Enantiospecific Total Synthesis of the Potent Antitumor Macrolides Cryptophycins 1 and 8

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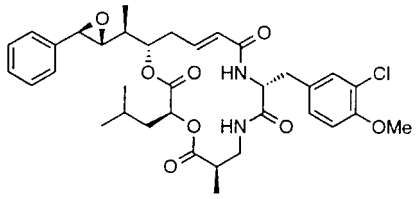
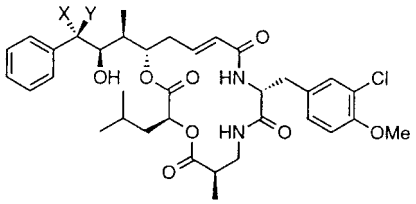
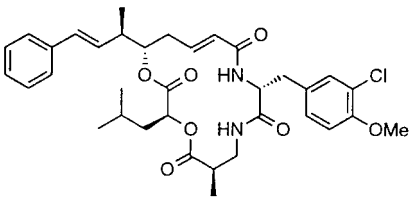
In 1990, Schwartz and co-workers reported the isolation of a novel depsipeptide from a *Nostoc* cyanobacterium that was extremely active against filamentous fungi and yeast of the genus *Cryptococcus*.[1] Subsequently, Moore and co-workers determined the structure of this compound (cryptophycin 1, **1**)[2] and found that it was a member of a family of macrolides that could be isolated from *Nostoc* sp GSV 224,[3] and that these compounds exhibited extraordinary activity against a variety of tumor cell lines.[4] For example, **1** has an IC_{50} cytotoxicity value of 20 pM against SKOV3 human ovarian carcinoma.[5] In addition to the natural cryptophycins, Moore found that the synthetically derived cryptophycin 8 (**2**) was more active in vivo than **1**.[5] Other modifications about this epoxide portion (natural or synthetic) have led to a significant loss of biological activity (e.g. cryptophycin 3 (**3**)).[5]



Cryptophycin 1 (**1**)



Cryptophycin 8 (**2**) (X = Cl, Y = H)
4 (X = H, Y = OH)



Cryptophycin 3 (**3**)

Given the profound activity of the cryptophycins, it is not surprising that it has attracted considerable synthetic interest.[2,6] All efforts to date have focused on the synthesis of **3**, while subsequent epoxidation of this olefin does not occur with good selectivity.[2,6] We wish to report here an enantiospecific synthesis of both cryptophycins 1 and 8 that allows for the exclusive generation of the desired products.

We recognized from the outset that the stereospecific introduction of the requisite epoxide/chlorohydrin could best be accomplished from an appropriately functionalized precursor, so we chose diol **4** as a suitable target. Further disconnection about the amide and ester linkages led to our first retrosynthetic targets.

The requisite carbon backbone of the cryptophycins was prepared from aldehyde **5** (Scheme 1).[7,8] Reaction of this aldehyde with **6**[9] under standard Evans aldol conditions afforded an excellent yield of a single crystalline product which was revealed to be the desired adduct **7**.[10,11] Following transamidation via the Weinreb protocol,[12] addition of allylmagnesium bromide gave β,γ-unsaturated ketone **8**. The remaining stereocenter was introduced with concomitant differentiation of the hydroxyl groups via intramolecular Tishchenko reaction with acetaldehyde.[13] The remaining alcohol was protected as the *p*-methoxybenzyl ether followed by conversion of the acetate into TIPS ether **9**. Oxidative cleavage of the olefin was followed by Horner−Emmons olefination and deprotection to afford the cryptophycin backbone **10**.

The depsipeptoid portion of the cryptophycins was prepared in a convergent fashion from the appropriately protected building blocks. Condensation of **11**[2] (Scheme 2) with amine **12**[14] was followed by desilylation and oxidation to give acid **13**.[15] Esterification[16] and debenzylation gave the fully elaborated depsipeptoid **14**, which was coupled with **10** under Yamaguchi conditions.[17] The secoamide, which was revealed via exposure to acid, was closed to the macrolide in excellent yield. Fluoride

(1) 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.

(2) See: Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479 and references cited within.

(3) See: Subbaraju, G. V.; Golakoti, T.; Patterson, G. M. L.; Moore, R. E. *J. Nat. Prod.* **1997**, *60*, 302 and references cited within.

(4) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.

(5) Golakoti, T.; 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.

(6) (a) de Muys, J.-M.; Rej, R.; Nguyen, D.; Go, B.; Fortin, S.; Lavallée, J.-F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1111. (b) Salamonczyk, G. M.; Han, K.; Guo, Z.-w.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893. (c) Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.

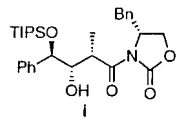
(7) Prepared from (*R*)-ethyl mandelate via a two-step procedure (1. Triisopropylsilyl (TIPS) chloride, imidazole (92%). 2. DIBAL, −78 °C (94%)). The use of a TIPS protecting group was crucial, as the corresponding TBS group was subject to migration in subsequent steps.

(8) All new compounds gave satisfactory ^{1}H and ^{13}C NMR data and were within acceptable combustion analytical limits.

(9) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *69*, 83.

(10) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(11) This aldol reaction is apparently sensitive to the scale of the reaction. While attempts to perform the transformation on large scale has led to the formation of an undesired diastereomer (**i**), the desired product could reliably and reproducibly be formed when less than 2 g of **5** were used. It has previously been reported that aldol additions to α-siloxy aldehydes gave rise to an undesired diastereomer.[10]



i

(12) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(13) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(14) Prepared via reduction (BH_3•THF (100%)) of the known amide (Hioki, H.; Okuda, M.; Miyagi, W.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 6131).

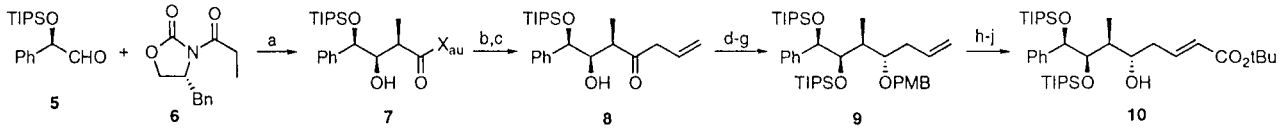
(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(16) Fredrick, D.; Bengt, F.; Leif, G.; Ulf, R. *J. Chem. Soc., Perkin Trans. 1* **1993**, *1*, 11.

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

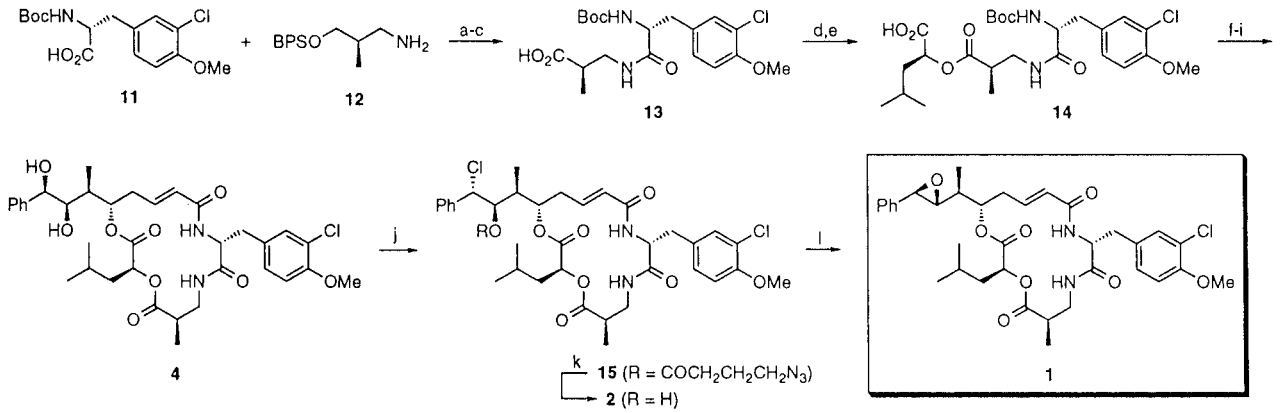
S0022-3263(97)01645-9 CCC: $14.00

Scheme 1



a) Bu_2BOTf, iPr_2NEt (84%); b) Me_3Al, MeONHMe•HCl (93%); c) CH_2=$CHCH_2MgBr$ (92%); d) MeCHO, SmI_2 (96%); e) PMBOC(NH)CCl_3, cat. TfOH (70%); f) DIBAL (90%); g) TIPSOTf, iPr_2NEt (93%); h) OsO_4, NMO; $NaIO_4$ (91%); i) $(EtO)_2POCH_2CO_2tBu$, DBU, LiCl (90%); j) DDQ (95%)

Scheme 2



a) EDC, HOBt (97%); b) Bu_4NF (96%); c) $RuCl_3$•xH_2O, $NaIO_4$ (83%); d) HIeuOBn, DCC (95%); e) H_2, Ra-Ni (84%); f)**10**, 2,4,6-trichlorobenzoyl chloride, iPr_2NEt (91%); g) HCl, EtOAc; h) *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-bis(pentamethylene)uroniumhexafluorophosphate (76%, 2 steps); i) Bu_4NF (95%); j) $N_3CH_2CH_2CH_2C(OMe)_3$, Me_3SiCl (63%); k) PPh_3, H_2O (63%); l) K_2CO_3, Me_2CO (98%).

deprotection then gave the desired cryptophycin diol **4** in 21% overall yield from **5**.

With our advanced target in hand, all that remained was the stereospecific introduction of the epoxide functionality. Sharpless has developed an excellent method for the in situ conversion of vicinal diols into epoxides.[18] In the case of the cryptophycins, however, the basic transesterification required in the final step is incompatible. We therefore sought an alternative that would allow for the selective cleavage of the ester formed at the homobenzylic position. In this regard, we chose 4-azido-1,1,1-trimethoxybutane[19] as our ortho ester since it would allow for the stereospecific introduction of the chloride and would give a 4-azidobutyrate ester in the process.[20] Employing Sharpless's conditions with this novel ortho ester gave the anticipated **15**. The azidobutyrate was chosen because, under reductive conditions, the azide could be transformed into the amine, causing it to undergo intramolecular lactamization and thus deprotection. Indeed, selective reduction under Staudinger conditions[21] resulted in the cleavage of the butyrate and gave exclusively cryptophycin 8 (**2**). The epoxide could be closed under the previously disclosed conditions[5] to give **1** which is identical in all respects to authentic cryptophycin 1.

In summary, we have achieved a highly efficient and enantiospecific total synthesis of cryptophycins 1 and 8. The use of these methods for the preparation of novel analogues as well as the elucidation of the mechanism of biological activity are currently underway. Furthermore, we have generated a novel ortho ester to be used in conjunction with known methodology to allow for the stereospecific formation of epoxides in the presence of other base sensitive functionality. Studies on other diol systems will be reported in due course.

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Supporting Information Available: Full experimental details for the synthesis of **1**−**15** (21 pages).

JO971645T

(18) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

(19) Generated from 4-chlorobutyronitrile via formation of the ortho ester followed by azide displacement (NaN_3, 18-c-6 (99%)). See also Ueno, H.; Maruyama, A.; Miyake, M.; Nakao, E.; Nakao, K.; Umezu, K.; Nitta, I. *J. Med. Chem.* **1991**, *34*, 2468.

(20) See Shoichi, K.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1296.

(21) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.