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A new asymmetric synthesis of (*S*)-(+)-pipecoline and (*S*)-(+)- and (*R*)-(−)-coniine by reductive photocyclization of dienamides

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Abstract

(*S*)-(+)-Pipecoline and both enantiomers of coniine were synthesized, in good yields, by a reductive photocyclization of chiral dienamides. Enantioselectivities of up to 75% were obtained. © 2000 Published by Elsevier Science Ltd.

Keywords: reductive photocyclization; dienamides; 2-substituted piperidines; (*S*)-(+)- and (*R*)-(−)-coniine; (*S*)-(+)-pipecoline.

The development of synthetic routes to 2-substituted piperidine alkaloids **1** is of great interest due to their occurrence in nature and their significant biological and pharmacological properties.[1]

Numerous asymmetric syntheses of optically active piperidines with a stereogenic carbon at the 2-position have been described. Most of them involved chiral intermediates which were cyclized into enantioenriched or enantiopure 2-substituted piperidines. These intermediates were prepared from a variety of chiral auxiliaries derived from phenylglycinol,[2] 2-substituted pyrrolidines,[3] 8-phenyl menthol,[4] sultam,[5] α-methylbenzylamine[6] or amino acids.[7] Other methodologies involved catalytic methods[8] or the chiral lithiation–intramolecular cyclization sequence of appropriate *N*-Boc-*N*-(3-halopropyl)-allylamines.[9]

More recently, different strategies to prepare 2-substituted piperidines from an already built piperidine ring have been reported, such as asymmetric reduction of cyclic imines,[10] enzymatic resolution,[11] alkylation of chiral 1,3,4-oxadiazinane[12] or nucleophilic addition on *N*-acyliminium ion.[13]

Moreover, since the work of Ninomiya[14] little attention has been paid to photochemical methods to synthesize monocyclic piperidine alkaloids.

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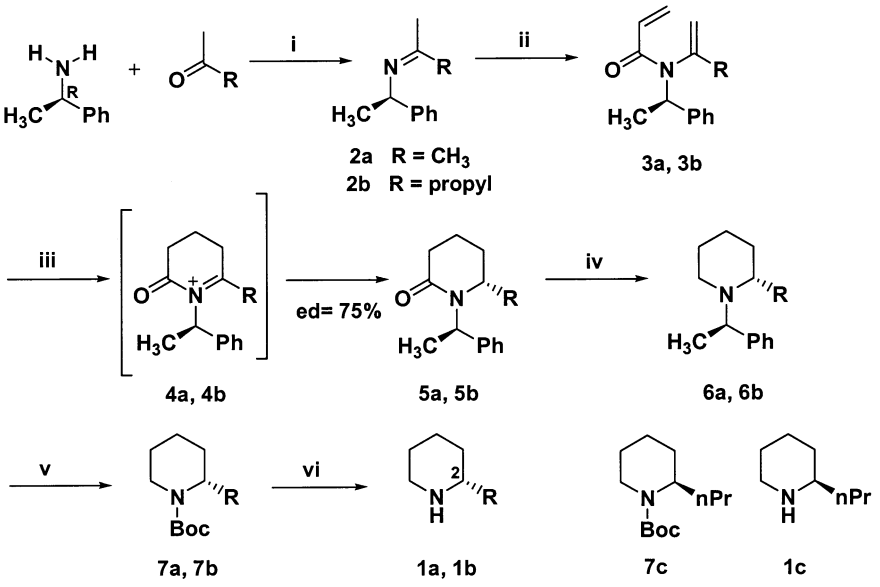
We now report a new, short and enantioselective synthesis of (*S*)-(+)-pipecoline,[2b,15] an alkaloid of *P. sabiniana* Dougl. and of both enantiomers of coniine,[2b,10–12,15] a hemlock alkaloid, based on the reductive photocyclization of the readily available chiral dienamides **3** (Scheme 1). The chiral auxiliary was (*R*)- or (*S*)-α-methylbenzylamine, allowing access to both enantiomers of the desired piperidines.



Scheme 1. **Reagents**: **i**, benzene, $ZnCl_2$, reflux, Dean–Stark; **ii**, acryloyl chloride, NEt_3 (1.5 equiv.), THF, rt; **iii**, *hv*, quartz reactor, low pressure mercury lamp, $NaBH_4$ in benzene:toluene:methanol; 58:28:14; **iv**, LAH, THF, reflux; **v**, H_2, $Pd(OH)_2$, Boc_2O, MeOH; **vi**, TFA, anisole, CH_2Cl_2

The imine **2** was obtained in excellent yield (**2a**, 77%; **2b**, 74%) by condensation of (*R*)-α-methylbenzylamine on acetone or pentan-2-one. *N*-acylation of the imine **2** with acryloyl chloride in the presence of 1.5 equivalents of triethylamine at room temperature gave the dienamide **3**, which is the key intermediate in our synthesis (**3a**, 77%; **3b**, 51%).

The photocyclization of the dienamide **3** was the crucial step and its irradiation led to the intermediate acyliminium ion **4** which was reduced in situ by sodium borohydride to give the piperidin-2-one **5**[16] (50%).

The solvents and the temperature of irradiation were chosen after optimization trials. The best results, in chemical yield and stereoselectivity, were obtained when the irradiation of the dienamide **3** was run in a mixture of benzene:toluene:methanol (58:28:14) at −20°C in a quartz reactor with a low pressure mercury lamp. The diastereomeric excess, determined by ^1H and by using an ^{13}C inverse gated decoupling sequence, was 75%.

The stereochemical outcome of this reaction could be explained by the nucleophilic addition of hydride on the non-isolated intermediate iminium ion **4** by the less hindered of its two diastereotopic faces.[17,18]

The lactam **5** was then reduced to piperidine **6** with $LiAlH_4$ (**6a**, 91%; **6b**, 77%). The piperidine **6** was debenzylated and the alkaloids thus obtained, (*S*)-(+)-pipecoline and (*S*)-(+)-coniine, were converted in situ to their *tert*-butoxycarbamate derivatives **7a** and **7b** in order to avoid the manipulation of volatile and toxic alkaloids.[19]

The antipodal (*R*)-(−)-*N*-Boc-coniine **7c** was obtained by the same procedure using (*S*)-α-methylbenzylamine as the chiral auxiliary.

Cleavage of the carbamoyl group by treatment of small quantities of compound **7** with trifluoroacetic acid and anisole led to (*S*)-(+)-pipecoline, (*S*)-(+)- and (*R*)-(−)-coniine in 90% enantiomeric excess.[20]

In conclusion, we described a short, efficient and enantioselective synthesis of 2-substituted piperidines: (*S*)-(+)-pipecoline, (*S*)-(+)- and (*R*)-(−)-coniine, in excellent enantiomeric excess, by means of reductive photocyclization of dienamides prepared from (*R*)- or (*S*)-α-methylbenzylamine as chiral auxiliary.

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16. A typical procedure is given for the preparation of *N*-(α-methylbenzyl)-6-propylpiperidin-2-one **5b**: sodium borohydride (660 mg, 17.4 mmol) was added to a stirred solution of the dienamide **3b** (500 mg, 2.05 mmol) in a mixture of benzene (85 ml)/toluene (45 ml)/methanol (20 ml) at −20°C. When the added sodium borohydride was dissolved, the resulting solution was irradiated, in a quartz reactor with a low pressure mercury lamp, for 48 hours. The reaction mixture was then evaporated. Water was added to the residue and the mixture was extracted with CH_2Cl_2 (3×15 ml). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on SiO_2 (AcOEt:hexane; 30:70) of the crude product gave the compound **5b** (250 mg, 1.02 mmol), shown to be a mixture of two diastereoisomers (ratio = 87:12) as determined by ^1H and ^{13}C NMR; IR ($CHCl_3$) 1635 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 0.58 (t, 3H, $J = 7.5$ Hz), 0.63–0.67 (m, 1H), 0.77–0.90 (m, 1H), 1.01–1.13 (m, 1H), 1.17–1.28 (m, 1H), 1.54 (d, 3H, $J = 7.0$ Hz), 1.56–1.71 (m, 2H), 1.73–1.84 (m, 2H), 2.32–2.46 (m, 2H), 3.32–3.40 (m, 1H), 5.67 (q, 1H, $J = 7.0$ Hz), 7.05–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 13.9, 15.9, 16.3, 19.4, 25.6, 31.0, 34.5, 52.5, 53.1, 127.1–128.2, 140.9, 169.8. The spectral data for this compound matched in all aspects those reported in the literature[17].
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19. Preparation of (*S*)-(+)-*N*-Boc-2-propylpiperidine **7b**: to a solution of piperidine **6b** (220 mg, 0.96 mmol) in 10 ml of AcOEt was added Boc_2O (230 mg, 1.05 mmol) and $Pd(OH)_2$ (22 mg). The suspension was vigorously stirred in a Paar apparatus under hydrogene (4 atm.) at room temperature for 15 hours. After filtration of catalyst, the solvent was evaporated. A solution of NaOH (4N) (5 ml) and THF (10 ml) was added to the residue and the mixture was stirred at room temperature for 1 hour. After addition of ether to the mixture and extraction, the extract was dried and evaporated. Chromatography on SiO_2 (AcOEt:hexane; 1:20 with a few drops of NEt_3) of the crude product gave the expected piperidine **7b** with an enantiomeric excess better than 90%; $[\alpha]_D^{20}$ 28.5 (*c* 1.35 $CHCl_3$) {lit.[10] $[\alpha]_D^{20}$ 30.5 (*c* 1.30 $CHCl_3$)}; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 0.90 (t, 3H, $J=7.2$ Hz), 1.20–1.67 (m, 6H), 1.44 (s, 9H), 2.73 (t, 1H, $J=13.3$ Hz), 3.95 (m, 1H), 4.19 (m, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 14.1, 19.1, 19.5, 25.7, 28.5, 31.9, 38.7, 50.2, 78.9, 155.2. Specific rotation of other *N*-Boc-piperidines: (*S*)-(+)-*N*-Boc-2-methylpiperidine **7a**: $[\alpha]_D^{20}$ 46 (*c* 0.86 $CHCl_3$) {lit.[15] $[\alpha]_D^{20}$ 50.9 (*c* 0.83 $CHCl_3$)}; (*R*)-(−)-*N*-Boc-2-propylpiperidine **7c**: $[\alpha]_D^{23}$ −28.4 (*c* 1.36 $CHCl_3$) {lit.[3] $[\alpha]_D^{23}$ −31.5 (*c* 0.86 $CHCl_3$)}.
20. ^{1}H and ^{13}C spectroscopic data are in agreement with those reported in literature.[15]