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A Convergent Synthesis of (+)-Cryptophycin B, a Potent Antitumor Macrolide from *Nostoc* sp. Cyanobacteria

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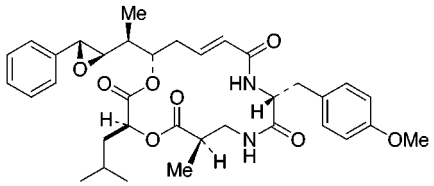
ABSTRACT



Cryptophycin B (2)

An efficient and highly stereoselective synthesis of cryptophycin B (2), a potent cytotoxic agent, is described. The ester-derived titanium-enolate-mediated *syn*-aldol reaction was employed to generate the stereocenters C(5) and C(6). The route is convergent and provides a convenient access to the synthesis of structural variants of cryptophycin B as well as members of its family.

Macrocyclic marine natural products continue to be a rich source for diverse antitumor agents with significant clinical potential.[1] Of particular interest, the cryptophycins, a group of depsipeptides isolated recently, have exhibited remarkably potent antitumor properties. The first cryptophycin (**1**) was isolated from terrestrial *Nostoc sp*. ATCC 53789 by researchers at Merck and was found to be very active against *Cryptococcus*, a fungus that often infects persons with immunodeficiencies.[2] In 1994, Moore et al. isolated a host of cyclic depsipeptides including cryptophycin A (**1**) and B (**2**) from *Nostoc. sp.* GSV 224 and established their absolute stereochemistry (Figure 1).[3] Cryptophycins A and B exhibited cytotoxic IC_{50} values of 5 and 7 pg/mL, respectively, against KB cells. In addition, the compounds were equally effective against drug-sensitive and drug-resistant tumor cells.[3,4] Arenastatin A (**3**), another member of the cryptophycin family, was isolated from the Okinawan marine sponge *Dysidea arenaria*.[5,6] It has displayed a cytotoxic IC_{50} value of 5 pg/mL against KB cells.[6]

Cryptophycin A and other members of the family have been shown to promote depletion of microtubules.[4] Furthermore, a number of these compounds effectively inhibited in vitro tubulin polymerization.[7] The significant clinical potential of the cryptophycins and their relatively low natural abundance has attracted immense interest in their synthesis and structural modification. Several total syntheses and synthetic approaches to cryptophycins and arenastatin A have been described in recent years.[8,9] As part of our interest in the structure−function studies of cryptophycins, we sought a flexible, enantioselective synthesis of cryptophycin B. Herein we report a convergent and stereocontrolled total synthesis of cryptophycin B.

As outlined in Figure 1, we planned to assemble cryptophycin B in a convergent manner from the protected

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(6) Koiso, Y.; Morita, K.; Kobayashi, M.; Wang, W.; Ohyabu, N.; Iwasaki, S. *Chem.-Biol. Interact.* **1996**, *102*, 183.
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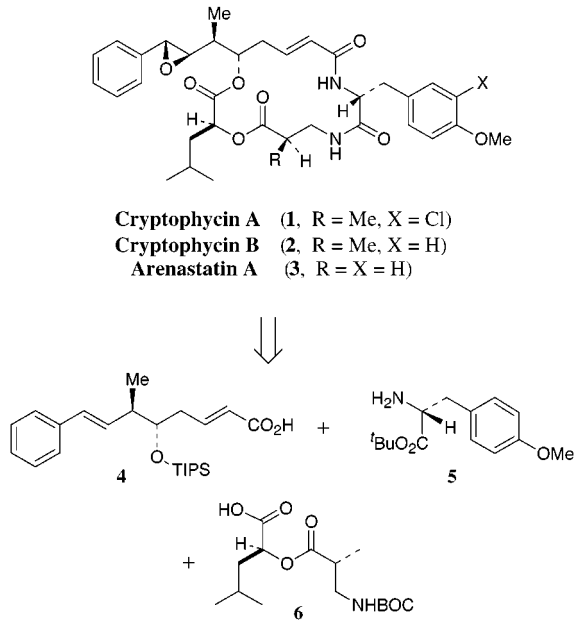
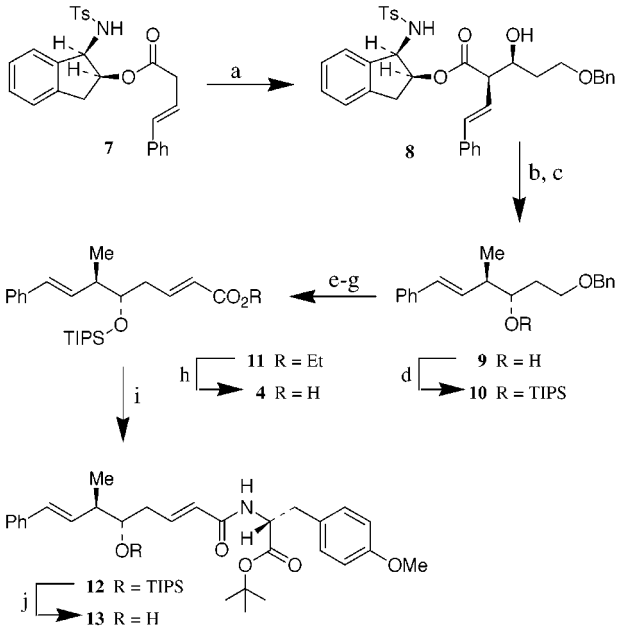


Figure 1.

octadienoic acid **4**, D-tyrosine ester **5**, and protected β-amino acid derivative **6**. The fragments were planned to be connected by Yamaguchi esterfication and cycloamidation reactions. Introduction of the sensitive epoxide functionality was planned at the final stage of the synthesis. The key elements of our synthesis involved an ester-derived titanium-enolate-mediated *syn*-aldol reaction to set the stereocenters at C(5) and C(6) of fragment **4**[10a,b] Thus, acylation of *trans*-4-phenyl-3-butenoic acid and (+)-(1*R*,2*S*)-1-(*N*-tosylamino)-2-indanol with DCC and DMAP afforded the ester **7** in 98% yield.[10c] As shown in Scheme 1, exposure of **7** to $TiCl_4$ and *N*,*N*-diisopropylethylamine in CH_2Cl_2 at 23 °C generated the corresponding titanium enolate. Subsequent reaction of the enolate with (benzyloxy)propionaldehyde at −78 °C furnished the aldol adduct **8** as a single diastereomer in 98% yield after silica gel chromatography. Reduction of **8** by lithium aluminum hydride in THF at 0 °C for 1 h afforded the diol in 92% yield. The primary hydroxyl group of the

Scheme 1[a]



[a] (a) $TiCl_4$, iPr$_2$NEt, 0 to 23 °C, 1 h then BnO(CH$_2$)$_2$CHO, −78 °C, 20 min (98%); (b) LAH, THF, 0 °C, 1 h (92%); (c) PhLi, THF, −78 °C, 30 min, TsCl, −20 °C, 30 min, then LAH, 0 °C, 20 min (96%); (d) TIPSOTf, 2,6-lutidine (99%); (e) K_2CO_3, BBr_3, CH_2Cl_2, 0 °C, (83%); (f) PCC, MS 4 Å, 23 °C, 10 min (98%); (g) NaH, triethylphosphonoacetate, THF, 0 °C, 30 min (92%); (h) aq LiOH, EtOH (1:1), 23 °C, 2 h (94%); (i) **5**, DCC, DMAP, 23 °C, 12 h (79%); (j) TBAF, THF, 23 °C (99%).

resulting diol was selectively converted to the corresponding methyl group in an one-pot, two-step sequence. Thus, treatment of the diol with phenyllithium and *p*-toluenesulfonyl chloride at −78 °C to −20 °C followed by reduction of the resulting tosylate with lithium aluminum hydride provided the alcohol **9** in 96% yield.

Protection of the secondary alcohol using triisopropylsilyl triflate and 2,6-lutidine in CH_2Cl_2 gave **10** in 99% yield.[11] Selective removal of the benzyl protecting group was effectively achieved by treatment of **10** with boron tribromide in CH_2Cl_2 in the presence of potassium carbonate to provide the corresponding alcohol in 83% yield.[12] Initial attempts with other conditions such as TMSCl/nBu$_4$N$^+$I$^-$, $FeCl_3$, or Na/NH_3 were unsuccessful.[13] Oxidation of the resulting alcohol with PCC in CH_2Cl_2 followed by Horner−Emmons olefination of the aldehyde with sodium hydride and triethyl phosphonoacetate provided the α,β-unsaturated ester **11** in 92% yield. Ester hydrolysis with aqueous lithium hydroxide in a mixture (1:1) of EtOH and H_2O gave the octadienoic acid fragment **4** in 94% yield. Coupling of this acid with

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(10) (a) Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937. (b) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171. (c) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527.

(11) Rücker C. *Chem. Rev.* **1995**, *95*, 1009 and references cited therein.

(12) Treatment of **10** with boron tribromide in CH_2Cl_2 afforded the corresponding alcohol in only 32% yield. The major side product was the desilylation product.

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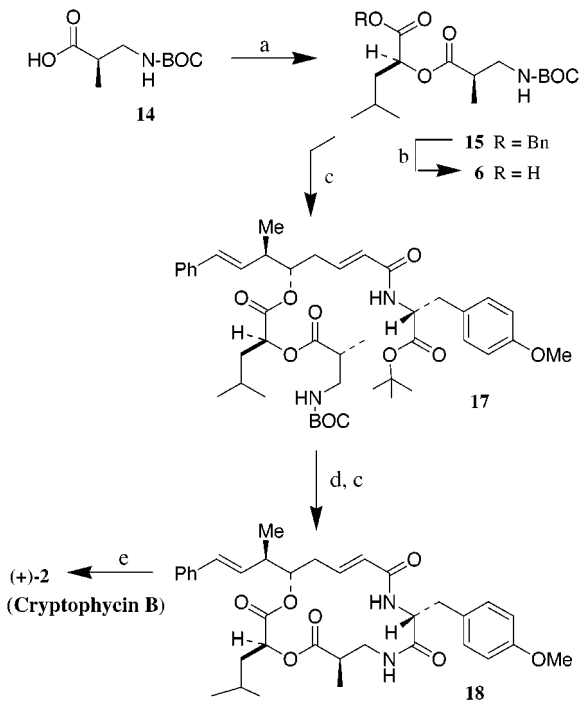
O-methyl-D-tyrosine *tert*-butyl ester[14] in the presence of DCC and DMAP in CH_2Cl_2 resulted in the amide **12** in 79% yield.[15] Exposure of **12** with $nBu_4N^+F^-$ in the presence of a trace of water in THF furnished the alcohol **13** in near quantitative yield.[16]

The synthesis of β-amino acid derivative **6** was carried out in two steps as shown in Scheme 2. Esterification of optically active *N*-Boc-3-amino-2-methylpropionic acid **14**[17] and benzyl (*S*)-(−)-2-hydroxyisocaproate[18] with dicyclohexylcarbodiimide and DMAP in CH_2Cl_2 at 23 °C for 12 h afforded the diester **15** in 91% yield. Catalytic hydrogenation of diester **15** over 10% Pd/C in ethyl acetate under a hydrogen-filled balloon for 5 h furnished the acid **6** in 95% yield. The acid **6** was subjected to esterification by reaction with 2,4,6-trichlorobenzoyl chloride, *N*,*N*-diisopropylethylamine, and alcohol **13** in the presence of DMAP under Yamaguchi conditions to provide diester **17** in 84% yield.[19] Exposure of **17** to trifluoroacetic acid at 23 °C for 2 h resulted in the removal of both the *tert*-butyl ester and the Boc-protecting group to furnish the requisite amino acid precursor for the macrocyclization. Thus, subjection of the resulting amino acid to Yamaguchi conditions with 2,4,6-trichlorobenzoyl chloride, *N*,*N*-diisopropylethylamine, and DMAP at 23 °C for 12 h furnished the cycloamide **18** ($[\alpha]^{23}_D$ +36.2, *c* 0.72, MeOH; lit.[3] $[\alpha]_D$ +36.7, *c* 1.93, MeOH) in 74% yield (from **17**). Epoxidation of **18** with dimethyldioxirane in CH_2Cl_2 at −30 °C to 23 °C for 12 h provided a 3:1 mixture of epoxides in 87% yield. The major epoxide was separated by reverse-phase HPLC on a C-18 column[20] (eluent, 3:1 MeOH/H_2O) to provide the synthetic cryptophycin B (**2**, $[\alpha]^{23}_D$ +20.6, *c* 0.24, MeOH; lit.[3] $[\alpha]_D$ +20.4, *c* 0.54, MeOH). Spectral data (500 MHz ^1H NMR, IR, and ^{13}C NMR) for the synthetic cryptophycin B are in full agreement with that reported by Moore et al. for the natural cryptophycin B.[3]

Scheme 2[a]



[a] (a) DCC, benzyl (*S*)-(−)-2-hydroxyisocaproate, DMAP, CH_2Cl_2, 23 °C, 12 h (91%); (b) H_2, 10% Pd−C, EtOAc, 5 h (95%); (c) 2,4,6-(Cl_3)PhCOCl, *i*Pr_2NEt, DMAP, alcohol **13**, 23 °C; (d) CF_3CO_2H, 23 °C, 2 h; (e) dimethyldioxirane, CH_2Cl_2, −30 to 23 °C, 12 h (87%, 3:1 mixture).

In summary, a stereocontrolled synthesis of cryptophycin B has been accomplished in 14 steps from **7** in 22% overall yield. The present synthetic route is easily amenable to the synthesis of other members of the cryptophycin family. Further studies of cryptophycins are ongoing in our laboratory.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **2** and **4**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) *O*-Methyl-D-tyrosine *tert*-butyl ester was prepared in a three-step sequence involving (1) treatment of commercially available *N*-Cbz-D-tyrosine with Me_2SO_4 and NaOH in aqueous EtOH at reflux; (2) reaction of the resulting *O*-methyltyrosine with 2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt, DMAP, and *t*BuOH; and (3) removal of Cbz group by hydrogenation over 10% Pd−C in MeOH (55% overall).

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(16) Reaction rate was accelerated in the presence of a trace amount of water.

(17) Amino acid **14** was prepared by tosylation of commercially available methyl (*R*)-(−)-3-hydroxy-2-methylpropionate with TsCl and NEt_3 in CH_2Cl_2 for 1 h. Displacement of tosylate with NaN_3 in DMSO at 23°C for 6 h. Hydrogenation of the resulting azide over 10% Pd/C in the presence of Boc_2O in EtOAc followed by saponification with aqueous LiOH at 23°C for 30 min (90% overall).

(18) Benzyl (*S*)-(−)-2-hydroxyisocaproate was prepared from commercially available (*S*)-(−)-2-hydroxyisocaproate by treatment with $CsCO_3$ in MeOH/H_2O (6:1) for 30 min followed by reaction with BnBr in DMF at 0 °C (91%).

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

(20) The major epoxide was cleanly separated by an isocratic reverse phase HPLC (see ref 8g for similar separation) on a YMC-Pack ODS-AQ 5S 120 Å column (4.6 × 250 mm) with flow rate 1 mL/min and UV detection at 254 nm. Retention times for **2**: 31.58 min; and diastereomer: 37.20 min.