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Synthesis of New Perhydro-(1,4)-diazepin-2-ones as Constrained Peptidomimetics

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Abstract : New access to substituted perhydro-(1,4)-diazepin-2-ones has been developed through either a Mitsunobu reaction or an amide bond formation for the cyclisation key step.

Peptidomimetics represent a growing class of biomolecules expected to largely overcome the limitations of natural peptides which preclude their uses as therapeutic tools.[1] Progression from peptides to drugs is currently attempted through their partial substitution by constrained scaffolds resulting in an increase of their selectivity[2] as well as their lipophilicity related to the newly formed hydrophobic collapse.[3]

Beside the well-known benzodiazepines, some other 7-membered heterocycles (as for example tetrahydro-azepinones[4,6-8] or diazepine-diones[4,5]) lacking the fused aryl nucleus and thus, more difficult to prepare, gave very interesting γ-turn mimetics to define the peptide secondary structure. In that way, RGD-dependent binding between fibrinogen and GP IIb/IIIa integrin receptor[6] , angiotensin II receptor ligands[7] as well as HIV-1 protease inhibition[8] were examined. A library of perhydro-diazepine-diones have just been obtained by combinatorial chemistry on solid support.[9] Chiral 1,4-Dia(or Thia)zepin-5-ones were elegantly prepared by intramolecular aminolysis.[10]

As compared to the tetrahydro-azepinone structure already published,[4,6-8] it seemed to us that the perhydrodiazepinone heterocycle depicted in the scheme I could be a better mimetic structure according to the presence of a second nitrogen atom (N_4) on the cycle. In a previous work,[11] we have already achieved the synthesis of a diazepinone mimicking the Ile-Ala-Gly sequence, we wanted to extend this result and develop general methods yielding these heterocycles. We describe herein 2 complementary routes giving readily access to these new class of scaffolds :

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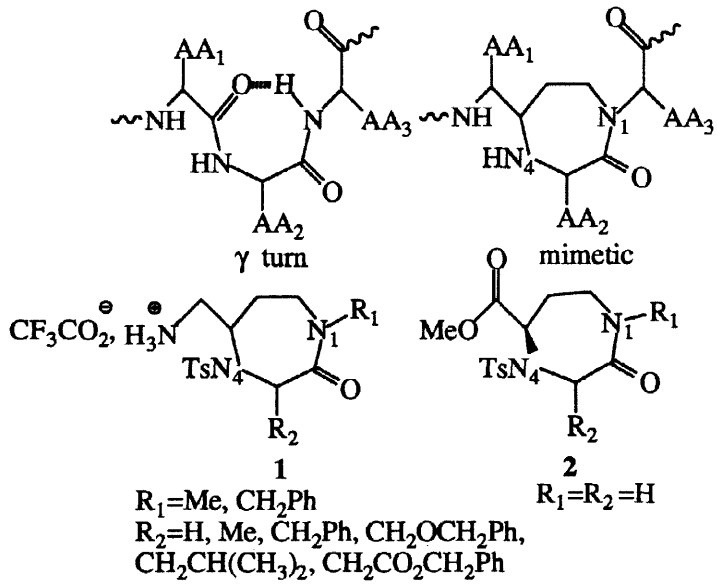
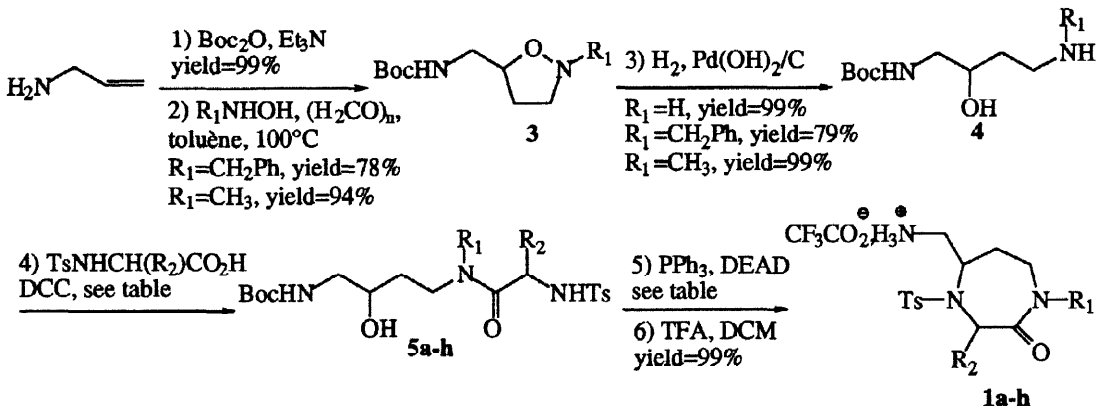


Scheme 1 : perhydrodiazepinone as γ-turn mimetic and target molecules

In the first route, the key step is an intramolecular Mitsunobu cyclisation[12] (Scheme 2) :



Scheme 2

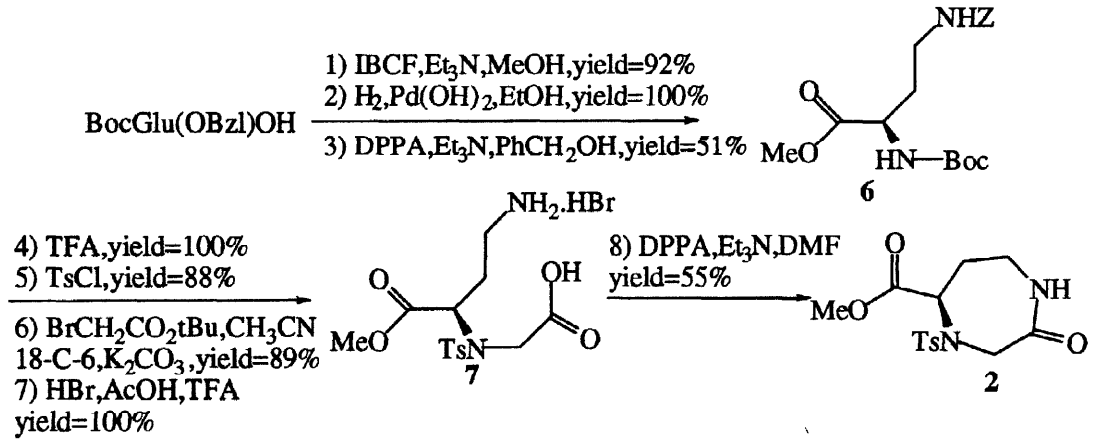
Starting from the readily available Boc-allylamine, the isoxazolidines **3** were easily obtained in one-pot in good yield through nitrone formation performed by addition of hydroxylamines (RNHOH) on a double bond in presence of $(H_2CO)_n$. The ring opening and eventually the N-debenzylation were obtained by hydrogenolysis over $Pd(OH)_2/C$. The resulting diaminoalcohols **4** were N-acylated by N-tosyl α-amino acids to give the linear precursors **5a-h**. Preliminary study of the Mitsunobu cyclisation step has shown that two structural features are required : the NH proton must be sufficiently acidic as with NH-Tos in order to achieve the O-phosphonium group substitution[13] and the presence of a tertiary amide is necessary to yield more easily the right folded conformation leading to cyclisation

which failed with unsubstituted compound **5b** (See Table). When an alkyl group (Me or a Bzl) is grafted on the N_1 atom, the cyclisation is taking place with a very satisfactory yield allowing a reasonably good expectation in the future solid phase version of this reaction.

Compounds	R_1	R_2	Yield (%) of **5** from **4**	Yield (%) of the cyclisation
a	$PhCH_2$	CH_3	65	88
b	H	CH_3	69	0
c	CH_3	CH_3	75	86
d	CH_3	CH_2OCH_2Ph	72	72
e	CH_3	$CH_2CO_2CH_2Ph$	43	65
f	CH_3	$CH_2CH(CH_3)_2$	82	36
g	CH_3	H	30	97
h	CH_3	CH_2Ph	71	70

Table : Synthesis of perhydro-diazepinones **1a-h**.

The second route is dealing with the enantiospecific synthesis of **2** (Scheme 3) :



Scheme 3 : Enantiospecific synthesis of perhydro-diazepinone **2**

Withdrawn from the chiral pool, BocGlu(OBzl)OH was readily methylated, debenzylated and subjected to a modified Curtius reaction[14] using diphenylphosphorylazide (DPPA) on the lateral free carboxylic group in a benzylic alcohol medium containing triethylamine (TEA). The resulting fully protected diamino acid **6** was successively N-Boc deprotected, N-Tosylated and N-alkylated by $BrCH_2CO_2tBu$ in the presence of 18-C-6

crown ether. After acid deprotection, the resulting linear precursor **7** containing both free acid and amine groups was treated with DPPA in DMF,TEA[15] to give the new perhydro diazepinone **2** in acceptable overall yield. It must be stressed that using directly an N-Tos-Glu derivative revealed unsuccessful for the Curtius reaction : instead of the expected product, a pyroGlu derivative was mainly formed. Furthermore, contrary to the previous results, the Mitsunobu reaction with the benzyl glycolate failed to produce the N-alkylated product, problably owing to the peculiar structure of the entering α-hydroxy-ester.[16]

In summary, we have performed, following two complementary routes, the synthesis of different perhydrodiazepinones in good yield. This new scaffolds would be readily inserted in peptidic sequence in order to obtain new peptidomimetics.

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