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Synthesis and [4 + 2]-Annulation of Enantioenriched (*Z*)-Crotylsilanes: Preparation of the C1–C13 Fragment of Bistramide A

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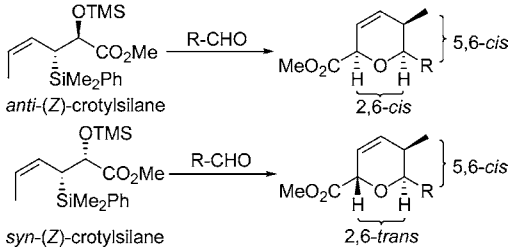
ABSTRACT



New chiral crotylsilanes that bear a (*Z*)-olefin geometry were synthesized in high enantiopurity. The reagents participate in [4 + 2]-annulations with aldehydes to give stereochemically complementary pyrans (relative to (*E*)-crotylsilanes) bearing 2,6-*cis*-5,6-*cis* and 2,6-*trans*-5,6-*cis* relationships of peripheral functionalities. A stereoselective synthesis of the C1–C13 fragment of bistramide A is also described highlighting this annulation strategy.

Functionalized pyran ring systems are embedded in a vast array of biologically active natural products.[1] Several methods are presently available allowing for their synthesis in high yields and diastereoselectivities.[2]

Previous work described the synthesis and utility of (*E*)-crotylsilanes **1** and **2** (Scheme 1) in the formation of dihydropyrans through a [4 + 2]-annulation pathway[3] and subsequent applications of these reagents in natural product synthesis.[4] Access to trisubstituted pyrans with a 5,6-*cis* relationship has not been possible using crotylsilane reagents with (*E*)-olefin geometry.[3] Direct access, in a stereocontrolled manner, to the complementary 5,6-*cis* dihydropyran system would be a useful contribution to the field and broaden the scope of the silane-based methodology.[5]

An efficient synthesis of the complimentary (*Z*)-crotylsilanes **3** and **4** and their use in the stereochemically complimentary [4 + 2]-annulation are described in this paper. This strategy allows for straightforward access to 2,6-*trans*-5,6-*cis*- and 2,6-*cis*-5,6-*cis*-dihydropyrans **7** and **8** whose stereochemistry could not be established using (*E*)-crotylsi-

(1) For examples, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (b) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 2041. (c) Norcross, R. D.; Patterson, I. *Chem. Rev.* **1995**, *95*, 2041. (d) O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205. (e) Westly, J. W., Ed. *Polyether Antibiotics*; Marcel Dekker: New York, 1983; Vols. I and II.

(2) For examples of crotyl- and allylsilanes used in the formation of pyrans, see: (a) Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* **2001**, 1042. (b) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (c) Chelle, F.; Markó, I. E. *Tetrahedron Lett.* **1997**, *38*, 2895.

(3) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

(4) (a) Huang, H.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383. (b) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991. (c) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626. (d) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693. (e) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223. (f) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (g) Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995. (h) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529.

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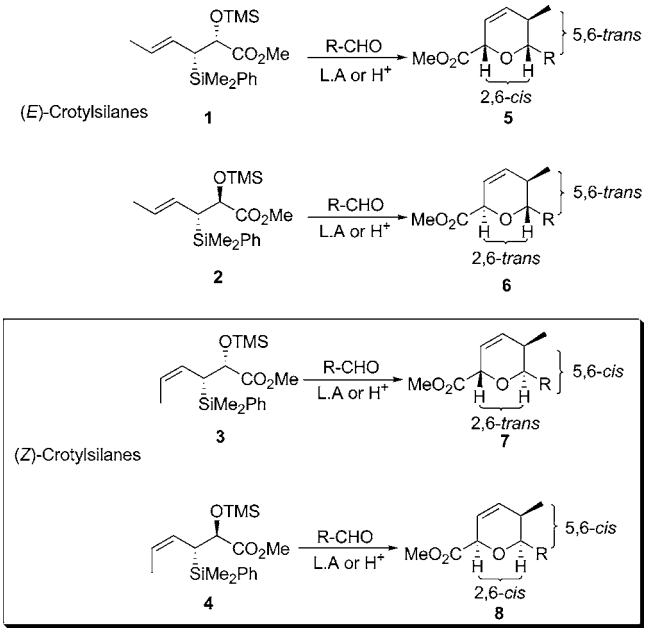
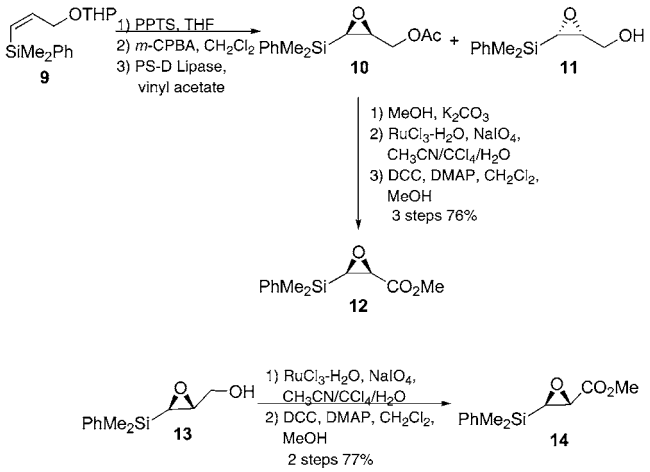
Scheme 1. (*Z*)- and (*E*)-Crotylsilane Reagents Accessing Dihydropyrans



lanes (Scheme 1). The use of *ent*-**3** for the synthesis of the C1−C13 fragment of bistramide A has also been described.

To obtain the desired (*Z*)-crotylsilanes **3** and **4** in multigram quantities, we envisioned their synthesis from both *cis*- and *trans*-silyl epoxy esters **12** and **14** (Scheme 2). Accordingly, the synthesis of the *cis*-epoxy ester began with (*Z*)-vinylsilane **9**.[6] Deprotection of the primary alcohol in the presence of PPTS followed by epoxidation with *m*-CPBA gave a racemic mixture of silyl epoxy alcohols, which underwent kinetic resolution in the presence of PS-D lipase[7] and vinyl acetate to give enantiomerically enriched acetate **10** and alcohol **11**.[8] The complimentary *trans*-epoxy alcohol **13** was obtained in accord with Chauret.[9] Upon removal of the acetate group in **10** the remaining steps in the sequence are identical. Oxidation with $NaIO_4$ and catalytic $RuCl_3$ provided the respective acids,[10] which were immediately

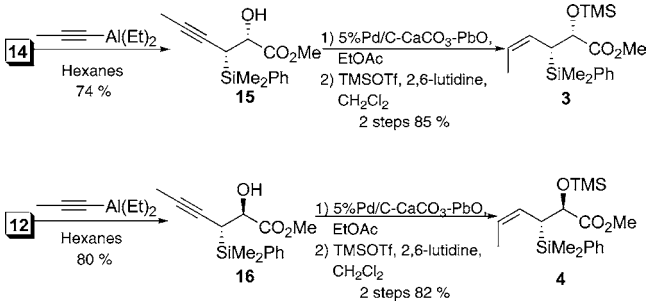
Scheme 2. Preparation of *cis*- and *trans*-Silyl Epoxy Esters



esterified to give epoxy esters **12** and **14** (76% from **10** and 77% from **13**, respectively). Using this route, the epoxy esters were prepared in greater than 10 g quantities with high enantiomeric purity.

To complete the synthesis of the silanes, a regioselective epoxide ring opening with diethylpropynylaluminum[11] was used to give 2,3-*syn* (**15**) and 2,3-*anti* (**16**) hexyne methyl esters. Finally, Lindlar reduction of the individual alkynes followed by protection of the secondary alcohols as their TMS ethers gave *syn*- (**3**) and *anti*-(*Z*)-crotylsilanes (**4**) (Scheme 3).

Scheme 3. Preparation of *syn*- and *anti*- (*Z*)-Crotylsilanes



Once a synthetic sequence for the synthesis of (*Z*)-crotylsilanes was established, our attention turned to their use in [4 + 2]-annulations: a number of different aldehydes were evaluated to determine the reaction scope. On exposure to a Lewis acid or Brønsted acid the desired 2,6-*trans* 5,6-*cis* **7** (from **4**) and 2,6-*cis* 5,6-*cis* **8** (from **3**) dihydropyrans were obtained (Scheme 1, Table 1).[12]

Aliphatic aldehydes and (*Z*)-crotylsilanes are effective reaction partners in the annulation giving good yields and

(5) For examples of natural products containing 5,6-*cis*-di- and tetrahydropyrans, see: (a) Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. *J. Am. Chem. Soc.* **1978**, *100*, 6786. (b) Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015. (c) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (d) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazon, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 1993. (e) Fusetanai, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977. (f) Higa, T.; Tanaka, J.; Komesu, M.; Gravalos, D. C.; Puentes, J. L. F.; Bernardinelli, G.; Jefford, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 7587.

(6) Vinylsilane **9** may be prepared in three steps from commercially available propargyl alcohol. See the Supporting Information.

(7) Lipase PS-D "Amano" I from Lot No. ILPSAY0352205K may be purchased from Amano Enzyme USA Co., Lomdard, IL 60148.

(8) The free alcohol of **10** was obtained in 94% yield (two steps from the racemic epoxide) and found to have 94−96% ee. Alcohol **11** was obtained in 89% yield and 94−97% ee.

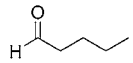
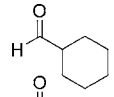
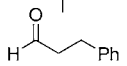
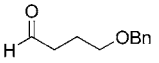
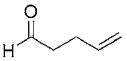
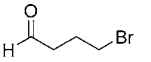
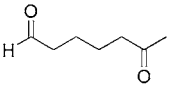
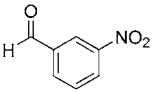
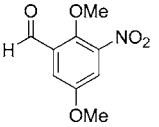
(9) (a) Chauret, D. C.; Chong, J. M.; Ye Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3601. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(11) Kim, K.; Okamoto, S.; Takayama, Y.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 4237.

(12) See the Supporting Information for experimental details.

Table 1. [4 + 2]-Annulation with (*Z*)-Crotylsilanes **3** and **4**

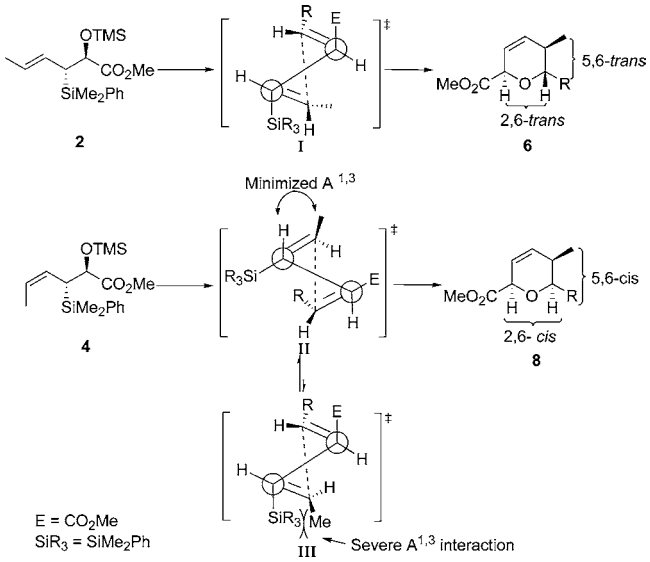
entry	aldehyde	reaction with **3**[a] product[c]	%yield[d]	dr[e]	rection with **4**[b] product[c]	%yield[d]	dr[e]
1		**7a**	92	>20:1	**8a**	91	>20:1
2		**7b**	80	12:1	**8b**	74	8:1
3		**7c**	71	15:1	**8c**	88	10:1
4		**7d**	74	>20:1	**8d**	78	>20:1
5		**7e**	76	>20:1	**8e**	73	6:1
6		**7f**	80	>20:1	**8f**	83	>20:1
7		**7g**	90	>20:1	**8g**	91	>20:1
8		**7h**	48	>20:1	**8h**	45	6:1
9		**7i**	75	>20:1	**8i**	81	>20:1
10		**7j**	60	>20:1	**8j**	50	>20:1

[a] Reaction of **3** was run in CH_2Cl_2 (0.05 M) using 1−2 equiv of aldehyde in the presence of triflic acid (1.0 equiv) at −78 °C unless otherwise noted. [b] Reaction of **4** was run in CH_2Cl_2 (0.05 M) using 1−2 equiv of aldehyde in the presence of triflic acid (1.0 equiv) at −90 °C unless otherwise noted. [c] Stereochemical assignments were determined through NOE and direct comparison with known materials from ref 3. [d] All yields are based on isolated product after purification by chromatography. [e] The ratio of products is determined by ^{1}H NMR (400 MHz).

diastereoselectivities.[13] Reaction conditions required for the annulation are compatible with a number of functional groups such as ethers (Table 1, entry 5 and 10), primary alkyl bromides (Table 1, entry 7), alkenes (Table 1, entry 6), nitro groups (Table 1, entries 9 and 10), and ketones (Table 1, entry 8). In addition, α-branched substrates (Table 1, entries 2 and 3) participate in the described annulation albeit with some loss of diastereoselectivity. Some aromatic aldehydes (Table 1, entries 9 and 10) are also effective in the annulation.

Interestingly, the stereochemical outcome of the annulations reported in Table 1 was not entirely anticipated. Previous results with (*E*)-crotylsilanes gave a 2,6-*cis*-dihydropyran **5** with the *syn*-(*E*)-crotylsilane **1** and 2,6-*trans*-dihydropyran **6** for the *anti*-(*E*)-crotylsilane **2** (Scheme 1).[14] In the case of the (*Z*)-crotylsilanes, a 2,6-*cis*-dihydropyran was observed for *anti*-(*Z*)-crotylsilane **3** and a 2,6-*trans*-dihydropyran when using *syn*-(*Z*)-crotylsilane **4**.[15] These results may suggest that the silicon adopts a pseudoequatorial orientation for silane **4** (**II** avoids potential A^{1,3} destabilizing interactions arising from a (*Z*)-olefin and axial silicon **III**)[16] giving the major diastereomer[17] as shown in Scheme 4 (**I** gives **6** and **II** gives **8**).[18,19]

Scheme 4. Comparison of (*E*)- and (*Z*)-Crotylsilanes in [4 + 2]-Annulation



Having established an efficient means to access both 2,6-*cis*-5,6-*cis* and 2,6-*trans*-5,6-*cis* dihydropyran systems, we then applied the annulation strategy in the synthesis of the C1−C13 fragment of bistramide A.

Bistramide A (**17**) was first isolated in 1988 from *Lissoclinum* bistramide sluiter.[20] It belongs to a class of natural products[21] that has been known to display high neuro- and cytotoxic properties[22] as well as profound effects on cell cycle regulation.[23] Its potent activity along with its chal-

(13) Minor amounts of side products of the reaction include homo-aldol coupling followed by dehydration and Peterson olefination to give the conjugated esters of **3** and **4**.

(14) For an interpretation of the stereochemical course of (*E*)-crotylsilanes in the [4 + 2]-annulations, see: Huang, H. Ph.D. Thesis, Boston University, 2005.

(15) Enantiomeric excess (ee) analysis was preformed using chiral HPLC analysis with a CHIRALCEL OD column. See the Supporting Information.

(16) It has been suggested that silicon prefers an axial orientation for both electronic and steric reasons but may still eliminate even without optimal orbital overlap. For a detailed discussion and relevant examples, see: Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.

(17) Intramolecular silyl-modified Sakurai condensations of vinylsilanes suggest allylic strain plays a role in stereochemical outcome: Bayston, D. J.; Chelle, F.; Scheirmann, V.; Dobbs, A. P.; Markó, I. E. *Tetrahedron Lett.* **1997**, *38*, 2899.

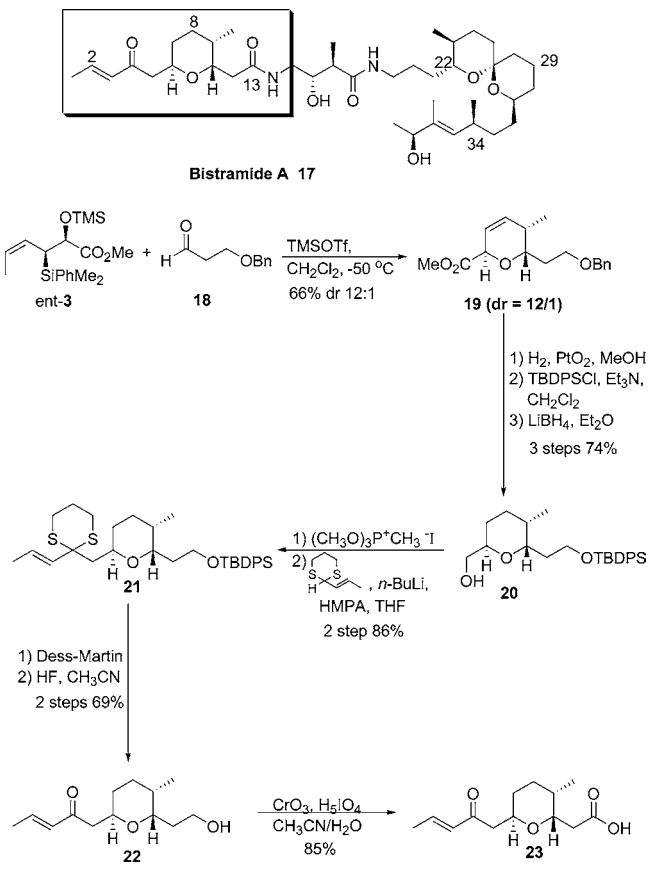
(18) It is conceivable that an *oxonia*-Cope rearrangement could play a role in the stereochemical outcome of these reactions; however, no byproducts from this pathway were observed. For an example of *oxonia*-Cope rearrangements in allyl systems, see: Roush, W. R.; Dilley, G. J. *Synlett* **2001**, *SI*, 955.

(19) For an example of *oxonia*-Cope rearrangement of ester-substituted oxycarbenium vinylsilanes to form dihydropyrans, see ref 2b.

(20) Gouiffes, D.; Moreau, S.; Helbecque, N.; Bernier, J. L.; Henichart, J. P.; Barbin, Y.; Laurent, D.; Verbist, J. F. *Tetrahedron* **1988**, *44*, 451.

(21) (a) Biard, J. F.; Roussakis, C.; Kornprobst, J. M.; Gouiffes-Barbin, D.; Verbist, J. F.; Cotelle, P.; Foster, M. P.; Ireland, C. M.; Debitus; C. *J. Nat. Prod.* **1994**, *57*, 1336. (b) Foster, M. P.; Mayne, C. L.; Dunkel, R.; Pugmire, R. J.; Grant, D. M.; Kornprobst, J. M.; Verbist, J. F.; Biard, J. F.; Ireland, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 1110. (c) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.

Scheme 5. Synthesis of the C1−C13 Fragment of Bistramide A



lenging structure has stimulated much attention from the synthetic community.[24]

Scheme 5 illustrates our synthesis of the C1−C13 fragment of bistramide A. Aldehyde **18** underwent TMSOTf-promoted annulation with crotylsilane *ent*-**3** to give the desired dihydropyran **19** in 66% yield (dr = 12/1). Catalytic hydrogenation using Adam's catalyst concomitantly reduced the double bond and deprotected the benzyl ether. Protection of the resulting alcohol followed by reduction of the methyl ester gave **20** in 74% yield over three steps. To introduce the unsaturated ketone, the primary alcohol was transformed to the corresponding iodide upon treatment with $(PhO)_3P^+CH_3I^-$ followed by displacement of the resulting iodide with the lithium anion of 2-propenyl-dithiane **21**.[25] The resulting dithiane was unmasked with Dess−Martin periodinane,[26] followed by deprotection of the TBDPS ether with HF in acetonitrile. Finally, oxidation of the primary alcohol directly to the acid with catalytic chromium in wet acetonitrile completed the C1−C13 fragment of bistramide A **23** in a nine-step sequence (25% overall).[24c]

In summary, we have developed a reliable protocol for the preparation of (*Z*)-crotylsilane reagents with high enantiopurity. These reagents were shown to undergo [4 + 2]-annulations with aldehydes to produce both 2,6-*cis*-5,6-*cis* and 2,6-*trans*-5,6-*cis* dihydropyran systems in high yield and diastereoselectivities. Having ready access to all four diastereomeric silanes **1**−**4** (and their enantiomers), we are able to generate all stereochemical permutations with the annulation strategy. Application in the synthesis of the C1−C13 fragment of bistramide A was also achieved. These experiments further underscore the point that subtle structural changes in the silane reagents are manifested in profound alterations in the stereochemical outcome of the annulation. Further studies on the application and mechanistic understanding of these reagents will be reported in due course.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Gouiffes, D.; Juge, M.; Grimaud, N.; Welin, L.; Sauviat, M. P.; Barbin, Y.; Laurent, D.; Roussakis, C.; Henichart, J. P.; Verbist, J. F. *Toxicon* **1988**, *26*, 1129.

(23) Johnson, W. E. B.; Watters, D. J.; Suniara, R. K.; Brown, G.; Bunce, C. M. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 80.

(24) (a) Synthesis of the C1−C13 fragment was described: Gallagher, P, O.; McErlean, S. P.; Jacobs, M, F.; Watters, D. J.; Kitching, W. C. *Tetrahedron Lett.* **2002**, *43*, 531. (b) Synthesis of a stereoisomer of bistramide A is described: Wipf, P.; Uto, Y.; Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670. (c) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546.

(25) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357. (c) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.

(26) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575.