film): 3064.6, 3029.8, 2930.0, 2889.0, 2867.8, 1640.2, 1496.1, 1453.9, 1347.3, 1319.0, 1205.4, 1066.4, 1028.0, 1013.5, 954.7, 912.3, 733.7, 696.5 cm^{-1}. HRMS Calcd for $C_{24}H_{33}O_2$ (M + 1): 353.2480. Found: 353.2469.

(2*R,5*S**)-2,5-Bis(benzyloxy)-6-methylheptanenitrile (2w).** Isolated by flash chromatography in 95% yield as a 6:1 ratio of diastereomers. ^{1}H NMR: δ 7.35 (m, 10 H), 4.83 (d, J = 11.7 Hz, 1 H), 4.53 (d, J = 11.5 Hz, 1 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 4.15 (t, J = 6.6 Hz, 1 H), 3.17 (m, 1 H), 2.20–1.50 (m, 5 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.68, 136.02, 128.64, 128.40, 128.37, 128.22, 127.79, 127.57, 118.34, 83.19, 72.19, 71.56, 67.74, 30.14, 29.59, 24.96, 18.64, 17.41. IR (thin film): 3050.6, 3013.7, 1485.3, 1417.1, 1228.9, 1165.8, 790.6, 717.5, 656.3, 531.9 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07. Found: C, 78.53; H, 8.20.

5-Acetoxy-2-hydroxy-6-methylheptanenitrile (10a). Isolated by flash chromatography in 80% yield as a 1:1 mixture of diastereomers. ^{1}H NMR: δ 4.77 (m, 1 H), 4.55 (m, 1 H), 3.10 (m, 1 H), 2.10 (s, 3 H), 1.75 (m, 5 H), 0.91 (d, J = 8.4 Hz, 6 H). ^{13}C NMR: δ 171.92, 119.92, 77.79, 60.77, 31.34, 31.04, 26.33, 20.98, 18.20, 17.49. IR (thin film): 3450.0, 2981.3, 2887.5, 1725.0, 1375.0, 1250.0, 1022.5, 975.0, 893.7 cm^{-1}.

5-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-6-methylheptanenitrile (10b). Isolated by flash chromatography in 80% yield as a 1:1 mixture of diastereomers. ^{1}H NMR: δ 4.60 (m, 1.5 H), 3.55 (m, 1 H), 3.34 (d, J = 5.4 Hz, 0.5 H), 2.17–1.60 (m, 5 H), 0.92 (s, 4.5 H), 0.88 (s, 4.5 H), 0.84 (d, J = 5.4 Hz, 3 H), 0.82 (d, J = 5.4 Hz, 3 H), 0.16 (s, 2 H), 0.08 (s, 2 H), 0.05 (s, 2 H). ^{13}C NMR: δ 120.06, 76.46, 61.55, 32.53, 31.13, 28.18, 25.92, 19.21, 18.04, 17.90, –4.34. IR (thin film): 3436.3, 2942.7, 2848.7, 1466.6, 1390.2, 1249.1, 1061.1, 831.9, 767.3 cm^{-1}.

(2*R,5*S**)-5-(Allyloxy)-2-hydroxy-6-methylheptanenitrile (10c).** Isolated by flash chromatography in 70% yield as a 7:1 mixture of diastereomers. ^{1}H NMR: δ 5.86 (m, 1 H), 5.23 (d, J = 18.5 Hz, 1 H), 5.16 (d, J = 10.3 Hz, 1 H), 4.54 (t, J = 6.8 Hz, 1 H), 4.49 (d, J = 5.6 Hz, 1 H), 3.97 (dd, J = 4.2, 5.4 Hz, 2 H), 3.11 (m, 1 H), 2.01–1.58 (m, 5 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 134.16, 120.05, 117.70, 83.69, 70.39, 61.29, 31.76, 29.51, 24.68, 18.73, 16.59. IR (thin film): 3342.3, 2860.5, 1419.6, 1108.1, 1025.9, 990.6, 920.1 cm^{-1}.

(2*R,5*S**)-5-(Benzyloxy)-2-hydroxy-6-methylheptanenitrile (10d).** Isolated by flash chromatography in 50% yield as a 7:1 mixture of diastereomers. ^{1}H NMR: δ 7.35 (m, 5 H), 4.64 (d, J = 11 Hz, 1 H), 4.25 (d, J = 11 Hz, 1 H), 4.44 (q, J = 6.8 Hz, 1 H), 4.01 (d, J = 6.8 Hz, 1 H), 3.22 (m, 1 H), 2.18–1.71 (m, 5 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H). ^{13}C NMR: δ 137.64, 128.50, 128.37, 128.10, 120.03, 83.55, 71.41, 61.20, 31.55, 29.47, 24.51, 18.79, 16.68. IR (thin film): 3424.6, 2954.5, 2872.2, 1448.9, 1067.0, 737.9, 690.9 cm^{-1}.

(2*R,5*S**)-2-Hydroxy-5-methoxy-6-methylheptanenitrile (10e).** Isolated by flash chromatography in 85% yield as a 10:1 mixture of diastereomers. ^{1}H NMR: δ 4.91 (d, J = 6.6 Hz, 1 H), 4.54 (m, 1 H), 3.35 (s, 3 H), 2.98 (m, 1 H), 2.06–1.65 (m, 5 H), 0.90 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 120.06, 86.07, 61.45, 56.81, 32.15, 28.69, 24.40, 18.81, 16.09. IR ($CDCl_3$): 2964.2, 2253.9, 1466.7, 1386.4, 1096.8, 1054.3, 907.6, 731.3, 650.4 cm^{-1}.

(4*R,6*R**)-4,7-Bis(benzyloxy)-6-methyl-1-heptene (13a).** Isolated by flash chromatography in 92% yield as an 11:1 mixture of diastereomers. Major isomer ^{1}H NMR: δ 7.30 (m, 10 H), 5.83 (m, 1 H), 5.08 (d, J = 17 Hz, 1 H), 5.05 (d, J = 9 Hz, 1 H), 4.55 (d, J = 11.5 Hz, 1 H), 4.44 (m, 2 H), 4.41 (d, J = 11.5 Hz, 1 H), 3.53 (m, 1 H), 3.28 (dd, J = 5.4, 9.0 Hz, 1 H), 3.20 (dd, J = 5.4, 9.0 Hz, 1 H), 3.20 (t, J = 6 Hz, 2 H), 1.96 (m, 1 H), 1.60–1.38 (m, 2 H), 0.95 (d, J = 6.9 Hz, 3 H). ^{13}C

NMR: δ 138.78, 138.74, 134.79, 128.23, 127.73, 127.44, 127.38, 127.34, 116.97, 76.57, 75.30, 72.82, 70.64, 38.31, 38.15, 30.13, 18.09. IR (thin film): 3029.6, 2928.1, 2857.0, 1496.0, 1453.8, 1361.4, 1205.5, 1095.9, 1028.0, 995.2, 913.1, 734.9, 696.9 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.43; H, 8.70. Found: C, 81.54; H, 8.74.

(4*R,6*S**)-4,7-Bis(benzyloxy)-6-(1-methylethyl)-1-heptene (13b).** Isolated by flash chromatography in 86% yield as an 18.4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30 (m, 10 H), 5.80 (m, 1 H), 5.10 (d, J = 11 Hz, 1 H), 5.04 (d, J = 6 Hz, 1 H), 4.56 (d, J = 11.5 Hz, 1 H), 4.39 (d, J = 11.5 Hz, 1 H), 4.45 (d, J = 13 Hz, 1 H), 4.37 (d, J = 13 Hz, 1 H), 3.50 (m, 1 H), 3.33 (d, J = 5.5 Hz, 2 H), 2.35 (m, 2 H), 1.80 (m, 2 H), 1.60-1.30 (m, 2 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.90, 138.79, 134.93, 128.21, 127.69, 127.46, 127.34, 127.32, 116.92, 76.90, 72.87, 71.38, 70.78, 40.14, 38.73, 33.15, 28.85, 19.85, 18.94. IR (thin film): 2956.1, 2886.4, 2869.8, 1453.9, 1365.2, 1094.6, 1028.0, 994.0, 912.5, 734.2, 696.6 cm^{-1}. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.76; H, 9.15. Found: C, 81.77; H, 9.13.

(2*R,4*S**)-2,5-Bis(benzyloxy)-4-methylpentanenitrile (13c).** Isolated by flash chromatography in 90% yield as a 6:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (m, 10 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.44 (d, J = 11.4 Hz, 1 H), 4.42 (s, 2 H), 4.27 (dd, J = 5.8, 8.4 Hz, 1 H), 3.27 (dd, J = 2.6, 8.7 Hz, 1 H), 3.24 (dd, J = 2.6, 8.7 Hz, 1 H), 2.20-1.65 (m, 3 H), 0.95 (d, J = 6.7 Hz, 3 H). ^{13}C NMR: δ 138.23, 135.98, 128.49, 128.29, 128.26, 128.14, 127.51, 127.48, 118.48, 74.53, 72.85, 72.12, 66.32, 37.70, 29.74, 17.28. IR (thin film): 3031.2, 2959.1, 2930.0, 2869.4, 1496.3, 1454.4, 1396.2, 1363.7, 1331.8, 1254.2, 1207.8, 1094.0, 1027.8, 912.2, 738.3, 698.7, 610.9 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.73; H, 7.72.

(2*R,4*R**)-2,5-Bis(benzyloxy)-4-phenylpentanenitrile (13d).** Isolated by flash chromatography in 87% yield as a 4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25 (m, 15 H), 4.72 (d, J = 12 Hz, 1 H), 4.43 (m, 2 H), 4.37 (d, J = 12 Hz, 1 H), 4.03 (t, J = 8.1 Hz, 1 H), 3.55 (d, J = 8.1 Hz, 2 H), 2.42 (m, 1 H), 2.21 (m, 1 H), 2.18 (m, 1 H). ^{13}C NMR: δ 140.58, 137.92, 135.86, 128.63, 128.40, 128.26, 128.17, 127.98, 127.59, 127.52, 127.45, 127.07, 118.06, 73.83, 72.83, 72.08, 66.72, 41.68, 36.41. IR (thin film): 3059.8, 3027.0, 2863.1, 1494.9, 1451.1, 1396.3, 1363.5, 1333.3, 1204.6, 1092.4, 1026.6, 911.6, 741.8, 698.0 cm^{-1}. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.82; H, 6.78. Found: C, 80.60; H, 6.75.

(2*R,4*R**)-2,5-Bis(benzyloxy)-4-(1-methylethyl)pentanenitrile (13e).** Isolated by flash chromatography in 89% yield as a 9.5:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30 (m, 10 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.36 (d, J = 5.3 Hz, 2 H), 4.28 (dd, J = 2.5, 4.2 Hz, 1 H), 3.33 (d, J = 4.8 Hz, 2 H), 2.05-1.65 (m, 4 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H). ^{13}C NMR: δ 138.24, 136.11, 128.48, 128.32, 128.23, 128.16, 127.56, 127.54, 118.91, 72.97, 72.12, 71.12, 66.47, 39.81, 33.76, 29.14, 19.61, 19.17. IR (thin film): 3064.1, 3031.1, 2960.0, 1496.1, 1454.6, 1388.8, 1380.2, 1369.2, 1251.7, 1207.5, 1090.0, 1036.1, 1027.8, 738.2, 696.6 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07. Found: C, 78.25; H, 8.11.

(4*R,5*R**)-4,7-Bis(benzyloxy)-5-methyl-1-heptene (20a).** Isolated by flash chromatography in 81% yield as a 1:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31 (m, 10 H), 5.90 (m, 1 H), 5.07 (d, J = 16 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 4.50 (m, 4 H), 3.50 (m, 2 H), 3.29 (m, 1 H), 2.30 (m, 2 H), 1.90 (m, 2 H), 1.50 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.93, 138.57, 135.66, 128.26, 128.16, 127.60, 127.54, 127.39, 127.29, 116.50, 82.19, 72.68, 71.55, 68.47, 35.34, 32.57, 32.45, 14.41. IR (thin film): 3060.3, 3025.0, 2931.0, 2860.5, 1495.9, 1448.9, 1360.8, 1096.4, 908.3, 732.1, 696.8 cm^{-1}. HRMS Calcd for $C_{22}H_{29}O_2$ (M + 1): 325.2160. Found: 325.2171.

(4*R,5*S**)-4,7-Bis(benzyloxy)-5-(1-methylethyl)-1-heptene (20b).** Isolated by flash chromatography in 70% yield as an 4:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29 (m, 10 H), 5.84 (m, 1 H), 5.06 (d, J = 13.8 Hz, 1 H), 5.02 (d, J = 8.3 Hz, 1 H), 4.46 (m, 4 H), 3.45 (m, 3 H), 2.31 (m, 2 H), 1.95-1.38 (m, 4 H), 0.88 (t, J = 6.5 Hz, 6 H). ^{13}C NMR: δ 138.97, 138.67, 136.02, 128.31, 128.21, 127.59, 127.43, 127.31, 116.43, 80.50, 72.72, 71.38, 70.15, 42.85, 35.35, 27.93, 26.72, 21.55, 19.43. IR (thin film): 2942.8, 2860.5, 1490.1, 1448.9, 1360.8, 1084.6, 908.3, 732.1, 696.8 cm^{-1}. HRMS Calcd for $C_{24}H_{33}O_2$ (M + 1): 353.2480. Found: 353.2473.

(2*R,3*S**)-2,5-Bis(benzyloxy)-3-methylpentanenitrile (20c).** Isolated by flash chromatography in 74% yield as a 3:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33 (m, 10 H), 4.82 (d, J = 11.7 Hz, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 4.43 (m, 2 H), 4.07 (d, J = 4.5 Hz, 1 H), 3.45 (t, J = 6.5 Hz, 2 H), 2.17 (m, 1 H), 1.89 (m, 1 H), 1.56 (m, 1 H), 1.06 (d, J = 6.8 Hz, 3 H). ^{13}C NMR: δ 138.27, 136.13, 128.67, 128.49, 128.43, 128.30, 128.23, 127.76, 117.87, 72.92, 72.31, 71.97, 67.39, 33.98, 31.81, 15.09. IR (thin film): 3022.2, 2922.2, 2855.6, 1455.6, 1361.1, 1205.6, 1094.4, 738.9, 694.4 cm^{-1}. HRMS Calcd for $C_{20}H_{23}NO_2$: C, 309.1729. Found: 309.1716.

(2*R,3*R**)-2,5-Bis(benzyloxy)-3-(1-methylethyl)pentanenitrile (20d).** Isolated by flash chromatography in 72% yield as a 12:1 mixture of diastereomers. Major isomer ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (m, 10 H), 4.80 (d, J = 11.6 Hz, 1 H), 4.42 (d, J = 11.6 Hz, 1 H), 4.44 (m, 2 H), 4.21 (d, J = 4.3 Hz, 1 H), 3.50 (m, 2 H), 2.10-1.70 (m, 4 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H). ^{13}C NMR: δ 138.35, 136.06, 128.54, 128.34, 128.27, 128.09, 127.59, 127.54, 118.16, 72.75, 72.14, 70.34, 68.60, 44.05, 28.66, 26.97, 20.49, 19.03. IR (thin film): 3048.5, 2954.5, 2860.5, 1496.0, 1454.8, 1366.7, 1208.0, 1084.6, 737.9, 696.8 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07. Found: C, 78.03; H, 8.31.

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Enantioselective Total Synthesis of (-)-Subergorgic Acid

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Abstract: A completely stereocontrolled total synthesis of (-)-subergorgic acid (**1**) has been accomplished. The starting β-hydroxy ketone was prepared in optically pure condition by lipase-promoted hydrolysis of the racemic chloroacetate. Following arrival at **5**, ring A was introduced by a reaction sequence that included a Mukaiyama-type aldol condensation and subsequent photochemical oxidation with (diacetoxyiodo)benzene and iodine. To permit proper functionalization within ring C, the carbonyl group in **16** was transformed into an internal double bond by Pd(II)-promoted reduction of the derived enol triflate with formate ion. Elaboration to **1** from **18** proceeded via a series of regio- and stereoselective reactions, several of which had to cope with the high steric compression levels associated with neopentyl sites. Notwithstanding, the progressive advance to more highly functionalized intermediates was accomplished with very reasonable efficiency.

In 1982, during the course of an investigation of the chemical constituents of gorgonians from the South China Sea, Wu, Yiao, and Long discovered subergorgic acid (**1**),[2] a substance that they came to regard as the near-perfect agent for chemical self-protection available to Pacific corals.[3] In actual fact, **1** is an unusually powerful cardiotoxic agent having the capacity for inhibiting neuromuscular transmission at levels below 0.20 μg/mL.[4] The

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