ORGANIC LETTERS

2006
Vol. 8, No. 14
2993−2996

Total Synthesis of Cryptophycin Analogues via a Scaffold Approach

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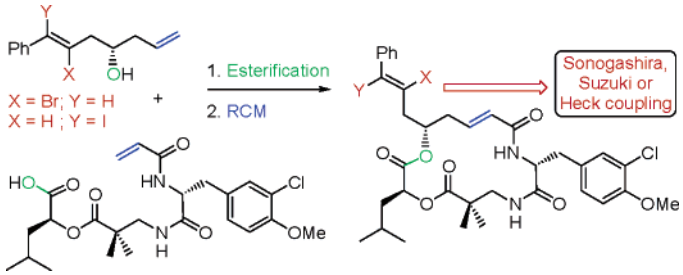
Received April 18, 2006

ABSTRACT



Allylation of in situ generated β,γ-unsaturated aldehydes affords rapid access to vinyl halide analogues of fragment A of the cryptophycins. Three scaffolds are prepared in gram quantities by a ring-closing metathesis approach. Derivatization via a variety of cross-coupling protocols is possible, which affords novel analogues of these potent antimitotic agents.

Antimitotic agents[1] display remarkable structural variety and are arguably the most useful class of pharmaceuticals for the chemotherapeutic treatment of a variety of cancers.[2] Within this group of molecules, the cryptophycin depsipeptides[3] (Figure 1) are among the most potent thus far described, operating at picomolar concentrations, and 40- to 400-fold more active than paclitaxel[4] or vinblastine[5] in several tumor cell lines.[6] Of additional import is a reduced susceptibility to Pgp (P-glycoprotein)[7] mediated multiple drug resistance (MDR) relative to other anticancer agents.[8] The low abundance of the cryptophycins combined with extraordinary clinical potential[9] and their modular nature has made them an ideal target for total synthesis.[10]

Allylation of β,γ-unsaturated aldehydes generated by the treatment of 2-vinyloxiranes (e.g., **8** and **9**, Figure 2) with a Lewis acid[11] affords the basic core structure of fragment A [(*S*)-**6** or (*S*)-**7**] of the cryptophycins. In particular, we were interested in substrates that contained functionality that could

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(9) (a) Liang, J.; Moore, R. E.; Moher, E. D.; Munroe, J. E.; Al-awar, R. S.; Hay, D. A.; Varie, D. L.; Zhang, T. Y.; Aikins, J. A.; Martinelli, M. J.; Shih, C.; Ray, J. E.; Gibson, L. L.; Vasudevan, V. Polin, L.; White, K.; Kushner, J.; Simpson, C.; Pugh, S.; Corbett, T. H. *Invest. New Drugs* **2005**, *23*, 213. (b) Drew, L.; Fine, R. L.; Do, T. N.; Douglas, G. P.; Petrylak, D. P. *Clin. Cancer Res.* **2002**, *8*, 3922.

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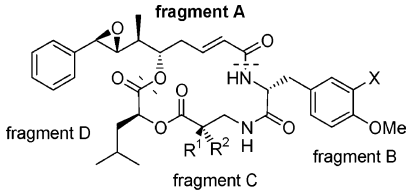
10.1021/ol0609356 CCC: $33.50
Published on Web 06/16/2006



1 cryptophycin 1 (R^1 = Me, R^2 = H, X = Cl)
2 cryptophycin 52 (R^1 = R^2 = Me, X = Cl)
3 arenastatin A (R^1 = R^2 = H, X = H)

Figure 1. Various cryptophycin structures.

be readily derivatized (e.g., scaffolds **4** or **5**) via a variety of metal cross-coupling reactions.[12] Functionalization would allow for the synthesis of a wide variety of analogues that have not previously been prepared. As evidenced by the structural diversity of other antimitotic agents that are accommodated by the active site of β-tubulin,[13] it may be possible to discover new pharmacologically active compounds based on substitution on this olefin.

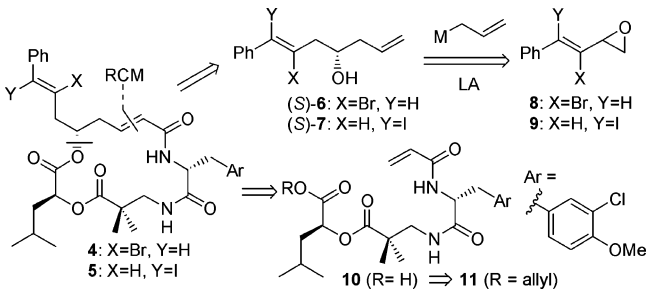


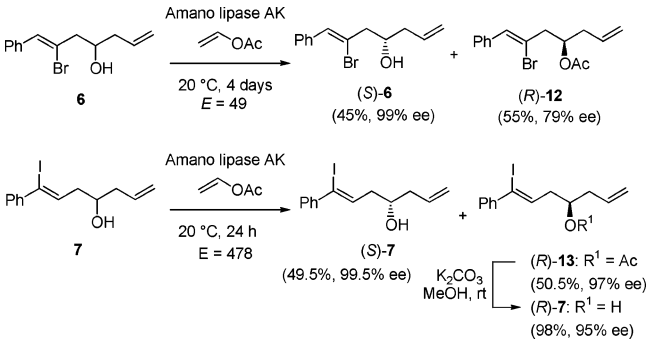
Figure 2. Retrosynthetic analysis of the cryptophycin scaffolds.

Based on our recent study[14] concerning the selective terminal homologation of bishomoallylic alcohols and a precedent established by Georg,[10(b)] our strategy involves ring-closing metathesis (RCM) as the final step for scaffold formation, following esterification of the depsipeptide fragment **11** with the appropriate bishomoallylic alcohol (**6** or **7**, Figure 2).

The depsipeptide portion (**11**) was prepared by known literature procedures or slight modifications thereof.[15] To prepare enantiomerically pure vinyl halide bishomoallylic alcohols (**6** and **7**), we decided to employ enzymatic resolution[16] of racemic bishomoallylic alcohols to gain ready access to both antipodes of the desired products. Lipases have been widely employed for this purpose, and from the list of available alternatives we selected Amano lipase AK on the basis of its commercial availability and success in similar systems.[17]

With some optimization,[18] we were pleased to find that after 4 days at room temperature, the fully resolved alcohol (*S*)-**6**[19] and the optically enriched acetate (*R*)-**12**[20] were recovered (Scheme 1).[21]

Scheme 1



The resolution of the vinylic iodide (**7**) under the same conditions gave both the resolved alcohol (*S*)-**7**[22] and acetate (*R*)-**13** in near perfect ee (E = 478). The enantiomerically enriched acetate was hydrolyzed to (*R*)-**7** without a significant loss of optical purity. With suitable substrates now in hand ((*S*)-**6**, (*S*)-**7**, and (*R*)-**7**) we began construction of the macrocylic cryptophycin scaffolds.

Purification of the free acid coupling partner (**10**, Figure 2) was both ineffective and difficult; moreover we were concerned about its stability to storage. Consequently, we investigated a one-pot procedure for the synthesis of **17** from the allyl-protected depsipetide (**11**, Scheme 2).[23] Palladium-catalyzed deallylation of **11**, followed by esterification with (*S*)-**6** under Yamaguchi conditions afforded the macrocyclic precursor (**17**) in excellent yield. Esterification of (*S*)-**7** and (*R*)-**7** under identical conditions afforded **18** and ***epi*-18** respectively in comparable yields. The macrocycle (**4**) was

(11) (a) Lautens, M.; Maddess, M. L.; Sauer, E. L.; Ouellet, S. G. *Org. Lett.* **2002,** *4*, 83. (b) Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079.
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(15) See Supporting Information for details.
(16) For reviews, see: (a) Roberts, S. M. In *Preparative Biotransformations*; Wiley: Chichester, 1992−1997. (b) Faber, K. In *Biotransformations in Organic Chemistry*, 3rd ed.; Springer: Weinheim, 1997. (c) Wong, C.-H.; Whitesides, G. M. In *Enzymes in Synthetic Organic Chemistry*; Elsevier Science: New York, 1994.
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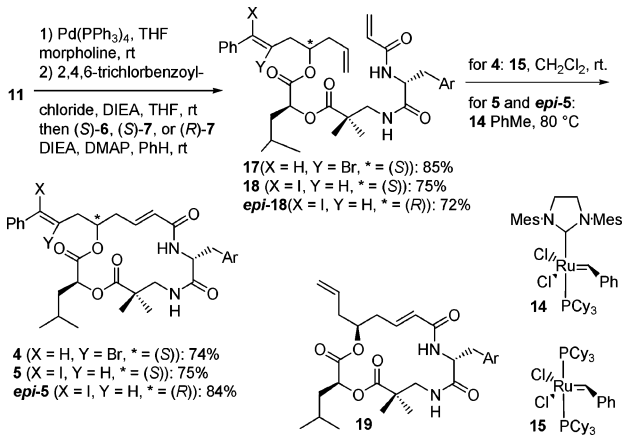
(18) We first subjected the corresponding homoallylic homopropargylic alcohol to the resolution conditions of Taber (3 mass equiv AK, 60 °C, neat vinyl acetate) and observed that regardless of conversion, both the acetate and unreacted alcohol were racemic.
(19) Stereochemistry was confirmed by comparison of HPLC traces of this alcohol and of the identical substrate prepared previously. See ref 11a
(20) Currently, this acetate is not of sufficient optical purity to be useful in the preparation of cryptophycin analogues. We are investigating solutions to this problem.
(21) Calculated according to: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Shi, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(22) Absolute stereochemistry was proven by X-ray analysis of **22**.
(23) For details on the synthesis of **11**, see Supporting Information.

Scheme 2

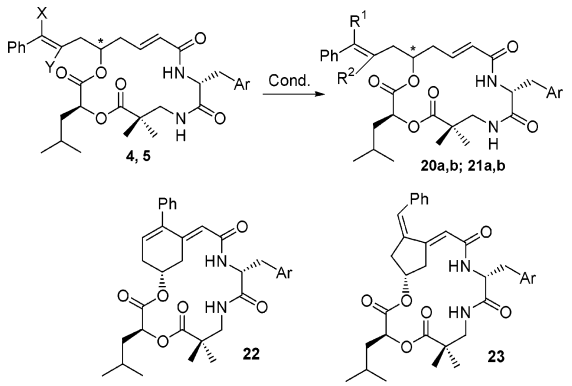


smoothly formed under treatment with Grubbs' second generation catalyst (**14**) in CH_2Cl_2 (0.014 M) at room temperature (Scheme 2). Attempted ring-closure of ***epi*-18** under the same conditions was very sluggish and required more forcing conditions. Moreover, along with the formation of the desired product (***epi*-5**) a second macrocylic compound was isolated that appears to be the terminal olefin **19**.[24]

Fortunately, use of the less active catalyst (**15**) suppressed the pathway leading to **19** and provided the desired macrocycle (***epi*-5**) in good yield. The latter method was used for the preparation of the third cryptophycin scaffold (**5**), which proceeded without incident and in good yield. With gram quantities of the three macrocylic scaffolds (**4**, **5**, and ***epi*-5**) in hand, we initiated preliminary investigations directed toward derivatization of the vinylic halides, Table 1.

Sonogashira[25] coupling of **4** with phenyl acetylene gave the cross-coupled product **20a** in good yield. The vinyl iodide substrates (**5** and ***epi*-5**) were notably more reactive, affording **21a** and ***epi*-21a**, respectively, in improved yield under milder reaction conditions. We have also demonstrated examples of Suzuki−Miyaura[26] reactions on all three scaffolds (**4**, **5**, and ***epi*-5**) with phenylboronic acid and CsF that afforded analogues **20b**, **21b**, and ***epi*-21b**, respectively, in high yield. We were surprised to find that in the case of **5**, when the base is changed to K_2CO_3, no coupling product was observed, but rather the intramolecular Heck product **22** was isolated in good yield. Similarly, attempted Stille coupling of **4** with tributylphenyltin gave the isomeric product **23**. For the former product (**22**) a crystal structure has been obtained that confirms both the structure and relative stereochemistry about the macrocycle (Figure 3).[27]

Table 1. Cryptophycin Scaffold Coupling Reactions



4/5	conditions[a]	R^1	R^2	config (*)	product (yield, %)
4	a	H	CCPh	(*S*)	**20a** (69)
4	b	H	Ph	(*S*)	**20b** (77)
4	c				**23** (84)
5	a	CCPh	H	(*S*)	**21a** (98)
5	b	Ph	H	(*S*)	**21b** (80)
5	d				**22** (85)
***epi*-5**	a	CCPh	H	(*R*)	***epi*−21a** (97)
***epi*-5**	b	Ph	H	(*R*)	***epi*−21b** (87)

[a] (a) Phenylacetylene, $Pd(PPh_3)_4$, CuI, dioxane, 80 °C; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, CsF, dioxane, 80 °C; (c) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 80 °C; (d) $PhSnBu_3$, $Pd(PPh_3)_4$, dioxane, 80 °C.

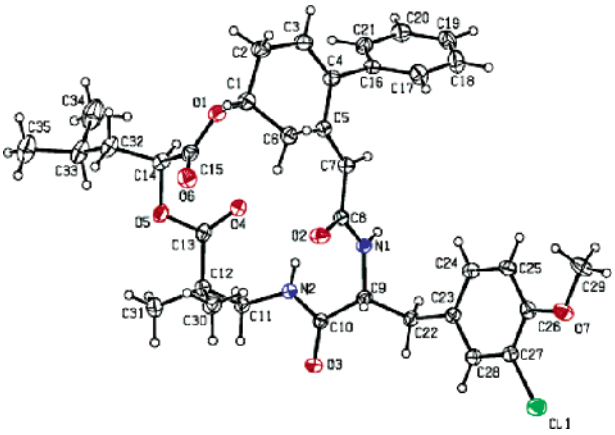


Figure 3. Crystal structure of **22**.

Finally, we have initiated investigations aimed at the installation of the epoxide moiety upon the trisubstituted

(24) This product was a single disasteromer, suggesting it was not formed by RCM with the internal olefin, followed by ROM/RCM to form the macrocycle.

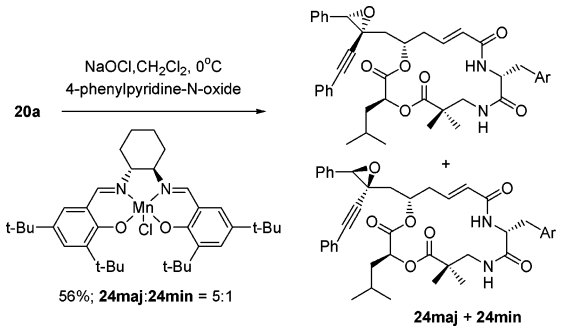
(25) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(26) (a) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(27) Colorless needles, dimensions 0.30 × 0.16 × 0.15 mm^3, orthorhombic, P 21 21 21, a = 10.4580(3), b = 17.8240(5), c = 21.1220(7) Å, α = 90°, β = 90°, γ = 90°, V = 3937.2(2) $Å^3$, ρ = 1.248 g cm^{-3}, T = 150(2) K, θ_{max} = 27.49°, Nonius Kappa-CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Of 28907 reflections collected, 8968 were independent (R_{int} = 0.0665). The data frames were integrated and scaled using the Denzo-SMN package (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326.). Solution and refinement with SHELXTL V6.12 (G. M. Sheldrick, SHELXTL-Windows NT. V6.12, Bruker Analytical X-ray Systems Inc., Madison, WI, 2001), non-hydrogen atoms were refined with anisotropic parameters, hydrogen atoms were refined on calculated positions using a riding model, goodness of fit 1.038, R1 = 0.0479, wR2 = 0.0953, residual electron density 0.217 to −0.289 e $Å^{-3}$. CCDC-288364 (**22**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

olefins. For example, treatment of **20a** (Scheme 3) under

Scheme 3



Jacobsen's conditions[28] afforded the epoxides **24** and **25** in moderate yield and with good diastereoselectivity.[29] Further screening of epoxidation conditions is currently underway.

In summary, we have demonstrated that products arising from the rearrangement/allylation of 2-vinyloxiranes are efficiently converted to derivatizable des-epoxy cryptophycin analogues. Three scaffolds have been constructed in two steps from enzymatically resolved bishomoallylic alcohols, and we have demonstrated that the vinyl halide they contain is convertible to a variety of C−C bonds via cross-coupling protocols. On the basis of these findings, we are currently studying the selective introduction of the epoxide moiety and building a library of compounds for biological testing.

Acknowledgment. We thank Merck Frosst Canada and NSERC (Canada) for an Industrial Research Chair and the University of Toronto for financial support of this work. We also thank Dr. Alan Lough for X-ray structure determination. M.M. thanks NSERC (Canada) for financial support in the form of a postgraduate fellowship.

Supporting Information Available: Crystallographic data in CIF format, full experimental details, and characterization, including ^{1}H and ^{13}C NMR spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0609356

(28) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.

(29) The configurations at the epoxide functionalities for **24maj** and **24min** have not yet been established.