ORGANIC LETTERS

2007
Vol. 9, No. 5
817−819

Short and Efficient Synthesis of Cryptophycin Unit A

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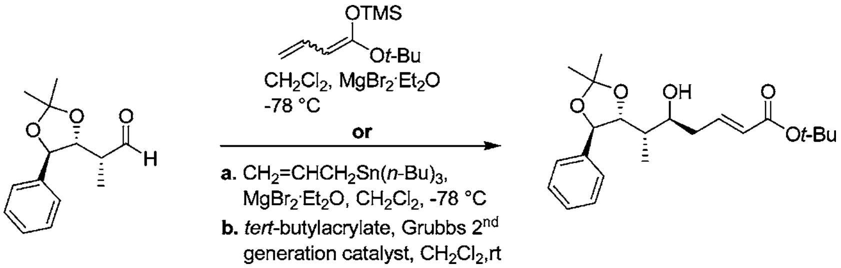
Received December 15, 2006

ABSTRACT

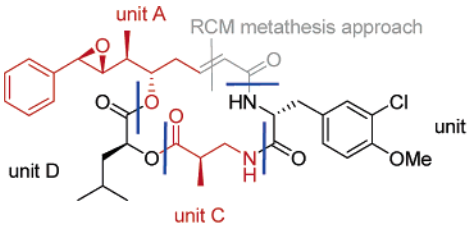


Two short synthetic approaches toward cryptophycin unit A comprise a catalytic asymmetric dihydroxylation as the sole source of chirality, while all further stereogenic centers are introduced under substrate control. The key step of the first route is a vinylogous Mukaiyama aldol addition, which introduces the α,β-unsaturated ester moiety with defined configuration at the δ-carbon atom. Likewise, allylation with allyltributylstannane diastereoselectively gives the homoallylic alcohol that can be converted by a metathesis reaction to a unit A precursor.

Cryptophycins are a class of 16-membered macrocyclic depsipeptides. The first representative, cryptophycin-1, was isolated more than 15 years ago by Schwartz et al. at Merck from the cyanophyte *Nostoc* sp. ATCC 53789[1] and later by Moore et al. from *Nostoc* sp. GSV 224, who made a first proposal regarding the stereochemistry in 1994.[2] At the same time, Kobayashi et al. reported on the isolation of the close analogue arenastatin A (later renamed cryptophycin-24) from the marine sponge *Dysidea arenaria*, providing the absolute configuration and a first total synthesis.[3]

Cryptophycin-1 and related cryptophycins display tumor-selective cytotoxicity even against multidrug-resistant cell lines. Many syntheses of naturally occurring cryptophycins and analogues have been published since then, providing detailed insight into the structure−activity relationship of cryptophycins.[4]

Retrosynthetic disconnection at the depsipeptide ester and amide bonds of cryptophycin-1 leads to four building blocks corresponding to units A−D (Figure 1): unit A is a structurally unique δ-hydroxy acid with four stereogenic



cryptophycin-1

Figure 1. Retrosynthetic disconnection of cryptophycin-1 leading to the four building block units A, B, C, and D.

[†] Organic and Bioorganic Chemistry.

[‡] Inorganic Chemistry.

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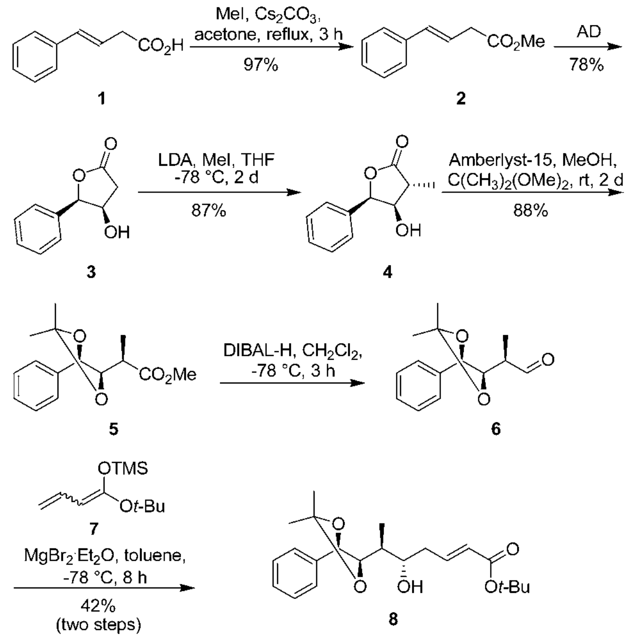
10.1021/ol063032l CCC: $37.00 © 2007 American Chemical Society
Published on Web 02/07/2007

centers; unit B is a D-tyrosine-derived α-amino acid; unit C is a *β*-alanine derivative, and unit D is L-leucic acid. Usually, the individual building blocks are synthesized as protected precursors which are sequentially coupled to give an acyclic depsipeptide and then cyclized. Ring closure can be effected by either macrolactamization or ring-closing metathesis (RCM) as pioneered by Georg and Tripathy in 2004.[5] The RCM strategy tolerates the highly sensitive benzylic epoxide function. However, the epoxide is usually introduced at the end of the synthesis. In most recent syntheses, the configuration of the future epoxide is preformed as a *syn*-diol, which is later converted into the epoxide according to Sharpless' protocol,[6] which was adapted for base-sensitive substrates by Moher[7] and co-workers and introduced into cryptophycin synthesis by Leahy and Gardinier in 1997.[8]

Moher and co-workers were the first to establish the stereochemistry of the *syn*-diol by an asymmetric dihydroxylation (AD), though at the *seco*-cryptophycin stage after introduction of all other stereogenic centers.[7] We recently reported on a stereodivergent 13-step synthesis of a unit A precursor relying on an asymmetric dihydroxylation as the sole source of chirality and subsequent diastereoselective reactions.[9]

The unit A synthesis discussed in the following obeys the same principle but features a different set of disconnections. The key step is the conversion of intermediate **6** to unit A precursor **8** (Scheme 1). A similar approach was followed by Sih and co-workers to a simpler unit A precursor with only two stereogenic centers, but introduction of the α,*β*-unsaturated ester moiety by a Reformatsky-type reaction with *tert*-butyl 4-bromocrotonate and a Pb/Zn couple proceeded without satisfactory regio- and diastereoselectivity.[10] In contrast to the Reformatsky reaction, vinylogous Mukaiyama aldol additions with silylketene acetals[11] proceed with regioselective attack of the *γ*-carbon atom, a method recently applied by Kalesse and co-workers to the total synthesis of ratjadone.[12]

Scheme 1. Unit A Precursor Synthesis



Our synthesis starts with (*E*)-4-phenylbut-3-enoic acid **1**, which was converted to methyl ester **2** by treatment with cesium carbonate and methyl iodide in 97% yield. Methyl ester **2** could also be obtained from phenylacetaldehyde by a modified Knoevenagel condensation in 58% yield.[13] The previously described asymmetric dihydroxylation of **2** under concomitant lactonization[14] gave *β*-hydroxylactone **3** in 78% yield after purification by crystallization and chromatography of the residue. α-Methylation of the dianion derived from **3** with LDA/methyl iodide occurred without any O-methylation and with complete diastereoselectivity according to the ^1H NMR spectrum of the crude product. After purification by chromatography, lactone **4** was obtained in 87% yield. Georg and co-workers used a Fráter alkylation to introduce the *δ*-methyl substituent in a unit A synthesis before,[15] though with an acyclic substrate. In the case of lactone **4**, however, α-methylation occurs diastereoselectively in the absence of the *β*-hydroxyl substituent as well, as was demonstrated in the unit A synthesis of Ghosh and Swanson.[16] Both protection of the diol as acetonide and esterification to methyl ester **5** were effected by treatment with 2,2-dimethoxypropane, methanol, and Amberlyst-15 at room temperature in 88% yield.[17] Selective reduction of methyl ester **5** with diisobutylaluminum hydride gave aldehyde **6** in virtually quantitative yield. Aldehyde **6** was used without prior purification, though flash chromatography was possible without epimerization.

The magnesium bromide diethyl etherate mediated vinylogous Mukaiyama aldol addition of (*E*,*Z*)-(1-*tert*-butoxybuta-1,3-dienyloxy)trimethylsilane **7**[18] to aldehyde **6** gave unit A precursor **8**[9] in 42% yield and 95% de. The relative configuration of **8** was proven by X-ray crystal structure analysis (Figure 2). Because the enantioselectivity of the asymmetric dihydroxylation[14,17] is known, there is no doubt regarding the absolute configuration of **8** as well.

The aldol addition step gave only a moderate yield and was inconvenient insofar as the synthesis of silyl keteneacetal

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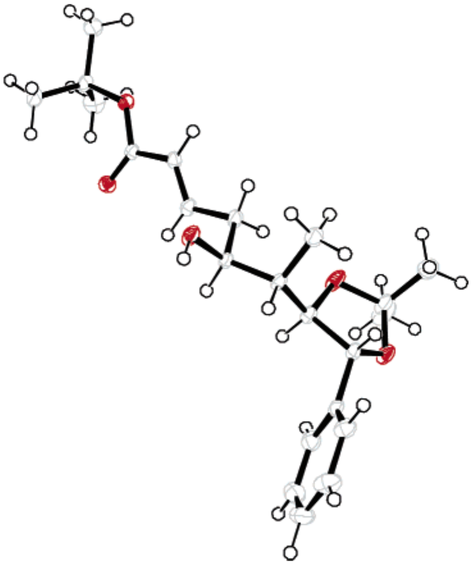
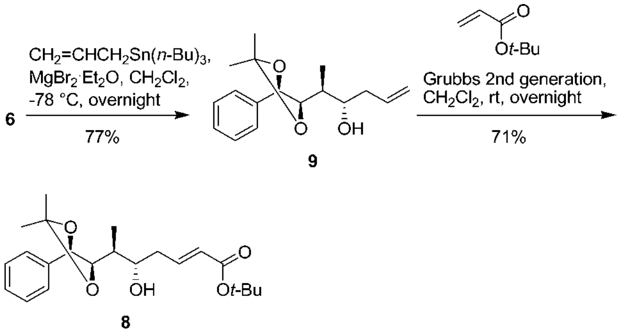


Figure 2. X-ray structure of unit A precursor **8** after crystallization from *n*-hexane.

7 requires the addition of hexamethylphosphoric triamide.[18] Alternatively, we investigated the allylation of aldehyde **6** with allyltributylstannane, which gave homoallylic alcohol **9** in 76% yield and 98% de (Scheme 2). Although **9** is a potential unit A precursor for RCM,[5] we used a metathesis reaction with *tert*-butylacrylate and Grubbs' second-generation catalyst to prepare unit A precursor **8** in 71% yield, which confirmed the anticipated diastereoselectivity of the allylation step.

In summary, two syntheses of cryptophycin unit A precursor **8** were developed, providing the compound in 24% and 32% yield over six and seven steps, respectively. Though the synthesis outlined in Scheme 1 is the shortest one of a unit A precursor with four stereogenic centers so far, the overall yield is limited by the moderate efficiency of the Mukaiyama aldol addition step. In contrast, the almost equally short allylation/metathesis approach outlined in Scheme 2 is one of the most efficient syntheses. Nevertheless, an RCM approach starting from intermediate **9** (45% overall yield) seems even more promising.

Scheme 2. Metathesis Approach from Aldehyde **6**



Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for financial support.

Supporting Information Available: Synthetic procedures and full spectroscopic data for compounds **2**−**6**, **8**, and **9** and the complete crystal data for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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