## **Total Synthesis of Bistramide A**

Jason T. Lowe, Iwona E. Wrona, and James S. Panek\*

Department of Chemistry and Center for Chemical Methodology and Library Development, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

panek@bu.edu

Received December 6, 2006

## ORGANIC LETTERS 2007 Vol. 9, No. 2 327–330



An asymmetric synthesis of the marine metabolite bistramide A is reported. The synthesis relies on the utility of three different organosilane reagents to construct all principle fragments and 8 of the 11 stereogenic centers of the natural product.

Bistramide A (1) is a marine metabolite initially isolated in 1988 from *Lissoclinum bistratum* Sluiter near New Caledonia.<sup>1</sup> Four additional members of the bistramide family (bistramides B–D and K) have been identified since this initial report.<sup>2</sup> These compounds have been shown to exhibit numerous biological properties, including antiproliferative,<sup>3</sup> antiparasitic,<sup>4</sup> immunomodulatory,<sup>5</sup> neurotoxic,<sup>3</sup> and cytotoxic activities.<sup>2</sup> Bistramide A was further implicated in a unique protein kinase C $\delta$ -activation.<sup>6</sup> However, recent studies indicate actin as the primary cell receptor of the natural product.<sup>7</sup>

(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) 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.

The structure of bistramide A was originally proposed to be a 19-membered macrocyclic lactam.<sup>8</sup> Extensive 2D NMR analysis,<sup>9</sup> however, revealed an acylic compound containing a substituted tetrahydropyran and spiroketal subunit, connected by a central  $\gamma$ -amino acid linker. Further NMR analysis<sup>10</sup> and chiroptical measurements<sup>11</sup> of other members of the bistramide family (B–D) allowed for the accurate prediction of the absolute stereochemistry of **1**. Kozmin's total synthesis of bistramide A<sup>12</sup> then confirmed the predicted stereochemistry and structure as illustrated in Figure 1. Subsequent to Kozmin's report, an additional synthesis of bistramide A<sup>13</sup> and one of structurally related bistramide C<sup>14</sup>

<sup>(3)</sup> Riou, D.; Roussakis, C.; Robillard, N.; Biard, J. F.; Verbist, J. F. Biol. Cell 1993, 77, 261.

<sup>(4)</sup> Gautret, P.; Le Pape, P.; Biard, J. F.; Menard, D.; Verbist, J. F.; Marjolet, M. Acta Parasitol. 1998, 43, 50.

<sup>(5)</sup> Pusset, J.; Maillere, B.; Debitus, C. J. Nat. Toxins 1996, 5, 1.

<sup>(6)</sup> 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.

<sup>(7) (</sup>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.

<sup>(8)</sup> Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.

<sup>(9)</sup> 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.

<sup>(10) (</sup>a) Gallagher, P. O.; McErlean, C. S. P.; Jacobs, M. F.; Watters, D. J.; Kitching, W. *Tetrahedron Lett.* **2002**, *43*, 531. (b) Solladié, G.; Baudet, C.; Biard, J.-F. *Tetrahedron Lett.* **2000**, *41*, 7747.

<sup>(11) (</sup>a) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem.-Eur. J.* 2002, *8*, 1670.
(b) Zuber, G.; Goldsmith, M.-R.; Hopkins, T. D.; Beratan, D. N.; Wipf, P. *Org. Lett.* 2005, *7*, 5269.

<sup>(12)</sup> Statsuk, A. V.; Liu, D.; Kozmin, S. A. J. Am. Chem. Soc. 2004, 126, 9546.

<sup>(13)</sup> Crimmins, M. T.; DeBaillie, A. C. J. Am. Chem. Soc. 2006, 128, 4936.



Figure 1. Retrosynthetic analysis of bistramide A.

have been completed. The diverse biological activity and challenging molecular architecture of 1 motivated us to explore the utility of crotylsilane-based bond construction to prepare this interesting marine metabolite. Herein, we report a convergent, enantioselective synthesis of bistramide A using organosilane-based methodology to construct 8 of the 11 stereogenic centers of the natural product.

The retrosynthesis of bistramide A, shown in Figure 1, reveals three subunits of varying complexity. Each of these fragments, tetrahydropyran 2, masked amino acid 3, and spiroketal 4, are accessible from different organosilane reagents developed in our laboratory. Tetrahydropyran 2 was previously assembled through a [4+2]-annulation utilizing (*Z*)-crotylsilane reagent 5.<sup>15</sup> The  $\gamma$ -amino acid subunit 3 of bistramide A can be constructed through a chelation-controlled crotylation using (*R*)-silane reagent 6.<sup>16</sup> Finally, disconnection of the anomeric C–O and C28–C29 bonds of spiroketal fragment 4 provides tetrahydropyran 7 and phosphonium salt 8. The relative and absolute stereochemistry of tetrahydropyran 7 is readily accessible from our [4+2]-annulation of crotylsilane 9.<sup>17</sup>

The preparation of the  $\gamma$ -amino acid fragment of bistramide A is illustrated in Scheme 1. The known homoallylic alcohol **10**<sup>18</sup> was protected as its silyl ether using TBSOTf in 99% yield. Ozonolysis followed by reduction with NaBH<sub>4</sub> provided a primary alcohol (92%, two steps), which was protected as its silyl ether **11**. Removal of the benzyl ether was followed with azide formation using (PhO)<sub>2</sub>P(O)N<sub>3</sub> under Mitsunobu conditions (78%, two steps). Selective silyl ether deprotection using CSA afforded the desired alcohol



**12** in 90% yield.<sup>13</sup> Formation of the protected TIPS acid was achieved though a two-step oxidation/protection sequence in 76% yield.<sup>14,19</sup> Reduction of the azide provided the fully functionalized C14–C18 fragment **3**.

The construction of the C29–C40 segment is illustrated in Scheme 2. This fragment was synthesized by incorporating known building blocks, which are directly accessible from the chiral pool.<sup>20</sup> Thus, (*S*)-1,2,4-butanetriol derivative  $13^{21}$ was subjected to a Wittig olefination with phosphonium salt  $14^{22}$  to give olefin 15 as a mixture of geometric isomers (*Z*:*E* =10/1) in 70% yield. One-pot reduction of the olefin and benzyl ether deprotection with Raney nickel gave a primary alcohol in 78% yield. Swern oxidation of this material provided an aldehyde, which was directly converted to the  $\alpha,\beta$ -unsaturated ketone 16 using the diethyl 1-methyl-2-



oxopropyl phosphonate reagent.<sup>23</sup> Reduction of the resulting ketone using Corey's chiral oxazaborolidine<sup>24</sup> and protection of the resulting secondary allylic alcohol as a TBS ether gave

<sup>(14)</sup> Wipf, P.; Hopkins, T. D. Chem. Commun. 2005, 3421.

<sup>(15) (</sup>a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (b) Lowe, J. T.; Youngsaye, W.; Panek, J. S. J. Org. Chem. **2006**, *71*, 3639.

<sup>(16)</sup> Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. Tetrahedron Lett. 1995, 36, 8727.

<sup>(17)</sup> Huang, H.; Panek, J. S. J. Am. Chem. Soc. 2000, 122, 9836.

<sup>(18)</sup> For the synthesis of the enantiomer of **10**, see: Huang, H.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383.

<sup>(19)</sup> For TEMPO oxidation of alcohols to carboxylic acids, see: Zhao,

M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. J. Org. Chem. **1999**, 64, 2564.

<sup>(20)</sup> For examples of chiral pool reagents, see: Blaser, H. U. Chem. Rev. 1992, 92, 935.

<sup>(21)</sup> Blakemore, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831.

<sup>(22)</sup> Gaeta, F. C. A.; Lehman de Gaeta, L. S.; Kogan, T. P.; Or, Y. S.; Foster, C.; Czarniecki, M. J. Med. Chem. 1990, 33, 964.

<sup>(23)</sup> Altenbach, H. J.; Korff, R. Tetrahedron Lett. 1981, 22, 5175.

<sup>(24)</sup> Corey, E. J.; Helal, C. J. Angew. Chem., Int. Ed. 1998, 37, 1986 and references cited therein.



**17** in 77% yield (two steps). Reductive opening of the PMP acetal with Dibal-H generated the primary alcohol along with the secondary PMB ether in 98% yield. Bromination of the primary alcohol followed by displacement with PPh<sub>3</sub> afforded the advanced coupling partner **8**.

Our synthesis of the spiroketal portion of bistramide A is depicted in Scheme 3 and was initiated with a [4+2]annulation employing syn-(E)-crotylsilane reagent  $9.1^{7}$  Accordingly, the annulation of aldehyde  $18^{25}$  gave the desired dihydropyran 19 as a single diastereomer in 97% isolated vield. The endocyclic olefin was isomerized into conjugation using tetra-*n*-butyl ammonium hydroxide. The resulting  $\alpha,\beta$ unsaturated ester was converted to its methyl glycoside by treatment with CSA in MeOH, and reduction of the ester with Dibal-H afforded aldehyde 7 in 76% yield (two steps). The key transformation in this synthetic sequence involved the olefination of aldehyde 7 with phosphonium salt 8. Gratifyingly, the union through phosphorus-based olefination provided the PMB-protected (Z)-alkene 21 as a single olefin isomer in 86% yield. Selective hydrogenation of the C28-C29 olefin of 21 with Wilkinson's catalyst provided the saturated system in 79% yield. The incorporation of a fully functionalized C40-C32 side chain prior to spirocyclization underscores the convergent nature of this synthesis.

Our initial approach for the remainder of the synthesis of **4** required a deprotection of the C31 PMB group of the C28–C29 saturated analogue of **21** followed by spirocyclization.<sup>26</sup> However, the unmasking of the alcohol proved to be difficult (Table 1). Deprotection under standard DDQ conditions (CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O) did not provide the free secondary alcohol **22** as hoped but instead gave a complex mixture of compounds. Interestingly, the major product identified from this reaction was spirocycle **23** (Table 1, entry 1).<sup>27</sup> In an effort to optimize the reaction, phosphate buffered water (pH 7) was added to remove any adventitious acid. Unfortunately, this modification gave only a slightly higher yield of **23** (Table 1, entry 2). Anhydrous conditions<sup>28</sup> gave only trace amounts of the desired product upon workup (Table 1, entry 3). Addition of pyridine to the reaction at room temperature gave useful

quantities of **23** (Table 1, entry 4). The best result was obtained at 0 °C under anhydrous conditions in the presence of pyridine to provide the spirocycle in 76% yield (Table 1, entry 5).<sup>29</sup> This transformation presumably occurred through an intermediate oxocarbenium ion that was trapped by the nascent homoallylic alcohol after PMB removal. Other conditions including TMSI,<sup>30</sup> I<sub>2</sub> in MeOH<sup>31</sup> and, the Me<sub>2</sub>S·BCl<sub>3</sub> complex<sup>32</sup> did not provide the desired secondary alcohol or spiroketal.



 $^a\,$  All yields are based on isolated product after chromatography over silica gel.  $^b$  Phosphate buffer (pH 7).

Birch reduction of the primary benzyl ether followed by a Mitsunobu displacement of the alcohol with  $(C_6H_5O)_2P$ - $(O)N_3$  afforded the primary azide. Formation of the primary amine **4** was carried out by conversion of the azide to an

<sup>(25)</sup> Cloarec, J.-M.; Charette, A. B. Org. Lett. 2004, 6, 4731.

<sup>(26)</sup> Fénézou, J. P.; Gauchet-Prune, J.; Julia, M.; Pancrazi, A. Tetrahedron Lett. 1988, 29, 3667.

<sup>(27)</sup> For a previous example of spirocyclization in the presence of DDQ,
see: Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. Org. Lett. 2002, 4, 391.
(28) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. Synlett 1998, 1102.

<sup>(29)</sup> The conditions found in Table 1 were also applied to  ${\bf 21}$  with little success.

<sup>(30)</sup> Gordon, D. M.; Danishefsky, S. J. J. Am. Chem. Soc. 1992, 114, 659.

<sup>(31)</sup> Vaino, A. R.; Szarek, W. A. Synlett 1995, 1157.

<sup>(32)</sup> Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward. S. E. *Synlett* **1993**, 663.

iminophosphorane by treatment with  $Me_3P$  followed by in situ hydrolysis of the resulting phosphine imine.<sup>33</sup>

With reproducible and reliable routes to advanced subunits 2-4, we were positioned to complete the total synthesis of bistramide A. Accordingly, fragment coupling commenced with the union of tetrahydropyran subunit 2 and amine 3 as facilitated by the PyBOP peptide coupling reagent (Scheme 4). Deprotection of the TIPS acid permits the final peptide



coupling of acid **24** and amine **4**, completing the carbon framework of the natural product. Removal of the remaining silyl protecting groups with PPTS completed the synthesis of bistramide A.

In summary, a highly convergent, enantioselective synthesis of bistramide A has been described. The synthesis illustrates considerable synergy derived from the design and application of three different enantioenriched organosilane reagents 5, 6, and 9 to construct 8 of the 11 stereogenic centers. The robust nature of the silane chemistry is demonstrated in the rapid and efficient assembly of three principle subunits 2-4 prior to fragment coupling. Synthesis and biological evaluation of bistramide-like analogues will be reported at a later date.

Acknowledgment. Financial support for this research is obtained from NIH CA56304. J.S.P. is grateful to Amgen, Johnson & Johnson, Merck Co., Novartis, Pfizer, and GSK for financial support. J.T.L. acknowledges an ACS Graduate Fellowship sponsored by Bristol-Myers Squibb Pharmaceuticals and Merck Graduate Fellowship. I.E.W. acknowledges a Novartis Graduate Fellowship.

**Supporting Information Available:** Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## OL062957Y

<sup>(33)</sup> For a review of the Staudinger reaction, see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.