Two-Directional Chain Synthesis and Terminus Differentiation

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Introduction

Macrolide antibiotics (polypropionates) and terpenes (polyisoprenoids) are examples of natural products that contain repeating elements within their structure. Not surprisingly, laboratory syntheses of these molecules often use reactions that introduce the repeating element on mulitple occasions. Several years ago, we began to explore the potential of performing these reactions at different positions within the target molecule at the same time. We focused our attention on molecules that comprise, or contain within their structure, acyclic chains. Our plan was to simultaneously elongate the two ends of a nascent chain. The two-directional chain synthesis strategy offers the possibility of reducing the number of synthetic transformations required to synthesize a chain-containing molecule.[1] To realize this goal, it was clear that we would have to overcome at least one problem that is intrinsic to the strategy.

Since the ends of the homologated chain are prepared by the same type of reaction(s), they will be either identical or similar to each other. In the common case of a target molecule with dissimilar chain termini, a method to distinguish them will be required in order for the two-directional strategy to be an efficient one. Realizing this, we have focused our attention on group selective reactions that can effectively distinguish the terminal groups of two-directionally homologated chains. In this Account, we will survey representative examples of natural product syntheses that use the two-directional strategy and examine the group selective reactions that have been used to differentiate chain termini.

In general, four strategies exist for the synthesis of acyclic chains: *Linear synthesis* involves the one-directional homologation of an acyclic chain and is well-suited for the preparation of short chains in either racemic or optically active form (Figure 1). The advantages of a *convergent synthesis* (one-directional) have been widely recognized by organic chemists. This strategy has been used commonly in recent years as the

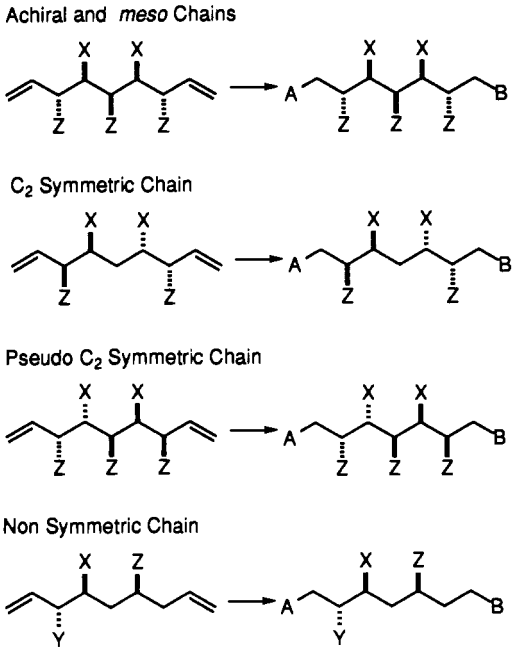
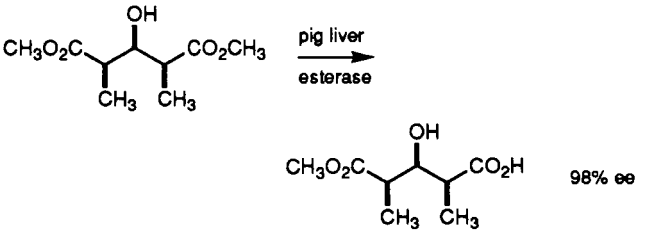


Figure 1. Four types of chain synthesis strategies.

Scheme 1



targets for chemical synthesis have grown in complexity.[2] Of course, a convergent synthesis does not necessarily involve fewer total transformations, but it can increase significantly the throughput of intermediates in a synthesis. In the unlikely case that a racemic product is required, a convergent synthesis necessitates the coupling of racemic subunits with mutual kinetic resolution. More often, this approach entails the coupling of enantioenriched fragments with their absolute stereochemistry matched in a way that is dictated by the structure of the target. The alternative chain synthesis strategy that is the topic of this Account involves the homologation of a chain in two directions. A *sequential two-directional synthesis* is indistin-

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(1) For an earlier discussion of this strategy, see: Schreiber, S. L. *Chem. Scr.* 1987, *27*, 563.

(2) Examples include the following. (a) Palytoxin: Kishi, Y. *Chem. Scr.* 1987, *27*, 573. (b) X-206: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* 1988, *110*, 2506. (c) Avermectin A_{1a}: Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* 1989, *111*, 2967.

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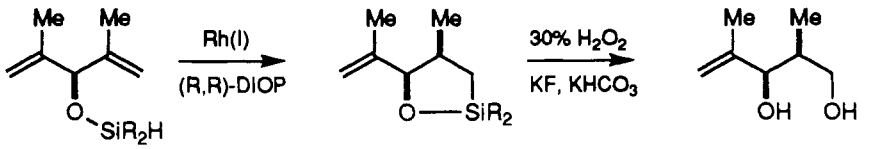
Scheme 2



Hypothetical Terminus Differentiation

guishable from the one-directional linear synthesis with regard to its intrinsic efficiency. Many examples of this type of chain synthesis can be found in the literature.[3] However, the *simultaneous two-directional synthesis* not only can decrease the number of reactions required in a synthesis but also can result in the preparation of materials with extremely high levels of enantiomeric purity.[1]

Performing two reactions on a substrate at the same time requires a consideration of potential symmetry elements within the target molecule. Four different subclasses of acyclic chains that contain symmetry elements suitable for this strategy have been identified.[4] In Figure 1, representative, symbolic chains of each class are shown. Vinyl groups are used to represent any functional group that can be further manipulated.

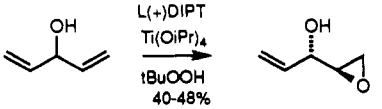
Methods of Two-Directional Chain Synthesis

Two-Directional Synthesis of Achiral and Meso Chains. The two-dimensional synthesis of a meso chain results in a molecule with enantiotopic termini. The synthesis of chains that contain stereocenters requires the use of substrate-controlled reactions. Enantiopure reagents will be useful only if they are used in a sequential manner, and even then they will require the intermediacy of enantioenriched products on the route to the achiral target. An attractive feature of these chains is that they can be prepared with extremely high levels of enantiomeric purity when group and face selective reactions are used in the step that differentiates the enantiotopic ends of the chain (see below).

Early examples of terminus differentiaton of achiral and meso chains used enzymes to monofunctionalize the chain termini.[5] In the work of Mohr et al.[6] (Scheme 1), the hydrolyses of 14 symmetrical dimethyl esters were studied using pig liver esterase. Hydrolytic enzymes are not the only ones that may be used for this purpose: examples of terminus differentiation using oxidative[7] and reductive[8] enzymes have also been reported.

Although enzymes have proved to be valuable catalysts for synthetic organic chemists, their scope can be limited by their inherent substrate specificity. Nonenzymatic transformations that proceed with high enantiotopic group and diastereotopic face selectivity have provided a highly effective solution to the problem of distinguishing the ends of achiral and meso chains. These processes can couple a kinetic resolution with an initial asymmetric synthesis to provide products with extremely high levels of enantiomeric purity. The first

Table 1



	%ee	%de
3 h -25 °C	84	92
24 h -25 °C	93	99.7
140 h -25 °C	>97	>99.7

reaction converts a prostereogenic center (or centers) into a stereogenic center (or centers) in unequal amounts (asymmetric synthesis) while the second reaction enhances the enantiomeric excess (ee) via a kinetic resolution. A mathematical model describing these reactions predicted that the enantiomeric excess of the monofunctionalized compound would increase as the reaction proceeds to completion.[9] Experimental support was provided in a study of the Sharpless asymmetric epoxidation reaction[10] (Table 1). As shown, the enantiomeric excess (as well as the diasteroemeric excess (de)) of divinyl carbinol monoepoxide increased greatly during the course of the reaction.

Recently, Ito and co-workers reported a catalytic, asymmetric hydrosilation (Scheme 2).[11] A hypothetical reaction process is also provided in order to illustrate how the reaction might be used to distinguish the ends of achiral and meso chains.

In a formal total synthesis of both (+)- and (−)-riboflavin (vitamin B_2),[12] an asymmetric epoxidation reaction was used to differentiate the enantiotopic ends

(3) Examples include the following. (a) Calcimycin: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. (b) Monensin: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (c) Rifamycin: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(4) In the earlier discussion,[1] the first three subclasses were described as classes A, B, and C.

(5) Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1985; Vol. 5, Chapter 9.

(6) (a) Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501. (b) For a recent example, see: Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597.

(7) Jakovac, I. J.; Goodbrand, B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659.

(8) Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.

(9) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.

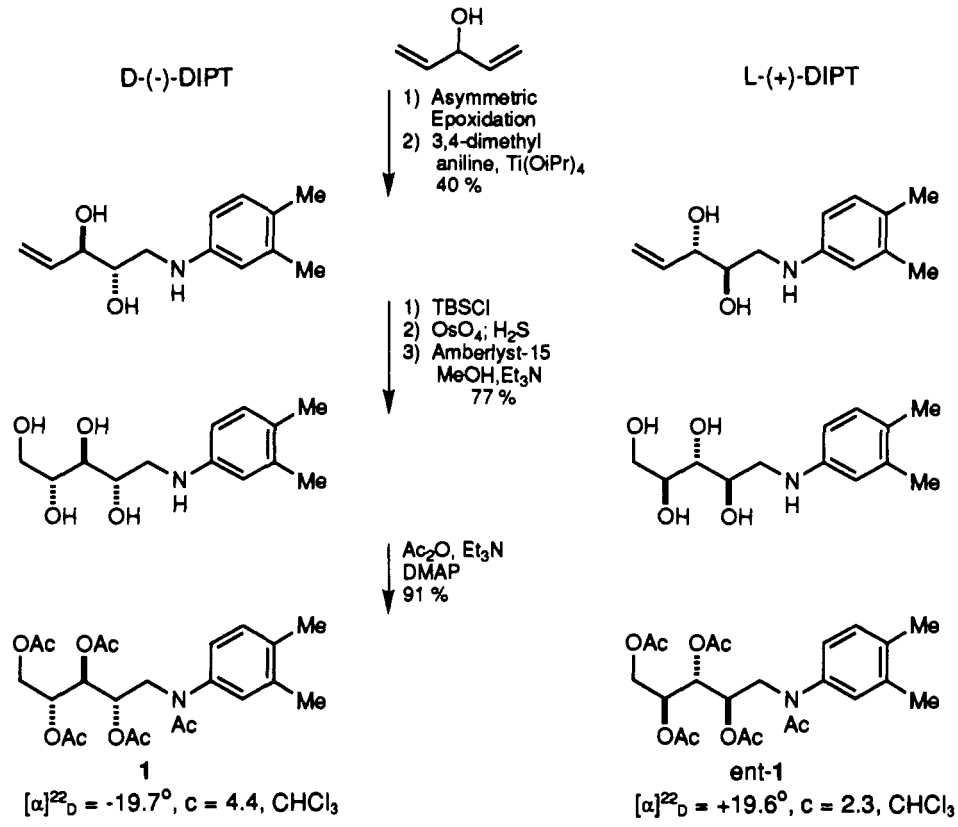
(10) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(11) Tamao, K.; Tohma, T.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333.

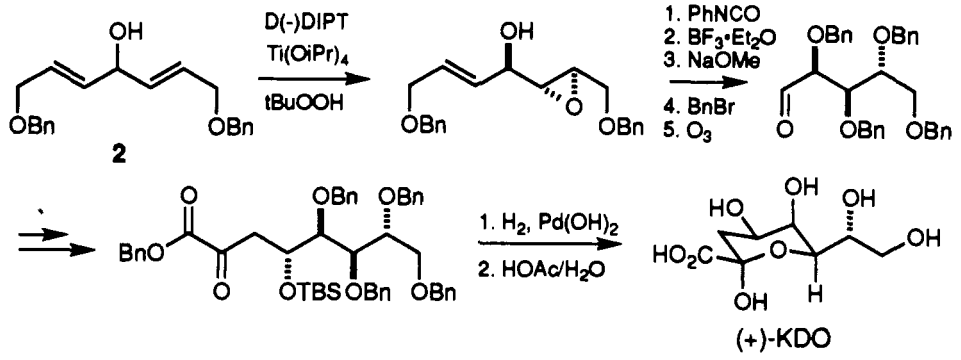
(12) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793.

(13) For an example, see: Yoneda, F.; Sakuma, Y.; Shimomura, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 348 and references therein.

Scheme 3



Scheme 4



of divinyl carbinol (Scheme 3). After a series of steps, the protected amino tetrol 1 (and *ent*-1) was produced. This compound (1) had previously been converted to riboflavin by several groups.[13]

A similar strategy was also used in the synthesis of (+)-KDO[12] (Scheme 4). Again, the terminus differentiation step was performed early in the synthesis to provide epoxide **2**, which was then converted into the natural product via an arabinose derivative.

Several meso skipped-polyol chains were prepared by two-directional synthesis in studies leading to the structure determination of (+)-mycoticins A and B[14] (Scheme 5). The termini of these meso chains were differentiated using an enantiotopic group selective epoxidation. Further homologation of these products led to the complete relative and absolute stereochemical assignment of the mycoticins.

Recently, a different solution to the problem of meso chain terminus differentiation has been described. Harada et al. have developed a method for the enantiodifferentiating transformation of 1,3-alkanediols using a kinetically controlled acetalization with a menthone derivative. This method was described in the context of a two-directional synthesis of the C(19)–C(27) segment of rifamycin S[15] (Scheme 6). The meso-tetrol **3** was treated with *d*-menthone silyl alkenyl ether and catalytic TfOH to produce a 4.5:1 mixture of the separable menthonides **4** and **5**, respectively. Here the problem of differentiating the enantiotopic termini was converted into the simpler problem of separating diastereomers. Compound **4** was converted into an intermediate used in the Kishi synthesis of rifamycin S,[16] thereby completing a formal total synthesis.

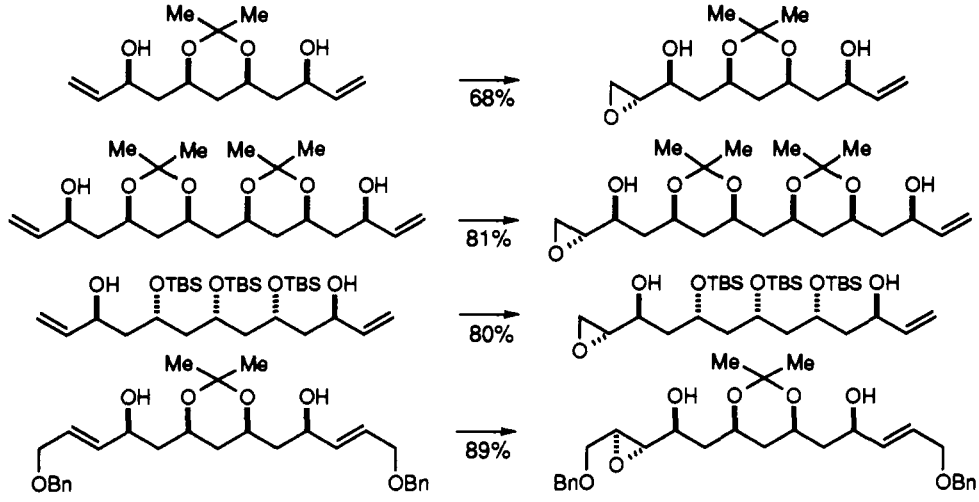
(14) (a) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (b) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (c) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001. (d) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, *28*, 6005.

(15) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637.

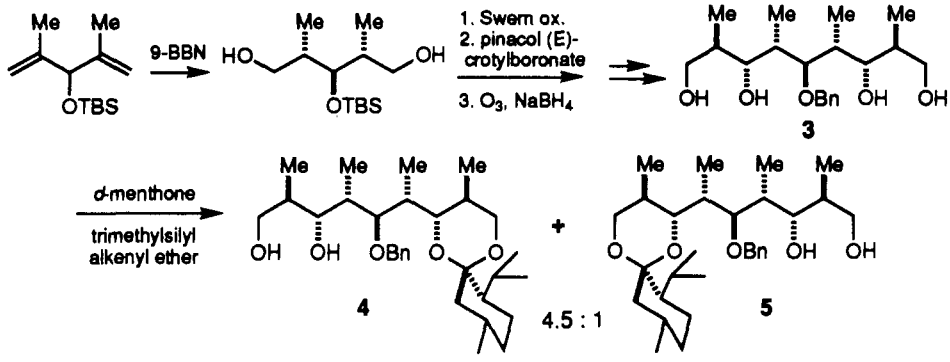
(16) (a) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

Scheme 5

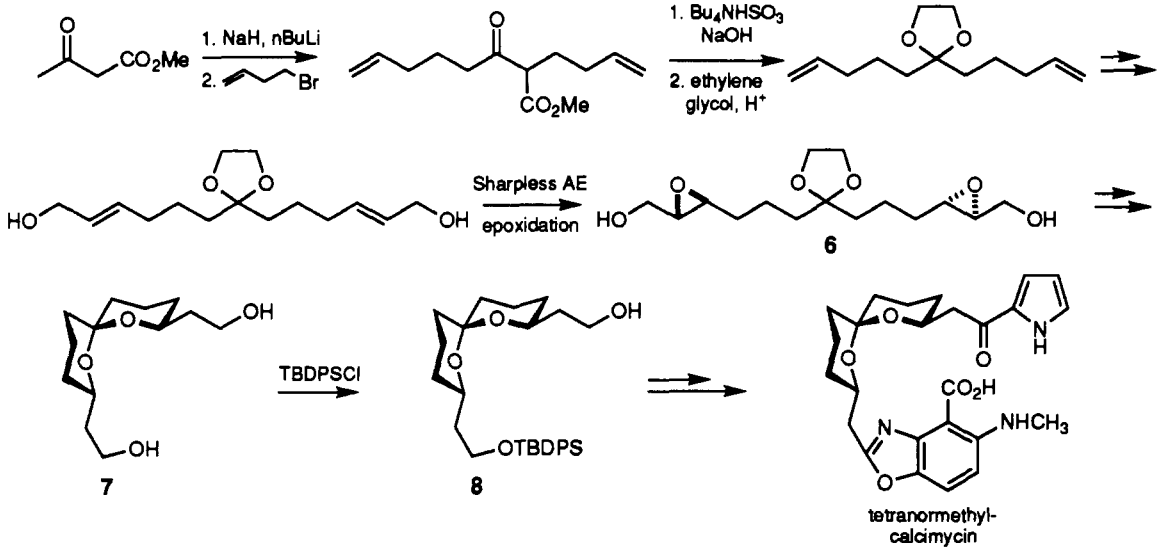
Sharpless AE with L-(+)-DIPT



Scheme 6



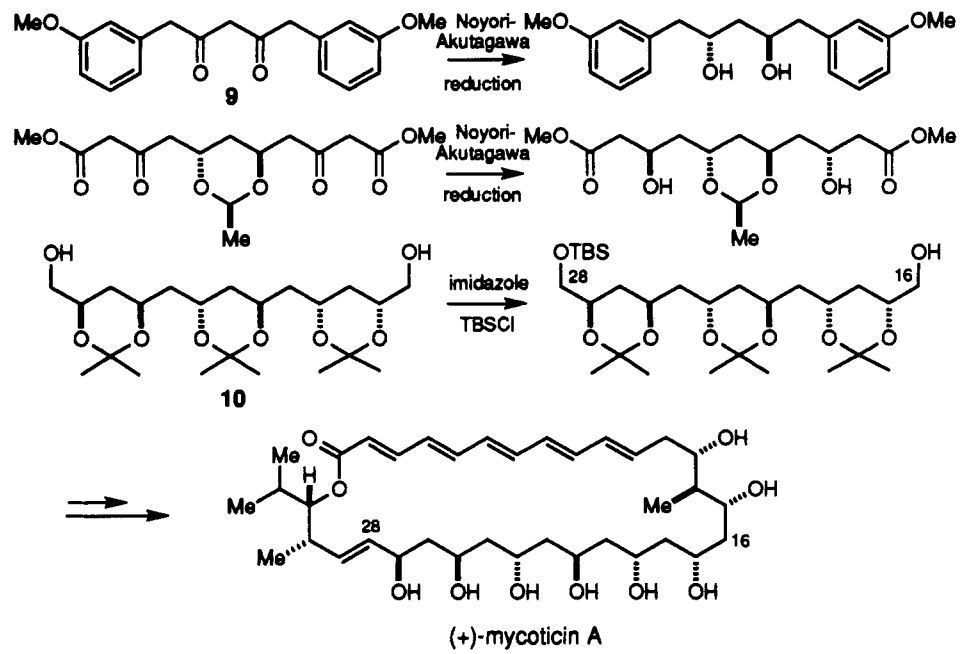
Scheme 7



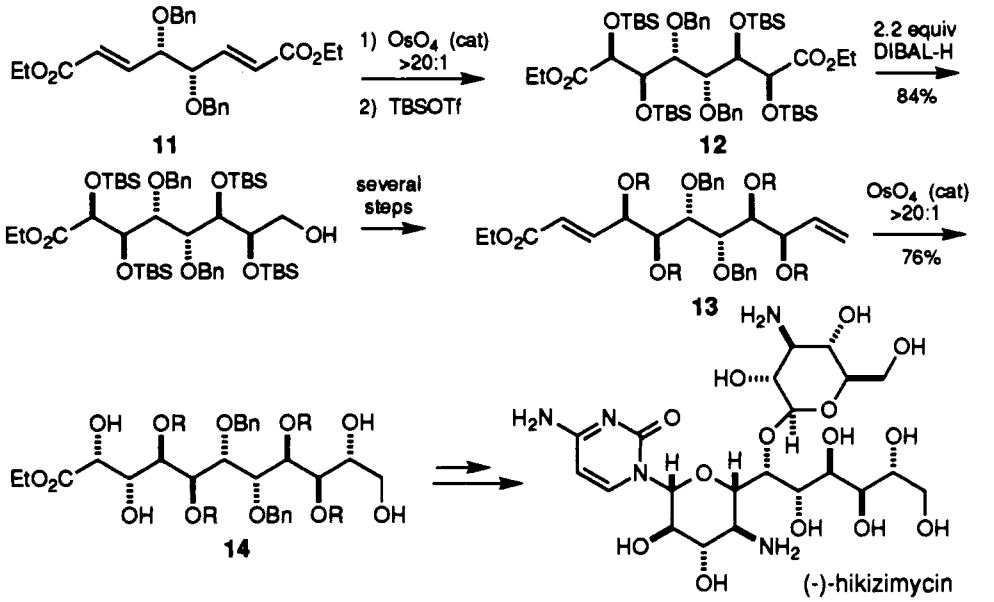
Two-Directional Synthesis of C_2-Symmetric Chains. Two-directional syntheses of C_2-symmetric chains result in the construction of molecules with homotopic groups at their termini. These targets are prepared by the simultaneous homologation of C_2-symmetric starting materials, or by the double addition of a chiral reagent to an achiral precursor that does not contain a prostereogenic center. High levels of enantio- and diastereoselectivity are expected in the formation of these chains due to a process described by Eliel and Midland.[17] As an illustration, in the case of a two-directional (simultaneous homologation) synthesis, a reaction that proceeds at each of two sites with 20:1 enantioselectivity is expected to produce a ca. 400:1 mixture of enantiomers (in addition to small quantities of the more readily separable diastereomers). Differentiation of the termini of C_2-symmetric chains is simplified relative to the other classes because the two ends are homotopic and therefore require only a

(17) (a) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (b) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1144.

Scheme 8



Scheme 9



monofunctionalization reaction: no selectivity is involved in this process.

An early example of a two-directional synthesis of a C_2-symmetric chain comes from the work of Nakahara et al., who described the total synthesis of tetranormethylcalcimycin.[18] As is shown in Scheme 7, diepoxide **6** was synthesized in a two-directional manner and converted into the C_2-symmetric spiroketal **7**. Differentiation of the two homotopic alcohols by a monoprotection reaction provided alcohol **8**, which after a series of steps was transformed into tetranormethylcalcimycin.

While the two-directional synthesis of a meso chain was useful in determining the absolute stereostructure of the mycoticins (see above), the application of a two-directional C_2-symmetric chain synthesis led to the preparation of the C(16)–C(28) polyol fragment of the natural products (Scheme 8). Thus, conversion of the achiral diketone **9** into the enantioenriched diol **10** was achieved by two iterations of the catalytic asymmetric hydrogenation reaction developed by Noyori, Akutagawa, and co-workers.[19] Monoprotection of diol **10** produced a C(16)–C(28) fragment, which was subsequently transformed into (+)-mycoticin A.[20]

A two-directional chain synthesis strategy was also used in the total synthesis of (−)-hikizimycin.[21] For this synthesis, the requisite C_2-symmetric chain was prepared from (+)-diisopropyl tartrate (Scheme 9). The

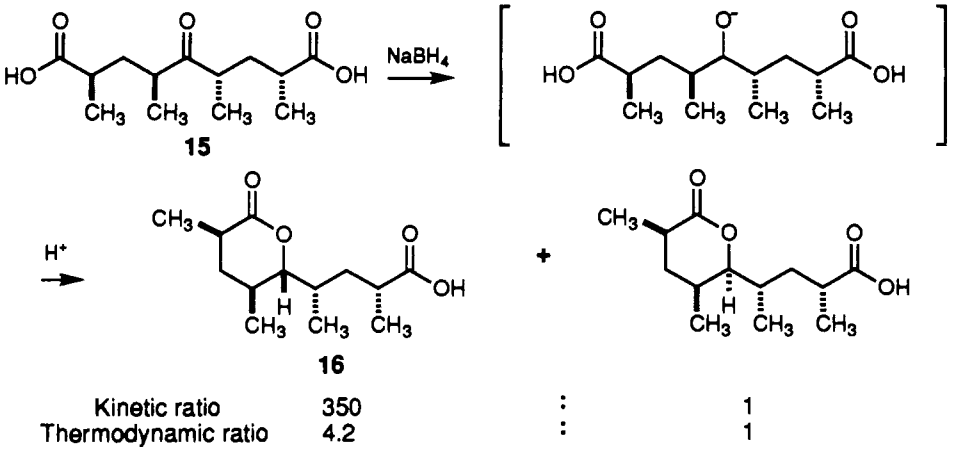
(18) Nakahara, Y.; Fujita, A.; Ogawa, T. *Agric. Biol. Chem.* **1987**, *51*, 1009.

(19) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5956. (b) Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 87.

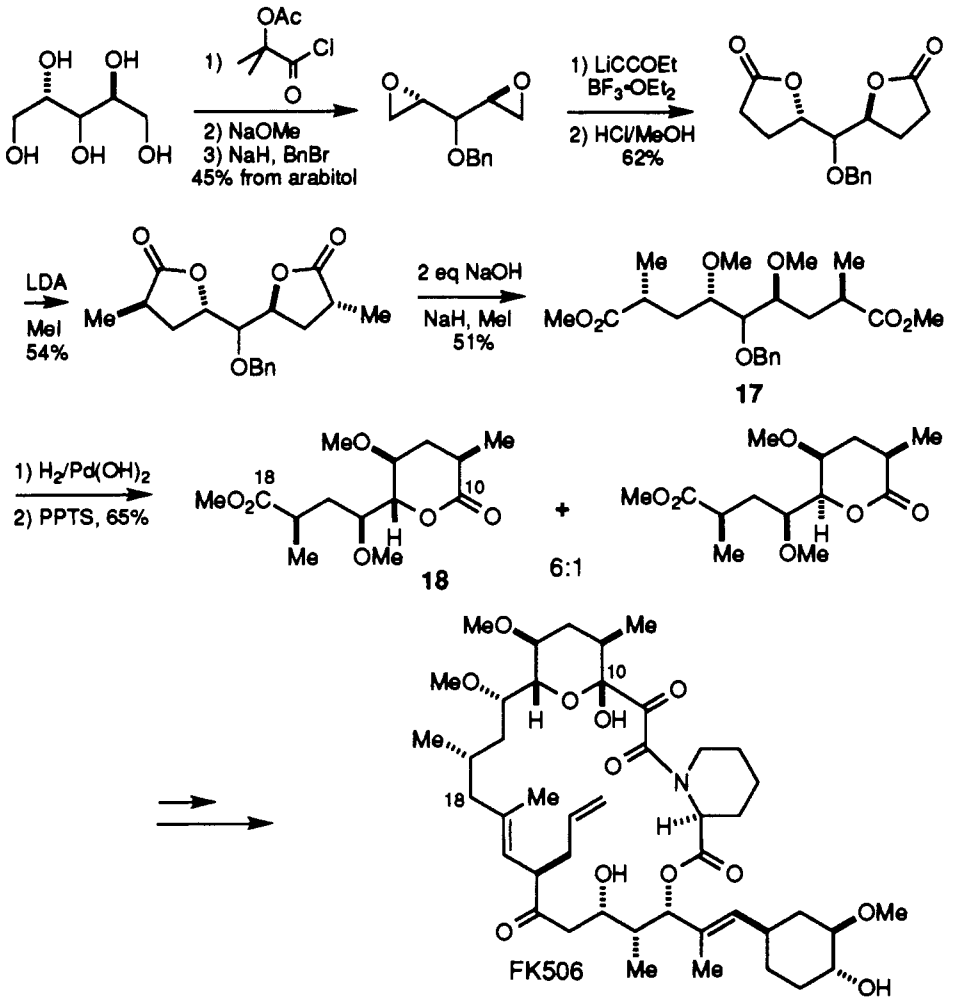
(20) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.

(21) (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657. (b) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524.

Scheme 10



Scheme 11

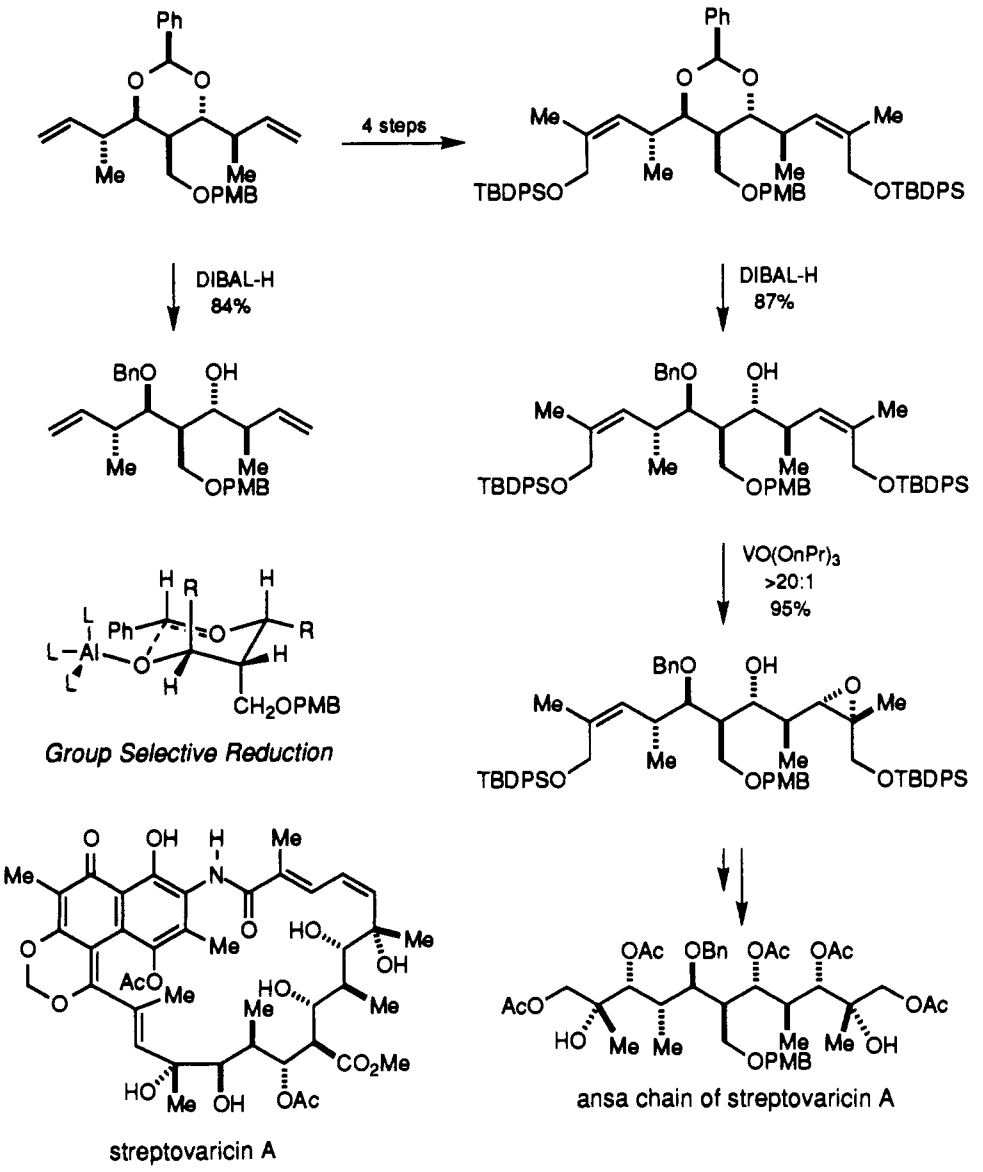


two-directional, double diastereoselective osmylations of **11** and **13** afforded **12** and **14**, respectively, with greater than 20:1 diastereoselectivity. Differentiaton of the termini in **12** was achieved in 84% yield by reduction of one of the two homotopic ester groups. Elaboration of **14** completed the total synthesis of (−)-hikizimycin.

Two-Directional Synthesis of Pseudo-C_2-Symmetric Chains. We use the term "pseudo-C_2-symmetric" to characterize chains that would be C_2-symmetric if they did not contain a central chirotopic, nonstereogenic center. These chains can be efficiently prepared by the double addition of chiral reagents to the termini of achiral or meso chains. As in the construction of C_2-symmetric chains, products with high levels of enantiomeric excess can be anticipated as a result of the "Eliel" effect. However, selective differentiation of the terminal groups in this case requires a diastereotopic, group selective transformation that simultaneously converts the central chirotopic atom(s) into a stereogenic atom(s).

(22) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

Scheme 12



In 1984, Hoye et al. utilized a diastereotopic group selective lactonization for both terminus differentiation and selective lactone construction in an insightful synthesis of invictolide[22] (Scheme 10). Reduction of the C_2-symmetric ketone **15** followed by a kinetic quench provided a 350:1 ratio of lactone isomers. All substituents on the ring are equatorial in the major isomer **16**.

A similar tactic was used in a total synthesis of the signal transduction inhibitor FK506[23,24] (Scheme 11). The pseudo-C_2-symmetric diester **17** was prepared by a two-directional strategy involving simultaneous epoxide opening, lactonization, and alkylation. The diastereotopic, group selective lactonization of **17** proceeded with 6:1 diastereoselectivity using pyridinium *p*-toluenesulfonate as a catalyst to provide **18**, a C(10)–C(18) fragment of FK506.

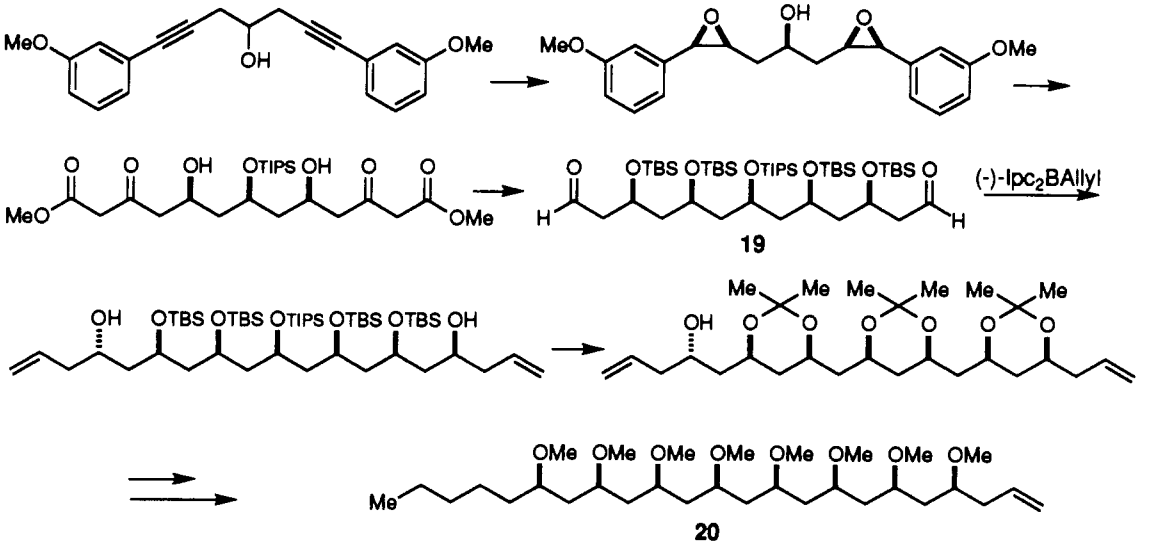
In a synthesis of the ansa bridge of streptovaricin A,[25] a pseudo-C_2-symmetric chain was also prepared using a two-directional strategy. In this work, the group selective reductive cleavage of a benzylidene acetal by diisobutylaluminum hydride facilitated the differentiation of the diastereotopic termini (Scheme 12).

An ingenious diastereotopic group selective process for differentiating the ends of a two-directionally synthesized chain was recently described.[26] In this example, the enantiotopic termini of a meso chain were converted into diastereotopic groups and then differentiated via a diastereotopic group selective reaction. meso-Dialdehyde **19** (Scheme 13) was prepared by two-directional synthesis and reacted with either (+)- or (−)-*B*-allyldiisopinocampheylborane (Ipc_2BAll) to convert the C_s-symmetric substrate into either antipode of an elongated polyol (only one is shown). Thus, a single enantiomeric reagent introduced two new stereocenters and simultaneously fixed the absolute stereochemistry of the five preexisting stereocenters. Terminus differentiation was carried out using a selective acetonide-forming reaction. The diastereotopic group selectivity

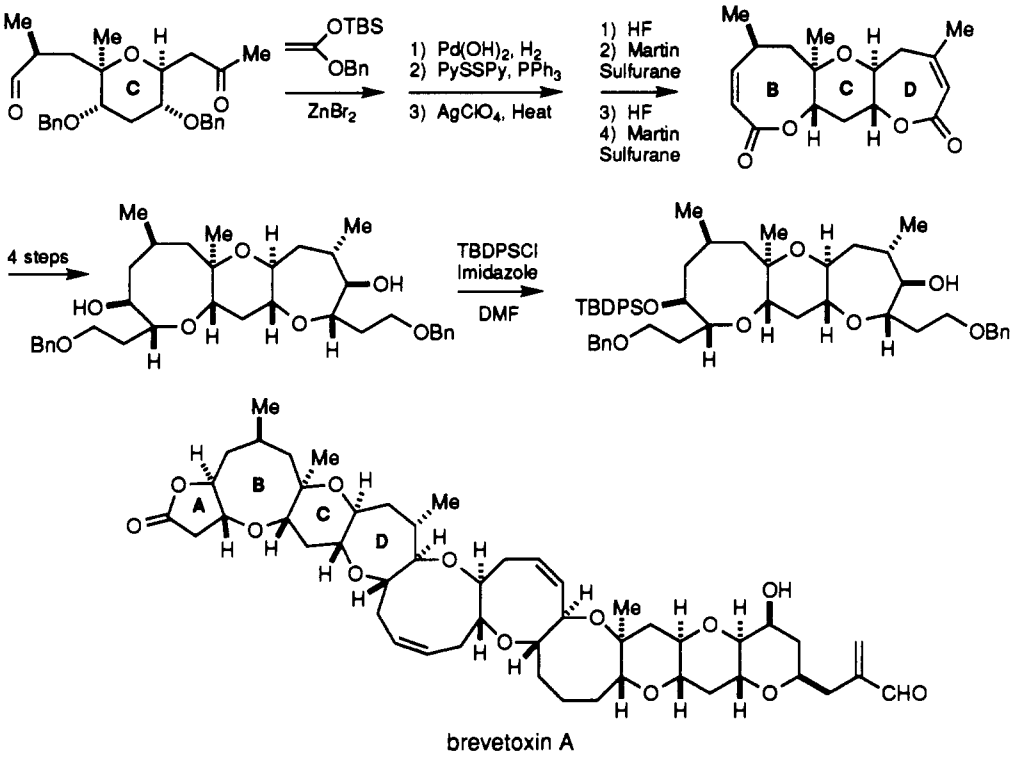
(23) (a) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.
(24) For a similar strategy, see: Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776.

(25) (a) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085. (b) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31.
(26) Wang, Z.; Deschênes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090.

Scheme 13



Scheme 14



(15:1) can be rationalized by the thermodynamic preference of a *syn*-1,3-acetonide over an *anti*-1,3-acetonide due to the 1,3-diaxial interaction of methyl groups present in the latter. The differentiated product was then converted into the isotactic polymethoxy-1-alkene **20** isolated from the tolytoxin-producing algae *Tolypothrix conglutinata*.

Two-Directional Synthesis of Nonsymmetric Chains. At times the synthesis of a nonsymmetric chain using a two-directional strategy may be desirable. These compounds can be constructed either by the double addition of chiral reagents to the termini of an enantioenriched chain or by the double addition of an achiral reagent (in a substrate-controlled process) to either racemic or nonracemic chains. Terminus differentiaton of these chains requires the selective transformation of similar functional groups in differing chemical environments. The studies by Nicolaou and co-workers of brevetoxin A[27] provide an elegant example of this strategy (Scheme 14). Here the B and D rings of brevetoxin A were simultaneously constructed and extended from the central C ring. Differentiation of the termini was readily achieved using a monosilylation reaction, which occurred at the less hindered alcohol.

Conclusion

The examples provided in this Account illustrate the potential of two-directional chain synthesis in a diverse

(27) (a) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K. *J. Am. Chem. Soc.* **1990**, *112*, 3696. (b) Somers, P. K. Ph.D. Thesis, University of Pennsylvania, May 1989.

(28) Babine, R. E.; Zhang, N.; Jurgens, A. R.; Schow, S. R.; Desai, P. R.; James, J. C.; Semmelhack, M. F. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 541.

array of challenging synthetic problems. Most applications of the two-directional strategy require that the ends of the nascent chain be differentiated. The examples chosen demonstrate that a number of interesting solutions to this problem have already been uncovered. (Other examples of two-directional synthesis not discussed here include the syntheses of HIV-1 protease inhibitors[28] and a C(22)–C(34) halichondrin precursor.[29] These illustrate synthetic targets that do not require terminus differentiation.) With the increased focus in recent years on group-selective reactions, the differentiation of the ends of two-directionally synthesized chains should be even less of an obstacle in the future.

On a personal note, we have also found that the planning of two-dimensional syntheses has been an intellectually stimulating exercise that led us to undertake synthetic challenges, especially in the development of group selective reactions, that we would not have otherwise encountered. This was an unexpected and satisfying reward that, judging from the examples provided in this Account, others may have experienced as well.

(29) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961.