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Diastereoselective synthesis of enantiopure differentially protected *cis*-4,5-diaminopiperidin-2-one through intramolecular transamidation

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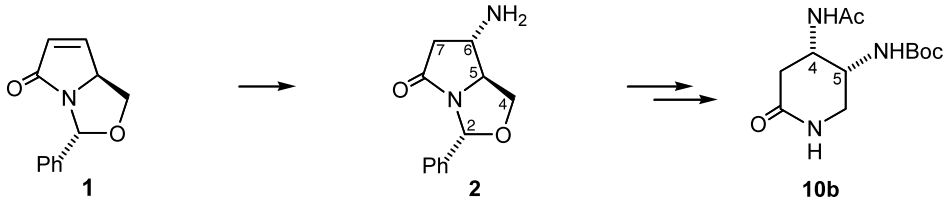
Abstract—The diastereoselective synthesis of enantiopure differentially protected *cis*-4,5-diaminopiperidin-2-one was achieved by means of conjugate addition of ammonia to an unsaturated γ-lactam and transamidation reaction with ring expansion as the main steps.

During our studies on the synthesis of enantiopure polysubstituted piperidines,[1,2] and piperidin-2-ones,[3,4] we developed the first route to *cis*-4,5-diaminopiperidin-2-ones via an intramolecular Mitsunobu reaction of hydroxamates, followed by N_1–O bond cleavage with SmI_2.[3] Compounds of this type were unknown before and could constitute structural sub-units in interesting more complex molecules.[5] Particularly, the possibility of orthogonal protections on the amino groups and their use as peptidomimetics,[6,7] make these compounds attractive as intermediates in the synthesis of conformationally constrained peptides analogues. Here is reported a novel access to enantiopure protected *cis*-4,5-diaminopiperidinone involving a transamidation of (4*S*,5*R*)-4-acetylamino-5-aminomethylpyrrolidinone **9b** derived from (*S*)-pyroglutaminol.[8]

The easy diastereoselective conjugate addition of benzylamine to unsaturated bicyclic lactam **1** in the presence of water has already been described.[9] Taking these results in account, the direct introduction of a primary amino group at C-6 was investigated. Thus, looking for a simple protocol, it was observed that the 6-amino derivative **2** could be obtained (62%) by stirring a mixture of unsaturated lactam **1** and 32% NH_4OH solution in a closed flask at 20°C (Scheme 1).[10]

However, compound **2** was not very stable and slowly afforded another product **3** on standing at room temperature (Scheme 2). The NMR data of **2** and **3** (Table 1) indicate a change in C-6 substitution. Indeed, the chemical shifts of H-6 (**2**: 3.58 ppm, **3**: 3.34 ppm) and C-6 (**2**: 53.27 ppm, **3**: 57.88 ppm) constitute the main differences, all coupling constants being very similar in both compounds.

The elementary analysis of adduct **3** ($C_{24}H_{25}N_3O_4$) confirmed by HRMS [$(MH)^+$ at m/z 420.1945] provided evidence for its dimeric structure. Partial β-elimination of ammonia and 1,4-addition of one molecule of **2** to the resulting unsaturated γ-lactam could explain its formation (Scheme 2).



Scheme 1.

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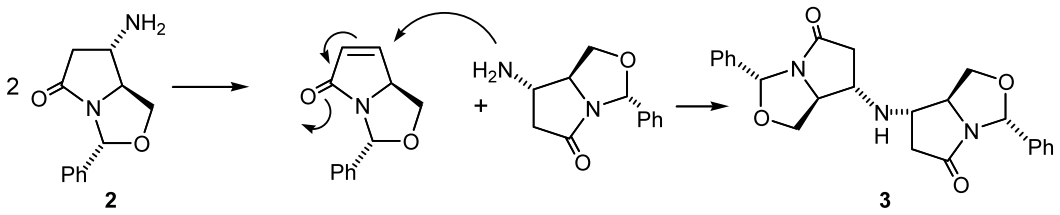


Scheme 2.

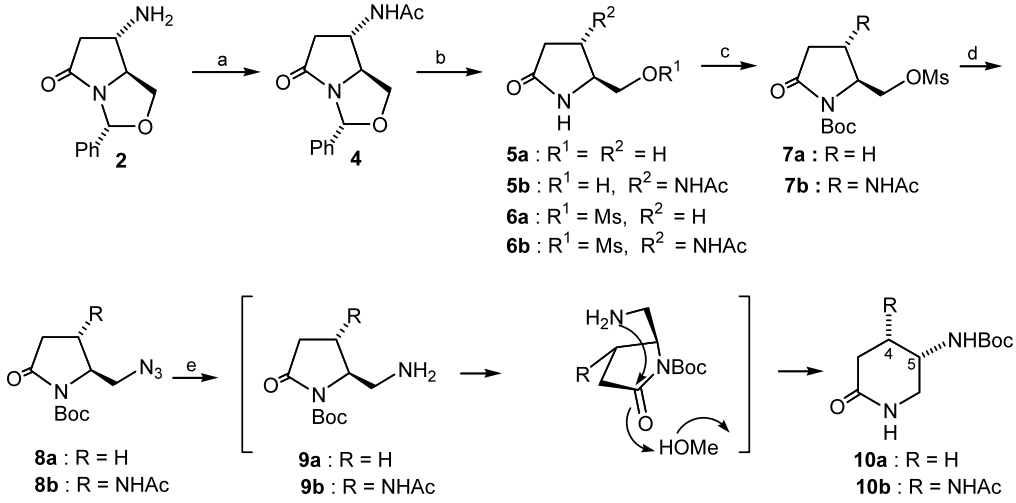
Table 1. Comparison of relevant chemical shifts (^1H, ^{13}C) of **2** and **3** ($CDCl_3$)

δ (ppm)	C-2	H-4	C-4	H-5	C-5	H-6	C-6	H-7	C-7
2	87.39	4.22 3.70	70.04	3.82	67.79	3.58	53.27	2.80 2.62	44.52
3	87.21	4.24 3.65	70.34	3.84	65.84	3.34	57.88	2.78 2.60	41.98

Ring expansion of amino-lactams through transamidation have already been described and applied to the synthesis of macrocyclic amino-lactams in the 'Zip' reaction.[11] But until now, the construction of 5-amino-δ-lactams by this route was poorly explored.[4,8] For an efficient transamidation reaction with ring extension, the presence of electron-withdrawing groups, such as alkoxycarbonyl residues, on the nitrogen atom was required to enhance the reactivity of lactam carbonyl. Azide **8a**, prepared from (*S*)-5-hydroxymethylpyrrolidin-2-one **5a** (88% overall yield),[12] was used as a model for this purpose. The reduction of the azido group (H_2, 10% Pd/C) was followed by heating in methanol to complete the formation of the known (*S*)-5-(*N*-Boc)aminopiperidin-2-one **10a** (95%).[13] In order to extend the scope of this finding, a similar sequence was applied to 4-*N*-acetylamino-5-hydroxymethylpyrrolidinone **5b** (Scheme 3).

Accordingly, after a classical *N*-acylation step, lactam **2** was transformed to the corresponding lactam **4** (Ac_2O–pyridine, 20°C, 99% yield);[10] thus, the oxaziridine ring was hydrolyzed selectively and quantitatively by treatment with aqueous trifluoroacetic acid affording **5b**.[14] Then, compound **5b** was converted into *N*-Boc mesylate **7b** in two steps (67 and 89%, respectively). 5-Azidomethyl derivative **8b** (NaN_3, DMF, 91%) was reduced in methanol (H_2, 10% Pd/C). Under these mild conditions, complete transamidation occurred directly affording **10b** in 96% yield (Scheme 3).[15] In the particular case of the *N*-Boc aminomethyl intermediates **9**, no additive base was needed for the ring opening by intramolecular nucleophilic attack of the primary amino group. Electrophilic assistance of the solvent, and activation of the pyrrolidinone carbonyl by the presence of *N*-Boc protecting group, account for the efficiency of the process.

In conclusion, a concise and efficient method has been developed for the synthesis of 5-aminopiperidin-2-one **10a** and differentially *N*,*N*′-protected (4*S*,5*R*)-4,5-diaminopiperidin-2-one **10b** from (*S*)-pyroglutaminol in



Scheme 3. *Reagents and conditions*: (a) Ac_2O, py, 20°C; (b) CF_3CO_2H, THF–H_2O, rt; (c) MsCl, py, 0°C to rt; Boc_2O, DMAP, CH_3CN; (d) NaN_3, DMF, 50°C; (e) H_2, 10% Pd/C, CH_3OH.

very mild conditions. This methodology could be extended to 5-hydroxymethylpyrrolidin-2-ones bearing various other substituents in 3 and 4 positions and to their N_1-sulfonyl analogues.

References

1. Langlois, N.; Calvez, O. *Synth. Commun.* **1998**, *28*, 4471–4477.
2. Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, *39*, 9447–9450.
3. Langlois, N.; Calvez, O. *Tetrahedron Lett.* **2000**, *41*, 8285–8288.
4. Langlois, N. *Org. Lett.* **2002**, 185–187.
5. Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 1587–1589.
6. Weber, K.; Gmeiner, P. *Synlett* **1998**, 885–887.
7. Lehmann, T.; Michel, D.; Glänzel, M.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 1389–1400.
8. Preliminary communication: Langlois, N. IXth Conference, French–American Chemical Society, June 2–6, 2002, Saint-Malo, France.
9. Langlois, N.; Calvez, O.; Radom, M. O. *Tetrahedron Lett.* **1997**, *38*, 8037–8040.
10. *Preparation of **2** and **4***: To a solution of unsaturated lactam **1** (504 mg, 2.5 mmol) in THF (2.5 mL) was added NH_4OH (32% solution, 5.0 mL) and the mixture was stirred at rt until complete conversion. After dilution with CH_2Cl_2, the organic phase was washed twice with water, dried over $MgSO_4$ and evaporated to dryness. The residue could be purified by chromatography on silica gel (eluent: CH_2Cl_2–MeOH 93:7) to afford the compound **2** (62%), or directly acylated with Ac_2O (0.46 mL) in pyridine (5.7 mL) at rt for 18 h. Then, the mixture was cooled to 0°C, and methanol (4 mL) was added. After being stirred for 0.5 h, the solvents were evaporated under reduced pressure and the product was purified by chromatography on silica gel (eluent: CH_2Cl_2–MeOH 96:4) giving rise to **4** (398 mg, 61% for two steps): $[\alpha]_D^{25} = +92$ (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, $\delta = 0$: TMS): 7.37 (m, 5H, H-Ar), 6.60 (m, 1H, NH), 6.28 (s, 1H, H-2), 4.37 (1H), 4.31 (m, 1H, H-6), 3.86 (m, 2H), 2.85 (dd, 1H, $J_{7a,7b} = 16.6$, $J_{7a,6} = 8.9$ Hz, Ha-7), 2.73 (dd, 1H, $J_{7a,7b} = 16.6$, $J_{7b,6} = 9.8$ Hz, Hb-7), 1.96 (s, 3H, $COCH_3$); ^{13}C NMR (75.0 MHz, $CDCl_3$): 174.29 (CO), 170.76 (CO), 138.23 (qC, Ar), 128.86, 128.58, 126.01 (CH, Ar), 87.09 (C-2), 71.32 (C-4), 66.41 (NCH), 50.03 (NCH), 40.15 (C-7), 22.87 ($COCH_3$). Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.61; H, 6.34; N, 10.71%.
11. (a) Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. *Angew. Chem., Int. Ed. Engl.* **1977**, 861–862; (b) Kramer, U.; Schmid, H.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 811–815; (c) Wasserman, H. H.; Matsuyama, H.; Robinson, R. P. *Tetrahedron* **2002**, *58*, 7177–7190.
12. Ackerman, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122–132.
13. Panday, S. K.; Langlois, N. *Tetrahedron Lett.* **1995**, *36*, 8205–8208.
14. Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G. *Tetrahedron Lett.* **1997**, *38*, 5891–5894.
15. *Preparation of **10b***: 5-Azidomethyl derivative **5b** (53.0 mg, 0.178 mmol) in MeOH (1.0 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (9.0 mg) for 48 h. The catalyst was filtered on Celite® and washed with MeOH. The solution was evaporated under reduced pressure affording **10b** (46.4 mg, 96%) after crystallization by addition of CH_2Cl_2: mp 123–126°C; $[\alpha]_D^{25} = -63.5$ (*c* 0.62, MeOH); IR: 3430, 3407, 3318, 3005, 1697 (sh), 1669, 1505 cm^{-1}; MS (ESI): 294 [$(MNa)^+$, 100%)], 272 $(MH)^+$, 248, 216; ^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (m, 1H, $NHCOCH_3$), 6.64 (m, 1H, NH), 5.98 (m, 1H, $NHCO_2$), 4.38 (m, 1H, H-4), 4.05 (m, 1H, H-5), 3.63, 3.23 (2 br dd, 2H, H_2-6), 2.83, 2.31 (2 br dd, 2H, H_2-3), 2.01 (s, 3H, $COCH_3$), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR (75.0 MHz, $CDCl_3$): 171.50 (CO), 170.33 (CO), 156.46 (NCO_2), 80.38 (qC, *t*-Bu), 48.12, 47.13, 43.68 (C-4, C-5, C-6), 28.32 (CH_3, *t*-Bu), 23.11 ($COCH_3$).