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Synthesis of a Platform To Access Bistramides and Their Analogues

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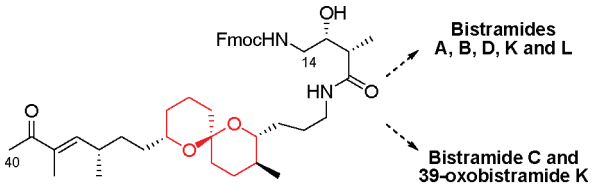
ABSTRACT



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 *Trididemnum 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.

(2) (a) For isolation of bistramide A, see: Gouiffès, D.; Moreau, S.; Helbecque, N.; Bernier, J. L.; Hénichart, J. P.; Barbin, Y.; Laurent, D.; Verbist, J. F. *Tetrahedron* **1988**, *44*, 451–459 and cited references. (b) For isolation of bistratenes, which were deduced to be identical with bistramides, see: Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354–1359.

(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.

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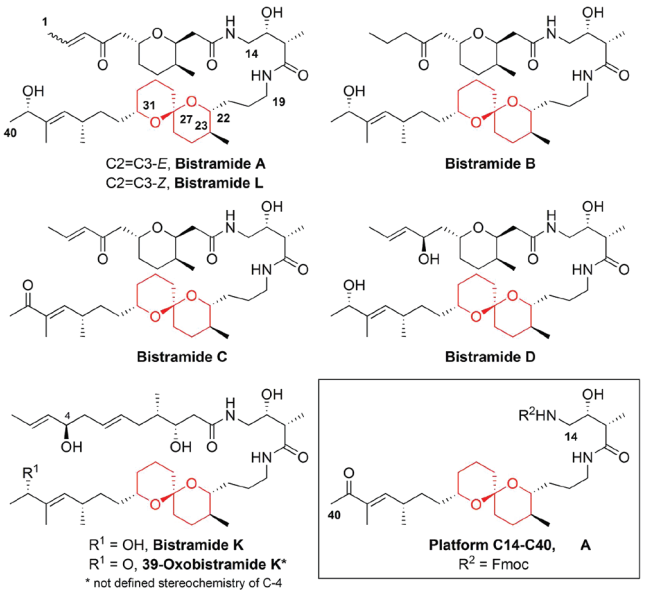
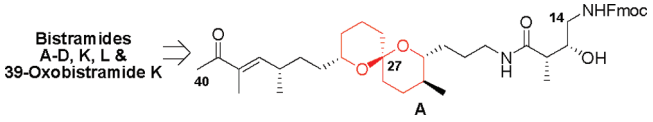
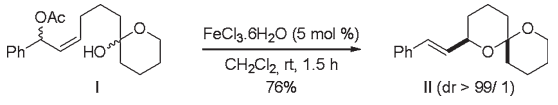
Scheme 1. Bistramides A–D, K, L and 39-Oxobistramide K



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



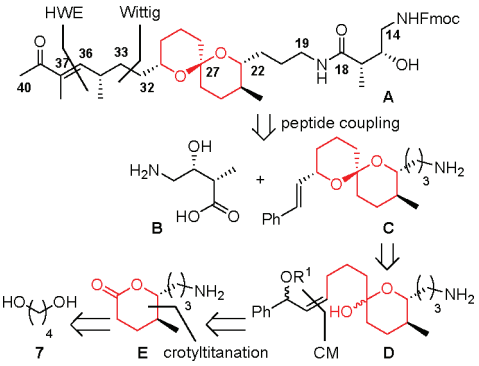
Scheme 3. $FeCl_3$-Catalyzed Spiroketalization of Unsaturated Lactol



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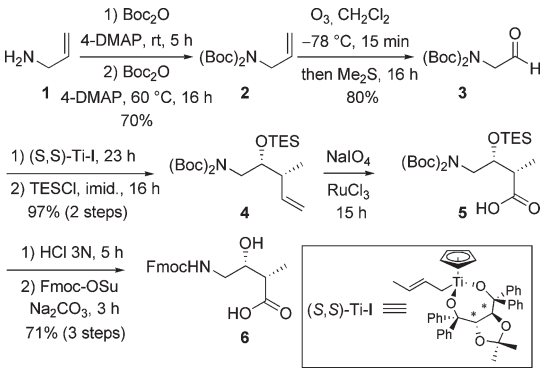
(10) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

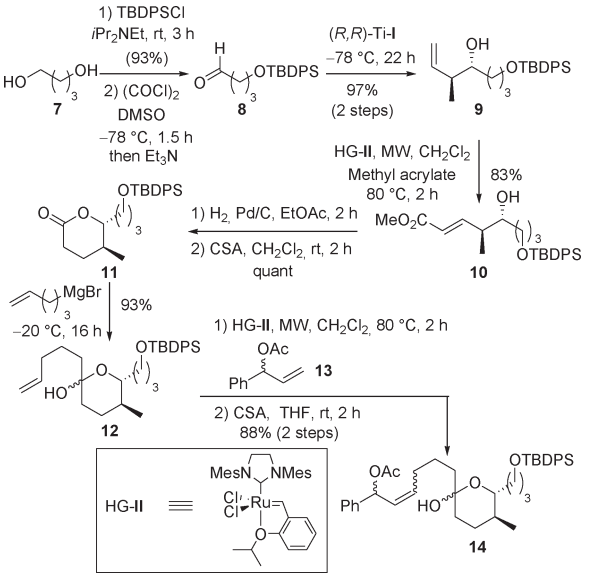
(11) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rhote-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Cossy, J.; Bouzbouz, S.; Pradaux, F.; Willis, C.; Bellosta., V. *Synlett* **2002**, 1595–1606.

(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 (iPr_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.

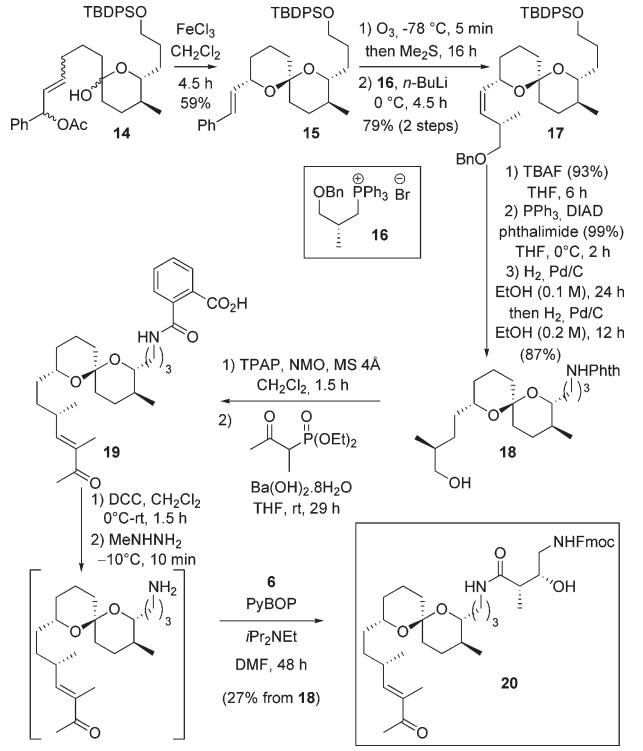
(17) Compound **16** was prepared according to the following synthetic sequence: (a) (Benzylation) Widmer, U. *Synthesis* **1987**, 568–570. (b) (Ester reduction) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292–5300. (c) (Bromination) Boons, G.-J.; Clase, J. A.; Lennon, J. C.; Ley, S. 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.

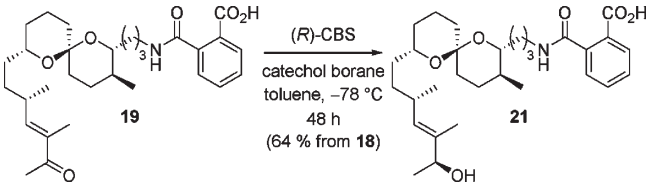
(20) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

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.

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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.