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)]BF₄ 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].

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\textsubscript{2}Cl\textsubscript{2}, AcOH, rt, 90 min, (75%); b) Boc\textsubscript{2}O, NaOH, t-BuOH/H\textsubscript{2}O, rt, 16 h (quant.) c) Me\textsubscript{2}SO\textsubscript{4}, K\textsubscript{2}CO\textsubscript{3}, acetone, reflux, 4 h (99%); d) LiOH, H\textsubscript{2}O/THF/MeOH, rt, 1 h (93%).

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\textsubscript{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\textsubscript{2}CO\textsubscript{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\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 16 h (84%); b) [(COD)Rh-(R,R)-Et-DuPhos]BF\textsubscript{4} (1.9 mol %), H\textsubscript{2}, dry and degassed MeOH, 3–6 bar, 21.5 h (97%; 98% ee); c) 10% Pd/C, H\textsubscript{2}, MeOH, 16 h, (76%).

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 \( \alpha \)-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 \( \alpha \)-amino acids is well-established [12]. In the first step of the developed synthesis 3-chloro-4-methoxybenzaldehyde is reacted with rac-Boc-\( \alpha \)-phosphono-glycine 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\textsubscript{4} catal-

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].
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]BF4).

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]BF4 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]

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