ORGANIC LETTERS

2011
Vol. 13, No. 22
6018–6021

Synthesis of a Platform To Access Bistramides and Their Analogues

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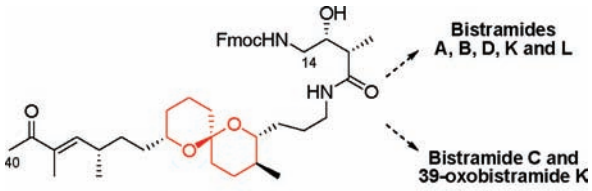
Received September 13, 2011

ABSTRACT



Platform C14-C40

The platform C14−C40, which can be used to prepare bistramide C and 39-oxobistramide K, was synthesized in 19 steps with an overall yield of 6.2%. Furthermore, the chemoselective reduction of the ketone at C-39 was performed giving an easy access to bistramides A, B, D, K, and L. Finally, the versatility of the synthesis of the C14−C40 fragment can allow the preparation of a large variety of stereoisomers to produce bistramide analogues.

Bistramides A−D, K, and L belong to a family of natural products isolated from an ascidian, *Lissoclinum bistratum*, which was collected in New Caledonia (Nouméa).[1] Since their isolation in 1988[2] and 1994,[3] a new member of this family, 39-oxobistramide K, has been isolated in 2009 from *Tridemnum cyclops* in Madagascar (Scheme 1).[4] Bistramides have shown to exhibit numerous biological properties such as antiparasitic,[5] immunomodulatory,[6] neurotoxic,[1] antiproliferative,[7] and cytotoxic activities.[8] Due to the biological properties and the challenging molecular structure of bistramides, it is not surprising that bistramides have elicited considerable interest from the synthetic community.[9]

Herein, we report a convergent approach to a platform that could allow the synthesis of all bistramides and their analogues. In considering a retrosynthetic scheme for the bistramides, the C14−C40 spiroketalic subunit **A** could be considered as a common fragment to all bistramides and, accordingly, was selected as our target molecule (Scheme 2).

Recently, we have shown that a spiroketal of type **II** can be formed in good yield and diastereoselectivity from an ω-unsaturated lactol of type **I** when treated with $FeCl_3$ (Scheme 3).[10]

(1) Gouiffès, D.; Jugé, M.; Grimaud, N.; Welin, L.; Sauviat, M. P.; Barbin, Y.; Laurent, D.; Roussakis, C.; Hénichart, J. P.; Verbist, J. F. *Toxicon* **1988**, *26*, 1129–1136.

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(3) (a) For isolation of bistramides A−D and K: Biard, J. F.; Roussakis, C.; Komprobst, J. M.; Gouiffès-Barbin, D.; Verbist, J. F.; Cotelle, P.; Foster, M. P.; Ireland, C. M.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1336–1345. (b) For isolation of bistramides D, K, and L: Biard, J. F.; Cortadellas, D.; Debitus, C.; Laurent, D.; Roussakis, C.; Verbist, J. F. WO 9420503 A1, 1994.

(4) Murphy, B. T.; Cao, S.; Brodie, P.; Maharavo, J.; Andriamanantoanina, H; Ravelonandro, P.; Kingston, D. G. *J. Nat. Prod.* **2009**, *72*, 1338–40.

(5) (a) Gautret, P.; Le Pape, P.; Biard, J. F.; Menard, D.; Verbist, J. F.; Marjolet, M. *Acta Parasitol.* **1998**, *43*, 50–53. (b) See ref 3b.

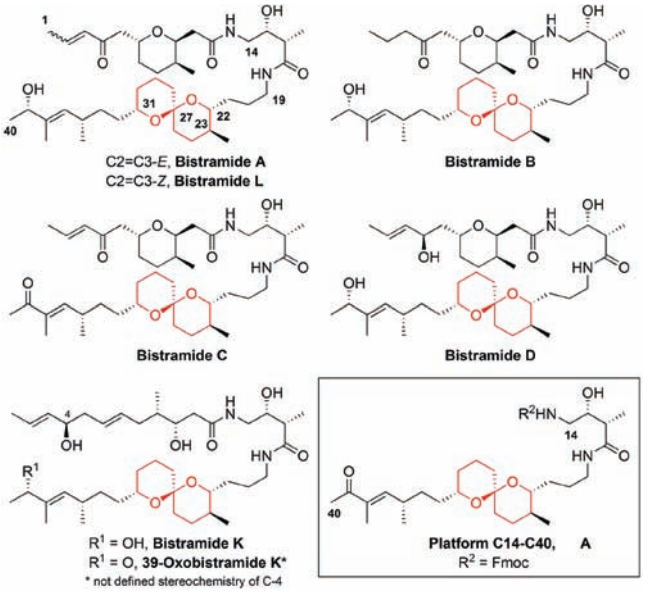
(6) (a) Pusset, J.; Maillere, B.; Debitus, C. *J. Nat. Toxins* **1996**, *5*, 1–6. (b) See also ref 5a.

(7) (a) See ref 3a. (b) Rizvi, S. A.; Liu, S.; Chen, Z.; Skau, C.; Pytynia, M.; Kovar, D. R.; Chmura, S. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 7288–7290. (c) Kozmin, S. A.; Rizvi, S. US 20100217019 A1, 2010. (d) Rizvi, S. A.; Courson, D. S.; Keller, V. A.; Rock, R. S.; Kozmin, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 4088–4092. (e) Rivzi, S. A.; Tereshko, V.; Kossiakoff, A. A.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 3882–3883. (f) Statsuk, A. V.; Bai, R.; Baryza, J. L.; Verma, V. A.; Hamel, E.; Wender, P. A.; Kozmin, S. A. *Nat. Chem. Biol.* **2005**, *1*, 383–388. (g) Johnson, W. E. B.; Watters, D. J.; Suniara, R. K.; Brown, G.; Bunce, C. M. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 80–88.

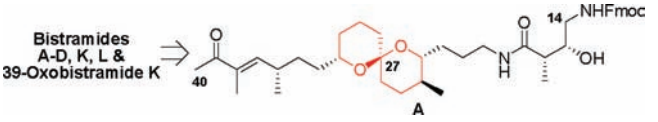
(8) (a) Riou, D.; Roussakis, C.; Biard, J. F.; Verbist, J. F. *Anticancer Res.* **1993**, *13*, 2331–2334. (b) Liscia, E.; Riou, D.; Siavoshian, S.; Boesch, S.; Lebert, V.; Tomasoni, C.; Dabouis, G.; Biard, J. F.; Roussakis, C. *Anticancer Res.* **1996**, *16*, 1209–1212. (c) Siavoshian, S.; Jacquot, C.; Biard, J. F.; Briand, G.; Roussakis, C. *Anticancer Res.* **1999**, *19*, 5361–5365. (d) see also ref 7.

10.1021/ol202483u
Published on Web 10/17/2011

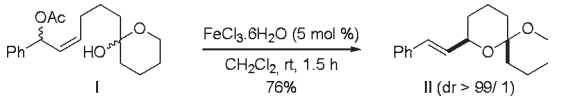
Scheme 1. Bistramides A–D, K, L and 39-Oxobistramide K



Scheme 2. Retrosynthetic Approach to All Bistramides from **A**



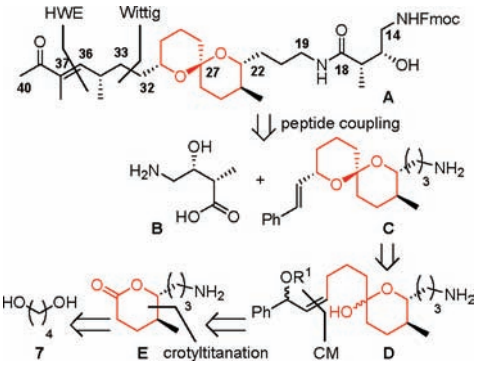
Scheme 3. $FeCl_3$-Catalyzed Spiroketalization of Unsaturated Lactol



With the aim of developing a convergent route to **A**, an appropriate disconnection point appeared to be at the C18–C19 bond which led to two fragments **B** and **C**. Our strategy for fragment **C** would rely on four key reactions, a Horner–Wadsworth–Emmons (HWE) reaction to introduce the unsaturation at C36–C37, a Wittig reaction to form the C32–C33 bond, a spiroketalization of an unsaturated lactol of type **D**, and a cross-metathesis to introduce the unsaturation in lactol **D**. Lactol **D** would be synthesized from lactone **E** whose stereogenic centers would be controlled by enantioselective crotyltitanation.[11] Lactone **E** would itself be available from the cheap commercially available 1,4-butanediol (**7**) (Scheme 4).

The C14–C18 region of the target represented by amino acid **6** was synthesized from allylamine **1**. The first step consisted of a bis-protection of the amine (Boc_2O,

Scheme 4. Retrosynthetic Approach towards **A**



4-DMAP, CH_3CN, rt then 60 °C) to obtain the corresponding bis-carbamate **2** (70% yield).[12] After ozonolysis (O_3, CH_2Cl_2, −78 °C then Me_2S), aldehyde **3** (80% yield)[12] was treated with the highly face-selective titanium complex (*S*,*S*)-Ti-**I** (Et_2O, −78 °C, 18 h),[11] leading to the corresponding homoallylic alcohol in good diastereoselectivity and enantioselectivity (dr > 95/5; ee > 95%). In order to transform the latter to the corresponding carboxylic acid **5**, the hydroxyl group was protected (TESCl, imid.) and the resulting silyl ether **4** was oxidatively cleaved ($NaIO_4$, $RuCl_3$, CCl_4/MeCN/H_2O, rt, 16 h).[9n] After a deprotection/protection sequence, the Fmoc-protected amino acid **6** was isolated in 71% yield over three steps (Scheme 5). Thereby, fragment C14–C18 was synthesized in an overall yield of 34% yield over seven steps which, according to our knowledge, is the most efficient synthesis for compound **6**.[9j,n]

The synthesis of spiroketal **20** was next undertaken (Schemes 6, 7) from the commercially available 1,4-butanediol (**7**). The first step entailed monoprotection of one of the primary hydroxyl groups as a *tert*-

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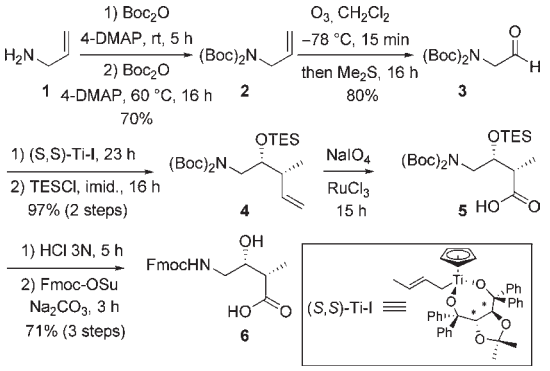
(10) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

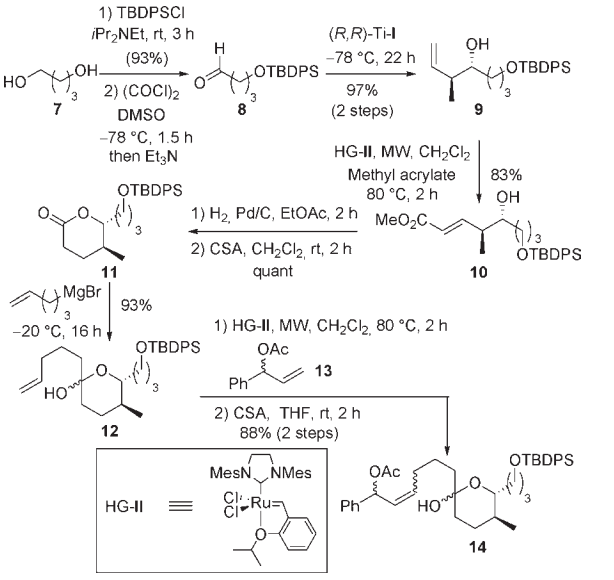
(11) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rhote-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Cossy, J.; Bouzbouz, S.; Pradaux, F.; Willis, C.; Bellosta., V. *Synlett* **2002**, 1595–1606.

(12) Varney, M. D.; Romines, W. H.; Palmer, C. L. U.S. Patent 5,594,139, 1997, 20 pp.

Scheme 5. Synthesis of C14–C18 Fragment **6**



Scheme 6. Synthesis of Intermediate **14**



butyldiphenylsilyl ether (TBDPS) (Scheme 6).[13] Oxidation of the second primary hydroxyl group to aldehyde **8** was performed by using a Swern oxidation under standard conditions [$(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N]. This oxidation was followed by a diastereoselective crotyltitanation using the highly face-selective titanium complex (*R*,*R*)-[Ti]-**I** (Et_2O, −78 °C);[11] it led to the corresponding homoallylic alcohol **9** (97% over two steps, dr > 95/5, ee > 95%, $[\alpha]_D^{20} = +4.5$ (*c* = 6.4, EtOH)).[14]

In order to access the six-membered ring lactone **11**, homoallylic alcohol **9** was first converted to the unsaturated ester **10** in 83% yield, by performing a cross-metathesis with an excess of methyl acrylate in the presence of the Grubbs–Hoveyda second generation catalyst (HG-**II**, 5–8 mol %)[15] under microwave irradiation, for 2 h. After hydrogenation [H_2, (1 atm), Pd/C (10 mol %), EtOAc, 2 h] and treatment under acidic conditions (cat. CSA, CH_2Cl_2, rt, 2 h), lactone **11** was isolated in quantitative yield. Lactone **11** was then transformed to lactol **14** in three steps. The first step involved the addition of 4-pentenyl magnesium bromide to **11** (Et_2O, −20 °C), and lactol **12** was produced in 93% yield. This latter was then condensed with allyl acetate **13**[16] utilizing the Grubbs–Hoveyda second generation catalyst[15] (HG-**II**, 10 mol %, microwave irradiation, CH_2Cl_2, 2 h) to furnish a mixture of two products: lactol **14** and its glycal derivative. Upon treatment with a catalytic amount of CSA in wet THF, the crude mixture gave the functionalized lactol **14** (88%), the precursor of spiroketal **15**.

Following treatment of **14** with $FeCl_3 \cdot 6H_2O$ (5 mol %, CH_2Cl_2, rt)[10] the desired spiroketal **15** was isolated in 59% yield (Scheme 7). Spiroketal **15** was then cleaved with O_3 (−78 °C, CH_2Cl_2, then Me_2S), to produce the corresponding aldehyde which was directly used for a Wittig reaction with phosphonium salt **16**[17] (*n*-BuLi, THF, 0 °C) to generate alkene **17** in 79% yield (two steps). In order to install the amino group at C19, the silyl ether was cleaved (TBAF, THF, 93%) and the resulting hydroxyl group was transformed to a phthalimido group under Mitsunobu conditions (phthalimide, PPh_3, DIAD). A two-step one-pot hydrogenation/deprotection sequence (1 atm of H_2, Pd/C) led to hydroxyl-phthalimido spiroketal **18** which was isolated in 87% yield. Oxidation of **18** (TPAP, NMO, MS 4 Å, CH_2Cl_2) to the corresponding aldehyde and a HWE reaction, using activated $Ba(OH)_2 \cdot 8H_2O$ as a base, afforded enone **19** in 75% yield, when the phthalimido group had been cleaved.

The formation of this amido carboxylic acid was not a dramatic issue as the treatment of **19** with DCC (CH_2Cl_2, 0 °C, 30 min then rt, 1 h) and then with *N*-methylhydrazine (THF, −10 °C, 10 min) produced the desired amino group at C19.[18] The resulting amine was then coupled with the previously synthesized amino acid **6**, using PyBOP (*i*Pr_2NEt, DMF, rt), to afford compound **20** which can give access to bistramide C and 39-oxobistramide K after Fmoc removal[9n] and immediate peptide coupling with the appropriate C1–C13[19] lateral chain of bistramides.

(13) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1992**, *57*, 1722–1727.

(14) Due to the very small value of optical rotation for compound **9**, when the analysis was performed in aprotic solvent, $[\alpha]_D^{20} = -0.2$ (*c* = 1, $CHCl_3$); measurement was done in protic solvent at higher concentration to obtain a stable value ($[\alpha]_D^{20} = +4.5$ (*c* = 6.4, EtOH).

(15) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(16) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653–2656.

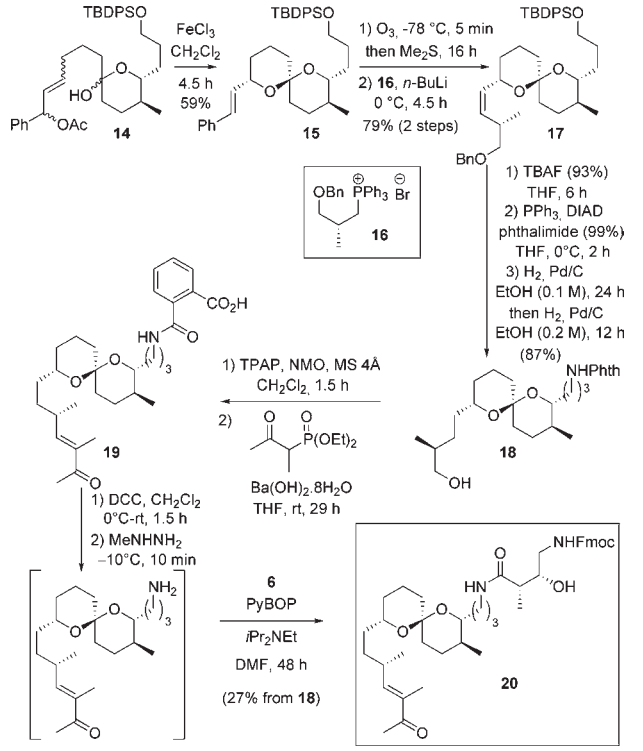
(17) Compound **16** was prepared according to the following synthetic sequence: (a) (Benzylation) Widmer, U. *Synthesis* **1987**, 568–570. (b) (Ester reduction) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292–5300. (c) (Bromination) Boons, G.-J.; Clase, J. A.; Lennon, J. C.; Ley, S. V.; Staunton, J. *Tetrahedron* **1995**, *51*, 5417–5446. (d) (Preparation of phosphonium salt) See ref 9f.

(18) Stocksdale, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 1221–1225.

(19) See ref 9a, 9c–9h, 9j, 9l–9o.

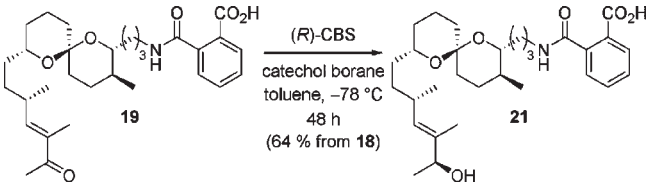
(20) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

Scheme 7. Synthesis of Spiroketal **20**



It is worth noting that enone **19** was reduced to alcohol **21** using (*R*)-CBS and catechol borane[20] in 64% yield over three steps, starting from **18**, with good diastereoselectivity (dr >95:5) (Scheme 8). Alcohol **21**, through the sequence described previously [phthalimide removal, peptide coupling with **6** (Scheme 7), Fmoc removal, and

Scheme 8. Chemoselective Reduction of the Enone of **19**



peptide coupling with the appropriate C1−C13 chain], can potentially lead to bistramides A, B, D, K, and L.

In summary, compound **20** was synthesized in 19 steps with an overall yield of 6.2% and can be utilized to synthesize bistramide C and 39-oxobistramide K by realizing a peptide coupling with the appropriate carboxylic acid C1−C13.[19] On the other hand, **21** can be the precursor of bistramides A, B, D, K, and L. Based on recent SAR studies,[7b,d] showing that the biological activity of bistramide derivatives is strongly dependent on the C14−C40 subunit, our platform offers a straightforward access to a range of analogues. Furthermore, due to the versatility of allyl metals for controlling the stereogenic centers at C15−C16 and at C22−C23, a great diversity of stereoisomers can, in principle, be easily reached.

Acknowledgment. Dr. Serge Sablé (Sanofi-Aventis, Vitry-sur-Seine, France) is acknowledged for his contribution for the structural determinations.

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