Beilstein Journal of Organic Chemistry

# A two step synthesis of a key unit B precursor of cryptophycins by asymmetric hydrogenation

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Full Research Paper

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Keywords:
amino acid; asymmetric hydrogenation; cryptophycin; DuPhos

*Beilstein J. Org. Chem.* **2011,** *7,* 243–245.
doi:10.3762/bjoc.7.32

Received: 02 November 2010
Accepted: 27 January 2011
Published: 22 February 2011

Editor-in-Chief: J. Clayden

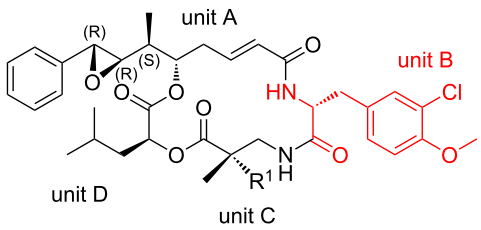


## Abstract

A novel highly enantioselective two step access to a unit B precursor of cryptophycins in good yields from commercially available starting materials has been developed. The key step is an asymmetric hydrogenation using the commercially available [(COD)Rh-(*R*,*R*)-Et-DuPhos]$BF_4$ catalyst. The synthetic route provides the advantage of less synthetic steps, proceeds with high yields and enantioselectivity, and avoids hazardous reaction conditions.

## Introduction

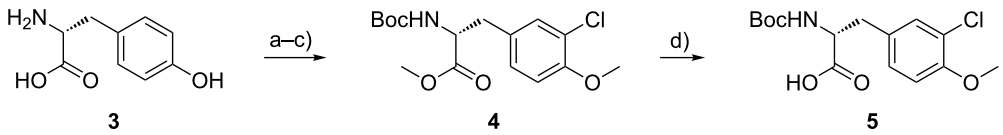
Cryptophycins are macrocyclic depsipeptides, which show very high cytotoxicity even against multidrug-resistant cell lines. They inhibit mitosis of eukaryotic cells by interacting with the β-subunit of α/β-tubulin heterodimers. Numerous natural and artificial analogs have been analysed in structure–activity relationship (SAR) studies. The unit B of cryptophycins contains a considerably modified D-tyrosine derivative (Figure 1). Substituent variations at unit B are not well tolerated. Both the methoxy and the chloro substituent are required for full biological activity [1-4].




$R^1$ = H: cryptophycin-1 (**1**)
$R^1$ = Me: cryptophycin-52 (**2**)

**Figure 1:** The four building blocks (units) A–D of cryptophycin-1 (**1**) and cryptophycin-52 (**2**).

The previously published synthetic route to unit B precursor **4** involves a three-step modification of D-tyrosine by chlorina-



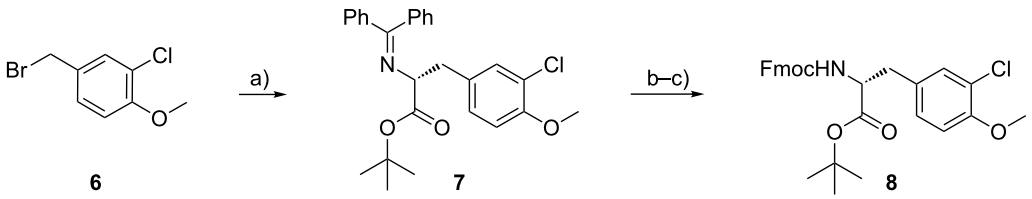

**Scheme 1:** Synthesis of the unit B precursor from D-tyrosine (**3**). Reagents and conditions [7]: a) $SO_2Cl_2$, AcOH, rt, 90 min, (75%); b) $Boc_2O$, NaOH, *t*-BuOH/$H_2O$, rt, 16 h (quant.) c) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 4 h (99%); d) LiOH, $H_2O$/THF/MeOH, rt, 1 h (93%).

tion, protecting group introduction and double methylation followed by a final saponification reaction to give carboxylic acid **5** (Scheme 1). A number of experimental procedures for this route have been published [5-7]. The selective monochlorination of D-tyrosine is quite cumbersome since the formation of the dichlorinated product must be minimized and the presence of unreacted D-tyrosine after the reaction must be completely avoided. The dichlorinated by-product has to be separated by column chromatography when purifying the desired methyl ester **4** [7,8]. In addition, another major drawback of this synthetic route is the use of highly toxic and carcinogenic dimethyl sulfate.

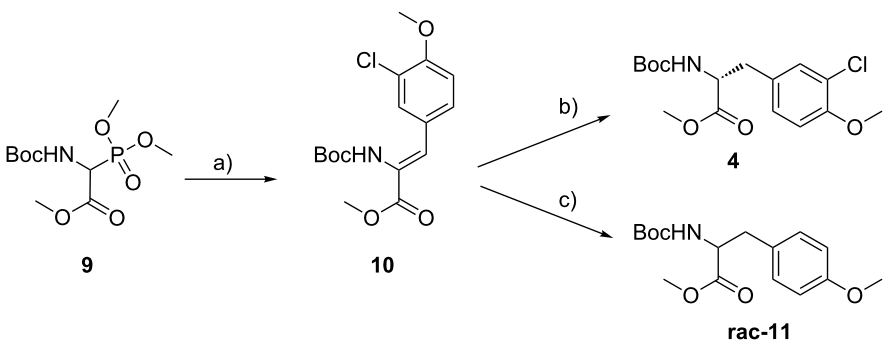
A completely different route to unit B precursor **8** (Scheme 2) is based on a phase transfer catalyst (PTC) mediated asymmetric alkylation. However, the required cinchonine derived chiral catalyst is not commercially available [9].

## Results and Discussion

We envisaged a two step synthesis for the unit B precursor **4** (Scheme 1) from commercially available non-toxic starting materials based on an asymmetric hydrogenation approach to make the unit B precursor synthesis shorter and safer. In general, there is also a whole variety of possible stereoselective synthetic methods available to synthesize modified α-amino acids, such as the classical Schöllkopf-method [10] or catalytic approaches [11,12]. The unit B precursor of cryptophycin is a phenylalanine derivative. An asymmetric hydrogenation approach for the synthesis of such α-amino acids is well-established [12]. In the first step of the developed synthesis 3-chloro-4-methoxybenzaldehyde is reacted with *rac*-Boc-α-phosphonoglycine trimethyl ester (**9**) [13,14] to yield olefin **10** in a completely *Z*-selective Horner–Wadsworth–Emmons (HWE) reaction (Scheme 3). Asymmetric hydrogenation using the commercially available [(COD)Rh-(*R*,*R*)-Et-DuPhos]$BF_4$ cata-




**Scheme 2:** Unit B synthesis by a chiral PTC approach. Reagents and conditions [9]: a) *N*-(Diphenylmethylene)glycine *tert*-butyl ester, 50% KOH, toluene/$CHCl_3$, chiral phase transfer catalyst (0.01 equiv), 0 °C, 20 h (87%; 96% *ee*); b) 15% citric acid, THF, rt, 16 h; c) FmocCl, $Na_2CO_3$, THF, rt, 14 h, (72% over two steps).




**Scheme 3:** Unit B precursor **4** synthesis by asymmetric hydrogenation. Reagents and conditions: a) 3-Chloro-4-methoxybenzaldehyde, 1,1,3,3-tetramethylguanidine, $CH_2Cl_2$, 0 °C to rt, 16 h (84%); b) [(COD)Rh-(*R*,*R*)-Et-DuPhos]$BF_4$ (1.9 mol %), $H_2$, dry and degassed MeOH, 3–6 bar, 21.5 h (97%; 98% *ee*); c) 10% Pd/C, $H_2$, MeOH, 16 h, (76%).

lyst [14,15] gave the anticipated methyl ester **4** (Scheme 1) in 97% yield with an *ee* exceeding 98% (determined by chiral HPLC). Hydrogenation of **10** with 10% Pd/C was envisaged to obtain ***rac*-4** as a reference for the determination of the *ee*. Interestingly, due to this more reactive catalyst a complete reductive dehalogenation was observed to give *rac*-Boc-Tyr(Me)-OMe (***rac*-11**) as reported for a similar case [16]. Therefore, ***ent*-4** was synthesized analogously also using the commercially available enantiomeric catalyst ([(COD)Rh-(*S*,*S*)-Et-DuPhos]$BF_4$).

## Conclusion

A novel two step synthesis of the important cryptophycin unit B precursor **4** is disclosed based on a HWE reaction followed by a highly enantioselective [(COD)Rh-(*R*,*R*)-Et-DuPhos]$BF_4$ mediated asymmetric hydrogenation. This high-yielding access is more convenient and avoids hazardous chemicals in contrast to the established method.

## Supporting Information

### Supporting Information File 1

Full experimental procedures and detailed analytical data for the synthesis of **10** and **4** including chiral HPLC spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-32-S1.pdf]

## Acknowledgements

We wish to thank F. Mertink, K.-P. Mester and G. Lipinski for running the NMR spectra, and Dr. M. Letzel, O. Kollas and S. Heitkamp for recording the mass spectra (all Bielefeld University). Financial support by Deutsche Forschungsgemeinschaft (DFG) is gratefully acknowledged.

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