Pergamon

Tetrahedron Letters 39 (1998) 5951–5954

TETRAHEDRON LETTERS

SYNTHESIS AND APPLICATIONS OF NONRACEMIC β-AMINO ALDEHYDES TO THE ASYMMETRIC SYNTHESIS OF PIPERDINES: (+)-DIHYDROPINIDINE

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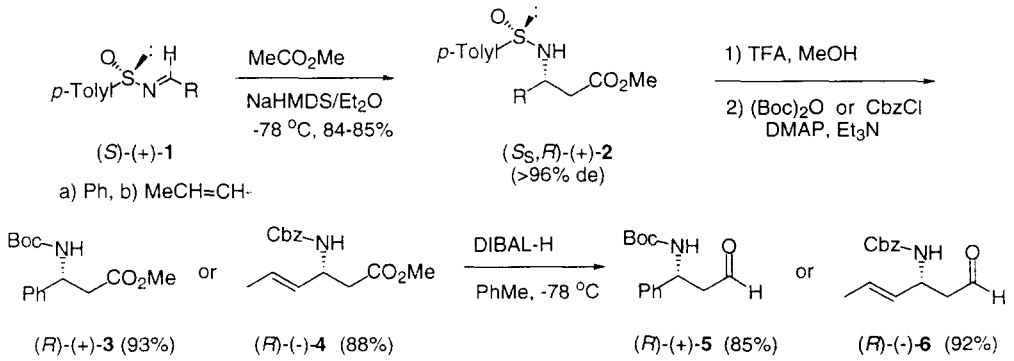
Received 27 May 1998; accepted 9 June 1998

Summary: New methodology for the enantioselective synthesis of stable N-protected β-amino aldehydes **5** and **6**, and their application to the asymmetric synthesis of (+)-2-phenylpiperdine (**11**) and (+)-dihydropinidine (**14**) is described.

N-Protected α-amino aldehydes are widely used building blocks in the asymmetric synthesis of natural products and are readily prepared from α-amino acids.[1] These compounds have found utility in the synthesis of 1,2-amino alcohols via the addition of organometallic reagents, in aldol reactions, [4+2] cycloadditions and Wittig type condensations.[1,2] By contrast there are relatively few reported applications for nonracemic β-amino aldehydes.[3] This situation is undoubtedly due their tendency to self-condense,[4] and the lack of convenient methods for their preparation.[3] Enantiopure N-protected β-amino aldehydes have been prepared by reduction of N-Boc-β-amino nitriles,[3] N-tosyl β-amino esters,[5] β-amino N-methyl-N-methoxy amides[4c,6] as well as other methods.[7,8] The problem with most of these procedures is in the synthesis of the precursor β-amino acid derivative which is often multi-step and inconvenient. Removal of the N-protecting group, necessary for further elaboration of the amino aldehyde, is also problematic. In this letter we describe a simple four step asymmetric synthesis of *N*-protected β-amino aldehydes from sulfinimines **1** and their application to the synthesis of nonracemic piperdine alkaloids (Scheme 1). Sulfinimines (thiooxime S-oxides (*S*)-**1**), prepared in "one pot" from commercially available (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate and aromatic or aliphatic aldehydes,[9] are important chiral imine building blocks for the asymmetric synthesis of amine derivatives.[10,11]

Scheme 1



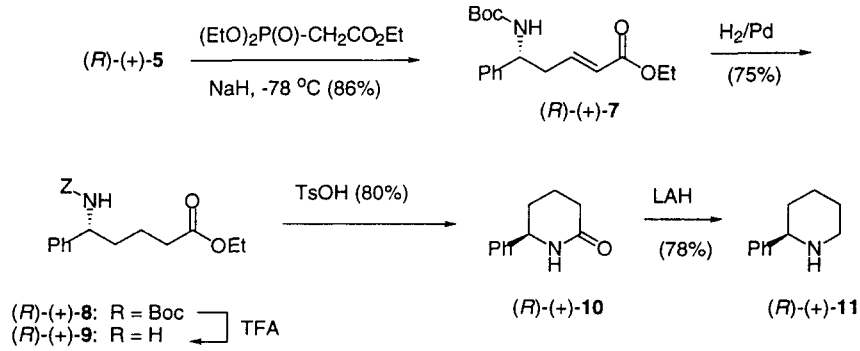
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01223-4

N-Sulfinyl β-amino acid (+)-**2b** was prepared in 88% yield and 97% de by addition of (*S*)-(+)-**1b**[9] (typically 12.0 mmol) to the sodium enolate of methyl acetate, prepared from methyl acetate and sodium bis(trimethylsilyl) amide (NaHMDS), as previously described for (+)-**2a**.[12] The sulfinamide **2** is probably a consequence of the anion stabilizing sulfinyl group; analogous reactions of *N*-alkyl and *N*-arylimines produced cyclized β-lactams.[13] An added feature of the *N*-sulfinyl group is that it is easily removed under mild conditions. Thus, treatment of sulfinamides **2a** and **2b** with 4 equivalents of trifluoroacetic acid (TFA) in MeOH for 2 h at rt, removal of the solvent to dryness gave a residue that was dissolved in THF. Addition of excess triethylamine, a few crystals of dimethylaminopyridine (DMAP) and di-*tert*-butyl dicarbonate or benzyl chloroformate afforded (*R*)-**3** and (*R*)-**4** in 93 and 88% yield, respectively, for the two steps following flash chromatography.

β-Amino aldehydes (*R*)-**5** and (*R*)-**6** were prepared by DIBAL-H reduction of N-Boc and N-Cbz amino esters **3** and **4** at -78 °C in toluene. Careful monitoring of the reaction time is necessary or over-reduction to the alcohols occurs. For example **4** with 2.0 equiv. of DIBAL-H at -78 °C for 20 min gave (*R*)-**6** in 93% yield whereas the yield was reduced to 75% after 45 min. Significantly, and in apparent contrast to other β-amino aldehydes, **5** and **6** are stable crystalline solids amenable to purification by flash chromatography. These aldehydes exhibit characteristic absorption for the aldehydic proton at δ 9.74 ppm in the ^{1}H NMR.

We next turned our attention to the application of these amino aldehydes to the enantioselective synthesis of (*R*)-2-phenylpiperdine (**11**) and (2*R*,6*S*)-dihydropinidine (**14**). The piperdine alkaloids, mono and 2,6-disubstituted analogues, are widely distributed in nature and exhibit a range of biological activities.[14] While these alkaloids have been the subject of a number of syntheses their synthesis in enantiopure form has received less attention until recently.[15] Our preparation of (+)-**11** is outlined in Scheme 2 and begins with Horner-Wadsworth-Emmons reaction of (*R*)-**5** with NaH/triethylphosphonoacetate at -78 °C to afford a single isomer of *trans* (*R*)-**7** (J = 15.5 Hz) as an oil in 86% yield. Hydrogenation, H_2/Pd/MeOH, gave amino ester (*R*)-**8** in 75% yield. Deprotection with TFA gave a mixture of amino ester **9** and (*R*)-(+)-6-phenylpiperidin-2-one (**10**) in a 1.5:1.0 ratio. Refluxing the crude mixture in benzene with TsOH for 2 h resulted in an 80% yield of (*R*)-(+)-**10** as white crystals, mp 119-121 °C, after flash chromatography. Subsequent treatment of (*R*)-**10** with $LiAlH_4$ produced (*R*)-(+)-2-phenylpiperdine (**11**) as a volatile oil; $[\alpha]^{20}_D$ +57.3 (*c* 1.7, CH_2Cl_2), [Lit.[16] $[\alpha]^{20}_D$ +54.7 (*c* 1.7, $CHCl_3$) for 92% ee]. Attempts to determine the ee of (*R*)-**11** independently using

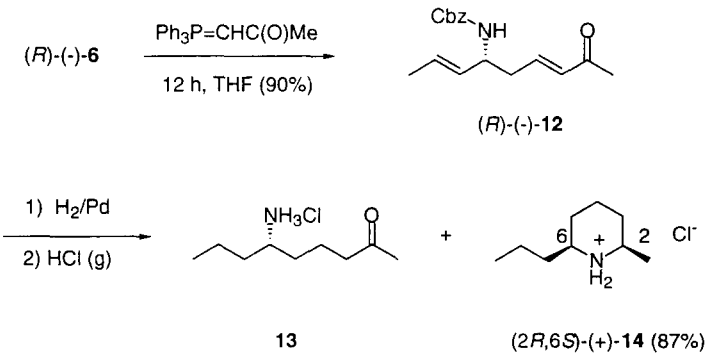
Scheme 2



chiral shift reagents or preparing the Mosher amide were unsuccessful. However, there is no reason to believe that any step in the synthesis (Scheme 2) would lead to epimerization, and it is assumed that the ee of (*R*)-**11** is the same as the starting β-amino aldehyde; e.g. >97% ee. Earlier enantioselective synthesis of this alkaloid included asymmetric ring closure using a chiral organoselenium reagent (92% ee)[16] and asymmetric hydrogenation of the corresponding imine with a chiral titanocene catalyst (97% ee).[17]

A similar approach was used to prepare (2*R*,6*S*)-(+)-dihydropinidine (**14**) and is outlined in Scheme 3. Refluxing of 1.1 equivalents of 1-triphenylphosphoranylidene-2-propanone with β-amino aldehyde (*R*)-(-)-**6** in THF for 12 h gave a 90% yield of a 4.6:1 *E*/*Z* mixture of the ketone from which (*R*)-**12** was isolated in 74% yield by flash chromatography. The reason that the unsaturated aldehyde (*R*)-**6** was chosen as the starting material rather than its saturated analog is that the corresponding N-sulfinyl β-amino acid **2** (R = *n*-propyl) was obtained as an oil in 90% de and could not be upgraded to diastereomeric purity. Next, in a single operation, we planned to remove the Cbz protecting group, hydrogenate each of the double bonds, cyclize the amino ketone **13** to the cyclic imine and stereoselectivity reduce it to (+)-**14**. However, hydrogenation (Pd/H_2) in MeOH containing a catalytic amount of PTSA or HCl afforded a complex mixture of products which could not be separated. In the presence of methanolic HCl a single product was formed whose spectral properties suggested it was the amino ketone **13**. Finally, hydrogenation of (*R*)-**12** for 12 h, removal of the solvent, dissolving the crude product in ether and passing dry HCl gas through the solution for a few minutes afforded a white solid. Crystallization from EtOAc/EtOH gave (2*R*,6*S*)-(+)-dihydropinidine (**14**)[18] in 87% overall yield for the 6 steps from (-)-**12**. The enantiomeric purity of **14** was >96%; $[\alpha]^{20}_D$ +12.6 (*c* 1.09, EtOH); [Lit.[19a] $[\alpha]^{20}_D$ +12.7 (*c* 1.0, EtOH), Lit.[19b] $[\alpha]^{20}_D$ +12.5 (*c* 1.00, EtOH). Dihydropinidine (**14**) has been from amino acids,[19a] using chiral auxilaries,[19b] and kinetic resolution using Sharpless asymmetric epoxidation.[20]

Scheme 3



In summary, a convenient new method for the preparation of stable, enantiopure *N*-protected β-amino aldehydes from sulfinimines was developed. The application of these chiral building blocks to the efficient asymmetric synthesis of piperdine alkaloids, (*R*)-(+)-2-phenylpiperdine (**11**) and (2*R*,6*S*)-(+)-dihydropinidine (**14**) was described.

Acknowledgments. This work was supported by a grant from the National Institutes of Health.

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21. Selected properties: (+)-**3**: mp 92-93.5 °C, $[\alpha]^{20}_D$ +29.9 (*c* 1.4, $CHCl_3$), >97% ee; (-)-**4**: oil, $[\alpha]^{20}_D$ −10.7 (*c* 1.2, $CHCl_3$), 97% ee; (+)-**5**: mp 92-93.5 °C, $[\alpha]^{20}_D$ +28.0 (*c* 1.3, $CHCl_3$); (-)- **6**: mp 56-57 °C, $[\alpha]^{20}_D$ −11.4 (*c* 1.2, $CHCl_3$); (+)-**10**: mp 119-121 °C, $[\alpha]^{20}_D$ +73.6 (*c* 1.4, $CHCl_3$); (-)-**12**: oil, $[\alpha]^{20}_D$ −12.5 (*c* 1.5, $CHCl_3$).