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Toward the Synthesis of Peloruside A: Fragment Synthesis and Coupling Studies

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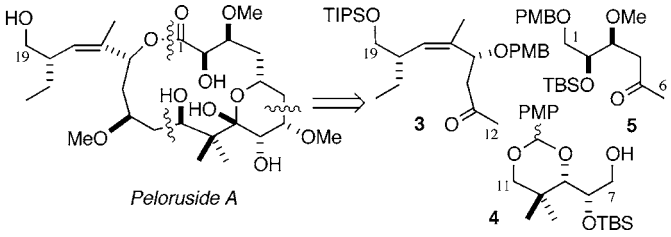
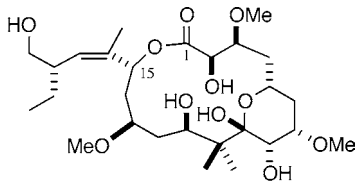
ABSTRACT



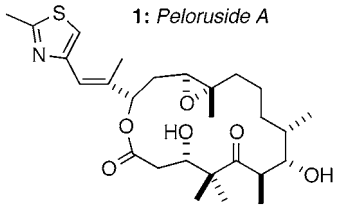
The asymmetric synthesis of building blocks 3, 4, and 5, corresponding to C_{12}–C_{19}, C_7–C_{11}, and C_1–C_6 segments of peloruside A, is reported, along with boron-mediated aldol coupling studies directed toward the assembly of the complete carbon skeleton of this microtubule-stabilizing macrolide.

Peloruside A (**1**) is a novel cytotoxic polyketide, isolated by Northcote and co-workers,[1a] from a New Zealand marine sponge, *Mycale hentscheli*. Elucidation of its structure and relative stereochemistry by extensive NMR studies revealed a polyoxygenated 16-membered macrolide, containing a pyranose ring, with a branched unsaturated side chain at C_{15}. Acting as a potent antimitotic agent, peloruside A inhibits the growth of a range of cancer cell lines at nanomolar concentrations.[1]

Like paclitaxel (Taxol), recent studies[1b] have demonstrated that peloruside functions by promoting tubulin polymerization and interfering with microtubule dynamics, inducing apoptosis following arrest of the cell cycle in the G2-M phase. Thus, peloruside now joins an elite group of nontaxane microtubule-stabilizing agents (including the epothilones, discodermolide, eleutherobin, and laulimalide) that have potential as drug candidates for the treatment of solid tumors.[2] Notably, the apparent[1b] structural resemblance of peloruside A to the 16-membered macrolide epothilone B (**2**),[3] currently in clinical trials as an anticancer drug, hints that it may act as a Taxol/epothilone surrogate by binding in a common site on β-tubulin.



1: *Peloruside A*



2: *Epothilone B*

As the current supply of peloruside A from the sponge source is limited, an efficient total synthesis is required to

(1) (a) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445. (b) Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356. (c) Hood, K. A.; Bäckström, B. T.; West, L. M.; Northcote, P. T.; Berridge, M. V.; Miller, J. H. *Anti-Cancer Drug Des.* **2001**, *16*, 155.

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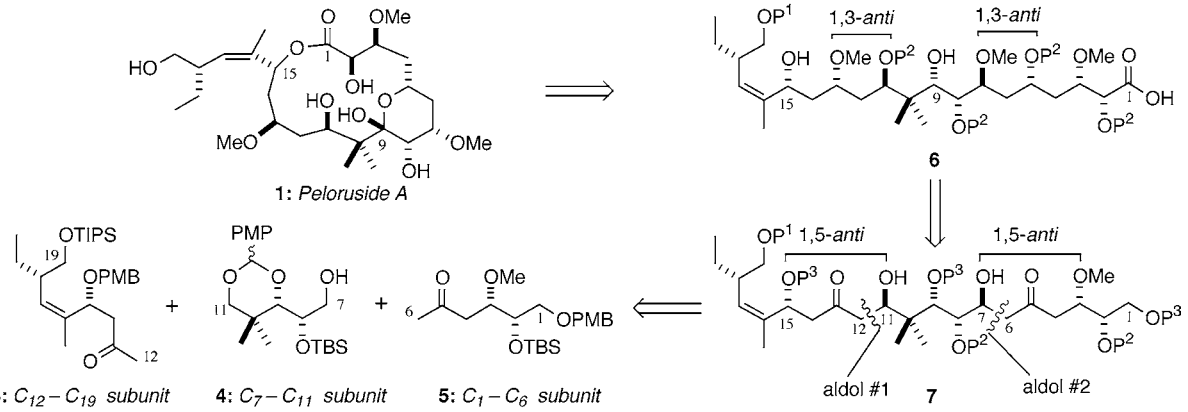
Scheme 1



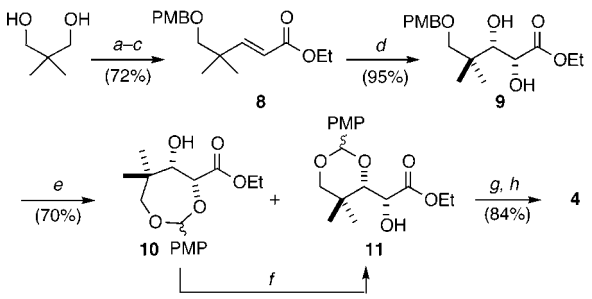
enable further biological and preclinical evaluation, as well as to initiate analogue chemistry. To this end, we now report the asymmetric synthesis of three peloruside subunits (**3**, **4**, and **5**), along with studies directed toward the assembly of the complete carbon skeleton.

Allowing for the uncertainty over the absolute configuration,[1a,4] we planned a flexible strategy (Scheme 1) to introduce the 10 stereocenters in **1**. We envisaged an endgame based on a selective macrolactonization of a suitable seco acid derivative such as **6**, whereby, after oxidation of the remaining C_9 hydroxyl group, final deprotection would induce hemiacetal formation and thus generate peloruside A. Retrosynthetic analysis of advanced intermediate **6**, involving disconnections at C_6-C_7 and $C_{11}-C_{12}$, revealed the three subunits **3**, **4**, and **5**, selected as building blocks of comparable complexity. Stereoselective aldol couplings involving methyl ketones **3** and **5** might then be used to assemble **6** in a convergent manner and install the elaborate polyol sequence. To establish the correct 1,3- and 1,5-diol stereorelationships, as indicated in **6** and **7**, respectively, we planned to make use of our 1,5-anti aldol methodology[5,6] for implementing the key coupling steps, in combination with 1,3-anti reductions of the resulting β-hydroxy ketones. The required 1,2-syn diol relationships embedded in subunits **4** and **5** would be installed by appropriate Sharpless asymmetric dihydroxylations,[7] while subunit **3** should be available with use of suitable aldol methodology.

First, an efficient and scaleable synthesis of the C_7-C_{11} subunit **4** was developed by starting from neopentylglycol via a highly stereoselective HWE homologation to give **8** (Scheme 2). Installation of the 1,2-syn diol was then

Scheme 2[a]

ligand	ee (%)
$(DHQ)_2PHAL$	82
$(DHQ)_2PYR$	88
(DHQ)PHN	96



[a] Conditions: (a) PMBBr, NaH, Bu_4NI, THF, 0 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; NEt_3; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, PhMe/THF, 0 °C; (d) (DHQ)PHN, K_2CO_3, $K_3Fe(CN)_6$, K_2OsO_4, $MeSO_2NH_2$, *t*-BuOH/H_2O, 4 °C; (e) DDQ, 4 Å MS, CH_2Cl_2; (f) CSA, 4 Å MS, CH_2Cl_2; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (h) DIBAL, CH_2Cl_2/hexane, −50 °C.

accomplished by catalytic Sharpless dihydroxylation methodology.[8] When the (*E*)-enoate **8** was treated with AD-mix-α, containing the $(DHQ)_2PHAL$ ligand, the desired diol **9** was obtained in high yield, albeit in moderate enantiomeric purity (82% ee).[9] From a screening of structurally related chiral ligands, the monomeric (DHQ)PHN[10] was found to improve the enantioselectivity of the dihydroxylation step, providing **9** in 95% yield and with 96% ee. DDQ-mediated

(2) For recent reviews, see: (a) Altmann, K. H. *Curr. Opin. Chem. Biol.* **2001**, *5*, 424. (b) He, L. F.; Orr, G. A.; Horwitz, S. B. *Drug Discovery Today* **2001**, *6*, 1153. (c) Stachel, S. J.; Biswas, K.; Danishefsky, S. J. *Curr. Pharm. Des.* **2001**, *7*, 1277.

(3) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.

(4) The absolute configuration of peloruside A has not yet been determined.

(5) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (b) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187.

(6) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(8) For related studies on *gem*-dimethyl-containing substrates, see: Ohmori, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 6519.

(9) The enantiomeric purities of **9** and **14** were determined by chiral HPLC, using the racemic diol as the reference. The absolute configurations were determined by the advanced Mosher method (ref 18 and Supporting Information).

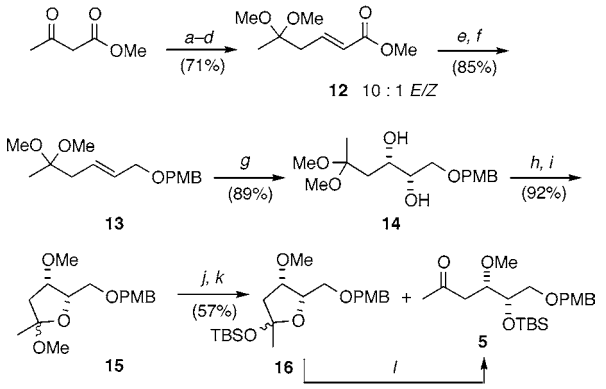
(10) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.

oxidative cyclization[11] of this mono-PMB protected triol resulted in an unexpected mixture of PMP acetals. The intermediate oxocarbenium ion is trapped by either of the two hydroxyl groups, resulting in a ca. 1:1 mixture of seven- and six-membered cyclic acetals, **10** and **11**. Advantageously, this crude product mixture could be subjected to equilibrating conditions (CSA, CH_2Cl_2) to afford solely the desired, and thermodynamically more stable, six-membered cyclic acetal **11** in 70% overall yield. Silylation of alcohol **11** and DIBAL reduction of the ester group then completed the synthesis of the C_7-C_{11} subunit **4**.

The preparation of the C_1-C_6 methyl ketone **5** commenced from methyl acetoacetate (Scheme 3). Formation of the

Scheme 3[a]

ligand	ee (%)
$(DHQ)_2PHAL$	54
$(DHQ)_2PYR$	92
(DHQ)PHN	86

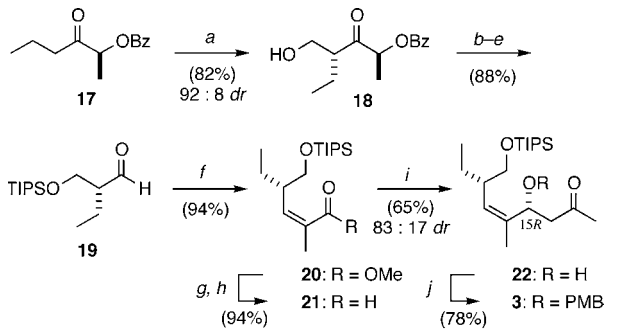


[a] Conditions: (a) $(MeO)_3CH$, CSA, MeOH; (b) $LiAlH_4$, THF, 0 °C; (c) PDC, 4 Å MS, CH_2Cl_2; (d) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C; (e) DIBAL, CH_2Cl_2, −78 °C; (f) PMBBr, NaH, THF, 0 °C; (g) $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, K_2OsO_4, $MeSO_2NH_2$, *t*-BuOH/H_2O, 4 °C; (h) PPTS, MeOH; (i) NaH, MeI, THF, 0 °C; (j) HCl_{aq}, CH_2Cl_2, 0 °C; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (l) cat. TBAF, THF.

methyl acetal, followed by a 3-step homologation sequence, afforded enoate **12** (10:1 *E*/*Z*; 71%). Reduction and PMB ether formation then provided the allylic ether **13** in 85% yield. Again, the Sharpless asymmetric dihydroxylation reaction on **13** required an extensive screening of ligands to enhance the enantioselectivity from 54% ee when using AD-mix-α, containing $(DHQ)_2PHAL$, to 92% ee in 89% yield when using $(DHQ)_2PYR$. Upon treatment of the resulting diol **14** with mild acid (PPTS, MeOH), the adjacent hydroxyl groups were differentiated by engaging one of them in formation of a tetrahydrofuranyl acetal, while the other was subsequently methylated (NaH, MeI) to provide **15** (92%). Careful acid-mediated hydrolysis of the acetal,[12] followed by silylation with TBS triflate, afforded a mixture of the desired methyl ketone **5** and the cyclic silylated acetal **16**. Upon treatment with catalytic TBAF, the latter was converted cleanly into **5**.

Next, the remaining peloruside subunit **3**, containing 1,4-related stereocenters at C_{15} and C_{18} and the trisubstituted (*Z*)-alkene of the side chain, was prepared by application of our asymmetric boron aldol methodology, making use of the (*S*)-lactate-derived ketone **17** (Scheme 4).[13,14] Here an aldol

Scheme 4[a]



[a] Conditions: (a) *c*-Hex_2BCl, Me_2NEt, Et_2O; HCHO, −78 °C; MeOH, H_2O_2, pH 7 buffer; (b) TIPSCl, imidazole, DMAP, CH_2Cl_2; (c) $NaBH_4$, MeOH; (d) K_2CO_3, MeOH; (e) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C; (f) $(CF_3CH_2O)_2P(O)CHMeCO_2Me$, 18-crown-6, KHMDS, THF, −78 °C; (g) DIBAL, CH_2Cl_2, −40 °C; (h) DMP, CH_2Cl_2; (i) (−)-Ipc_2BCl, Me_2CO, Et_3N, Et_2O, −78 °C; MeOH, H_2O_2, pH 7 buffer; (j) PMBTCA, TfOH, Et_2O.

reaction of **17** with formaldehyde when using *c*-Hex_2BCl/Me_2NEt (Et_2O, −78 °C) gave a separable mixture of diastereomers, favoring the expected[13,15] adduct **18** (92:8 dr, 82% yield of **18**). TIPS ether formation, followed by a sequence[13a] involving ketone reduction with $NaBH_4$, benzoate hydrolysis, and glycol cleavage with $Pb(OAc)_4$, provided the enantiomerically pure aldehyde **19** (88%). Using the Still−Gennari HWE variant,[16] homologation of **19** gave the desired (*Z*)-enoate **20** exclusively (94%). Following conversion into aldehyde **21**, an aldol reaction with acetone required reagent control to achieve a good level of diastereoselectivity. Thus, (−)-Ipc_2BCl/Et_3N in Et_2O was employed[17] to give a separable mixture (83:17 dr) from which the desired (15*R*)-adduct **22**[18] was isolated in 65% yield. Finally, PMB ether formation led to the $C_{12}-C_{19}$ methyl ketone **3**.

(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

(12) This reaction was accompanied by the formation of the elimination product 2-(4-methoxybenzyloxymethyl)-5-methylfuran.

(13) (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639. (b) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.

(14) Ketone **17** was prepared from ethyl (*S*)-lactate in 62% yield by an identical 3-step sequence to that described in ref 13a for the enantiomeric series.

(15) See the Supporting Information for a proof of stereochemistry of aldol adduct **18**.

(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(17) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935. (c) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.

(18) The configurations of **22**, **24**, **26**, and **28** were established by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters, using the advanced Mosher method, see: Kusumi, T.; Hamada, T.; Ishitsuka, M. O.; Ohtani, I.; Kakisawa, H. *J. Org. Chem.* **1992**, *57*, 1033.

Scheme 5

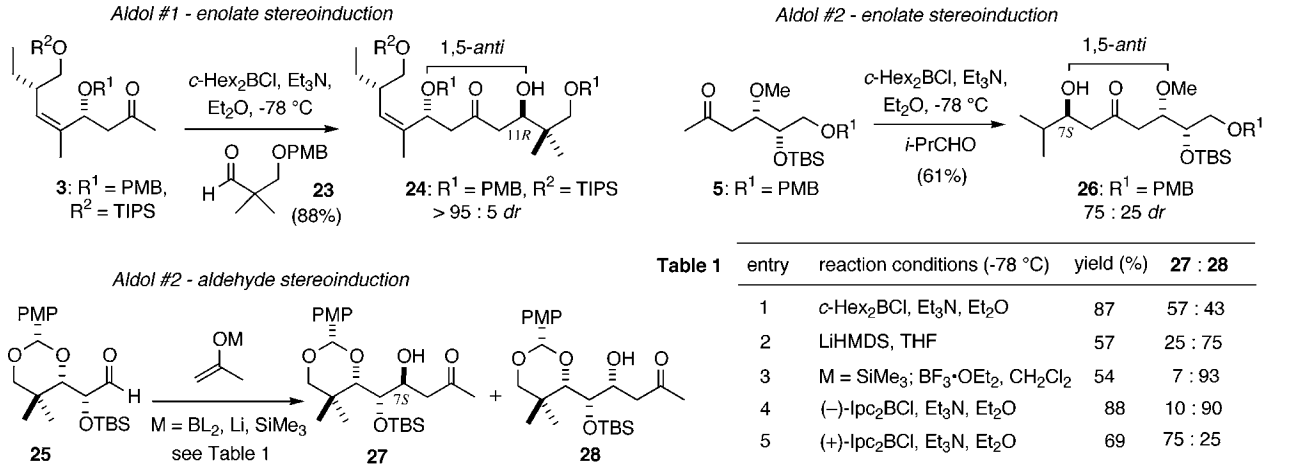


Table 1

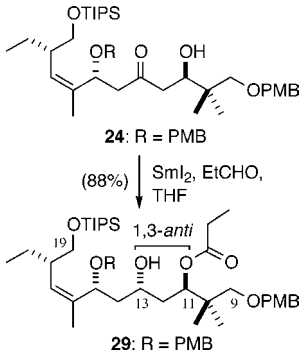
entry	reaction conditions (-78 °C)	yield (%)	**27** : **28**
1	*c*-Hex_2BCl, Et_3N, Et_2O	87	57 : 43
2	LiHMDS, THF	57	25 : 75
3	M = $SiMe_3$; $BF_3{\cdot}OEt_2$, CH_2Cl_2	54	7 : 93
4	(–)-Ipc_2BCl, Et_3N, Et_2O	88	10 : 90
5	(+)-Ipc_2BCl, Et_3N, Et_2O	69	75 : 25

With all three building blocks **3**, **4**, and **5** in hand, we set out to investigate the two key aldol couplings required to assemble the carbon skeleton of peloruside (i.e. aldols #1 and #2, Scheme 1). The results are presented in Scheme 5. With *c*-Hex_2BCl/NEt_3 the coupling of methyl ketone **3** with the achiral aldehyde **23** proceeded, as expected,[5] with an excellent level of remote 1,5-anti induction (>95:5 dr) in favor of the desired (11*R*)-adduct **24** (88%).[18] Hence, it should be possible to exploit this high level of substrate-based induction arising from the boron enolate of **3** in combination with a suitable C_{11} aldehyde derived from **4**.

We next sought to explore the potential influence of the stereogenic centers contained in ketone **5** and aldehyde **25**, obtained by Dess−Martin oxidation of **4**, in the planned C_6−C_7 coupling (i.e. aldol #2). The *c*-Hex_2BCl-mediated aldol reaction between ketone **5** and isobutyraldehyde served to confirm the anticipated role[5,19] of the β-methoxy group in securing the desired 1,5-anti stereoinduction, giving ketone **26** with moderate selectivity of 75:25 dr (Scheme 5). The π-facial selectivity of aldehyde **25** was then evaluated in aldol reactions with acetone. Not only did we observe low diastereoselectivity with *c*-Hex_2BCl (Table 1, entry 1), but the undesired all-syn product **28** was preferred under a variety of other conditions, particularly using the Mukaiyama protocol (entry 3), thus indicating that 1,2-stereoinduction follows the Felkin−Anh model, where the steric effect from the large alkyl group overrides any electronic control from the α-oxygen substituent in the aldehyde **25**. Fortunately, it proved possible by using (+)-Ipc_2BCl[17] to favor the desired (7*S*)-configuration in **27** with 75:25 dr (entry 5). We anticipate that in the (+)-Ipc_2BCl-mediated aldol coupling between ketone **5** and aldehyde **25**, triple asymmetric induction should amplify this selectivity.[17c]

Having constructed the β-hydroxy ketone **24** in an efficient manner by employing 1,5-anti stereoinduction in the aldol coupling step, we turned to achieving a suitable reduction to set in place the 1,3,5-triol sequence (Scheme 6). An

Scheme 6



Evans−Tishchenko reduction[20] on **24** with SmI_2 and EtCHO gave the alcohol **29** exclusively in 88% yield. This 1,3-anti reduction differentiates the C_{11} and C_{13} hydroxyls and provides the C_9−C_{19} subunit of peloruside.

In summary, we have achieved highly stereoselective syntheses of several peloruside subunits (**3**, **4**, **5**, and **29**), and established that they can be coupled together in the desired manner. Studies toward completing a total synthesis of peloruside A are underway.

Acknowledgment. We thank the EPSRC (GR/S19929), EC (HPRN-CT-2000-00018), Merck Sharp and Dohme, and DAAD (Fellowship to T.K.) for support.

Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The reduced level of 1,5-anti induction is attributed to the bulky C_2 TBS ether adversely affecting the conformation of the stereodirecting methyl ether at C_3 (for a related example, see ref 5b) and/or an opposing influence from the C_2 stereocenter. For a situation where more remote stereocenters win out over the 1,5-effect, see: Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055.

(20) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.