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Handy Access to Chiral N,N'-Disubstituted 3-Aminopyrrolidines.

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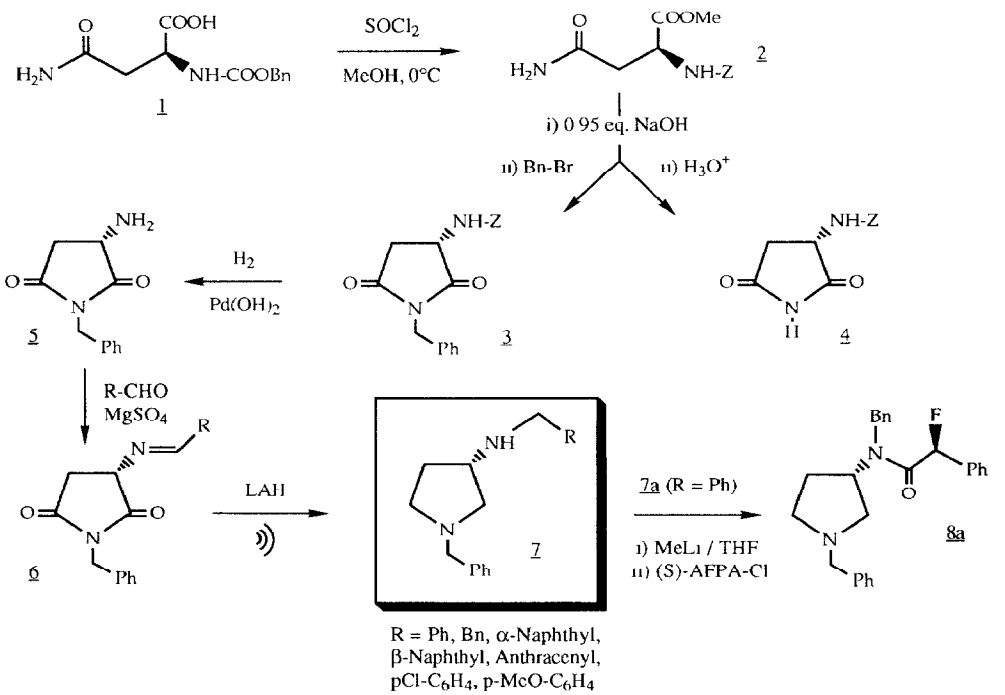
Abstract: A new and rapid synthesis of (S)-3-aminopyrrolidines 7 is proposed from N-protected (S)-Asparagine. Basic cyclization of methyl N-Z-(S)-Asparaginate 1 followed by one-pot N-benzylation directly leads to (S)-aminosuccinimide 3 which, after cleavage of the Z-protecting group, is converted to corresponding imines and readily reduced to disubstituted chiral 3-aminopyrrolidines 7. Almost no racemization (≤5%) of the original amino-acid asymmetric center may be observed.

The 3-pyrrolidinol and 3-aminopyrrolidine structures are found in several important molecules such as cyclopeptide alkaloids[1], neurotoxic fungal metabolites[2], antifilarial[3] and anti-emetic[4] agents as well as antibiotics of the quinolone carboxylic acid series[5]. However, if the access to racemic[1,3] or optically active[6] 3-pyrrolidinols is well documented, the only asymmetric route to its amino counterpart proposed to date is also based on 3-pyrrolidinol[5]. The previous interest of our laboratory in chiral amide utilization in enantioselective synthesis[7], as well as excellent results recently obtained by several groups using diamines as chiral inductors in alkylation[8] or hydroxyalkylation[9] reactions prompted us to search for a convenient access to large amounts of diversely substituted 3-aminopyrrolidines. We have therefore developed a gram-scale versatile process based on commercially available N-benzyloxycarbonyl-L-asparagine (Z-Asp) 1.

Indeed, according to literature[10], this latter compound may be readily cyclized through a low temperature $SOCl_2$ treatment; in our hands however this process turned out to be rather erratic and we therefore decided to first esterify the aminoacid into its' methyl ester 2 (3 eq. $SOCl_2$ in dry MeOH, 15 min. at 0°C, yield = 97%). This compound undergoes easy cyclization when treated by 0.95 eq.[11] of sodium hydroxide (0.5N sol.) in water for 15 min at room temperature[12]. Advantage may then be taken of the *in-situ* sodium imidate formation to directly N-alkylate by phase transfer (1.8 eq. Ph-CH_2-Br in CH_2Cl_2, 0.1 eq. $N(Bu)_4I$, RT, 4h, yield = 65%)

the newly formed imide into its N-benzyl equivalent 3 (Scheme 1). At that point the absence of racemization may be checked by α_D comparison to literature[12] of aminosuccinimide 4. The obtained solid 3 was conveniently purified by washing with small amounts of methanol. Selective cleavage of the carbobenzyloxy (Z) group was then achieved by catalytic hydrogenolysis (1 atm. H_2, $Pd(OH)_2$, MeOH, RT, 12h, quantitative) leading to 3-amino-N-benzyl-succinimide 5. The thus obtained primary amine may then be condensed with benzaldehyde (THF, $MgSO_4$, RT, 6h) leading to corresponding imine 6a (R=Ph) which may be directly reduced by a large excess of lithium-aluminium hydride[13] under ultrasonic conditions[14] (3 molar eq., THF, 35°C, 8h). The N,N'-disubstituted amino-3-pyrrolidines 7 are recovered after work-up and flash chromatography (SiO_2, CH_2Cl_2 + 5% MeOH eluant) in good overall yields (≈ 50% in 5 steps) and spectral features are in full agreement with expected structure[15]. This same procedure could be succesfully applied to a large variety of aromatic aldehydes in similar yields and has also be extended to benzophenone using O'Donnell's methodology[16] to prepare the intermediate imine.



Scheme 1

Enantiomeric excess has been checked on 3-(N-benzylamino)-N-benzyl-pyrrolidine 7a (R=Ph) through chemical derivatization using the α-fluorophenylacetic acid chloride (AFPA-Cl), a chiral auxiliary recently developed mainly by Beguin and Hamman[17]. Bulky 7a was converted to its lithium amide (1 eq. MeLi, THF, -78°C, 0.5h), to which was added the AFPA-Cl (THF, -78°C, 3h) according to the conditions recently described by Brown and colleagues[18] for application of Mosher's α-(methoxy-trifluoromethyl-phenyl)-acetic acid

(MTPA)[19] derivatization process to hindered secondary amines. This procedure leads in excellent yield[20] to expected fluoramide 8a while neither MTPA nor camphorsulfonic chloride could give satisfactory results in these conditions. Aqueous $NaHCO_3$ washing of the AFPA derivatization medium followed by ^{19}F NMR examination of the crude mixture ($CDCl_3$) leads to two pairs of doublets (J^2_{H-F} = 48Hz) of very different intensities. Displayed on Figure 1 are the spectra obtained from derivatization of an identical 80% e.e. amino-3-pyrrolidine sample by either S-(+) or R-(-)-AFPA. It is clear from these that both outer doublets correspond to a same diastereoisomer while inner doublets represent the other one.

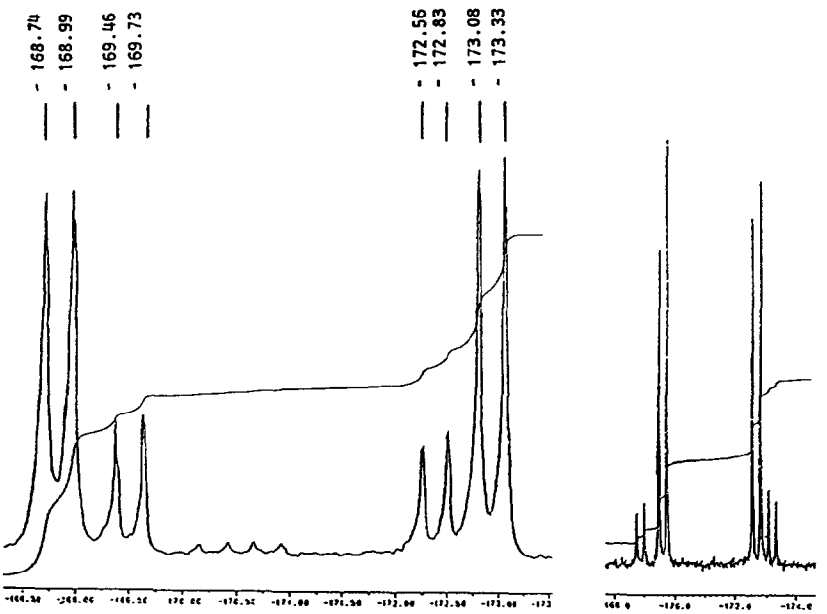


Figure 1: ^{19}F NMR Spectra (190MHz, ppm, $CDCl_3$, $CFCl_3$ internal standard) of fluoramides 8a as obtained from R-(-) *(left)* or S-(+)-AFPA *(right)*.

This splitting is more than likely due to the coexistence in solution of two conformers for each diastereoisomer, a well-known phenomenon for tertiary amides[21]. This hypothesis could unfortunately not be checked by solvent nor temperature effect (no coalescence of signals observed up to 65°C). The fair gap ($\Delta\delta$ = 0.7 ppm) between doublets makes the sharp assignment of d.e. easy; we thus measure final e.e. of 7a to be 86%, starting from a 91% e.e. commercial sample (Sigma) of Z-Asp 1

Generalization to related structures and application of these new compounds as chiral templates to different types of reaction (aldolization, alkylation, cycloaddition,...) are currently under investigation in our laboratory.

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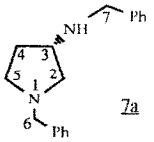

7a

400MHz ^{1}H NMR (ppm, $CDCl_3$): 7.25 (m, 10H, Ph), 3.71 (s, 2H^6), 3.60 (dd$_{AB}$, 2H^7), 3.35 (m, 1H^3), 2.75 (dd, J_{gem} = 9.0, ^{3}J = 6.5, 1H^2), 2.64 (m, 1H^5), 2.52 (m, 1H^5), 2.40 (dd, J_{gem} = 9.0, ^{3}J = 5.0, 1H^2), 2.13 (m, 1H^4), 1.75 (s, NH), 1.61 (m, 1H^4). 50MHz ^{13}C NMR (ppm, $CDCl_3$): 139.9, 138.7 (Ar^{IV}), 128.5, 128.0, 127.8, 126.5 (Ar^{III}), 60.3 (C^2), 60.1 (C^6), 56.4 (C^3), 52.7 (C^5), 52.0 (C^7), 31.8 (C^4). MS (EI, 70eV): m/z = 266 (M+1, 4%), 175 (8%), 161 (15%), 91 (Bn, 100%).

$[\alpha]_D^{27}$ = +1.7 (c = 2.0, $CHCl_3$).

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