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Asymmetric Synthesis. XXXI[1]. Synthesis of 2-Substituted Piperazines from Chiral Non-racemic Lactams.

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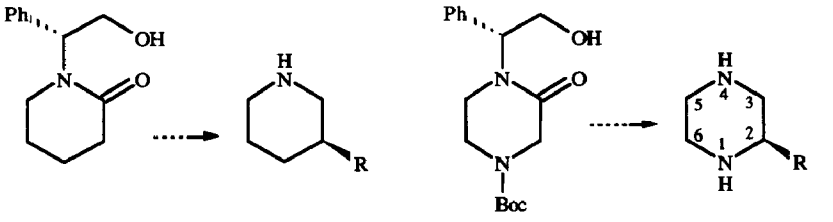
Key-words : Asymmetric synthesis ; 2-substituted piperazines; diastereoselective alkylation of lactams.

Abstract : The preparation of lactam **2** from R-(-)-phenylglycinol and N-Boc glycine is described. Diastereoselective alkylation of **2** allowed the preparation of piperazine derivatives in an optically pure form.

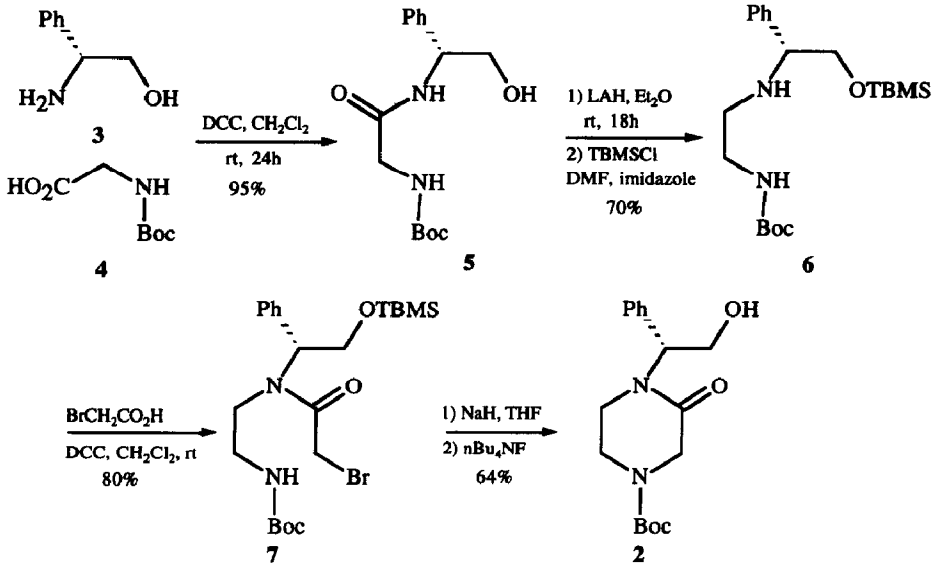
Although the piperazine ring is often encountered in biologically active compounds (antibiotics[2], CNS acting drugs[3], antiarrhythmic agents[4]...) there is a lack of general methods for the asymmetric synthesis of 2 and/ or 6-substituted derivatives. The simplest approach consists of preparation of 2,5-dioxopiperazines *via* the cyclodimerization of amino acids[5a,b] or peptides.[5c,d,6] However this method suffers from formation of linear products by intermolecular condensation, appreciable racemization, and is limited to the substituents of natural amino-acids. A few methods exist which might lead to unsymmetrical piperazine derivatives[7] but they are not generally applicable to enantiomerically pure compounds.

In connection with our program of asymmetric synthesis of piperidines[1], *via* diastereoselective alkylation of chiral non-racemic lactam **1**, we decided to investigate the application of this methodology to the preparation of 2-substituted piperazines from the analog lactam **2**.

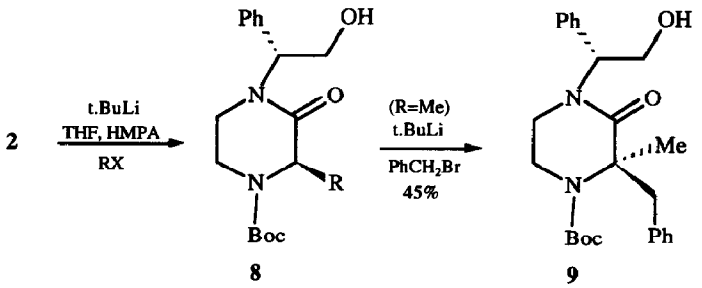


1 2

We used the N-Boc substituent, reasoning that the presence of a carbamate function located at N-1 would allow a good differentiation between the reactivity of the nitrogens and the possibility of an easy selective deprotection. Furthermore, the presence of a carbamate function should permit the introduction of a substituent on C-6 *via* a metalation process.[8]



(R) (-)-Phenylglycinol **3** was condensed with N-Boc glycine in the presence of DCC to furnish amide **5**. Reduction of the carbonyl group of the amide, followed by protection of the hydroxyl as a silyl ether was achieved in 70 % yield. Selective condensation with bromoacetic acid was carried out in the presence of DCC. The key step was the cyclization of bromo derivative **7** which was performed with NaH in THF. A single product was obtained which was deprotected under classical conditions leading to required synthon **2**.[9] This synthesis allowed the preparation of **2** on a multigram scale, with some steps requiring no purification. Optical purity of compound **2** was proved to be superior to 99% by chiral HPLC.

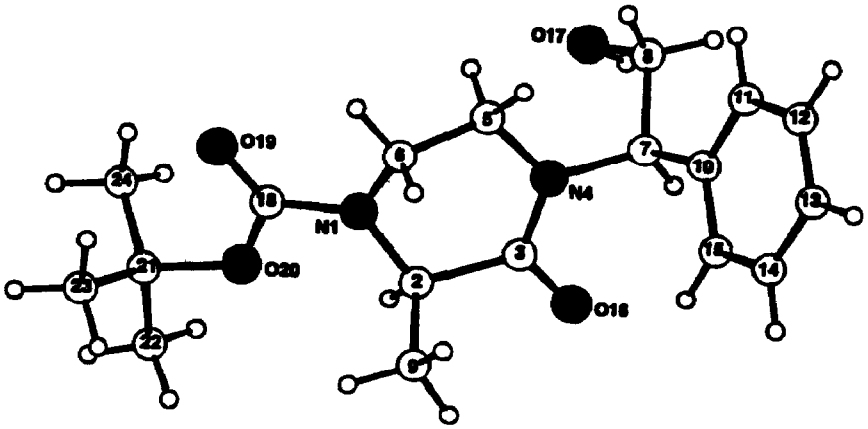


Table

RX	Compound	yield[a] (%)	de (%)
CH_3I	**8a**	80	≥ 92[b]
$PhCH_2Br$	**8b**	60	≥ 90[c]
$CH_2=CHCH_2Br$	**8c**	65	≥ 90[c]

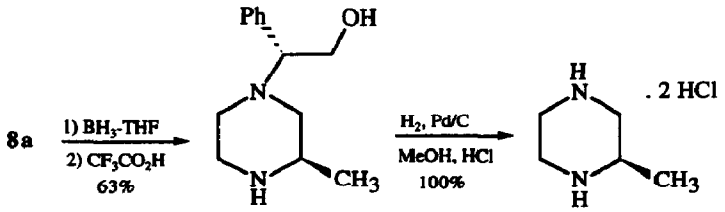
a) Based on isolated products, b) Determined by HPLC and NMR, c) determined by ^1H and ^{13}C NMR.

With compound **2** in hand, we investigated the alkylation under the conditions previously described in the piperidine series.[1] **2** was reacted with t.BuLi (2.0 eq) in THF in the presence of HMPA, then halogeno reagent was added at -78°C.[10] Compounds **8** were obtained as a mixture of diastereomeric compounds (de ≥ 90%) (Table) easily separable by flash chromatography. It was impossible to determine the configuration of the newly created asymmetric center by NMR studies. This problem was solved by an X-ray analysis of the methylated derivative **8a**.[11](Figure)



Figure

Bis-alkylation was performed starting from compound **8a** ; the second substituent was introduced with complete diastereoselection affording compound **9** in moderate yield (Y = 45 %). In order to demonstrate the efficiency of our method for the preparation of substituted piperazines we synthesized (R)-(+)-2-methylpiperazine **11**[6] in 3 steps from **8a** in 63 % yield.



When O-silylated derivative of **2** was submitted to alkylation conditions, a loss of diastereoselectivity was observed (de < 20 %). This result is in favour of the model proposed previously to explain the diastereoselectivity observed in the piperidine series.[1]

Application of this methodology to the preparation of multisubstituted piperazines is under investigation.

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References and notes

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9. All new compounds were fully characterized by IR, MS, ^{1}H and ^{13}C NMR spectroscopy and exhibit satisfactory combustion analyses for C, H and N. **2a**: ^{1}H NMR (δ ppm) 1.4 (s, 9 H Boc), 2.82 (s, OH), 3.08 (m, 1H), 3.3 (m, 1H), 3.45 (ddd, 1H, J = 13.3; 7.2 and 3.8 Hz), 3.62 (m, 1H), 4.15 (m, 2xH-2; 2xH-8),5.76 (dd, H-7 J = 8.6 and 5.6 Hz), 7.3 (m, 5H ar). ^{13}C NMR: 28.4 (C-22, C-23 and C24), 40.3 (C-6), 42.4 (C-5), 48.0 (C-2), 58.7 (C-7), 61.6 (C-8), 80.9 (C-21), 127.9 ; 128.3 ; 129 ; 136.1 (C ar), 154.2 (C-18), 167.5 (C-3). IR (film): 1696 and 1636.5 cm^{-1}. MS: 321 (MH^+), 302 (M-18), 289 (M-31), 264 (M-54), 261 (M-57).[α] $_D^{20}$ = -81 (c=0.88 ; $CHCl_3$).
10. Preparation of **8a** is typical. To a solution of lactam **2** (500 mg, 1.56 mmol), HMPA (0.550 ml) in THF (20 ml) under nitrogen was added t.BuLi (2 eq) at - 78°C. The mixture was stirred for 20 min and MeI (3 eq, 300 µl) was then added dropwise. After stirring at - 78°C for 2 h, the mixture was treated with satured NH_4Cl, extracted with CH_2Cl_2, washed with brine and concentrated to give an oil which was purified by chromatography on silica gel with cyclohexane/ ethyl acetate 50/50 (420 mg 80 %).
11. **X-ray structure analysis** : Crystal data . $C_{18}H_{26}O_4N_2$, M_w = 334.42, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 9.001 (4), b = 9.707 (5), c = 21.186 (16) Å, V = 1851 (2) $Å^3$, d_c = 1.20 g cm^{-3}, F(000) = 720, λ (Cu Kα) = 1.5418 Å, µ = 0.65 mm^{-1} ; 2963 Nonius diffractometric intensities measured, 1583 unique of which 993 with I > 2.5 σ(I) considered as observed.The structure was solved by direct methods using *SHELXS86* and refined by full matrix least-squares with *SHELX76*, minimizing the function $\Sigma w (Fo-|Fc|)^2$. The hydrogen atoms, located in difference Fourier maps, were replaced at theoretical positions (d C-H = 1.00 Å) - except that of the hydroxyl group HO17, refined - and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.051 and R_w = 0.065 (with $R_w = \{\Sigma w(Fo-|Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.001672\ Fo^2]$]. No residual was higher than 0.20 e $Å^{-3}$ in the final difference map. In the crystal structure, the molecules are linked in chains by means of intermolecular hydrogen bonds observed between the hydroxyl O17-H of one molecule and the oxygen atom O16 of the neighbouring one (distances O17...O16 = 2.732 (6), H17...O16 = 1.75 (6) Å, angle O17-H...O16 = 161°). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

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