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Synthesis of perhydrodiazepinones as new putative peptidomimetics

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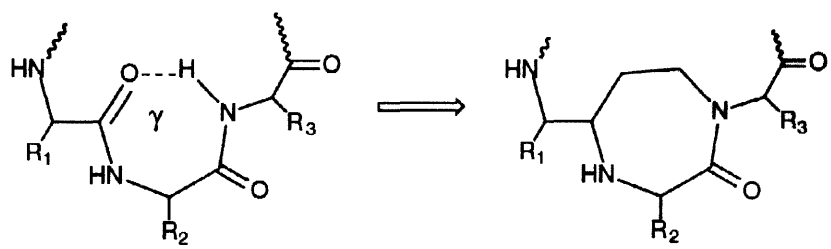
Abstract: New functionalized 7-membered azaheterocycles (perhydrodiazepinones) have been designed as new scaffolds supposed to mimick peptide γ-turns constrained by an ethylene bridge. They were synthesized by either lactam cyclisation on an aminoacid compound outcoming from a glutamic acid derivative starting material or through an intramolecular Mitsunobu reaction on diaminoalcohol linear precursors. Furthermore, as a new strategy useful for combinatorial chemistry, the second synthesis has been investigated on a soluble polymer support (PEG).

Keywords: Mitsunobu reactions, peptide/mimetics, sulfonamides, polymer support.

Introduction

In attempts to replace peptides by orally available molecules, peptide bonds or fragments have been substituted by several structural moieties. Among them, the use of heterocyclic rings as constrained peptidomimetics have appeared in the literature as for example 5-membered hetero-aromatic rings : imidazoles [1], oxazoles [2], thiazoles [2,3], oxadiazoles and triazoles [4 and ref. therein], or non-aromatics : imidazolidines [5], isoxazolines [6] oxazolines and thiazolines [7]. Along these series, the 6-membered cycles, piperazines [8], morpholines [9] are also well represented whereas the 7-membered rings are much less abundant except some didehydroazepinones [10] and benzodiazepines [11] or their benzothia(xa)zepines analogs [12]. Despite a good structural analogy with γ-turn which could arise from the replacement of intramolecular hydrogen bond by a more stable ethylene bridge as shown (Scheme 1), the perhydro-(1,4)-diazepinone series have retained little attention [13]. We have been involved in their syntheses for the last few years and we would like to describe our recent results.



Scheme 1 : Analogy between Perhydrodiazepinone and γ–turn.

Two complementary approaches have been followed for the synthesis of these molecules in solution and one of them adapted to liquid phase synthesis on PEG.

Results and discussion

The first strategy (Scheme 2) started from a chiral pool derivative.

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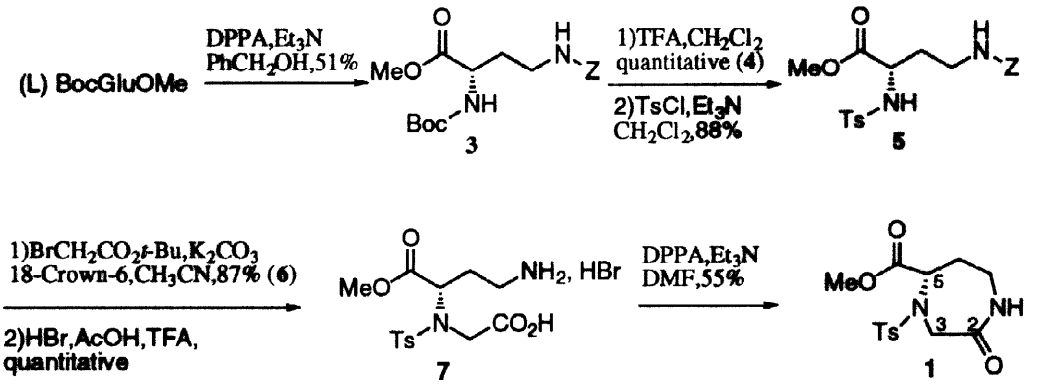
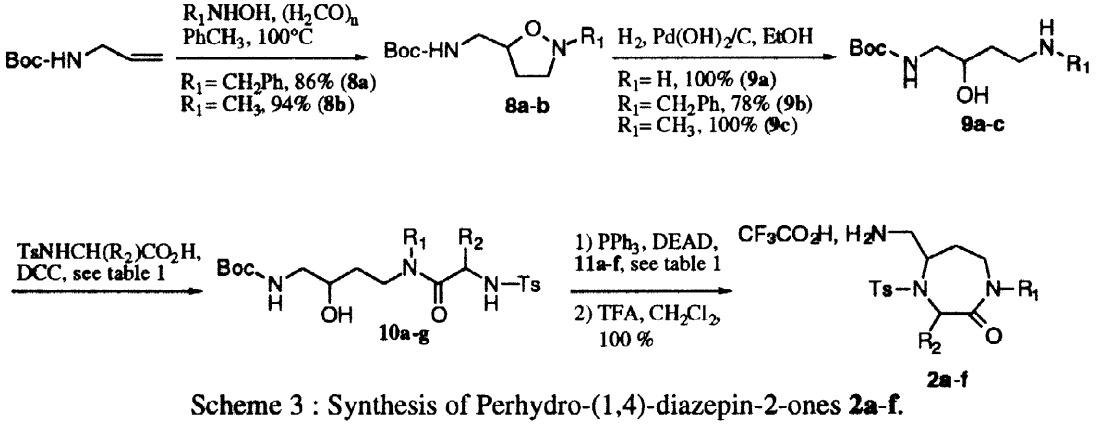


Scheme 2 : Synthesis of diazepinone **1**.

Boc-Glu-OMe was transformed by a Curtius reaction performed with DPPA dissolved in toluene followed by a benzylalcohol solvolysis of the intermediate isocyanate into a diamine ester **3** orthogonally protected. The Boc protection was replaced by a Ts group. In our first approach, the Boc protection was not efficient in presence of the activated transient acylazide prevailing during the Curtius reaction : undesired pyroGlu-OMe was obtained (data not shown). The resulting sulfonamide **5** was sufficiently reactive and was smoothly N-alkylated by tertiobutyl bromoacetate in the presence of crown ether (18-Crown-6) as catalyst yielding 87% of compound **6**. After quantitative cleavage of both the t-Butyl ester and the Z group (HBr, in a mixture of AcOH/TFA as solvent), a cyclisation of the free amino-acid linear precursor **7** in DMF under diluted condition (1.33mM) led to the diazepinone **1** in 55% yield of the purified product. The above preparation could be indeed easily extended using other α-bromo ester derivatives.

In addition to the described route, the cyclisation step has been also designed to take place at another cycle position, namely by the formation of the C-N (sulfonamide) bond. As the linear precursor contained a secondary OH-function, it was decided to cyclise by an intramolecular Mitsunobu reaction (Scheme 3).



Scheme 3 : Synthesis of Perhydro-(1,4)-diazepin-2-ones **2a-f**.

Starting from the easily available Boc-allylamine, a 1,3-dipolar cycloaddition of the olefin on the nitrone generated in-situ from Me- or Bn-hydroxylamine and paraformaldehyde yielded the corresponding isoxazolidines (**8a-b**) that were opened smoothly by hydrogenolysis. By carefully controlling the reduction process, it was possible to preserve the N-benzyl protection. The new amines obtained either free, benzylated or methylated (**9a-c**) were successfully acylated by N-tosyl amino acid anhydrides preformed at 0°C in the presence of DCC. This was the best way of activation, avoiding both racemization and O-acylation.

Cyclisation of the linear precursors (**10a-f**) was achieved in good yield by an intramolecular Mitsunobu reaction [14] between the free secondary -OH and the sulfonamide group (table 1). Study of the Mitsunobu cyclisation step has shown that the presence of a tertiary amide is necessary to yield more easily the correct folded conformation leading to cyclisation. That this reaction failed with unsubstituted compound **10g** (Table

1) is in agreement with what is known about the ring closure of short peptides : the free-energy barrier between *syn* (favourable) and *anti* peptide bond conformation is greatly reduced by the N-substitution [15].

The sulfonamide group was found to be essential for the cyclisation step : other tested N-substituents (-Z, -Troc, or -Ac, unpublished results) were inefficient whatever the redox system that was used : DEAD, DIAD, ADDP/PPh_3, PBu_3, $P(OEt)_3$, $P(OPh)_3$ or cyanomethylenetrialkylphosphoranes [16]. This confirm the good ability of sulfonamides, highly related to their NH pKa, for the successful preparation of amines via the Mitsunobu reaction[17].

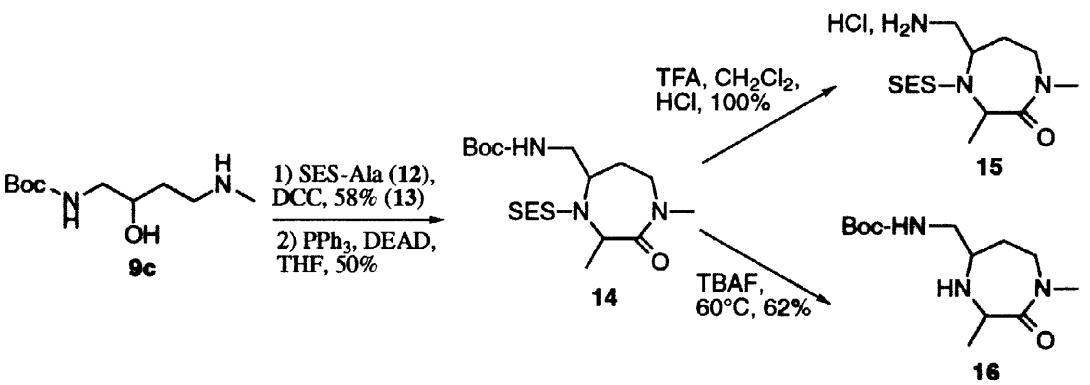
Compounds 10 and 11	R_1	R_2	Yield (%) of **10** from **9a-c**	Yield (%) of cyclisation (**11**)
a	$PhCH_2$	CH_3	65	88
b	CH_3	CH_3	75	86
c	CH_3	CH_2Ph	70	70
d	CH_3	CH_2OCH_2Ph	71	72
e	CH_3	$CH_2CO_2CH_2Ph$	42	65
f	CH_3	H	30	97
g	H	CH_3	69	0

Table 1 : Synthesis of Perhydro-(1,4)-diazepin-2-ones **11a-f**.

Applied to the diastereomeric mixture of linear precursors examined so far, the cyclisation step proceeded without any significant diastereoselectivity. Our attempts to separate easily the diastereomeric diazepinones were so far unsuccessful. However by ^{1}H-NMR analysis in almost all cases, the corresponding ratio was determined on the fully protected heterocycles.

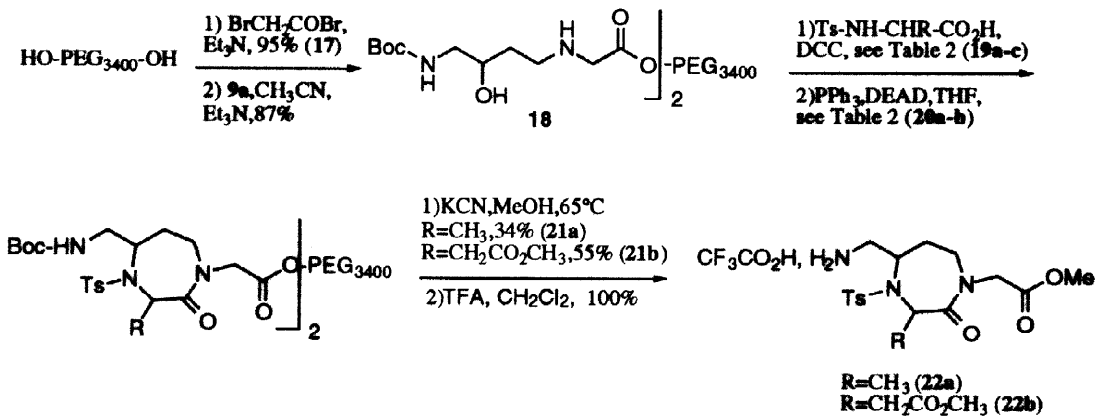
The free exocyclic amines **2a-f** easily obtained by TFA cleavage in nearly quantitative yield were subjected to analytical HPLC for an efficient diastereomeric separation (See experimental part).

In a further step, to allow a much easy intracyclic amine recovery, the Tosyl moiety has been efficiently replaced by the trimethylsilylethylsulfonyl (SES) group [18]. The resulting fully protected diazepinone was either hydrolysed in acidic medium or treated by F^- ions [19], yielding respectively the free amino compounds **15** or **16** (Scheme 4).



Scheme 4 : Orthogonal deprotection using the SES group.

To have in hands a new tool that could be useful for combinatorial chemistry we have adapted this synthesis on polymeric support. Since we have shown that to synthesize these perhydro-(1,4)-diazepin-2-ones (**11a-f**), the linear compound should contain a tertiary amide. This position was considered as a good anchor site for the diazepinone synthesis in the liquid phase [20] using a medium-sized bifunctional poly(ethyleneglycol), (PEG, M_w=3400).



Scheme 5 : PEG-supported synthesis of perhydrodiazepinones.

The linker was prepared by esterification at both ends of the PEG using $BrCH_2COBr$ (see scheme 5) [21]. Treatment with an excess of **9a** followed by acylation of the new supported amine using various anhydrides in excess yielded compound **18**. The Mitsunobu reaction led to the supported 7-membered heterocycles **20a-b** (see Table 2). Owing to the polymer solubility in usual organic solvents but cold EtOAc and diethyl ether, the Ph_3PO could be removed very easily. All the steps were followed by standard solution ^{1}H-NMR. Surprisingly and conversely to **10d**, for the O-benzyl serine derivative **19c**, no cyclisation occured.

Compounds **19** and **20**	R	Yield (%) of **19** from **18**	Yield (%) of the cyclisation (**20**)
a	CH_3	91	89
b	$CH_2CO_2CH_3$	88	80
c	CH_2OCH_2Ph	80	0

Table 2 : Synthesis of PEG-supported perhydro-(1,4)-diazepin-2-ones **20a-b**.

Finally, transesterification by KCN in refluxing MeOH led to the expected 7-membered heterocycles (**21a-b**). To our knowledge, this is the first synthesis of perhydro-(1,4)-diazepin-2-ones performed on liquid phase using a medium-sized polyethyleneglycol as soluble polymer.

Experimental section

Commercial solvents (ethyl ether or THF) were dried by redistillation in presence of sodium. All water-sensitive reactions were conducted under a dry argon atmosphere. All reactions were followed by thin layer chromatography (TLC) using silica gel $60/F_{254}$ plastic-backed plates and revealed by UV light, iodine vapors or exposition to ninhydrin (5% EtOH solution). Uncorrected melting points were taken on a Büchi apparatus and rotatory power $[\alpha_D]$ measured at 20°C using a Perkin-Elmer polarimeter. Analytical or semi-preparative HPLC experiments were conducted with a Waters equipment using nucleosil or Delta Pack C^{18} columns or Chiralcel OD for optical resolution. Except when notified a gradient run of 30 minutes (min) from 10 to 100% CH_3CN was applied for analytical HPLC. ^{1}H- and ^{13} C-NMR analyses were performed with a Brucker AC-250MHz or an Advance DPX-200MHz. Mass spectra (FAB mode) were recorded on Jeol DX 300 or SX102A

using either metanitrobenzyl alcohol (NBA) or glycerol/thioglycerol mixture as matrix. Mass spectra (electrospray ionization mode ESIMS) were taken on Micromass platform equipment using H_2O/MeCN/AcOH (49/49/2 in vol.) as solvent. The diastereoisomeric ratio was determined by ^{1}H-NMR and/or by analytical HPLC.

Methyl (2S) 2-N-tert-butyloxycarbonyl-4-N-benzyloxycarbonyl-(2,4)-diaminobutyrate **3** : A solution containing (L) Boc-Glu-OMe (0.391g, 1.5mmol), triethylamine (0.303g, 3mmol), diphenylphosphoryl azide (0.826g, 3mmol) and benzyl alcohol (0.324g, 3 mmol) in toluene (7mL) was heated at 100°C overnight [22]. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (Hexane/EtOAc : 55/45) to afford a yellow oil (0.28g, 51%). TLC Hexane/EtOAc (50/50) R_f=0.60. $[\alpha]_D^{20}$: -17° (c=1, CH_2Cl_2). HPLC : Tr=24.74 min. ESIMS ($C_{18}H_{26}N_2O_6$) : m/z 367 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.65-1.80 (m, 1H), 2.00-2.15 (m, 1H), 3.02-3.18 (m, 1H), 3.44-3.60 (m, 1H), 3.76 (s, 3H), 4.31-4.50 (m, 1H), 5.12 (s, 2H), 5.15-5.25 (m, 1H), 5.40-5.50 (m, 1H), 7.30-7.42 (m, 5H).

Methyl (2S) 4-N-benzyloxycarbonyl-(2,4)-diaminobutyrate **4** : To a solution of **3** (0.361g, 1mmol) in CH_2Cl_2 (2mL) was added at -20°C trifluoroacetic acid (2mL). The mixture was stirred at 20°C for 3h, then the solution was concentrated in vacuo to afford a yellow oil (0.38g, quantitative). $[\alpha]_D^{20}$: -12° (c=1, methanol). HPLC : Tr=16.00min. ESIMS ($C_{13}H_{18}N_2O_4$) : m/z 267 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.97-2.25 (m, 2H), 3.25-3.40 (m, 2H), 3.80 (s, 3H), 4.07 (t, 1H, J=7Hz), 5.11 (s, 2H), 7.22-7.50 (m, 5H).

Methyl (2S) 2-N-tosyl-4-N-benzyloxycarbonyl-(2,4)-diaminobutyrate **5**. To a solution of **4** (0.38g, 1mmol) in CH_2Cl_2 (7mL) was added at -20°C paratoluenesulfonyl (tosyl) chloride (0.191g, 1mmol) and triethylamine (0.203g, 2mmol). The solution was stirred at 20°C overnight. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (Hexane/EtOAc : 1/1) to afford a white powder (0.37g, 88%). TLC Hexane/EtOAc (50/50) R_f=0.47. M.P.=84-86°C. $[\alpha]_D^{20}$: 27° (c=1, CH_2Cl_2). HPLC : Tr=25.90min. ESIMS ($C_{20}H_{24}N_2O_6S$) : m/z 421 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.60-1.78 (m, 1H), 2.00-2.18 (m, 1H), 2.44 (s, 3H), 3.20-3.38 (m, 1H), 3.41-3.57 (m, 1H), 3.51 (s, 3H), 3.95 (dt, 1H, J= 4Hz and 9Hz), 5.15 (s, 2H), 5.11-5.25 (m, 1H), 5.32 (d, 1H, J=4Hz), 7.30-7.40 (m, 5H), 7.33 (d, 2H, J=9Hz), 7.73 (d, 2H, J=9Hz).

Methyl (2S) 2-N-tosyl-2-N-tert-butylcarboxymethyl-4-N-benzyloxycarbonyl-(2,4)-diaminobutyrate **6**. A solution of compound **5** (0.399g, 0.95mmol), 18-Crown-6 (0.251g, 0.95mmol), potassium carbonate (0.131g, 0.95mmol) and *tert*-butyl bromoacetate (0.556g, 2.85mmol) in MeCN (8mL) was stirred at 20°C for 24h. The mixture was filtered and concentrated in vacuo. The residue was chromatographed on silica gel (Hexane/EtOAc : 60/40) to afford a colorless oil (0.441 g, 87%). TLC Hexane/EtOAc (50/50) R_f=0.73. $[\alpha]_D^{20}$: 32° (c=1, CH_2Cl_2). HPLC : Tr=29.54min. ESIMS ($C_{26}H_{34}N_2O_8S$) : m/z 535 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.65-1.85 (m, 1H), 2.05-2.25 (m, 1H), 2.43 (s, 3H), 3.45 (s, 3H), 3.40-3.57 (m, 2H), 3.82 (d, 1H, J=18Hz), 4.10 (d, 1H, J=18Hz), 4.47 (dd, 1H, J=3Hz and 11Hz), 5.12 (s, 2H), 5.30 (t, 1H, J=6Hz), 7.29-7.40 (m, 7H), 7.75 (d, 2H, J=9Hz).

(2S) 2-N-tosyl-2-N-tert-butylcarboxymethyl-(2,4)-diamino butyric acid **7**. To **6** (0.267g, 0.5mmol) was added at 20°C a solution of 33% of hydrobromic acid in acetic acid (10mL) and trifluoroacetic acid (5mL). The mixture was stirred vigorously at 20°C for 1h and concentrated in vacuo to afford a colorless oil (0.212g, quantitative). $[\alpha]_D^{20}$: -50° (c=1, MeOH). HPLC : Tr=16.50min. ESIMS ($C_{14}H_{20}N_2O_6S$) : m/z 344 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.97-2.40 (m, 2H), 2.47 (s, 3H), 3.15-3.60 (m, 2H), 3.42 (s, 3H), 3.88 (d, 1H, J=18Hz), 4.17 (d, 1H, J=18Hz), 4.67 (dd, 1H, J=4Hz and 10Hz), 7.41 (d, 2H, J=8Hz), 7.78 (d, 2H, J=8Hz).

(5S) 4-Tosyl-5-methoxycarbonyl-perhydro-(1,4)-diazepin-2-one **1**. To a solution of compound **7** (0.07g, 0.2mmol) in DMF (150mL) was added dropwise at 20°C triethylamine (0.102g, 1mmol) and diphenylphosphoryl azide [22]. The mixture was stirred vigorously at 20°C for 36 h and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc) to afford a white powder (0.036g, 55%). M.P.=130-132°C. TLC MeOH/EtOAc (10/90) R_f=0.50. $[\alpha]_D^{20}$: -40° (c=1, CH_2Cl_2). HPLC : Tr=17.85min. FABMS (GT) m/z ($C_{14}H_{19}N_2O_5S$) : 327 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 327.1042 and found : 327.1015. ^{1}H-NMR ($CDCl_3$) δ 2.05-2.27 (m, 1H), 2.31-2.50 (m, 1H), 2.45 (s, 3H), 3.20-3.35 (m, 2H), 3.66 (s, 3H), 3.97 (d, 1H, J=18Hz), 4.32 (d, 1H, J=18Hz), 4.87 (dd, 1H, J=4Hz and 9Hz), 6.25-6.40 (m, 1H), 7.30 (d, 2H, J=8Hz), 7.73 (d, 2H, J=8Hz). RMN ^{13}C ($CDCl_3$) δ 21.81, 31.67, 39.34, 48.11, 52.74, 57.65, 127.44, 129.94, 136.51, 144.25, 170.82, 172.25.

2-Benzyl-5-tert-butyloxycarbonylaminomethyl-(1,2)-isoxazolidine **8a**. Boc-allylamine (1.57g, 10mmol), N-benzylhydroxylamine (1.84g, 15mmol) and paraformaldehyde (2.25g, 75mmol) in toluene (105mL) were heated at 100°C for 20h [23]. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (CH_2Cl_2/EtOAc : 70/30) to afford a yellow oil (2.51g, 86%). TLC CH_2Cl_2/EtOAc (50/50) R_f=0.55. HPLC : Tr=18.07min. FABMS (NBA) ($C_{16}H_{24}N_2O_3$) : m/z 293 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.95-2.05 (m, 2H), 3.05-3.15 (m, 2H), 3.25-3.40 (m, 2H), 3.95 (s, 2H), 4.00-4.10 (m, 1H), 4.85-5.00 (m, 1H), 7.30-7.50 (m, 5H).

2-Methyl-5-tert-butyloxycarbonylaminomethyl-(1,2)-isoxazolidine **8b**. Boc-allylamine (1.57g, 10mmol), N-methylhydroxylamine hydrochloride (1.25g, 15mmol), paraformaldehyde (2.25g, 75mmol) and triethylamine (2.09g, 15mmol) were heated in toluene/ethanol (105mL/35mL) at 100°C for 20h. The solution was concentrated in vacuo and the triethylamine hydrochloride was precipitated after addition of EtOAc (30mL) and filtered. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (EtOAc/MeOH : 95/5) to afford a yellow oil (2.03g, 94%). TLC EtOAc/MeOH (75/25) R_f=0.52. FABMS (NBA) ($C_{10}H_{20}N_2O_3$) : m/z 217 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.85-2.05 (m, 1H), 2.30-2.50 (m, 1H), 2.50-2.70 (m, 1H), 2.59 (s, 3H), 3.10-3.50 (m, 3H), 3.95-4.15 (m, 1H), 4.90-5.05 (m, 1H).

1-N-tert-Butyloxycarbonyl-(1,4)-diaminobutan-2-ol **9a**. To the isoxazolidine **8a** (1.46g, 5mmol) in 95% EtOH (15mL) was added $Pd(OH)_2$/C 20% (0.50g). The mixture was stirred vigorously under hydrogen atmosphere at 20°C overnight. The mixture was filtered through celite and the solution was concentrated in vacuo to afford a white powder (1.02g, quantitative). F=62-64°C. FABMS (NBA) ($C_9H_{20}N_2O_3$) : m/z 205 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.46 (s, 9H), 1.58-1.67 (m, 2H), 2.80 (t, 2H, J=7Hz), 3.00-3.15 (m, 2H), 3.67-3.77 (m, 1H).

1-N-tert-Butyloxycarbonyl-4-N-benzyl-(1,4)-diaminobutan-2-ol **9b**. To the isoxazolidine **8a** (1.46g, 5mmol) in 95% ethyl alcohol (10mL) was added $Pd(OH)_2$/C 20% (0.50g). The mixture was stirred vigorously under hydrogen atmosphere at 20°C. After the disappearance of the isoxazolidine **8a** (controlled by HPLC) the mixture was filtered through Celite and the solution was concentrated in vacuo to afford a colorless oil (1.15g, 78%). HPLC : Tr=7.56 min. FABMS (GT) ($C_{16}H_{26}N_2O_3$) : m/z 295 $(M+H)^+$. ^{1}H-NMR (D_2O) δ 1.55 (s, 9H), 1.70-1.95 (m, 2H), 3.10-3.30 (m, 4H), 3.80-3.95 (m, 1H), 4.30 (s, 2H), 7.50 (large broad, 5H).

1-N-tert-Butyloxycarbonyl-4-N-methyl-(1,4)-diaminobutan-2-ol **9c**. To the isoxazolidine **8b** (1.73g, 8mmol) in 95% ethyl alcohol (25mL) was added $Pd(OH)_2$/C 20% (0.80 g). The mixture was stirred overnight vigorously under hydrogen atmosphere at 20°C. The catalyst was filtered through Celite and the solution was concentrated in vacuo to afford a colorless oil (1.74 g, quantitative). FABMS (NBA) ($C_{10}H_{22}N_2O_3$) : m/z 219 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.46 (s, 9H), 1.61-1.66 (m, 2H), 2.41 (s, 3H), 2.69-2.76 (m, 2H), 3.04-3.11 (m, 2H), 3.64-3.75 (m, 1H).

1-N-tert-Butyloxycarbonyl-4-N-benzyl-4-N-(α-N-tosylalanyl)-(1,4)-diaminobutan-2-ol **10a** (typical procedure). To a solution of (L) N-tosyl alanine (0.61g, 2.5mmol) in CH_2Cl_2 (30mL) was added at 0°C dicyclohexylcarbodiimide (0.26g, 1.25mmol). The mixture was stirred at 0°C for 1 h then the dicyclohexylurea was removed by filtration. To the filtrate were added at 20°C the compound **9b** (0.37g, 1.25mmol) and triethylamine (0.126g, 1.25mmol). The solution was stirred overnight then the mixture was concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2/EtOAc : 70/30) to afford a colorless oil (0.42g, 65%). TLC CH_2Cl_2/EtOAc (50/50) R_f=0.51. HPLC : Tr=18.07 min. FABMS (NBA) ($C_{26}H_{37}N_3O_6S$) : m/z 520 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.25-1.58 (m, 14H), 2.34 (s, 3H), 2.78-2.90 (m, 1H), 2.95-3.05 (m, 1H), 3.20-3.40 (m, 2H), 3.65-3.85 (m, 1H), 4.05-4.15 (m, 2H), 4.20-4.40 (m, 1H), 4.50-4.70 (m, 1H), 4.95-5.05 (m, 1H), 5.85-5.60 (m, 1H), 7.00-7.80 (m, 9H).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-(α-N-tosylalanyl)-(1,4)-diaminobutan-2-ol **10b**. The synthesis of **10b** was carried out in the same manner as for the linear compound **10a** by coupling this time **9c** and (L) N-tosyl alanine. The product is a white foam (0.6g, 75% yield). TLC EtOAc R_f=0.43. HPLC : Tr=21.25 min. FABMS (NBA) ($C_{20}H_{33}N_3O_6S$) : m/z 444 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.25-1.60 (m, 14H), 2.43 (s, 3H), 2.89 (s, 3H), 2.90-3.05 (m, 2H), 3.10-3.30 (m, 2H), 4.05-4.12 (m, 1H), 4.13-4.30 (m, 1H), 5.00-5.13 (m, 1H), 5.85-5.97 (m, 1H), 7.23-7.32 (m, 2H), 7.68-7.77 (m, 2H).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-(α-N-tosyl-phenylalanyl)-(1,4)-diaminobutan-2-ol **10c**. The synthesis of **10c** was carried out in the same manner as for linear compound **10a** by coupling **9c** and (L) N-tosyl phenylalanine. The product is a white powder (0.40 g, 70% yield). TLC (EtOAc/hexane : 70/30) R_f=0.26. HPLC : Tr=24.47min. FABMS (NBA) ($C_{26}H_{37}N_3O_6S$) : m/z 520 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.46

(s, 9H), 1.65-1.75 (m, 1H), 1.90-2.00 (m, 1H), 2.39 (s, 3H), 2.47 (s, 3H), 2.65-3.00 (m, 4H), 3.05-3.30 (m, 2H), 3.70-3.90 (m, 1H), 4.05-4.20 (m, 1H), 4.30-4.50 (m, 1H), 5.03-5.09 (m, 1H), 5.80-5.93 (m, 1H), 7.05-7.40 (m, 7H), 7.69 (d, 2H, J=8Hz).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-(α-N-tosyl–β-O-benzylseryl)-(1,4)-diaminobutan-2-ol **10d**. The synthesis of **10d** was carried out in the same manner as for linear compound **10a** by coupling **9c** and (L) N-tosyl-(β-O-benzyl)serine. The product is a white foam (0.96g, 71% yield). TLC EtOAc R_f=0.60. HPLC : Tr=24.73 min. FABMS (GT) ($C_{27}H_{39}N_3O_7S$) : m/z 550 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.49 (s, 9H), 1.65-1.75 (m, 1H), 1.90-2.00 (m, 1H), 2.42 (s, 3H), 2.82 (s, 3H), 2.80-3.00 (m, 2H), 3.00-3.30 (m, 2H), 3.80-3.90 (m, 3H, H), 4.40 (s, 2H), 4.37-4.50 (m, 1H), 4.90-5.00 (m, 1H), 5.70-5.80 (d, 1H, J=9Hz), 7.18-7.28 (m, 2H), 7.30-7.40 (m, 5H), 7.65-7.78 (m, 2H).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-(α-N-tosyl–β-benzylaspartyl)-(1,4)-diaminobutan-2-ol **10e**. The synthesis of **10e** was carried out in the same manner as for linear compound **10a** by coupling **9c** and (L) N-tosyl-(β-O-benzyl)aspartic acid.The product is a white foam (0.40g, 42% yield). TLC EtOAc R_f=0.47. HPLC : Tr=24.90 min. FABMS (NBA) ($C_{28}H_{39}N_3O_8S$) : m/z 578 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.65-1.75 (m, 1H), 1.90-2.00 (m, 1H), 2.40-2.50 (m, 1H), 2.70-2.95 (m, 3H), 2.39 (s, 3H), 2.91 (s, 3H), 3.20-3.45 (m, 2H), 3.75-3.85 (m, 1H), 4.60-4.70 (m, 1H), 4.95-5.05 (m, 2H), 5.10-5.20 (m, 1H), 6.40-6.60 (m, 1H), 7.10-7.40 (m, 7H), 7.75 (d, 2H, J=8Hz).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-(α-N-tosyl-glycyl)-(1,4)-diaminobutan-2-ol **10f**. The synthesis of **10f** was carried out in the same manner as for linear compound **10a** by coupling **9c** and N-tosyl glycine. The product is a colorless oil (0.17g, 30% yield). TLC EtOAc R_f=0.42. HPLC : Tr=20.67 min. FABMS (GT) ($C_{19}H_{31}N_3O_6S$) : m/z 430 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.45-1.75 (m, 2H), 2.44 (s, 3H), 2.88 (s, 3H), 2.90-3.05 (m, 2H), 3.17-3.39 (m, 2H), 3.78 (d, 2H, J=5Hz), 3.82-4.05 (m, 2H), 5.01-5.16 (m, 1H), 5.70-5.85 (m, 1H), 7.30 (d,2H, J=8Hz),7.78 (d,2H, J=8Hz).

1-N-tert-Butyloxycarbonyl-4-N-(α-N-tosylalanyl)-(1,4)-diaminobutan-2-ol **10g**. The synthesis of **10g** was carried out in the same manner as for linear compound **10a** by coupling **9a** and (L) N-tosyl alanine. The product is a colorless oil (0.60g, 69% yield). TLC EtOAc R_f=0.40. HPLC : Tr=19.10 min. FABMS (NBA) ($C_{19}H_{31}N_3O_6S$) : m/z 430 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.17 (d, 3H, J=7Hz), 1.45 (s, 9H), 1.50-1.65 (m, 2H), 2.45 (s, 3H), 3.05-3.20 (m, 2H), 3.40-3.60 (m, 2H), 3.62-3.70 (m, 1H), 3.75-3.85 (m, 1H), 4.15-4.25 (m, 1H), 5.10-5.15 (m, 1H), 5.95-6.10 (m, 1H), 7.10-7.20 (m, 1H), 7.30 (d, 2H, J=8Hz), 7.80 (d, 2H, J=8Hz).

1-Benzyl-3-methyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11a** (typical procedure). To a solution of triphenylphosphine (131mg, 0.5mmol) in THF (3mL) under an argon atmosphere was added dropwise at 0°C diethylazodicarboxylate (87.4mg, 0.5mmol) dissolved in THF (0.5mL). The mixture was stirred at 0°C for 30min. The substrate **10a** (130mg, 0.25mmol) in THF (3.5mL) was added dropwise at 0°C during 2 h. The mixture was stirred at 20°C for 36h. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc : 50/50) to afford a white powder (110mg, 88%) as a mixture of two diastereoisomers in a 40/60 ratio established by HPLC analysis: Tr=26.93min and 27.11min. TLC hexane/EtOAc (30/70) R_f=0.59. FABMS (GT) ($C_{26}H_{35}N_3O_5S$) : m/z 502 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 502.2376. Found : 502.2359. ^{1}H-NMR ($CDCl_3$) δ 1.21-1.90 (m, 14H), 2.46 (s, 3H), 3.15-3.30 (m, 2H), 3.35-3.55 (m, 2H), 4.05-4.40 (m, 3H), 4.57-4.85 (m, 1H), 5.00-5.17 (m, 1H), 7.00-7.80 (m, 9H).

1-Methyl-3-methyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11b**. The synthesis of **11b** was carried out in the same manner as for **11a** using the linear compound **10b** (110mg, 0.25mmol). The product is a white foam (91mg, 86% yield) as a mixture of two diastereoisomers in a 55/45 ratio, HPLC : Tr=23.71min and 23.95min. TLC EtOAc R_f=0.48 FABMS (GT) ($C_{20}H_{31}N_3O_5S$) : m/z 426 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) of the main diastereoisomer δ 1.47 (s, 9H), 1.65 (d, 3H, J=8Hz), 1.80-2.15 (m, 3H), 2.44 (s, 3H), 2.57 (s, 3H), 2.80-2.96 (m, 1H), 3.20-3.55 (m, 2H), 3.90-4.05 (m, 1H), 5.00 (q, 1H, J=8Hz), 5.12-5.25 (m, 1H), 7.29 (d, 2H, J=7Hz), 7.70 (d, 2H, J=7Hz). ^{1}H-NMR ($CDCl_3$) of the minor diastereoisomer δ 1.43 (s, 9H), 1.57 (d, 3H, J=8Hz), 1.70-2.00 (m, 2H), 2.45 (s, 3H), 2.85 (s, 3H), 3.00-3.20 (m, H), 3.40-3.60 (m, 1H), 3.28 (t, 2H, J=7Hz), 3.96-4.11 (m, 1H), 4.17 (q, 1H, J=8Hz), 4.50-4.70 (m, 1H), 7.31 (d, 2H, J=8Hz), 7.75 (d, 2H, J=8Hz).

1-Methyl-3-benzyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11c**. The synthesis of **11c** was carried out in the same manner as for **11a** using the linear compound **10c** (130mg,

0.25mmol). The product is a white powder (87mg, 70% yield) as a mixture of two diastereoisomers in a 65/35 ratio, HPLC : Tr=26.98min and 27.53min. TLC EtOAc R_f=0.56. FABMS (NBA) m/z ($C_{26}H_{35}N_3O_5S$) : 502 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.50-1.70 (m, 2H), 2.42 (s, 3H), 2.65 (s, 3H), 2.80-3.00 (m, 2H), 3.05-3.15 (m, 2H), 3.40-3.60 (m, 2H), 3.88-4.05 (m, 1H), 4.20-4.40 (m, 1H), 5.40-5.50 (m, 1H), 7.25-7.80 (m, 9H).

1-Methyl-3-(benzyloxymethyl)-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11d**. The synthesis of **11d** was carried out in the same manner as for **11a** using the linear compound **10d** (137mg, 0.25mmol). The product is a white powder (96mg, 72% yield) as a mixture of two diastereoisomers in a 70/30 ratio, HPLC : Tr=27.72min and 28.01min . TLC EtOAc R_f=0.50. FABMS (NBA) ($C_{27}H_{37}N_3O_6S$) : m/z 532 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) of the main diastereoisomer δ 1.45 (s, 9H), 2.00-2.25 (m, 3H), 2.43 (s, 3H), 2.68 (s, 3H), 2.75-2.90 (m, 1H), 3.00-3.15 (m, 1H), 3.32-3.55 (m, 1H), 3.92-4.20 (m, 3H), 4.45-4.68 (m, 2H), 5.20-5.35 (m, 2H), 7.20-7.70 (m, 9H). ^{1}H-NMR ($CDCl_3$) of the minor diastereoisomer δ 1.41 (s, 9H), 1.80-1.90 (m, 1H), 1.95-2.05 (m, 1H), 2.20-2.35 (m, 2H), 2.42 (s, 3H), 2.88 (s, 3H), 3.28-3.45 (m, 2H), 4.00-4.35 (m, 6H), 5.20-5.35 (m, 1H), 7.05-7.80 (m, 9H).

1-Methyl-3-(benzyloxycarbonylmethyl)-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11e**. The synthesis of **11e** was carried out in the same manner as for **11a** using the linear compound **10e** (144mg, 0.25mmol). The product is a colorless oil (91mg, 65% yield) as a mixture of two diastereoisomers in a 65/35 ratio, HPLC : Tr=27.35min and 27.85min. TLC EtOAc R_f=0.41. FABMS (NBA) ($C_{28}H_{37}N_3O_7S$) : m/z 560 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) of the main diastereoisomer δ 1.42 (s, 9H), 1.75-1.90 (m, 1H), 1.95-2.05 (m, 1H), 2.20-2.30 (m, 1H), 2.42 (s, 3H), 2.68 (s, 3H), 2.62-2.90 (m, 3H), 3.00-3.20 (m, 2H), 4.05-4.13 (m, 1H), 5.02-5.25 (m, 3H), 5.40-5.55 (m, 1H), 7.20-7.80 (m, 9H). ^{1}H-NMR ($CDCl_3$) of the minor diastereoisomer δ 1.42 (s, 9H), 1.75-1.90 (m, 1H), 1.95-2.05 (m, 1H), 2.20-2.30 (m, 1H), 2.36 (s, 3H), 2.78 (s, 3H), 2.62-2.90 (m, 3H), 3.00-3.20 (m, 2H), 4.20-4.35 (m, 1H), 4.40-4.50 (m, 1H), 5.02-5.25 (m, 3H), 7.20-7.80 (m, 9H).

1-Methyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **11f**. The synthesis of **11f** was carried out in the same manner as for **11a** using the linear compound **10f** (107mg, 0.25mmol). The product is a colorless oil (100mg, 97% yield). TLC EtOAc R_f=0.35. HPLC : Tr=23.05 min. FABMS (NBA) ($C_{19}H_{29}N_3O_5S$) : m/z 412 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.70-1.90 (m, 2H) 1.91-2.05 (m, 1H), 2.43 (s, 3H), 2.55 (s, 3H), 2.95-3.30 (m, 3H), 3.85 (d, 1H, J=18Hz), 4.50 (d, 1H, J=18Hz), 3.90-4.09 (m, 1H), 5.00-5.10 (m, 1H), 7.30 (d, 2H, J=8Hz), 7.70 (d, 2H, J=8Hz).

1-Benzyl-3-methyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2a** (typical procedure). To a solution of perhydro-(1,4)-diazepin-2-one **11a** (100mg, 0.2mmol) in CH_2Cl_2 (2mL) was added at -20°C trifluroacetic acid (2 mL). The mixture was stirred at 20°C for 4 h, then the solution was concentrated in vacuo. The oil was purified by preparative HPLC to afford a white foam (103mg, quantitative yield) as a mixture of two diastereoisomers in a 40/60 ratio. HPLC Tr=8.84min and 9.73min (H_2O 65%/MeCN 35%TFA 0.1%). FABMS (NBA) ($C_{21}H_{27}N_3O_3S$) : m/z 402 $(M+H)^+$. LC/MS : Water/MeCN (30 → 40% MeCN in 20minutes). Tr_1=12.33min. ESIMS= m/z 402.0 $(M+H)^+$. Tr_2=13.55min. ESIMS= m/z 402.0 $(M+H)^+$. ^{1}H-NMR (CD_3OD) of the main diastereoisomer δ 1.79 (d, 3H, J=8Hz), 1.88-2.20 (m, 3H), 2.50 (s, 3H), 2.89-3.20 (m, 3H), 3.52 (d, 1H, J=6Hz), 4.10-4.30 (m, 1H), 4.68 (d, 1H, J=6Hz), 5.25 (q, 1H, J=8Hz), 7.05-7.35 (m, 5H), 7.39 (d, 2H, J=8Hz), 7.75 (d, 2H, J=8Hz).^{13}C-NMR (CD_3OD) of the main diastereoisomer δ 20.16, 20.55, 29.85, 43.36, 45.25, 52.23, 56.17, 57.69, (127.28, 127.56, 127.73, 127.81, 127.90, 128.08, 128.65, 128.77, 129.32, 129.49, 129.74, 130.01, 130.22, 131.15, 136.58, 136.93, 145.35) : benzenic carbons of both diastereoisomers, 172.39.^{1}H-NMR (CD_3OD) of the minor diastereoisomer δ 1.78 (d, 3H, J=7Hz), 1.80-1.90 (m, 2H), 2.51 (s, 3H), 2.55-2.70 (m, 1H), 2.98 (d, 1H, J=5Hz), 3.08 (d, 1H, J=5Hz), 3.22-3.35 (m, 1H), 3.47 (d, 1H, J=10Hz), 4.20-4.38 (m, 1H), 4.50 (q, 1H, J=7Hz), 4.80 (d, 1H, J=10Hz), 7.08-7.30 (m, 5H), 7.47 (d, 2H, J=8Hz), 7.78 (d, 2H, J=8Hz).^{13}C-NMR (CD_3OD) of the minor diastereoisomer δ 17.38, 20.16, 28.67, 40.71, 44.66, 51.42, 52.28, 55.29, (127.28, 127.56, 127.73, 127.81, 127.90, 128.08, 128.65, 128.77, 129.32, 129.49, 129.74, 130.01, 130.22, 131.15, 136.58, 136.93, 145.35) : benzenic carbons of both diastereoisomers, 171.24.

1-Methyl-3-methyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2b**. The synthesis of **2b** was carried out in the same manner as for **2a** by action of trifluoroacetic acid on **11b** (106mg, 0.25mmol). The mixture was concentrated in vacuo. To the residue 10mL of 1N HCl was added and this phase was extracted three times with EtOAc (3x10mL). The aqueous phase was concentrated in vacuo to afford an oil. The oil was purified by preparative HPLC to afford a colorless oil (90mg, quantitative yield) as a mixture of

two diastereoisomers in a 55/45 ratio. HPLC Tr=8.54min and 9.36 min (H_2O 80%/MeCN 20%/TFA 0.1%). FABMS (NBA) ($C_{15}H_{23}N_3O_3S$) : m/z 326 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 326.1538. Found : 326.1504. LC/MS : Water/MeCN 10% during 15 minutes then MeCN % (10 → 15) in 15minutes. Tr_1=21.36min. ESIMS=326.0 $(M+H)^+$. Tr_2=22.16 min. ESIMS=326.1 $(M+H)^+$. ^{1}H-NMR (CD_3OD) of the main diastereoisomer δ 1.60 (d, 3H, J=7Hz), 1.90-2.10 (m, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 2.80-3.15 (m, 3H), 3.98-4.10 (m, 1H), 5.00 (q, 1H, J=7Hz), 7.25-7.34 (m, 2H), 7.54-7.63 (m, 2H). ^{13}C-NMR (CD_3OD) of the minor diastereoisomer δ 19.71, 20.48, 29.48, 36.28, 43.42, 47.58, 55.30, 57.62, (127.31, 130.09, 136.10, 145.35) : benzenic carbons of both diastereoisomers, 172.05. ^{1}H-NMR (CD_3OD) of the minor diastereoisomer δ 1.59 (d, 3H, J=8Hz), 1.90-2.10 (m, 2H), 2.30-2.40 (m, 1H), 2.35 (s, 3H), 2.42 (s, 3H), 2.90-3.10 (m, 2H), 3.15-3.25 (m, 1H), 3.98-4.10 (m, 1H), 4.28 (q, 1H, J=8Hz), 7.25-7.34 (m, 2H), 7.54-7.63 (m, 2H). ^{13}C-NMR (CD_3OD) of minor diastereoisomer δ 17.53, 20.48, 28.58, 35.52, 40.91, 47.37, 56.37, 52.00, (127.87, 129.90, 137.00, 144.99) : benzenic carbons of the 2 diastereoisomers, 170.59.

1-Methyl-3-benzyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2c**. The synthesis of **2c** was carried out in the same manner as for **2a** by action of trifluoroacetic acid on **11c** (100mg, 0.2 mmol). The mixture was concentrated in vacuo and the resulting oil was purified by preparative HPLC to afford an colorless oil (103mg, quantitative yield) as a mixture of two diastereoisomers in a 65/35 ratio. HPLC : Tr=16.79min and 17.67min. FABMS (GT) ($C_{21}H_{27}N_3O_3S$) : m/z 402 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 402.1851. Found : 402.1801. LC/MS : MeCN 32% Tr_1=14.19 min. ESIMS=m/z 402.1 $(M+H)^+$; Tr_2=16.29 min. ESIMS=m/z 402.1 $(M+H)^+$. NMR (CD_3OD) of the main diastereoisomer : ^{1}H-NMR, δ 1.95-2.12 (m, 2H), 2.15-2.30 (m, 1H), 2.36 (s, 3H), 2.43 (s, 3H), 2.80-2.95 (m, 3H), 3.10-3.42 (m, 2H), 3.92-4.05 (m, 1H), 5.38-5.47 (m, 1H), 7.15-7.62 (m, 9H). ^{13}C-NMR, δ 20.51, 29.23, 36.45, 38.91, 43.66, 47.99, 55.31, 62.13, (124.23, 126.88, 127.17, 127.36, 127.49, 128.22, 128.36, 128.70, 128.98, 129.34, 129.63, 129.68, 130.03, 130.13, 130.19, 135.73, 136.25, 136.89, 139.55, 145.50, 145.53 : benzenic carbons of both diastereoisomers), 171.04. NMR (CD_3OD) of the minor diastereoisomer : ^{1}H-NMR, δ 1.43-1.52 (m, 1H), 1.70-1.80 (m, 1H), 1.95-2.12 (m, 1H), 2.15-2.30 (m, 1H), 2.36 (s, 3H), 2.46 (s, 3H), 2.60-2.66 (m, 1H), 3.10-3.22 (m, 2H), 3.75-3.85 (m, 1H), 3.92-4.05 (m, 1H), 4.21-4.28 (m, 1H), 7.15-7.62 (2m, 9H). ^{13}C-NMR, δ 20.51, 27.67, 35.21, 35.73, 40.75, 47.37, 55.21, 59.03, (124.23, 126.88, 127.17, 127.36, 127.49, 128.22, 128.36, 128.70, 128.98, 129.34, 129.63, 129.68, 130.03, 130.13, 130.19, 135.73, 136.25, 136.89, 139.55, 145.50, 145.53 : benzenic carbons of both diastereoisomers), 169.52).

1-Methyl-3-(benzyloxymethyl)-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2d**. The synthesis of **2d** was carried out in the same manner as for **2a** by action of trifluoroacetic acid on **11d** (58mg, 0.11mmol). The mixture was concentrated in vacuo. The oil was purified by preparative HPLC to afford a white powder (60mg, quantitative yield) as a mixture of two diastereoisomers in a 70/30 ratio. HPLC analysis : Tr=18.64 min and 18.85 min. FABMS (GT) ($C_{22}H_{29}N_3O_4S$) : m/z 432 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 432.1957. Found : 432.2012. LC/MS : MeCN 32% Tr_1=20.85min. ESIMS=m/z 432.0 $(M+H)^+$; Tr_2=24.37min. ESIMS=m/z 432.1 $(M+H)^+$. ^{1}H-NMR (CD_3OD) of the main diastereoisomer δ 1.95-2.35 (m, 3H), 2.48 (s, 3H), 2.58 (s, 3H), 2.82-2.97 (m, 1H), 3.00-3.20 (m, 2H), 3.85-4.18 (m, 2H), 4.20-4.30 (m, 1H), 4.62 (d, 2H, J=5Hz), 5.30-5.42 (m, 1H), 7.30-7.40 (m, 5H), 7.45 (d, 2H, J=8Hz), 7.72 (d, 2H, J=8Hz). ^{13}C-NMR (CD_3OD) of the main diastereoisomer δ 20.51, 29.13, 36.55, 42.45, 47.37, 54.87, 61.58, 69.96, 73.12, (127.26, 127.88, 128.28, 128.39, 128.43, 128.52, 128.71, 128.80, 130.06, 130.18, 136.25, 137.02, 137.33, 137.71, 145.26, 145.50) : benzenic carbons of both diastereoisomers, 168.96. ^{1}H-NMR (CD_3OD) of the minor diastereoisomer δ 1.61-1.75 (m, 2H), 2.48 (s, 3H), 2.63 (s, 3H), 2.70-2.85 (m, 1H), 3.00-3.30 (m, 2H), 3.50-3.70 (m, 1H), 3.72-3.80 (m, 2H), 3.90-4.00 (m, 1H), 4.45-4.55 (m, 1H), 4.25-4.40 (m, 1H), 4.60 (s, 2H), 7.32-7.40 (m, 5H), 7.45 (d, 2H, J=8Hz), 7.75 (d, 2H, J=8Hz). ^{13}C-NMR (CD_3OD) of the minor diastereoisomer δ 20.51, 27.32, 34.75, 38.90, 46.66, 47.58, 54.50, 68.68, 73.81, (127.26, 127.88, 128.28, 128.39, 128.43, 128.52, 128.71; 128.80, 130.06, 130.18, 136.25, 137.02, 137.33, 137.71, 145.26, 145.50) : benzenic carbons of both diastereoisomers, 169.32.

1-Methyl-3-(benzyloxycarbonylmethyl)-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2e**. The synthesis of **2e** was carried out in the same manner as for **2a** by action of trifluoroacetic acid on **11e** (56mg, 0.1 mmol). The mixture was concentrated in vacuo and the resulting oil was purified by preparative

HPLC to afford a colorless oil (57 mg, quantitative yield) as a mixture of two diastereoisomers in a 65/35 ratio. HPLC : Tr=19.30 min and 20.06 min. FABMS (GT) ($C_{23}H_{29}N_3O_6S$) : m/z 460 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 460.1906. Found : 460.1917. LC/MS : MeCN 33% Tr_1=11.80 min. ESIMS=m/z 460.1 $(M+H)^+$. Tr_2=15.25 min. ESIMS=m/z 460.2 $(M+H)^+$. ^{1}H-NMR (CD_3OD) of the main diastereoisomer δ 1.90-2.02 (m, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.70-3.30 (m, 5H), 4.02-4.12 (m, 1H), 5.12 (s, 2H), 5.32-5.40 (m, 1H), 7.20-7.38 (m, 7H), 7.57 (d, 2H, J=7Hz). ^{13}C-NMR (CD_3OD) of the main diastereoisomer δ 20.52, 29.70, 36.38, 38.87, 43.30, 48.87, 56.36, 59.26, 67.51, (124.22, 127.00, 127.46, 127.57, 127.99, 128.03, 128.13, 128.25, 128.36, 128.46, 128.61, 128.66, 130.03, 130.11, 130.22, 135.76, 136.00, 136.30, 136.35, 145.38, 145.66) : benzenic carbons of both diastereoisomers, (168.80, 169.62, 170.42, 170.82) : carboxylic carbons of both diastereoisomers. ^{1}H-NMR (CD_3OD) of the minor diastereoisomer δ 1.58-1.68 (m, 1H), 1.72-1.82 (m, 1H), 2.33 (s, 3H), 2.38 (s, 3H), 2.35-2.45 (m, 1H), 2.90-3.40 (m, 4H), 3.50-3.60 (m, 1H), 4.20-4.28 (m, 1H), 4.60-4.68 (m, 1H), 5.05 (s, 2H), 7.20-7.38 (m, 7H), 7.57 (d, 2H, J=7Hz). ^{13}C-NMR (CD_3OD) of the minor diastereoisomer δ 20.52, 28.20, 35.35, 35.48, 40.18, 47.81, 52.13, 56.36, 66.82, (124.22, 127.00, 127.46, 127.57, 127.99, 128.03, 128.13, 128.25, 128.36, 128.46, 128.61, 128.66, 130.03, 130.11, 130.22, 135.76, 136.00, 136.30, 136.35, 145.38, 145.66) : benzenic carbon of both diastereoisomers, (168.80, 169.62, 170.42, 170.82) : carboxylic carbon of both diastereoisomers.

1-Methyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **2f**. The synthesis of **2f** was carried out in the same manner as for **2a** by action of trifluoroacetic acid on **11f** (123mg, 0.3mmol). The mixture was concentrated in vacuo and the resulting oil was purified by preparative HPLC to afford a colorless oil (127mg, quantitative yield). HPLC : Tr=13.24 min. FABMS (GT) ($C_{14}H_{21}N_3O_3S$) : m/z 312 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 312.1382. Found : 312.1407. ^{1}H-NMR (CD_3OD) δ 1.65-1.75 (m, 2H), 1.88-1.98 (m, 1H), 2.23 (s, 3H), 2.24 (s, 3H), 2.69-2.90 (m, 3H), 3.82-3.92 (m, 1H), 3.95 (d, 1H, J=18Hz), 4.15 (d, 1H, J=18Hz), 7.20 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz). ^{13}C-NMR (CD_3OD) δ 20.49, 29.29, 35.44, 40.43, 46.26, 47.36, 54.83, (127.46, 130.04, 136.26, 145.25) : benzenic carbons, 169.17.

(L) N-[2-(Trimethylsilyl)ethylsulfonyl]-alanine **12**. To a suspension of L-alanine (0.22g, 2.5mmol) in 5mL of CH_2Cl_2 was added trimethylsilylchloride (0.27g, 2.5mmol) at room temperature.The mixture was heated under reflux for 2h then triethylamine (0.51g, 5mmol) was added followed by addition of a solution of 2-(trimethylsilyl)ethylsulfonyl chloride (0.50g, 2.5mmol) in CH_2Cl_2 (2.5mL). The resulting mixture was vigorously stirred for 1h at room temperature then MeOH (10 mmol) was added. Evaporation was followed by addition of aqueous K_2CO_3 in order to obtain pH=8 and extraction with diethyl ether. The aqueous layer was acidified to pH=1 with 1N HCl and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated to afford a yellow oil of SES-Ala **12** (0.40g, 63%). ESIMS ($C_8H_{19}NO_4SSi$) : m/z 254 $(M+H)^+$. FT-IR=3271 cm^{-1} (m), 2953 cm^{-1} (m), 1730 cm^{-1} (s), 1250 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ=0.05 (s, 9H), 1.05-1.10 (m, 2H), 1.50-1.55 (d, 3H, J=7.2 Hz), 2.95-3.05 (m, 2H), 4.20-4.30 (m, 1H), 5.14 (d, 1H, J=8 Hz), 5.70-5.90 (m,1H).

1-N-tert-Butyloxycarbonyl-4-N-methyl-4-N-[N-(2-trimethylsilylethylsulfonyl)alanyl]-(1,4)-diaminobutan-2-ol **13**. To a solution of SES-Ala (0.23g, 0.91mmol) in CH_2Cl_2 (6mL) was added at 0°C dicyclohexylcarbodiimide (0.10g, 0.20mmol). The mixture was stirred at 0°C for 1 h then the formed dicyclohexyl urea was removed by filtration. To the filtrate were added at 20°C the compound **9c** (83mg, 0.38mmol) and triethylamine (38mg, 0.38mmol). The solution was stirred for 8 h, then the mixture was concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2/EtOAc : 15/85) to afford a colorless oil (0.10g, 58%) as a mixture of two diastereomers. TLC EtOAc R_f=0.58. ESIMS ($C_{18}H_{39}N_3O_6SSi$) : m/z 454 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 0.10 (s, 9H), 1.00-1.10 (m, 2H), 1.35-1.40 (d, 3H, J=6.9 Hz), 1.45 (s, 9H), 1.65-1.85 (m, 2H), 2.80-2.90 (m, 2H), 2.90-3.05 (m, 2H), 3.10 (s, 3H), 3.20-3.45 (m, 2H), 3.50-3.60 (m, 1H), 4.15-4.35 (m, 1H), 4.35-4.55 (m, 1H), 4.90-5.15 (m, 1H), 5.20-5.40 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 0.01, 12.40, 21.73, 22.10, 30.35, 33.65, 33.78, 37.15, 50.84, 50.90, 52.20, 68.60, 69.05, 69.20, 81.75, 158.45, 174.29, 175.70.

1-Methyl-3-methyl-4-N-(2-trimethylsilyl)ethylsulfonyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **14**. To a solution of triphenylphosphine (463mg, 1.76mmol) in THF (10mL) under an argon atmosphere was added dropwise at 0°C diethylazodicarboxylate (0.31g, 1.76mmol) dissolved in THF (3.5mL). The mixture was stirred at 0°C for 30min. Compound **13** (398mg, 0.88mmol) in THF (10mL) was added dropwise at 0°C during 4h. The mixture was stirred at 20°C for 36h. The solution was

concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc : 25/75) to afford a yellow oil (0.19g, 50%) as a mixture of two diastereoisomers in a 65/35 ratio. TLC EtOAc R_f=0.43 and 0.33. ESIMS ($C_{18}H_{37}N_3O_5SSi$) : m/z 436 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) of the main diastereoisomer δ 0.05 (s, 9H), 0.90-0.95 (m, 2H), 1.40 (s, 9H), 1.60 (d, 3H, J=7.6 Hz), 1.80-2.30 (m, 2H), 2.90-2.95 (m, 2H), 2.95 (s, 3H), 3.20-3.25 (m, 2H), 3.40-3.45 (m, 1H), 3.50-3.55 (m, 1H), 3.95-4.05 (m, 1H), 4.75 (q, 1H, J=7.6 Hz), 5.00-5.10 (m, 1H). ^{13}C-NMR ($CDCl_3$) of the major diastereoisomer δ 0.01, 10.10, 21.40, 28.80, 30.75, 37.75, 46.10, 49.10, 49.60, 57.05, 57.75, 66.30, 156.30, 171.90. ^{1}H-NMR ($CDCl_3$) of the minor diastereoisomer δ 0.05 (s, 9H), 1.00-1.05 (m, 2H), 1.40 (s, 9H), 1.55 (d, 3H, J=7.0 Hz), 1.80-2.30 (m, 2H), 2.90-2.95 (m, 2H), 2.95 (s, 3H), 3.10-3.15 (m, 1H), 3.30-3.35 (m, 1H), 3.50-3.55 (m, 2H), 3.95-4.05 (m, 1H), 4.10 (q, 1H, J=7 Hz), 4.85-4.95 (m, 1H). ^{13}C-NMR ($CDCl_3$) of the minor diastereoisomer δ 0.01, 10.10, 17.60, 28.80, 30.75, 37.75, 42.70, 48.15, 53.20, 53.30, 57.55, 66.30, 156.40, 172.20.

1-Methyl-3-methyl-4-N-(2-trimethylsilyl)ethylsulfonyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **15**. To a solution of the perhydro-(1,4)-diazepin-2-one **14** (100mg, 0.23mmol) in CH_2Cl_2 (3mL) was added at -20°C trifluroacetic acid (3mL) The mixture was stirred at 20°C for 4h, then the mixture was concentrated in vacuo. To the residue 10mL of 1N HCl was added and this phase was extracted three times with EtOAc (3x10mL). The aqueous phase was concentrated in vacuo to afford a translucent oil (77mg, quantitative yield) as a mixture of two diastereoisomers in a 65/35 ratio. ESIMS ($C_{13}H_{29}N_3O_3SSi$) : m/z 336 $(M+H)^+$. ^{1}H-NMR (CD_3OD) of the major diastereoisomer δ 0.10 (s, 9H), 0.75-0.85 (m, 2H), 1.60-1.65 (d, 3H, J=7.7 Hz), 2.00-2.40 (m, 2H), 2.90 (s, 3H), 2.95-3.05 (m, 2H), 3.05-3.15 (m, 2H), 3.50-3.55 (m, 2H), 4.15-4.25 (m, 1H), 4.75 (q, 1H, J=7.7 Hz). ^{13}C-NMR (CD_3OD) of the major diastereoisomer δ 0.01, 12.20, 22.25, 32.50, 39.00, 46.15, 50.15, 54.60, 57.50, 59.70, 175.25. ^{1}H-NMR (CD_3OD) of the minor diastereoisomer δ 0.10 (s, 9H), 0.90-0.95 (m, 2H), 1.50-1.55 (d, 3H, J=6.9 Hz), 2.00-2.40 (m, 2H), 2.90 (s, 3H), 2.95-3.05 (m, 2H), 3.05-3.15 (m, 2H), 3.40-3.45 (m, 1H), 3.55-3.60 (m, 1H), 4.15-4.35 (m, 2H). ^{13}C-NMR (CD_3OD) of the minor diastereoisomer δ 0.01, 12.10, 18.70, 32.00, 38.35, 43.20, 49.90, 50.35, 54.80, 57.00, 175.50.

1-Methyl-3-methyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **16**. To a solution of Perhydro-(1,4)-diazepin-2-one **14** (100 mg, 0.23 mmol) in THF (13 mL) was added tetrabutylammonium fluoride (1M in THF, 0.23 mL, 0.23 mmol). The mixture was heated under reflux for 7 h. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (EtOAc/MeOH : 90/10) to afford a yellow oil (38 mg, 62%) as a mixture of two diastereoisomers in a 65/35 ratio. TLC EtOAc/MeOH R_f=0.55 and 0.41. ESIMS m/z ($C_{13}H_{25}N_3O_3$) : 272 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) of major diastereoisomer δ 1.15 (d, 3H, J=7.2 Hz), 1.40 (s, 9H), 1.45-1.55 (m, 1H), 1.80-1.90 (m, 1H), 2.90-3.00 (m, 1H), 2.95 (s, 3H), 3.15-3.20 (m, 1H), 3.20-3.25 (m, 2H), 3.65-3.70 (m, 1H), 4.05 (q, 1H, J=7.2 Hz), 4.90-5.00 (m, 1H). ^{13}C-NMR ($CDCl_3$) of major diastereoisomer δ 19.25, 28.80, 31.15, 36.65, 49.35, 51.30, 59.35, 60.70, 79.90, 156.60, 175.35. ^{1}H-NMR ($CDCl_3$) of minor diastereoisomer δ 1.25 (d, 3H, J=7.2 Hz), 1.25-1.30 (m, 1H), 1.65-1.75 (m, 1H), 1.40 (s, 9H), 2.95 (s, 3H), 3.00-3.05 (m, 1H), 3.10-3.15 (m, 2H), 3.65-3.70 (m, 2H), 3.70-3.75 (q, 1H, J=7.2 Hz), 4.90-5.00 (m, 1H). ^{13}C-NMR ($CDCl_3$) of minor diastereoisomer δ 18.70, 28.80, 32.85, 36.50, 43.15, 47.00, 51.30, 53.25, 79.90, 156.60, 175.55.

Poly(ethyleneglycol-3400) bis(bromocarbonylmethyl) ether **17**. To a solution of PEG_{3400} (1g, 2.94 10^{-4}moles) in 5mL of dry CH_2Cl_2 was added at -20°C $BrCH_2COBr$ (0.39 g, 1.94 mmoles) and triethylamine (60 mg, 2.94 10^{-4}moles). The resulting solution was stirred at 20°C for one day, then the solvent was evaporated under reduced pressure to give an oil, after precipitation of $Et_3N.HBr$ in EtOAc, the polymer **17** was precipitated in cold EtOAc to give a white powder (1.02 g, 95%). FT-IR=3600-3150 cm^{-1} (m), 2882 cm^{-1} (s), 1738 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 3.50-3.85 (m, 306 H), 3.90 (s, 4H), 4.30-4.40 (m, 4H).

Poly(ethyleneglycol-3400) di-6-hydroxy-7-tert-butyloxycarbonylamino-3-azaheptanoate **18**. To a solution of **9a** (0.50g, 2.47mmol) in MeCN (8mL) was added triethylamine (0.28g, 2.72mmol) and **17** (0.75g, 0.2mmol). The mixture was vigorously stirred for one day and then concentrated in vacuo. To the resulting oil was added EtOAc (20mL) for precipitating triethylamine hydrochloride which was discarded by filtration. The product was purified by precipitation in EtOAc (20mL) at -5°C, and filtration. This purification was repeated three times. The product was dissolved in CH_2Cl_2 (10mL), precipitated in diethyl ether (250mL) to afford a white powder (0.68g, 87%). FT-IR=3500-3200 cm^{-1} (m), 2880 cm^{-1} (s), 1745 cm^{-1} (s), 1713 cm^{-1} (s), 1276 cm^{-1} (s), 1248 cm^{-1} (s). ^{1}H-NMR (CD_3OD) δ 1.47 (s, 9H), 1.52-1.80 (m, 2H), 2.80-2.95 (m, 2H), 3.00-3.20 (m, 2H), 3.50-3.80 (m, 309H),4.28-4.38(m, 2H).

Poly(ethyleneglycol-3400) di-3-(N'-tosylalanyl)-6-hydroxy-7-tert-butyloxycarbonylamino-3-azaheptanoate **19a**. To a solution of (L) N-Tosyl alanine (0.29g, 1.2mmol) in CH_2Cl_2 (15mL) was added at 0°C dicyclohexylcarbodiimide (0.12g, 0.6mmol). The mixture was stirred at 0°C

for 1 h then the dicyclohexylurea was removed by filtration. To the filtrate were added at 20°C the compound **18** (0.80g, 0.2mmol) and triethylamine (0.06g, 0.6mmol). The solution was stirred overnight then the mixture was concentrated in vacuo. To the resulting oil was added EtOAc (20mL) and the solution was filtrated. The product was purified by precipitation in EtOAc (20 mL) at -5°C and filtration. This purification was repeated three times. The product was dissolved in CH_2Cl_2 (10mL), precipitated in diethyl ether (250mL) and filtered to afford a white powder (0.79g, 91%) as a mixture of two diastereoisomers. FT-IR=(3550-3200) cm^{-1} (m), 2877 cm^{-1} (s), 1750 cm^{-1} (s), 1718 cm^{-1} (s), 1684 cm^{-1} (s), 1289 cm^{-1} (s), 1252 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 1.38-1.55 (m, 12H), 1.60-1.80 (m, 1H), 1.85-2.00 (m, 1H), 2.42 (s, 3H); 2.60-2.85 (m, 1H), 2.90-3.15 (m, 1H), 3.37-3.50 (m, 2H), 3.52-3.85 (m, 309 H), 4.08-4.20 (m, 1H), 4.22-4.38 (m, 2H), 5.00-5.20 (m, 1H), 5.60-5.75 (m, 1H), 7.22-7.32 (m, 2H), 7.65-7.78 (m, 2H).

Poly(ethyleneglycol-3400) di-3-[N'-tosylaspartyl(β-O-methyl)]-6-hydroxy-7-tert-butyloxycarbonylamino-3-azaheptanoate **19b**. The synthesis of **19b** was carried out in the same manner as for **19a** by coupling **18** (0.80g, 0.2mmol) and (L) N-tosyl aspartic acid(β-O-methyl) (0.36 g, 1.2 mmol). The product is a white powder (0.78 g, 88%) as a mixture of two diastereoisomers. FT-IR=(3550-3100) cm^{-1} (m), 2889 cm^{-1} (s), 1748 cm^{-1} (s), 1745 cm^{-1} (s), 1704 cm^{-1} (s), 1694 cm^{-1} (s), 1278 cm^{-1} (s), 1248 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.60-1.90 (m, 2H), 2.41 (s, 3H); 2.80-3.40 (m, 6H), 3.58-3.80 (m, 312 H), 4.10-4.35 (m, 3H), 5.00-5.20 (m, 1H), 5.42-5.60 (m, 1H), 7.30 (d, 2H, J=8Hz), 7.78 (d, 2H, J=8Hz).

Poly(ethyleneglycol-3400) di-3-[N'-tosylseryl(β-O-benzyl)]-6-hydroxy-7-tert-butyloxycarbonylamino-3-azaheptanoate **19c**. The synthesis of **19c** was carried out in the same manner as for **19a** by a coupling between **18** (0.80g, 0.2mmol) and (L) N-tosyl serine(β-O-benzyl) (0.42g, 1.2mmol). The product is a white powder (0.73g, 80%) as a mixture of two diastereoisomers. FT-IR=(3500-3000) cm^{-1} (m), 2893 cm^{-1} (s), 1752 cm^{-1} (s), 1718 cm^{-1} (s), 1695 cm^{-1} (s), 1284 cm^{-1} (s), 1248 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.60-1.75 (m, 1H), 1.80-1.95 (m, 1H), 2.39 (s, 3H), 2.85-3.20 (m, 4H), 3.55-3.75 (m, 309 H), 3.75-3.85 (m, 2H), 4.18-4.40 (m, 3H), 4.42 (s, 2H), 5.00-5.10 (m, 1H), 5.60-5.80 (m, 1H), 7.10-7.30 (m, 7H), 7.70 (d, 2H, J=8Hz).

Poly(ethyleneglycol)yl-bis1-carboxymethyl-3-methyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **20a**. To a solution of triphenylphosphine (121mg, 0.46mmol) in THF (1mL) under an argon atmosphere was added dropwise at 0°C diethylazodicarboxylate (81 mg, 0.46mmol) dissolved in THF (0.5 mL). The mixture was stirred at 0°C for 30 min. Substrate **19a** (252mg, 0.058mmol) in THF (1.7mL) was added dropwise at 0°C during 2h. The mixture was stirred at 20°C for 36h then the solution was concentrated in vacuo. The product was purified by precipitation in EtOAc (15mL) at -5°C and filtration. This purification was repeated three times. The product was dissolved in CH_2Cl_2 (10mL) and precipitated in diethyl ether (250mL), filtered to afford a white powder (222mg, 89%) as a mixture of two diastereoisomers. FT-IR=2880 cm^{-1} (s), 1734 cm^{-1} (s), 1713 cm^{-1} (s), 1706 cm^{-1} (s), 1287 cm^{-1} (s), 1251 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 1.40-1.55 (m, 12H), 1.75-1.95 (m, 2H), 2.10-2.30 (m, 1H), 2.46 (s, 3H), 2.55-2.75 (m, 1H), 3.20-3.40 (m, 2H), 3.42-3.80 (m, 309 H), 4.20-4.35 (m, 2H), 5.02 (q, 1H, J=6Hz), 5.08-5.20 (m, 1H), 7.30 (d, 2H, J=9Hz), 7.72 (d, 2H, J=9Hz).

Poly(ethyleneglycol)yl-bis1-carboxymethyl-3-methylcarboxymethyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **20b**. The synthesis of **20b** was carried out in the same manner as for **20a** using the linear compound **19b** (258mg, 0.058mmol). The product is a white powder (204mg, 80%) as a mixture of two diastereoisomers. FT-IR=2885 cm^{-1} (s), (1750-1700) cm^{-1} (s), 1278 cm^{-1} (s), 1242 cm^{-1} (s). ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.80-1.95 (m, 2H), 2.30-2.45 (m, 1H), 2.45 (s, 3H), 2.60-3.10 (m, 3H), 3.32-3.50 (m, 2H), 3.52-3.80 (m, 311 H), 4.10-4.30 (m, 3H), 4.90-5.00 (m, 1H), 5.00-5.20 (m, 1H), 7.25-7.35 (m, 2H), 7.70-7.82 (m, 2H).

1-Methylcarboxymethyl-3-methyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **21a**. To a solution of **20a** (200mg, 0.0465mmol) in MeOH (8mL) was added potassium cyanide (6 mg, 0.093 mmol). The mixture was heated under reflux for 4 h then concentrated in vacuo. The polyethylene glycol was precipitated at -5°C in EtOAc (10mL) and filtrated. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc : 20/80) to afford a white powder (15.2mg, 34%) as a mixture of two diastereoisomers. TLC EtOAc R_f=0.67. HPLC : Tr=22.80min. ESIMS ($C_{22}H_{33}N_3O_7S$) : m/z 506 $(M+Na)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.42 (d, 3H, J=6Hz), 1.49 (s, 9H), 1.60-1.75 (m, 2H), 2.10-2.25 (m, 1H), 2.90-3.05 (m, 1H), 2.47 (s, 3H), 3.28-3.40 (m, 2H), 3.70 (s, 3H), 3.97-4.35 (m, 3H), 5.04 (q, 1H, J=6Hz), 5.08-5.15 (m, 1H), 7.30 (d, 2H, J=8Hz), 7.73 (d, 2H, J=8Hz).

1,3-Dimethylcarboxymethyl-4-tosyl-5-tert-butyloxycarbonylaminomethyl-perhydro-(1,4)-diazepin-2-one **21b**. To a solution of **20b** (205mg, 0.0465mmol) in methanol (8mL) was added potassium cyanide (6mg, 0.093mmol). The mixture was heated under reflux for 4 h then concentrated in vacuo. The polyethylene glycol was precipitated at -5°C in EtOAc (10mL) and filtrated. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc : 20/80) afforded an colorless oil (27.7mg, 55%) as a mixture of two diastereoisomers. TLC EtOAc R_f=0.70. HPLC : Tr=24.31 min. ESIMS ($C_{24}H_{35}N_3O_9S$) : m/z 564 $(M+Na)^+$. ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.65-1.90 (m, 2H), 2.32-2.48 (m, 1H), 2.70-2.85 (m, 1H), 2.43 (s, 3H), 2.92-3.17 (m, 2H), 3.20-3.40 (m, 2H), 3.70 (broad s, 6H), 3.90-4.00 (m, 1H), 4.10-4.25 (m, 1H), 4.30-4.50 (m, 1H), 4.70-4.85 (m, 1H), 4.90-5.10 (m, 1H), 7.30-7.40 (m, 2H), 7.70-7.80 (m, 2H).

1-Methylcarboxymethyl-3-methyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **22a**. To a solution of compound **21a** (9.6mg, 0.02mmol) in CH_2Cl_2 (1mL) was added at -20°C trifluroacetic acid (1mL). The mixture was stirred at 20°C for 3h, then the solution was concentrated in vacuo to afford a colorless oil (9.9mg, quantitative) as a mixture of two diastereoisomers in a 50/50 ratio. HPLC : Tr_1=13.80 min, Tr_2=14.00 min. FABMS (GT) ($C_{17}H_{25}N_3O_5S$) : m/z 384 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 384.1590. Found : 384.1593. LC/MS : Tr_1=12.60 min. ESIMS=m/z 384.0 $(M+H)^+$. Tr_2=13.15 min. ESIMS= m/z 383.9 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.68 (d, 3H, J=7Hz), 1.90-2.02 (m, 1H), 2.11-2.27 (m, 2H), 2.48 (s, 3H), 2.60-2.75 (m, 1H), 3.00-3.20 (m, 2H), 3.67 (s, 3H), 3.90-4.12 (m, 2H), 4.20-4.30 (m, 1H), 5.12 (q, 1H, J=7Hz), 7.35-7.45 (m, 2H), 7.67-7.77 (m, 2H).

(1,3)-Dimethylcarboxymethyl-4-tosyl-5-aminomethyl-perhydro-(1,4)-diazepin-2-one **22b**. To a solution of compound **21b** (10.8mg, 0.02mmol) in CH_2Cl_2 (1mL) was added at -20°C trifluroacetic acid (1mL). The mixture was stirred at 20°C for 3h, then the solution was concentrated in vacuo to afford a colorless oil (11.1mg, quantitative) as a mixture of two diastereoisomers in a 60/40 ratio. FABMS (GT) ($C_{19}H_{27}N_3O_7S$) : m/z 442 $(M+H)^+$. High-resolution mass spectrum, exact mass calculated : 442.1648. Found : 442.1590. LC/MS : Tr_1=15.95 min. ESIMS= m/z 442.0 $(M+H)^+$. Tr_2=16.70 min. ESIMS= m/z 442.1 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ 1.82-2.00 (m, 2H), 2.47 (s, 3H); 2.40-2.50 (m, 1H), 2.72-2.95 (m, 3H), 3.00-3.20 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 3.90-4.05 (m, 1H), 4.15-4.30 (m, 1H), 4.52-4.70 (m, 1H), 5.00-5.10 (m, 1H), 7.35-7.45 (m, 2H), 7.75-7.85 (m, 2H).

References

[1] Thompson, S.K.; Murthy, K.H.M.; Zhao, B.; Winborne, E.; Green, D.W.; Fischer, S.M.; DesJarlais, R.L.; Tomaszek, T.A.; Meek, T.D.; Gleason, J.G.; Abdel-Meguid, S.S. *J. Med. Chem.* **1994**, *37*, 3100-3107.

[2] Gordon, T.D.; Singh, J.; Hansen, P.E.; Morgan,B.A. *Tetrahedron Lett.* **1993**, *34*, 1901-1904.

[3] Gordon, T.D.; Hansen, P.E.; Morgan,B.A.; Singh, J.; Baizman,E.; Ward, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 915-920.

[4] Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csöregh, I.; Hesselink, W.; Hacksell,U. *J. Org. Chem.* **1995**, *60*, 3112-3120.

[5] Gilbert, I.; Rees, D.C.; Ridcharson, R.S. Singh, J. *Tetrahedron Lett.* **1991**, *32*, 2277-2280.

[6] Kim, B.H.; Chung, Y.J.; Keum, G.; Kim, J.; Kim, K. *Tetrahedron Lett.* **1992**, *33*, 6811-6814.

[7] Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807-2810.

[8] (a) Goodfellow, V.S.; Lauderman, C.P.; Gerrity, G.I.; Burkard, M.; Strobel, E.; Zuzack, J.S.; McLeod, D.A. *Mol. Div.* **1996**, *2*, 97-102. (b) Yamashita, T.; Hatamoto, E.; Takenaka, H.; Kojima, Y.; Inoue, Y.; Gemba, M.; Yasuda, M. *Chem. Pharm. Bull.* **1996**, *44*, 856-859.

[9] (a) Brickmann, K.; Somfai, P.; Kihlberg, J. *Tetrahedron Lett.* **1997**, *38*, 3651-3654. (b) Scott, B.O.; Siegmund, A.C.; Marlowe,C.K.; Pei,Y.; Spear,K.L. *Mol. Div.* **1995**, *1*, 125-134.

[10] Callahan, J.F.; Bean, J.W.; Burgess, J.L.; Eggleston, D.S.; Hwang, S.M.; Kopple, K.D.; Koster, P.F.; Nichols, A.; Peishoff, C.E.; Samanen, J.M.; Vasko, J.A.; Wong, A.; Huffman, W.F. *J. Med. Chem.* **1992**, *35*, 3970-3972.

[11] (a) Ripka, W.C.; De Lucca, G.V.; Bach II, A.C.; Pottorf, R.S.; Blaney, J.M. *Tetrahedron* **1993**, *49*, 3593- 3628. (b) Evans, B.E.; Bock, M.G.; Rittle,K.E.; Di Pardo, R.M.; Whitter, W.L.; Veber, D.F.; Anderson, P.F.; Freidinger, R.M. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 4918-4922.

[12] (a) Robl, J.A.; Simpkins, L.M.; Stevenson, J.; Sun, C. Q.; Murugesan, N.; Barrish, J.C.; Asaad, M.M.; Bird,J.E.; Schaeffer,T.R.; Trippodo,N.C.; Petrillo,E.W.; Karanewsky,D.S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1789-1794. (b) Kawanishi, Y.; Ishihara, S.; Tsushima,T.; Seno, K.; Hagishita,S.; Ishikawa,M.; Ishihara, Y. *Bioorg. Med. Chem.* **1997**, *5*, 1411-1423.

[13] (a) Ma, X.; Passaro, G.; Rolland Fulcrand, V.; Fauchère, J.L.; Lazaro, R.; Roumestant, M.L.; Viallefont, P. *Protein and Peptide Letters* **1995**, 347-350. (b) Nouvet, A.; Lamaty, F.; Lazaro, R. *Tetrahedron Lett.* **1998**, *39*, 2099-2102.

[14] (a) Mitsunobu, O. *Synthesis*, **1981**, 1-28. (b) Hughes, D.L. The Mitsunobu reaction. In: Beak, P. *et al* Editors. Organic Reactions. New York: John Wiley & Sons, **1992**, *Vol.42*, 335-656.

[15] Cavelier-Frontin, F.; Achmad, S. Verducci, J.; Jacquier, R.; Pepe, G. *J. Mol. Struct. (Theochem)* **1993**, *286*, 125-130.
[16] Tsunoda, T.; Nagino, C.; Oguri, M.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2459-2462.
[17] Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2457-2458.
[18] Weinreb, S.M.; Demko, D.M.; Lessen, T.A. *Tetrahedron Lett.* **1986**, *27*, 2099-2102.
[19] (a) Ward, D.A.; Gai, Y.Z.; Kaller, B.F. *J. Org. Chem.* **1996**, *61*, 5498. (b) Wifp, P.; Venkatraman, S.; Miller, C.P. *Tetrahedron Lett.* **1995**, *36*, 3639.
[20] Gravert, D.J.; Janda, K.D. *Chem. Rev.* **1997**, *97*, 489-509.
[21] Nouvet, A.; Lamaty, F.; Lazaro, R. *Tetrahedron Lett.* **1998**, *39*, 3469-3470.
[22] (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151-2157.
[23] Wityak, J.; Gould, S.J.; Hein, S.J.; Douglas, A.K. *J. Org. Chem.* **1987**, *52*, 2179-2183.