ORGANIC LETTERS

2002
Vol. 4, No. 2
177−180

Total Synthesis of Crambescidin 359

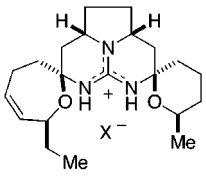
Kazuo Nagasawa,*,‡ Angelina Georgieva,† Hiroyuki Koshino,† Tadashi Nakata,† Tetsuya Kita,‡ and Yuichi Hashimoto‡

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0011, Japan, and Institute of Molecular and Cellular Biosciences, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

nagasawa@iam.u-tokyo.ac.jp

Received September 27, 2001

ABSTRACT



Crambescidin 359 (4)

Crambescidin 359 (4), which is the "vessel part" of the pentacyclic guanidine alkaloid ptilomycalin A (1), was synthesized for the first time based upon successive 1,3-dipolar cycloaddition reaction. This synthesis established the absolute stereochemistry of 4.

Ptilomycalin A (**1**)[1] from the sponges *Ptilocaulis spiculifer* and *Hemimycale* sp. and related crambescidins[2] (e.g., isocrambescidin (**2**)) from the sponge *Crambe crambe* are a characteristic family of marine alkaloids, which consist of unique pentacyclic guanidine units (so-called "vessel part") and a spermidine or hydroxyspermidine units (so-called "anchor part") linked by a linear long chain fatty acid. They show significant antitumor, antiviral, and antifungal activities,[1a,b] Ca^{2+} channel blocker activity,[2b,3] and inhibitory activity toward Na^+, K^+, and Ca^{2+} -ATPases.[4] Because of this unique structure and the biological activities of ptilomycalin A (**1**, Figure 1) and its analogues, many synthetic studies have been reported.[5−8] The Snider group and Murphy group independently reported the synthesis of the pentacyclic guanidine part based upon a biomimetic route,[5,6] and recently, Overman et al. succeeded in the first total synthesis of **1**[7a] and **2**[7b] based upon the efficient tethered Biginelli condensa-

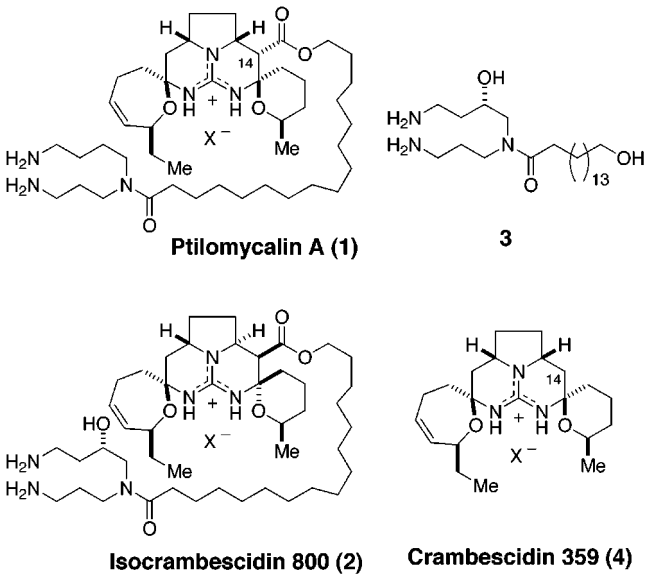


Figure 1. Ptilomycalin A (**1**) and related natural alkaloids.

† RIKEN.
‡ The University of Tokyo.

(1) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirst, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472. (c) Ohtani, I.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2525.

(2) (a) Jares-Eriyama, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (b) Jares-Eriyama, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L. *J. Org. Chem.* **1993**, *58*, 4805.

(3) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007.

(4) Ohizumi, Y.; Sasaki, S.; Kusumi, T.; Ohtani, I. I. *Eur. J. Pharmacol.* **1996**, *310*, 95.

(5) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526. (b) Snider, B. B.; Shi, Z. *Tetrahedron Lett.* **1993**, *34*, 2099. (c) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828. (d) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549.

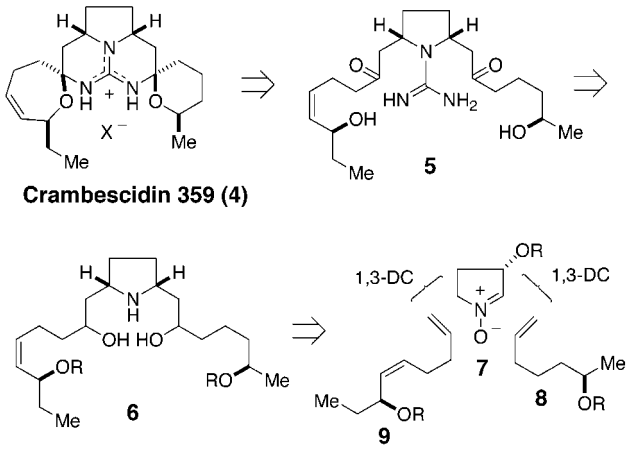
10.1021/ol0168263 CCC: $22.00 © 2002 American Chemical Society
Published on Web 12/29/2001

tion reaction. In 1995, Minale et al. reported the isolation of two new types of pentacyclic guanidine alkaloids, celeromycalin and fromiamycalin, from two New Caledonian starfishes, *Celerina heffernani* and *Fromia mononilis*, together with known ptilomycalin A (**1**), crambescidin 800, and the hydroxyspermidine **3** linked to a long chain fatty acid.[6] Those five compounds were examined in a CME 4 cell infection assay with HIV-1 and were found to be highly cytotoxic toward the target cells except for the hydroxyspermidine **3**. On the basis of these investigations, Minale and co-workers proposed that the biological activities of these ptilomycalin A type alkaloids are mostly caused by the pentacyclic guanidine portion (vessel part) in the molecule.[9]

In 2000, Braekman reported the isolation of new pentacyclic guanidine alkaloids dehydrobatzelladine C, crambescidin 359 (**4**), and crambescidin 431 from the marine sponge of the genus *Monanchora*, guided by the toxic activities against nauplii of brine shrimp *Artemia salina*.[10] Among them, crambescidin 359 (**4**) is the first derivative which lacks the side chain of carboxylate at C14 of ptilomycalin A. Though those structures were elucidated with 1D and 2D NMR experiments, the absolute configurations were not determined. Intrigued by the structure of crambescidin 359 (**4**) and the poorly defined biological activities of the "vessel part" of ptilomycalin A, we planned to synthesize **4** stereoselectively on the basis of the successive 1,3-dipolar cycloaddition protocol.[11]

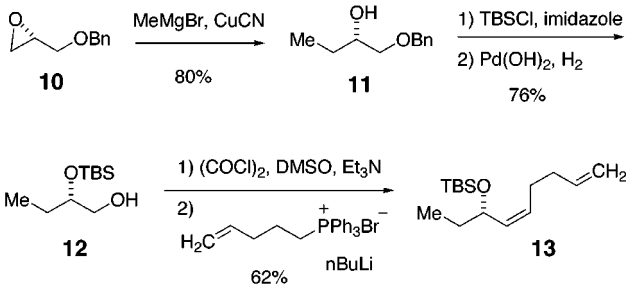
Our synthetic plan is outlined in Scheme 1. Pentacyclic guanidine **4** could be prepared from double *N*,*O*-acetalization of guanylated dihydroxy-diketone **5**, which can be obtained via **6** through successive 1,3-dipolar cycloaddition (1,3-DC) between the nitrone **7** and olefins **8** and **9**.

Scheme 1. Retrosynthetic Analysis for Crambescidin 359 (**4**)



Synthesis of the olefin **13** corresponding to **9** is summarized in Scheme 2. The optically active epoxide **10**[12] derived from the D-mannitol was reacted with methylmagnesium bromide in the presence of copper(I) cyanide to give the alcohol **11** in 80% yield. The secondary alcohol of **11** was protected as the *tert*-butyldimethylsilyl ether, and subsequent deprotection of the benzyl group with Pearlman's catalyst[13] gave the alcohol **12** in 76% yield. Oxidation of the alcohol **12** under Swern conditions followed by elongation of the side chain with the Wittig reaction using 1-pentenyl-5-triphenylphosphonium bromide gave **13** in 62% yield.

Scheme 2. Synthesis of Olefin (+)-**13**



With the olefins **13** and **15**[14] in hand, a successive 1,3-DC reaction protocol was next applied (Scheme 3). The 1,3-DC reaction of the optically active nitrone **14**[15] with (2*R*)-2-*tert*-butyldimethylsilyloxy-6-heptene (**15**) in toluene stereoselectively gave the isoxazolidine **16**[16] in 67% yield. The secondary alcohol on the pyrrolidine ring was removed by means of the following stepwise reactions: (1) thiocarbonate formation with phenyl chlorothionoformate[17] and (2) reduction with $^{n}Bu_3SnH$ in the presence of AIBN catalyst. The resulting isoxazolidine **17** was subjected to m-CPBA oxidation in dichloromethane at 0 °C, and a nitrone moeity was regenerated regioselectively to give **18**.[18] The second 1,3-DC reaction of **18** and the olefin **13** took place regio- and

(6) (a) Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Abdul Malik, K. M. *J. Chem. Soc., Chem. Commun*. **1994**, 119. (b) Murphy, P. J.; Williams, H. L. *J. Chem. Soc., Chem. Commun*. **1994**, 819. (c) Murphy, P. J.; Williams, H, L.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron* **1996**, *52*, 8315.

(7) (a) Overman, L. E.; Rabinowitz, M. H.; Renhowe P. A. *J. Am. Chem. Soc*. **1995**, *117*, 2657. (b) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc*. **1999**, *121*, 6944.

(8) For other synthetic studies, see: (a) Grillot, A. L.; Hart, D. J. *Tetrahedron* **1995**, *51*, 11377. (b) Anderson, G. T.; Alexander, M. D.; Taylor, S. D.; Smithrud, D. B.; Benkovic, S. J.; Weinreb, S. M. *J. Org. Chem*. **1996**, *61*, 125.

(9) Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carre, J. B.; Debitus, C.; Lucarain, L.; Provost, J. *Tetrahedron* **1995**, *51*, 3675.

(10) Braekman, J. C.; Daloze, D.; Tavares, R.; Hajdu, E.; Van Soest, R. W. M. *J. Nat. Prod*. **2000**, *63*, 193.

(11) Nagasawa, K.; Georgieva, A.; Nakata, T. *Tetrahedron* **2000**, *56*, 187.

(12) Takano, S.; Inamura, Y.; Ogasawara, K. *Tetrahedron Lett*. **1981**, *22*, 4479.

(13) Pearlman, W. M. *Tetrahedron Lett*. **1967**, 1663.

(14) Nagasawa, K.; Georgieva, A. Takahashi, H.; Nakata, T. *Tetrahedron* **2001**, *57*, 9726.

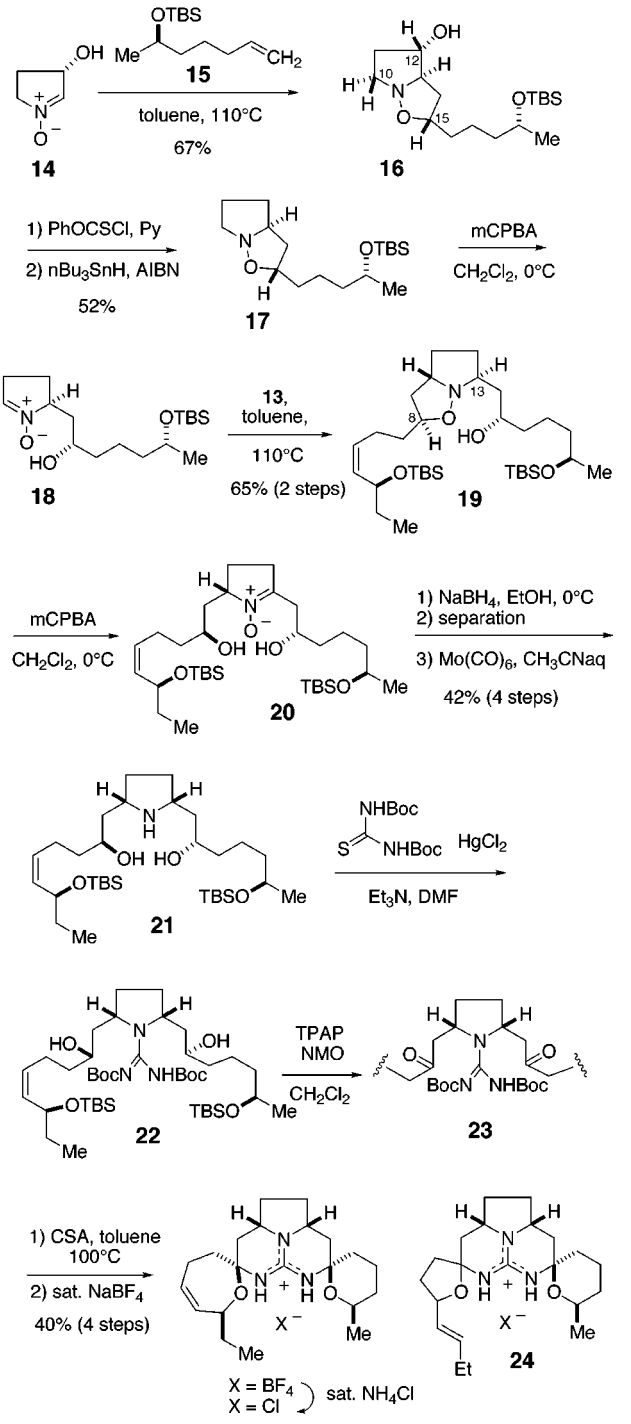
(15) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett*. **1999**, *40*, 2853.

(16) NOEs were observed from H-10β to H-12 and H-15, from H-15 to H12.

(17) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett*. **1989**, *30*, 2619.

(18) (a) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, Sk. A. *J. Am. Chem. Soc*. **1979**, *101*, 2435. (b) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett*. **1986**, *27*, 1489.

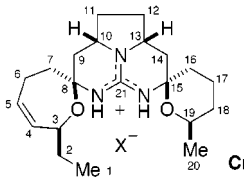
Scheme 3. Total Synthesis of (−)-Crambescidin (**4**)



stereoselectively from the less hindered side in the "*exo*-mode" to give the isoxazolidine **19**[19] in 65% yield from **17**. The second oxidative cleavage of the isoxazoline **19** with 1 equiv of m-CPBA in dichloromethane effectively furnished the nitrone **20** regioselectively.[20] Reduction of the nitrone with sodium borohydride gave 2,5-*cis*-*N*-hydoxypyrrolidine with 7:1 diastereoselection.[20] After removal of the minor *trans*-isomer by silica gel column chromatography, the *cis*-isomer was subjected to reduction with molybdenium hexacarbonyl[21] in aqueous acetonitrile to give the 2,5-*cis*-pyrrolidine **21** in 42% yield from **19**. Reaction of **21** with bis-*N*-Boc-thiourea and $HgCl_2$[22] gave the *N*-protected guanidine **22**, which was subjected to oxidation with the TPAP−NMO system[23] to give the diketone **23**. Though the deprotection of the *tert*-butyldimethylsily ether and Boc group under acidic conditions took place smoothly, the subsequent *N*,*O*-double acetalization reaction was troublesome. On treatment of **23** with hydrogen chloride, rearranged cyclization product **24** was obtained as the major product.[7b]

After investigation of various acidic conditions, CSA was found to be effective for giving the desired *N*,*O*-acetalization product. To the diketone **23** in toluene was added CSA (1 equiv), and the resulting mixture was heated at 100 °C for 20 h to give **4** as a camphorsulfonate. The countercamphorsulfonate anion was exchanged to tetrafluoroborate with saturated sodium tetrafluoroborate and gave crambescidin 359 (**4**) in 40% yield from **22**. A comparison of the ^1H and ^{13}C NMR spectral data of our synthetic **4** and the natural product revealed some slight differences in their ^1H and ^{13}C NMR chemical shifts (Table 1).[24]

Table 1. ^{13}C NMR (150 MHz) Spectra of **4**



position	X = BF_4^-	X = Cl^-	natural[10,26]
1	10.1	10.1	10.1
2	29.1	29.1	29.1
3	70.8	70.9	70.9
4	133.5	133.7	133.7
5	129.6	129.7	129.7
6	23.6	23.5	23.5
7	36.4	37.0	37.0
8	83.9	83.5	83.5
9	37.0	37.3	37.3
10	53.3	53.0	53.0
11	29.9	30.0[a]	30.0
12	29.9	30.1[a]	23.5
13	51.8	51.4	51.4
14	39.7	39.7	39.7
15	80.3	80.1	80.1
16	33.5	33.8	33.7
17	17.9	18.6	18.5
18	32.1	32.3	32.3
19	67.0	67.0	67.0
20	21.5	21.5	21.5
21	147.7	148.4	148.4

[a] Indistinguishable.

(19) NOE was observed from H-8 to H-13.
(20) (a) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron Lett.* **1993**, *34*, 137. (b) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron* **1993**, *49*, 4339.

We carefully analyzed the spectral data of 2D PFG-DQFCOSY, HMQC, and HMBC spectra, and completely assigned the ^{1}H and ^{13}C NMR data of our synthetic **4**. Stereochemistries of the synthetic **4** were confirmed to be the same as those of natural crambescidin 359 by NOE differential spectral data as follows: from Me-1 to H-10 and H-19, from H-3 to H-7α, from H-7β to H-9α. We speculated that the discrepancies of the NMR chemical shifts were due to the difference of the counteranion of **4**. Thus, the counteranion of **4** was reexchanged into chloride anion by treatment with saturated ammonium chloride to furnish **4** as a chloride salt. Its spectral data were completely consistent with those reported for natural crambescidin 359 (**4**) (Table 1). Since the optical rotation of synthetic crambescidin 359 (**4**) chloride salt was −8° (lit. −9°),[10] this also established the absolute stereochemistry of **4**.[25]

In summary, the first total synthesis of crambescidin 359 (**4**), a novel pentacyclic guanidine alkaloid, was accomplished based upon the successive 1,3-DC reaction protocol, and this synthesis has established the absolute stereochemistry of **4**. Since crambescidin 359 (**4**) is the first isolated ptilomycalin A type derivative which lacks the "anchor part", studies to evaluate the biological activities of **4** (the "vessel part" of ptilomycalin A) are in progress in our laboratories.

Acknowledgment. A.G. thanks JST (Japan Science and Technology Corporation) for the STA postdoctoral fellowship. Tore Co., Ltd. is greatly acknowledged for the financial support. This research was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and spectral data for **13**, **16**, **17**, **19**, **21**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0168263

(21) Ritter, A. R.; Miller, M. J. *J. Org. Chem*. **1994**, *59*, 4602.

(22) (a) Kim, K. S.; Qian, L. *Tetrahedron Lett*. **1993**, *34*, 7677. (b) Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Synth. Comm*. **1993**, *23*, 1443.

(23) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(24) We thank Prof. Braekman for providing copies of spectra of crambescidin 359 (**4**).

(25) The counteranion of natural **4** was not reported. The coincidence of the spectral data as well as the optical rotation of synthetic **4** chloride salt and the natural products would suggest that the counteranion of the natural product is chloride.

(26) On the basis of detailed analysis of the spectral data of synthetic **4**, we assigned the C12 signal at 30.0 or 30.1 ppm, though the original assignment of C12 was 23.5 ppm, which overlaps with C6.