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Synthetic Studies Towards MPC1001: Preparation of a β -hydroxyl-Tyrosine Derivative

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Abstract

A procedure for the asymmetric synthesis of a novel β -hydroxy- α -amino acid derivative to be used in the preparation of the natural product MPC1001 and analogs has been developed. The amino acid was efficiently prepared in six steps *via* a Mukaiyama aldol reaction via a diphenyloxazinone and 3-bromo-4-methoxybenzaldehyde.

Keywords

MPC1001; β -hydroxyl- α -amino acid; Mukaiyama aldol reaction; Oxazinone; Epipolythiodioxopiperazine

The epipolythiodioxopiperazine (ETP) family of natural products has interested the scientific community due to their unique chemical structure and potent biological activity.¹ Since the discovery of Gliotoxin by Weindling and coworkers in 1932, there have been more than fourteen distinct structural classes of these fungal metabolites isolated to date.¹ The sulfur-bridged diketopiperazine moiety that distinguishes the ETP family of natural products has been shown to be responsible for their biological activity. (Figure 1)²

In 2004, MPC1001 and congeners were isolated from the mycelium of the *Cladorrhnmum* sp. by Hasegawa and coworkers³ These compounds are structurally unique because they contain an oxepin moiety fused to the ETP core. To date, a total synthesis of MPC1001 has not been reported. However, two approaches toward the tricyclic core have been published. In 2009, Clive and coworkers completed the synthesis of the complex ring system from *trans*-4-hydroxyl-L-proline utilizing an acid-promoted ring closure of the primary alcohol onto a vinylogous amide.⁴ Recently, Bräse and coworkers utilized a late-stage ring closing metathesis to afford an advanced oxepin derivative that was also made from *trans*-4-hydroxyl-L-proline.⁵ In addition to the MPC family of natural products, the aranotin⁶, emethallicins⁷, and emestrian⁸ classes also contain an oxepin subunit. MPC1001 is unique because it also possesses an interesting β -hydroxyl- α -amino acid moiety.

MPC1001 is especially intriguing due to its biological activity against the human prostate cell cancer line DBU.³ MPC1001 displays an IC₅₀ value of 9.3 nM which is more potent than the therapeutic agents etoposide (400 nM), mitomycin C (25 nM), and adriamycin (20 nM). The complex structure and potent biological activity of MPC1001 render this compound an attractive synthetic target.

Herein, we report a general method for the synthesis of a β -hydroxy- α -amino acid derivative **15** using an asymmetric Mukaiyama aldol reaction. The flexibility in our design provides the

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opportunity for the preparation of analogs of MPC1001. Our approach employs a commercially available aldehyde **6** and an optically pure oxazinone **5** as our template.

We envisioned disconnecting MPC1001 to provide isovanillic acid (**1**), the complex oxepin ring-containing amino acid **2**, and the β -hydroxy- α -amino acid derivative **3**. Amino acid **3** could arise from the Mukaiyama aldol reaction of 3-bromo-4-methoxybenzaldehyde (**6**) and the silyl enol ether derived from oxazinone **5** (Scheme 1)

The synthetic approach to the unnatural amino acid portion is devised around a chiral diphenyloxazinone glycine template (**5**) that allows for the synthesis of either L or D amino acid derivatives. Lactone **5** can be easily prepared commercially available from (1*S*,2*R*)-(+)-2-amino-1,1-diphenylethanol in three steps in high yield with no chromatography required.⁹ The diphenyloxazinone template have been utilized in a wide range of synthetic transformations including enolate alkylation, glycine electrophilic reactivity, radical chemistry, dipolar cycloadditions, as well as homologation at the lactone carbonyl which provides access to highly functionalized amino acids.¹⁰

The synthesis commenced with the formation of the silylenol ether derivative **7** from oxazinone **5** (Scheme 2).¹¹ Unfortunately, utilizing conditions previously developed for the preparation of β -hydroxy- α -amino acids via oxazinone **5** resulted in the recovery of starting materials.¹¹ After some experimentation, we found that dropwise addition of silylenol ether **7** to a mixture of aldehyde **6** and 8 mol % Cu(OTf)₂ in CH₂Cl₂ provided compound **8** in a 99% yield.¹² Removal of the Cbz protecting group under hydrogenation conditions afforded the secondary amine **4** in a 74% yield along with the *R,R*-diastereomer **9**. The amine **4** was deprotected without cleaving the template or reducing the aromatic bromide. Exposure of the free amine **4** to ZnCl₂ in a 2:1 methanol/THF mixture in a sealed tube for 24 hours provided the methyl ester **10** in 90% yield. The newly formed amino ester **10** was then immediately methylated under reductive amination conditions to afford tertiary amine **11** in 88% yield. Final removal of the oxazinone template with Pb(OAc)₄ at 0 °C gave the *N*-methyl amine **12** in 73% yield.

The stereochemical rationalization for the diastereoselectivity of the Mukaiyama aldol reaction is described by an open transition state (Figure 2). Given that Lewis acids prefer the *anti* preferences,¹³ there are two main contributing transition states that can dictate the outcome of the reaction. **T1** is disfavored due to the steric interactions between the Lewis acid and the lactone ring, as well as the silyl protection group and the aromatic portion of the aldehyde. Therefore, the less sterically hindered transition state, **T2**, is favored resulting in the *anti*-product.

A corroborating X-ray crystal structure analysis was obtained of the amino acid methyl ester **14** as shown in Scheme 3. Removal of the oxazinone template from **10** yielded **13** in good yield followed by deprotection of the silyl ether with TBAF, which gave the crystalline amino ester **14**. X-ray crystallography analysis of this species confirmed the relative stereochemistry (Scheme 3).

In summary, *N*-methyl amino acid **12** was synthesized in six steps from oxazinone **5** employing a diastereoselective Mukaiyama aldol with commercially available 3-bromo-4-methoxybenzaldehyde **6**. The amino acid derivative **12** is currently under investigation for use in the synthesis of (*ent*)-MPC1001.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structure of Gliotoxin and the ETP Core.

Figure 2.
Transition State Analysis for the aldol condensation.

Scheme 1.
Synthetic Strategy.

Scheme 2.
Synthesis of N-Methyl Amino Ester **12**.

Scheme 3.
Synthesis and crystal structure of compound **14**.