Tetrahedron: Asymmetry Vol. 4, No. 2, pp. 189-192, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
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Enantiospecific Synthesis of *N*-Benzyl-2-alkyl Pyrrolidines and Piperidines Mediated by Chiral Organoborane Reagents

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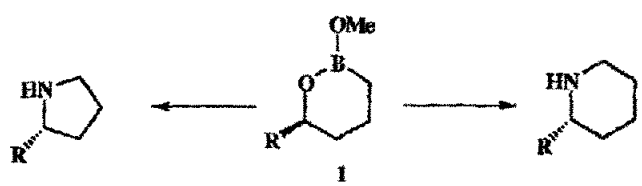
(*Received in UK 22 December* 1992; *accepted 5 January* 1993)

Abstact: *A new general method for synthesizing N-benzyl-2-alkylpyrrolidines and N-benzyl-2-alkylpiperidines, having very high enantiomeric excess, has been achieved starting from aldehydes and organoborane reagents.*

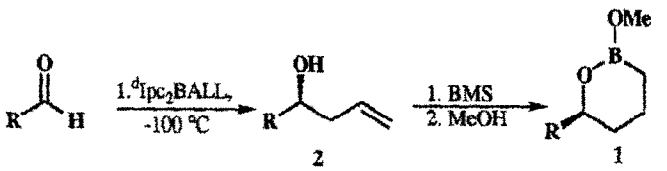
Substituted pyrrolidine and piperidine derivatives are abundant in nature and have diverse physiological activities.[2] Although a number of groups have reported the synthesis of 2-substituted pyrrolidines and piperidines in the racemic form,[3] the asymmetric synthesis of these compounds has been a relatively recent development.[4] However, only a few studies describe a single, unified method for the synthesis of both the five- and the six-membered nitrogen heterocycles.[5] During the course of our program on the asymmetric hydroboration of enamines, [6] we became interested in the synthesis of enantiomerically pure 2-alkylpyrrolidines and 2-alkylpiperidines. We have found that a hydroboration-methanolysis protocol converts homoallylic alcohols[7] predominantly into 6-alkyl-2-methoxy-1,2-oxaborinanes 1. We were interested in developing a method for converting 1 into 2-alkylpyrrolidines and 2-alkylpiperidines (eq. 1).



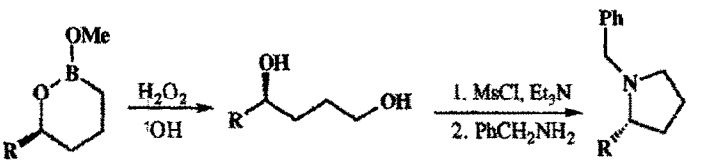
1 (1)

We now wish to describe our preliminary results on the conversion of **1** into *N*-benzyl-2-alkylpyrrolidines and *N*-benzyl-2-alkylpiperidines. This procedure is experimentally convenient and provides final products in >98% enantiomeric purity. Additionally, starting material **1** is readily accessible from enantiomerically pure homoallylic alcohols.[7]

Our synthesis of *N*-benzyl-2-alkylpyrrolidines and *N*-benzyl-2-alkylpiperidines began with the hydroboration-methanolysis reaction of the known homoallylic alcohols **2**, prepared from ^{d}B-allyl-diisopinocampheylborane ($^{d}Ipc_2BALL$) and aldehydes.[7] Thus, the hydroboration-methanolysis of (*R*)-1-octen-4-ol with borane-dimethylsulfide (BMS) provided (*R*)-6-butyl-2-methoxy-1,2-oxaborinane in essentially quantitative yield. This boronic ester was oxidized to the corresponding 1,4-diol which was converted into a dimesylate and cyclized with benzylamine [8] to give (*S*)-N-benzyl-2-butylpyrrolidine.[9,10] Similarly, (*S*)-1-octen-4-ol was converted into (*R*)-*N*-benzyl-2-butylpyrrolidine. Following this general procedure several *N*-benzyl-2-alkylpyrrolidines of known configuration were synthesized (eqs. 2 and 3, Table 1).



(2)

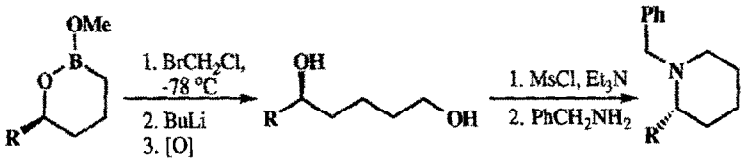


(3)

R = *n*-Bu, *n*-Heptyl, 3-Pentyl

For analytical purpose, a portion of these *N*-benzyl-2-alkylpyrrolidines were debenzylated[11] using $Pd(OH)_2$-C/H_2 and converted into the corresponding MTPA-amides.[12] Capillary GC analysis on a 30 m Methylsilicone column showed that these 2-alkylpyrrolidines were >98% enantiomerically pure.

The synthesis of *N*-benzyl-2-alkylpiperidines was achieved from the corresponding optically active 1,5-diols. These were readily prepared from the common boronic ester intermediate (**1**) by an one-carbon homologation-oxidation sequence.[13] Thus, hydroboration-methanolysis of (*R*)-1-hepten-4-ol followed by an one-carbon homologation-oxidation gave (*R*)-1,5-octanediol in essentially quantitative yield. As above, mesylation and subsequent cyclization with benzylamine[8] produced (*S*)-*N*-benzyl-2-propylpiperidine(*N*-benzylconiine) (eq. 4, Table 1).[9,14]



(4)

R = Me, *n*-Pr

In summary, we have shown that chiral homoallylic alcohols (99% ee), obtained from aldehydes and $^{d}Ipc_2BALL$, are easily converted into *N*-benzyl-2-alkylpyrrolidines and piperidines of high enantiomeric purity. We are currently evaluating this method for the synthesis of optically active *cis*- and *trans*- 2,5-dialkylpyrrolidines and 2,6-dialkylpiperidines.

Table 1. *N*-Benzyl-2-alkylpyrrolidines and *N*-Benzyl-2-alkylpiperidines of Very High Enantiomeric Purity[a]

heterocyclic product	yield, %[b]	bp °C, (Torr)	α^{25}_{D}, (deg)[c]	% ee[d]	config.
N-benzyl-2-butylpyrrolidine	76	90-92 (0.5)	+49.2	>98	*S*
N-benzyl-2-butylpyrrolidine	65	90-92 (0.5)	-49.4	>98	*R*
N-benzyl-2-heptylpyrrolidine	62	128-132 (0.3)	+50.5	>98	*S*
N-benzyl-2-heptylpyrrolidine	54	129-133 (0.3)	-50.6	>98	*R*
N-benzyl-2-(3-pentyl)pyrrolidine	75	100-102 (0.3)	+69.2[e]	>98	*R*[f]
N-benzyl-2-(3-pentyl)pyrrolidine	70	101-104 (0.3)	-69.1[e]	>98	*S*[f]
N-benzyl-2-methylpiperidine	71	72-74 (0.5)	+68.2	>98	*S*
N-benzyl-2-propylpiperidine	64	67-69 (0.5)	+86.7	>98[g]	*S*

[a]Prepared starting from the corresponding homoallylic alcohols of 99 % ee. [b]Isolated yield. [c]Observed rotations (neat, *l* 1.0). [d]Determined by capillary GC analysis of the MTPA amides of the debenzylated amines. [e]Specific rotations (*c* 2, *n*-pentane). [f]Change in configuration is due to change in the priority assignment. [g]Predicted in analogy with the other results.

Acknowledgments. This research was supported by faculty research funds granted by the University of California, Santa Cruz.

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9. All new compounds were characterized by ^{1}H and ^{13}C NMR and Mass spectroscopy.
10. The following procedure for the synthesis of (*S*)-*N*-benzyl-2-butylpyrrolidine is representative. Hydroboration of the homoallylic alcohol was achieved by the dropwise addition of BMS (2.5 mL, 25 mmol) to a 1.0 M THF solution of (*R*)-1-octen-4-ol (25 mmol, 99% ee) at 0 °C. After an hour, methanol (25 mmol) was added and the solution was stirred for one more hour. It was then oxidized using 30% H_2O_2 (30 mmol) in the presence of 3 M NaOH (10 mL). Separation, extraction with diethyl ether, drying and solvent removal afforded the crude (*R*)-1,4-octanediol in essentially quantitative yield. Mesylation of the diol and cyclization with benzylamine was carried out according to the literature procedure[8] to afford (*S*)-*N*-benzyl-2-butylpyrrolidine in 76% yield: bp 90-92 °C/0.5 Torr; α^{25}_{D} +49.2 (Neat, *l* 1.0).
11. Debenzylation of the *N*-benzyl-2-alkylpyrrolidines and piperidines were sluggish at ambient temperature and pressure. We are currently investigating the use of p-methoxybenzylamine for the ring closure.
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14. The following procedure for the synthesis of (*S*)-*N*-benzylconiine is representative. Hydroboration of the homoallylic alcohol was achieved by the dropwise addition of BMS (2.5 mL, 25 mmol) to a 1.0 M THF solution of (*R*)-1-hepten-4-ol (25 mmol, 99% ee) at 0 °C. After an hour, methanol (25 mmol) was added and the solution was stirred for one more hour. After the addition of bromochloromethane (33 mmol) the reaction mixture was cooled to -78 °C and *n*-butyllithium (13.2 mL, 33 mmol) was added with stirring over a period of 0.5 h. The solution was allowed to warm to 25 °C and then refluxed for 1.5 h, during which time a white precipitate was formed. The reaction mixture was cooled to 25 °C and oxidized with alkaline hydrogen peroxide.[10] Separation, extraction with diethyl ether, drying and solvent removal afforded the crude (*R*)-1,5-octanediol in essentially quantitative yield. Mesylation of the diol and cyclization with benzylamine was carried out according to the literature procedure[8] to afford (*S*)-*N*-benzylconiine in 64% yield: bp 67-69 °C/0.5 Torr; α^{25}_{D} +86.7 (Neat, *l* 1.0).