



## 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.

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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 medically valuable compounds.<sup>1</sup> 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.<sup>2</sup> 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).<sup>3,4</sup> 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 (Fig. 1).<sup>4</sup> 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.<sup>5</sup> In the absence of water, an excess of this enolate afforded the *syn*-2,3-diamino esters.<sup>5</sup> Our asymmetric synthesis of the novel tetracyclic marine antitumor agent (–)-agelastatin A (**6**)<sup>6</sup> and the potent neurokinin substance P receptor antagonist (2*S*,3*S*)-(+)-CP-99,994 (**7**)<sup>7</sup> relied on the fact that the two amino groups in the *syn*-2,3-diamino esters were differentially protected.<sup>8</sup> 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*-CP-99,994 (**8**) from *anti*-2,3-diamino ester (–)-**5**.<sup>9</sup>

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.<sup>7</sup> 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/H<sub>2</sub>O 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 H<sub>3</sub>PO<sub>4</sub> the sulfinamide group was left intact.<sup>10</sup> They attributed the remarkable chemoselectivity of this acid to the low nucleophilicity of the phosphate counterion.

Significantly, treatment of (–)-**5** with 4 equiv of H<sub>3</sub>PO<sub>4</sub> (85 wt % in H<sub>2</sub>O) in THF at 0 °C for 4 h produced an 86% isolated yield of the C-2 deprotected amine (*S*<sub>S</sub>,2*S*,3*S*)-(+)-**9** (Scheme 1). While reaction of (+)-**9** with benzyl bromide gave (+)-**10** in excellent yield,

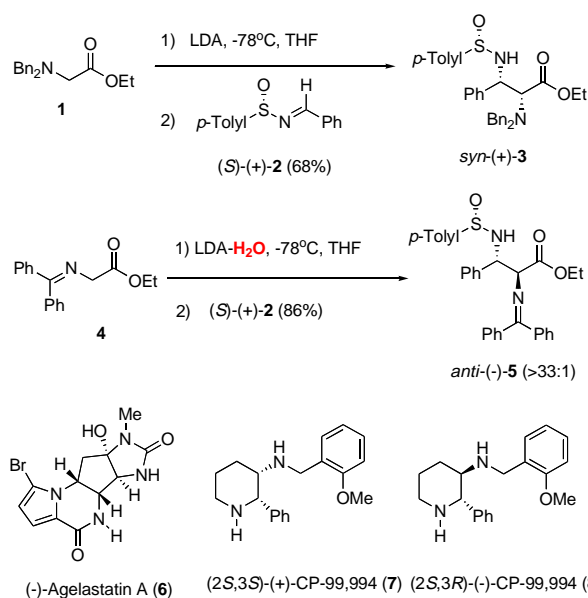
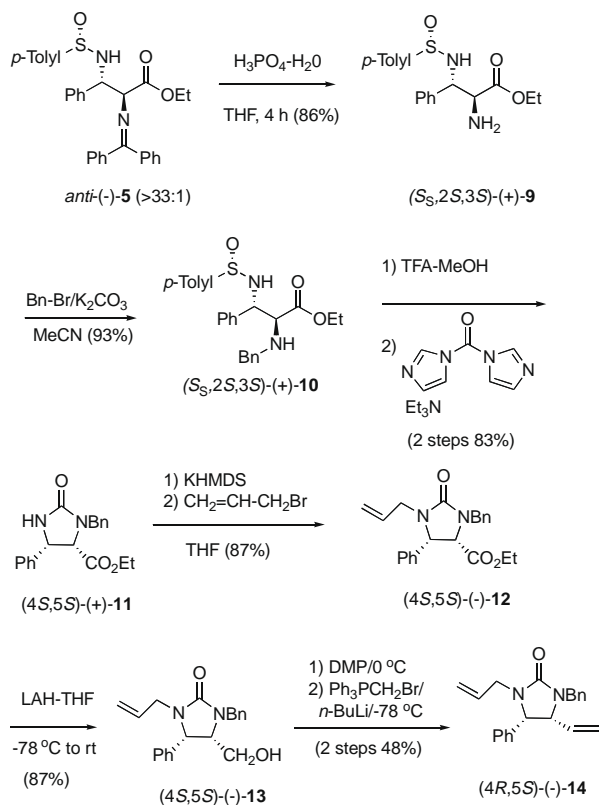
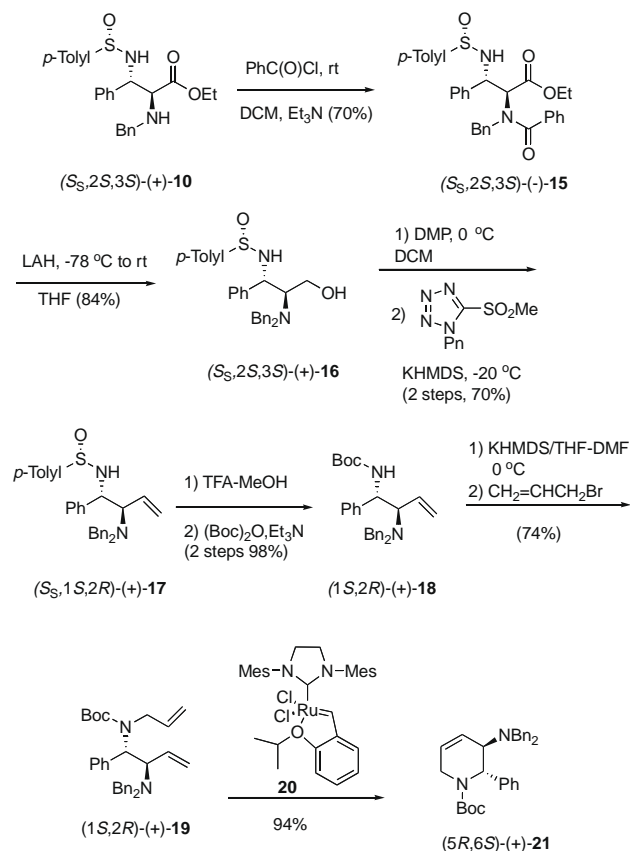


Figure 1. Applications of *N*-sulfinyl 2,3-diamino esters.

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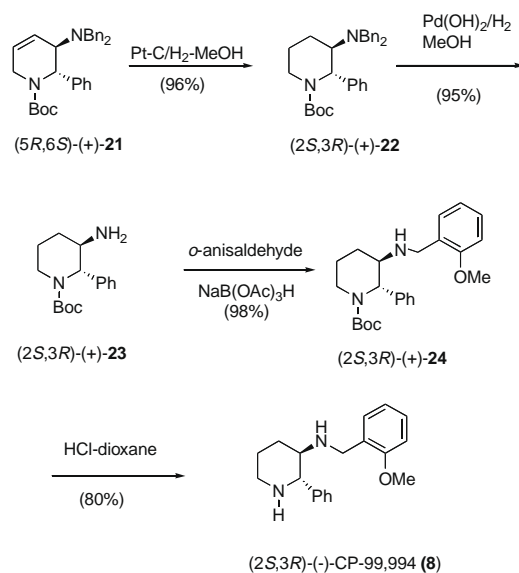
Scheme 1. Synthesis of diamino diene (–)-14.



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

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/Et<sub>3</sub>N. 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 Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and added to a –78 °C THF solution of the Wittig reagent (Ph<sub>3</sub>PCH<sub>2</sub>Br/*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 H<sub>2</sub>SO<sub>4</sub>) or base (NaOH, Ba(OH)<sub>2</sub>) 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 the *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 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 Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and immediately used in the next step. The Kocienski-modified Julia olefination<sup>11</sup> 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**<sup>12</sup> to give the ami-



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

no 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.<sup>13</sup>

The conversion of (+)-21 into the target (2*S*,3*R*)-(–)-*epi*-CP-99,994 (**8**) followed the procedure that we used to prepare (+)-CP-99,994 (**7**).<sup>7</sup> The double bond in the key tetrahydropyridine

intermediate (+)-**21** was reduced (Pt–C, H<sub>2</sub>) to give (+)-**22**. Deprotection (Pd(OH)<sub>2</sub>–C, H<sub>2</sub>) of the dibenzyl amino group gave (+)-**23** which was subjected to a one-pot reductive amination reaction with *o*-anisaldehyde/NaB(OAc)<sub>3</sub>H affording (+)-**24** in 98% isolated yield (Scheme 3).<sup>14</sup> Finally, removal of the *N*-Boc group (HCl–dioxane) gave (2*S*,3*R*)-(–)-*epi*-CP-99,994 (**8**) in 80% yield as the hydrochloride salt.<sup>15</sup>

In summary, a new synthesis of (2*S*,3*R*)-(–)-*epi*-CP-99,994 (**8**), the *anti*-analog of the potent neurokinin substance P receptor antagonist (2*S*,3*S*)-(+)-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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## References

- For a review on the syntheses and significance of 2,3-diamino esters see: Viso, A.; Pradilla, R. F. d. I.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3198.
- For reviews highlighting the importance of vicinal diamines see: (a) Sababu Kotti, S. R. S.; Cody, T.; Li, G. *Biol. Drug Des.* **2006**, *67*, 101; (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
- For recent reviews on the chemistry of sulfinimines see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030; (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93–104; (c) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905; (d) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993–9003.
- Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789–2792.
- Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* **2007**, *9*, 833–836.
- (a) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621–623; (b) Davis, F. A.; Zhang, J.; Zhang, Y.; Qiu, H. *Synth. Commun.* **2009**, *39*, 1914–1919.
- Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838–7840.
- For other examples of the asymmetric synthesis of heterocycles using sulfinimine-derived 2,3-diamino esters see: (a) Viso, A.; Fernandez de la Pradilla, R.; Urena, M. *Tetrahedron* **2009**, *65*, 3757–3766; (b) Viso, A.; Fernandez de la Pradilla, R.; Flores, A.; Garcia, A. *Tetrahedron* **2007**, *63*, 8017–8026, and references cited therein; (c) Viso, A.; Fernandez de la Pradilla, R.; Flores, A.; Garcia, A.; Tortosa, M.; Lopez-Rodriguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448.
- For an asymmetric synthesis of the (+)-(2*R*,3*S*) isomer of CP-99,994 see: Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473–2479.
- Viso, A.; Fernandez de la Pradilla, R.; Lopez-Rodriguez, M. L.; Garcia, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542–1547.
- Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955–968.
- Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- For a review see: (a) Felpin, F.-X.; Lebreton, J. *Curr. Org. Syn.* **2004**, *1*, 83–109; For leading references see: (b) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046–2052.
- Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
- Selected data: (+)-**9**, oil, [α]<sub>D</sub><sup>20</sup> +92.5 (c 1.3, CHCl<sub>3</sub>); (+)-**10**, oil, [α]<sub>D</sub><sup>20</sup> +102.8 (c 1.3, CHCl<sub>3</sub>); (+)-**11**, oil, [α]<sub>D</sub><sup>20</sup> +33.6 (c 2.4, CHCl<sub>3</sub>); (–)-**12**, oil, [α]<sub>D</sub><sup>20</sup> –77.8 (c 2.0, CHCl<sub>3</sub>); (–)-**13**, oil, [α]<sub>D</sub><sup>20</sup> –34.8 (c 1.3, CHCl<sub>3</sub>); (–)-**14**, oil, [α]<sub>D</sub><sup>20</sup> –53.4 (c 0.55, CHCl<sub>3</sub>); (–)-**15**, oil, [α]<sub>D</sub><sup>20</sup> –50.8 (c 0.6, CHCl<sub>3</sub>); (+)-**16**, oil, [α]<sub>D</sub><sup>20</sup> +27.1 (c 0.45, CHCl<sub>3</sub>); (+)-**17**, oil, [α]<sub>D</sub><sup>20</sup> +62.5 (c 0.4, CHCl<sub>3</sub>); (+)-**18**, oil, [α]<sub>D</sub><sup>20</sup> +59.0 (c 0.5, CHCl<sub>3</sub>); (+)-**19**, oil, [α]<sub>D</sub><sup>20</sup> +95.0 (c 0.8, CHCl<sub>3</sub>); (+)-**21**, oil, [α]<sub>D</sub><sup>20</sup> +21.4 (c 0.85, CHCl<sub>3</sub>); (+)-**22**, oil, [α]<sub>D</sub><sup>20</sup> +48.0 (c 0.2, CHCl<sub>3</sub>); (+)-**23**, oil, [α]<sub>D</sub><sup>20</sup> +62.7 (c 0.5, CHCl<sub>3</sub>); (+)-**24**, oil, [α]<sub>D</sub><sup>20</sup> +35.2 (c 0.5, CHCl<sub>3</sub>); (–)-**8**, oil, [α]<sub>D</sub><sup>20</sup> –74.2 (c 0.4, CHCl<sub>3</sub>) [lit.<sup>16</sup> [α]<sub>D</sub><sup>20</sup> –78 (c 1.0, MeOH)].
- Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911–4913.