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# A Concise Synthesis of the Cytotoxic Depsipeptide Arenastatin A

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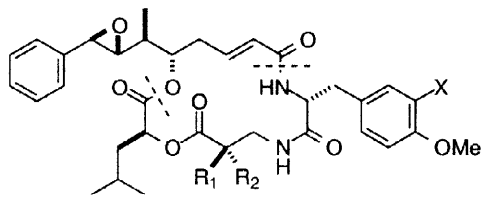
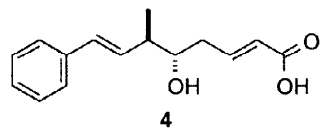
**Abstract:** Arenastatin A (**1**, cryptophycin 24) was synthesized by convergence of hydroxy ester **16** with amino acid derivative **27**; two independent and highly efficient routes to **16** are disclosed. 

Arenastatin A (**1**),[1] along with the closely related cryptophycins (e.g. **2**),[2] comprise a large family of cyclic and acyclic depsipeptides with potent cytotoxic activity. For example, **1** isolated from the Okinawan sponge *Dysidea arenaria* is reported to posses an $IC_{50}$ value of 5 pg/mL in KB cells.[1b] This level of bioactivity[3] combined with the scarcity of natural material has stimulated vigorous efforts towards synthesis of these natural products. To date, one total synthesis of **1** has been reported,[4] and several routes to members of the cryptophycin family and various analogues have appeared.[5] Among the latter is a synthesis by a group at Eli Lilly of the promising clinical candidate cryptophycin 52 (**3**).[6] We now describe a convergent synthesis of arenastatin A which makes this substance available in quantity for further evaluation as a potential candidate in cancer chemotherapy.

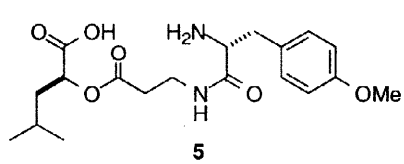
The strategy most frequently adopted for assembly of the macrocyclic framework of the cryptophycins has employed convergence of a hydroxy acid, e.g. **4**, with an amino acid, e.g. **5**, and our approach to **1** was designed along similar lines. Herein, we report two efficient routes to the "upper" portion **4** of arenastatin A, a pathway to the "lower" amino acid segment **5** of **1**, and their merger to afford the natural depsipeptide.



**1**, $R_1 = R_2 = X = H$ (Arenastatin A)
**2**, $R_1$ = Me, $R_2$ = H, X = Cl (Cryptophycin A)
**3**, $R_1=R_2$=Me, X=Cl (Cryptophycin 52)



**4**



**5**

Chelation-controlled addition of allyltri-*n*-butylstannane to (*R*)-aldehyde **6**[7] under Linderman's modification[8] of Keck's conditions[9] yielded *anti* homoallylic alcohol **7** (dr > 20:1).[10] Protection of **7** as its silyl ether **8** followed by Lemieux-Johnson oxidation gave **9**, and Wittig reaction of this aldehyde with

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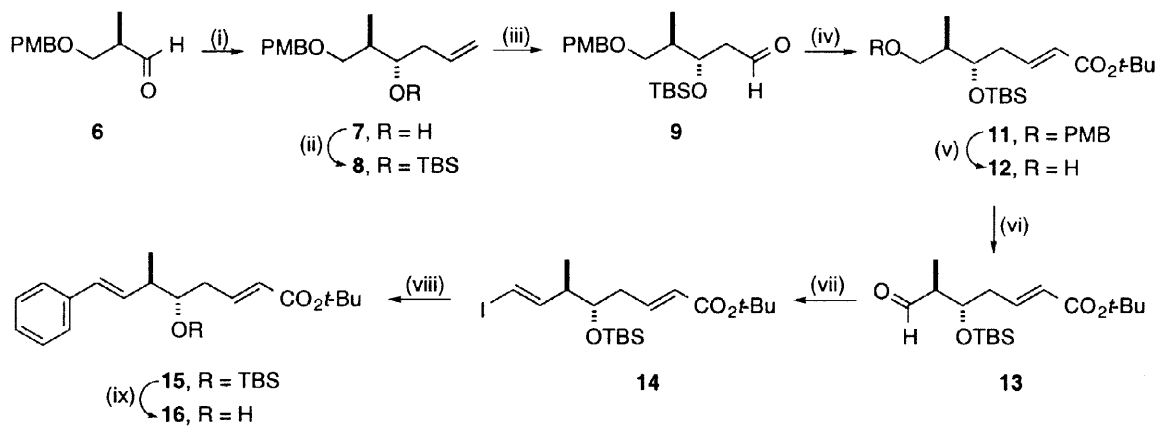
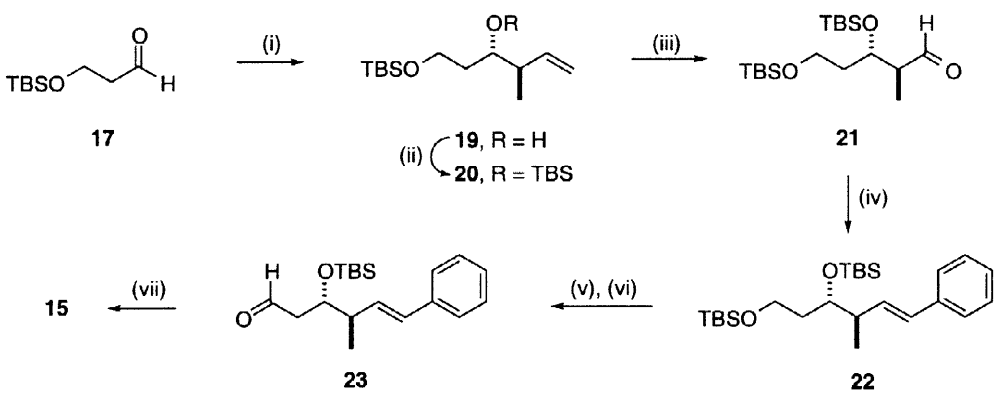
phosphorane **10** furnished α,β-unsaturated *t*-butyl ester **11**. After removal of the *p*-methoxybenzyl group, the resultant alcohol **12** was oxidized to aldehyde **13** which was subjected to a Takai reaction[11] with iodoform. The (*E*)-iodoalkene **14** was coupled in a Stille process[12] with phenyltrimethylstannane to afford **15**, from which the silyl ether was cleaved. This sequence produced hydroxy ester **16** in an overall 12% yield for the nine steps from **6**.



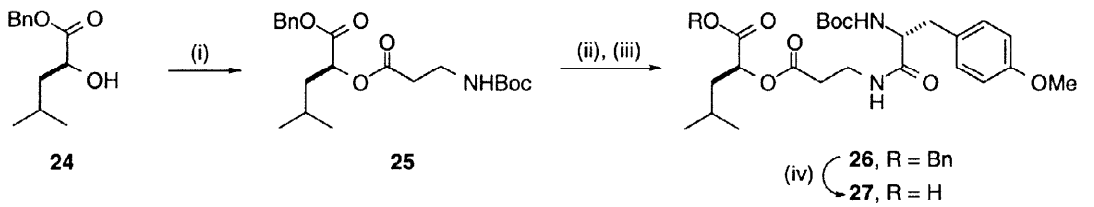

**Scheme 1**: (i) *n*-$Bu_3SnCH_2CH{=}CH_2$, $SnCl_4$, $CH_2Cl_2$, –100 °C, 76% (20:1); (ii) TBSCl, Imid, DMF, rt, 91%; (iii) $OsO_4$ (cat), $NaIO_4$, THF–$H_2O$ (76%); (iv) $Ph_3P{=}CHCO_2t$-Bu (**10**), $CH_2Cl_2$, rt, 95%; (v) DDQ, $CH_2Cl_2$–$H_2O$, 0 °C→ rt, 92%; (vi) Dess-Martin periodinane, $CH_2Cl_2$, 92%; (vii) $CHI_3$, $CrCl_2$, THF, 0 °C, 62%; (viii) $Me_3SnPh$, $PdCl_2(MeCN)_2$, DMF, rt, 67%; (ix) TBAF, THF, 75%.

A second, more efficient route to **16** began from the known aldehyde **17**,[13] which upon reaction with (*E*)-crotyldiisopinylcampheylborane prepared from the (+)-methoxyborane **18**[14] gave *anti* alcohol **19** (dr >50:1, er >12:1).[15] After protection, alkene **18** was ozonized, and the aldehyde **21** was condensed with the anion of benzyl diethyl phosphonate to provide styrene derivative **22**. Selective cleavage of the primary silyl ether was accomplished quantitatively, and Dess-Martin oxidation of the resulting alcohol yielded **23**. Wittig reaction of this aldehyde with **10** gave **15**, leading to an overall yield for **16** of 20% for the seven steps from **17**.




**Scheme 2**: (i) *trans* $CH_3CH{=}CHCH_3$, *t*-BuOK, *n*-BuLi, –75 °C → –45 °C, (+)-$(Ipc)_2BOMe$ (**18**), $BF_3.OEt_2$, –78 °C, then **17**, –78 °C → rt, 71%; (ii) TBSCl, Imid, DMF, rt, 93%; (iii) $O_3$, $CH_2Cl_2$, –78 °C, then $Me_2S$, –78 °C → rt, 62%; (iv) $PhCH_2P(O)(OEt)_2$, *n*-BuLi, THF, –78 °C → rt, 79%; (v) HF-pyr, THF, rt, 99%; (vi) Dess-Martin periodinane, $CH_2Cl_2$, rt, 98%; (vii) **10**, $CH_2Cl_2$, rt, 85%.

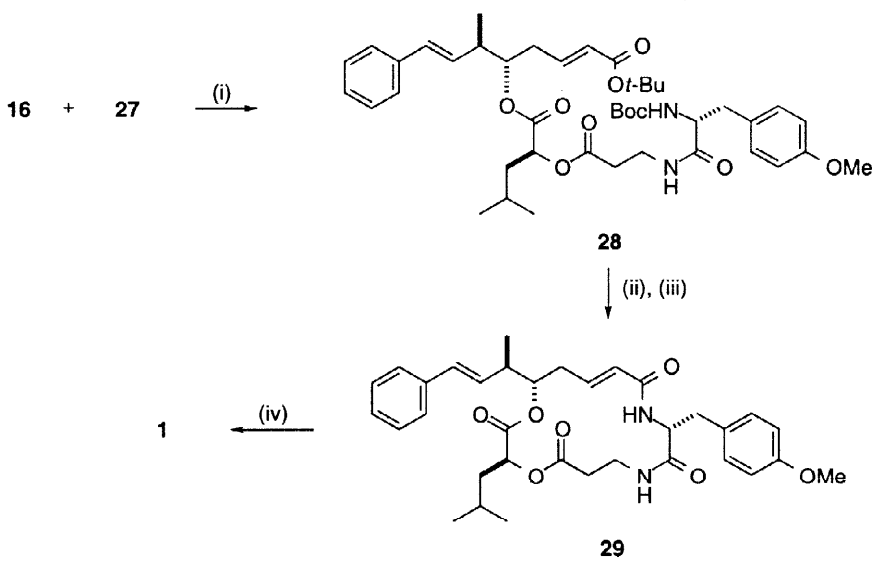
Synthesis of the lower segment of **1** began with esterification of benzyl (–)-2-hydroxyisocaproate (**24**) with Boc-protected β-alanine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and gave diester **25** in quantitative yield. The Boc group was removed and the resulting amine was condensed with N-Boc-O-methyl-*D*-tyrosine using 1-hydroxybenzotriazole (HOBT) and EDCI. Hydrogenolysis of the benzyl ester **26** over Pearlman's catalyst led to the amino acid derivative **27**.




**24** **25**

**Scheme 3**: (i) $HO_2CCH_2CH_2NHBoc$, EDCI, DMAP, 99%; (ii) TFA, $CH_2Cl_2$, 0 °C; (iii) (*R*)-*p*-$MeOC_6H_4CH_2CH(NHBoc)CO_2H$, EDCI, HOBT, $Et_3N$, 99%; (iv) $H_2$, $Pd(OH)_2$, EtOAc.

Coupling of **27** with hydroxy ester **16** was carried out in the presence of diisopropylcarbodiimide (DIC) and afforded **28** in high yield. After simultaneous removal of the Boc protecting group and *t*-butyl ester with trifluoroacetic acid, the amino acid was treated with diphenylphosphoryl azide (DPPA) to furnish desepoxyarenastatin A (**29**). Epoxidation of **29** with dimethyldioxirane, as described by Kobayashi,[4] led to arenastatin A (**1**), $[\alpha]_D^{23}$ + 48.7 (c 0.87, $CHCl_3$), and its epimeric epoxide in a 3:1 ratio, respectively. The two epoxides were separated by HPLC (ODS–AQ, MeOH–$H_2O$ 3:1), and the identity of **1** was confirmed by exact correspondence of its $^1H$ and $^{13}C$ NMR spectra with those of natural arenastatin A.




**Scheme 4**: (i) DIC, DMAP, $CH_2Cl_2$, rt, 93%; (ii) TFA, $CH_2Cl_2$, 0 °C; (iii) DPPA, $NaHCO_3$, DMF, 0 °C, 57% from **28**; (iv) $Me_2CO_2$,$CH_2Cl_2$, –30 °C, 24 h, dr 3:1, 80%.

In summary, we have developed a practical synthesis of arenastatin A which can be readily adapted to the preparation of related depsipeptides. Extension of this route to other cryptophycins as well as SAR studies of synthetic analogues will be described in due course.

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