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Asymmetric synthesis of (2*S*,3*R*)-(-)-*epi*-CP-99,994 using sulfinimine-derived *anti*-2,3-diamino esters

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Abstract

A differentially protected C-3 *N*-sulfinyl, C-2 *N,N*-(diphenylmethylene) 2,3-diamino ester was employed in the synthesis of the amino piperidine (2*S*,3*R*)-(-)-*epi*-CP-99,994. Key steps in the synthesis included the chemoselective hydrolysis of the C-2 *N,N*-(diphenylmethylene) group and its reprotection as a dibenzylamino group

Optically active *syn*- and *anti*-2,3-diamino acids are an important class of non-protein amino acids. They are key components of natural products including peptide antibiotics, antifungal agents, as well as other medicinally valuable compounds.¹ They are also useful precursors of chiral 1,2-diamines (vicinal diamines) which are found in a broad variety of natural products, are useful ligands for catalysis, and are building blocks for asymmetric syntheses.² In 2004 we reported the enantioselective synthesis of *syn*-2,3-diamino esters via the addition of the enolate of ethyl (dibenzylamino) acetate (**1**) to sulfinimines (*N*-sulfinyl imines).^{3,4} For example, the lithium *E*-enolate of **1** was added to sulfinimine (*S*)-(+)-**2** to give *syn*-2,3-diamino ester (+)-**3** in 68% yield of the major diastereoisomer (Figure 1).⁴ In 2007 we disclosed that the *Z*-lithium enolate of *N,N*-(diphenylmethylene)glycine ethyl ester (**4**), *in the presence of water*, adds to (*S*)-(+)-**2** to give the *anti*-2,3-diamino ester (-)-**5** in high dr and in excellent yield.⁵ In the absence of water, an excess of this enolate afforded the *syn*-2,3-diamine esters.⁵ Our asymmetric synthesis of the novel tetracyclic marine antitumor agent (-)-agelastatin A (**5**)⁶ and the potent neurokinin substance P receptor antagonist (2*S*,3*S*)-(+)-CP-99,994 (**6**)⁷ relied on the fact that the two amino groups in the *syn*-2,3-diamino esters were differentially protected.⁸ A key step in these syntheses was the selective removal of the *N*-sulfinyl group. We describe here an efficient asymmetric synthesis of (2*S*,3*R*)-(-)-*epi*-CP99,994 (**8**) from *anti*-2,3-diamino ester (-)-**5**.⁹

In considering the synthesis of (-)-**8** from (-)-**5** we envisioned a route similar to that used in the preparation of (+)-**7**, namely the construction of a diamino diene and using ring closing metathesis (RCM) to form the piperidine ring.⁷ However this requires selective hydrolysis of the *N,N*-(diphenylmethylene)amino group in (-)-**5** without disturbing the *N*-sulfinylamino group. Initial attempts to accomplish this with TFA/MeOH or HCl/H₂O under various reaction conditions failed, always resulting in removal of both protecting groups. Recently, Viso and co-workers reported that in the hydrolysis of *N*-sulfinylimidazolidines with H₃PO₄ the sulfonamide group was left intact.¹⁰ They attributed the remarkable chemoselectivity of this acid to the low nucleophilicity of the phosphate counterion.

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Significantly, treatment of (-)-**5** with 4 equiv of H₃PO₄ (85 wt % in H₂O) in THF at 0 °C for 4 h produced an 86% isolated yield of the C-2 deprotected amine (S_S,2S,3S)-(+)-**9** (Scheme 1). While reaction of (+)-**9** with benzyl bromide gave (+)-**10** in excellent yield, attempts to add a second *N*-benzyl group resulted in complex mixtures of products. In an effort to prepare a diamine in which the C-3 amino group could be selectively allylated, (+)-**10** was hydrolyzed (TFA-MeOH) and urea (+)-**11** was prepared in 83% yield using excess 1,1-carbonyldiimidazole/Et₃N. Allylation with 8 equiv of allyl bromide/KHMDS afforded (-)-**12** that on reduction with LAH gave alcohol (-)-**13** all in good yields (Scheme 1). Next, (-)-**13** was oxidized to the aldehyde with Dess-Martin periodinane (DMP). The aldehyde was treated with Na₂S₂O₃, dried (Na₂SO₄) and added to a -78 °C THF solution of the Wittig reagent (Ph₃PCH₃Br/*n*-BuLi) to give the diamino diene (-)-**14** in 48% isolated yield. Unfortunately, all attempts to hydrolyze the urea under acid (5 N HCl, 5 N H₂SO₄) or base (NaOH, Ba (OH)₂) conditions failed, and starting material was recovered under all conditions.

For this reason we returned to (+)-**10** in hopes of finding conditions for the chemoselective modification of one of the amino groups. Reasoning that the *N*-benzyl protected amine was a harder nucleophile than then *N*-sulfinyl amine, (+)-**10** was treated with benzoyl chloride, a hard Lewis acid. Remarkably, (-)-**15** was selectively formed in 70% yield (Scheme 2). Next, reduction of (-)-**15** with 4.0 equiv of LAH at -78 °C to rt accomplished the reduction of both the amide and ester groups to give the *N,N*-dibenzylamino alcohol (+)-**16** in 84% yield. Oxidation of the alcohol with DMP gave the aldehyde, which quickly decomposed on isolation. For this reason the crude aldehyde was treated with Na₂S₂O₃, dried (Na₂SO₄), and immediately used in the next step. The Kocienski-modified Julia olefination¹¹ using phenyltetrazole methyl sulfone (1.5 equiv) and KHMDS (3.6 equiv) at -20 °C gave (+)-**17** in 70 % yield for the two steps (Scheme 3). The sulfinyl group was removed (TFA-MeOH), replaced with a Boc group and (+)-**18** was allylated with excess allyl bromide/KHMDS at 0 °C to give the diamino diene (+)-**19** in 74% yield. This highly-aminated diene smoothly underwent RCM with the Grubbs-Hoveyda catalyst **20**¹² to give the amino tetrahydropyridine (+)-**21** in 94% isolated yield. 1,2,4,6-Tetrahydropyridines such as (+)-**21** are useful chiral building blocks for the synthesis of natural products because of the many methods available for ring functionalization of the C-C double bond.¹³

The conversion of (+)-**21** into the target (2S,3R)-(-)-*epi*-CP99,994 (**8**) followed the procedure that we used to prepare (+)-CP99,994 (**7**).⁷ The double bond in the key tetrahydropyridine intermediate (+)-**21** was reduced (Pt-C, H₂) to give (+)-**22**. Deprotection (Pd(OH)₂-C, H₂) of the dibenzyl amino group gave (+)-**23** which was subjected to a one-pot reductive amination reaction with *o*-anisaldehyde/NaB(OAc)₃H affording (+)-**24** in 98% isolated yield (Scheme 3). Finally, removal of the *N*-Boc group (HCl-dioxane) gave (2S,3R)-(-)-*epi*-CP99,994 (**8**) in 80% yield as the hydrochloride salt.¹⁵

In summary, a new synthesis of (2S,3R)-(-)-*epi*-CP99,994 (**8**), the *anti*-analog of the potent neurokinin substance P receptor antagonist (2S,3S)-(+)-CP-99,994 (**8**) has been achieved. Highlights of this synthesis include the chemoselective hydrolysis of the *N,N*-(diphenylmethylene) protected C-2 amino group in (-)-**5** to give *N*-sulfinyl diamino ester (-)-**9** and the chemoselective *N*-benzoylation of the C-2 *N*-benzyl group in (+)-**10** to give (-)-**15**.

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Figure 1.
Applications of *N*-sulfinyl 2,3,-diamino esters

Scheme 1.
Synthesis of diamino diene (-)-14

Scheme 2.
Synthesis of amino tetrahydropyridine (+)-**21**.

Scheme 3.
Conversion to (-)-CP-99,994 (**8**)