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Enantio- and diastereoselective synthesis of 2,5-disubstituted pyrrolidines through a multicomponent Ugi reaction and their transformation into bicyclic scaffolds

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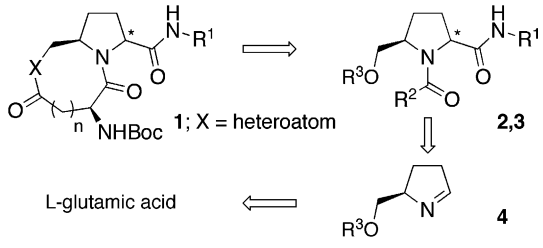
Abstract—A new enantio- and diastereoselective synthesis of 2,5-disubstituted pyrrolidines through a multicomponent approach has been developed, using highly reactive pyrrolines **4** as preformed cyclic imines. The pyrrolidines obtained using protected aspartic acid as acid component in the Ugi condensation have been transformed into two epimeric bicyclic lactones **18**, **19**, which may find an application as external reverse turn inducers.

Recently, the replacement of natural amino acids in peptides with non-proteinogenic derivatives has become an important goal in synthetic organic chemistry. In particular the synthesis of peptidomimetics that mimic natural dipeptides is very attractive, since these motifs, if characterized by a suitable conformation, can induce a reverse turn in an oligopeptidic chain connected to them.[1] This fact is of great importance for the synthesis of ligands of receptors, such as the integrins, involved in many diseases connected with cell-adhesion processes, like angiogenesis and tumor metastasis.[2] We recently reported the synthesis of a new semi-rigid derivative, having the characteristics of 'external reverse turn scaffold',[3] employing an Ugi four component (4CR) reaction, followed by a highly stereoselective ring closing metathesis.[4] Within the same project we explored also the possibility of synthesizing a novel family of epimeric bicyclic scaffolds through a highly convergent strategy, exploiting the Ugi condensation of chiral pyrrolines, followed by an appropriate cyclization. These derivatives may behave as reverse turn inducers, in line with previous results obtained with other bicylic lactams.[5]

For our purposes we first studied the enantioselective synthesis of monosubstituted pyrrolines **4a**,**b** (Scheme 2),[6] to be used as common intermediates for the preparation of a small library of epimeric 2,5-disubstitued pyrrolidines **2**, **3** (Scheme 1). Among several recently reported methods for the synthesis of pyrrolines,[7,8] we choose, for the preparation of **4a**,**b**, the strategy involving the formation of the heterocyclic ring as the last step, through a Staudinger Aza–Wittig reaction.[7] We started therefore from diprotected triol **5**, readily obtained from L-glutamic acid by a known procedure (Scheme 2).[9] Further elaboration of **5** required an independent manipulation of the three alcoholic functionalities: among the primary hydroxy groups only one is conserved in a protected form in the pyrrolines **4a**,**b**, while the other one had to be oxidized to an aldehyde to give **9a**,**b**. The stereospecific transformation of the secondary hydroxy group into an azide was performed in excellent yield by a nucleophilic displacement.[10] This synthesis allowed the preparation of two pyrrolines through a non-racemizing sequence[11] in an excellent overall yield [59% (**4a**) and 54% (**4b**) from **5**].



Scheme 1.

Keywords: Multicomponent Ugi reaction; Pyrrolines; Reverse turn inducer.
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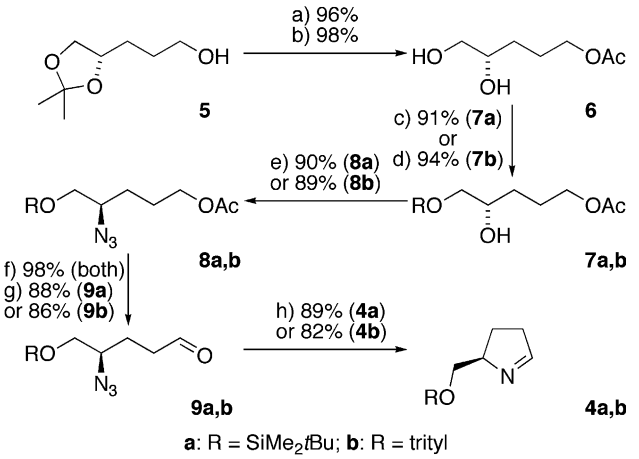
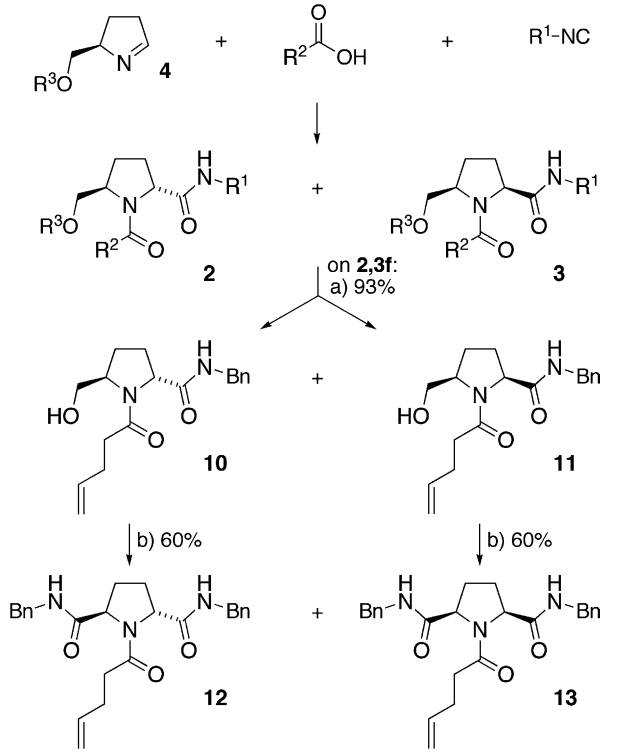


Scheme 2. Reagents and conditions: (a) Ac_2O, Py, rt; (b) AcOH, H_2O, rt; (c) *t*-$BuMe_2SiCl$, imidazole, DMAP, THF, rt; (d) trityl chloride, Py, CH_2Cl_2, rt; (e) (i) MsCl, Et_3N, CH_2Cl_2, −30 °C; (ii) NaN_3, DMF, 65 °C; (f) KOH, MeOH, 0 °C; (g) $(COCl)_2$, DMSO, Et_3N, −78 °C → −50 °C; (h) PPh_3, THF, 50 °C.

With compounds **4a**,**b** in hand we turned our attention on the Ugi multicomponent reaction (Scheme 3).[12] Only one example of Ugi reaction employing pyrrolines was previously reported[13] and, in general, only few examples involving cyclic imines are known.[14] Pyrrolines **4a**,**b** showed a high degree of reactivity and, under standard conditions, the reaction was usually complete within 1–2 h. The yields ranged from moderate to excellent (Table 1). On the other hand the diastereomeric ratio was in all cases only moderate. Surprisingly, when the bulkier trityl O-protecting group was employed, the reaction was nearly not stereoselective at all (entry 2).



Scheme 3. Reagents and conditions: (a) HF, CH_3CN, 0 °C, then separation of the alcohols and independent transformation on both; (b) (i) Jones oxidation; (ii) benzyl amine, 2,4,6-collidine, HATU [(O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate], DMF/CH_2Cl_2, rt.

The relative configuration was unambiguously demonstrated, in the case of **2**, **3f**, by converting them into symmetric triamides **12** and **13** (Scheme 3). Compound **12**, deriving from the prevailing diastereoisomer, showed itself to be optically active {$[\alpha]_D$ +6.0 (*c* 0.68, EtOH)}, demonstrating therefore a *trans* relationship of the substituents in the parent compound **2f**. On the contrary, the epimer, derived from **3f**, showed, as expected, no optical activity, being a meso compound.

Although we do not have yet a definite proof for the relative stereochemistry of the other adducts, we can reasonably assume that, especially for compounds **2** and **3a**,**g**,**h**,**i**, all deriving from the same pyrroline and the same isocyanide, the major stereoisomer has a *trans* relative configuration as well. It is highly unlikely, indeed, that the nature of the carboxylic component can have such a great influence on the stereoselection as to reverse the stereoselectivity.[15] It should be noted that the single previous example of Ugi condensation with chiral pyrrolines[13] afforded preferentially the *cis* isomers. The stereogenic centre was however placed in a different position. On the other hand, Ugi reaction with other cyclic imines[14] afforded usually the *trans* isomer as major product.

Finally, we demonstrated that the Ugi reaction did not cause racemization on the stereocentre of **4**. Using L- and D-Fmoc-Ala as acid component (entries 7 and 8) only two different diastereoisomers were identified by HPLC analysis.

Compounds **2**, **3i**, obtained using a N-protected bifunctional amino acid (aspartic acid in this case), showed the opportunity for the first synthetic application of these derivatives, which is summarized in Scheme 4.

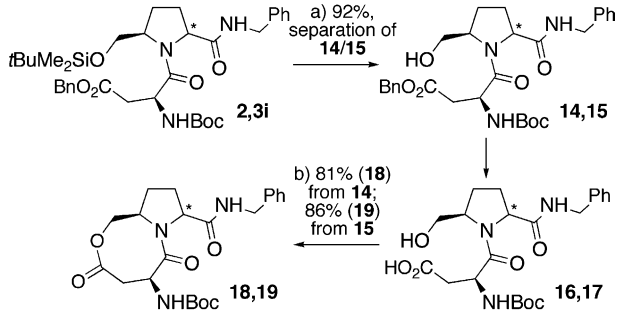
For preparative purposes we separated the two epimers after removal of the silyl ether. We then independently submitted hydroxymethyl pyrrolidines **14** and **15** to the cleavage of the ester moiety under hydrogenolytic conditions. The final step, that is, the formation of an eight-membered lactone, was realized using PyBop [(benzotriazolyl-1-oxy)tripyrrolidinophosphonium hexafluorophosphate] as condensing agent under high dilution conditions. In this case only the bicyclic lactones **18**, **19** were isolated in excellent overall yield.[16]

The size of the lactone/lactam ring can of course be decided before performing the Ugi reaction, just by a correct choice of the diacid. Moreover, the two protected functionalities of **2**, **3i** can be elaborated in a different fashion, in order to create bicyclic derivatives[1] with different structures (Scheme 1). The presence of a protected amine and of an amide functionality bonded to these scaffolds allows the introduction of amino acid units in order to assemble various acyclic or cyclic pep-

Table 1. Ugi reaction of pyrrolines **4**

Entry[a]	R^1	R^2–CO_2H	R^3	Products	Yield% (**2**+**3**)	Dr (**2**:**3**)
1	Bn	*n*-C_3H_7–CO_2H	$SiMe_2$*t*-Bu	**2**, **3a**	45	68:32[b]
2	Bn	*n*-C_3H_7–CO_2H	Trityl	**2**, **3b**	70	53:47[c]
3	CH_2CO_2*t*-Bu	Ph–CO_2H	$SiMe_2$*t*-Bu	**2**, **3c**	62[d]	53:47[e,f]
4	*n*-Bu	Ph–CO_2H	$SiMe_2$*t*-Bu	**2**, **3d**	44[d]	64:36[b]
5	*t*-Bu	Ph–CO_2H	$SiMe_2$*t*-Bu	**2**, **3e**	46[d]	63:37[b]
6	Bn	CH_2=$CH(CH_2)_2$–CO_2H	$SiMe_2$*t*-Bu	**2**, **3f**	60	68:32[e]
7	Bn	Fmoc-L-Ala	$SiMe_2$*t*-Bu	**2**, **3g**	80	64:36[e]
8	Bn	Fmoc-D-Ala	$SiMe_2$*t*-Bu	**2**, **3h**	69	65:35[e]
9	Bn	Boc-L-Asp(OBn)	$SiMe_2$*t*-Bu	**2**, **3i**	85	66:34[e]

[a] All the reactions were carried out in MeOH (0.30 M) at rt for 1–2 h.
[b] By GC–MS.
[c] By weight.
[d] Yield from **9a**.
[e] By HPLC.
[f] Determined after $SiMe_2$*t*-Bu removal (*n*-Bu_4NF, THF, rt, 69%).



Scheme 4. Reagents and conditions: (a) HF, CH_3CN, 0 °C; (b) (i) H_2, Pd/C, EtOH, rt; (ii) PyBOP, Et_3N, CH_2Cl_2 2 mM, reflux.

tidomimetics. Studies in these fields are still under investigation in our group and will be reported in due course.

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10. In our case the displacement, promoted by sodium azide on the mesylate, worked well, contrary to a previous report on similar compounds,[7] and we obtained a complete conversion of **7a**,**b** into **8a**,**b** in excellent yields. Moreover this two-step sequence is safer than the one-step Mitsunobu reaction involving hydrazoic acid used by the same authors to overcome the decomposition of the mesylate.
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15. The ^1H and ^{13}C NMR spectra of compounds **2**, **3**, registered at room temperature in d_6-DMSO, show the presence of two rotamers, deriving from restricted rotation around the N(ring)–CO bond. When registered at 100 °C, the ^{13}C spectra gave only a single set of signals. At the same temperature, the ^1H spectra show usually collapsed signals as well, but they were rather broad. Interestingly in the trans adducts, the NH proton of the major conformer was always downfield (with a typical difference of 0.3–0.6 ppm and a regular rotamer ratio around 2:1), while in the *cis* compounds it fell upfield [with a typical difference

of 0.2–0.5 ppm and a lower (although more varied) rotamer ratio] (^{1}H NMR at room temperature). This trend furtherly confirms that the major stereoisomers have always the same relative configuration.

16. The structure of **18**, **19** was demonstrated by ^{1}H, ^{13}C NMR and IR. Moreover an additional support for ruling out the possibility of dimeric compounds was furnished by HPLC–MS analysis.