ORGANIC LETTERS

2001
Vol. 3, No. 12
1813−1815

Rapid Entry into the Cryptophycin Core via an Acyl-β-lactam Macrolactonization: Total Synthesis of Cryptophycin-24

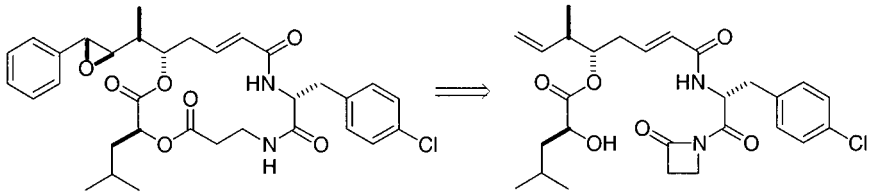
MariJean Eggen,[†] Sajiv K. Nair,[†] and Gunda I. Georg*

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

georg@ukans.edu

Received March 7, 2001

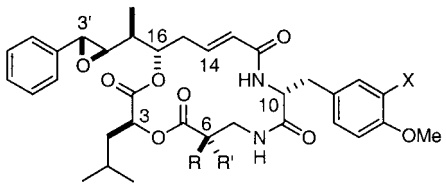
ABSTRACT



An efficient, concise approach to the macrolide core of the cryptophycins, potent antimitotic agents, has been achieved. The reaction sequence features a novel macrolactonization utilizing a reactive acyl-β-lactam intermediate that incorporates the β-amino acid moiety within the 16-membered macrolide core. This highly modular approach, which allows for multiple alterations throughout the structure, was successfully applied to the total synthesis of cryptophycin-24.

The cryptophycins are exceptionally potent, novel 16-membered macrolides isolated from the blue-green algae *Nostoc* sp.[1] The simplest of the macrolides, cryptophycin-24 (arenastatin A, **1**, Figure 1), was also isolated from the Okinawan marine sponge *Dysidea arenaria*.[2] The most abundant component, cryptophycin-1 (**2**), has demonstrated both antifungal and antimitotic properties.[1a,b] In vivo studies in human tumor xenografts in mice demonstrated remarkable tumor burden reduction when compound **2** was administered intravenously.[3] A hydrolytically more stable synthetic analogue, cryptophycin-52 (**3**), is currently in Phase II clinical trials.[4]

Microtubules are eukaryotic cellular structures involved in the movement and positioning of chromosomes during mitosis as well as the movement of vesicles and organelles



Cryptophycin-24 (Arenastatin A) R, R', X= H (**1**)
Cryptophycin-1 R = Me, R' = H, X = Cl (**2**)
Cryptophycin-52 R, R' = Me, X = Cl (**3**)

Figure 1. Structures of the cryptophycins.

[†] Current address: Pharmacia Corp., Kalamazoo, MI 49001.

(1) (a) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113. (b) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729. (c) Subbaraju, G. V.; Golakoti, T.; Patterson, G. M. L.; Moore, R. E. *J. Nat. Prod.* **1997**, *60*, 302.

(2) Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kuroso, M.; Wang, W.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 7969.

(3) (a) Shih, C.; Gossett, L. S.; Gruber, J. M.; Grossman, C. S.; Andis, S. L.; Schultz, R. M.; Worzalla, J. F.; Corbett, T. H.; Metz, J. T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 69. (b) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729.

(4) Shih, C.; Al-Awar, R.; Norman, B.; Patel, V.; Toth, J.; Varie, D.; Fray, A.; Moher, E.; Martinelli, M.; Corbett, T.; Moore, R. *Abstract of Papers*, 219th National Meeting of the American Chemical Society; San Francisco, CA; American Chemical Society: Washington, DC, **2000**; ORG 291.

10.1021/ol010044s CCC: $20.00
Published on Web 05/10/2001

within these cells. The dynamic nature of the equilibrium between microtubules and tubulin along with their involvement in cell division has made them an important target in anticancer research.[5] Several agents that interact with tubulin, such as the Vinca alkaloids, colchicine, podophyllotoxin, maytansine, and the cryptophycins,[6] disrupt this equilibrium in favor of tubulin protein. Cryptophycin's exceptional potency has led to studies of other possible modes of action.[7] Cryptophycin-1 (**2**) and -52 (**3**) stabilize microtubule dynamics at low nanomolar concentrations which exhibit no effect on the overall concentration of microtubules within the cell but still lead to apoptosis.[7b,8] Cryptophycin-52 (**3**) was recently reported to be the most potent agent to cause the expression of hyperphosphorylated Bcl2, rendering cancer cells susceptible to apoptosis.[4]

The potent bioactivity of the cryptophycins raised interest in our group and others, leading to numerous reported formal[9] and total syntheses.[10] Significant structure−activity relationship studies have also been carried out involving both semisynthetic analogues derived from modifications of the epoxide[11] and synthetic analogues which differ in the tyrosine fragment,[12] β-amino acid moiety,[13] or octadienoate ester fragment[14] or contain an isosteric replacement of the C5 ester with an amide.[15]

Our continued interest in the interactions of these compounds with tubulin protein led us to develop a novel, concise approach toward the synthesis of the macrolide core of the cryptophycins. Previous research with paclitaxel derivatives in our laboratory utilized chiral β-lactam precursors as reactive intermediates for incorporation of the phenylisoserine side chain.[16] Likewise, the presence of the β-amino acid within the cryptophycin core provided a basis for our retrosynthetic strategy (Figure 2). The key step would be

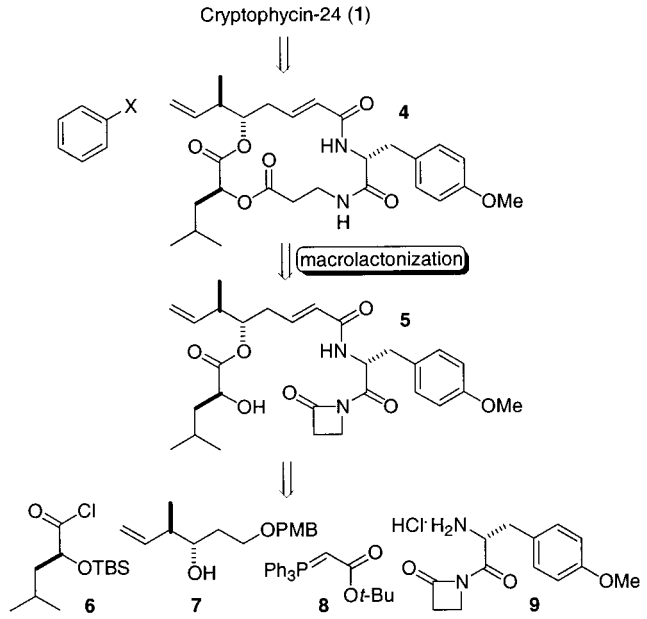


Figure 2. Retrosynthetic analysis of cryptophycin-24.

the closure to the macrocycle via an intramolecular reaction[17] of the β-hydroxy group in the leucic acid ester component with the activated acyl β-lactam.

To make the synthesis as concise as possible, the leucic acid segment was introduced first by esterification of the secondary alcohol[9b] **7** with acid chloride **6** derived from bis-silylated L-leucic acid (Scheme 1).[18] The *p*-methoxybenzyl ether was deblocked using DDQ to provide the desired primary alcohol. Oxidation of this alcohol was somewhat problematic as basic oxidation conditions led to decomposi-

(5) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259.

(6) (a) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779. (b) Kerksiek, K.; Mejillano, M.; Schwartz, R. E.; Georg, G. I.; Himes, R. *FEBS Lett.* **1995**, *377*, 59. (c) Smith, C. D.; Zhang, X. *J. Biol. Chem.* **1996**, *271*, 6192. (d) Bai, R.; Schwartz, R. E.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Cancer Res.* **1996**, *56*, 4398. (e) Koiso, Y.; Morita, K.; Kobayashi, M.; Wang, W.; Ohyabu, N.; Iwasaki, S. *Chem.-Biol. Interact.* **1996**, *102*, 183.

(7) (a) Mooberry, S. L.; Busquets, L.; Tien, G. *Int. J. Cancer* **1997**, *73*, 440. (b) Panda, D.; Himes, R. H.; Moore, R. E.; Wilson, L.; Jordan, M. A. *Biochemistry* **1997**, *36*, 12048. (c) Kessel, D. *J. Chromatogr. B* **1999**, *735*, 121.

(8) Panda, D.; DeLuca, K.; Williams, D.; Jordan, M. A.; Wilson, L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9313.

(9) (a) Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703. (b) Eggen, M.; Georg, G. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3177. (c) Furuyama, M.; Shimizu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 1351. (d) Varie, D. L.; Brennan, J.; Briggs, B.; Cronin, J. S.; Hay, D. A.; Rieck, J. A. I.; Zmijewski, M. J. *Tetrahedron Lett.* **1998**, *39*, 8405. (e) Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 1459. (f) Fray, A. H. *Tetrahedron: Asymmetry* **1998**, *9*, 2777.

(10) (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479. (b) Kobayashi, M.; Wang, W.; Ohyabu, N.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1995**, *43*, 1598. (c) Salamonczyk, G. M.; Han, K.; Guo, Z.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893. (d) Rej, R.; Nguyen, D.; Go, B.; Fortin, S.; Lavallee, J.-F. *J. Org. Chem.* **1996**, *61*, 6289. (e) de Muys, J.-M.; Rej, R.; Go, B.; Fortin, S.; Lavallee, J.-F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1111. (f) Dhokte, U. P.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *Tetrahedron Lett.* **1998**, *39*, 8771. (g) White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1998**, *39*, 8779. (h) Kobayashi, M.; Kuroso, M.; Wang, W.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2394. (i) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206. (j) Gardinier, K. M.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 7098. (k) Ghosh, A. K.; Bischoff, A. *Org. Lett.* **2000**, *2*, 1573. (l) Christopher, J. A.; Kocienski, P. J.; Kuhl, A.; Bell, R. *Synlett* **2000**, *4*, 463. (m) Liang, J.; Moher, E. D.; Moore, R. E.; Hoard, D. W. *J. Org. Chem.* **2000**, *65*, 3143. (n) Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792.

(11) (a) Trimurtulu, G.; Ogino, J.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030. (b) Georg, G. I.; Ali, S. M.; Stella, V. J.; Waugh, W. N.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1959.

(12) Patel, V. F.; Andis, S. L.; Kennedy, J. H.; Ray, J. E.; Schultz, R. M. *J. Med. Chem.* **1999**, *42*, 2588.

(13) Varie, D. L.; Shih, C.; Hay, D. A.; Andis, S. L.; Corbett, T. H.; Gossett, L. S.; Janisse, S. K.; Martinelli, M. J.; Moher, E. D.; Schultz, R. M.; Toth, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 369.

(14) Al-Awar, R. S.; Ray, J.; Schultz, R.; Andis, S.; Worzalla, J.; Kennedy, J.; Corbett, T. In *American Association of Cancer Research*; New Orleans, LA, 1998; p 425.

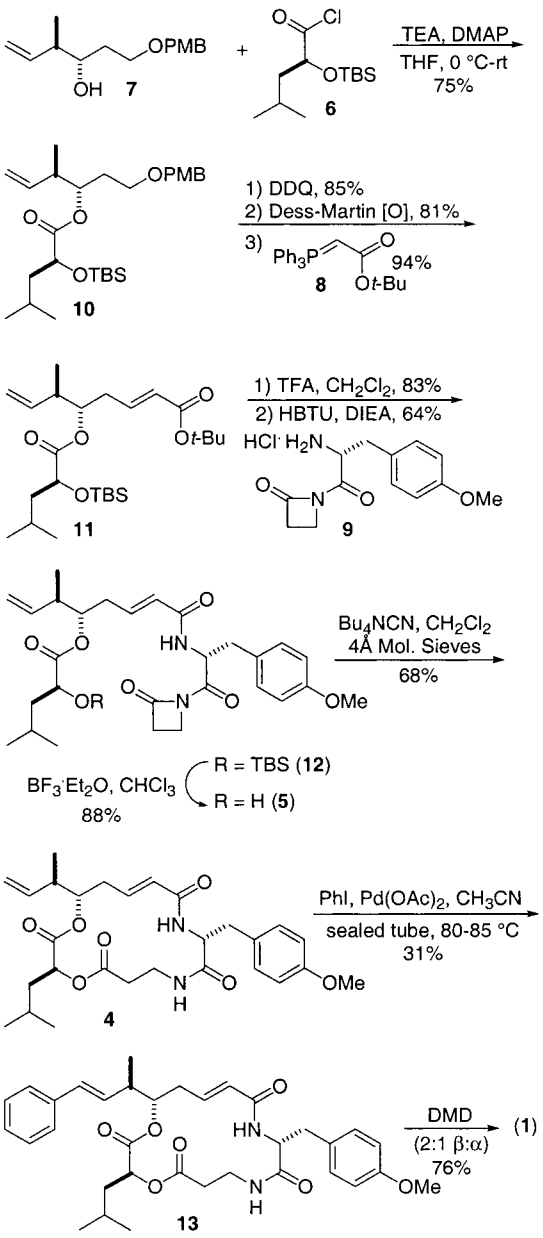
(15) Norman, B. H.; Hemscheidt, T.; Schultz, R. M.; Andis, S. L. *J. Org. Chem.* **1998**, 63, 5288.

(16) Georg, G. I.; Ali, S. M.; Zygmunt, J.; Jayasinghe, L. R. *Exp. Opin. Ther. Pat.* **1994**, *4*, 109 and references therein.

(17) For other examples of β-lactam-mediated cyclizations, see: (a) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237. (b) Gardner, B.; Nakanishi, H.; Kahn, M. *Tetrahedron* **1993**, *49*, 3433. (c) Saragovi, H. U.; Fitzpatrick, D.; Raktabutr, A.; Nakanishi, H.; Kahn, M.; Greene, M. I. *Science* **1991**, *253*, 792.

(18) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972.

Scheme 1



tion and the production of numerous byproducts. However, the Dess−Martin oxidation cleanly provided the required aldehyde. Attempts to carry out a standard Horner−Emmons homologation under basic conditions once again provided numerous undesired products with little isolable olefin. Even the Masamune and Roush conditions (LiCl/DBU),[19] which are normally utilized when substrates or reagents are base sensitive, failed in this case. Gratifyingly, the neutral phosphorane **8** produced the desired bond linkage leading to the ester **11**.

Deprotection of the *tert*-butyl ester with TFA followed by coupling with aminoacylazetidinone **9** using HBTU/DIEA incorporated all the elements necessary for macrocycle formation. Deprotection of the *tert*-butyldimethylsilyl ether with $BF_3{\cdot}Et_2O$ provided the acyl-β-lactam intermediate **5** for macrolactonization. The key macrolactonization using CH_2Cl_2-soluble Bu_4NCN[17a] cleanly provided the 16-membered macrolide **4**. The end game involved the attachment of the C3′-phenyl under Heck conditions and epoxidation utilizing dimethyldioxirane (DMD) to provide cryptophycin-24 (**1**).[20]

In summary, a unique and convergent synthesis of cryptophycin-24 (**1**) has been developed. The modular approach allows for multiple alterations throughout the structure by modification of the amino acyl β-lactam, hydroxy acid, and C3′-aromatic group. The reaction sequence features a novel macrolactonization approach utilizing the reactive acyl-β-lactam for the incorporation of the β-amino acid moiety. The acyl-β-lactam macrolactonization strategy provides a concise and efficient entry into the macrocyclic core of this promising family of antitumor macrolides.

Acknowledgment. We thank the National Institutes of Health for financial support (RO1 CA 70369). The Department of the Army is acknowledged for financial support of M.E. through a postdoctoral fellowship (DAMD 17-97-1-7051). S.K.N. thanks the Kansas Health Foundation for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra for compounds **1**, **4**, **5**, **7**, **10**−**12**, and all other intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010044S

(19) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(20) For separation of epoxides by RP-HPLC, see ref 10i. Alternatively, for separation of epoxides using a halohydrin approach see ref 13.