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Synthesis of Azepane Scaffolds on Solid Support for Combinatorial Chemistry

Laurence Gauzy, Yves Le Merrer,* Jean-Claude Depezay

Université René Descartes, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, 45, rue des Saints-Pères, 75270 Paris Cedex 06, France.

François Clerc, Serge Mignani

Rhône-Poulenc Rorer S.A. Centre de Recherche de Vitry-Alfortville, 13, quai Jules Guesde, BP14, 94403 Vitry sur Seine Cedex, France.

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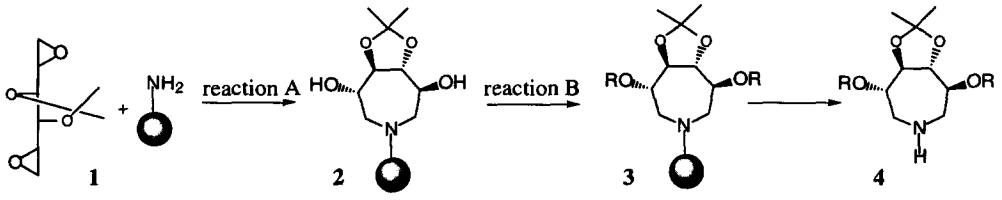
Abstract : Enantiopure C_2-symmetric azepanes have been synthesized on solid support as scaffolds for the synthesis of peptidomimetics in combinatorial chemistry. The key step involves Rink resin as a formal equivalent of ammonia in the nucleophilic opening of L-iditol bis-epoxide.

Keywords : azepane, solid phase synthesis, combinatorial chemistry, Rink resin

In the aim of discovering new drugs, an attractive strategy lies in the development of peptidomimetics. In that goal, former works on somatostatin (SRIF) have shown that the use of different scaffolds[1] could lead to compounds exhibiting more or less affinity for the SRIF receptors. In particular, we developed the utilization of azasugars,[1a] and among them a 3,4,5,6-tetrahydroxy-azepane, as non-peptidic scaffolds in the synthesis of somatostatin analogs.

Recently, a great interest has been devoted to the development of combinatorial chemistry in order to synthesize libraries of small molecules,[2] such as β-turn mimetics,[2g] as an answer to high-throughput biological screening. In particular, a critical issue is the choice of the scaffold that could provide drug candidates for various diseases. Therefore, having azasugars at our disposal as scaffolds in the synthesis of a new potentiel class of bioavailable organic compounds, we wanted to apply their synthesis to combinatorial chemistry. Thus, we present herein our preliminary results concerning the solid phase synthesis of azepanes and their use as scaffolds in the synthesis of new libraries of peptidomimetics.

Scheme 1



The strategy we developed consists in the use of an amine-type resine as a nucleophile, equivalent of ammonia,[3] in the opening of L-iditol bis-epoxide **1**[4] to provide resin-bound azepane **2** (Scheme 1, reaction A). Furthermore, the free alcohol functions of **2** could be transformed into other functional groups (reaction B) to introduce side chains required for biological activity.

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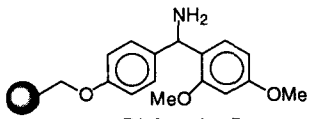
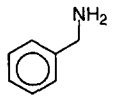
In our point of view, a key feature was the use of a readily cleavable linker, as the Rink linker **5** which is fairly close to benzylamine **6**. It was clear that crowded amine derived from Rink resin **5**, after removal of the Fmoc group,[5] might hinder the opening of bis-epoxide **1**. So, we initially carried out the reaction in liquid-phase on 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **1** with amines **6**, **7** and **8**[6] to evaluate their reactivity. The corresponding *N*-substituted azepane was obtained by reaction in DMF at 80°C, or most easily in methanol at room temperature in about 80% yield after chromatographic purification, even with the more crowded amine **8** which mimics the Rink resin.



Rink resin **5**



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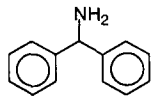

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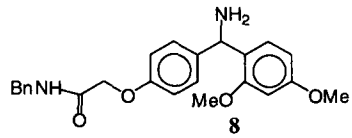

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Next, we attempted to form the azepane on the Rink resin (Table 1) in DMF at 80°C or in $MeOH/CH_2Cl_2$ at room temperature. In the later case, CH_2Cl_2 was used as cosolvent to improve the swelling properties of the resin.

Table 1 : Solid-phase synthesis of azepane

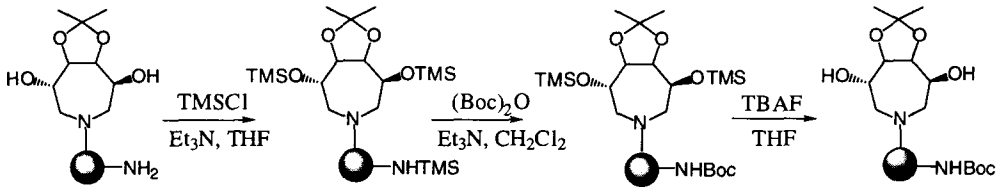
Entry	Reaction conditions A	Loading in azepane[7] **2**[a]
1	**1** (2eq.),[b] DMF, 80°C, 2 days	0.20 mmol/g
2	**1** (2eq.),[b] DMF, 80°C, 5 days	0.45 mmol/g
3	**1** (5eq.),[b] $MeOH/CH_2Cl_2$ 1/1, rt, 2 days	0.23 mmol/g
4	**1** (5eq.),[b] $MeOH/CH_2Cl_2$ 1/1, rt, 5 days	0.21 mmol/g
5	**1** (5eq.),[b] $MeOH/CH_2Cl_2$ 1/4, rt, 3 days	0.12 mmol/g

(a) Initial loading of Rink resin **5** : 0.50 mmol/g.
(b) Equivalent of bis-epoxide **1** for one Rink linker on solid support.

Apparently, the best loading in azepane was obtained by reaction in DMF after heating during 5 days (entry 2), and to a lesser extent by reaction in $MeOH/CH_2Cl_2$ (1/1) at room temperature during 2 days (entry 3). However, after benzoylation of secondary alcohols of **2** (PhCOCl, pyridine, CH_2Cl_2) and cleavage of the resulting **3** from the resin (10% TFA in CH_2Cl_2), the better yield of the free azepane **4** (88%) was obtained *via* the experimental cyclization procedure described in entry 3 (to compare with 43% *via* the experimental cyclization procedure described in entry 2[8]). These results proved that degradation[9] of the resin beads occurred during heating in DMF, so although the overall yields (≅ 20%) were analogues, conditions described in entry 3 revealed to be the best ones.

Before modifying secondary alcohols of **2**, the amine-linkers which were not involved in azepanes were protected to prevent further secondary reactions.[10] Thus, using a modification of a method described by Bolin,[11] the following procedure was developed (Scheme 2). Silylation of secondary hydroxyl groups and free amine-linkers provided both protection for the former and activation for the latter which were then protected as *tert*-butyl-carbamate with $(Boc)_2O$. Subsequent deprotection of silyl ethers involved tetrabutylammonium fluoride in THF.[12]

Scheme 2



Then, in an effort to extend the utilization of resin-bound **2** in combinatorial chemistry, we examined the functionalization of secondary alcohols into esters or carbamates (Table 3). On one hand, considering that carboxylic ester could be introduced *via* a reaction between alcohol and carboxylic acid, anhydride or acyl halide, glycine, acetic anhydride and benzoyl chloride were respectively chosen. Esterification involving glycine could be accomplished in the presence of *N,N'*-diisopropylcarbodiimide (entry 1), while reaction with acetic anhydride and benzoyl chloride was efficiently catalyzed by pyridine as cosolvent with CH_2Cl_2 (entries 2 and 3). On the other hand, alcohol could be converted into carbamate, by successive treatment with 1,1'-carbonyldiimidazole,[13] and primary or secondary amine (entries 4 and 5). However, these conditions revealed to be incompatible with an aromatic amine (no reaction with aniline). In that case, the use of an isocyanate[14] proved to be successful (entry 6).

Table 2 : Reaction B and cleavage

Entry	R	Reaction conditions B[a]	Yield after cleavage[b]
1	FmocNH-CH_2-CO	Fmoc-Gly-OH, DIC,[c] DMAP, CH_2Cl_2	90%
2	Ac	$(Ac_2)O$, pyridine, CH_2Cl_2	64%
3	PhCO	PhCOCl, pyridine, CH_2Cl_2	88%
4	BnNH-CO	CDI,[d] THF then $BnNH_2$	80%
5	(-$(CH_2)_5$-)N-CO	CDI,[d] THF then piperidine	53%
6	PhNH-CO	PhNCO, Et_3N, CH_2Cl_2	93%

(a) 10 eq. of reactant for one azepane on solid support. (b) Yields based on support-bound azepane **2**, the final products are obtained without purification with a purity ≥ 90% (based on ^1H NMR). (c) DIC : *N,N'*-diisopropylcarbodiimide. (d) CDI : 1,1'-carbonyldiimidazole.

Our results demonstrate that such resin-bound azepanes can be used as scaffolds in the synthesis of peptidomimetics after choosing appropriate pharmacophores. The introduction of aminoacid side chains by one the methods described as well as eventual subsequent alkylation of the nitrogen atom should allow the synthesis of a library of peptidomimetics. Our current efforts are also directed towards the introduction of other functional groups.

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5. Deprotection was carried out by 30% piperidine in DMF.
6. The amine **8** was prepared from the commercialy available Fmoc-Rink linker by amidification with benzylamine in presence of DCC and *N,N*-diisopropylethylamine, and subsequent Fmoc removal with piperidine in THF.
7. The formation of the desired azepane was indicated by the disappearance of the free amine of the linker. In order to quantify reaction yields directly on beads, we have used a protocol involving ninhydrin.
8. Typical procedure at room temperature : To a mixture of the deprotected Rink resin (2 g, 1 mmol) and CH_2Cl_2 (10 mL) in a fritted reaction vessel was added bis-epoxide **1** (1 g, 5.38 mmol) and MeOH (10 mL). After shaking 2 days, the resin was filtered and successively washed with CH_2Cl_2 (3 x 10 mL) and Et_2O (2 x 10 mL), then dried under reduced pressure to give **2**. Resin loading of "Rink-azepane resin" **1** was determined to be 0.23 mmol/g by ninhydrin test.
9. Degradation has been confirmed by heating the deprotected Rink resin in DMF at 80°C during 2, 5 or 7 days. Treatment of each batch with *N*-Fmoc glycine (DIC, DMAP) and subsequent measurement of the Fmoc group introduced allowed to quantify the remaining free amino group after heating. The ratio of remaining amine relative to the initial quantity was respectively 87, 35 or 26% after heating during 2, 5 or 7 days.
10. For example, without caping free amines, the azepane **4** isolated after benzoylation and cleavage was contamined with benzamide.
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12. To cap the free amino group (0.27 mmol/g), a portion of the resin-azepane (50 mg) was successively treated with : 1) THF (1 mL), Et_3N (17 µL) and trimethylsilyl chloride (16 µL) during 15h, then filtration; 2) a solution of di-*tert*-butyl dicarbonate (27 mg) in CH_2Cl_2 (1 mL) in presence of Et_3N (17 µL) for 8h, then filtration and washing with CH_2Cl_2 (5 x 1 mL), CH_2Cl_2-acetic acid (1/1, 5 x 1 mL) and CH_2Cl_2 (5 x 1 mL); and 3) THF (700 µL) and a solution of tetrabutylammonium fluoride (300 µL, 1M in THF) for 15h, then filtration, washing with THF (5 x 1 mL), CH_2Cl_2 (5 x 1 mL), Et_2O (2 x 1 mL) and drying under reduced pressure. After protection of the remaining free amines as carbamates, only 0.07 mmol/g of Rink-linker remains free.
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