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RCM approach for the total synthesis of cryptophycin-24 (Arenastatin A)

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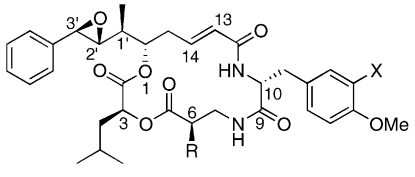
This article is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—An efficient total synthesis of cryptophycin-24 (arenastatin A) is reported, which features two novel synthetic strategies, the use of a RCM reaction to form the macrocycle, and the introduction of the styrene epoxide moiety prior to the macrocyclization reaction.

The cryptophycins, a unique family of 16-membered macrolides, are currently considered to be one of the most promising new leads in cancer therapy.[1–3] The first member of this family, cryptophycin-1 (**1**), whose structure was established by Moore and co-workers[4] was isolated from blue-green alga (*Nostoc* sp. ATCC 53789).[5] A biologically equivalent and structurally simpler analog cryptophycin-24 (**2**, arenastatin A) was obtained from the marine sponge *Dysidea arenaria*[6] (Fig. 1). These compounds interact with tubulin in a vinca alkaloid-like fashion[7–11] and exhibit selective anticancer activity. Because of their interesting biological activity and challenging molecular structure, several total and partial syntheses of cryptophycins and their analogs have been reported.[4,12–26]



R = Me; X = Cl Cryptophycin-1 (**1**)
R = X = H Arenastatin A (Cryptophycin-24) (**2**)

Figure 1. Structures of cryptophycins.

Herein we wish to report the first RCM approach for the synthesis of cryptophycin-24 (**2**), featuring the introduction of the β-epoxide prior to macrolide formation.[27]

Earlier syntheses typically introduce the C13–C14 *trans*-olefin moiety in a Wittig-type reaction and use a macrolactamization or macrolactonization approach for the construction of the 16-membered ring system. Another strategic theme common to the majority of these syntheses has been the late-stage introduction of the epoxide pharmacophore using *m*-CPBA or dimethyl dioxirane, which produces a mixture of epoxide diastereomers and necessitates a chromatographic separation of the desired β-isomer. Three prior syntheses in which the epoxide moiety was introduced stereoselectively via diol formation have been reported.[13,16,23] These syntheses first constructed the cryptophycin macrocyclic skeleton in the presence of the diol and then formed the epoxide after macrocyclization.

Our retrosynthetic analysis, shown in Figure 2, demonstrates that cryptophycin-24 (**2**) could be synthesized from diene **3** using RCM conditions and that intermediate **3** could be assembled from epoxy alcohol **4** and acid **5**.

For the synthesis of the targeted epoxy olefin **4**, we chose to prepare the β-epoxide via the Sharpless asymmetric dihydroxylation reaction (Scheme 1).[16] Olefin **6**[15] furnished styrene **7** under standard Heck coupling conditions with iodobenzene and $Pd(OAc)_2$. When styrene **7**

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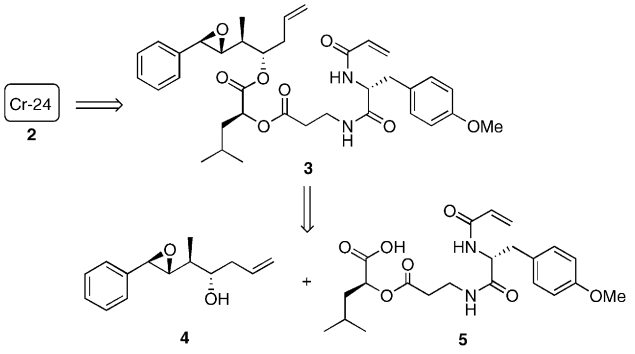
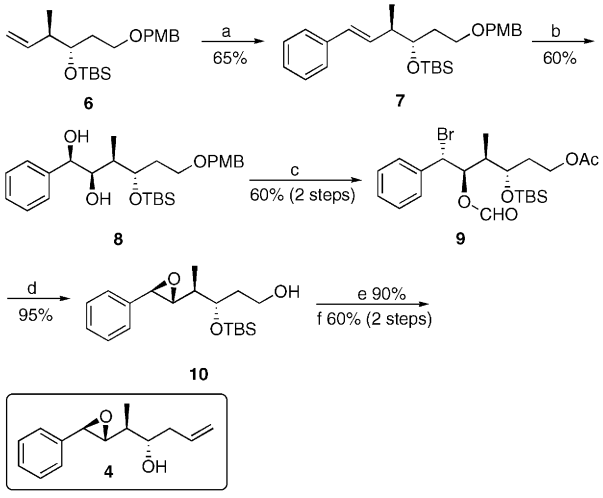
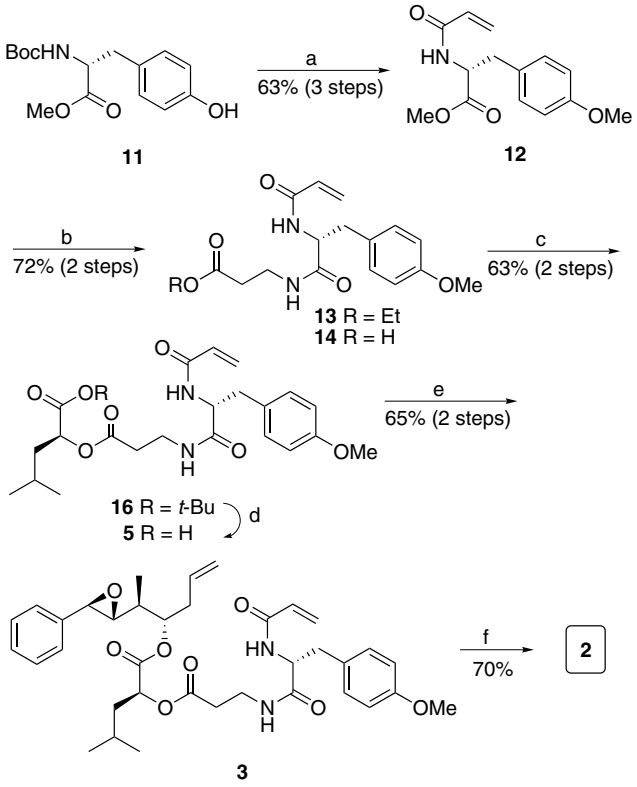


Figure 2. Retrosynthetic analysis for cryptophycin-24.



Scheme 1. Reagents and conditions: (a) $Pd(OAc)_2$, PhI, Et_3N, MeCN, reflux, 12 h; (b) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, rt, 24 h; (c) (i) $HC(OMe)_3$, cat. PPTS, CH_2Cl_2, rt, 3 h, (ii) AcBr, CH_2Cl_2, rt, 6 h; (d) K_2CO_3, THF/MeOH, 0 °C to rt, 8 h; (e) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 3 h; (f) (i) $Cp_2TiCH_2ClAlMe_2$, THF, 0 °C, 2 h, (ii) TBAF, rt, 6 h.



Scheme 2. Reagents and conditions: (a) (i) Me_2SO_4, K_2CO_3, acetone, reflux, 8 h, (ii) TFA, CH_2Cl_2, rt, 3 h, (iii) DIEA, acryloyl chloride, 0 °C, 2 h; (b) (i) LiOH, THF/MeOH/H_2O, rt, 3 h, (ii) EDCI, THF/DMF, HOBT, DMAP, rt, 2 h, β-alanine ethyl ester, rt, 16 h; (c) (i) LiOH, THF/MeOH/H_2O, rt, 3 h, (ii) EDCI, DMAP, rt, 2 h, then **15**, rt, 16 h; (d) TFA, CH_2Cl_2, rt, 5 h (**5** used in next step without purification); (e) 2,4,6-trichlorobenzoyl chloride, DIEA, DMAP, rt, 2 h, then **4**, rt, 16 h; (f) Grubbs 1 catalyst (10 mol%), CH_2Cl_2, reflux, 6 h.

was subjected to the Sharpless asymmetric dihydroxylation reaction in the presence of the $(DHQD)_2PHAL$ ligand, diol **8** was obtained in 60% yield with >95% diastereoselectivity (by NMR) favoring the desired β-isomer (Scheme 1).

Subsequent conversion of diol **8** to the corresponding cyclic orthoformate, followed by treatment with AcBr,[16] provided the bromoformate **9**, and included an unexpected simultaneous transformation of the OPMB group to the more labile OAc functionality. The epoxide ring closure and the acetate hydrolysis were achieved in a single step using K_2CO_3/THF–MeOH, which produced the epoxy alcohol **10**. Dess–Martin periodinane oxidation of alcohol **10**, followed by Tebbe olefination and subsequent TBS deprotection with TBAF, provided the crucial homoallylic alcohol **4**.[28]

The synthesis of the depsipeptide unit **5** was achieved in excellent yield following the sequence of straightforward and high yielding reactions described in Scheme 2. Methylation of the phenol group of commercially available (D)-*N*-Boc-tyrosine methyl ester **11**, followed by removal of the *N*-Boc protecting group (TFA), and subsequent amide formation with acryloyl chloride provided intermediate **12**. The methyl ester of **12** was hydrolyzed and coupled with β-alanine ethyl ester to yield amide **13**. Saponification of the ethyl ester of **13** and subsequent coupling of acid **14** with L-leucic acid *t*-butyl ester (**15**)[29] furnished the desired depsipeptide **16**. Removal of the *t*-butyl group of **16** with TFA and subsequent coupling of the acid **5** with alcohol **4** under Yamaguchi coupling conditions afforded the RCM precursor **3**. The final metathesis reaction of diene **3** with the Grubbs 1 catalyst[30] proceeded with exclusive formation of the *E*-isomer to provide **2** in good yield.[28,31]

In conclusion, a *trans*-selective RCM approach for the convergent and efficient synthesis of cryptophycin-24 (arenastatin A) has been achieved in the presence of the chemically reactive styrene epoxide moiety.

Acknowledgements

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