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Total synthesis of cryptophycin-24 (arenastatin A) via Prins cyclization

J.S. Yadav [a,*], K.V. Purnima [a], B.V. Subba Reddy [a], K. Nagaiah [a], A.K. Ghamdi [b]

[a] CSIR, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Engineer Abdullah Baqshan for Bee Research, King Saudi University, Saudi Arabia

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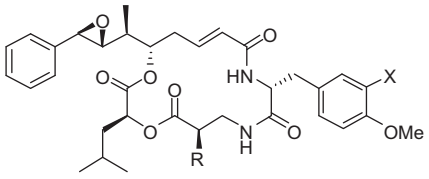
ABSTRACT

A stereoselective synthesis of fragment A of cryptophycin is achieved utilizing the versatile Prins cyclization. Subsequently, the total synthesis of cryptophycin-24 (arenastatin A) has been accomplished by coupling it with the depsipeptide subunit.

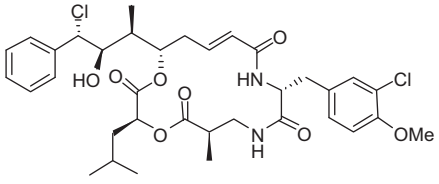
Cryptophycins were isolated by Schwartz and co-workers from *Nostoc* sp. strains ATCC 53789.[1] While these authors established their structures, details of absolute stereochemistry were not demonstrated. Subsequently, a variety of cytotoxins were isolated by Moore and co-worker from a crude lipophilic extract of *Nostoc* sp. GSV 224 and they established their absolute stereochemistry.[2a] Cryptophycins are cyclic depsipeptides and are remarkably potent against tumor cell lines.[2b]

Cryptophycin A (**1**) and B (**2**) exhibit cytotoxic IC_{50} values of 5 and 7 pg/mL, respectively, against KB cells. In 1994, arenastatin A (**3**) (renamed as cryptophycin-24), another member of the cryptophycin family, was isolated **3** by Kobayashi et al. from the Okinawa marine sponge *Dysidea arenaria*. It also exhibits cytotoxicity with IC_{50} value of 5 pg/mL against KB cells.[3] Moore and co-worker have discovered that the synthetically derived cryptophycin 8 (**4**) is more active in vivo than (**1**) (Fig. 1).[4]

Cryptophycin A (**1**) was found to be very active against the fungus *Cryptococcus*, which causes immunodeficiency.[2] The significant clinical potential of cryptophycins and their low natural abundance have made them attractive synthetic targets. Consequently, some reports on the total synthesis of cryptophycins following multi-step synthetic sequences have been published.[5–13] However; many of these syntheses employ asymmetric dihydroxylation as a key step to generate *syn*-diols. In view of their fascinating structures and biological activity, we were interested in the synthesis of cryptophycins using Prins cyclization as a key step for the synthesis of non-peptidic part.[14,15] We have explored the utility of Prins cyclization in the synthesis of various polyketide intermediates for the total synthesis of natural products[16] and report the total synthesis of cryptophycin-24. In our retrosynthetic analysis (Scheme 1), we envisaged that cryptophycin-24 could be divided into two parts, homoallyl alcohol with four stereogenic centers (Fragment A) and a peptidic subunit (Fragment B). It was proposed to obtain an *anti*-1,3-diol derivative from 2,4,5,6-tetrasubstituted tetrahydropyran **8**, which in turn could be obtained via the Prins cyclization of the homoallylic alcohol **9** with an aldehyde **10**. The synthesis of



cryptophycin A (**1**) X=Cl, R=CH_3
cryptophycin B (**2**) X=Cl, R=H
cryptophycin-24 (**3**) X=H, R=H



cryptophycin 8 (**4**)

Figure 1.

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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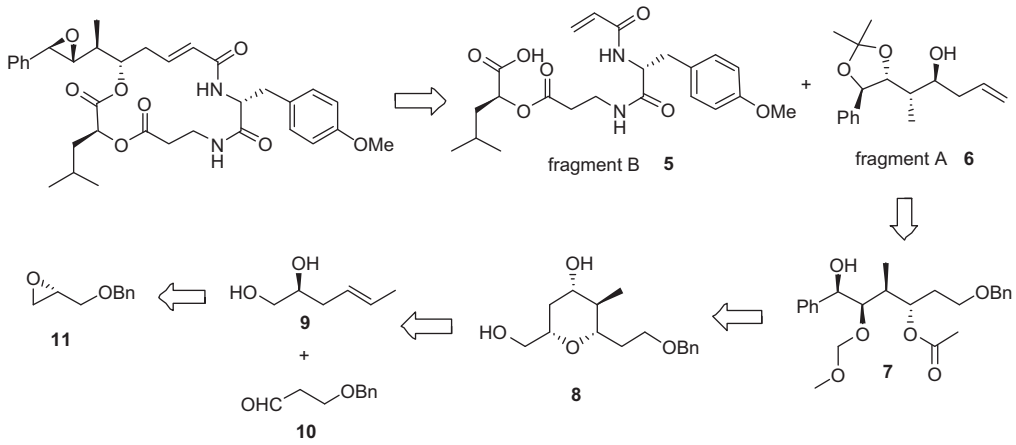


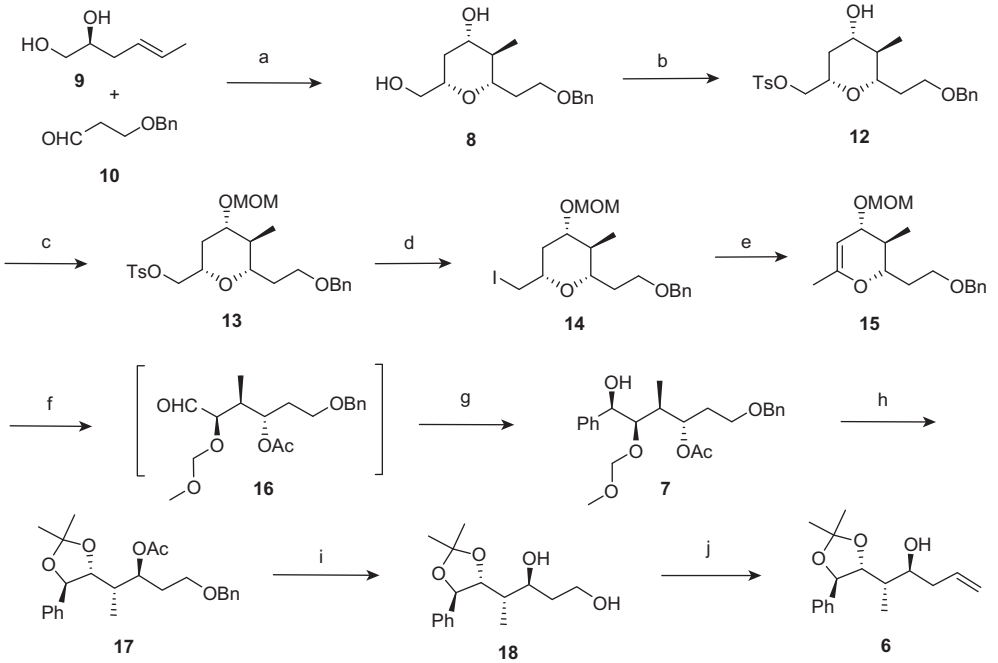
Scheme 1. Retrosynthetic analysis of cryptophycin-24 (arenastatin A) (**3**).

fragment A began with the homoallylic alcohol **9** which was prepared from (*S*)-benzyl glycidyl ether **11**.[17] Prins cyclization of **9** with aldehyde **10** in the presence of TFA (10 equiv) followed by hydrolysis of the resulting trifluoroacetate with K_2CO_3 in methanol gave 4-hydroxytetrahydropyran **8** with 94% de.

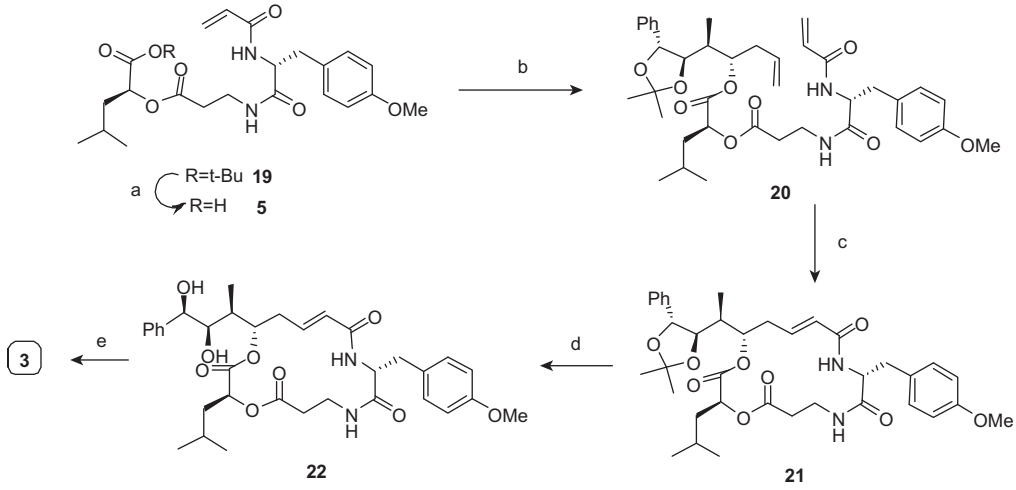
This was separated by column chromatography (Scheme 2). The stereochemistry was assumed to be in line with previous results.[16] It was later proved by the elaboration of compound **8** to the target fragment which was found to be identical to a sample reported earlier.[13] Chemoselective tosylation of primary alcohol **8** with 1.1 equiv of tosyl chloride in the presence of TEA in CH_2Cl_2 gave the corresponding tosylate **12** in 82% yield. MOM protection of the secondary alcohol in **12** with methoxymethyl chloride provided the corresponding MOM ether **13** in 76% yield. Treatment of tosylate **13** with NaI in refluxing acetone gave the respective iodide **14** in 86% yield, which on exposure to potassium *t*-butoxide[18] in THF and a subsequent rearrangement on silica gel gave the key intermediate **15** in 55% yield.[16d]

Ozonolysis of alkene **15** afforded the corresponding aldehyde **16**, which on treatment with phenylmagnesium bromide in the presence of magnesium bromide diethyl etherate in CH_2Cl_2 at −78 °C afforded *syn*-selective alcohol **7** in 72% overall yield with 94% de. The presence of $MgBr_2$ led to high *syn*-selectivity in phenyl Grignard reaction, while in the absence of $MgBr_2$ an inseparable mixture of diastereomers was obtained in a 1:1 ratio.[19] The MOM group in **7** was deprotected using *p*-TSA in methanol to furnish the corresponding diol in 65% yield, which in turn was protected as its acetonide **17** by treatment with 1,2-dimethoxypropane in the presence of catalytic amounts of PPTS in 92% yield. The acetate **17** was hydrolyzed with K_2CO_3 in methanol to yield an alcohol.

This was subsequently debenzylated with Pd/C under H_2 atmosphere in methanol to furnish diol **18** in 82% yield. Oxidation of primary hydroxyl group in **18** using TEMPO and BAIB in CH_2Cl_2 followed by Wittig olefination of the resulting aldehyde with an excess C-1 ylide generated in situ by the reaction of ICH_3PPh_3 with



Scheme 2. Synthesis of **6**. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, 0 °C to rt, 4 h; (ii) K_2CO_3, MeOH, rt, 2 h, 65% over two steps; (b) *p*-TSCl, CH_2Cl_2, TEA, 0 °C to rt, 8 h, 82%; (c) MOM-Cl, CH_2Cl_2, DIPEA, 0 °C to rt, 6 h, 76%; (d) NaI, acetone, reflux, 24 h, 86%; (e) *t*-BuOK, THF, 0 °C, 30 min, silica gel promoted rearrangement, 55%; (f) O_3, CH_2Cl_2, −78 °C, 15 min; (g) PhMgBr in Et_2O, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 45 min, 72% over two steps; (h) (i) *p*-TSA, MeOH, reflux, 6 h, 65%; (ii) 2,2-DMP, PPTS, rt, 3 h, 92%; (i) (i) K_2CO_3, MeOH, rt, 2 h, quant; (ii) 5% Pd/C, MeOH, H_2, 3 h, 82%; (j) (i) TEMPO, BAIB, CH_2Cl_2, rt, 1 h; (ii) ICH_3PPh_3, *t*-BuOK, THF, 0 °C to rt, 4 h, 76% from **18**.



Scheme 3. Synthesis of **3**. Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 4 h, quant; (b) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, 0 °C to rt, 2 h, then **6**, DMAP, rt, 18 h, 80% from **19**; (c) Grubbs' II catalyst (10 mol %), CH_2Cl_2, reflux, 2 h, 75%; (d) TFA, CH_2Cl_2, 0 °C to rt, 4 h, 80%; (e) (i) $(MeO)_3CH$, PPTS, CH_2Cl_2, rt, 1 h; (ii) AcBr, CH_2Cl_2, rt, 2 h; (iii) $KHCO_3$, DME/EtOH/MeOH (6:4:1), 40 °C, 6 h, 65% from **22**.

potassium *t*-butoxide gave the target fragment A of cryptophycin-24 **6** in 76% yield. The data of a target fragment A of cryptophycin-24 were identical in all respects to that reported in literature.[13]

The depsipeptide subunit (Fragment B) was constructed from D-*N*-Boc-tyrosine methyl ester, β-alanine, and L-leucic acid *t*-butyl ester.[7d] The *t*-butyl group of **19** was removed with TFA and the resulting acid **5** was coupled with alcohol **6** under Yamaguchi conditions to afford the compound **20** in 80% overall yield.[7d] The diene **20** was subjected to Grubbs' second generation catalyst in CH_2Cl_2 under reflux conditions to afford the RCM product **21** in 75% yield (Scheme 3).[11] The compound **21** was subjected to TFA in CH_2Cl_2 to afford diol **22** (80%). The *syn*-diol **22** was then converted into the epoxide in three sequential steps in 65% yield. Initially, the diol was treated with trimethylorthoformate in the presence of PPTS in CH_2Cl_2, followed by acetyl bromide to produce the anticipated bromohydrin formate, which was taken for the next step without purification. The formation of the desired epoxide was achieved using solid $KHCO_3$ in a mixture of DME/ethanol/methanol (6:4:1) at 40 °C for 6 h.[11] The data of the target molecule **3**, cryptophycin-24 (arenastatin A) were identical in all respects to that reported in.[4]

In conclusion, we have proved the versatility of the Prins cyclization in natural product synthesis by achieving the stereoselective synthesis of cryptophycin-24 (arenastatin A). Further applications of the Prins cyclization in the synthesis of natural products are in progress.

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