Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7147–7149

A highly efficient, asymmetric synthesis of blastidic acid: the β-amino acid component of the antibiotic, (+)-blasticidin S

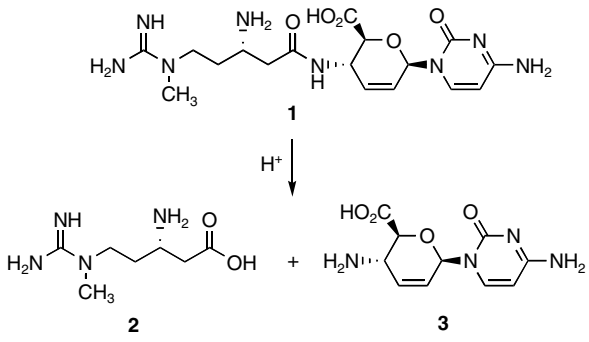
Roland Bischoff, Niall McDonald and Andrew Sutherland*

WestChem, Department of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK

Received 4 August 2005; accepted 18 August 2005
Available online 6 September 2005

Abstract—A new approach for the asymmetric synthesis of blastidic acid, the β-amino acid component of the antibiotic, (+)-blasticidin S has been achieved in 11 steps and 30% overall yield. The key transformations involve a one-pot Swern/Wittig reaction sequence to prepare the carbon backbone followed by a stereoselective conjugate addition to introduce the β-amino functionality.

(+)-Blasticidin S **1**, a peptidyl-nucleoside antibiotic first isolated from *Streptomyces griseochromogenes* has been used extensively as a fungicide against *Pyricularia oryzae*, the cause for the serious rice blast disease in Asia.[1–3] Structural characterisation of (+)-blasticidin S **1** using both chemical degradation (Scheme 1) and X-ray analysis revealed two main components, the β-amino acid, blastidic acid **2** and the hexopyranosyl nucleoside, cytosinine **3**.[4,5] (+)-Blasticidin S **1** has also been the subject of intense biosynthetic studies with cytosine, D-glucose, L-arginine and L-methionine shown to be the primary building blocks.[6] More recently, Gould and co-workers have shown, using labelled precursors, that the β-amino acid component of **1**, blastidic acid **2** is biosynthesised from L-arginine via an intramolecular migration of the α-nitrogen to the β-position.[7]



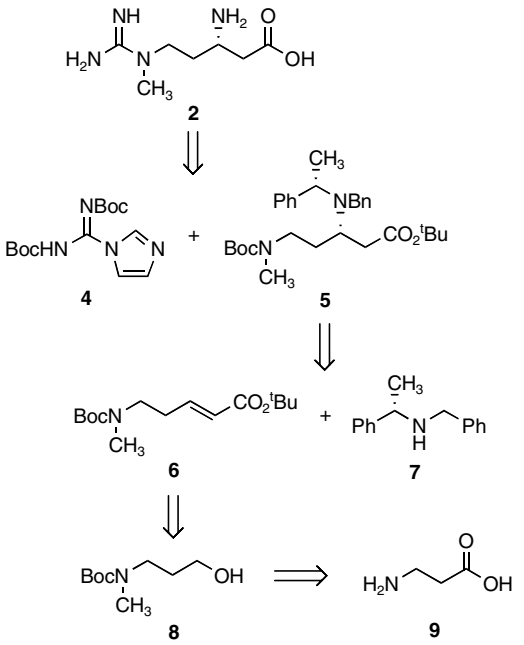
Scheme 1.

While the biosynthesis of **1** and its components have been extensively studied, reports on the chemical synthesis of these compounds are much more limited. Goto and co-workers outlined the first synthesis of cytosinine **3** in 1972, [8] but it was not until 2001 that two routes for the synthesis of blastidic acid **2** by the groups of Nomoto and Ichikawa were first reported.[9,10] Further work by Ichikawa and co-workers has led to the first total synthesis of (+)-blasticidin S **1**.[11] Although two routes have already been developed for the synthesis of blastidic acid **2**, we were interested in developing a novel, efficient approach, which would also provide a suitably protected derivative for the total synthesis of (+)-blasticidin S **1**. We now report our 11 step synthesis of (+)-blastidic acid **2** from readily available β-alanine using a one-pot Swern oxidation/Wittig olefination reaction sequence to prepare the key *E*-allylic ester followed by a stereoselective conjugate addition to introduce the β-amino functionality.

Our retrosynthesis of blastidic acid **2** is outlined in Scheme 2. It was proposed that **2** could be prepared by coupling commercially available *N*,*N*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **4** and a suitably protected β-ornithine derivative **5**. We intended to synthesise **5** from β-alanine **9** by methylation at an early stage followed by a one-pot oxidation and Wittig

Keywords: Blastidic acid; β-Amino acid; Antibiotic; Asymmetric synthesis; Conjugate addition.
* Corresponding author. Tel.: +44 141 330 5936; fax: +44 141 330 4888; e-mail: andrews@chem.gla.ac.uk

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.096

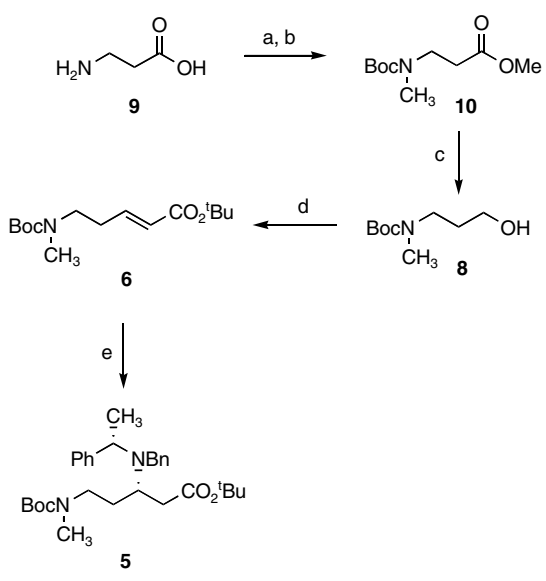


Scheme 2.

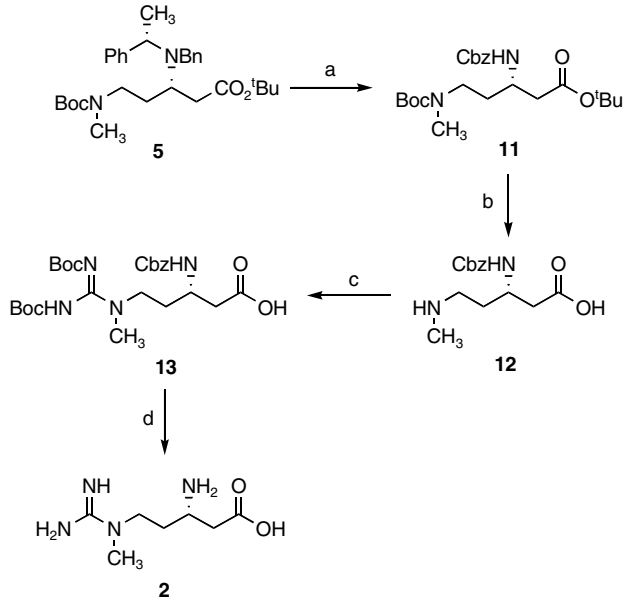
reaction to give the desired carbon skeleton. Asymmetric conjugate addition with chiral amine **7** using the Davies protocol would complete the synthesis of **5**.[12]

The first stage of the synthesis involved the preparation of β-ornithine derivative **5** (Scheme 3). β-Alanine **9** was converted in a one-pot reaction to *N*-Boc-β-alanine methyl ester in essentially quantitative yield using chlorotrimethylsilane and methanol to form the ester followed by treatment with triethylamine and di-*tert*-butyl dicarbonate resulting in protection of the amino functionality.[13] The β-nitrogen was then methylated using sodium hydride and methyl iodide to give derivative **10** in 93% yield. Attempts at reducing **10** to the corresponding aldehyde using 1.2 equiv of DIBAL-H returned a mixture of the starting material, the desired aldehyde and alcohol **8**. Moreover, purification of the aldehyde by column chromatography led to significant decomposition. To overcome these problems, methyl ester **10** was reduced to alcohol **8** in 79% yield using 2.2 equiv of DIBAL-H. Alcohol **8** was then converted directly to *E*-allylic ester **6** using a one-pot Swern oxidation/Wittig olefination reaction process thereby, avoiding any problems associated with isolation of the aldehyde intermediate.[14] Having prepared a suitably derived *E*-allylic ester, the next stage of the synthesis required the introduction of the β-amino functional group in an asymmetric fashion. This was carried out using the approach established by Davies and co-workers involving deprotonation of (*S*)-benzyl-α-methylbenzylamine **7** with *n*-butyl lithium at −78 °C followed by reaction with *E*-allylic ester **6**.[15] After work-up of this reaction, the ^{1}H NMR spectrum of the crude material showed the presence of the addition product in a diastereomeric ratio of 24:1. Subsequent purification by column chromatography gave diastereomer **5** in 85% yield.

As well as developing an efficient route to blastidic acid, we were also interested in preparing an orthogonally protected intermediate **13**, which could be easily coupled to a cytosinine derivative for the total synthesis of (+)-blastidicin S **1**. Thus, the β-amino functional group of **5** was deprotected using transfer hydrogenation conditions[16] and then subsequently reprotected with benzyl chloroformate to give β-ornithine derivative **11** in 74% yield over two steps (Scheme 4). The next stage of the



Scheme 3. Reagents and conditions: (a) (i) TMSCl, MeOH, (ii) NEt_3, Boc_2O, 99% over two steps; (b) MeI, NaH, THF, 93%; (c) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt, 79%; (d) (i) $(COCl)_2$, DMSO, NEt_3, −78 °C to rt, (ii) $Ph_3P{=}CHCO_2{}^tBu$, 97% over two steps; (e) **7**, ^{n}BuLi, THF, −78 °C, 85%.



Scheme 4. Reagents and conditions: (a) (i) 5% Pd/C, ammonium formate, ^{t}BuOH, Δ, (ii) Cbz–Cl, $NaHCO_3$, acetone, H_2O, 74% over two steps; (b) TFA, CH_2Cl_2; (c) **4**, DIPEA, MeOH, 82% over two steps; (d) TMSI, $CHCl_3$ then HCl, MeOH, 82%.

synthesis required deprotection of the side-chain amino functional group and addition of the guanidine unit. This was carried out by treatment of **11** with TFA resulting in the deprotection of both the Boc-group and the *tert*-butyl ester. Reaction of **12** with Hünig's base (2 equiv) and *N*,*N*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **4**[17] then gave orthogonally protected **13** in 82% yield for the two steps. This stage in the Ichikawa synthesis proved problematic due to easy lactamisation during deprotection of the side-chain amino functional group.[10,11] In our own synthesis of selectively labelled L-arginine, cyclic amide products were also isolated during a similar reaction sequence.[18] Hence, in designing our route to blastidic acid, the *tert*-butyl ester was used not only to maximise 1,4-addition during the conjugate addition step but also, to allow the use of reaction conditions to deprotect both the δ-amino group and the ester, thus preventing formation of the six-membered lactam. Finally, **13** was converted to blastidic acid **2** by reaction with trimethylsilyl iodide and acidic methanol.[19] This method for deprotection of carbamates results in protonation of the amino groups as they are formed, again preventing any untoward cyclisation reactions.[11] Purification by ion exchange chromatography gave blastidic acid in 82% yield.[20]

In conclusion, a simple and efficient, 11-step synthesis of blastidic acid has been achieved from commercially available β-alanine giving the target molecule in 30% overall yield. This route also provides intermediate **13**, which is suitably protected for coupling with a cytosinine derivative for the total synthesis of (+)-blasticidin S. Further efforts towards the total synthesis of (+)-blasticidin S are currently underway.

Acknowledgements

The authors gratefully acknowledge the University of Glasgow and AstraZeneca, for financial support.

References and notes

1. Takeuchi, S.; Hirayama, K.; Ueda, K.; Sakai, H.; Yonehara, H. *J. Antibiot. Ser. A.* **1958**, *11A*, 1–5.
2. Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739.
3. Yamaguchi, H.; Yamamoto, C.; Tanaka, N. *J. Biochem.* **1965**, *57*, 667–677.
4. Yonehara, H.; Takeuchi, S.; Otake, N.; Endo, T.; Sakagami, Y.; Sumiki, Y. *J. Antibiot.* **1963**, *16A*, 195–222; Otake, N.; Takeuchi, S.; Endo, T.; Yonehara, H. *Tetrahedron Lett.* **1965**, *6*, 1405–1409.
5. Onuma, S.; Nawata, Y.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1091.
6. Seto, H.; Yamaguchi, I.; Otake, N.; Yonehara, H. *Tetrahedron Lett.* **1966**, *7*, 3793–3799; Seto, H.; Yamaguchi, I.; Otake, N.; Yonehara, H. *Agric. Biol. Chem.* **1968**, *32*, 1292–1298.
7. Prabhakaran, P. C.; Woo, N.-T.; Yorgey, P.; Gould, S. J. *Tetrahedron Lett.* **1986**, *27*, 3815–3818; Prabhakaran, P. C.; Woo, N.-T.; Yorgey, P. S.; Gould, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 5785–5791.
8. Kondo, T.; Nakai, H.; Goto, T. *Tetrahedron Lett.* **1972**, *13*, 1881–1884; Kondo, T.; Nakai, H.; Goto, T. *Tetrahedron* **1973**, *29*, 1801–1806.
9. Nomoto, S.; Shimoyama, A. *Tetrahedron Lett.* **2001**, *42*, 1753–1755.
10. Ichikawa, Y.; Ohbayashi, M.; Hirata, K.; Nishizawa, R.; Isobe, M. *Synlett* **2001**, 1763–1766.
11. Ichikawa, Y.; Hirata, K.; Ohbayashi, M.; Isobe, M. *Chem. Eur. J.* **2004**, *10*, 3241–3251.
12. Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183–186; Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999–2008.
13. Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W. A.; Martín, V. S. *J. Org. Chem.* **1998**, *63*, 3741–3744; Padrón, J. M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W. A.; Martín, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381–3394.
14. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198–2200.
15. For a recent example, see: Bunnage, M. E.; Davies, S. G.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2763–2776.
16. Langenhan, J. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 6440–6443.
17. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389–3392; Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Org. Lett.* **2002**, *4*, 3767–3769.
18. Hamilton, D. J.; Sutherland, A. *Tetrahedron Lett.* **2004**, *45*, 5739–5741.
19. Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315–316.
20. Optical rotation for **2**: $[\alpha]_D^{20}$ +21.5 (*c* 1.0, H_2O); Lit.[9] $[\alpha]_D^{18}$ +21.0 (*c* 1.0, H_2O). Spectroscopic data was entirely consistent with that published for blastidic acid **2**.[9–11]