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Sulfinimine-derived 2,3-diamino esters in the asymmetric synthesis of piperidine (2*S*,3*S*)-(+)-CP-99,994

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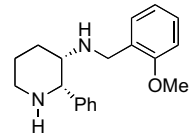
Abstract—Sulfinimine-derived, differentially protected, 2,3-diamino esters are useful building blocks for the asymmetric synthesis of heterocycles and is illustrated by an efficient synthesis of amino piperidine (+)-CP-99,994.

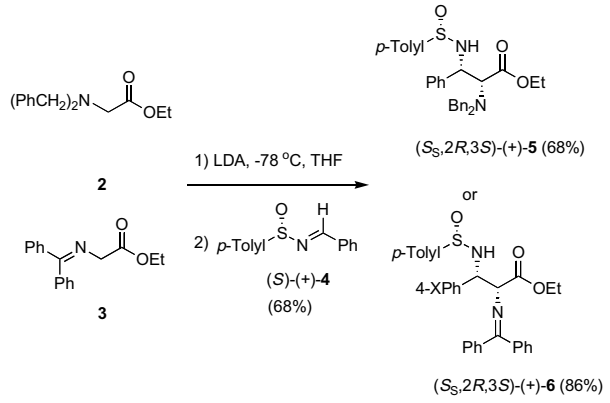
2,3-Diamino acids are non-protein amino acids, which are key components of natural and synthetic biologically active compounds.[1] For example (2*S*,3*S*)-(+)-CP-99,994 (**1**), a synthetic 2,3-disubstituted piperidine, is a potent neurokinin substance P receptor antagonist, which exhibits antiemetic activity.[2] Several asymmetric syntheses of this compound or its epimer have been reported, however, with few exceptions,[3] most of these syntheses are multi-step procedures that provide (+)-**1** in low overall yield (Fig. 1).[4,5] An additional problem is that most of these methods begin with an optically active monoamine.[5] This means that the second amino group needs to be introduced stereospecifically later in the synthesis resulting in the undesirable separation of diastereomers and resulting in lower efficiencies.



(2*S*,3*S*)-(+)-CP-99,994 **1**

Figure 1. Substance P receptor antagonist.

We have been exploring the addition of prochiral enolate species to sulfinimines (*N*-sulfinyl)[6] where two new stereogenic centers are created in a single operation, and with the possible formation of four diastereoisomers.[7] In this context we reported the addition of the *E*-lithium enolate of ethyl (dibenzylamino)acetate (**2**)[7a] or a large excess of the *Z*-lithium enolate of *N*-(diphenylmethylene)glycine ethyl ester (**3**)[7d] to (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**4**) gives differentially N-protected (S_S,2*R*,3*S*)-(+)-*syn*-2,3-diamino-3-phenylpropanoate (+)-**5** and (+)-**6**, respectively in good to excellent yields (Scheme 1). Employing (S_S,2*R*,3*S*)-(+)-**5** we describe here a highly efficient 12-step (nine operations) asymmetric synthesis of (+)-**1** in 38% overall yield from (+)-**5**. Furthermore, because of the diversity of available sulfinimines, our synthesis is particularly suited for analogue synthesis.[6]



Scheme 1.

The *N*-sulfinyl group in (+)-**5** was removed with TFA–MeOH to give the mono amine, which was not isolated, but was treated, after concentration, with $(Boc)_2O$–Et_3N–THF to give the *N*-Boc protected diamine

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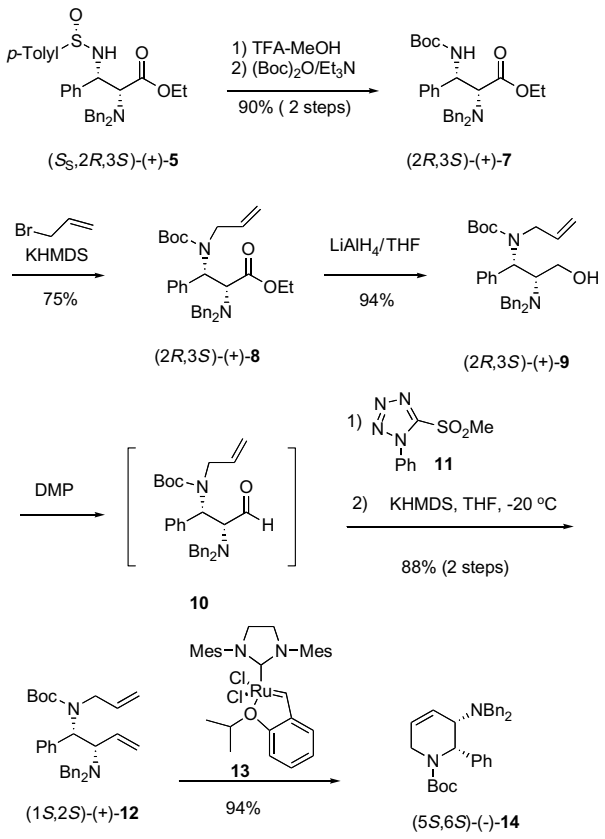


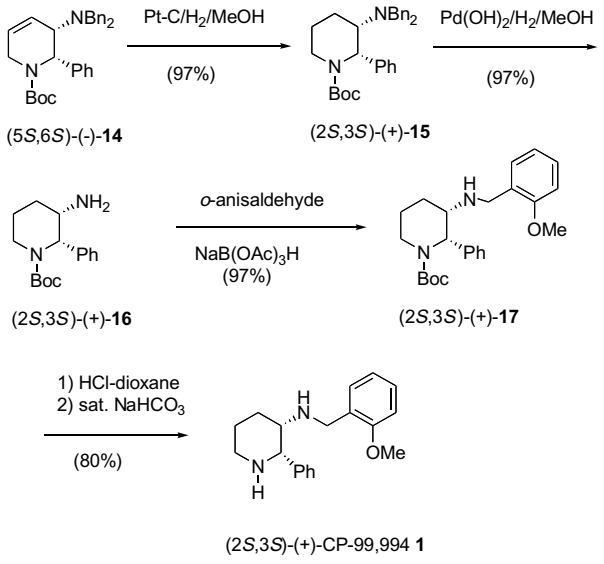
Scheme 2.

(2*R*,3*S*)-(+)-**7** in 90% yield for the two steps (Scheme 2). Initial attempts to allylate the *N*-Boc amino group with allyl bromide and NaH or K_2CO_3 were unsuccessful. However, reaction of (+)-**7** with 1.5 equiv of KHMDS followed with 6 equiv of allyl bromide at 0 °C gave (2*R*,3*S*)-(+)-**8** in 75% yield. Alcohol (1*S*,2*R*)-(+)-**9** was obtained in 94% yield by reduction of the ester group in (+)-**8** with 5 equiv of $LiAlH_4$ in THF at rt. With (+)-**9** in hand the idea was to oxidize the alcohol to aldehyde **10** and use a Wittig-type olefination reaction to generate the diene. Reaction of (+)-**9** with 1.5 equiv of the Dess–Martin periodinane (DMP) reagent did indeed give the aldehyde as evidenced by the appearance of an aldehyde proton at δ 9.7 ppm, but all attempts to isolate it proved unsuccessful because it quickly decomposed at room temperature. For this reason the crude aldehyde, isolated by treating with $Na_2S_2O_3$ and drying, was used directly in the next step. However, attempts to effect the Wittig reaction using $Ph_3PCH_3^+Br^-/t\text{-}BuO^-K^+$ resulted in decomposition. More successful was the Kocienski-modified Julia olefination.[8] Gratifyingly a THF solution of crude **10** and phenyltetrazole methyl sulfone **11** (1.4 equiv) on treatment with 3.6 equiv of KHMDS at −20 °C afforded diamino diene (1*S*,2*S*)-(+)-**12** in 93% yield (Scheme 2).

1,2,5,6-Tetrahydropyridines such as (−)-**14** are useful chiral building blocks for the asymmetric synthesis of natural products because of the many methods available for ring functionalization of the C–C double bond.[9] One method for their preparation employs ring-closing metathesis (RCM) of amino dienes.[9a] However, to the best of our knowledge there are no reports of diamino dienes and RCM being used to prepare amino piperidines. Furthermore, RCM's functional group tolerance problems with amines have been reported.[10] Significantly, highly-aminated diene (+)-**12** smoothly undergoes RCM with the Grubbs–Hoveyda catalyst[11] **13** to give amino tetrahydropyridine (−)-**14** in 94% yield (Scheme 2).

The double bond in the key tetrahydropyridine intermediate (−)-**14** was selectively reduced with Pt–C, H_2 to give (2*S*,3*S*)-(+)-**15** in 97% yield (Scheme 3). The *N*-benzyl groups were removed using $Pd(OH)_2$, H_2 affording amino piperidine (2*S*,3*S*)-(+)-**16** in 97% yield. It was not necessary to isolate (+)-**15** and the reaction sequence, reduction and deprotection was carried out in one-pot to give (+)-**16** in 95% yield for the two steps. Attempts to reduce the double bond and remove *N*-benzyl groups using $Pd(OH)_2$, H_2 resulted in decomposition. Importantly, one-pot reductive amination of *o*-anisaldehyde with (+)-**16** using $NaB(OAc)_3H$ gave (2*S*,3*S*)-(+)-**17** in 97% yield.[12] Earlier reports using $NaBH_3CN$ or $NaBH_4$ as the reducing agents reportedly give this material in lower yield (ca. 80%).[5a,b] Removal of the Boc group (HCl–dioxane) gave the title compound, (2*S*,3*S*)-(+)-CP-99,994 (**1**) in 80% yield.[13]

In summary, a concise 12-step, nine operations, asymmetric synthesis of the neurokinin substance P receptor antagonist amino piperidine (+)-CP-99,994 (**1**) was developed. The overall yield from the sulfinimine-derived differentially N-protected diamino ester (+)-**5** was 38%. Highlights of the synthesis include an efficient Kocienski-modified Julia olefination and ring-closing metathesis of a diamino diene using the Grubbs–Hoveyda catalyst **13** to give tetrahydropyridine (−)-**14**. The flexibility of the synthesis using sulfinimines makes this methodology well suited for enantiomer and analogue preparation.



Scheme 3.

Acknowledgments

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13. Selected data: (+)-**8**, $[\alpha]_D^{20}$ +121.2 (*c* 1.05, $CHCl_3$); (+)-**12**, $[\alpha]_D^{20}$ +29.4 (*c* 0.87, $CHCl_3$); (−)-**14**, $[\alpha]_D^{20}$ −6.9 (*c* 1.1, $CHCl_3$); (+)-**15**, $[\alpha]_D^{20}$ +69.1 (*c* 0.6, $CHCl_3$); (+)-**16**, $[\alpha]_D^{20}$ +27.0 (*c* 0.8, $CHCl_3$); (+)-**17**, $[\alpha]_D^{20}$ +27.5 (*c* 0.3, $CHCl_3$); (+)-**1**, $[\alpha]_D^{20}$ +74.2 (*c* 0.5, $CHCl_3$).