

HETEROCYCLES, Vol. 77, No. 7, 2009, pp. 417 - 432. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd July, 2008, Accepted, 18th August, 2008, Published online, 21st August, 2008.
DOI: 10.3987/COM-08-S(F)37

SYNTHESIS OF 5-AMINO- AND 4-HYDROXY-2-PHENYLSULFONYLMETHYLPYPERIDINES

Julien Massé and Nicole Langlois*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette,
France

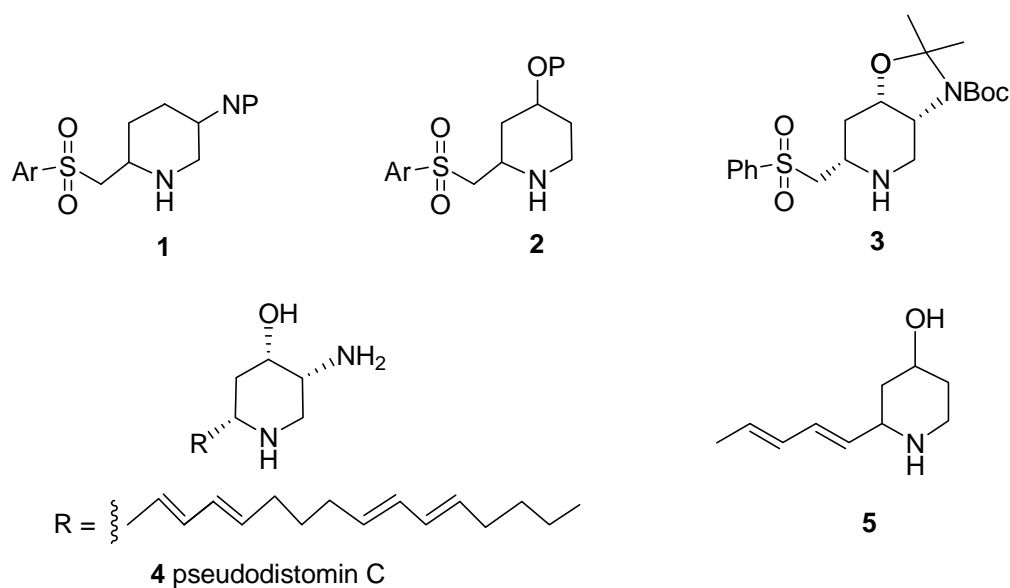
E-mail: nicole.langlois@icsn.cnrs-gif.fr

Abstract – Suitable protected 5-amino- and 4-hydroxy-2-phenylsulfonylmethylpiperidines were synthesized from functionalized *N*-benzyloxycarbonylpiperidin-2-ones through the opening of lactam ring by methyl phenyl sulfone carbanion followed by reductive aminocyclization.

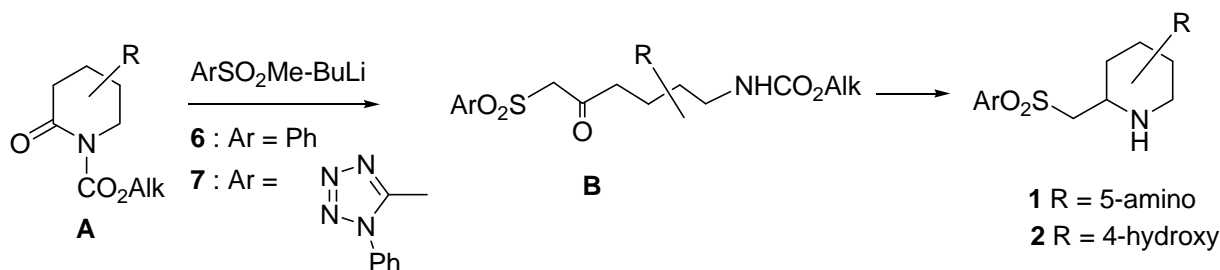
INTRODUCTION

Many functionalized piperidines constitute structural subunits in natural as well as synthetic products which could exhibit interesting biological activities and a wide range of methodologies have been reported for their syntheses.¹ In this context, 5-amino and 4-hydroxy-2-phenylsulfonylmethylpiperidines **1** and **2** are interesting targets as scaffolds to synthesize, respectively, simplified deoxy- or deamino-analogues of pseudodistomins such as **4**, by further elaboration of poly-unsaturated chains at C-2. Pseudodistomin C (**4**) is an all *cis* 2,4,5-trisubstituted piperidine of marine origin which displays cytotoxic activities.² We developed some years ago a stereoselective and original access to the intermediate **3**,³ which has been previously converted into **4**,⁴ through Julia or Julia-Kocienski olefination to generate the 2-(1*E*,3*E*)-dienyl chain at C-2.^{5,6} In addition, *O*-protected 4-hydroxy-2-phenylsulfonylmethylpiperidines **2** could also be the precursors of 4-hydroxy-2-(1,3-pentadienyl)piperidines **5**. Several diastereomers of **5** have been isolated from *Streptomyces* strains.⁷ Whereas *trans* (2*S*,4*S*)-**5** exhibits antibacterial and anticonvulsant activities, DNA-binding properties have been attributed to its enantiomer,^{7b} and the *cis* derivative (2*S*,4*R*) was proposed as an intermediate in the biosynthesis of the potent antimicrobial agent streptazolin.^{7a,8} Therefore, the synthesis of these compounds have attracted much interest.⁹

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



We report herein the preparation of substituted 2-arylsulfonylmethylpiperidines of general structure **1** and **2** by a similar route depicted in the Scheme 1. This involved the opening of appropriate functionalized *N*-alkoxycarbonylpiperidinones **A** with anion of a methyl sulfone such as **6** or **7**, and reductive aminocyclization of the corresponding β -ketosulfones **B**, leading to target substituted piperidines.

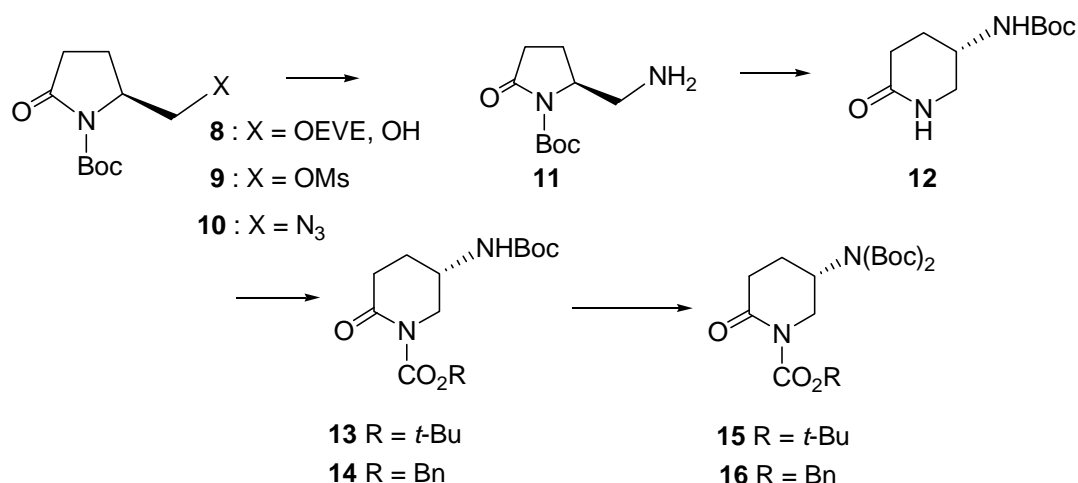


Scheme 1

RESULTS AND DISCUSSION

Accordingly, our investigations began with the preparation of appropriate protected 5-amino- and 4-hydroxy-piperidinones **15**, **16** and **21**.

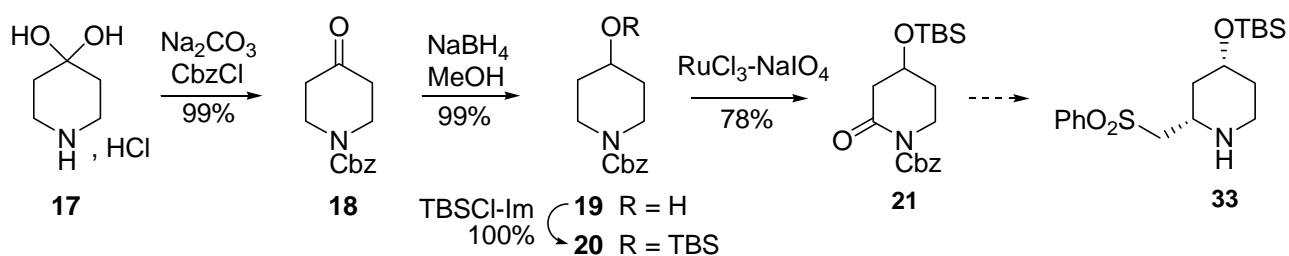
The protected 1-alkoxycarbonyl-5-aminopiperidinones **15** and **16** were prepared from enantiopure (*S*)-5-*tert*-butoxycarbonylamino-piperidin-2-one **12**, following the Scheme 2. The intermediate **12** has been obtained from (*S*)-pyroglutaminol derivative **8**¹⁰ by a convenient, short and efficient route previously developed in our laboratory.^{3,11} It involved an intramolecular transamidation of 1-alkoxycarbonyl-5-aminomethylpyrrolidin-2-one **11** obtained from **8** through the mesylate (**9**) (95%) and the azidomethyl derivative (**10**) (96%). Without isolation of **11**, the conversion of **10** into **12** was almost quantitative. We demonstrated the superiority of this route to the pathways involving intramolecular Mitsunobu reactions,^{12,13} and its interest has been confirmed afterwards by several recent examples.¹⁴



Scheme 2

Dually protected 5-amino group was needed to prevent side reactions. Accordingly, *N,N'*-tricarbamates **15** and **16** were stepwise prepared. These sequential protections are not obvious since the possibility of ring contraction could not be excluded. Thus, the 5-substituted piperidinone **12** was first protected as 1-*tert*-butylcarbamate **13** or 1-benzylcarbamate **14**. *N-tert*-Butylcarbamate **13** was obtained in 90% yield under classical conditions (DMAP, Boc₂O in MeCN), whereas orthogonally protected 1-benzyloxycarbonyl compound **14** could be isolated only in moderate yield (60%) under Kikugawa's conditions using LiHMDS as base and benzyl chloroformate at -78 °C.¹⁵ Subsequent *N*-Boc protections to provide **15** and **16** were introduced respectively with 77% and 67% yield. The presence of six-membered ring in **15** and **16** was confirmed by IR absorption in the range of carbonyl, excluding a reverse transamidation reaction.

In the 4-hydroxypiperidine series, we chose to focus our study toward the synthesis of racemic *cis*-4-*tert*-butyldimethylsilyloxy-2-phenylsulfonylmethylpiperidine **33** from 1-benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypiperidin-2-one **21**. Starting from inexpensive piperidinone monohydrate hydrochloride **17**, the piperidinone **21** was prepared in high yields as outlined in the Scheme 3.

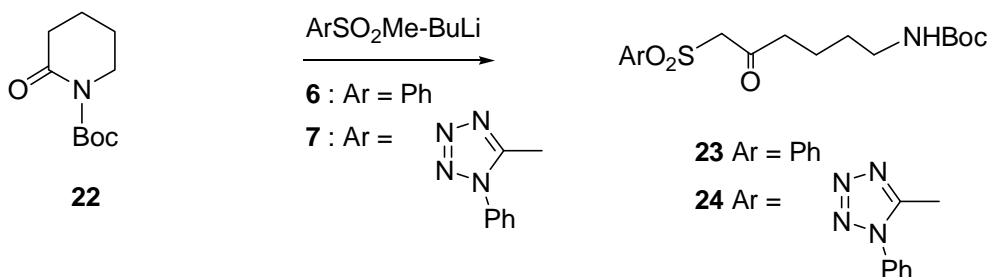


Scheme 3

In our hands, benzyl chloroformate was shown to be more efficient than *N*-benzyloxycarbonyloxysuccinimide to protect nitrogen,¹⁶ affording **18** in 99% yield. Further reduction with NaBH₄ under classical conditions provided the known *N*-Cbz-piperidin-4-ol **19** in 99% yield.¹⁷ The corresponding TBS ether **20**^{17c,18} was oxidized into lactam **21**¹⁹ in 78%, with RuCl₃/NaIO₄ under biphasic conditions.²⁰

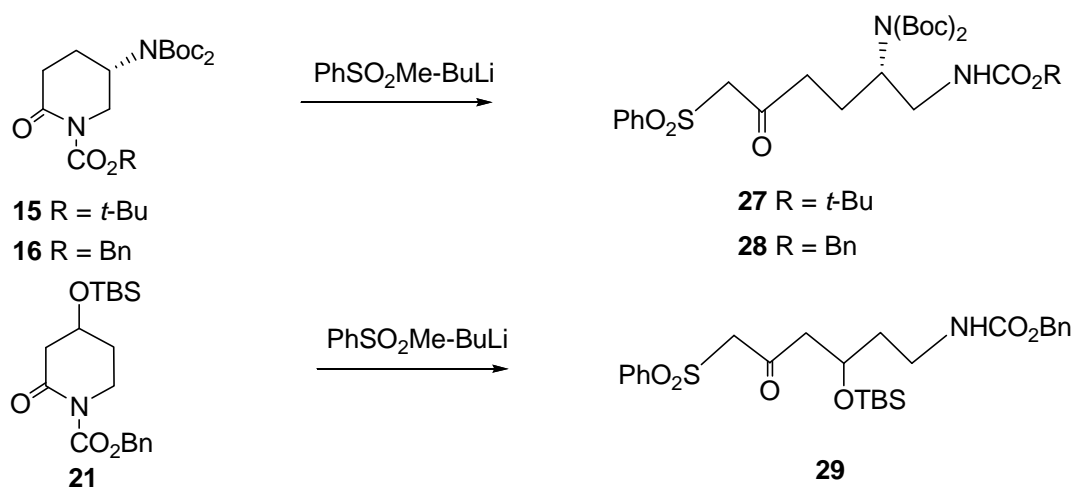
With the piperidinones **15**, **16** and **21** in hands, we investigated their conversion into acyclic β-ketosulfones.

N-*tert*-Butoxycarbonylvalerolactam **22** was used as a model to compare the ring opening step with carbanions of methyl phenyl sulfone **6** and methyl 1-phenyl-1*H*-tetrazol-5-yl sulfone **7**, respectively. As we observed in the cases of 1-alkoxycarbonylpyrrolidinone nucleophilic opening,²¹ methyl sulfones **6** and **7** in THF were deprotonated with *n*BuLi, at -78 °C and the *N*-alkoxycarbonylpiperidinone gave rise rapidly at the same temperature to the expected acyclic β-ketosulfones **23**²² and **24** (Scheme 4).



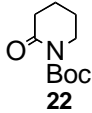
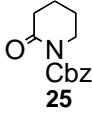
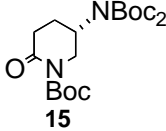
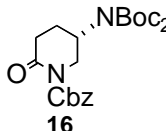
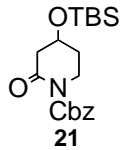
Scheme 4

β-Ketosulfone **23** obtained by using methyl phenyl sulfone **6** was isolated in better yields (91%) than **24** (71%) formed with methyl sulfone **7**, the difference being significant. For this reason, the other functionalized *N*-alkoxycarbonylpiperidinones **15**, **16** and **21** were opened with **6** carbanion (Scheme 5), and the results are summarized in the Table 1.



Scheme 5

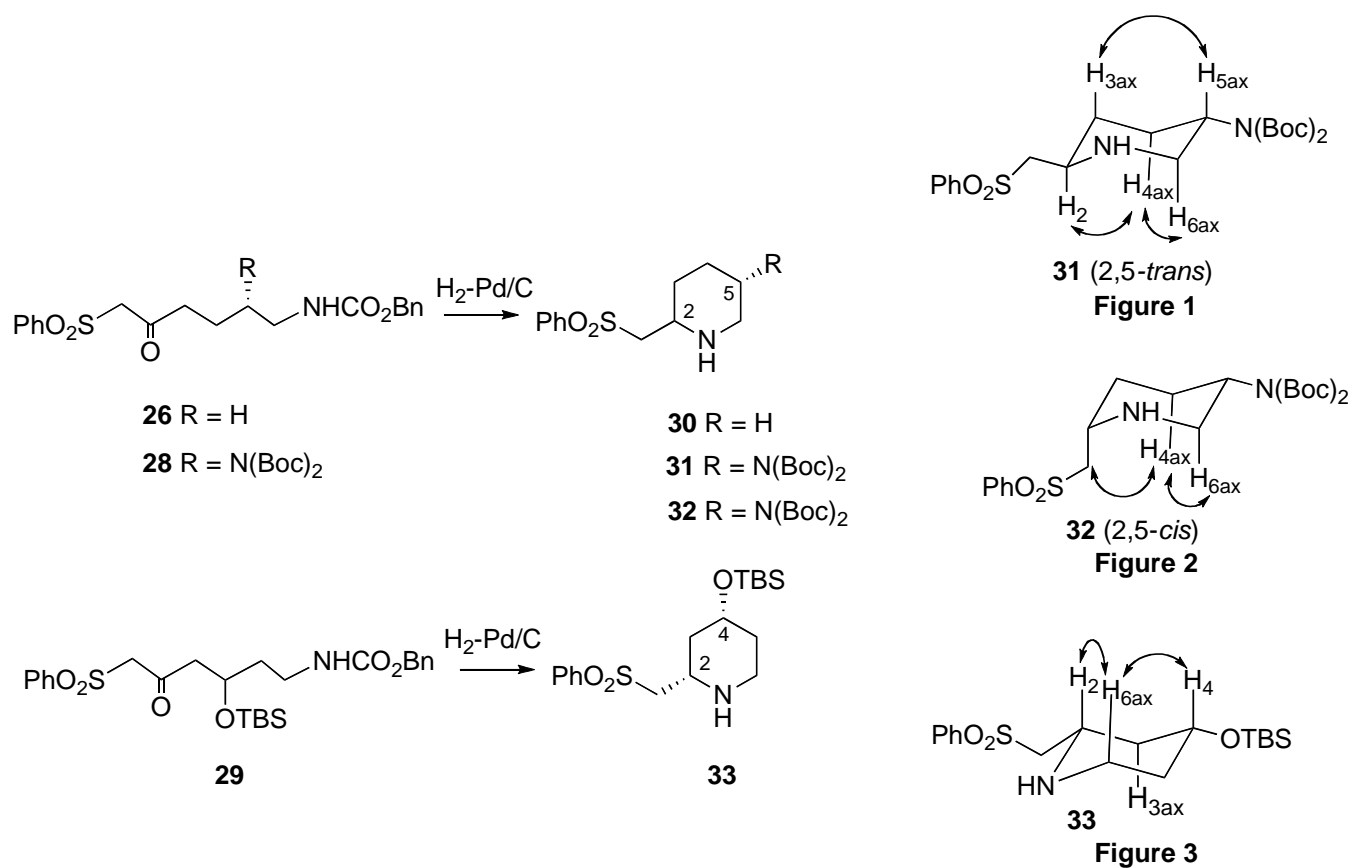
Table 1. Preparation of β -ketosulfones by opening lactams with methyl phenyl sulfone **6** carbanion

Piperidinones					
Ketosulfones	23	26	27	28	29
(yield)	(91%)	(75%)	(74%)	(67%)	(78%)

The opening of *N*-Boc protected piperidinone **22** and **25** occurred with high regioselectivity, and the β -ketosulfones **23** and **26** were the sole products obtained. In the case of **15**, some nucleophilic attack of one of nitrogen Boc protecting groups was also observed (probably N_1 Boc) with the formation of an acyclic disulfone (ca 9%), while the treatment of **21** afforded **29** in 78% yield, together with small amount (less than 4%) of 4-*tert*-butyldimethylsilyloxypiperidin-2-one by loss of the Cbz protecting group.

Reductive aminocyclizations were investigated on the *N*-Cbz ketosulfones **26**, **28** and **29**.

With the model ketosulfone **26**, one-pot hydrogenolysis of benzyl carbamate (H_2 , 10% Pd/C) and cyclization–reduction into **30** occurred in good yields after 30 h (80%). With substituted ketosulfone **28**, the reaction was much slower under the same conditions and some starting material was recovered after 48 h (ca 20%). An equilibrium between the imine intermediate and a conjugate enamine could be involved during this aminocyclization step.²² Two diastereomers of 2,5-disubstituted piperidines **31** and **32** were formed (70% yield) in *ca* 1:2 ratio. Their configurations were deduced from NMR spectroscopy. To avoid overlapping of several signals, C_6D_6 was used as solvent for 1H and 2D experiments with minor diastereomer **31**. The doublet of doublet at 3.23 ppm (with two large coupling constants $J = J' = 10.9$ Hz) could be assigned to H-6ax confirming the axial position of vicinal H-5. The coupling pattern of the signal at 3.03 ppm attributed to H-2 is also compatible with an axial position, and NOE were observed between H-5 and H-3ax, H-6ax and H-4ax, H-4ax and H-2, supporting a *trans* 2,5 configuration as shown in Figure 1. In the major diastereomer **32**, a small NOE effect between H-4ax and the methylene of the phenylsulfonylmethyl group is compatible with an axial position of this group and a *cis* 2,5 relative configuration as shown in Figure 2.



Scheme 6

With benzyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-6-(phenylsulfonyl)hexylcarbamate **29**, the *cis*-2,4-substituted piperidine **33** was isolated only in moderate yield (53%), together with starting material. It is worthy of note that the product of *O*-desilylation was not identified under these conditions of hydrogenolysis.²³ The attribution of relative *cis* configuration of 4-*tert*-butyldimethylsilyloxy-2-phenylsulfonylmethylpiperidinone **33** was based on steric factors and supported by the comparison of the chemical shifts and coupling constants with the data described for the two diastereomers of 4-hydroxy-2-(1,3-pentadienyl)piperidines **5**.^{7,9a,b} NOESY experiment indicated correlations between H-6ax and H-4 and between H-6ax and H-2 as shown in Figure 3.

In conclusion, *cis* and *trans* 5*S*-(bis(*tert*-butoxycarbonyl)amino)-2-phenylsulfonylmethylpiperidines were prepared through opening of appropriate substituted *N*-Cbz-lactam, followed by reductive aminocyclization. These polysubstituted piperidines constitute interesting building blocks for the synthesis of pseudodistomin deoxy analogues owing to the presence of a phenyl sulfone function which would allow the introduction of various polyunsaturated side chains at position α to the nitrogen. Starting from **21**, the synthesis of **33** occurred with good stereoselectivity, and this work could be extended to the synthesis of enantiopure counterparts.²⁴

EXPERIMENTAL

General. Melting points were uncorrected. NMR spectra were recorded on a Bruker spectrometer at 300 or 500 MHz for ^1H NMR, 75 or 125 MHz for ^{13}C NMR; chemical shifts are given in ppm relative to residual CHCl_3 (7.27 ppm for ^1H NMR and 77.14 ppm for the middle line in ^{13}C NMR); s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. Mass spectra and high-resolution mass spectra (m/z) were measured using ESI. All moisture sensitive reactions were performed under argon. THF was freshly distilled from the sodium complex of benzophenone before use. Dichloromethane was freshly distilled from CaH_2 . Column chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography (TLC) on silica gel (Merck HF 254 + 366).

(*S*)-*tert*-Butyl 2-(methylsulfonyloxy)methyl-5-oxopyrrolidine-1-carboxylate (**9**)

Mesyl chloride (3.3 mL, 42.4 mmol) was added dropwise under inert atmosphere to a stirred solution of *N*-Bocpyroglutaminol (4.563 g, 21.2 mmol) in dry pyridine (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt for 3 h. After cooling at 0 °C, the mixture was diluted with CH_2Cl_2 and aqueous Na_2CO_3 (10% w/v, 150 mL), was added. The mesylate was extracted with CH_2Cl_2 , purified by filtration on silica gel (eluent : EtOAc-MeOH 9 : 1) and obtained as colorless crystals (5.91 g, 95%). Mp 80-81 °C. $[\alpha]_{\text{D}}^{26} - 65$ (c 2.0, CHCl_3) lit.,²⁵ **ent-9**: + 64.4 (c 1.00, EtOH). IR: 3030, 2933, 1787, 1748(sh), 1707, 1364 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): 4.60, 4.35 (2 dd, 2H, H_2 -6), 4.41 (masked m, 1H, H-5), 3.03 (s, 3H, SMe), 2.70, 2.50, 2.25, 2.07 (4 m, 4H, H_2 -3, H_2 -4), 1.54 (s, 9H, *t*-Bu) ppm.

(*S*)-*tert*-Butyl 2-(azidomethyl)-5-oxopyrrolidine-1-carboxylate (**10**)

NaN_3 (5.78 g, 89.0 mmol) was added to a solution of mesylate **9** (5.214 g, 17.8 mmol) in DMF (53.4 mL). The mixture was stirred under argon at 50 °C for 10 h, cooled to rt, diluted with H_2O and extracted with Et_2O . The organic layers were washed with H_2O and afforded azido-derivative **10** as colorless gum after usual workup (4.10 g, 96%). $[\alpha]_{\text{D}}^{26} - 43$ (c 0.65, CHCl_3). IR: 2990, 2111, 1786, 1746, 1711 cm^{-1} . MS (ESI, CH_2Cl_2 -MeOH) m/z : 263 $[(\text{MNa})^+, 100\%]$. ^1H NMR (300 MHz, CDCl_3): 4.27 (m, 1H, H-5), 3.67 (dd, 1H, $J = 12.3$, $J' = 5.7$ Hz, Ha-6), 3.54 (dd, 1H, $J = 12.3$, $J' = 3.0$ Hz, Hb-6), 2.70, 2.43, 2.16, 1.93 (4m, 4H, H_2 -3, H_2 -4), 1.55 (s, 9H, *t*-Bu) ppm. ^{13}C NMR (75 MHz, CDCl_3): 173.9, 149.8, 83.5, 56.6, 53.7, 31.4, 28.0, 21.3 ppm. HRMS (ESI, CH_2Cl_2 -MeOH) m/z : calcd for $\text{C}_{10}\text{H}_{16}\text{N}_4\text{O}_3\text{Na}$ $(\text{MNa})^+$: 263.1120, found 263.1116.

(*S*)-5-*N*-*tert*-Butoxycarbonylamino-piperidin-2-one (**12**)

A solution of compound **10** (706 mg, 2.94 mmol) in dry MeOH (14 mL) and 10% Pd/C (180 mg) were

stirred under H₂ (1 atm.) for 26 h. The catalyst was filtered off on Celite[®] and washed with MeOH. Evaporation to dryness under reduced pressure gave rise to the crude product which was heated in MeOH at 65 °C for 24 h to afford (*S*)-5-*N*-*tert*-butoxycarbonylamino-piperidin-2-one **12** (623 mg, 99%) as colorless crystals. Mp 128-129 °C. $[\alpha]_D^{25} - 36.4$ (*c* 0.72, CHCl₃). IR: 3687, 3631, 3031, 1718, 1662, 1506 cm⁻¹. MS (CI, isobutane) *m/z*: 215 (MH)⁺, 159, 115. ¹H NMR (300 MHz, CDCl₃): 6.12 (broad s, NH), 4.74 (broad s, 1H, NHCO₂), 3.97 (m, 1H, H-5), 3.56 (broad d, 1H, *J* = 11.5 Hz, Ha-6), 3.16 (dd, 1H, *J* = 11.5, *J'* = 6.6 Hz, Hb-6), 2.47 (m, 2H, H₂-3), 2.03 (m, 1H, Ha-4), 1.87 (m, 1H, Hb-4), 1.45 (s, 9H, *t*-Bu) ppm. ¹³C NMR (75 MHz, CDCl₃): 171.73, 155.26, 79.98, 46.89, 44.22, 28.62, 28.44, 26.49 ppm. Anal. Calcd for C₁₀H₁₈N₂O₃: C, 56.06; H, 8.47; N, 13.07. Found: C, 55.90; H, 8.07; N, 12.87.

(*S*)-*tert*-Butyl 5-(bis(*tert*-butoxycarbonyl)amino)-2-oxopiperidine-1-carboxylate (**15**)

a) (*S*)-*tert*-Butyl 5-(*tert*-butoxycarbonylamino)-2-oxopiperidine-1-carboxylate (**13**)

To a solution of lactam **12** (749 mg, 3.5 mmol) in MeCN (10 mL) were successively added DMAP (214 mg, 1.75 mmol) and Boc₂O (1.146g, 5.25 mmol) in MeCN (4 mL) and the mixture was stirred at rt for 8 h. After evaporation of the solvent at rt, the residue was purified by chromatography on silica gel (eluent : Et₂O) to afford **13** (988 mg, 90%). MS (ESI, MeOH) *m/z*: 337 (MNa)⁺, 237 (100%). ¹H NMR (300 MHz, CDCl₃): 4.65 (broad d, 1H, NH), 4.03 (m, 1H, H-5), 3.80 (d, 1H, *J* = 12.5, *J'* = 4 Hz, Ha-6), 3.57 (dd, 1H, *J* = 12.5, *J'* = 6 Hz, Hb-6), 2.56 (m, 2H), 2.12 (m, 1H), and 1.75 (m, 1H): H₂-3 and H₂-4, 1.52 and 1.45 (2s, 18H, 2 *t*-Bu) ppm. The compound **13** was further protected as tricarbamate **15**.

To a solution of *tert*-butyl 5-(*tert*-butoxycarbonyl)amino-2-oxopiperidine-1-carboxylate **13** (941 mg, 2.99 mmol) in MeCN (9.5 mL) were successively added DMAP (208 mg, 1.7 mmol) and Boc₂O (1.028g, 4.5 mmol) in MeCN (4.0 mL) and the mixture was stirred at rt for 18 h. After evaporation of the solvent at rt, the product was purified by chromatography on silica gel (eluent : heptane-Et₂O 3 : 7 to give **15** as colorless crystals (955 mg, 77%). Mp 100 °C. $[\alpha]_D^{26} + 13.2$ (*c* 3.17, CHCl₃). IR: 2980, 2937, 1727, 1716, 1690, 1477, 1453, 1413, 1391, 1364, 1297 cm⁻¹. MS (ESI, MeOH) *m/z*: 437 (MNa⁺, 100%), 337. ¹H NMR (300 MHz, CDCl₃): 4.50 (m, 1H, H-5), 3.96 (dd, 1H, *J* = 12.5, *J'* = 6.1 Hz, Ha-6), 3.86 (dd, 1H, *J* = 12.5, *J'* = 10.9 Hz, Hb-6), 2.78 and 2.47 (2m, 2H, H₂-3), 2.17 and 2.06 (2m, 2H, H₂-4), 1.50-1.49 (27H, 3x *t*-Bu) ppm. ¹³C NMR (75 MHz, CDCl₃): 171.24, 152.84, 151.96, 83.31, 83.23, 50.74, 46.04, 33.90, 28.12, 23.77 ppm. Anal. Calcd for C₂₀H₃₄N₂O₇: C, 57.95; H, 8.27; N, 6.76. Found: C, 57.68; H, 8.26; N, 6.54.

(*S*)-Benzyl 5-(bis(*tert*-butoxycarbonyl)amino)-2-oxopiperidine-1-carboxylate (**16**)

(*S*)-Benzyl 5-(*tert*-butoxycarbonyl)amino-2-oxopiperidine-1-carboxylate (**14**)

LiHMDS (1M in THF, 2.4 mL) was added under argon to a solution of lactam **12** (512 mg, 2.39 mmol) in

dry THF (30 mL) under stirring at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 0.25 h at the same temperature before the addition of benzyl chloroformate (0.39 mL, 2.75 mmol). After being stirred for additional 0.5 h at $-78\text{ }^{\circ}\text{C}$, a saturated aqueous NH_4Cl solution was added, and the cooling bath was removed. The dicarbamate was extracted with EtOAc and purified by filtration on silica gel (eluent: Et_2O) to give **14** (500 mg, 60%). MS (ESI, MeOH) m/z : 371 (MNa^+), HRMS calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$: 371.1583, found: 371.1584. The compound **14** was further protected as tricarbamate **16**, by treatment with DMAP and Boc_2O under the conditions described for **13** and the tricarbamate **16** was isolated after chromatography on silica gel (eluent : heptane- Et_2O 3 : 7) as colorless crystals (431 mg, 67%). Mp 124-125 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{26} + 16$ (c 3.08, CHCl_3). IR: 2985, 2936, 1723, 1691, 1458, 1386, 1336 cm^{-1} . MS (ESI, CH_2Cl_2 -MeOH) m/z : 919 (2MNa^+), 471 (MNa^+ , 100%). ^1H NMR (300 MHz, CDCl_3): 7.44 and 7.35 (2m, 5H, H-Ar), 5.30 (s, 2H, OCH_2), 4.55 (m, 1H, H-5), 4.08 (dd, 1H, $J = 12$, $J' = 6$ Hz, Ha-6), 3.96 (dd, 1H, $J = 12$, $J' = 9.7$ Hz, Hb-6), 2.84 and 2.51 (2m, 2H, H_2 -3), 2.21 and 2.08 (2m, 2H, H_2 -4), 1.49 (s, 18H, t -Bu) ppm. ^{13}C NMR (75 MHz, CDCl_3): 171.06, 153.41, 152.76, 135.38, 128.62, 128.34, 128.10, 68.68, 50.52, 46.26, 33.88, 27.98, 23.61 ppm. HRMS (ESI, CH_2Cl_2 -MeOH) m/z : calcd for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_7\text{Na}$ (MNa^+): 471.2107, found 471.2078.

***N*-Benzyloxycarbonylpiperidin-4-one (18)**

Na_2CO_3 (711 mg, 6.77 mmol) was added at rt to a mixture of 4-piperidone monohydrate hydrochloride (825 mg, 4.81 mmol) in THF- H_2O 1:1 (20 mL). Then, benzyl chloroformate (0.57 mL, 3.99 mmol) was added under stirring. After 70 min., the mixture was diluted with CH_2Cl_2 and aqueous solution of Na_2CO_3 (5% w/v). The organic layer was separated and the aqueous layer was further extracted 3 times with CH_2Cl_2 to afford, after usual workup and filtration on silica gel (eluent: Et_2O) the *N*-Cbz derivative **18** (922 mg, 99%) as a colorless oil. IR: 3031, 2960, 2879, 1693, 1497, 1473, 1426, 1362, 1352, 1310, 1271, 1226, 1116 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): 7.37 (5H, H-Ar), 5.19 (apparent s, 2H, CH_2Ph), 3.81 (dd, 4H), 2.47 (m, 4H) ppm. ^{13}C NMR (75 MHz, CDCl_3): 207.24, 155.14, 136.34, 128.54, 128.24, 128.14, 67.74, 43.04, 41.04 ppm (in full agreement with described data).^{17a}

***N*-Benzyloxycarbonylpiperidin-4-ol (19)**

To a solution of **18** (533 mg, 2.29 mmol) in MeOH (4.6 mL) was added NaBH_4 (42 mg, 1.11 mmol) and the mixture was stirred at rt for 30 min before addition of CH_2Cl_2 and H_2O . The aqueous phase was extracted with CH_2Cl_2 and the organic phases were washed with H_2O to afford after usual workup the alcohol **19** pure enough for the next step (532 mg, 99%). IR: 3397, 2942, 2862, 1672, 1428, 1363, 1270, 1221, 1128, 1069 cm^{-1} . ^1H NMR (300MHz, CDCl_3): 7.35 (m, 5H, H-Ar), 5.13 (s, 2H, OCH_2Ph), 3.93 and 3.88 (2m, 3H, 2x CHaN , H-4), 3.15 (ddd, 2H, $J = 13.6$, $J' = 9.5$, $J'' = 3.5$ Hz, 2 x CHbN), 2.00 (m, 1H,

OH), 1.85 (m, 2H) and 1.49 (m, 2H): H₂-3 and H₂-5. ¹³C NMR (75 MHz, CDCl₃): 155.37, 136.85, 128.56, 128.07, 127.90, 67.38, 67.21, 41.44, 34.10 ppm.^{17a,b}

***N*-Benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypiperidine (20)**

Imidazole (409 mg, 6.0 mmol) and TBSCl (446 mg, 2.96 mmol) were successively added to a solution of **19** (489 mg, 2.08 mmol) in DMF (1.18 mL) and the mixture was stirred at rt for 24 h. After addition of aqueous Na₂CO₃ (10% w:v) and Et₂O, the product was extracted with Et₂O. The organic layers were washed twice with H₂O and gave rise to **20** after usual workup (728 mg, 100%). IR: 2949, 2928, 2855, 1698, 1428, 1358, 1272, 1253, 1222, 1098, 1043 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): 7.37 (m, 5H, H-Ar), 5.14 (s, 2H, OCH₂Ph), 3.92 (m, 1H, H-4), 3.69 (m, 2H, 2 x CHaN) and 3.40 (m, 2H, 2 x CHbN): H₂-2 and H₂-6), 1.72 (m, 2H) and 1.53 (m, 2H): H₂-3 and H₂-5, 0.91 (s, 9H, *t*-Bu), 0.07 (s, 6H, 2 SiMe) ppm. ¹³C NMR (75 MHz, CDCl₃): 155.45, 137.10, 128.57, 128.01, 127.91, 67.08, 66.93, 40.77, 34.27, 25.90, 18.18, -4.62 ppm.^{17c}

***N*-Benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypiperidin-2-one (21)**

EtOAc (13 mL) and H₂O (9 mL) were added to piperidine **20** (380 mg, 1.09 mmol). To the mixture stirred at rt were successively added Na₂CO₃ (340 mg, 3.2 mmol), NaIO₄ (1.10 g, 5.14 mmol) and RuCl₃·H₂O (40 mg, 0.177 mmol). After stirring for 4 h, NaIO₄ (550 mg, 2.57 mmol) was added and the mixture was stirred for 20 h before extraction with EtOAc. The crude product was purified by chromatography on silica gel (eluent : heptane-EtOAc 1 : 1) affording **21** (308 mg, 78%) as a colorless gum. IR: 2953, 2928, 2855, 1774 (sh), 1713, 1471, 1462, 1378, 1276, 1219, 1106, 1076 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 386 (MNa)⁺. ¹H NMR (300 MHz, CDCl₃): 7.43 and 7.36 (2m, 5H, H-Ar), 5.30 (centre of 2d, *J* = 12.6 Hz, OCH₂Ph), 4.21 (m, 1H, H-4), 3.89 (m, 1H, Ha-6), 3.72 (m, 1H, Hb-6), 2.70 (dd, 1H, *J* = 17.2, *J'* = 4.5 Hz, Ha-3), 2.55 (dd, 1H, *J* = 17, *J'* = 5.3 Hz, Hb-3), 1.94 and 1.85 (2m, 2H, H₂-5), 0.89 (s, 9H, *t*-Bu), 0.07 (s, 6H, 2 SiMe) ppm. ¹³C NMR (75 MHz, CDCl₃): 169.74, 154.20, 135.54, 128.67, 128.38, 128.16, 68.61, 64.95, 44.39, 42.29, 31.35, 25.82, 18.12, -4.75 ppm.¹⁹ HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₁₉H₂₉NO₄NaSi (MNa)⁺: 386.1764, found 386.1765.

1-Boc valerolactam (22)

To a solution of valerolactam (420.0 mg, 4.24 mmol) in MeCN (15 mL) were successively added DMAP (270.0 mg, 2.21 mmol) and Boc₂O (1.157 g, 5.3 mmol) and the mixture was stirred at rt for 1h. After evaporation of the solvent at rt under reduced pressure, the residue was purified by chromatography on silica gel (eluent : heptane-Et₂O 4 : 1) to give **22** as colorless crystals (810 mg, 96%).

***tert*-Butyl 5-oxo-6-(phenylsulfonyl)hexylcarbamate (23)**

*n*BuLi (1.88 mL, 1.6 M, 3.0 mmol) was added under argon to a stirred solution of PhSO₂Me (484.2 mg, 3.1 mmol) in dry THF (8 mL) at –78 °C. The mixture was stirred at the same temperature for 45 min before the addition of a solution of **22** (299 mg, 1.5 mmol) in THF (4.6 mL). The mixture was then stirred at –78 °C for 1.5 h. A saturated aqueous solution of NH₄Cl was added and the cooling bath was removed. After extraction with CH₂Cl₂ and usual workup, the product was purified by chromatography on silica gel (eluent : heptane-EtOAc 1 : 1) to give **23** (485 mg, 91%) as colorless crystals. Mp 82-3 °C. IR: 3338, 2976, 2928, 1716, 1686, 1525, 1446, 1361, 1322, 1290 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 378 (MNa⁺, 100%). ¹H NMR (300 MHz, CDCl₃): 7.89 (d, 2H), H-Ar, 7.70 (dd, 1H, H-Ar), 7.59 (dd, 2H, H-Ar), 4.58 (NH), 4.15 (s, 2H, SO₂CH₂), 3.10 (m, 2H, NCH₂) and 2.74 (dd, *J* ~ *J'* ~ 7.0 Hz, COCH₂), 1.58 (m, 2H) and 1.46 (masked m): H₂-3 and H₂-2, 1.46 (s, 9H, *t*-Bu) ppm. ¹³C NMR (75 MHz, CDCl₃): 197.93, 156.07, 138.85, 134.41, 129.47, 128.35, 79.27, 66.95, 43.99, 40.11, 29.26, 28.52, 20.28, ppm.²² HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₁₇H₂₅NO₅SNa: 378.1351, found: 378.1358.

***tert*-Butyl 5-oxo-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexylcarbamate (24)**

The same protocol was applied to **22** (2.5 mmol) and **7**, leading to β-ketosulfone **24** as colorless crystals (71% yield). Mp 78 °C. IR: 3368, 2948, 2911, 2876, 1731, 1682, 1595, 1517, 1501, 1456, 1366, 1344, 1292, 1270, 1249, 1161 cm⁻¹. MS (ESI, MeOH) *m/z*: 446 (MNa⁺). ¹H NMR (300 MHz, CDCl₃): 7.68-7.14 (H-Ar), 4.73 (s, 2H, SO₂CH₂), 4.57 (NH), 3.10 (CH₂), 2.68 (CH₂), 1.62 (CH₂), 1.48 (CH₂), 1.44 (s, 9H, *t*-Bu) ppm. ¹³C NMR (75MHz, CDCl₃): 196.54, 156.16, 131.7-125.6, 79.66, 64.83, 43.71, 39.90, 29.18, 28.51, 20.09 ppm. HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₁₈H₂₅N₅O₅SNa: 446.1474, found: 446.1495.

1-Benzylloxycarbonylvalerolactam (25)

A solution of valerolactam (427.7 mg, 4.31 mmol) in THF (5 mL) was added under argon to a mixture of NaH (80%, 155.4 mg, 5.18 mmol) and KI (899 mg, 5.42 mmol) in THF (4 mL), stirred at 0 °C. The mixture was stirred at rt for 1 h, cooled again at 0 °C before the addition of benzyl chloroformate (0.614 mL, 4.3 mmol). After being stirred for additional 20 min, a saturated aqueous solution of NH₄Cl was added. The product was extracted with EtOAc, and purified by chromatography on silica gel (eluent : heptane-Et₂O 1 : 1) affording **25** (895 mg, 89% yield). ¹H NMR data in full agreement with those of literature.²⁶

Benzyl 5-oxo-6-(phenylsulfonyl)hexylcarbamate (26)

*n*BuLi (1.6 M, 5.73 mL, 9.17 mmol) was added under argon to a stirred solution of PhSO₂Me (1.433 g,

9.17 mmol) in dry THF (22 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at the same temperature for 50 min before the addition of a solution of **25** (997.4 mg, 4.28 mmol) in THF (13 mL). The mixture was then stirred at $-78\text{ }^{\circ}\text{C}$ for 1.5 h. A saturated aqueous solution of NH_4Cl was added and the cooling bath was removed. After extraction with CH_2Cl_2 and usual workup, the product was purified by chromatography (eluent : heptane-EtOAc 55:45) to give **26** (1.247 g, 75%) as colorless crystals. Mp $83\text{ }^{\circ}\text{C}$. IR: 3451, 3021, 2944, 2871, 1720, 1516, 1448, 1325, 1216, 1222, 1156 cm^{-1} . MS (ESI, MeOH) m/z : 412 (MNa^+ , 100%). ^1H NMR (300 MHz, CDCl_3): 7.88 (dd, 2H, H-Ar), 7.68 (dd, 1H, H-Ar), 7.58 (dd, 2H, H-Ar), 7.34 (m, 5H, H-Ar), 5.09 (2H, OCH_2Ph), 4.89 (1H, NH), 4.13 (s, 2H, SO_2CH_2), 3.17 (m, 2H, NCH_2), 2.72 (m, 2H, COCH_2), 1.58 (2H), 1.48 (2H): H_2 -3, H_2 -2, ppm. ^{13}C NMR (75 MHz, CDCl_3): 197.91, 156.51, 138.79, 136.68, 134.40, 129.46, 128.59, 128.32, 128.17, 66.89, 66.69, 43.90, 40.59, 29.10, 20.15 ppm. HRMS (ESI, CH_2Cl_2 -MeOH) m/z : calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{NaS}$ (MNa^+): 412.1195, found: 412.1193.

***tert*-Butyl (*S*)-2-(bis(*tert*-butoxycarbonyl)amino)-5-oxo-6-(phenylsulfonyl)hexylcarbamate (**27**)**

*n*BuLi (1.6 M, 0.39 mL, 0.62 mmol) was added under argon to a stirred solution of PhSO_2Me (110 mg, 0.70 mmol) in dry THF (2.52 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at the same temperature for 50 min before the addition of a solution of **15** (166.0 mg, 0.40 mmol) in THF (0.73 mL). The mixture was then stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. A saturated aqueous solution of NH_4Cl was added at the same temperature. After extraction with CH_2Cl_2 and usual workup, the product was purified by chromatography (eluent : CH_2Cl_2 -EtOAc 9 : 1) to give **27** (169 mg, 74%) as colorless gum. IR: 3389, 2978, 2933, 1697, 1510, 1448, 1392, 1366, 1246, 1232 cm^{-1} . MS (ESI, MeOH) m/z : 593 (MNa^+ , 100%). ^1H NMR (300 MHz, CDCl_3): 7.88 (d, 2H, $J = 7.5\text{ Hz}$, H-Ar), 7.68 (dd, 1H, $J = J' = 7.5\text{ Hz}$, H-Ar), 7.57 (dd, 2H, $J = J' = 7.5\text{ Hz}$, H-Ar), 4.83 (m, 1H, NH), 4.16 (m, 3H, NCH, SO_2CH_2), 3.5-3.2 (2m, 2H, NCH_2), 2.75 (m, 2H, COCH_2), 1.95, 1.81 (2m, 2H, CH_2), 1.50, 1.42 (3 *t*-Bu) ppm. ^{13}C NMR (75 MHz, CDCl_3): 197.32, 155.83, 153.46, 138.82, 134.37, 129.44, 128.41, 82.90, 79.34, 67.09, 56.28, 43.27, 41.09, 28.47, 28.07, 23.72 ppm. HRMS (ESI, CH_2Cl_2 -MeOH) m/z : calcd for $\text{C}_{27}\text{H}_{42}\text{N}_2\text{O}_9\text{SNa}$ (MNa^+): 593.2509, found 593.2506.

Benzyl (*S*)-2-(bis(*tert*-butoxycarbonyl)amino)-5-oxo-6-(phenylsulfonyl)hexylcarbamate (28**)**

The same protocol was applied to **16** (404 mg, 0.90 mmol) and **6** (299 mg, 1.91 mmol) leading after purification by chromatography (eluent : heptane-Et₂O 2:8) to β -ketosulfone **28** (365 mg, 67%), as a colorless gum. $[\alpha]_{\text{D}}^{22} + 9.8$ (*c* 0.79, CHCl_3). IR: 3382, 2978, 2930, 1714, 1697, 1519, 1448, 1393, 1367, 1345, 1322 cm^{-1} . MS (ESI, MeOH) m/z : 627 (MNa^+ , 100%), 527. ^1H NMR (300 MHz, CDCl_3): 7.90 (d, 2H, $J = 7.5\text{ Hz}$, Ar-H), 7.69 (dd, 1H, $J = J' = 7.5\text{ Hz}$, H-Ar), 7.57 (dd, 2H, $J = J' = 7.5\text{ Hz}$, H-Ar), 7.33 (5H, CH_2Ph), 5.13 (1H, NH), 5.08 (2d, 2H, CH_2Ph), 4.19 (1H, NCH), 4.13 (2H, SO_2CH_2), 3.50, 3.41 (2m, 2H, NCH_2), 2.77 (m, 2H, COCH_2), 1.98, 1.85 (2m, 2H, CH_2), 1.47 (s, 18H, 2 *t*-Bu) ppm. ^{13}C NMR (75

MHz, CDCl₃): 197.24, 156.36, 153.45, 138.83, 136.62, 134.35, 129.44, 128.58, 128.39, 128.16, 83.03, 67.10, 66.77, 56.04, 43.81, 40.99, 28.03, 23.67 ppm. HRMS (ESI, MeOH) *m/z*: calcd for C₃₀H₄₀N₂O₉NaS (MNa)⁺: 627.2352, found: 627.2373.

Benzyl 3-(*tert*-butyldimethylsilyloxy)-5-oxo-6-(phenylsulfonyl)hexylcarbamate (29)

*n*BuLi (1.6 M, 0.83 mL, 1.33 mmol) was added under argon to a stirred solution of PhSO₂Me (207.0 mg, 1.33 mmol) in dry THF (3.0 mL) at –78 °C. The mixture was stirred at the same temperature for 55 min before the addition of a solution of **21** (211.0 mg, 0.58 mmol) in THF (2.0 mL). The mixture was then stirred at –78 °C for 40 min. A saturated aqueous solution of NH₄Cl was added and then, the cooling bath was removed. After extraction with CH₂Cl₂ and usual workup, the product was purified by chromatography (eluent : CH₂Cl₂-EtOAc 30 : 1) to afford **29** as a colorless gum (235.0 mg, 78%). IR: 3382, 2927, 2855, 1713, 1518, 1471, 1447, 1322, 1250, 1152, 1083, 1042 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 542 (MNa)⁺. ¹H NMR (300 MHz, CDCl₃): 7.89 (d, *J* = 7.9 Hz, 2H, H-Ar), 7.69 (dd, 1H, *J* = *J*' = 7.9 Hz, H-Ar), 7.58 (dd, 2H, *J* = *J*' = 7.9 Hz, H-Ar), 7.35 (m, 5H, CH₂Ph), 5.10 (apparent s, 2H, OCH₂Ph), 5.05 (broad, NH), 4.24 (m, 1H, H-3), 4.18 (s, 2H, SO₂CH₂), 3.25 (m, 2H, NCH₂), 2.90 (2H, COCH₂CH), 1.68 (m, 2H, H₂-2), 0.86 (s, 9H, *t*-Bu), 0.06 (s, 3H, SiMe), 0.02 (s, 3H, SiMe) ppm. ¹³C NMR (75 MHz, CDCl₃): 196.87, 156.37, 138.87, 136.75, 134.45, 129.50, 128.60, 128.35, 128.14, 67.91, 67.03, 66.70, 51.14, 37.60, 36.70, 25.88, 18.00, –4.65 ppm. HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₂₆H₃₇NO₆NaSSi (MNa)⁺ : 542.2033, found 542.2009.

2-(Phenylsulfonylmethyl)piperidine (30)

To a solution of β-ketosulfone **26** (1.13 g, 2.9 mmol) in MeOH (28 mL) was added 10% Pd/C (300 mg), and the mixture was stirred at rt under H₂ (1 atm.) for 30 h. The catalyst was filtered off on Celite[®] and washed with MeOH. Evaporation of the solution under reduced pressure afforded **30** (557 mg, 80%) as a pale yellow oil. IR: 3336, 2929, 2853, 1698, 1446, 1332, 1300 cm⁻¹. MS (IE) *m/z*: 239 (M⁺), 238, 97, 84 (100%), 77. ¹H NMR (300 MHz, CDCl₃): 7.91 (d, 2H, *J* = 7.5 Hz, H-Ar), 7.66 (dd, 1H, *J* = *J*' = 7.5 Hz, H-Ar), 7.57 (dd, 2H, *J* = *J*' = 7.5 Hz, H-Ar), 3.20-3.12 (m, 2H, H-2, SO₂CHa), 3.02 (2H, SO₂CHb, Ha-6), 2.72 (exch, NH), 2.67 (ddd, 1H, Hb-6), 1.75 (m, 1H), 1.63-1.27 (5H): H₂-3, H₂-4, H₂-5, ppm. ¹³C NMR (75 MHz, CDCl₃): 139.80, 133.90, 129.47, 127.85, 62.44, 51.44, 46.49, 32.82, 25.50, 24.61 ppm. *N*-Boc derivative was prepared to compare spectroscopic data with literature.²⁷

5S-(bis(*tert*-Butoxycarbonyl)amino)-2-(phenylsulfonylmethyl)piperidines (31) and (32)

To a solution of **28** (81.3 mg, 0.135 mmol) in MeOH (0.55 mL) was added 10% Pd/C (20 mg), and the mixture was stirred at rt under H₂ (1 atm) for 56 h. The catalyst was filtered off on Celite[®] and washed

with MeOH. The solution was evaporated under reduced pressure. Purification by preparative TLC (eluent Et₂O) afforded, together with starting material (16.1 mg, 20%), compounds **31** (14.2 mg, 23%) and **32** (29.0 mg, 47%). **31**: Mp 71 °C. $[\alpha]_D^{25} + 8$ (*c* 0.45, CHCl₃). IR: 2976, 2931, 1736, 1697, 1447, 1392, 1366, 1347, 1303, 1235, 1140, 1120 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 477 (MNa⁺, 100%), 455, 377, 299. ¹H NMR (500 MHz, C₆D₆ δ = 7.16 ppm): 7.73 (split d, 2H, *J* = 7.9 Hz, H-Ar), 6.93 (dd, 1H, *J* = 7.9 Hz, H-Ar), 6.86 (dd, 2H, *J* = *J*' = 7.9 Hz, H-Ar), 4.31 (m, 1H, H-5), 3.23 (dd, 1H, *J* = *J*' = 10.9 Hz, Ha-6), 3.03 (m, 1H, H-2), 2.97 (m, 1H, *J* = 10.9 Hz, Hb-6), 2.80 (dd, 1H, *J* = 14.0, *J*' = 9.0, Ha-7), 2.54 (dd, 1H, *J* = 14.0, *J*' = 3.0, Hb-7), 2.08 (dddd, 1H, *J* = 12.6, *J*' ~ *J*'' ~ 12, *J*''' = 4 Hz, Ha-4), 1.70 (broad d, 1H, *J* = 12.6 Hz, Hb-4), 1.37 (s, 18H, 2 *t*-Bu), 1.18 (m, 1H, *J* ~ 12.5 Hz, Ha-3), 0.94 (m, 1H, Hb-3) ppm. ¹³C NMR (125 MHz, CDCl₃): 153.20, 139.79, 133.99, 129.55, 128.00, 82.45, 62.01, 54.30, 50.91, 48.95, 33.04, 28.14 ppm. HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₂₂H₃₄N₂O₆NaS (MNa)⁺: 477.2035, found 477.2021.

32: $[\alpha]_D^{24} + 24$ (*c* 0.82, CHCl₃). IR: 2977, 2931, 1736, 1694, 1446, 1392, 1366, 1340, 1304, 1238, 1140 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 477 (MNa⁺, 100%), 455, 377, 299, 255. ¹H NMR (500 MHz, CDCl₃): 7.94 (d, 2H, *J* = 7.6 Hz, H-Ar), 7.67 (dd, 1H, *J* = *J*' = 7.6 Hz, H-Ar), 7.58 (dd, 2H, *J* = *J*' = 7.6 Hz, H-Ar), 4.02 (m, 1H, H-5), 3.62 (dd, 1H, *J* = 14.0, *J*' = 7.9 Hz, Ha-7), 3.55 (m, 1H, H-2), 3.20 (dd, 1H, *J* = *J*' = 11.4 Hz, Ha-6), 3.10 (dd, 1H, *J* = 14.0, *J*' = 4.1 Hz, Hb-7), 2.76 (dd, 1H, *J* = 11.4, *J*' = 3.8 Hz, Hb-6), 2.08 (m, 1H, Ha-4), 1.87-1.64 (m, 3H, Ha-3, Hb-3, Hb-4), 1.49 (s, 18H, 2 *t*-Bu) ppm. ¹³C NMR (125 MHz, CDCl₃): 153.32, 140.00, 133.83, 129.46, 128.05, 82.43, 56.91, 54.16, 47.12, 43.05, 30.40, 28.16, 24.05 ppm. HRMS (ESI, CH₂Cl₂-MeOH) *m/z*: calcd for C₂₂H₃₄N₂O₆NaS (MNa)⁺: 477.2035, found 477.2046.

(2*S**,4*R**)-4-(*tert*-Butyldimethylsilyloxy)-2-(phenylsulfonylmethyl)piperidine (**33**)

To a solution of **29** (66.0 mg, 0.127 mmol) in MeOH (0.5 mL) was added 10% Pd/C (16 mg), and the mixture was stirred at rt under H₂ for 56 h. The catalyst was filtered off on Celite[®] and washed with MeOH. The solution was evaporated under reduced pressure. Purification by preparative TLC (eluent Et₂O) afforded **33** as a colorless gum (24.8 mg, 53%), together with starting material (6.3 mg, ca 10%). IR: 3337, 2949, 2927, 2886, 2854, 1462, 1446, 1377, 1359, 1304, 1251, 1147, 1085 cm⁻¹. MS (ESI, CH₂Cl₂-MeOH) *m/z*: 370 (MH)⁺. ¹H NMR (500 MHz, C₆D₆): 7.75 (d, 2H, *J* = 7.5, H-Ar), 6.92 (2m, 3H, H-Ar), 3.42 (m, 1H, H-4), 3.23 (m, 1H, *J* ~ *J*' ~ 10 Hz, H-2), 2.98 (broad dd, 1H, *J* = 14.0, *J*' = 10 Hz, Ha-7), 2.71 (m, 1H, *J* ~ 12 Hz, Ha-6), 2.61 (dd, 1H, *J* = 14.0, *J*' = 2.4 Hz, Hb-7), 2.26 (ddd, 1H, *J* ~ *J*' ~ 12, *J*'' = 2.4 Hz, Hb-6), 1.57 and 1.55 (2m, 2H, Ha-5 and Ha-3), 1.43 (m, 1H, Hb-5), 1.19 (ddd, 1H, *J* ~ *J*' ~ *J*'' ~ 11 Hz, Hb-3), 0.96 (s, 9H, Sit-Bu), 0.01 (s, 6H, 2 SiMe) ppm. ¹³C (75 MHz, C₆D₆ δ = 128.39 ppm): 141.48, 133.56, 129.52, 70.26, 62.45, 50.37, 44.21, 43.04, 36.37, 26.39, 18.57, -4.00, -4.10 ppm.

HRMS: calcd for C₁₈H₃₂NO₃SSi (MH)⁺: 370.1872, found: 370.1895.

ACKNOWLEDGEMENTS

We thank the Institut de Chimie des Substances Naturelles (CNRS, Gif-sur-Yvette) for financial support to J. Massé.

REFERENCES

1. for reviews see: a) P. D. Bayley, P. A. Millwood, and P. D. Smith, *Chem. Comm.*, 1998, 633. b) S. Laschat and T. Dickner, *Synthesis*, 2000, 1781. c) F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693. d) P. M. Weintraub, J. S. Sabol, J. M. Kane, and D. R. Borcharding, *Tetrahedron*, 2003, **59**, 2953. e) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701.
2. I. Ninomiya, T. Kiguchi, and T. Naito, *The Alkaloids*, vol 50, ed. by G. A. Cordell, Academic Press, Inc., London 1998, pp. 317-342.
3. N. Langlois, *Org. Lett.*, 2002, **4**, 185.
4. Y. Doi, M. Ishibashi, and J. Kobayashi, *Tetrahedron*, 1996, **52**, 4573.
5. a) J. B. Baudin, G. Hareau, S. A. Julia, and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, 336. b) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, 856.
6. P. R. Blakemore, W. J. Cole, P. J. Kocienski, and A. Morley, *Synlett*, 1998, 26.
7. a) S. Grabley, P. Hammann, H. Kluge, J. Wink, P. Kricke, and A. Zeek, *J. Antibiot.*, 1991, **44**, 797. b) C. Maul, I. Sattler, M. Zerlin, C. Hinze, C. Koch, A. Maier, S. Grabley, and R. Thiericke, *J. Antibiot.*, 1999, **52**, 1124.
8. M. Mayer and R. Thiericke, *J. Org. Chem.*, 1993, **58**, 3486.
9. a) Y. Takemoto, S. Ueda, J. Takeuchi, Y. Baba, and C. Iwata, *Chem. Pharm. Bull.*, 1997, **45**, 1906. b) I. Ripoche, J.-L. Canet, B. Aboab, J. Gelas, and Y. Troin, *J. Chem. Soc., Perkin Trans 1*, 1998, 3485. c) H. Yokoyama, K. Otaya, S. Yamaguchi, and Y. Hirai, *Tetrahedron Lett.*, 1998, **39**, 5971. d) F. A. Davis, B. Chao, T. Fang, and J. M. Szewczyk, *Org. Lett.*, 2000, **2**, 1041. e) M. Sabat and C. R. Johnson, *Tetrahedron Lett.*, 2001, **42**, 1209. f) P. Celestini, B. Danieli, G. Lesma, A. Sacchetti, A. Silvani, D. Passarella, and A. Viridis, *Org. Lett.*, 2002, **4**, 1367.
10. N. Langlois, N. Van Bac, N. Dahuron, J.-M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni, and C. Riche, *Tetrahedron*, 1995, **51**, 3571.
11. a) N. Langlois, IXth Conference French-American Chemical Society, June 2-6th 2002, Saint-Malo, France. b) N. Langlois, *Tetrahedron Lett.*, 2002, **43**, 9531.
12. S. K. Panday and N. Langlois, *Tetrahedron Lett.*, 1995, **36**, 8205.
13. N. Langlois and O. Calvez, *Tetrahedron Lett.*, 2000, **41**, 8285.
14. a) K.-i. Tanaka, H. Nemoto, and H. Sawanishi, *Tetrahedron: Asymmetry*, 2005, **16**, 809. b) K.-i.

- Tanaka, T. Maesoba, and H. Sawanishi, *Heterocycles*, 2006, **68**, 183.
15. a) H. Li, T. Sakamoto, M. Kato, and Y. Kikugawa, *Synth. Commun.*, 1995, **24**, 4045. b) X.-L. Qiu and F.-L. Qing, *Synthesis*, 2004, 334.
16. V. Semetey, D. Moustakas, and G. M. Whitesides, *Angew. Chem. Int. Ed.* 2006, **45**, 588.
17. a) K. Hattori, H. Sajiki, and K. Hirota, *Tetrahedron*, 2000, **56**, 8433. b) D. Chang, H.-J. Feiten, K.-H. Engesser, J. B. van Beilen, B. Witholt, and Z. Li, *Org. Lett.*, 2002, **4**, 1859. c) C.-E. Yeom, Y. J. Kim, S. Y. Lee, Y. J. Shin, and B. M. Kim, *Tetrahedron*, 2005, **61**, 12227.
18. R. K. Boeckman, Jr and J. C. Potenza, *Tetrahedron Lett.*, 1985, **26**, 1411.
19. D. I. MaGee, M. Ramaseshan, and J. D. Leach, *Canad. J. Chem.*, 1995, **73**, 2111.
20. a) J. C. Sheehan and R. W. Tulis, *J. Org. Chem.*, 1974, **39**, 2264. b) G. Bettoni, C. Franchini, F. Morlacchi, N. Tangari, and V. Tortorella, *J. Org. Chem.*, 1976, **41**, 2780. c) N. K. Sharma and K. N. Ganesh, *Tetrahedron Lett.*, 2004, **45**, 1403.
21. A. J. Mota, A. Chiaroni, and N. Langlois, *Eur. J. Org. Chem.*, 2003, 4187.
22. L. A. Arias, D. Arbelo, A. Alzérreca, and J. A. Prieto, *J. Heterocycl. Chem.*, 2001, **38**, 29.
23. a) J. F. Cormier, *Tetrahedron Lett.*, 1991, **32**, 187. b) S. Kim, S. M. Jacobo, C.-T. Chang, S. Bellone, W. S. Powell, and J. Rokach *Tetrahedron Lett.*, 2004, **45**, 1973. c) T. Ikawa, K. Hattori, H. Sajiki, and K. Hirota, *Tetrahedron* 2004, **60**, 6901.
24. a) D. Chang, H.-J. Feiten, B. Witholt, and Z. Li, *Tetrahedron: Asymmetry*, 2002, **13**, 2141 and ref. cited therein. b) M. K. S. Vink, C. A. Schortinghuis, J. Luten, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, and F. P. J. T. Rutjes, *J. Org. Chem.*, 2002, **67**, 7869.
25. J. Ackermann, M. Matthes, and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 122.
26. A. Giovannini, D. Savoia, and A. Umani-Ronchi, *J. Org. Chem.*, 1989, **54**, 228.
27. D. J. Hart, J. Li, W.-L. Wu, and A. P. Kozikowski, *J. Org. Chem.*, 1997, **62**, 5023.