ORGANIC LETTERS

2007
Vol. 9, No. 22
4587−4589

Stereoselective Total Synthesis of Bistramide A

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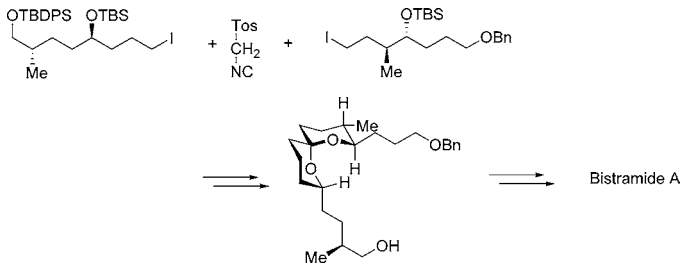
Received August 25, 2007

ABSTRACT



A highly stereoselective and convergent total synthesis of bistramide A is described. The salient feature of this synthesis is the construction of the spiroketal subunit by hydrolysis of dialkylated tosylmethyl isocyanide derivative derived via alkylation of TosMIC with suitably substituted halohydrin derivatives.

Bistramides, A−D and K, constitute a novel class of bioactive marine natural products that were isolated from the marine ascidian *Lissoclinum bistratum*.[1−3] They exhibit high cytotoxicity and significant effects on cell cycle regulation.[3] Bistramide A displayed an IC_{50} of 0.03−0.32 μg/mL for the P388/dox, B16, HT29, and NSCLC-N6 cell lines,[4] inhibits Na^+ conductance,[5] and is selective toward the activation of a single protein kinase C (PKC) isotype δ.[6] It is also believed that bistramide A can inhibit nucleotide exchange by stabilizing the closed actin conformation.[7] These promising biological activities of bistramide A have manifested it as a potential candidate for anticancer therapy.

The bistramide A skeleton consists of a substituted tetrahydropyran and spiroketal subunit connected by a central γ-amino acid linker. The first synthesis of bistramide A was reported by Kozmin and co-workers in 2004[8] confirming the assigned stereochemistry and structure as illustrated in Figure 1. Afterward, Kozmin, Crimmins[9] and Panek[10] have also reported the synthesis of this molecule using two different strategies. Additionally, Wipf et al.[11] reported the synthesis of bistramide C that is structurally related to bistramide A. Intrigued by its excellent biological activity and interesting molecular architecture, we became interested in the total synthesis of bistramide A. In continuation of the synthesis of complex natural products, we herein disclose the stereoselective total synthesis of bistramide A.

The retrosynthetic analysis of bistramide A is shown in Figure 1; disconnection at C13 and C18 amide linkages

(1) Gouiffès, D.; Moreau, S.; Helbecque, N.; Bernier, J. L.; Hénichart, J. P.; Barbin, Y.; Laurent, D.; Verbist, J. F. *Tetrahedron* **1988**, *44*, 451.
(2) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
(3) 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**, *7*, 1336.
(4) Johnson, W. E.; Watters, D. J.; Suniara, R. K.; Brown, G.; Bunce, C. M. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 80.
(5) (a) Sauviat, M. P.; Gouiffes-Barbin, D.; Ecault, E.; Verbist, J. F. *Biochim. Biophys. Acta* **1992**, *1103*, 109. (b) Sauviat, M. P.; Verbist, J. F. *Gen. Phys. Biophys.* **1993**, *12*, 465.
(6) Griffiths, G.; Garrone, B.; Deacon, E.; Owen, P.; Pongracz, J.; Mead, G.; Bradwell, A.; Watters, D.; Lord, J. *Biochem. Biophys. Res. Commun.* **1996**, *222*, 802.
(7) (a) Statsuk, A. V.; Bai, R.; Baryza, J. L.; Verma, V. A.; Hamel, E.; Wender, P. A.; Kozmin, S. A. *Nat. Chem. Biol.* **2005**, *1*, 383. (b) Rizvi, S. A.; Tereshko, V.; Kossiakoff, A. A.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 3882.
(8) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546.
(9) Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936.
(10) Lowe, J. T.; Wrona, I. E.; Panek, J. S. *Org. Lett.* **2007**, *9*, 327.

10.1021/ol702095n CCC: $37.00
Published on Web 10/06/2007

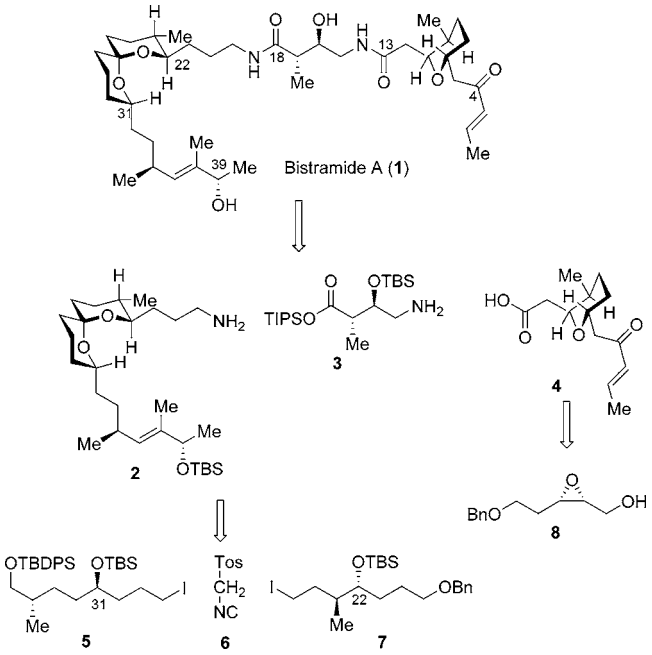
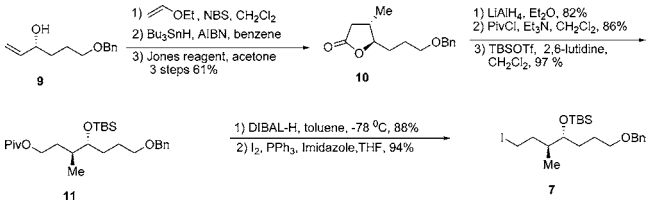


Figure 1. Retrosynthetic analysis of bistramide A.

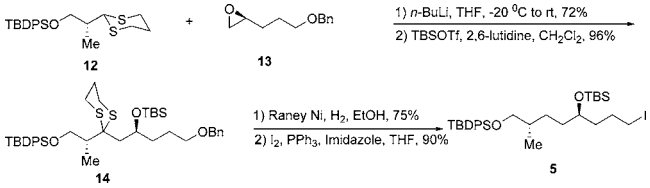
afforded spiroketal fragment **2**, γ-amino acid fragment **3**, and pyran fragment **4**. Fragment **2** was envisaged to be obtained by alkylation of TosMIC **6** with use of iodo compounds **5** and **7**.[12]

Scheme 1. Synthesis of Compound **7**



The synthesis of compound **7** is depicted in Scheme 1. Thus, lactone **10**, which was obtained (97% de, 61% yield over three steps) from allyl alcohol **9** (93% ee)[13] as reported earlier,[13,14] was reduced to the corresponding diol with $LiAlH_4$ (82%). The primary hydroxyl group of the diol was protected as its pivalate ester (86%) by using pivaloyl chloride and triethylamine and the secondary hydroxyl group as TBS ether by using TBSOTf and 2,6-lutidine to furnish **11** (97%). Deprotection of the pivalate ester by DIBAL reduction (88%) followed by treatment with iodine and triphenylphosphine yielded iodo compound **7** (94%).

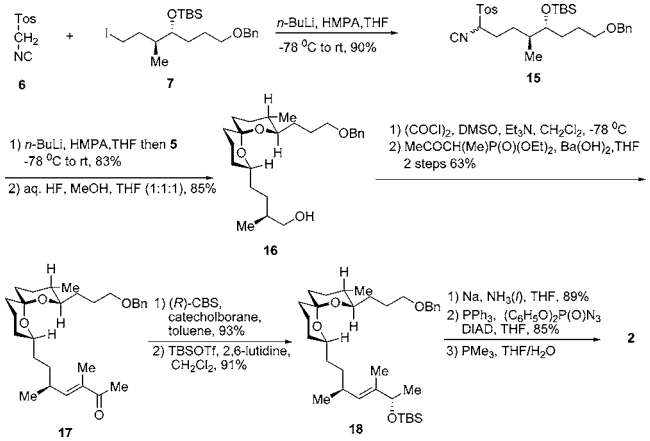
Scheme 2. Synthesis of Compound **5**



Compound **5** (Scheme 2) was synthesized starting from dithiane **12**, obtained by following a known procedure.[15] Metalation of dithiane **12** with *n*-BuLi at room temperature[16] followed by treatment of the anion with epoxide **13** afforded an alcohol (72%) and was protected as its TBS ether **14** (96%) with TBSOTf and 2,6-lutidine. Treatment of **14** with Raney-nickel under H_2 atmosphere in EtOH afforded the primary alcohol (75%) by a concomitant debenzylation, which was further converted into corresponding iodo compound **5** (90%).

Synthesis of spiroketal fragment **2** of bistramide A is shown in Scheme 3. TosMIC **6** was first alkylated with iodo

Scheme 3. Synthesis of Spiroketal Fragment **2**



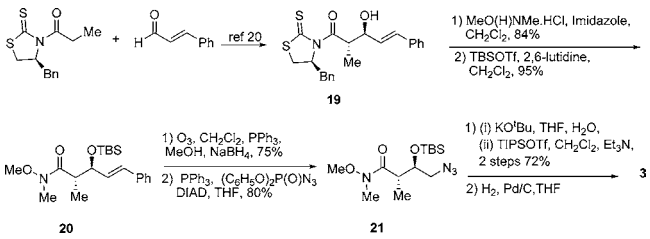
compound **7** in the presence of *n*-BuLi to afford **15** (90%). Further alkylation of the anion generated from **15** with iodo compound **5** gave dialkylated product (83%), which on treatment with aq. HF in MeOH/THF afforded spiroketal **16** (85%).[12] Swern oxidation of alcohol **16** followed by Horner−Wadsworth−Emmons olefination[17] with 1-methyl-2-oxopropyl phosphonate[18] provided an α,β-unsaturated ketone **17** (*E*/*Z*, 10:1). Reduction of ketone **17** with Corey's chiral

(11) (a) Wipf, P.; Hopkins, T. D. *Chem. Commun.* **2005**, 3421. (b) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670.
(12) Yadav, J. S.; Gadgil, V. R. *Tetrahedron Lett.* **1990**, *31*, 6217.
(13) A similar alcohol with opposite center at the C4 position was prepared earlier by our group as given in: Yadav, J. S.; Joyasawal, S.; Dutta, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2007**, *48*, 5335.
(14) (a) Yadav, J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1824. (b) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1983**, *105*, 3741.
(15) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.
(16) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491.
(17) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774.
(18) Corbel, B.; Medinger, L.; Haelters, J. P.; Sturtz, G. *Synthesis* **1985**, 1048.

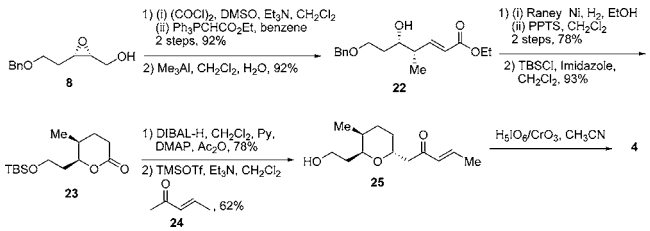
oxazaborolidine[19] (94% de, 93% yield) and protection of the resulting alcohol as its TBS ether yielded **18** (91%). Compound **18** was subsequently converted into **2** in three steps.[10]

After synthesizing amine **2**, we further proceeded to synthesize γ-amino acid fragment **3** (Scheme 4). Accordingly, the pure *anti* aldol adduct **19**[20] was converted into the corresponding Weinreb amide (84%)[21] and its free hydroxyl group was protected as TBS ether to afford **20** (95%). Ozonolysis of **20** followed by reductive workup provided a primary alcohol (75%), which was converted into the corresponding azide **21** (80%) by using $(PhO)_2P(O)N_3$ under Mitsunobu conditions. Hydrolysis of the amide[22] followed by protection of the resulting acid with TIPSOTf gave TIPS ester (72%, two steps) that was converted into γ-amino acid **3** via catalytic hydrogenation.[23]

Scheme 4. Synthesis of γ-Amino Acid Fragment **3**



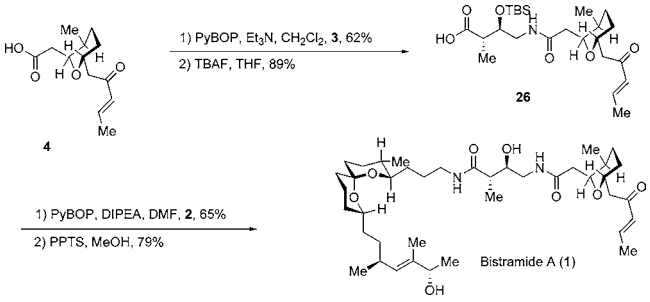
Scheme 5. Synthesis of Pyran Fragment **4**



Synthesis of pyran fragment **4** is shown in Scheme 5. The known *cis* epoxy alcohol **8** (92% ee)[24] was converted into a γ,δ-epoxy acrylate (92% in two steps) followed by treatment with Me_3Al in the presence of water following Miyashita's protocol[25] to furnish regio- and stereoselectively the *syn* product **22** (92%). One-pot olefin reduction and benzyl ether deprotection with Raney-nickel gave a mixture of hydroxy ester and lactone, which on treatment with PPTS in refluxing CH_2Cl_2 afforded the later exclusively (78%).[9] The free hydroxyl group was protected as TBS ether to obtain compound **23** (93%). The acetate (78%) derived from lactone **23** following Rychnovsky's protocol[26] was treated with silyl enol ether derived from ketone **24** in the presence of TMSOTf to afford exclusively alcohol **25** (62%),[9] which was further oxidized to corresponding acid **4**.[8,27]

Having synthesized all three fragments **2**, **3**, and **4**, their coupling to obtain bistramide A was accomplished by following a procedure reported in the literature (Scheme 6).[10]

Scheme 6. Completion of the Synthesis of Bistramide A



Coupling of tetrahydropyran subunit **4** and amine **3** in the presence of PyBOP furnished TIPS ester (62%), which was selectively deprotected with TBAF to yield acid **26** (89%). The final peptide coupling of acid **26** with amine **2** led to the formation of a complete carbon skeleton (65%). Removal of the silyl protecting groups with PPTS completed the synthesis of bistramide A (79%). The synthetic compound was found to be identical with that reported in earlier synthesis based on the comparison of ^{1}H NMR, ^{13}C NMR, HRMS, and optical rotation data.

In summary, we have accomplished a highly convergent and stereoselective synthesis of bistramide A. The spiroketal functionality was obtained via dialkylation of TosMIC with suitably substituted halohydrin derivatives. The C15 and C16 streocenters of the γ-amino acid fragment were prepared by Evans *anti* aldol method. The C9 and C11 stereocenters of the pyran fragment were prepared by Me_3Al-mediated opening of *cis* epoxide.

Acknowledgment. L.C. thanks CSIR, New Delhi, India, for financial assistance.

Supporting Information Available: Experimental details, selected spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.
(20) Adduct **19** (90% de) was prepared by following the known procedure as given in: Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.
(21) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.
(22) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
(23) To avoid the unwanted γ-lactone formation after ozonolysis/reduction reaction we did not prepare the methyl or TIPS ester by displacing the chiral auxiliary.
(24) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600.
(25) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483.
(26) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.
(27) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231.