Pergamon

Tetrahedron Letters 43 (2002) 6383–6385

TETRAHEDRON LETTERS

Stereoselective synthesis of tricyclic guanidine, the key component of the batzelladine alkaloids

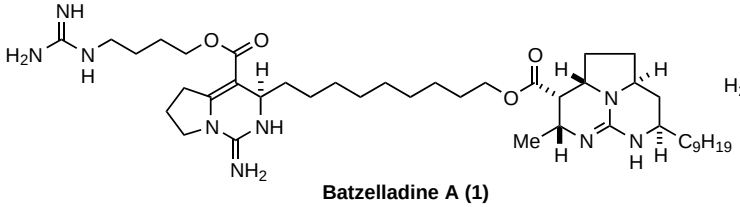
Kazuo Nagasawa,[a,*] Takanori Ishiwata,[c] Yuichi Hashimoto[a] and Tadashi Nakata[b,c]

[a]*Institute of Molecular and Cellular Biosciences, Univeristy of Tokyo, Bunkyo-ku, Tokyo 113-0032, Japan*
[b]*RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan*
[c]*Graduate School of Science and Engineering, Saitama University, Shimokubo, Saitama 338-8570, Japan*

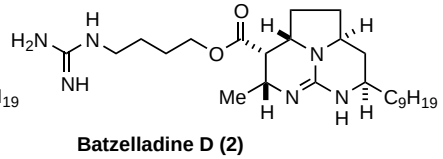
Received 7 June 2002; revised 28 June 2002; accepted 5 July 2002

Abstract—Stereoselective and efficient synthesis of tricyclic guanidine, the key component of batzelladines A and D, was accomplished based on successive 1,3-dipolar cycloadditions and successive cyclizations for the construction of the tricyclic guanidine ring. © 2002 Elsevier Science Ltd. All rights reserved.

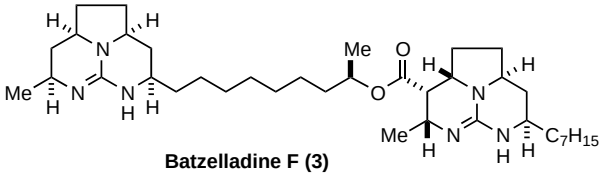
Batzelladines A–E, members of a novel class of guanidine alkaloids containing a tricyclic guanidine unit, were isolated from the Caribbean sponge *Batzella* sp.[1] Later, four further metabolites, termed batzelladines F–I, were obtained from the same source.[2] Batzelladines A (**1**) and B inhibit the binding of HIV glycoprotein gp-120 to the human CD4 receptor,[1] while batzelladines F (**3**), G, H, and I induce the dissociation of protein kinase $p56^{lck}$ from CD4.[2] Inspired by the novel structures of the batzelladines and their potential clinical importance in AIDS treatment, several synthetic studies have been reported.[3–9] In 1998, Snider's group succeeded in the total synthesis of batzelladine E; this was the first successful synthesis in this class of natural products.[5b] In 1999 and 2001, Overman's group accomplished the first total synthesis of batzelladines D (**2**)[7c] and F (**3**),[7d] respectively, which have the same tricyclic guanidine structure containing five stereogenic centers as batzelladine A. Though several total syntheses and other synthetic studies leading toward batzelladines have been reported, control of the stereochemistry on the tricyclic guanidine system is still an issue. In this communication, we report the synthesis of the tricyclic guanidine **4**, the key component of batzelladines, with complete stereocontrol of its five stereogenic centers by way of successive 1,3-dipolar cycloadditions and tricyclic guanidine formation by utilizing the Mitsunobu reaction conditions and an S_N2 type reaction.



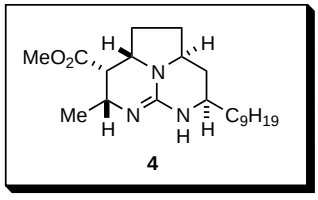
Batzelladine A (1)



Batzelladine D (2)



Batzelladine F (3)



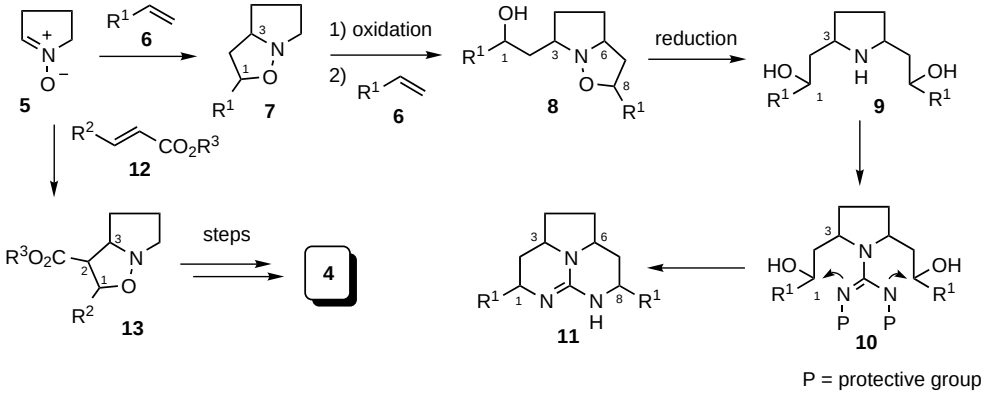
4

* Corresponding author. Tel.: +81-3-5841-7848; fax: +81-3-5841-8495; e-mail: nagasawa@iam.u-tokyo.ac.jp

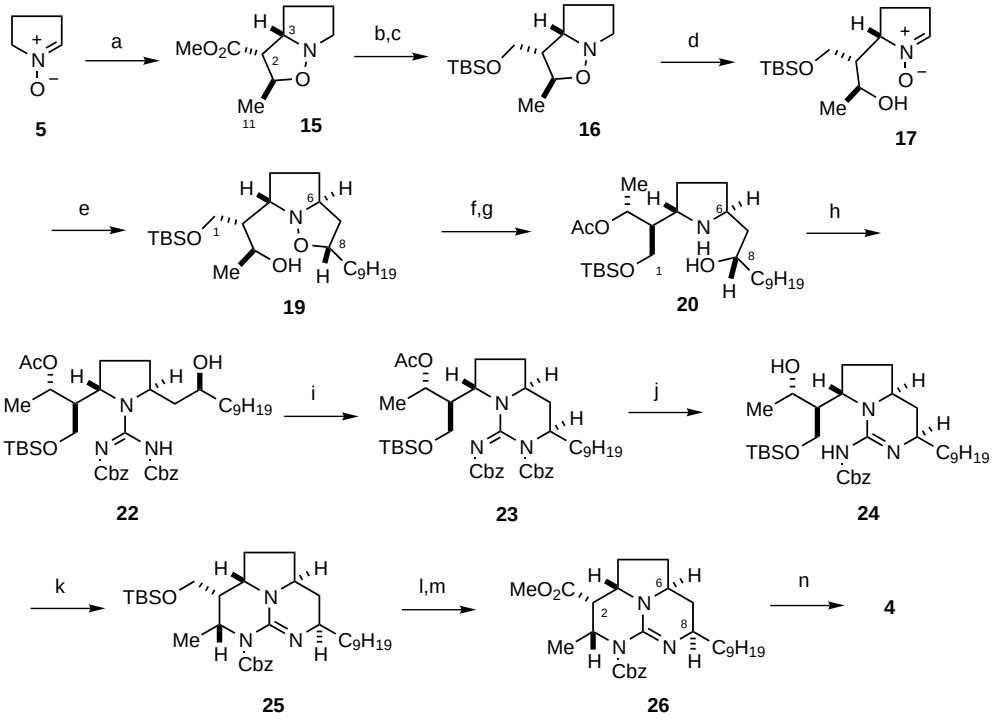
0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01371-0

Recently, we have developed an efficient strategy for stereoselective construction of the 3,6-*anti*- or 3,6-*syn*-fused tricyclic guanidine compound **11**.[10] Our strategy features 1) successive 1,3-dipolar cycloadditions to give 2,5-disubstituted pyrrolidine (**5** to **9**), 2) guanidine formation of 2,5-disubstituted pyrrolidine with a protected thiourea reagent (**9** to **10**), and 3) construction of the tricyclic guanidine by utilizing the Mitsunobu reaction and/or an S_N2 type reaction (**10** to **11**) (Scheme 1). In this protocol, the stereochemistry at C1 and C3 of **11** is controlled by the 1,3-dipolar cycloaddition reaction. Thus, if the unsaturated ester **12**, instead of the olefin **6**, is used for the 1,3-dipolar cycloaddition with **5**, the fully stereocontrolled cyclic guanidine compound **4** can be obtained. By means of this strategy, synthesis of the tricyclic guanidine **4**, a common key component of batzelladines A (**1**), D (**2**), and F (**3**), was achieved as shown in Scheme 2.

1,3-Dipolar cycloaddition of the nitrone **5** and methyl crotonate (**14**) in toluene gave the isoxazoline **15** in 82% yield.[11] The ester group of **15** was reduced with $LiAlH_4$ and subsequent protection of the hydroxyl group with *t*-$BuMe_2SiCl$ gave **16** in 95% yield. The oxidation of the isoxazoline **16** with *m*CPBA[12] effected regioselective ring cleavage to give the nitrone **17**, which was subsequently subjected to a second 1,3-dipolar cycloaddition with 1-undecene (**18**) to give **19** in 76% yield (two



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) methyl crotonate (**14**), toluene, 100°C, 82%; (b) $LiAlH_4$, Et_2O, 0°C; (c) TBDMSCl, imidazole, CH_2Cl_2, rt, 95% (two steps); (d) *m*CPBA, CH_2Cl_2, 0°C; (e) 1-undecene (**18**), toluene, 110°C, 76% (two steps); (f) Ac_2O, Py, rt; (g) Pd/C, H_2, EtOH, rt, 98% (two steps); (h) bis-Cbz-2-methyl-2-thiopseudourea (**21**), $HgCl_2$, Et_3N, DMF, 0°C to rt, 52%; (i) DEAD, PPh_3, THF, rt, 58%; (j) NaH, THF–MeOH (1:1), rt, 80%; (k) MsCl, Et_3N, CH_2Cl_2, 0°C, 82%; (l) Jones' reagent, acetone, 0°C; (m) $TMSCHN_2$, PhH–MeOH (7:2), rt, 47% (two steps); (n) Pd/C, H_2, EtOH, rt, 85%.

steps). In this cycloaddition, 1-undecene (**18**) approached **17** from the less-hindered side (β-face) in the *exo*-mode, and the newly generated stereochemistry of **19** at C6 and C8 was satisfactorily controlled.[10,13] After protection of the hydroxyl group of **19** with Ac_2O in pyridine, the N–O bond was reduced with hydrogen in the presence of 10% Pd/C to give the *trans*-2,5-disubstituted-β-hydroxypyrrolidine **20** in 98% yield. Treatment of **20** with bis-Cbz-2-methyl-2-thiopseudourea (**21**) in the presence of mercury (II) chloride[14] generated the guanylated pyrrolidine **22** in 51% yield. Treatment of **22** under the Mitsunobu reaction conditions[15] effected cyclization with inversion of the stereochemistry at C8 to give the bicyclic guanidine **23** in 58% yield. Deprotection of one of the Cbz groups and the acetyl group of **23** took place simultaneously with sodium hydride in MeOH–THF (1:1)[16] to give **24** in 80% yield. The tricyclic guanidine was formed on treatment of **24** with methanesulfonyl chloride in the presence of triethylamine to give **25** in 82% yield. Deprotection of the TBS ether of **25** and oxidation of the resulting primary alcohol were simultaneously carried out with Jones reagent to give the carboxylic acid, which was treated with trimethylsilyldiazomethane to give the methyl ester **26** in 47% yield. Finally, deprotection of the Cbz group was accomplished with hydrogen over 10% Pd/C to give **4** in 85% yield. The spectral data of **4** (^1H, ^{13}C NMR in CD_3OD, and high-resolution mass spectrum)[17] were consistent with the data reported by Overman.[7a]

In conclusion, we have succeeded in the stereoselective synthesis of the tricyclic guanidine **4**, the key component of batzelladines, based on successive 1,3-dipolar cycloadditions and successive cyclizations for the construction of tricyclic guanidine ring. This method should be applicable to various types of tricyclic guanidine class compounds. Efforts towards the synthesis of batzelladines A (**1**) D (**2**) and F (**3**) are in progress in our laboratories.

Acknowledgements

K.N. thanks Toray Co., Ltd. for an Award in Synthetic Organic Chemistry, Japan and the Pharmacy Research Encouragement Foundation for their financial support. This research was also supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; DeBrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
2. Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814.
3. Rao, A. V. R.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc. Chem. Commun.* **1995**, 1369.
4. Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905.
5. (a) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977; (b) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697.
6. (a) Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1996**, *37*, 6943; (b) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481; (c) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547.
7. (a) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512; (b) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520; (c) Cohen, F.; Overman, L. E.; Sakata, S. K. L. *Org. Lett.* **1999**, *1*, 2169; (d) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782.
8. Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551.
9. Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **2001**, *42*, 6637.
10. Nagasawa, K.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2001**, *42*, 4155.
11. Ali, S.k. A.; Khan, J. H.; Wazeer, M. I. M.; Perzanowski, H. P. *Tetrahedron* **1989**, *45*, 5979.
12. (a) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S.k. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435; (b) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1489; (c) Ali, S.k. A.; Wazeer, M. I. M. *Tetrahedron Lett.* **1993**, *34*, 137.
13. Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett.* **2002**, *4*, 177.
14. (a) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677; (b) Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Syn. Commun.* **1993**, *23*, 1443.
15. Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.
16. McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849.
17. Spectral data for **4**: ^1H NMR (CD_3OD, 400 MHz) δ 3.94 (m, 1H), 3.83 (m, 1H), 3.72 (s, 3H), 3.54 (m, 2H), 3.15 (t, $J=3.4$ Hz, 1H), 2.35 (ddd, $J=12.2$, 4.0, 2.1 Hz, 1H), 2.21 (m, 2H), 1.50–1.64 (m, 4H), 1.29 (brs, 14H), 1.25 (d, $J=6.3$ Hz, 3H), 0.89 (t, $J=6.4$ Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) 171.0, 151.5, 57.8, 57.3, 53.2, 49.9, 45.4, 37.0, 34.3, 33.0, 31.4, 30.6 (2 carbons), 30.4, 29.3, 26.2, 23.7, 18.4, 14.4 ppm; HRMS (FAB, MH^+) calcd for $C_{21}H_{38}N_3O_2$: 364.2964, found: 364.2963.