Tetrahedron Letters 50 (2009) 5205–5207

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Franklin A. Davis *, Yanfeng Zhang

Department of Chemistry, Temple University, Philadelphia, PA 19122, United States

ARTICLE INFO

Article history:
Received 18 May 2009
Revised 18 June 2009
Accepted 29 June 2009
Available online 3 July 2009

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 (Fig. 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*-CP-99,994 (**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/H_2O 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_3PO_4 the sulfinamide group was left intact.[10] 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_3PO_4 (85 wt % in H_2O) in THF at 0 °C for 4 h produced an 86% isolated yield of the C-2 deprotected amine (S_S,2*S*,3*S*)-(+)-**9** (Scheme 1). While reaction of (+)-**9** with benzyl bromide gave (+)-**10** in excellent yield,

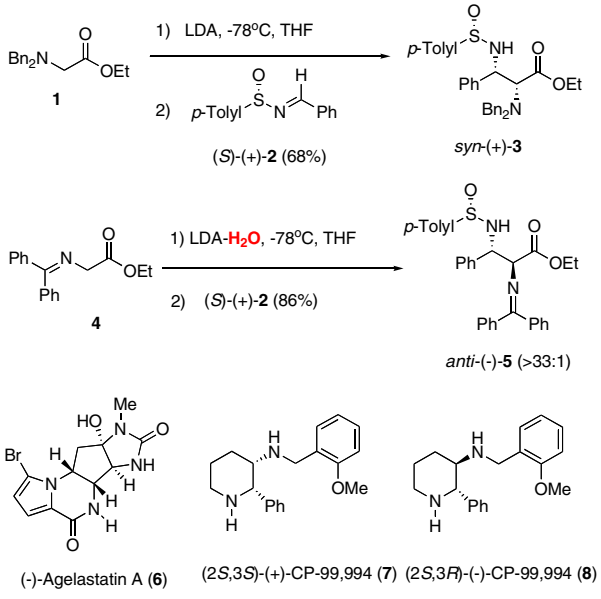
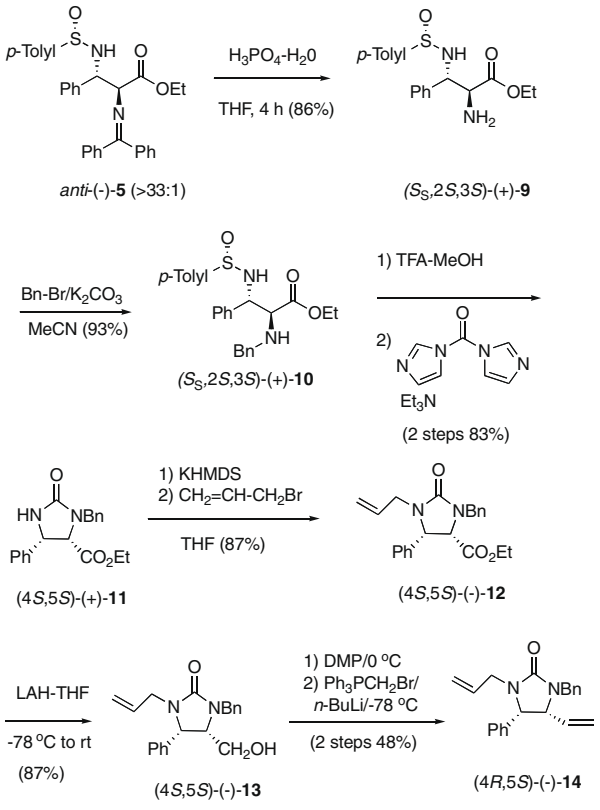


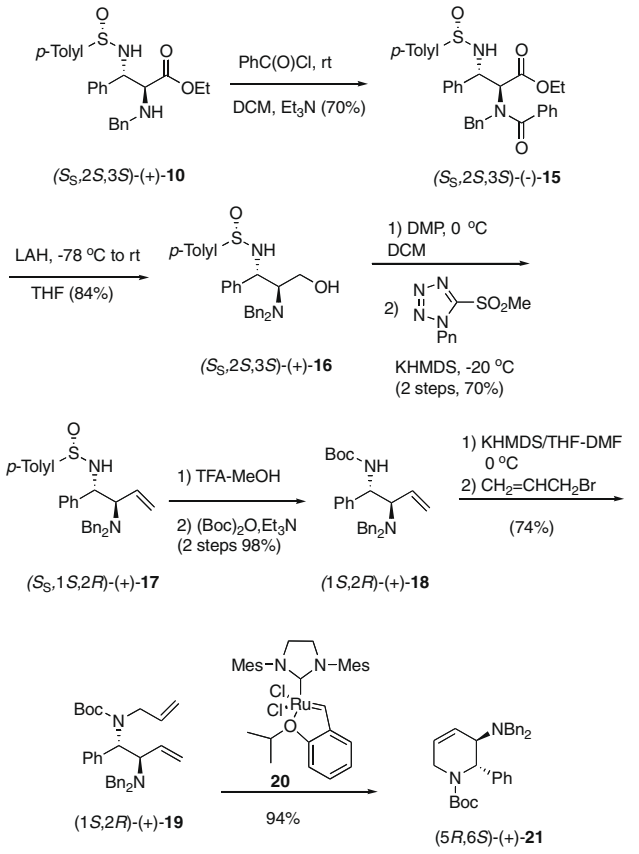
Figure 1. Applications of *N*-sulfinyl 2,3-diamino esters.

* Corresponding author. Tel.: +1 215 204 0477; fax: +1 215 204 0478.
E-mail address: fdavis@temple.edu (F.A. Davis).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.125



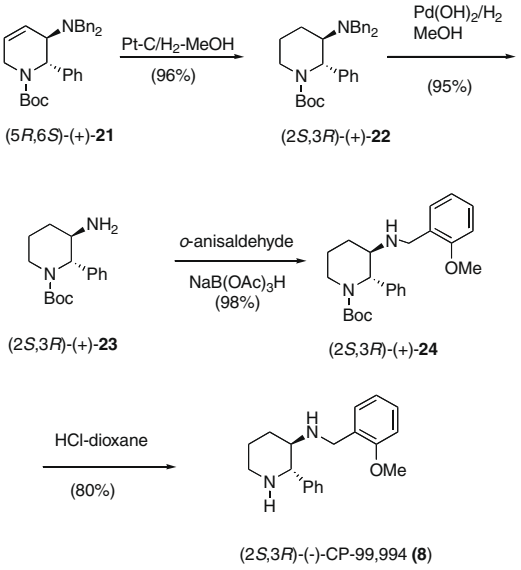
Scheme 1. Synthesis of diamino diene (−)-**14**.



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 selectivity allylated, (+)-**10** was hydrolyzed (TFA–MeOH) and urea (+)-**11** was prepared in 83% yield using excess 1,1-carbonyldiimidazole/Et_3N. 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 $Na_2S_2O_3$, dried (Na_2SO_4), and added to a −78 °C THF solution of the Wittig reagent (Ph_3PCH_3Br/*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_2SO_4) 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 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 $Na_2S_2O_3$, dried (Na_2SO_4), and immediately used in the next step. The Kocienski-modified Julia olefination[11] 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]



Scheme 3. Conversion to (−)-CP-99.994 (**8**).

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**).[7] The double bond in the key tetrahydropyridine

intermediate (+)-**21** was reduced (Pt–C, H_2) to give (+)-**22**. Deprotection ($Pd(OH)_2$–C, H_2) 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).[14] 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.[15]

In summary, a new synthesis of (2*S*,3*R*)-(−)-*e*pi-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**.

Acknowledgments

This work was supported by grants from the National Institutes of General Medical Sciences (GM57878 and GM51982) and Boehringer Ingelheim Pharmaceuticals.

References

1. For a review on the syntheses and significance of 2,3-diamino esters see: Viso, A.; Pradilla, R. F. d. l.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3198.
2. 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.
3. 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.
4. Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789–2792.
5. Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* **2007**, *9*, 833–836.
6. (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.
7. Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838–7840.
8. 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-Rodrigez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448.
9. 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.
10. Viso, A.; Fernandez de la Pradilla, R.; Lopez-Rodrigez, M. L.; Garcia, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542–1547.
11. Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955–968.
12. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
13. 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.
14. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
15. Selected data: (+)-**9**, oil, $[\alpha]_D^{20}$ +92.5 (*c* 1.3, $CHCl_3$); (+)-**10**, oil, $[\alpha]_D^{20}$ +102.8 (*c* 1.3, $CHCl_3$); (+)-**11**, oil, $[\alpha]_D^{20}$ +33.6 (*c* 2.4, $CHCl_3$); (−)-**12**, oil, $[\alpha]_D^{20}$ −77.8 (*c* 2.0, $CHCl_3$); (−)-**13**, oil, $[\alpha]_D^{20}$ −34.8 (*c* 1.3, $CHCl_3$); (−)-**14**, oil, $[\alpha]_D^{20}$ −53.4 (*c* 0.55, $CHCl_3$); (−)-**15**, oil, $[\alpha]_D^{20}$ −50.8 (*c* 0.6, $CHCl_3$); (+)-**16**, oil, $[\alpha]_D^{20}$ +27.1 (*c* 0.45, $CHCl_3$); (+)-**17**, oil, $[\alpha]_D^{20}$ +62.5 (*c* 0.4, $CHCl_3$); (+)-**18**, oil, $[\alpha]_D^{20}$ +59.0 (*c* 0.5, $CHCl_3$); (+)-**19**, oil, $[\alpha]_D^{20}$ +95.0 (*c* 0.8, $CHCl_3$); (+)-**21**, oil, $[\alpha]_D^{20}$ +21.4 (*c* 0.85, $CHCl_3$); (+)-**22**, oil, $[\alpha]_D^{20}$ +48.0 (*c* 0.2, $CHCl_3$); (+)-**23**, oil, $[\alpha]_D^{20}$ +62.7 (*c* 0.5, $CHCl_3$); (+)-**24**, oil, $[\alpha]_D^{20}$ +35.2 (*c* 0.5, $CHCl_3$); (−)-**8**, oil, $[\alpha]_D^{20}$ −74.2 (*c* 0.4, $CHCl_3$) [lit.[16] $[\alpha]_D^{20}$ −78 (*c* 1.0, MeOH)].
16. Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911–4913.