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A NEW ROUTE TO OPTICALLY PURE *cis*- AND *trans*-2,5-DISUBSTITUTED PYRROLIDINES

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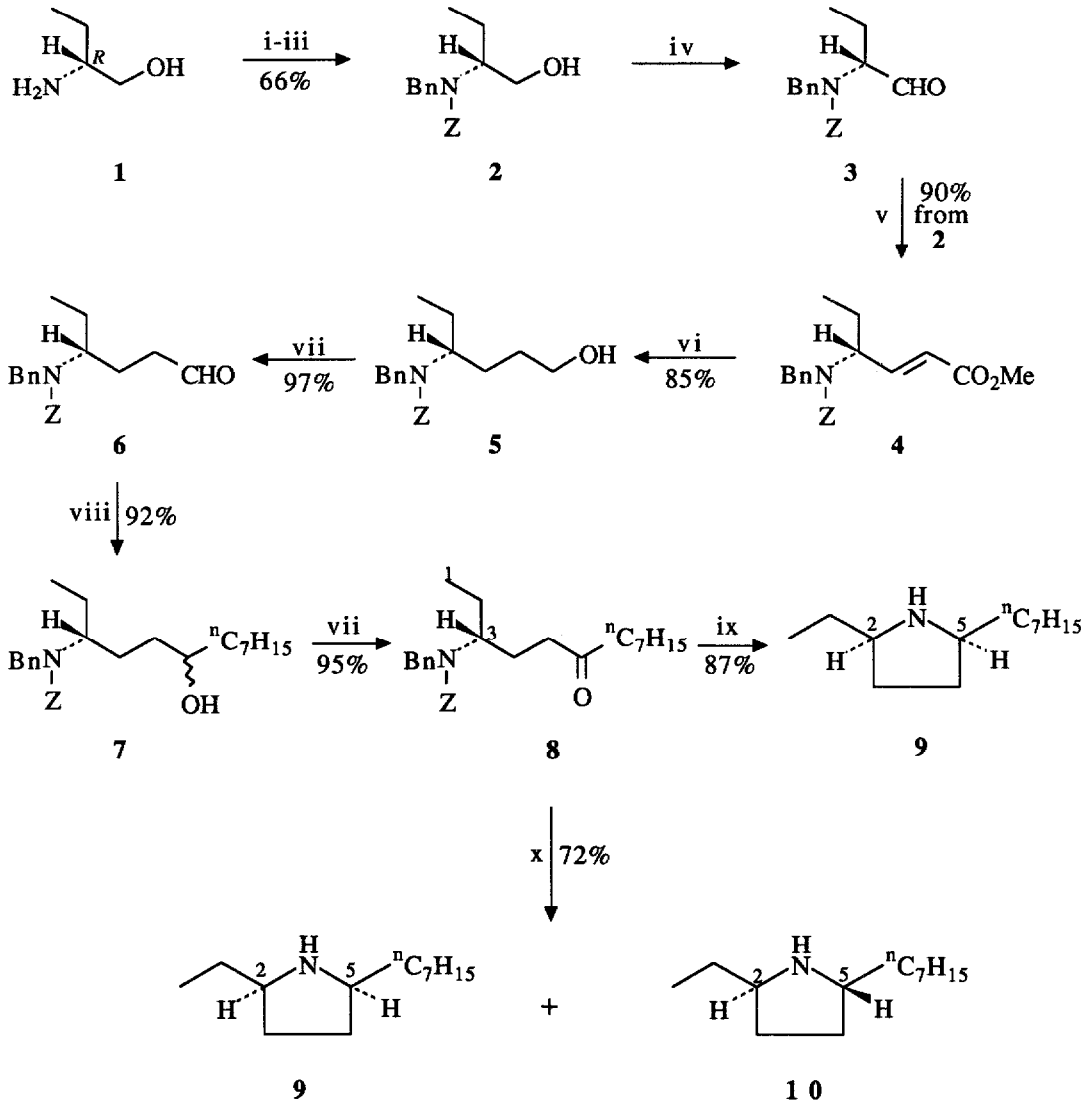
Abstract : A new route to optically pure *cis*- and *trans*-2,5-disubstituted pyrrolidines is described and is illustrated by the enantiospecific synthesis of (2*R*, 5*S*)-(+)-2-ethyl-5-heptylpyrrolidine **9** and (2*R*, 5*R*)-(-)-2-ethyl-5-heptylpyrrolidine **10** starting from (*R*)-(-)-2-amino-1-butanol **1**.

Several 2,5-disubstituted pyrrolidines, pyrrolines and 2-alkyl-6-methylpiperidines are known to occur among the predominant constituents of the venoms of ants belonging to different species of the genera *Solenopsis* and *Monomorium*. These compounds exhibit a wide range of physiological activities which include necrotic, hemolytic, phytotoxic, insecticidal, antibacterial, and antifungal properties.[1] A number of syntheses, mostly in the racemic mode,[2] have been reported for these bases. The only enantioselective syntheses of representative ant pyrrolidine toxins are those reported by Husson *et al.*[3] and by Shiosaki and Rapoport.[4]

In connection with our work relating to chiral synthesis of alkaloids using amino acids as the source of chirality,[5] we describe here a new route to optically pure *cis*- and *trans*-2,5-disubstituted pyrrolidines. Our approach is illustrated by the synthesis of *cis*-(2*R*, 5*S*)-2-ethyl-5-heptylpyrrolidine **9** and trans-(2*R*, 5*R*)-2-ethyl-5-heptylpyrrolidine **10** starting from commercially available (*R*)-(-)-2-amino-1-butanol **1** (see Scheme).

The amino group of the starting (*R*)-(-)-2-amino-1-butanol **1** was fully protected through successive introduction of a benzyl (Bn) and a benzyloxycarbonyl (Z) group to give the alcohol **2**. The aldehyde **3**, obtained by Swern oxidation[6] of **2**, was subjected to Wittig olefination with methyl(triphenylphosphoranylidene)acetate yielding the α,β–unsaturated ester **4**. Reduction of the conjugated ester group of **4** with sodium borohydride in the presence of lithium chloride[7] provided the saturated alcohol **5** which was oxidised with pyridinium chlorochromate (PCC) to the aldehyde **6**[8]. Grignard alkylation of **6** with n-$C_7H_{15}MgBr$ led to the mixture of alcohols **7** which, on PCC oxidation, afforded the ketone **8**. The latter was converted to the 2,5-disubstituted pyrrolidines **9** and **10** by way of two different hydrogenation procedures. Thus, hydrogenation of **8** with 10% Pd-C in methanol removed the amino protecting groups with concomitant ring closure and reduction to give exclusively the *cis*-2,5-disubstituted pyrrolidine **9**, namely, (2*R*, 5*S*)-(+)-2-ethyl-5-heptylpyrrolidine.

Scheme



Reagents and reaction conditions : i. $PhCHO$, $MgSO_4$, CH_2Cl_2, molecular seives 4Å, 25°C; ii. $NaBH_4$, MeOH, at 0°C and then 2h at room temperature; iii. $PhCH_2OCOCl$, NaOH, H_2O-dioxan (1:1), 5°C; iv. Me_2SO, $(COCl)_2$, , Et_3N, CH_2Cl_2, -78°C; v. $Ph_3P{=}CHCO_2Me$, THF, 25°C; vi. $NaBH_4$-LiCl (1:1), EtOH-THF (4:3), 25°C; vii. PCC, CH_2Cl_2, molecular sieves, 4Å, 25°C; viii. n-$C_7H_{15}MgBr$, Et_2O, 25°C; ix. H_2, 10% Pd-C, MeOH, 25°C; x. $HCOONH_4$, 10% Pd-C, MeOH, reflux, 1min.

By contrast, when the reductive deprotection was carried out with ammonium formate[9] in the presence of 10% Pd-C in refluxing methanol under nitrogen, a mixture of *cis*- and *trans*-2,5-disubstituted pyrrolidines **9** and **10** was obtained. The two isomers **9** and **10**, in the ratio 3:2, could be separated by silica gel column chromatography and their structure was established by the ^1H nmr studies of their N-benzyl derivatives using the method of Chan and Hill.[10]

The synthetic (+)-**9** and (-)-**10** had spectral data[11] which fully matched those previously reported.[3] Their enantiomeric homogeneity was established through HPLC and 400 MHz ^1H n.m.r. analysis of their (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivatives (Mosher amides).[12]

In conclusion, the route we have described here seems to be sufficeintly general in as much as it should be amenable to an array of amino acids leading to the synthesis of a variety of differently substituted 2,5-dialkylpyrrolidines. Furthermore, it should be possible to extend this method to 2,6-disubstituted piperidines and our current efforts are directed toward this goal.

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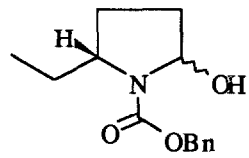
8. It is to be noted that, when the reaction sequence described for **1** to **6** was carried out with a singly protected amino group such as with a benzyloxycarbonyl (Z), the aldehyde corresponding to **6** (see Scheme) was obtained only in the cyclic form **6a** - an observation which is not without precedent in the literature [F.G. Salituro, N. Agarwal, T. Hoffmann and D.H. Rich, *J. Med. Chem.*, (1987), **30**, 286].



6 a

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11. All reported yields are for purified materials isolated from column chromatography and all compounds gave spectroscopic data in agreement with the assigned structures. Selected physical data include the following.

8 : colourless oil; ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.80 (t, 6H, 2 x Me), 1.43 (m, 14H, 7 x CH_2), 2.10 (m, 4H, 2 x CH_2), 3.83 (m, 1H, H-3), 4.30 (s, 2H, CH_2Ph), 5.13 (s, 2H, CO_2CH_2Ph), 7.23 (m, 10H, 2 x Ph); EIMS m/z 437($M^{+\cdot}$); $[\alpha]_D$ -4° (c 2, $CHCl_3$).

9 : colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.86 (t, 3H, Me, *J* 5.5), 1.02 (t, 3H, Me, *J* 7.5), 1.14-1.48 (m, 10H), 1.68-1.94 (m, 4H), 1.94-2.30 (m, 4H), 3.43 (m, 2H, H-2, H-5). ^{13}C NMR (50,2 MHz, $CDCl_3$) δ : 11.7, 14.1 (2 x Me), 22.7, 27.6, 28.9, 29.4, 29.9, 30.5, 30.9, 32.1, 36.6 (9 x CH_2), 59.5 (C-2), 61.0 (C-5). CIMS m/z 198 (MH^+); $[\alpha]_D$ +4° (c 2, $CHCl_3$), lit.[3] +7° (c 0.5, $CHCl_3$).

10 : colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.96 (t, 3H, Me, *J* 6), 1.00 (t, 3H, Me, *J* 7.5), 1.15-1.50(m, 10H), 1.50-2.00 (m, 4H), 2.20-2.90 (m, 4H), 3.41 (m, 2H, H-2, H-5). ^{13}C NMR (50,2 MHz, $CDCl_3$) δ : 11.4, 14.1 (2 x Me), 22.7, 27.3, 28.7, 29.3, 29.7, 31.8, 31.9, 32.2, 36.4 (9 x CH_2), 58.2(C-2), 59.8 (C-5); $[\alpha]_D$ -4° (c 0.6, $CHCl_3$), lit.[3] +4° (c 2, $CHCl_3$) for (+)-enantiomer.

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