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Enantioselective Total Synthesis of Bistramide A

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Bistramide A[1] (**1**) is a member of a new class of bioactive molecules isolated from the marine ascidian *Lissoclinum bistratum*. The bistramides demonstrate significant neuro- and cytotoxic properties as well as profound effects on cell cycle regulation.[2] In particular, bistramide A has an IC_{50} of 0.03−0.32 μg/mL for the P388/dox, B16, HT29, and NSCLC−N6 cell lines.[3] Studies have shown that bistramide A is cell permeable, blocks sodium channels,[4] and induces highly selective activation of a single protein kinase C (PKC) isotype δ.[5] The biological activity of bistramide A, as well as the other bistramides, has rendered them potential candidates for the treatment of slowly evolving tumors, such as nonsmall cell pulmonary carcinoma.[2]

From the time of their original isolation,[1a] the bistramides have presented a challenging stereochemical conundrum. Synthetic efforts toward the bistramides[6] were hampered by the lack of information regarding their relative and absolute configuration prior to Wipf's theoretical and synthetic studies.[6d,g] Kozmin and co-workers[7] have recently reported the first total synthesis of bistramide A, thus confirming Wipf's prediction of the stereochemical assignment of bistramide C.[6d,g]

Herein we disclose a convergent, enantioselective, total synthesis of bistramide A. At the onset of this project, the absolute configuration of bistramide A had not been established. Therefore, our goal was to devise a strategy that would allow either enantiomer of the three key subunits to be prepared, with the added requirement that either configuration at C39 could be accessed. Hence, it was envisioned that bistramide A would derive from three fragments: pyran **2**, carboxylic acid **3**, and spiroketal fragment **4** (Figure 1). The pyran fragment **2** was constructed as shown in Scheme 1. Exposure of aldehyde **5**[8] to the chlorotitanium enolate of *N*-propionyl thiazolidinethione **6**[9] proceeded smoothly (87%) with excellent diastereoselectivity (>98:2 dr). The chiral auxiliary was reductively cleaved, and the resulting aldehyde was exposed to $Ph_3P{=}CHCO_2Et$ to give α,β-unsaturated ethyl ester **8** in 78% yield over two steps. Hydrogenation of the resulting alkene provided the saturated ethyl ester, which was converted to the lactone in the presence of PPTS. Reductive acylation[10] of the lactone delivered acetate **9** as an inconsequential 7:1 mixture of anomers. Treatment of acetate **9** with the 2-trimethylsilyloxy-1,3-pentadiene,[11] in the presence of TMSOTf, installed the α,β-unsaturated ketone moiety of pyran **10** in 87% yield (9:1 dr). The TIPS ether was removed, and the resulting primary alcohol was oxidized to the acid.[6f] Esterification of the acid with hydroxysuccinimide gave pyran **2**.

The synthesis of carboxylic acid **3** began by transformation of allylic alcohol **11**[12] to the epoxy alcohol in 95% yield (98% ee) via a Sharpless asymmetric epoxidation[13] (Scheme 2). Treatment of the epoxy alcohol with lithium dimethylcuprate yielded the 1,3-diol accompanied by the undesired 1,2-diol (6:1). The minor isomer was readily removed by treating the mixture with sodium periodate to yield 1,3-diol **12** in 71% yield. Protection of diol **12** as the bis-silyl ether followed by oxidative cleavage of the PMB ether provided alcohol **13** in 95% yield over two steps. The azide moiety was then installed via a Mitsunobu reaction[14] with diphenylphosphoryl azide, whereupon the primary TBS ether was selectively cleaved with CSA in methanol to yield alcohol **14**. Oxidation[15] of the primary alcohol to the carboxylic acid, followed by deprotection of the TBS ether, gave the hydroxy acid in 66% yield over two steps. The azide moiety was readily reduced to the primary amine

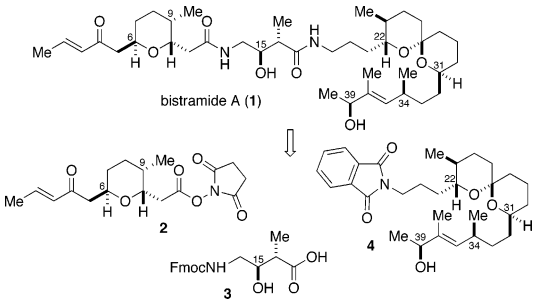
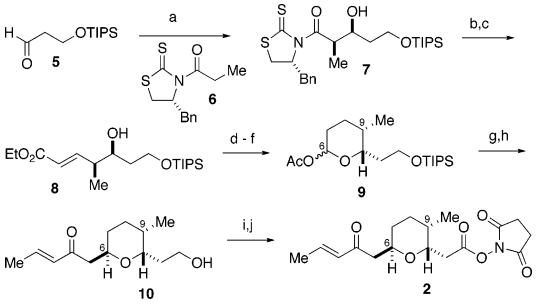


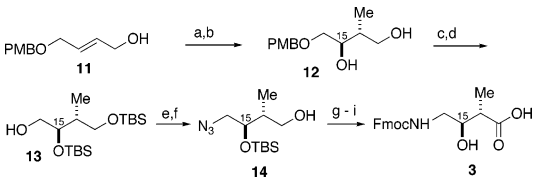
Figure 1. Retrosynthesis of bistramide A.

Scheme 1. Synthesis of Pyran **2**[a]



[a] Conditions: (a) $TiCl_4$, NMP, (−)-sparteine, CH_2Cl_2, −78 °C, **6**, 87%; (b) *i*-Bu_2AlH, THF, −78 °C; (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 78% (two steps); (d) H_2, Raney Ni, EtOH; (e) PPTS, CH_2Cl_2, 40 °C, 81% (two steps); (f) *i*-Bu_2AlH, pyridine, DMAP, Ac_2O, CH_2Cl_2, −78 to −20 °C, 96%; (g) Et_3N, TMSOTf, 3-penten-2-one, CH_2Cl_2, 0 °C then −78 °C, then add acetate **9**, 87%, 9:1 dr; (h) H_2SiF_6, CH_3CN, 0 °C, 75%; (i) H_5IO_6/CrO_3, CH_3CN, 77%; (j) *N*-hydroxysuccinimide, EDC·HCl, CH_2Cl_2, 100%.

Scheme 2. Preparation of Carboxylic Acid Fragment **3**[a]



[a] Conditions: (a) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, 4 Å sieves, −20 °C, 95%, 98% ee; (b) Me_2CuLi, Et_2O, −50 °C to 25 °C, 6:1 of 1,3- to 1,2-diol; $NaIO_4$, H_2O, 71%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%; (d) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C, 98%; (e) DEAD, PPh_3, $(PhO)_2PON_3$, THF, 0 °C, 90%; (f) CSA, MeOH, CH_2Cl_2, 0 °C, 85%; (g) $NaClO_2$, TEMPO, CH_3CN, 35 °C, 95%; (h) HF/pyr., THF, 70%; (i) H_2, Pd/C, Fmoc-OSu, THF, 70%.

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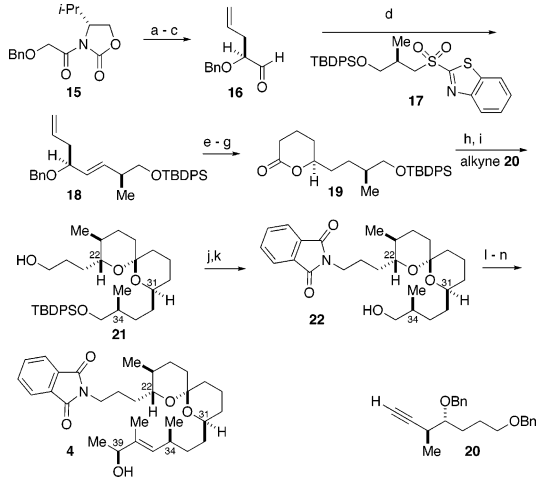
Scheme 3. Preparation of Spiroketal Fragment **4**[a]



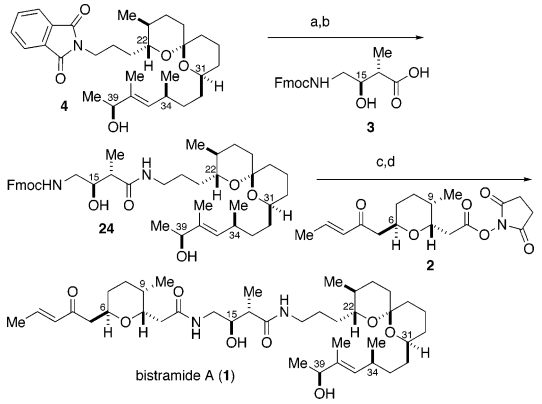
[a] Conditions: (a) NaHMDS, allyl iodide, THF, PhMe, −78 to −45 °C, 81%; (b) $LiBH_4$, MeOH, Et_2O, 98%; (c) Et_3N, DMSO, $(COCl)_2$, CH_2Cl_2, −78 to 25 °C, 98%; (d) LiHMDS, THF, sulfone **17**, then aldehyde **16**, −78 to −20 °C, 87%; (e) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, methyl acrylate, CH_2Cl_2, 40 °C, 87%; (f) H_2, Pd/C, EtOAc; (g) *p*-TSA, benzene, 80 °C, 70% (two steps); (h) alkyne **20**, *n*-BuLi, −78 °C, then lactone **19**; (i) H_2, Pd/C, MeOH, EtOAc, 83% (two steps); (j) PPh_3, DEAD, phthalimide, THF, 0 °C; (k) HF/pyr., THF, 84% (two steps); (l) Dess−Martin periodinane, CH_2Cl_2, pyr., 92%; (m) $Ba(OH)_2$, THF, $MeCOCH(Me)P(O)(OEt)_2$ (**23**), 58%; (n) (*R*)-CBS, catecholborane, toluene, −78 °C, 65%, >98:2 dr.

with hydrogen and Pd/C followed by in situ acylation to yield the desired carboxylic acid fragment **3**.

Construction of the spiroketal fragment **4** began with an asymmetric glycolate alkylation[16] of the sodium enolate of imide **15** with allyl iodide to produce the allylated acyl oxazolidinone in 81% yield (>98:2 dr; Scheme 3). Reductive cleavage of the auxiliary, followed by oxidation of the resulting primary alcohol under Swern[17] conditions, gave aldehyde **16**. Subjection of aldehyde **16** to a modified Julia reaction[18] with sulfone **17** gave diene **18** as a 60:40 mixture of *E*:*Z* isomers. A cross-metathesis reaction of diene **18** with methyl acrylate provided the unsaturated methyl ester in 87% yield. Hydrogenation of the two alkenes resulted in concomitant cleavage of the benzyl ether, whereupon treatment with acid gave lactone **19** (70% yield, two steps). Addition of lactone **19** to the lithium acetylide of alkyne **20** produced a keto alcohol, which was immediately exposed to hydrogen and Pd/C at 50 psi. As anticipated, the resulting trihydroxy ketone spontaneously cyclized to exclusively produce spiroketal **21** in 83% yield over two steps. Installation of the phthalimide under Mitsunobu[14] conditions, followed by deprotection of the TBDPS ether, gave alcohol **22** in 84% yield over two steps. Treatment of alcohol **22** with the Dess−Martin reagent[19] provided the aldehyde, which was subjected to a Horner−Wadsworth−Emmons olefination[20] with phosphonate **23** to install the *E*-olefin (C36−C37). The completed spiroketal fragment **4** was then obtained by stereoselective reduction of the resulting ketone with Corey's oxazoborolidine[21] to establish the C39 stereogenic center.

With the three required fragments in hand, their assembly to bistramide A was undertaken. Cleavage of the phthalimide protecting group of **4** with methanol and methylamine gave the amine, which was immediately exposed to a PyBOP-mediated condensation with acid **3** delivering amide **24** in 88% yield over two steps. Removal of the Fmoc group with subsequent exposure of the unpurified amine to ester **2** provided synthetic bistramide A, which

Scheme 4. Synthesis of Bistramide A[a]



[a] Conditions: (a) MeOH, $MeNH_2$, 65 °C; (b) PyBOP, **3**, DIEA, DMF 88% (two steps); (c) Et_2NH, DMF; (d) **2**, DMF 82% (two steps).

was identical in all respects (^1H, ^{13}C, $[\alpha]_D$, MS) to the natural product. The synthesis was completed with a longest linear sequence of 18 steps (Scheme 4).

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

References

(1) (a) Gouiffes, D.; Moreau, S.; Helbecque, N.; Bernier, J. L.; Henichart, J. P.; Barbin, Y.; Laurent, D.; Verbist, J. F. *Tetrahedron* **1988**, *44*, 451. (b) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
(2) Biard, J. F.; Roussakis, C.; Kornprobst, J. M.; Gouiffesbarbin, D.; Verbist, J. F.; Cotelle, P.; Foster, M. P.; Ireland, C. M.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1336.
(3) Johnson, W. E.; Watters, D. J.; Suniara, R. K.; Brown, G.; Bunce, C. M. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 80.
(4) Sauviat, M. P.; Gouiffesbarbin, D.; Ecault, E.; Verbist, J. F. *Biochim. Biophys. Acta* **1992**, *1103*, 109.
(5) Frey, M. R.; Leontieva, O.; Watters, D. J.; Black, J. D. *Biochem. Pharmacol.* **2001**, *61*, 1093.
(6) (a) 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. (b) Solladie, G.; Bauder, C.; Biard, J. F. *Tetrahedron Lett.* **2000**, *41*, 7747. (c) Gallagher, P. O.; McErlean, C. S. P.; Jacobs, M. F.; Watters, D. J.; Kitching, W. *Tetrahedron Lett.* **2002**, *43*, 531. (d) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem.−Eur. J.* **2002**, *8*, 1670. (e) Wipf, P.; Hopkins, T. D. *Chem. Commun.* **2005**, 3421. (f) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (g) Zuber, G.; Goldsmith, M.-R.; Hopkins, T. D.; Beratan, D. N.; Wipf, P.; *Org. Lett.* **2005**, *7*, 5269.
(7) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546.
(8) Hamdouchi, C.; Sanchez-Martinez, C. *Synthesis* **2001**, 833.
(9) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
(10) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.
(11) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717.
(12) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887.
(13) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(14) Mitsunobu, O. *Synthesis* **1981**, 1.
(15) Zhao, M. Z.; Li, J.; Mano, E.; Song, Z. G.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.
(16) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.
(17) Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem.* **1978**, *43*, 2480.
(18) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(20) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774.
(21) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1987.

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