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Two-Directional Desymmetrization by Double 1,4-Addition of Silicon and Boron Nucleophiles

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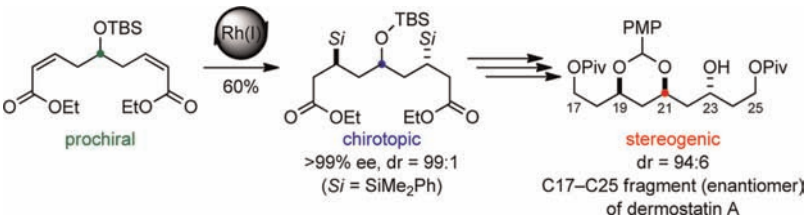
ABSTRACT



The two-directional desymmetrization of prochiral precursors with α,β-unsaturated branches by catalyst-controlled 1,4-addition of silicon and likewise boron nucleophiles allows for a general enantioselective access to *syn*,*anti*-triols with 1,*n* + 1,2*n* + 1 (*n* = 2 and 3) substitution patterns. The utility is demonstrated in the synthesis of the C17−C25 fragment of dermostatin A.

Two-directional desymmetrization of achiral precursors with a prochiral atom poses a remarkable stereochemical situation.[1] The twist in these enantioselective functionalizations[2,3] is that, when performed double, diastereofacial selectivity at the functional group of either enantiotopic branch sets the absolute configuration at the newly formed stereogenic center in the initial step. Its relative configuration to the former prochiral center is, in turn, irrelevant because, if the final step proceeds with the same diastereofacial selectivity at the remaining branch of the now chiral intermediate, that center becomes chirotopic. The net stereochemical result of such a two-step process is the transformation of a prochiral molecule into a pseudo-C_2-symmetric compound with a chirotopic atom flanked by the new stereocenters; all stereochemical options are schematically illustrated in the Supporting Information. Exceptional levels of enantio- and diastereoselectivity are foreseeable when the asymmetric method is highly enantioselective and exerts excellent catalyst control in both steps.[4]

Our laboratory developed a Rh(I)-catalyzed 1,4-addition of silicon nucleophiles to acylic α,β-unsaturated carboxyl compounds with very high enantiocontrol (>99% ee).[5−7] The use of this methodology in iterative

(1) For reviews of two-directional synthesis, see: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563–566. (b) Poss, C. R.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167–2213.

(2) For selected examples of reagent-controlled asymmetric two-directional syntheses with prochiral or *meso* precursors, see: (a) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090–1091. (b) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066–1070. (c) Zhang, Y.; Arpin, C. C.; Cullen, A. J.; Mitton-Fry, M. J.; Sammakia, T. *J. Org. Chem.* **2011**, *76*, 7641–7653.

(3) For selected examples of catalyst-controlled asymmetric two-directional syntheses with prochiral or *meso* precursors, see: (a) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915–3918. (b) Keller, V. A.; Kim, I.; Burke, S. D. *Org. Lett.* **2005**, *7*, 737–740. (c) Wysocki, L. M.; Dodge, M. W.; Voight, E. A.; Burke, S. D. *Org. Lett.* **2006**, *8*, 5637–5640. (d) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018–5021. (e) Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559–15561. (f) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795–12800.

(4) Kinetic resolution effects might also be considered when asymmetric induction of the used method is not high. For a scholarly example producing a highly enantiomerically enriched monofunctionalized carbinol, see: Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529.

(5) For a comprehensive overview of asymmetric conjugate addition reactions of silicon and boron nucleophiles, see: Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, *47*, 7917–7932.

(6) (a) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818–3820. (b) Walter, C.; Fröhlich, R.; Oestreich, M. *Tetrahedron* **2009**, *65*, 5513–5520.

(7) For the recently developed Cu(I)-catalyzed asymmetric conjugate silyl transfer, see: (a) Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900. (b) Harb, H. Y.; Collins, K. D.; Garcia Altur, J. V.; Bowker, S.; Campbell, L.; Procter, D. J. *Org. Lett.* **2010**, *12*, 5446–5449. (c) Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245–252.

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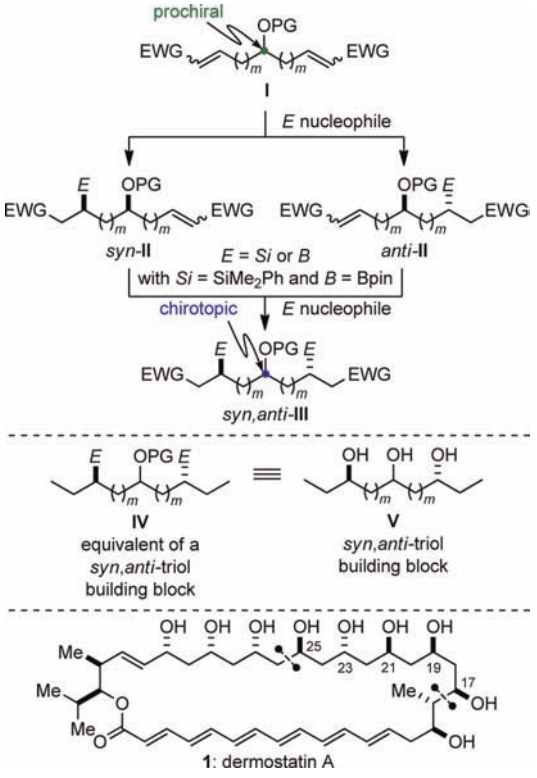
synthesis had already demonstrated its potential to override substrate control for chiral δ-substituted α,β-unsaturated acceptors.[8] Application of that catalyst-controlled conjugate silyl transfer to two-directional desymmetrization of carbinols with α,β-unsaturated substituents would provide a stereocontrolled one-pot access to triol surrogates with 1, $n+1$,$2n+1$ ($n = 2$ and 3) substitution patterns (**I**→*syn*-**II** and/or *anti*-**II**→*syn*,*anti*-**III**, Scheme 1, upper). Subsequent oxidative degradation of the C−Si bonds[9] and deprotection would then afford the targeted triols (**IV**≡**V**, Scheme 1, middle). An alternative indirect approach to the long-standing problem of asymmetric hydration of α,β-unsaturated acceptors[5] is the conjugate addition of a boron nucleophile (Scheme 1, upper),[10−12] again followed by stereospecific oxidation.[13] Both enantioselective methods, Rh(I)-catalyzed 1,4-addition of silicon[6,8] and Cu(I)-catalyzed 1,4-addition of boron,[11] in desymmetrization reactions would complement the existing repertoire of two-directional polyol syntheses.[1−3] We disclose herein the stereoselective preparation of 1,3,5-[3d,e,14] and 1,4,7-triols as well as the diastereoselective protection of the 1,3,5-triol to access the C17−C25 fragment of dermostatin A (**1**, Scheme 1, lower).[2c,15]

Scheme 1. Two-Directional Desymmetrization of Prochiral Carbinols with α,β-Unsaturated Substituents: Access to OH, OH,OH Building Blocks ($m = n-1$) with a Chirotopic Atom



(8) Hartmann, E.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6195–6198.

(9) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

At the outset of the project, we sought to learn about the capability of the chosen catalytic systems to outcompete substrate control. For this, we tested *S* configured δ-silyloxy-substituted α,β-unsaturated carboxyl compounds *Z*-**2** and *E*-**5** with defined double bond geometries in the 1,4-addition of silicon[16] and boron nucleophiles, respectively (Scheme 2).[5] As part of the aforementioned iterative approach,[8] we had already observed that, with (*R*)-binap, the Rh(I) catalysis yielded the *anti* diastereomer with dr = 95:5 (*Z*-**2**→*anti*-**3**, Scheme 2, left); (*S*)-binap as the ligand afforded the corresponding *syn* compound with dr = 99:1 (*Z*-**2**→*syn*-**3**). Apparently, there is only a small amount of influence of the existing stereocenter in *Z*-**2** on the stereochemical course, and a largely catalyst-controlled stereoinduction provides access to either of the diastereomers. Combined with subsequent oxidative degradation of the C−Si bond,[9] the strategy allows for the formation of *anti* and *syn* diols from the same precursor (*anti*-**3**→anti-**4** and *syn*-**3**→*syn*-**4**, Scheme 2, left).

Encouraged by these findings, we next turned our attention to Yun's Cu(I)-catalyzed conjugate addition of boron nucleophiles.[11] Diastereoselective additions had not been investigated yet. Control experiments with achiral α,β-unsaturated carboxyl acceptors showed that, in terms of stereoselectivity, the *E* configuration of the alkene is required. The reaction of *E*-**5** in the presence of (R,S_p)-josiphos then furnished the *anti* diastereomer with moderate dr = 89:11 (*E*-**5**→*anti*-**6**, Scheme 2, right); the *syn* diastereomer was obtained employing (S,R_p)-josiphos yet with the same level of diastereoselection (*E*-**5**→*syn*-**6**). The fact that no matched/mismatched selectivity is observed here indicates a fully catalyst-controlled transformation but with imperfect asymmetric induction. In analogy to the previous sequence, oxidation of the C−B bond[13] also

(10) For reviews of asymmetric conjugate boryl transfer, see: (a) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194–1196. (b) Mantilli, L.; Mazet, C. *ChemCatChem* **2010**, *2*, 501–504. (c) Bonet, A.; Sole, C.; Gulyás, H.; Fernández, E. *Curr. Org. Chem.* **2010**, *14*, 2531–2548.

(11) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147.

(12) For further examples with acyclic carboxyl acceptors, see: (a) Lillo, V.; Prieto, A.; Bonet, A.; Díáz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659–662. (b) Chen, I-H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098–4101. (c) O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (d) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008–5011. (e) Ibrahem, I.; Brestein, P.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12036–12041.

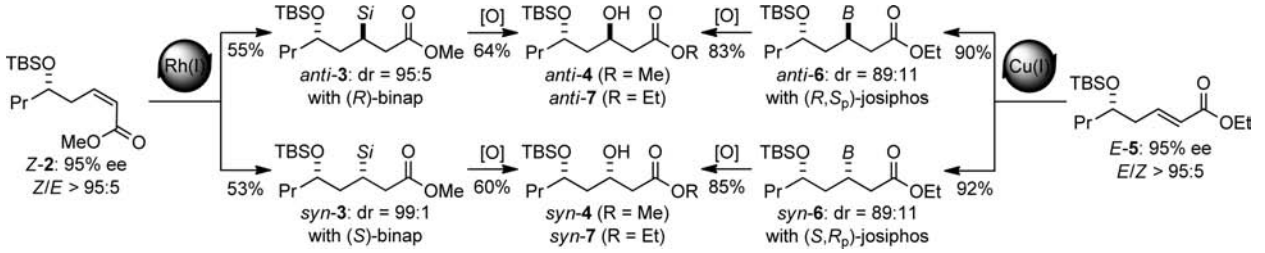
(13) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; pp 48−54.

(14) For more protocols on catalytic asymmetric construction of 1,3,5-triols, see: (a) Shepherd, J. N.; Na, J.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 4558–4559. (b) Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164–4166. (c) Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3077–3080. (d) Menz, H.; Kirsch, S. F. *Org. Lett.* **2009**, *11*, 5634–5637. (e) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112–3115. (f) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611–2614. (g) Kirsch, S. F.; Klahn, P.; Menz, H. *Synthesis* **2011**, 3592–3603.

(15) (a) Sinz, C. J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3224–3227. (b) Sinz, C. J.; Rychnovsky, S. D. *Tetrahedron* **2002**, *58*, 6561–6576.

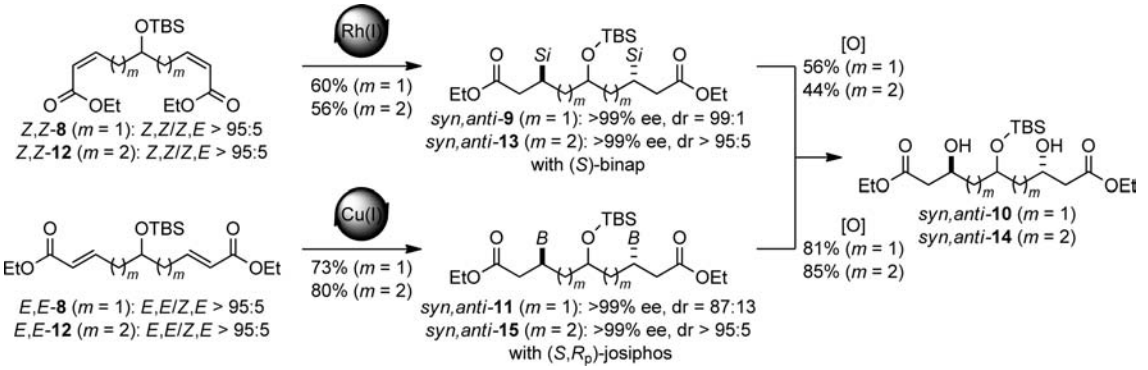
(16) For the preparation of $Me_2PhSi-Bpin$, see: (a) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647–4649. (b) Summary of Si−B chemistry: Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29–49.

Scheme 2. Catalyst vs Substrate Control in the Conjugate Silyl and Boryl Transfers onto δ-Silyloxy-Substituted α,β-Unsaturated Carboxyl Compounds[a]



[a] Rh(I)-catalyzed conjugate silyl transfer:[6,8] $[Rh(cod)_2]OTf$ (5.0 mol %), binap (10 mol %), $Me_2PhSi-Bpin$ (2.5 equiv), Et_3N (1.0 equiv), 1,4-dioxane/H_2O 10:1, 45 °C. Cu(I)-catalyzed conjugate boryl transfer:[11] CuCl (2.0 mol %), NaO*t*-Bu (3.0 mol %), josiphos (4.0 mol %), pinB−Bpin (1.1 equiv), MeOH (2.0 equiv), THF, rt. Oxidation of the C−Si bond:[9] KBr (1.5 equiv), NaOAc (30 equiv), AcOOH/AcOH 1:1, rt. Oxidation of the C−B bond:[13] $NaBO_3 \cdot 4H_2O$ (5.0 equiv), THF/H_2O 1:1, rt.

Scheme 3. Enantioselective Access to 1,3,5- and 1,4,7-Triols through Two-Fold Conjugate Addition of Silicon and Boron Nucleophiles to Bis(α,β-unsaturated) Compounds[a]



[a] See Scheme 2 for reagents and reaction conditions; double the amount of reagents and catalyst was used.

yielded the corresponding *anti* and *syn* diols (*anti*-**6**→*anti*-**7** and *syn*-**6**→*syn*-**7**, Scheme 2, right).

With these promising results, we were curious to apply these asymmetric 1,4-additions to the two-fold functionalization of bis(α,β-unsaturated) acceptors. We were then delighted to see that the Rh(I)-catalyzed silyl transfer[6,8] onto the prochiral δ-silyloxy-substituted *Z*,*Z*-**8** afforded desired *syn*,*anti*-**9** essentially as a single stereoisomer[17] in good chemical yield (*Z*,*Z*-**8**→*syn*,*anti*-**9**, Scheme 3, upper). Its conversion using standard oxidation conditions[9] made triol *syn*,*anti*-**10** with a 1,3,5-relationship of the hydroxy groups available (*syn*,*anti*-**9**→*syn*,*anti*-**10**). The Cu(I)-catalyzed borylation[11] was applied to isomeric acceptor *E*,*E*-**8**, and *syn*,*anti*-**11** was formed with 99% ee and dr = 87:13 (*E*,*E*-**8**→*syn*,*anti*-**11**, Scheme 3, lower).[17] As predicted on the basis of previous experiments (cf. Scheme 2, right), the individual steps do not proceed with perfect differentiation of the diastereotopic faces, and that is reflected in the moderate diastereomeric ratio with the *meso* configuration for the minor diastereomers *syn*,*syn*-**11** and *anti*,*anti*-**11** (not shown). It is only the wrong diastereotopic face selection in both steps on the same molecule that yields the undesired enantiomer (*ent*-*syn*,*anti*-**11**, not shown). As the probability of this incident is decreased in sequential functionalizations, enrichment of desired *syn*,*anti*-**11** is observed. Again, straightforward oxidative degradation[13] enabled the synthesis of the triol *syn*,*anti*-**10** in good chemical yield (*syn*,*anti*-**11**→ *syn*,*anti*-**10**).

In light of these stereoselectivities, we anticipated ε-silyloxy-substituted homologues *Z*,*Z*-**12** and *E*,*E*-**12** to be an equally effective entry into the asymmetric synthesis of 1,4,7-triols (Scheme 3). Indeed, *Z*,*Z*-**12** performed well in the Rh(I) catalysis,[6,8] and doubly silylated *syn*,*anti*-**13** was obtained with superb stereocontrol (*Z*,*Z*-**12**→*syn*,*anti*-**13**, Scheme 3, upper).[17] Subsequent oxidation[9] completed the sequence to yield the stereodefined 1,4,7-triol *syn*,*anti*-**14** (*syn*,*anti*-**13**→*syn*,*anti*-**14**). Similarly, substrate *E*,*E*-**12** was subjected to the boryl transfer[11] (*E*,*E*-**12**→*syn*,*anti*-**15**, Scheme 3, lower). This time, with the remote prochiral

(17) Diastereomeric ratios were determined by either GLC analysis or NMR spectroscopy. Minor stereoisomers were assigned by comparison with independently prepared samples using racemic ligands.

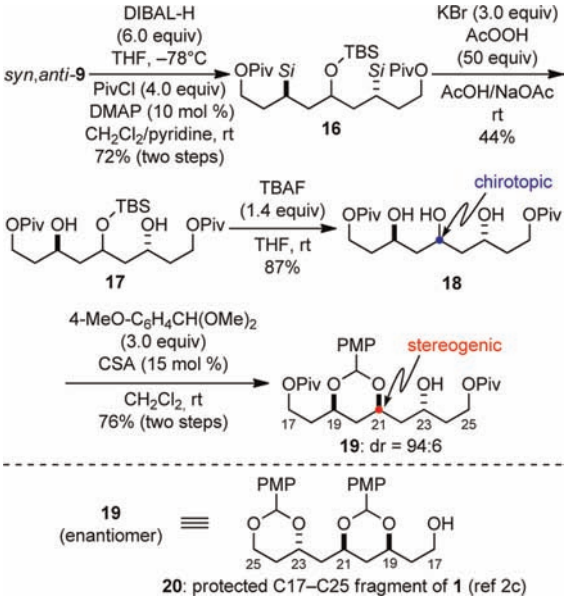
center, only a negligible amount of the *meso* diastereomers *syn*,*syn*-**15** and *anti*,*anti*-**15** (not shown) was formed.[17] With that improved diastereofacial discrimination, *syn*,*anti*-**15** was formed with >99% ee almost as a single diastereomer. After oxidative degradation[13] (*syn*,*anti*-**15**→*syn*,*anti*-**14**), the boron-based sequence arrives at the same 1,4,7-triol as the silicon-based strategy (*syn*,*anti*-**13**→*syn*,*anti*-**14**).

After conversion of the prochiral precursors into chiral compounds, one challenge remains. Unlike with C_2-symmetric molecules, the termini of pseudo-C_2-symmetric compounds are not equivalent, i.e., not homotopic. To break the symmetry with another functional group manipulation, one terminus must be selected over the other, in the course of which the chirotopic atom will become stereogenic.[1b] For pseudo-C_2-symmetric polyols, that differentiation is achieved by diastereoselective acetalization.[18] To demonstrate the utility of our approach, we performed such an acetalization on a polyol made by the above strategy. To this end, the terminal carboxyl groups of *syn*,*anti*-**9** were reduced, and the primary alcohols were protected as pivalates (*syn*,*anti*-**9**→**16**, Scheme 4, upper). Oxidative degradation of the C−Si bonds afforded orthogonally protected 1,3,5,7,9-pentol **17** in decent yield (**16**→**17**). Finally, removal of the TBS group at the central hydroxy group was followed by acetalization of the *syn*-configured hydroxy groups in **18** to afford compound **19** as the major diastereomer (**17**→**18**→**19**). The enantiomer of this fragment with different protecting groups (cf. **20**, Scheme 4, lower) is an intermediate in a recent total synthesis of dermostatin A (**1**) by Sammakia.[2c]

The present work compares indirect asymmetric conjugate hydration protocols,[5] that is enantioselective 1,4-additions of silicon and boron nucleophiles followed by oxidation, in a two-directional desymmetrization of prochiral bis(α,β-unsaturated) acceptors. Both methods exert excellent catalyst control, but the silylation is superior to the borylation in terms of asymmetric induction. In turn, the oxidative degradation of the C−element bond is more practical for the C−B than the C−Si bond. Yields are generally higher in the borylation/oxidation sequence.

(18) For selected examples of terminus differentiation through diastereoselective acetalization, see: (a) Reference 2a. (b) Reference 2c. (c) Reference 14a. (d) Shepherd, J. N.; Myles, D. C. *Org. Lett.* **2003**, *5*, 1027–1030.

Scheme 4. Terminus Differentiation through Diastereoselective Acetalization: Synthesis of the C17−C25 Fragment of **1**



By this general approach, stereodefined 1,3,5- and 1,4,7-triols become accessible. The differentiation of a pseudo-C_2-symmetric building block is achieved by diastereoselective acetalization as shown in the preparation of the enantiomeric C17−C25 fragment of dermostatin A (**1**).

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Supporting Information Available. Detailed starting material syntheses, general procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.