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Synthesis of New Perhydro-(1,4)-diazepin-2-ones as Constrained Peptidomimetics André Nouvet, Frédéric Lamaty and René Lazaro*

Laboratoire des Arnino acides, Peptides et Protéines (LAPP), UMR 5810 CNRS-Universités Montpellier I et II, Place E. Bataillon, 34095, Montpellier Cedex 05, France.

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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. © 1998 Elsevier Science Ltd. All rights reserved.

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 selectivity² 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 receptor⁶, angiotensin II receptor ligands⁷ as well as HIV-1 protease inhibition⁸ 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 (N₄) 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 :

* fax: + 33 (0) 4 67 14 48 66 e-mail: lazaro@univ-montp2.fr

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

In the first route, the key step is an intramolecular Mitsunobu cyclisation¹² (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 substitution¹³ and the presence of a tertiary amide is necessary to yield more easily the right folded conformation leading to cyclisation

Compounds	R ₁	R ₂	Yield (%) of 5 from 4	Yield (%) of the cyclisation
b	Н	CH ₃	69	0
с	CH3	CH3	75	86
d	CH ₃	CH ₂ OCH ₂ Ph	72	72
e	CH3	CH ₂ CO ₂ CH ₂ Ph	43	65
f	CH ₃	CH ₂ CH(CH ₃) ₂	82	36
g	CH ₃	Н	30	97
h	CH ₃	CH ₂ Ph	71	70

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.

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

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





Withdrawn from the chiral pool, BocGlu(OBzl)OH was readily methylated, debenzylated and subjected to a modified Curtius reaction¹⁴ 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, TEA¹⁵ 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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