Remote Stereochemical Control of Both Reacting Centers in Ketyl-Olefin Radical Cyclizations: Involvement of a Samarium Tridentate Ligate

Gary A. Molander,* J. Christopher McWilliams, and Bruce C. Noll†

Contribution from the Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received September 11, 1996[⊗]

Abstract: High diastereoselection in a samarium(II) iodide-promoted ketyl-olefin cyclization reaction has been achieved using tartramide-derived keto allylic acetals as chiral auxiliaries. The unique features of the reaction include the fact that remote diastereoselection is achieved in a radical process and that high levels of stereochemical induction are observed at both new stereocenters created in the transformation. The source of the asymmetric induction is postulated to be a highly ordered, tricyclic transition structure made possible by three-point chelation between the ketyl intermediate and the samarium counterion. As such, this transformation also demonstrates the first example of the use of a chelating metal to affect high levels of remote asymmetric induction in a radical reaction. Because of this chelation, the sense of relative stereoselectivity is unusual for a SmI_2-mediated cyclization, providing consistently high ratios of cis/trans isomers. A double-diastereodifferentiating experiment provides additional support for this mechanistic hypothesis. The preparation of enantiomerically enriched cyclopentanediols and -lactols can be achieved through this novel asymmetric cyclization protocol.

Introduction

The asymmetric formation of carbon−carbon bonds utilizing radical intermediates remains a challenging goal in organic synthesis.[1] In general, successful approaches to inducing asymmetry in radical reactions have relied on chiral auxiliaries that utilize steric bulk to block approach to one face of the radical or radical acceptor. When the reacting center is in close proximity to the auxiliary, this is a viable option. However, as the reacting center becomes further removed from the auxiliary (remote asymmetric induction), developing large auxiliaries with predictable conformational biases becomes a much more difficult endeavor. In heterolytic bond-forming processes, examples of remote asymmetric induction are well precedented.[2] These transformations take advantage of the ability of Lewis acids to organize substrates through chelation. Although the use of Lewis acids to control conformational preferences in radical chemistry has recently provided some impressive successes, few examples of applications to remote asymmetric induction are known.[1d−f,h−m,3]

Another issue that is unresolved in asymmetric carbon−carbon bond formation utilizing radical intermediates is that of controlling the stereochemistry at both reacting centers. Although currently developed methods employing chiral auxiliaries have demonstrated high stereoselectivity with regard to the chirality at the carbon atom bearing the radical, or at the alkene radical acceptor, simultaneous control of facial selectivity in both species remains an unchallenged field. Therefore, the currently available methods would necessitate a chiral auxiliary on each of the two reacting centers.[4] In heterolytic bond-forming reactions, controlling the facial selectivity of two reacting partners with a single chiral auxiliary can be achieved by chelation with a Lewis acid. Applications of this approach to radical reactions are lacking, presumably because of the absence of appropriate functional groups in close proximity to both reacting centers.

Herein we describe a samarium-mediated radical cyclization in which a single chiral auxiliary engenders high levels of asymmetric induction at both reacting carbon centers. High

† Author to whom correspondence should be addressed concerning the X−ray crystal structure.

⊗ Abstract published in *Advance ACS Abstracts,* February 1, 1997.

(1) For reviews of diastereoselection in radical reactions, see: (a) Smadja, W. *Synlett* **1994**, 1. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. See also: (c) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921. (d) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (e) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (f) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (g) Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron: Asymmetry* **1994**, *5*, 199. (h) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945. (i) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. (j) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481. (k) Renaud, P.; Gerster, M. *J. Am. Chem. Soc.* **1995**, *117*, 6607. (l) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (m) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.

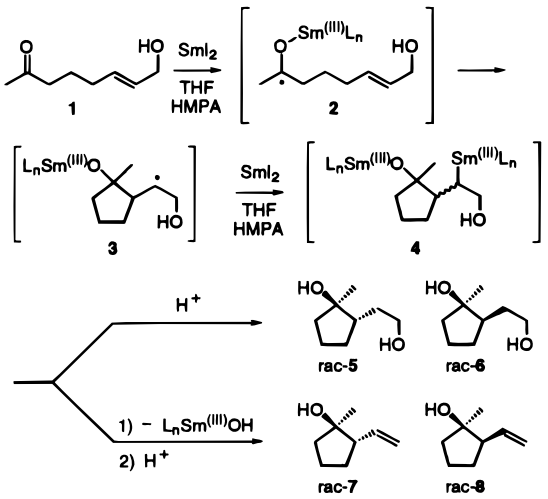
(2) For recent examples, see: (a) Molander, G. A.; Haar, Jr., J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40. (b) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517. (c) Teerawutgulrag, A.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2863. (d) Carey, J. S.; Coulter, T. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3933. (e) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935. (d) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1994**, *59*, 2676. (e) Carey, J. S.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1994**, 283. (f) Stanway, S. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1994**, 285. (g) Ahzng, H.-C.; Costanzo, M. J.; Maryanoff, B. E. *Tetrahedron Lett.* **1994**, *35*, 4891. (h) Hallett, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657. (i) Gruttadauria, M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1469. (j) Stanway, S. J.; Thomas, E. J. *Synlett* **1995**, 214. (k) Stanway, S. J.; Thomas, E. J. *Tetrahedron Lett.* **1995**, *36*, 3417.

(3) For recent examples of the application of Lewis acids to stereoselective radical transformations, see: (a) Renaud, P.; Ribezzo, M. *J. Am. Chem. Soc.* **1991**, *113*, 7803. (b) Guindon, Y.; Lavellée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. (c) Feldman, K. S.; Romanelli, A. L.; Ruckle, Jr., R. E. *J. Org. Chem.* **1992**, *57*, 100. (d) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547. (e) Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1601. (f) Guindon, Y.; Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Synlett* **1995**, 449. (g) Sibi, M. P.; Ji, J.; Hongliu, W.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200 and references therein.

(4) Presumably, this would also necessitate a matching between the chirality of the auxiliaries.

S0002-7863(96)03195-2 CCC: $14.00

Scheme 1



levels of remote asymmetric induction are observed at the radical center furthest removed from the auxiliary. The source of the observed stereoselectivity is postulated to be a highly ordered, tricyclic transition structure made possible by three-point chelation between the ketyl intermediate and the samarium cation.

Background

The SmI_2-mediated cyclization of keto olefins has been established as an excellent method for the synthesis of *trans*-1,2-dialkylcyclopentanols.[5] Initially, we were interested in extending this method to the cyclization of keto allylic alcohols, providing products with functionality readily amenable to further manipulation. Utilizing keto allylic alcohol **1** as an example (Scheme 1), four possible products could arise from cyclization with SmI_2. Thus, initial reduction with SmI_2 generates the ketyl radical **2**. Cyclization of **2** to **3**, followed by further reduction generates an intermediate organosamarium **4**. The intermediate **4** can either protonate to form the diols **5** and **6** or undergo elimination to the alkenes **7** and **8**.

Ideally, it would be desirable to develop conditions to produce each of the four possible products selectively. We had expected that formation of the trans isomers (**5** and **7**) would be preferred to the cis isomers (**6** and **8**) based upon substantial precedent. Earlier results from these laboratories on similar substrates indicated the presence or absence of proton sources (i.e., alcohols) had a distinct effect on the outcome of reactions conducted with intermediates analogous to **4**.[6] Indeed, cyclization of **1** in the presence of *tert*-butyl alcohol demonstrated selectivity for alkene formation (Table 1). In the absence of added alcohol, the diols were formed preferentially. However, the stereoselectivity of the cyclizations was very low, in stark contrast with the usual high selectivity observed with SmI_2 cyclizations of keto olefins.[5] The implication of these results was that the hydroxyl group was somehow involved in the stereodifferentiating, bond formation step.[7,8] This raised the possibility of employing a suitably disposed ligating auxiliary to reverse the inherent diastereoselectivity associated with SmI_2 cyclizations. Furthermore, if this ligating functionality was present in a chiral environment, it would be possible to control the absolute stereochemistry of the final product as well.

Table 1. Cyclization of **1** with SmI_2[a]

additive	ratio of **5**:**6**:**7**:**8**[b]
none	61:13:11:15
t-BuOH	07:00:56:37

[a] Reactions were run by adding a solution of **1** to a preformed solution of SmI_2 with HMPA in THF at room temperature. [b] Ratios were determined by GLC, uncorrected for response factors.

Our initial results with the cyclization of **1** implied that a chiral allylic alcohol or possibly an ether might provide the desired stereocontrolling element. However, the use of such functionalities has several disadvantages associated with it, including the difficulty of incorporating these moieties into the substrate, and dissociating them from the final product. With this in mind, we began our investigation with a series of chiral acetals. Acetals offer the advantages of ease of incorporation into the starting material, ease of removal from the products under conditions of protonation or elimination, and of being readily available in diverse forms. Furthermore, chiral acetals have been successful in directing asymmetric transformations with a variety of organometallics.[9] To our knowledge, no previous application of chiral acetals to organolanthanide chemistry has been demonstrated.

Results and Discussion

A representative series of keto allylic acetals was prepared from commercially available keto ester **9** (Scheme 2). Dithiane protection of the ketone functionality of **9** gave **10**.[10] Reduction of the ester, followed by oxidation,[11] provided the aldehyde **11**. A two-step homologation procedure yielded the enal **12**.[12] Direct acetalization, or transacetalization, from **12**, followed by deprotection to the ketone, yielded the dimethyl- (**13**), diester- (**14**), and diamide-substituted (**15a**) keto allylic acetals.[13]

Cyclization of the dimethyl-substituted acetal **13** with SmI_2/HMPA yielded mixtures of cyclopentanol products (Scheme 3). At low temperature (−78 °C), cyclization proceeded without elimination, producing the cyclopentanols with the dioxolane intact (**16** and **17**). At room temperature, elimination products (**18** and **19**) were observed along with **16** and **17**. Both **18** and **19** were mixtures of *E*- and *Z*-enol ethers. Although the relative stereoselectivity was typical for SmI_2-THF/HMPA cyclizations, no asymmetric induction from the chiral auxiliary was observed.[14] In the absence of HMPA, attempts to initiate cyclization of **13** with SmI_2 was met with low reactivity and

(5) (a) Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367. (b) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (c) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (e) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (f) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (g) Kan, R.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111. (h) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532. (i) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.

(6) Unpublished results.

(7) Alternative explanations, such as an equilibrating cyclization process, although less probable, cannot be excluded.

(8) Other examples in which a pendant hydroxyl group influences the stereoselectivity of SmI_2-mediated reactions are known. For examples of ketyl-olefin coupling, see ref 5e,h. (a) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. For a related example, see: (b) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloys Compounds* **1993**, *192*, 197.

(9) For a review, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. For more recent work in this field, see: (b) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998, and references cited therein. (c) Aubé, J.; Heppert, J. A.; Milligan, M. L.; Smith, M. J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563. (d) Parrain, J.-L.; Cintrat, J.-C.; Qintard, J.-P. *J. Organomet. Chem.* **1992**, *437*, C19. (e) Longobardo, L.; Mobbili, G.; Tagliavini, T.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron* **1992**, *48*, 1299. (f) For a recent example of the application of chiral acetals to asymmetric cyclopropanations, see: Armstrong, R. W.; Maurer, K. W. *Tetrahedron Lett.* **1995**, *36*, 357.

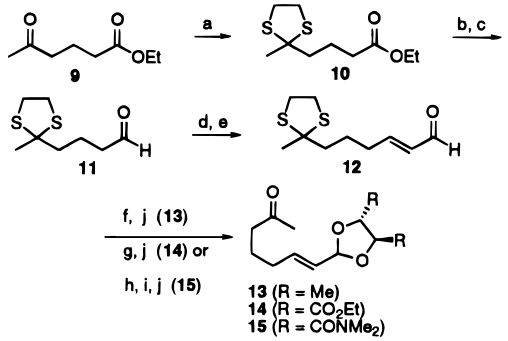
(10) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(11) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(12) Cresp, T. M.; Sargent, M. V.; Vogel, P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 37.

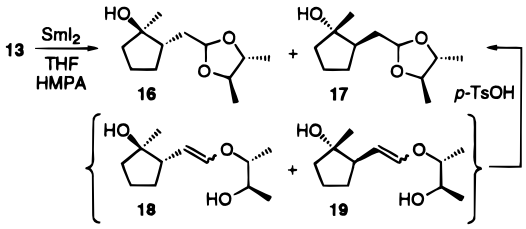
(13) The diamide acetal **15** was produced as a 9:1 mixture of *E*:*Z* stereoisomers. The mixture could be enriched by silica gel chromatography.

Scheme 2[a]



[a] (a) 1,2-Ethanediol, 0.4 equiv of $ZnCl_2$, CH_2Cl_2, 93%; (b) $LiAlH_4$, THF, 100%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 68%; (d) (1,3-dioxolan-2-yl-methyl)triphenylphosphonium bromide, KH, THF/HMPA, 75% (85:15 *Z*:*E*); (e) Amberlyst-15, H_2O, acetone, 96%; (f) (2*R*,3*R*)-2,3-butanediol, *p*-TsOH, benzene reflux, 60%; (g) diethyl-L-tartrate, *p*-TsOH, benzene, reflux, 66%; (h) $HC(OMe)_3$, dry Amberlyst, 82%; (i) *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, PPTS, toluene, 4Å mol. sieves, reflux, 86%; (j) NCS, $AgNO_3$, collidine, 9:1 CH_3CN/H_2O, **13** (65%), **14** (53%), **15a** (73%).

Scheme 3

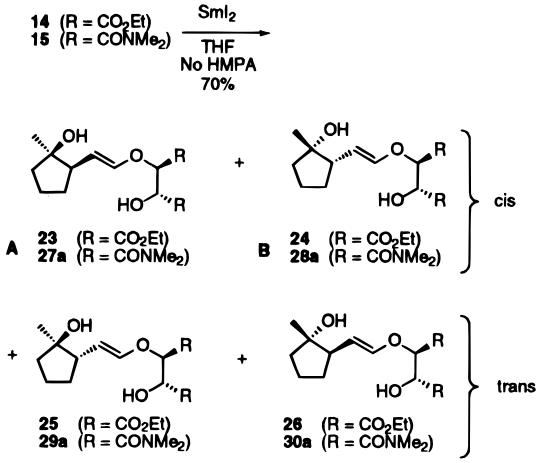


the observation of additional, uncharacterized products. It was quite apparent from these results that a simple acetal functionality, combined with modest steric biases far removed from the reacting center, would have an insignificant influence on the stereochemistry of the cyclization.

We then turned to the diester-substituted acetal **14**, which offered additional sites for metal ligation (i.e., the ester functionalities). Submitting **14** to typical cyclization conditions with SmI_2 in the presence of HMPA yielded intractable mixtures. However, we were pleased to discover that in the absence of HMPA, **14** cyclized readily, yielding products **23**−**26** (Scheme 4). Indeed, the enhanced reactivity of **14** toward SmI_2 was the first observation that distinguished this substrate from the acetal **13**. Although **13** displayed incomplete conversion after 24 h at room temperature, the cyclization of **14** was complete within 1 h at room temperature. A small amount of α-C−O bond cleavage of the enol ether was observed in the latter reaction. In spite of this, an overall combined yield of 70% could still be obtained in the cyclization of **14**.[15]

Several points concerning the stereoselectivity in the cyclization of **14** are worthy of note. The relative stereoselectivity in

Scheme 4

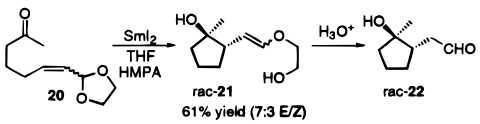


substrate	% isoltd yield	cis : trans	A : B
14	70	98 : 2	85 : 15
15a	79	>99 : < 1	97 : 03

the cyclization of **14** is excellent, providing the cis isomers (**23** + **24**) with ≥98:2 selectivity.[16] This result represents a complete reversal of the usually observed trans stereoselectivity associated with SmI_2-mediated ketyl-olefin cyclizations. In terms of asymmetric induction from the chiral auxiliary, the cyclization of **14** provided an 85:15 ratio of **23** and **24**, respectively. Although this level of stereoinduction is modest, *this provides the first example in which the stereochemistry at both reacting centers of a radical cyclization is controlled by a single chiral auxiliary*. Finally, the high stereoselectivity for the *E*-enol ether in both **23** and **24** is intriguing. When compared to the cyclization of the acetal **13**, this indicates another level of stereoselectivity associated with the diester-substituted acetal **14** that is not present in the simple dimethyl-substituted acetal system.

The diamide-substituted acetal **15a** was envisioned to be an improvement over the diester-substituted acetal **14** for two reasons. First, the amide functionalities should be better ligands for samarium ions, forming closer contacts with the samarium metal center. Shorter bond lengths in the transition structure should accentuate energetic differences in competing cyclization pathways. Secondly, an amide functionality would be less prone to α-C−O bond cleavage in the product enol ether.[15] In line with these predictions, cyclization of **15** with SmI_2 in the absence of HMPA proceeded with excellent relative stereochemistry and stereoinduction from the chiral auxiliary (Scheme 4). The cis (**27a** and **28a**) and trans (**29a** and **30a**) isomers were formed with ≥99:1 stereoselectivity, respectively. The ratio of the two cis isomers (**27a** and **28a**) was 97:3. The sense of relative and absolute stereochemistry was confirmed by chemical correlation (*vide infra*) and a single crystal X-ray structure of **27a** (Figure 1). No α-C−O bond cleavage was observed, and the overall combined yield of cyclization products was 79%. Not surprisingly, the diamide-substituted acetal

(14) Stereoselectivity was determined by submitting crude reaction mixtures to *p*-TsOH in toluene heated at reflux. These conditions yielded quantifiable mixtures of **16** and **17** from the cyclization of enol ethers, **18** and **19**. The relative stereoselectivity was assumed to be trans based upon the cyclization of the achiral keto allylic acetal **20**, which gave a 7:3 mixture of *E*- and *Z*-enol ethers rac-**21**. Submitting mixtures of **16**−**19** or rac-**21** to hydrolysis conditions yielded the hydroxy aldehyde rac-**22**. The corresponding cis isomers would be expected to give a cyclic hemiacetal (*vide infra*).



(15) Evidence for α-C−O cleavage of the enol ether bond comes from the observation of diethyl malate in crude reaction mixtures. We believe this process to be the source of several side reactions leading to intractable mixtures when **14** is submitted to stronger reducing conditions (i.e., SmI_2/THF-HMPA). (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (b) Molander, G. A. *Org. React.* **1994**, *46*, 211.

(16) The trans isomers, **25** and **26**, made up less than 2% of the product mixture. The minor isomers were not isolated or characterized, and the ratio of **25:26** is unknown.

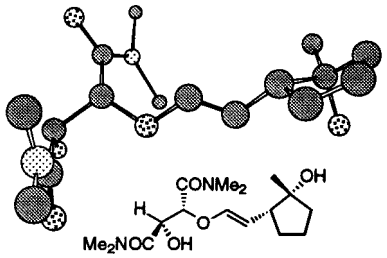
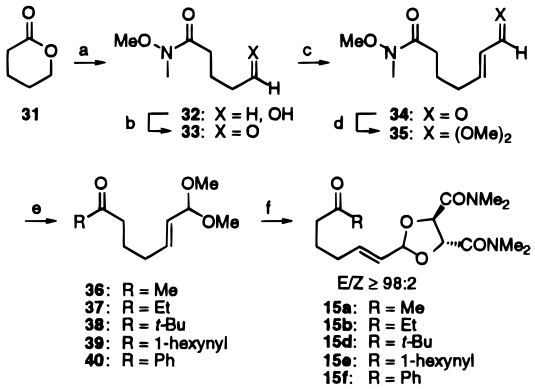


Figure 1. X-ray structure of **27a**.

Scheme 5[a]



[a] (a) $AlMe_3$, $Me(MeO)NH_2Cl$, CH_2Cl_2, 91%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 76%; (c) LDA (2 equiv), acetaldehyde *tert*-butylimine, THF, then diethyl chlorophosphate (1 equiv), then **33**, then oxalic acid, 38%; (d) TMSOMe, TMSOTf (catalyst), CH_2Cl_2, 96%; (e) RMgBr or RLi, THF, 63−80%; (f) *N*,*N*,*N*′,*N*′-tetramethylbis(*O*-trimethylsilyl)-L-tartaramide, TMSOTf, CH_2Cl_2, −20 °C, 41−57%, or *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, PPTS (catalyst), DMF, ≥79%.

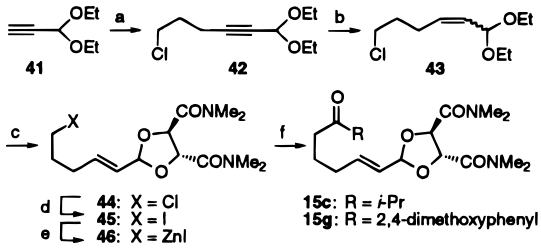
15a reacted faster than the corresponding diester-substituted acetal **14**.

Scope and Limitations

Cyclization of unactivated keto olefins with SmI_2-THF/HMPA provides trans cyclopentanols as the major products.[5] The relative stereoselectivity in these transformations is excellent when the steric bulk around the ketone is small but decreases with increasing alkyl substitution α to the carbonyl.[5i] We set out to determine what the effect of changing the steric and electronic properties around the carbonyl functionality might be on the reactivity and stereoselectivity of this related, but distinctly different, transformation in which the olefin was substituted with acetals.

Syntheses of representative unsaturated carbonyl substrates are outlined in Schemes 5, 6, and 8. Scheme 5 depicts a route in which diversity is incorporated through Weinreb amide intermediate **35**.[17] Starting with commercially available δ-valerolactone **31**, Weinreb amidation provided an acid- and base-sensitive hydroxyamide **32**.[18] Swern oxidation of **32** yielded the aldehyde **33**.[11] Using the procedure developed by Meyers, **33** was homologated to the enal **34**.[19] Acetalization of **34** by the method of Noyori provided the pivotal intermediate **35**.[20] Conversion of **35** to a variety of ketones (**36**−**40**) was generally successful, although low yields were obtained with the addition

Scheme 6[a]



[a] (a) *n*-BuLi, 1-chloro-3-iodopropane, DMSO/THF, 49%; (b) H_2, Lindlar catalyst, EtOAc, 97%; (c) *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, PPTS, DMF, 89%; (d) NaI, $NaHCO_3$, Na_2SO_3, acetone, 94%; (e) Zn, TMSCl (catalyst), 1,2-dibromoethane (catalyst), THF, 90%; (f) CuCN·LiCl, then isobutyryl chloride or 2,4-dimethoxybenzoyl chloride, 27% (**15c**), 21% (**15g**).

of isopropylmagnesium chloride or DIBAH (the latter was used in an attempt to generate the aldehyde).[21] Syntheses of these derivatives are described below. As previously noted, transacetalization of allylic methyl acetals with *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide in toluene heated at reflux provides products with only modest *E*/*Z*-stereoselectivity. Thus, the desired allylic diamide acetals (**15a**,**b**,**d**,**f**) were prepared by the method of Noyori[20] or by our newly developed transacetalization protocol.[22] This latter method was found to give the best yields, with little loss in stereoselectivity when compared to the Noyori method.

Scheme 6 outlines our syntheses of the isopropyl- and 2,4-dimethoxyphenyl-substituted derivatives, **15c** and **15g**, respectively. This route takes advantage of organozinc chemistry developed by Knochel.[23] The commercially available propiolaldehyde diethyl acetal **41** was monoalkylated with 1-chloro-3-iodopropane, yielding **42**.[24] After partial reduction under Lindlar conditions, the olefin **43** was obtained. Transacetalization to **44**, followed by a Finkelstein reaction, provided the pivotal iodide **45**. Conversion to the organozinc reagent **46** by the method of Knochel proceeded to 90% conversion.[23,25] After transmetalation to the copper species, the appropriate acid chlorides were added to yield the isopropyl and 2,4-dimethoxyphenyl ketones, **15c** and **15g**, respectively.[26]

The final substrate we wished to examine was an aldehyde derivative. We had hoped to acquire the aldehyde precursor **48** from a dithiane alkylation of the iodide **45** (Scheme 7). However, treating the lithium salt of **47** with **45** afforded products that displayed NMR resonances consistent with mono and bis-addition (**49** and **50**, respectively) of **47** to the amide functionalities of **45**. No evidence of iodide displacement from **45** was observed. Presumably, the amides direct the addition by prior ligation to the lithium cation.[27]

(17) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(18) (a) Lipton, M. F.; Basha, A.; Weinreb, S. M. In *Organic Syntheses*; Noland W. E., Ed.; John Wiley & Sons: New York, 1988; Collect. Vol. 6, pp 492−495. (b) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(19) Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.

(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(21) These comments should be taken in the context of single run, unoptimized experiments.

(22) Molander, G. A.; McWilliams, J. C., *Tetrahedron Lett.* **1996**, *40*, 7197.

(23) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *28*, 351. (b) For a recent review, see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

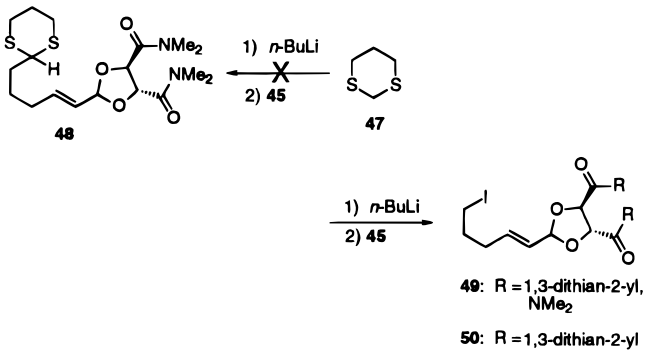
(24) Chong, J. M.; Wong, S. *Tetrahedron Lett.* **1986**, *27*, 5445.

(25) Determined by GC after hydrolysis of the crude mixture (uncorrected for response factors).

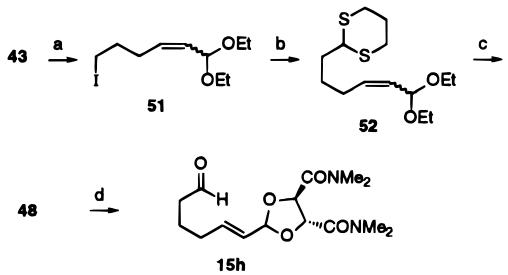
(26) The isolated yields of **15c** and **15g** were low overall, but this is a likely reflection of the isolation process. The relatively polar nature of the diamide acetals tends to swamp out subtleties in polarity differences between the impurities of this transformation (e.g., the chloride **44**, iodide **45**, and protonated material are all present in the crude mixture). For **15c**, isolation from the crude mixture required a reduction to an isolable mixture of epimeric alcohols, followed by oxidation back to **15c**. It should be noted that these yields represent single run, unoptimized reactions.

(27) We have found that lithium anions derived from hydrazones will alkylate **45** in good yield at low temperatures (−78 °C).

Scheme 7



Scheme 8[a]



[a] (a) NaI, $NaHCO_3$, Na_2SO_3, acetone, 93%; (b) 1,3-dithiane, *n*-BuLi, then **41**, THF, 65%; (c) *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, PPTS, DMF, 71%; (d) bis(trifluoroacetoxy)iodobenzene, 9:1 CH_3CN/H_2O, 76%.

To circumvent the problems associated with dithiane alkylation of **45**, we turned to alkylating the iodide **51**, derived from a precursor lacking the diamide acetal functionality **43** (Scheme 8). After Finkelstein conversion of **43** to the iodide **51**, alkylation proceeded without incident, providing **52**. Transacetalization of **52** to the diamide acetal **48**, followed by oxidative removal of the dithiane functionality,[28] yielded the aldehyde substrate **15h**.

With the desired substrates in hand, an investigation of the ketyl olefin cyclization reactions was begun. Addition of the keto allylic acetals (**15a**−**h**) to a THF solution of SmI_2 (Scheme 9) provided the results tabulated in Table 2. All of the aliphatic ketones cyclized to *cis*-cyclopentanols in good yields. Notably, even the bulky *tert*-butyl derivative **15d** cyclized readily without the need for HMPA as an additive. The relative stereoselectivity was excellent, providing high cis/trans ratios for the entire series of aliphatic ketone substrates. Again, the *tert*-butyl derivative **15d** showed little deviation from the smaller homologues. In terms of stereoinduction from the chiral auxiliary, some decrease was observed as the steric bulk around the ketone increased.

The unsaturated ketones **15e**−**g** did not show the same reactivity and stereoselectivity as their aliphatic counterparts. The propargylic ketone substrate **15e** appeared to give only pinacol coupling products. The unsubstituted phenyl substrate **15f** also indicated little propensity for cyclization, although some cyclopentanol products could be discerned from the crude reaction mixtures.

It seems unlikely that the low reactivity of substrates **15e**−**g** can be attributed to a high energy barrier in the initial reduction to the $Sm^{(III)}$-ketyl radical, especially when compared to the aliphatic ketones which should be more resistant to reduction. The poor reactivity of substrates **15e**−**f** may be a consequence of relatively large energy gaps between the SOMO of the $Sm^{(III)}$-ketyl radical and the LUMO of the alkene. The conjugated $Sm^{(III)}$-ketyl radicals in **15e**−**f** likely have lower SOMO energy levels relative to the $Sm^{(III)}$-ketyl radicals derived from aliphatic ketones.[29] Because the alkene LUMO remains unchanged for all the substrates, the net result is that conjugated $Sm^{(III)}$-ketyl radicals have less orbital overlap in the transition structure (i.e., less stabilization).[30]

We expected that additional alkoxy functionalities at the ortho and para positions of the aromatic ring in **15g** would increase the SOMO energy of the resultant $Sm^{(III)}$-ketyl radical relative to **15f** and, therefore, enhance reactivity. To test our hypothesis, the 2,4-dimethoxyphenyl ketone **15g** was submitted to cyclization with SmI_2. In this event, **15g** did display improved reactivity toward cyclization (Table 2), albeit with lower yield and stereoselectivity when compared to the aliphatic substrates. A small increase in the temperature of cyclization (40 °C instead of 23 °C) yielded cleaner reaction mixtures. Interestingly, we found that utilizing a large excess of SmI_2 resulted in an increase in the diastereoselectivity.[31] We believe these observations are consistent with the mechanism outlined in Scheme 10. An initial reduction of **15g** with SmI_2 yields the $Sm^{(III)}$-ketyl radical **53**. The cyclization of **53** to the intermediate carbon radicals **54** or **55** is a reversible process. It is this reversible step that differentiates **15g** from the aliphatic substrates **15a**−**d**.[32] The intermediates **54** and **55** are removed from the equilibrium by irreversible reduction to the organosamarium(III) species, **56** and **57**. At lower temperatures, the intermediate $Sm^{(III)}$-ketyl radical **53** has a longer lifetime and can undergo side reactions leading to other products. When excess SmI_2 is present, the rates of the irreversible reductions leading to **56** and **57** increase relative to the unimolecular equilibration of **54** and **55**. Thus, at higher temperatures and higher concentrations of SmI_2, the cyclization of **15g** proceeds more cleanly and with greater diastereoselectivity.

We examined the potential for aldehyde substrate **15h** to undergo stereoselective cyclization with SmI_2. In this event, good relative stereoinduction (98:2) and stereoinduction from the chiral auxiliary (95:5) was observed (Table 2). The combined yield for cyclization products was, however, only modest. Side reactions giving pinacol and reduction products appeared to be the source of diminished yields.[33] Optimized conditions consisted of slow addition of **15h** to an excess of SmI_2, thereby minimizing intermolecular side reactions.

The distinct features of this cyclization process have provided the basis for a reasonable mechanistic rationale. Although the overall diastereoselectivity decreases with increasing steric bulk around the ketyl center, the high relative cis-stereoselectivity of these cyclizations appears to be independent of the size of the ketone substituent. This is in stark contrast to the trans-selective SmI_2 cyclizations of unactivated keto olefins.[5] There is a large acceleration in the rate of cyclization when the diester-substituted acetal **14** is compared with the nonselective dimethyl-substituted acetal **13**. An additional, less dramatic, increase in

(28) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

(29) The stability of Sm(III)-ketyls derived from aromatic ketones is exemplified by the isolation and X-ray determination of the Sm(III)-ketyl derived from fluorenone: Hou, Z.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1995**, *117*, 4421.

(30) An analogous argument could be stated as a decrease in the electron density coefficient at the ketyl carbon orbital because of delocalization into the π-system.

(31) For example, the use of 2.7 and 8 equiv of SmI_2 yielded 60:40 and 75:25 mixtures of **59**/**60**, respectively. Also, the reactions appeared cleaner overall under these conditions.

(32) The cyclization of phenyl-substituted ketyl radicals has been shown to be a reversible process. Furthermore, the Sm(III)-ketyl derived from fluorenone was found to undergo reversible pinacol coupling: ref 29.

(33) When comparing the aldehyde substrate **15h** to the aliphatic ketone substrates **15a**−**d**, the rate of intermolecular pinacol coupling relative to cyclization is probably increased by diminished steric hindrance around the Sm(III)-ketyl, and this effect is compounded by the diminished nucleophilicity of the Sm(III)-ketyl.

Scheme 9

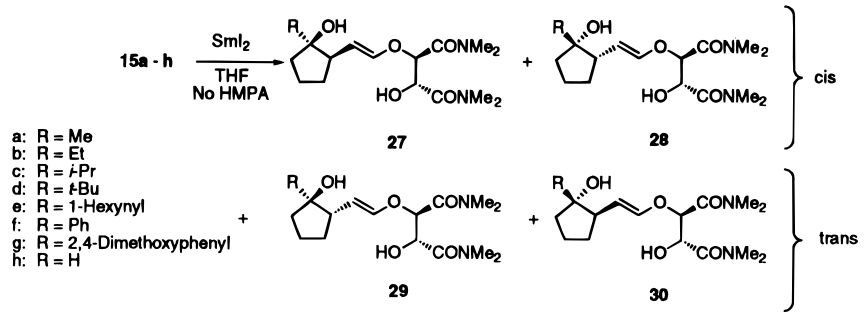


Table 2. Asymmetric Cyclization of Tartrate-Derived Keto Allylic Acetals[a]

substrate	R	*E*:*Z*[b]	% yield[c]	cis/trans[d]	**27**:**28**
14	Me	98:2	70	98:2[e]	85:15[f]
15a	Me	98:2	79	99:1	97:03
15b	Et	98:2	83	97:3	97:03
15c	*i*-Pr	97:3	82	97:3	93:07
15d	*t*-Bu	98:2	86	97:3	91:09
15e	1-hexynyl	98:2	0	N/A	N/A
15f	Ph	98:2	*g*	N/A	N/A
15g	Ar[h]	98:2	43	*g*	80:20[i]
15h	H	98:2	53	98:2	95:05

[a] Ratios of isomers (*E*/*Z*, cis/trans, **27**−**30**) were determined by GC (uncorrected for response factors). N/A = not applicable. [b] Ratio of alkene isomers in **14**, **15a**−**h**. [c] Combined isolated yield. [d] Ratio of (**27** + **28**)/(**29** + **30**). [e] Ratio of (**23** + **24**)/(**25** + **26**). [f] Ratio of **23**/**24**. [g] Not determined. [h] Ar = 2,4-dimethoxyphenyl. [i] Determined by ^{13}C NMR.

the rate of cyclization is observed when comparing the diamide-substituted acetal **15a** with the less selective diester-substituted acetal **14**. Finally, this cyclization process yields the *E*-enol ethers exclusively. We believe these observations are consistent with a tridentate-ligating transition structure in which the ketyl oxygen, an ether oxygen, and one of the carbonyl functionalities of the acetal are ligated to the samarium center. Several possible transition structure conformers that fit this criteria are shown in Chart 1.

Of the transition structures in Chart 1, conformers **58**, **59**, and **61** would yield the observed major cis diastereomer. Conformer **60** is the only transition structure in Chart 1 that would yield the observed minor cis diastereomer. The last two conformers in Chart 1, **62** and **63**, are those that would lead to the trans diastereomers. Only chair and boat conformers are considered for the cyclopentanol ring formation. The only boat conformer represented in Chart 1 is **59**. With regard to ligation around the samarium metal center, and to the resultant diastereoselectivity, conformer **59** is essentially equivalent to its chair counterpart **58**. For clarity, we have omitted analogous boat conformations that would correspond to conformers **60**−**63**. We believe this is justified based on the following argument. Although there are no flagpole interactions in **59**, two destabilizing torsional interactions (one consisting of eclipsing carbon−hydrogen bonds and the other a carbon−hydrogen bond eclipsing a carbon−carbon bond) more than compensate for any relief gained from the loss of the two 1,3-diaxial interactions in **58**. Similar arguments can be made for equivalent boat conformations of **60**−**63**. Therefore, for the consideration of only those low energy conformers having a distinctly different ligand sphere around samarium and those leading to different diastereomers, conformers **58** and **60**−**63** should suffice.[34]

Of the chair conformers in Chart 1, only **58** and **61** lead to the observed major diastereomer **27**. A distinct difference between conformers **58** and **61** is the orientation of the acetal-bearing carbon with respect to the alkene. In **58**, the acetal-bearing carbon is poised in an eclipsed conformation, but a bisected conformation is adopted in **61**. For propene, the eclipsed conformer has been calculated to be 2 kcal/mol lower in energy than the bisected conformer.[35] It is also interesting to note that elimination (following further reduction of the subsequently formed carbon radical) from any of the eclipsed conformations would provide the trans enol ether directly, whereas formation of the trans enol ether from the bisected conformer **61** would require a breakdown of the ligated structure in order to allow for bond rotation prior to the elimination event.[36] Furthermore, the samarium center in **61** is located on what may be considered the concave side of the acetal unit, whereas the samarium center occupies the convex side in **58**. We have reason to believe that the concave side of the acetal is a less stable environment for the samarium ion and its attached ligands (*vide infra*). Therefore, the chair conformer **58**, with an eclipsed conformation about the alkene-acetal carbon and with the samarium center located on the convex face of the acetal, likely represents the conformation of the transition structure leading to the major product **27**.

Conformer **60** represents the only conformation in Chart 1 that could lead to the minor diastereomer **28**. A bisected conformer analogous to **60** is not likely, for it would place the samarium center too far from the amide located on the convex face of the acetal for any significant bonding interaction. It is not obvious why conformer **58** is favored over that of conformer **60**. The distinct difference between **58** and **60** resides in the spatial placement of the samarium center. Although the metal center is located on the convex side of the acetal in **58**, it is on the concave side of the acetal in **60**. This suggests that locating the samarium center on the concave side of the acetal is relatively destabilizing. It is possible that there are more destabilizing van der Waals interactions between the ligands attached to samarium and the substrate on the concave side.[37]

Conformers **62** and **63** represent those that would lead to trans isomers **29** and **30**, respectively. Although some bonding between the amide oxygen and samarium may be possible in **62**, it would be very weak at best. In conformer **63**, no interaction between the amide and samarium is possible. Because the carbonyl functionalities serve to increase the oxidation potential of samarium, and it is likely this activation leads to enhanced reactivity, very little of the trans isomers

(34) In reality, a Boltzmann distribution of all reactive conformers would be more accurate, but with only semiquantitative approximations (i.e., energy approximations based upon correlation to related interactions), this is unworkable.

(35) (a) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035. (b) Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591.

(36) This is assuming an E2 elimination pathway.

(37) Although greater interaction between the R group of the ketyl with the ligands around samarium is suggested, it is difficult to rationalize a switch from conformer **58** to **60** as the size of R gets larger (i.e., the diastereoselectivity of the cyclization decreases as the size of R increases).

Table 3. Crystallographic Data for (2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*)-2-Hydroxy-2-methylcyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide, **27a**

compd no.	**27a**	transmission coeffs.	0.96 to 0.98
empirical formula	$C_{16}H_{28}N_2O_5$	*T* (K)	293(2)
formula mass	328.40	λ, Å	0.71069 (MoKα)
crystal system	triclinic	reflcns collected	1801
space group	*P*1	unique reflcns	1667 (*R*(int) = 0.0175)
a, Å	6.0950(10)	reflections observed	1324
b, Å	7.659(2)	*R* indices[a] [$I > 2\sigma(I)$]	R1 = 0.0390, wR2 = 0.0759
c, Å	10.042(2)	*R* indices[a] (all data)	R1 = 0.0549, wR2 = 0.0818
α, deg	101.89(3)	weighting coeffs[b]	$a = 0.0414$, $b = 0$
β, deg	93.06(3)	goodness-of-fit[c] on F^2	1.020
γ, deg	94.15(3)	ρ_{calc}, Mg/m^3	1.195
vol., Å^3	456.4(2)	μ, mm^{-1}	0.088
Z	1		

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR2 = \sqrt{\sum[w(F_o^2-F_c^2)^2]/\sum[w(F_o^2)^2]}$. [b] $w^{-1} = [\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$. [c] Goodness-of-fit $= \sqrt{\sum[w(F_o^2-F_c^2)^2]/(M-N)}$ where *M* is the number of reflections and *N* is the number of parameters refined.

Scheme 10

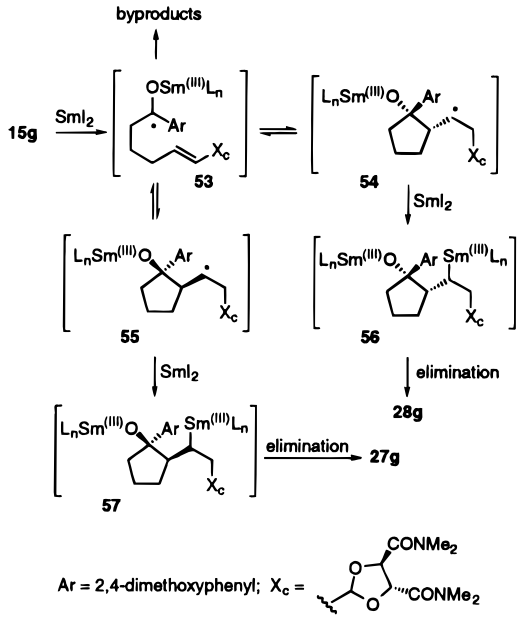
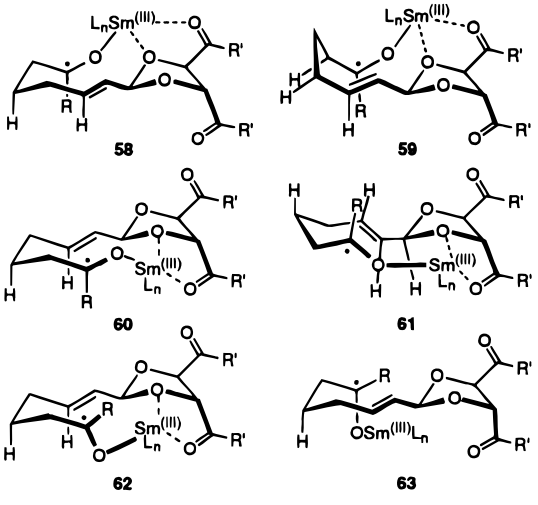


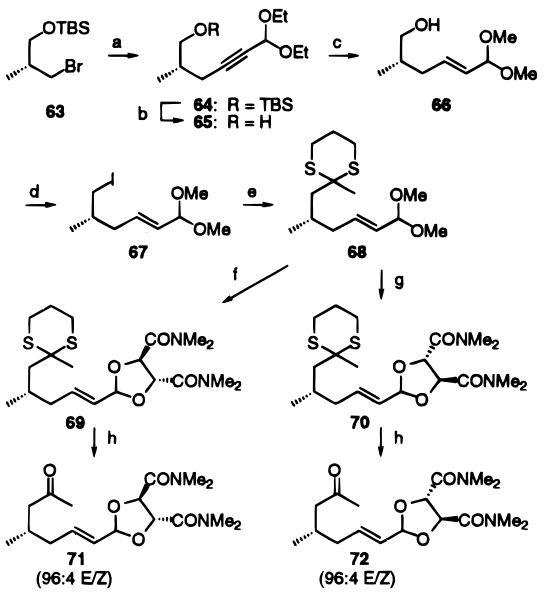
Chart 1



resulting from transition structures that proceed through conformers **62** and **63** are observed.

The methyl-substituted, diastereomeric keto allylic acetals **71** and **72** were prepared to test the hypothesis that **58** and **60** represent the transition structures leading to the major cis isomers, **27** and **28**, respectively (Scheme 11). Alkylation of propiolaldehyde diethyl acetal with the known bromide **63**

Scheme 11[a]



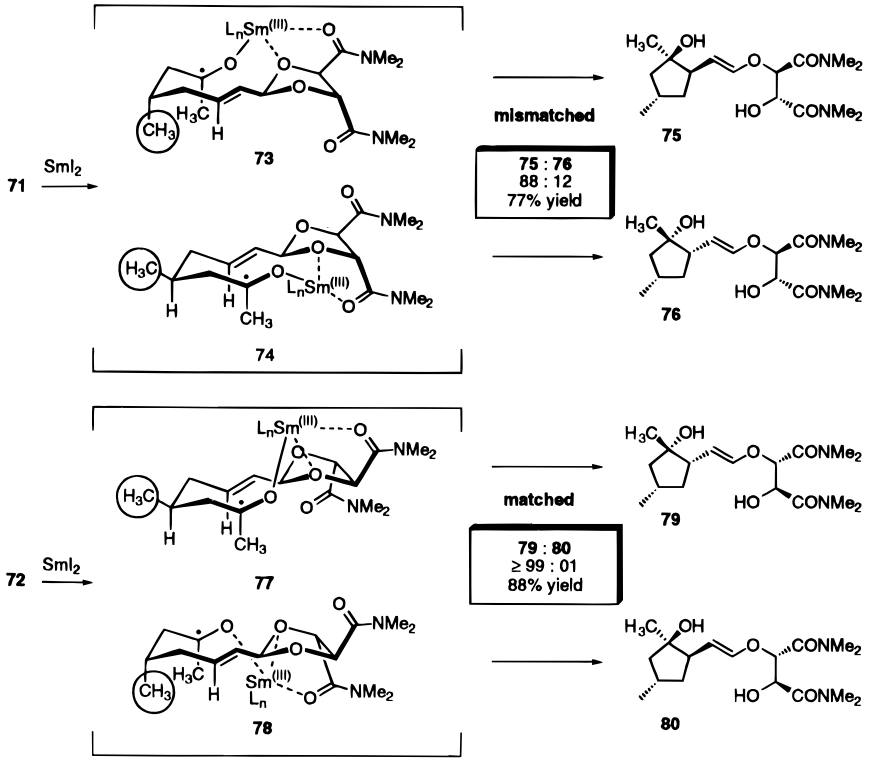
[a] (a) Propiolaldehyde diethyl acetal, *n*-BuLi, DMSO/THF, 72%; (b) *n*-Bu_4NF, THF/H_2O, 84%; (c) H_2, Lindlar catalyst, quinoline EtOAc, then MeOH, *p*-TsOH, 74%; (d) I_2, Ph_3P, imidazole, CH_3CN, 38%; (e) 2-methyl-1,3-dithiane, *n*-BuLi, 65%; (f) *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, PPTS (catalyst), DMF, 79%; (g) *N*,*N*,*N*′,*N*′-tetramethyl-D-tartaramide, PPTS (catalyst), DMF, 79%; (h) Chloramine-T, MeOH, H_2O, 55% (71), 50% (72).

yielded **64**.[38] Desilylation of **64** afforded **65**. Partial reduction of the alkyne **65**, followed by transacetalization produced the unsaturated methyl acetal **66**. After formation of the iodide **67**, alkylation with 2-methyl-1,3-dithiane yielded the protected ketone **68**.[39] From **68**, the synthesis diverged by transacetalization with both isomers of *N*,*N*,*N*′,*N*′-tetramethyltartaramide, yielding the L- and D-isomers, **69** and **70**, respectively. Deprotection of **69** and **70** provided the desired diastereomeric L- and D-substrates **71** and **72**, respectively.[40]

According to our mechanistic hypothesis regarding the source of stereoselectivity in these cyclizations, diastereomeric substrates **71** and **72** should represent mismatched and matched chirality, respectively. Cyclization of **71** through conformer **73**, which is analogous to **58**, places the methyl group in an unfavorable axial orientation (Scheme 12). However, conformer **74**, which is analogous to **60**, places the methyl group in a favorable equatorial orientation. Thus, we would expect to see

(38) McWilliams, J. C. Ph.D. Thesis, Cornell University, May, 1994.
(39) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.
(40) Huurdeman, W. F. J.; Wynberg, H.; Emerson, D. W. *Tetrahedron Lett.* **1971**, 3449.

Scheme 12

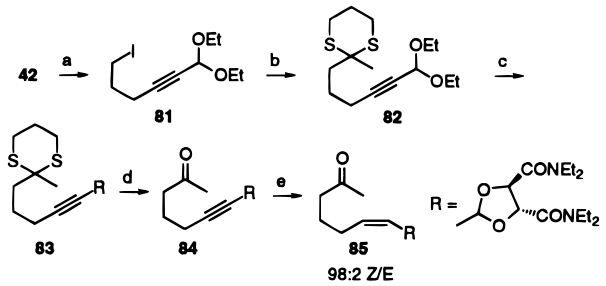


a decrease in the diastereoselectivity for the cyclization of **71** (i.e., the consequence of mismatched chirality). In contrast, cyclization of **72** through conformer **77**, which is analogous to **58**, places the methyl group in a favorable equatorial orientation. Conformer **78**, which is analogous to **60**, should be destabilized, because this conformer would place the methyl group in an unfavorable axial orientation. Thus, we would expect to see enhanced diastereoselectivity in the cyclization of **72**. It should be noted that if these cyclizations proceeded through conformers analogous to **61**, rather than **58**, we would expect no change in stereoselectivity for **71** (i.e., the methyl group is equatorial in both transition structures leading to major and minor cis diastereomers) and a mismatched effect for **72**.

The diastereomeric substrates **71** and **72** were submitted to cyclization under identical conditions (Scheme 12). In line with our predictions, cyclization of **71** yielded the diastereomers **75** and **76** with 88:12 diastereoselectivity, respectively (77% isolated yield). Cyclization of **72**, on the other hand, yielded the diastereomers **79** and **80** with ≥99:1 diastereoselectivity (88% isolated yield). Thus, the reactions of diastereomeric substrates **71** and **72** do indeed represent examples of mismatched and matched chirality, respectively, and reinforce the validity of the chelating model proposed.[41]

Another issue to be addressed was how the stereochemistry of the alkene in the starting material affected the diastereoselectivity of the cyclization. With this in mind, we prepared the *Z*-isomer, **85** (Scheme 13). The chloroalkyne **42** was converted to the iodide **81** under Finkelstein conditions. Alkylating 2-lithio-2-methyl-1,3-dithiane with **81** provided **82**.[40] Transacetalization with *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide provided the chiral acetal **83**, albeit in modest yield.[42] Following deprotection to the methyl ketone **84**,[43] Lindlar reduction then provided **85** as a 98:2 mixture of *Z*- and *E*-isomers, respectively.

Scheme 13[a]



[a] (a) NaI, $NaHCO_3$, Na_2SO_3, acetone, 86%; (b) *n*-BuLi, 2-methyl-1,3-dithiane, THF, 92%; (c) *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide, CSA (cat.), 4A mol. sieves, toluene, reflux, 42%; (d) NCS, $AgNO_3$, CH_3CN/H_2O, 56%; (e) H_2, Lindlar catalyst, quinoline, EtOAc, 90%.

Submitting the *Z*-isomer **85** to cyclization with SmI_2 yielded a 14:86:<1 ratio of **27a**:**28a**:(**29a** + **30a**), respectively. Thus, cyclization of **85** proceeded with the same high degree of relative stereoselectivity (≥99:1). Although stereoinduction from the chiral auxiliary was only modest (14:86), the major isomer **28a** was diastereomeric to the one formed upon cyclization of the *E*-isomers. Accordingly, the 2% impurity of **85** in the cyclization of the *E*-isomer **15a** should contribute 0.3% and 1.7% to the observed formation of **27a** and **28a** from **15a**. Thus, the diastereoselectivity resulting from cyclization of the pure *E*-isomer **15a** is actually 99:1.[44]

Although the stereochemistry of the major isomer **27a** had been established by an X-ray determination (*vide supra*), the conclusive proof for the stereochemical assignment of the minor isomer **28a** came from chemical correlation (Scheme 14). The enriched isomers of **27a** and **28a** (derived from the cyclization of **15a** and **85**, respectively) were hydrolyzed to the lactols **86**

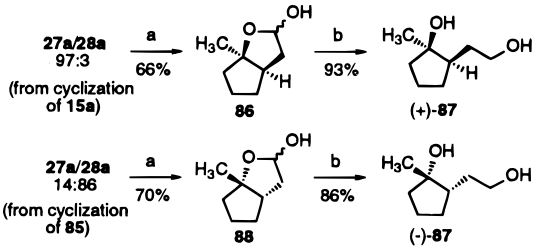
(41) Interestingly, the diastereoselectivity in the cyclization of **72** (≥99:1), exceeded the isomeric purity of the starting alkene geometry (96:4). Because transition structures for the *E*-isomers cannot be applied to the *Z*-isomer, this implies a matched case for the transition state with which *Z*-**72** cyclizes to yield **79** as well.

(42) Low yields were generally obtained for all propargylic acetals examined (i.e., transacetalization with *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide proceeded only at high temperatures and gave low yields of chiral products).

(43) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(44) This ratio of **27a**/**28a** was calculated as follows: **27a**/**28a** = (97 − 0.3)/(3 − 1.7) = 99/1.

Scheme 14[a]



[a] (a) 2 N HCl, THF; (b) $LiAlH_4$, THF.

and **88**. Reduction of each of these mixtures gave diols (+)-**87** and (−)-**87**, which differed only in their optical rotations. Thus, the two diastereomers **27a** and **28a** were of the same relative configuration about the cyclopentanol but differed in absolute stereochemistry.

The transformations depicted in Scheme 14 demonstrate the ease with which the chiral auxiliary can be removed. Although (−)-**87** is not available in high enantiomeric purity from the *Z*-isomer **85**, both enantiomers of *N,N,N′,N′*-tetramethyltartaramide are commercially available. Thus, both diols can be procured in high enantiomeric excess from the *E*-isomeric keto allylic acetal (**15** or its enantiomer) by selecting the corresponding enantiomer of the auxiliary.

Conclusions

In conclusion, the SmI_2-mediated cyclization of tartrate-derived keto allylic acetals provides the first example of an asymmetric radical cyclization in which high levels of stereochemical induction are achieved at both reacting centers. This transformation also demonstrates the first example of the use of a chelating metal to effect high levels of remote asymmetric induction in a radical reaction. The sense of relative stereoselectivity is also unusual for a SmI_2-mediated cyclization, providing consistently high ratios of cis/trans isomers. The stereoselectivity observed in this cyclization appears to arise from an intermediate tridentate ligate involving the ketyl oxygen and the acetal auxiliary. A double-diastereodifferentiating experiment provides additional support for this mechanistic hypothesis.

The preparation of enantiomerically enriched cyclopentanediols and -lactols can be achieved through this novel asymmetric cyclization protocol. We are currently exploring applications of this method to the synthesis of more complex structures as well as the extension of this method to acyclic substrates.

Experimental Section

Reagents. Unless otherwise noted, all reagents were purchased from Aldrich. Samarium metal was purchased from Cerac Inc., Milwaukee, WI, weighed, and stored under an inert atmosphere. Diiodomethane was purchased from Aldrich but was distilled and stored with copper over a nitrogen atmosphere prior to use. Propiolaldehyde diethyl acetal and δ-valerolactone were purchased from Lancaster. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl under argon prior to use. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were stored over 4 Å molecular sieves prior to use. All reactions were performed under a dry argon or nitrogen atmosphere.

(4*R*,5*R*)-*N,N,N′,N′*-Tetramethyl-2-((*E*)-6-oxo-1-heptenyl)-1,3-dioxolane-4,5-dicarboxamide (15a). Trimethylsilyl trifluoromethanesulfonate (0.11 mL, 0.57 mmol) was added to **36** (1.09 g, 5.84 mmol) and (2*R*,3*R*)-*N,N,N′,N′*-tetramethyl-2,3-bis(trimethylsilyloxy)succinbisamide (2.24 g, 6.43 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The solution was allowed to warm to −20 °C and stirred for 48 h at that temperature. Pyridine (0.23 mL, 2.8 mmol) was added to the solution. The solution was cannulated into ice-cold, saturated aqueous K_2CO_3, where it was stirred at room temperature for several hours. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×). The combined organic extracts were washed with brine and then concentrated. The resultant oil was diluted with THF (15 mL) and saturated aqueous K_2CO_3 (15 mL) and stirred for 60 min (until residual silyl ethers were completely hydrolyzed as judged by GC analysis). The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×). The combined organic extracts were washed with brine and dried over $MgSO_4$. The resultant oil was submitted to chromatography on silica gel (92:8 EtOAc/MeOH), yielding **15a** (1.09 g, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dt, J = 14.5, 6.7 Hz, 1H), 5.48 (ddt, J = 14.5, 6.9, 1.4 Hz, 1H), 5.44 (d, J = 6.9 Hz, 1H), 5.27 (d, J = 5.6 Hz, 1H), 5.18 (d, J = 5.6 Hz, 1H), 3.15 (s, 3H), 3.13 (s, 3H), 2.94 (s, 6H), 2.40 (t, J = 7.4 Hz, 2H), 2.09 (s, 3H), 2.08−2.03 (m, 2H), 1.69−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 168.7, 166.9, 138.1, 125.9, 106.0, 76.5, 74.4, 42.6, 37.07, 36.92, 35.71, 35.65, 31.1, 28.8, 22.2; IR (neat) 1713, 1650, 1503, 1149, 1056 cm^{-1}; $[\alpha]_D^{20}$ −19.0° (*c* 1.89, EtOAc).

(4*R*,5*R*)-2-((*E*)-6-Oxo-1-hexenyl)-*N,N,N′,N′*-tetramethyl-1,3-dioxolane-4,5-dicarboxamide (15h). To a solution of **48** (2.15 g, 5.34 mmol) in 9:1 CH_3CN/H_2O (75 mL) was slowly added bis(trifluoroacetoxy)iodobenzene (3.45 g, 8.03 mmol) at 0 °C. After stirring the mixture for 10 min, $NaHCO_3$ (2.10 g, 25.0 mmol), followed by brine (75 mL) were added. The aqueous phase was extracted with EtOAc (3×). The combined organic extracts were washed with brine and dried over $MgSO_4$. The resultant oil was chromatographed on silica gel (EtOAc → 93:7 EtOAc/MeOH), yielding **15h** (1.27 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (broad t, J = 1.4 Hz, 1H), 5.89 (dt, J = 15.1, 6.5 Hz, 1H), 5.50 (broad dd, J = 15.1, 6.5 Hz, 1H), 5.45 (d, J = 6.9 Hz, 1H), 5.28 (d, J = 5.8 Hz, 1H), 5.19 (d, J = 5.8 Hz, 1H), 5.15 (s, 3H), 3.14 (s, 3H), 2.94 (s, 6H), 2.42 (td, J = 7.4, 1.4 Hz, 2H), 2.13−2.07 (m, 2H), 1.75−1.61 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.0, 168.8, 167.0, 137.7, 126.2, 105.9, 76.5, 74.5, 42.9, 37.12, 36.98, 35.76, 35.72, 31.1, 20.6; IR (neat) 2727, 1722, 1652, 1505, 1152, 1059 cm^{-1}; $[\alpha]_D^{20}$ −21.5° (*c* 1.98, EtOAc).

Diethyl (2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*)-2-Hydroxy-2-methylcyclopentyl)vinyl)succinate (23). Samarium (104 mg, 0.69 mmol) was weighed into a flask in a glovebox. After sealing the flask with a septum, the flask was transferred to an argon manifold. To the solid samarium was added THF (3 mL), followed by diiodomethane (49 μL, 0.61 mmol). The mixture was stirred vigorously at room temperature for 2 h. A solution of **14** (95 mg, 0.29 mmol) in THF (3 mL) was added to the SmI_2 mixture by syringe pump over a period of 20 min. After stirring at room temperature for an additional 40 min, a minimum of saturated aqueous $NaHCO_3$ was added. The mixture was filtered through a bed of Celite and dried over K_2CO_3. The resultant crude oil was chromatographed on silica gel (1:1 hexanes/EtOAc), yielding an 85:15 ratio of **23** and **24**, respectively (67 mg, 70% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, J = 12.4 Hz, 1H), 4.87 (dd, J = 12.4, 8.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.62 (d, J = 2.2 Hz, 1H), 4.37−4.21 (m, 4H), 2.06−1.99 (m, 1H), 1.78−1.68 (m, 3H), 1.67−1.53 (m, 3H), 1.28 (q, J = 6.9 Hz, 6H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68, 168.0, 146.0, 106.0, 79.85, 78.62, 71.6, 62.3, 61.8, 48.8, 39.8, 30.04, 26.13, 21.22, 14.2, 14.1; IR (neat) 3500, 1747, 1732, 1668, 1652, 1264, 1200, 1156, cm^{-1}; MS (EI$^+$) calcd for $C_{16}H_{25}O_7$ (M − H): *m/e* 329.1601, found 329.1586; 329 (<5 (M − H)), 190 (10), 117 (100), 89 (15), 71 (13), 43 (40), 29 (32); $[\alpha]_D^{20}$ +18.6° (*c* 2.02, EtOAc). **Diethyl (2*R*,3*R*)-*O*-((*E*)-2-((1*S*,2*S*)-2-hydroxy-2-methylcyclopentyl)vinyl)succinate** (**24**): ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.65, 145.88, 105.78, 78.62, 30.14, 26.23, 21.31.

General Method for the Cyclization of Keto Allylic Acetals with SmI_2. Samarium metal (Cerac, 2.6−2.8 equiv) was weighed into a flask in a glovebox. After sealing the flask with a septum, the flask was transferred to an argon manifold. To the solid was added THF (9 mL/mmol diiodomethane), followed by diiodomethane (2.2−2.4 equiv). The mixture was stirred vigorously at room temperature for 2 h, during which time a deep blue color developed. A solution of the keto allylic acetals (0.3−0.4 mmol) in THF (6 mL/mmol) was added by syringe pump over a period of 30−90 min at 0 °C to 35 °C. After stirring at 0 °C to 35 °C for an additional 30−60 min, Celite was added until a viscous slurry formed. To this mixture was added saturated aqueous $NaHCO_3$ (2 mL), and stirring was continued for 10 min. After dilution with CH_2Cl_2, the mixture was filtered through a bed of Celite. The

filter bed was washed several times with CH_2Cl_2, and the combined filtrates were dried over $MgSO_4$. The resultant crude oil was chromatographed on silica gel.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*)-2-Hydroxy-2-methylcyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27a). Using the general procedure above, substrate **15a** was cyclized, and the products were isolated after chromatography (6:1 EtOAc/MeOH) to afford a 96:3:1 mixture of **27a**, **28a**, and (**29a** + **30a**), respectively (81% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, J = 12.7 Hz, 1H), 4.92 (dd, J = 12.7, 8.4 Hz, 1H), 4.80 (broad dd, J = 7.1, 4.7 Hz, 1H), 4.72 (d, J = 4.7 Hz, 1H), 4.10 (broad d, J = 7.1 Hz, 1H (OH)), 3.13 (s, 3H), 3.09 (s, 3H), 2.94 (s, 3H), 2.91 (s, 3H), 2.23−1.98 (m, 1H), 1.76−1.48 (m, 6H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.5, 106.1, 79.73, 79.14, 69.31, 48.9, 39.9, 36.92, 36.86, 36.19, 35.92, 30.0, 26.0, 21.1; IR (neat) 3408, 1644, 1504, 1149, 1058 cm^{-1}; MS (EI$^+$) calcd for $C_{16}H_{29}N_2O_5$ (M + H): *m*/*e* 329.2076, found 329.2070; 329 (<5 (M + H)), 188 (38), 116 (100), 98 (34), 72 (97), 43 (73); $[\alpha]_D^{20}$ +4.9° (*c* 2.47, EtOAc); Anal. Calcd for $C_{16}H_{28}N_2O_5$: C: 58.51; H: 8.59; N: 8.53. Found: C: 58.58; H: 8.83; N: 8.30.

X-ray Crystallography for 27a. A suitable crystal was selected and mounted on a Nicolet P3 4-circle diffractometer. Unit cell dimensions were determined after carefully centering 24 reflections chosen such that 20° < 2θ < 35°. Peak profiles examined from this group indicated a large mosaic spread, and an ω scan width of 1.2° was chosen to ensure that the entire intensity peak was recorded. Data were collected in two shells, the first, 0° < 2θ < 40° was measured at 3.91°/min and the second shell, to 45°, was measured at 2.02°/min. No decay was observed in the intensities of two standard reflections monitored every 198 reflections.

Structure solution via direct methods in the noncentrosymmetric space group *P*1 revealed all non-hydrogen atoms. Hydrogens were placed at calculated positions which were allowed to ride on the position of the parent atom in subsequent cycles of least-squares refinement. Absolute configuration was assigned from known stereochemistry of the precursor. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen thermal parameters were set at 1.2 times the equivalent isotropic value of the parent atom. Full details of the crystallographic results are included in the Supporting Information.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*)-2-Ethyl-2-hydroxycyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27b). Using the general procedure above, substrate **15b** was cyclized, and the products were isolated after chromatography (6:1 EtOAc/MeOH) to afford a 94:3:3 mixture of **27b**, **28b**, and (**29b** + **30b**), respectively (83% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J = 13.0 Hz, 1H), 4.90 (dd, J = 13.0, 8.4 Hz, 1H), 4.81 (broad dd, J = 6.8, 4.1 Hz, 1H), 4.70 (d, J = 4.1 Hz, 1H), 3.90 (broad d, 6.8H, 1 (OH)), 3.15 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.93 (s, 3H), 2.13−2.04 (m, 1H), 1.68−1.48 (m, 7H), 1.37−1.26 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.4, 106.3, 82.3, 79.3, 69.4, 47.5, 36.91, 36.85, 36.56, 36.22, 35.95, 32.0, 30.0, 21.1, 8.7; IR (neat) 3416, 1651, 1644, 1504, 1150, 1058 cm^{-1}; MS (CI$^+$, NH_3) calcd for $C_{17}H_{31}N_2O_5$ (M + H): *m*/*e* 343.2255, found 343.2233; 343 (100), 325 (50); (EI$^+$) 116 (100), 72 (48); $[\alpha]_D^{20}$ +5.2° (*c* 2.04, EtOAc). Anal. Calcd for $C_{17}H_{30}N_2O_5$: C: 59.63; H: 8.83; N: 8.18. Found: C: 59.69; H: 8.82; N: 8.16.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*S*)-2-Hydroxy-2-(1-methylethyl)cyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27c). Using the general procedure above, substrate **15c** was cyclized, and the products were isolated after chromatography (9:1 EtOAc/MeOH) to afford a 90:7:3 mixture of **27c**, **28c**, and (**29c** + **30c**), respectively (82% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, J = 13.0 Hz, 1H), 4.92 (dd, J = 13.0, 8.1 Hz, 1H), 4.81 (broad dd, J = 7.0, 4.2 Hz, 1H), 4.69 (d, J = 4.2 Hz, 1H), 3.88 (broad d, J = 7.0 Hz, 1H (OH)), 3.14 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.92 (s, 3H), 2.31 (broad dt, J = 10.3, 7.7 Hz, 1H), 1.79−1.57 (m, 5H), 1.53−1.44 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.3, 145.4, 106.2, 84.5, 78.9, 69.2, 44.5, 36.81, 36.78, 35.99, 35.74, 34.6, 32.6, 30.2, 20.9, 17.74, 17.63; IR (neat) 3417, 1644, 1503, 1148, 1058 cm^{-1}; MS (EI$^+$) calcd for $C_{18}H_{33}N_2O_5$ (M + H): *m*/*e* 357.2389, found 357.2406; 357 (M + H (<5)), 188 (15), 116 (100), 72 (95); $[\alpha]_D^{20}$ +6.5° (*c* 2.00, EtOAc). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C: 61.65; H: 9.05; N: 7.86. Found: C: 60.63; H: 9.29; N: 7.33.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*S*)-2-(1,1-Dimethylethyl)-2-hydroxycyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27d). Using the general procedure above, substrate **15d** was cyclized, and the products were isolated after chromatography (8:1 EtOAc/MeOH) to afford an 88:9:3 mixture of **27d**, **28d**, and (**29d** + **30d**), respectively (86% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J = 12.7 Hz, 1H), 5.01 (dd, J = 12.7, 9.0 Hz, 1H), 4.80 (broad dd, J = 6.7, 4.0 Hz, 1H), 4.67 (d, J = 4.0 Hz, 1H), 3.85 (broad d, J = 6.7 Hz, 1H (OH)), 3.14 (s, 3H), 3.09 (s, 3H), 2.97 (s, 3H), 2.92 (s, 3H), 2.48 (dt, J = 7.7, 9.0 Hz, 1H), 1.95−1.87 (m, 1H), 1.73−1.38 (m, 5H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.3, 144.7, 108.6, 85.6, 79.2, 69.4, 43.3, 37.50, 36.86, 36.79, 36.27, 36.20, 35.90, 33.2, 35.9, 22.2; IR (neat) 3416, 1644, 1504, 1146, 1058 cm^{-1}; MS (CI$^+$ (NH_3)) calcd for $C_{19}H_{35}N_2O_5$ (M + H): *m*/*e* 371.2511, found 371.2546; 388 (24 (M + NH_4)), 371 (100 (M + H)), 353 (57), 343 (50), 327 (33); (EI) 116 (100), 72 (53), 57 (29); $[\alpha]_D^{20}$ +2.5° (*c* 1.79, EtOAc). Anal. Calcd for $C_{19}H_{34}N_2O_5$: C: 61.60; H: 9.25; N: 7.56; found: C: 61.62; H: 9.16; N: 7.39.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*S*)-2-(2,4-Dimethoxyphenyl)-2-hydroxycyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27g). Using the general procedure above, substrate **15g** was cyclized, and the products were isolated after chromatography (9:1 EtOAc/MeOH) to afford a 4:1 mixture of **27g** and **28g**, respectively (43% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.40 (dd, J = 8.7, 2.0 Hz, 1H), 6.10 (d, J = 12.8 Hz, 1H), 4.87 (dd, J = 12.8, 7.5 Hz, 1H), 4.74 (broad m, 1H), 4.62 (d, J = 4.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.04 (s, 3H), 3.00 (s, 3H), 2.93 (s, 3H), 2.86 (s, 3H), 2.18−2.09 (m, 1H), 1.98−1.65 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.2, 159.5, 157.7, 145.4, 127.1, 125.6, 106.3, 103.6, 99.1, 82.5, 79.2, 69.2, 55.2 (2 carbons), 46.5, 39.7, 36.84, 36.67, 36.21, 35.90, 29.9, 21.7; IR (neat) 3418, 1651, 1644, 1583, 1504, 1207, 1158, 1048 cm^{-1}; MS (EI$^+$) calcd for $C_{23}H_{34}N_2O_7$ (M+): *m*/*e* 450.2366, found 450.2363; 432 (7), 188 (30), 116 (100), 72 (60); $[\alpha]_D^{20}$ +24.8° (*c* 2.07, EtOAc).

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*)-2-Hydroxycyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (27h). Samarium (465 mg, 3.09 mmol) was weighed into a flask in a glovebox. After sealing the flask with a septum, the flask was transferred to an argon manifold. To the solid samarium was added THF (25 mL), followed by diiodomethane (686 mg, 2.56 mmol). The mixture was stirred vigorously at room temperature for 2 h. A solution of **15h** (200 mg, 0.64 mmol) in THF (5 mL) was added by syringe pump over a period of 7 h at room temperature. After stirring at room temperature for an additional 12 h, air was bubbled into the mixture until the blue-green color had faded to brown. To this mixture was added saturated aqueous Na_2SO_3 (0.5 mL), saturated aqueous $NaHCO_3$ (6 mL), and enough Celite to produce a viscous slurry. After dilution with CH_2Cl_2, the mixture was filtered through a bed of Celite. The filter bed was washed several times with CH_2Cl_2, and the combined filtrates were dried over $MgSO_4$. The resultant crude oil was chromatographed on silica gel (6:1 EtOAc/MeOH), yielding a 93:5:2 mixture of **27h**, **28h**, and (**29h** + **30h**), respectively (107 mg, 53% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, J = 12.6 Hz, 1H), 5.00 (dd, J = 12.6, 7.9 Hz, 1H), 4.81 (broad dd, J = 6.3, 4.6 Hz, 1H), 4.57 (d, J = 4.6 Hz, 1H), 4.13 (broad s, 1H), 3.99 (broad s, 1 (OH)), 3.12 (s, 3H), 3.10 (s, 3H), 2.94 (s, 3H), 2.91 (s, 3H), 2.31−2.24 (m, 1H), 2.00 (broad s, 1 (OH)), 1.85−1.73 (m, 2H), 1.73−1.58 (m, 2H), 1.56−1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.4, 145.2, 106.5, 78.8, 75.4, 69.2, 44.4, 36.92, 36.89, 36.11, 35.85, 33.6, 28.6, 21.9; IR (neat) 3406, 1644, 1504, 1147, 1058 cm^{-1}; MS (EI$^+$) calcd for $C_{15}H_{27}N_2O_5$ (M + H): *m*/*e* 315.1920, found 315.1897; 315 (<5 (M + H)), 188 (15), 116 (100), 72 (89), 44 (21); $[\alpha]_D^{20}$ +2.8° (*c* 3.02, EtOAc).

(2*R*,3*R*)-*O*-((*E*)-2-((1*S*,2*S*)-2-Hydroxy-2-methylcyclopentyl)vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (28a). Using the general procedure above, substrate **85** was cyclized, and the products were isolated after chromatography to afford a 13:83:3 mixture of **27a**, **28a**, and (**29a** + **30a**), respectively (83% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, J = 12.6 Hz, 1H), 4.86 (dd, J = 12.6, 8.7 Hz, 1H), 4.82 (dd, J = 6.9, 4.3 Hz, 1H), 4.71 (d, J = 4.3 Hz, 1H), 3.92 (d, J = 6.9Hz, 1H (OH)), 3.15 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.93 (s, 3H), 2.05−1.99 (m, 1H), 1.81−1.68 (m, 3H), 1.67−1.50 (m, 3H), 1.159 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.22, 168.22, 145.55, 106.07,

79.76, 78.94, 69.1, 48.8, 39.82, 36.79 (2 carbons), 36.00, 35.69, 30.37, 25.96, 21.15; IR (neat) 3416, 1644, 1504, 1151, 1058 cm^{-1}; MS (EI^+) calcd for $C_{16}H_{29}O_5N_2$ (M + H): *m/e* 329.2076, found 329.2085; 329 (<5 (M + H)), 116 (84), 72 (75), 18 (100); $[\alpha]_D^{20}$ +43.3° (*c* 2.24, EtOAc).

5-Hydroxy-*N,O*-dimethylpentanohydroxamic Acid (32). Trimethylaluminum (450 mL, 0.90 mol) was slowly added over 2 h to *N,O*-dimethylhydroxylamine hydrochloride (88.0 g, 0.90 mol) in CH_2Cl_2 (500 mL) at −78 °C. The bath was removed, and the solution was allowed to stir overnight. Upon cooling the solution to 0 °C, δ-valerolactone (30.15 g, 0.298 mmol) was cannulated in over a 30 min period. The cooling bath was removed, and the solution was stirred for several hours. The solution was cooled to 0 °C, whereupon Rochelle's salt (100 g) in H_2O (150 mL) was added (very slowly at first). The mixture was filtered through a bed of Celite, washing several times with CH_2Cl_2. Drying the solution over $MgSO_4$ and concentration yielded **32** (43.62 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.60 (t, J = 6.3 Hz, 2H), 3.15 (s, 3H), 2.44 (broad t, J = 6.9 Hz, 2H), 1.74−1.67 (m, 2H), 1.61−1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (broad), 61.5, 60.9, 31.9, 31.8 (broad), 31.0 (broad), 20.3; IR (neat) 3424, 1644, 1179, 1060, 999 cm^{-1}.

***N,O*-Dimethyl-5-oxopentanohydroxamic acid (33).** Oxalyl chloride (2.4 mL, 28 mmol) was slowly added to DMSO (4.0 mL, 56 mmol) in CH_2Cl_2 (20 mL) at −78 °C. After stirring 5 min, 5-hydroxy-*N,O*-dimethylpentanohydroxamic acid (3.00 g, 18.6 mmol) in CH_2Cl_2 (5 mL) was cannulated into the solution over a 5 min period. The heterogeneous solution was stirred for 60 min, whereupon triethylamine (13 mL, 93 mmol) was added. The mixture was warmed to room temperature and stirred for several hours. The mixture was poured into Et_2O (100 mL) and filtered through Celite (washing with Et_2O). After concentration, the oil was diluted with EtOAc and Et_2O and then filtered through Celite. This solution was concentrated again, diluted with Et_2O, and filtered through Celite. After a final concentration, the homogenous oil was submitted to vacuum distillation, collecting **33** (4.4 g, 76%) at 70−74 °C (0.2 torr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, J = 1.5 Hz, 1H), 3.65 (s, 3H), 3.15 (s, 3H), 2.52 (td, J = 7.0, 1.5 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 1.98−1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 173.5 (broad), 61.0, 42.9, 31.9 (broad), 30.5 (broad), 16.8; IR (neat) 2726, 1722, 1661, 1180, 998 cm^{-1}.

(*E*)-*N,O*-Dimethyl-7-oxo-5-heptenohydroxamic acid (34). To a solution of diisopropylamine (28 mL, 200 mmol) in THF (450 mL) was added *n*-BuLi (80 mL, 203 mmol) at −78 °C. After stirring the solution for 2 h, acetaldehyde *N*-*tert*-butylimine (13.7 mL, 101 mmol) was added over 10 min. The solution was stirred at −78 °C for 90 min, and then diethyl chlorophosphate (14.6 mL, 101 mmol) was added over 20 min. The solution was stirred at −78 °C for 2 h and then allowed to warm to −10 °C over 3 h. After stirring for an additional 30 min at −10 °C, the solution was cooled again to −78 °C, whereupon **33** (14.7 g, 92 mmol) was added gradually. The solution was warmed to 0 °C overnight and then poured into an ice cold solution of oxalic acid (35 g, 277 mmol) in H_2O (400 mL). Benzene (400 mL) was added, and the resulting mixture was stirred for 36 h. The organic layer was separated, and to the aqueous phase was added solid NaCl until the solution was saturated. The aqueous phase was extracted with EtOAc until no more product was detected in the extract. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×) and brine, back-extracting with EtOAc (2×). After drying ($MgSO_4$) and concentration, the crude oil was submitted to chromatography on silica gel (1:2 hexanes/EtOAc), yielding **34** of 92% purity by GC (7.05 g, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 8.0 Hz, 1H), 6.80 (dt, J = 15.7, 6.6 Hz, 1H), 6.08 (ddt, J = 15.7, 8.0, 1.4 Hz, 1H), 3.62 (s, 3H), 3.12 (s, 3H), 2.42 (broad t, J = 7.2 Hz, 2H), 2.39−2.33 (m, 2H), 1.85−1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 173.5 (broad), 157.8, 133.2, 61.2, 32.1 (two carbons), 30.8, 22.5; IR (neat) 1689, 1661, 1130, 992 cm^{-1}.

(*E*)-7,7-Dimethoxy-*N,O*-dimethyl-5-heptenohydroxamic acid (35). Trimethylsilyl trifluoromethanesulfonate (0.8 mL, 4.13 mmol) was added to a solution of methoxytrimethylsilane (21 mL, 142 mmol) and **34** (7.0 g, 38 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The reaction was stirred overnight, whereupon pyridine (1.5 mL, 18 mmol) was added to the now heterogeneous mixture. After stirring for 20 min, the mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic extracts were washed with brine, back-extracting with CH_2Cl_2 (2×). The organic phase was dried ($MgSO_4$) and concentrated, yielding **35** (8.45 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dt, J = 15.8, 6.6 Hz, 1H), 5.46 (ddt, J = 15.8, 5.4, 1.2 Hz, 1H), 4.69 (d, J = 5.4 Hz, 1H), 3.64 (s, 3H), 3.28 (s, 6H), 3.15 (s, 3H), 2.41 (broad t, J = 7.4 Hz, 2H), 2.15−2.09 (m, 2H), 1.77−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (broad), 134.1, 126.8, 102.7, 60.6, 52.0, 31.5 (broad), 31.3, 30.5 (broad), 23.1; IR (neat) 1667, 1132, 1050, 993 cm^{-1}.

General Method for the Preparation of Ketones from Weinreb's Amide 35. A solution of the organolithium or Grignard reagent was added to **35** in THF (2.5 mL/mmol **35**) at −60 °C to 0 °C. After stirring 20−120 min at 0 °C to 23 °C, H_2O (for organolithium reagents) or a 10% solution of Rochelle's salt (for Grignard reagents) was added. The aqueous layer was extracted with Et_2O (2×). The combined organic extracts were washed with brine and dried over $MgSO_4$. The resultant oil was subjected to chromatography on silica gel.

(*E*)-8,8-Dimethoxy-6-octen-2-one (36). Utilizing the general procedure above, methylmagnesium bromide in Et_2O provided an oil that was subjected to chromatography on silica gel (3:1 hexanes/EtOAc), yielding **36** (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, J = 15.6, 6.2 Hz, 1H), 5.43 (ddt, J = 15.6, 5.3, 1.3 Hz, 1H), 4.69 (d, J = 5.3 Hz, 1H), 3.27 (s, 6H), 2.40 (t, J = 7.4 Hz, 2H), 2.09 (s, 3H), 2.08−2.02 (m, 2H), 1.69−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 134.4, 127.2, 103.1, 52.6, 42.8, 31.3, 29.9, 22.7; IR (neat) 1716, 1674, 1132, 1052 cm^{-1}.

(*E*)-9,9-Dimethoxy-7-nonen-3-one (37). Utilizing the general procedure above, ethylmagnesium bromide in Et_2O provided an oil that was subjected to silica gel chromatography (3:1 hexanes/EtOAc), yielding **37** (65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, J = 15.6, 6.8 Hz, 1H), 5.44 (ddt, J = 15.6, 5.3, 1.3 Hz, 1H), 4.69 (d, J = 5.3 Hz, 1H), 3.29 (s, 6H), 2.42−2.36 (m, 4H), 2.09−2.03 (m, 2H), 1.71−1.63 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 134.2, 127.0, 102.8, 52.3, 41.1, 35.5, 31.1, 22.5, 7.4; IR (neat) 1715, 1674, 1131, 1052 cm^{-1}.

(*E*)-9,9-Dimethoxy-2,2-dimethyl-7-nonen-3-one (38). Utilizing the general procedure above, *tert*-butyllithium in pentane provided an oil that was subjected to silica gel chromatography (7:2 hexanes/EtOAc), yielding **38** (169 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dt, J = 15.5, 6.9 Hz, 1H), 5.44 (ddt, J = 15.5, 5.3, 1.4 Hz, 1H), 4.69 (d, J = 5.3 Hz, 1H), 3.29 (s, 6H), 2.46 (t, J = 7.3 Hz, 2H), 2.07−2.02 (m, 2H), 1.68−1.61 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 134.9, 127.1, 103.2, 52.6, 44.1, 35.6, 31.5, 26.4, 22.9; IR (neat) 1705, 1131, 1052 cm^{-1}.

(*E*)-1,1-Dimethoxy-2-tridecen-8-yn-7-one (39). Utilizing the general procedure above, *n*-butyllithium in hexanes provided an oil that was subjected to silica gel chromatography (6:1 hexanes/EtOAc), yielding **39** (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, J = 15.8, 6.3 Hz, 1H), 5.44 (ddt, J = 15.8, 5.3, 1.2 Hz, 1H), 4.69 (d, J = 5.3 Hz, 1H), 3.28 (s, 6H), 2.50 (t, J = 7.4 Hz, 2H), 2.32 (t, J = 7.0 Hz, 2H), 2.10−2.05 (m, 2H), 1.78−1.70 (m, 2H), 1.56−1.49 (m, 2H), 1.44−1.35 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 133.8, 127.2, 102.6, 93.8, 80.5, 52.1, 44.3, 30.8, 29.3, 22.8, 21.5, 18.2, 13.1; IR (neat) 2212, 1674, 1131, 1052 cm^{-1}.

(*E*)-7,7-Dimethoxy-1-phenyl-5-hepten-1-one (40). Utilizing the general procedure above, phenyllithium in 7:3 cyclohexane: Et_2O provided an oil that was subjected to silica gel chromatography (5:2 hexanes/EtOAc), yielding **40** (76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.91 (m, 2H), 7.55−7.51 (m, 1H), 7.45−7.41 (m, 2H), 5.83 (dt, J = 15.6, 6.6 Hz, 1H), 5.48 (ddt, J = 15.6, 5.2, 1.5 Hz, 1H), 4.70 (d, J = 5.2 Hz, 1H), 3.29 (s, 6H), 2.96 (t, J = 7.3 Hz, 2H), 2.19−2.14 (m, 2H), 1.88−1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 136.6, 134.2, 132.6, 128.2, 127.6, 127.1, 102.8, 52.3, 37.3, 31.2, 23.0; IR (neat) 1686, 1598, 1131, 1050 cm^{-1}.

(2*R*,3*R*)-*O*-((*E*)-2-((1*R*,2*R*,4*S*)-2,4-Dimethyl-2-hydroxycyclopentyl)vinyl)-*N,N,N′,N′*-tetramethylsuccinamide (75). To a saturated (0.1 M) solution of SmI_2 (6.2 mL, 0.62 mmol) in THF was added a solution of **71** (81 mg, 0.24 mmol) in THF (2 mL) by syringe pump over a period of 40 min at 30 °C. After stirring at 30 °C for an additional 60 min, air was bubbled into the mixture until the blue-green color had faded to brown. To this mixture was added saturated aqueous Na_2SO_3

(0.3 mL), saturated aqueous $NaHCO_3$ (3 mL), and enough Celite to produce a viscous slurry. After dilution with CH_2Cl_2, the mixture was filtered through a bed of Celite. The filter bed was washed several times with CH_2Cl_2, and the combined filtrates were dried over $MgSO_4$. The resultant crude oil was chromatographed on silica gel (6:1 EtOAc/MeOH), yielding an 88:12 mixture of **75** and **76**, respectively (63 mg, 77% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, J = 12.3 Hz, 1H), 4.90 (dd, J = 12.3, 8.4 Hz, 1H), 4.82 (dd, J = 7.0, 4.0 Hz, 1H), 4.71 (d, J = 4.0 Hz, 1H), 3.88 (d, J = 7.0 Hz, 1H), 3.15 (s, 3H), 3.11 (s, 3H), 2.98 (s, 3H), 2.93 (s, 3H), 2.26−2.17 (m, 1H), 1.96 (dd, J = 13.5, 7.8 Hz, 1H), 1.88−1.80 (m, 2H), 1.37−1.31 (m, 1H), 1.18 (dd, J = 13.5, 8.7 Hz, 1H), 1.15 (s, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.3, 106.2, 80.7, 78.9, 69.3, 49.2, 47.4, 38.4, 36.90, 36.85, 36.14, 35.87, 29.2, 26.0, 22.3; IR (neat) 3417, 1644, 1504, 1145, 1058 cm^{-1}; MS (EI$^+$) calcd for $C_{17}H_{31}N_2O_5$ (M + H): *m*/*e* 343.2233, found 343.2220; 343 (9 (M + H)), 188 (58), 116 (99), 72 (100), 46 (58); $[\alpha]_D^{20}$ +6.8° (*c* 2.10, EtOAc).

(2*R*,3*R*)-*O*-((*E*)-2-((1*S*,2*S*,4*S*)-2,4-Dimethyl-2-hydroxycyclopentyl)-vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (76): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, J = 12.5 Hz, 1H), 1.01 (d, J = 6.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.3, 168.2, 145.5, 105.9, 80.0, 79.1, 49.9, 48.6, 40.2, 31.0, 27.5, 21.5.

(2*S*,3*S*)-*O*-((*E*)-2-((1*S*,2*S*,4*S*)-2,4-Dimethyl-2-hydroxycyclopentyl)-vinyl)-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide (79). To a saturated (0.1 M) solution of SmI_2 (6.2 mL, 0.62 mmol) was added a solution of **72** (78 mg, 0.23 mmol) in THF (2 mL) by syringe pump over a period of 40 min at 30 °C. After stirring at 30 °C for an additional 60 min, air was bubbled into the mixture until the blue-green color had faded to brown. To this mixture was added saturated aqueous Na_2SO_3 (0.3 mL), saturated aqueous $NaHCO_3$ (3 mL), and enough Celite to produce a viscous slurry. After dilution with CH_2Cl_2, the mixture was filtered through a bed of Celite. The filter bed was washed several times with CH_2Cl_2, and the combined filtrates were dried over $MgSO_4$. The resultant crude oil was chromatographed on silica gel (6:1 EtOAc/MeOH), yielding **79** as the major isomer of a ≥ 99:1 mixture of diastereomers (69 mg, 88% combined yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, J = 12.4 Hz, 1H), 4.93 (dd, J = 12.4, 8.0 Hz, 1H), 4.82 (dd, J = 6.9, 4.0 Hz, 1H), 4.71 (d, J = 4.0 Hz, 1H), 3.85 (d, J = 6.9 Hz, 1H (OH)), 3.15 (s, 3H), 3.11 (s, 3H), 2.98 (s, 3H), 2.93 (s, 3H), 2.11−2.05 (m, 1H), 2.00−1.90 (m, 2H), 1.82−1.75 (m, 1H), 1.41−1.28 (m, 2H), 1.15 (m, 3H), 1.01 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.5, 105.9, 79.9, 79.5, 69.4, 49.9, 48.5, 39.6, 36.98, 36.89, 36.35, 36.07, 30.9, 27.4, 21.8; IR (neat) 3421, 1644, 1503, 1148, 1057 cm^{-1}; MS (EI$^+$) calcd for $C_{17}H_{31}N_2O_5$ (M + H): *m*/*e* 343.2233, found 343.2230; 188 (50), 142 (20), 116 (100), 98 (37), 72 (90), 46 (50); $[\alpha]_D^{20}$ −12.9° (*c* 2.30, EtOAc).

(1*R*,2*R*)-2-(2-Hydroxyethyl)-1-methylcyclopentanol [(+)-87]. To a 97:3 mixture of **27a** and **28a** (116 mg, 0.35 mmol) in THF (4 mL) at room temperature was added 6 N HCl (2 mL). The solution was stirred for 30 min, and then solid Na_2CO_3 and saturated aqueous $NaHCO_3$ were added until no more effervescence was observed. The aqueous solution was extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over K_2CO_3. The resultant oil was chromatographed on silica gel (1:1 hexanes/EtOAc), yielding an epimeric mixture of lactols **86** (33 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ major: 5.52−5.51 (m, 1H), 3.91 (s, 1H (OH)), 2.47−2.43 (m, 1H), 2.16 (ddd, J = 13.3, 9.1, 1.1 Hz, 1H), 1.83−1.77 (m, 1H), 1.73−1.66 (m, 2H), 1.65−1.52 (m, 3H), 1.45 (s, 3H), 1.32 (ddd, J = 13.3, 11.2, 6.9 Hz, 1H), minor: 5.50−5.49 (m, 1H), 4.20 (broad s, 1H (OH)), 2.28−2.18 (m, 1H), 2.00−1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ major: 99.27, 93.7, 46.7, 41.7, 40.9, 33.1, 28.6, 24.0, minor: 99.31, 94.3, 47.3, 40.4, 33.6, 26.7, 24.6; IR (neat) 3405, 1037, 1005 cm^{-1}.

A solution of epimeric lactols **86** (33 mg, 0.23 mmol) in THF (2 mL) was cannulated into a mixture of $LiAlH_4$ (8 mg, 0.21 mmol) in THF (2.5 mL) at room temperature. After stirring for 30 min, the reaction was quenched with 2.5 N NaOH (1 mL). To the mixture was added Celite, followed by CH_2Cl_2. The slurry was filtered, washing with CH_2Cl_2. After drying over $MgSO_4$, the resultant oil was chromatographed on silica gel (100% EtOAc), yielding **(+)-87** (31 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dt, J = 10.5, 6.0 Hz, 1H), 3.61 (ddd, J = 10.5, 7.8, 5.7 Hz, 1H), 1.85−1.43 (m, 9H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.8, 61.7, 46.7, 41.6, 31.7, 30.0, 26.6, 21.2; IR (neat) 3362, 1056 cm^{-1}; MS (EI$^+$) calcd for $C_8H_{15}O_2$ (M − H): *m*/*e* 143.1072, found 143.1074; 126 (10 (M − H_2O)), 111 (23), 97 (38), 71 (87), 43 (100), 31 (36), 17 (15); $[\alpha]_D^{20}$ +14.4° (*c* 2.05, $CHCl_3$).

(1*S*,2*S*)-2-(2-Hydroxyethyl)-1-methylcyclopentanol ((−)-87). To a 14:86 mixture of **27a** and **28a**, respectively (87 mg, 0.27 mmol), in THF (4 mL) at room temperature was added 6 N HCl (2 mL). The solution was stirred for 30 min, and then solid Na_2CO_3 and saturated aqueous $NaHCO_3$ were added until no more effervescence was observed. The aqueous layer was extracted with EtOAc (3×). The combined organic extracts were washed with brine (2×) and dried over K_2CO_3. The resultant oil was chromatographed on silica gel (1:1 hexanes/EtOAc), yielding a mixture of epimeric lactols **88** (27 mg, 0.19 mmol, 70%). This mixture was diluted in THF (2 mL) and cannulated into a mixture of $LiAlH_4$ (7 mg, 0.18 mmol) in THF (2.5 mL) at room temperature. After stirring 20 min, the reaction was quenched with 2.5 N NaOH (1 mL). To the mixture was added Celite, followed by CH_2Cl_2. The slurry was filtered, washing with CH_2Cl_2. After drying over $MgSO_4$, the resultant oil was chromatographed on silica gel (100% EtOAc), yielding **(−)-87** (24 mg, 86%): $[\alpha]_D^{20}$ −11.7° (*c* 0.99, $CHCl_3$).

Acknowledgment. We thank the National Institutes of Health for their generous financial support of this program. We would also like to thank Dr. Todd Nelson for helpful comments regarding the preparation of the manuscript.

Supporting Information Available: Crystallographic data and tables for **27a**. Full experimental details for the preparation of **10**−**12**, **14**, **15b-g**, **42**−**45**, **48**, **51**, **52**, **64**−**72**, and **81**−**85**. Copies of ^{1}H and ^{13}C spectra of compounds for which no elemental analysis was obtained (134 pages). See any current masthead page for ordering and Internet access instructions.

JA963195C