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A Novel Method for Chirospecific Synthesis of 2,5-Disubstituted Pyrrolidines#

N. André Sasaki* and Isabelle Sagnard

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex France

Abstract : One-pot ring formation using (R)-1 or (S)-1 as a nucleophile and homochiral glycidyl triflate (R)-2 or (S)-2 as an electrophile provides a pivotal intermediate 4 which can be transformed into a 2,5-disubstituted pyrrolidine with any desired stereochemistry at the C-2 and C-5 positions

In recent years, asymmetric synthesis of 2,5-disubstituted pyrrolidines, represented by forms A, B, C, and D in Figure 1, has become an important subject of investigation. Various *trans*-2,5-dialkyl pyrrolidines of the form A or B in which alkyl groups R and R' differ from each other, have been isolated from several species of fire ants belonging to the *Solenopsis* and *Monomolium* families and poison frog *Dendrobates histrionicus*[1].

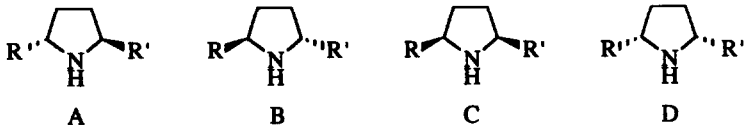


Figure 1

Due to the scarce quantities isolated, the structures of these natural products have only been determined by gas chromatography-mass spectrometry and their absolute configuration has, in most cases, not yet been established. Despite a broad range of physiological properties exibited by *trans*-2,5-dialkylpyrrolidines[2], there exist only a handful of methods for the enantioselective synthesis of this family of pyrrolidine derivatives[3]. One example is the enantioselective synthesis of pyrrolidines of the form A and B from specific non-proteinogenic α-amino acids[4]. However efficient these methods are, it is yet of great interest to develop a general methodology for the synthesis of *trans*-2,5-dialkylpyrrolidines of the form A and B with high diastereomeric and enantiomeric purity.

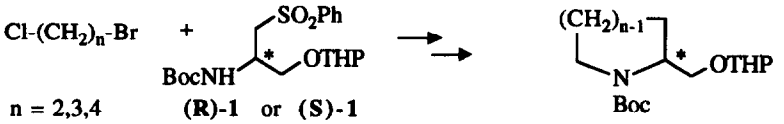
Trans-2,5-dialkyl and dialkoxymethylpyrrolidines of the form A and B in which alkyl or alkoxymethyl groups R and R' are identical to each other, on the other hand, have proved to be of considerable importance as chiral auxilliaries in numerous asymmetric syntheses owing to the presence of a C_2-axis of symmetry[5]. However, a major drawback to utilizing these amines lies in the difficulty of preparation of these compounds in diastereomerically pure form. To this end, optical resolution of racemates has been applied as an approach to obtain pyrrolidines in diastereomerically pure form[6]. Several enantioselective syntheses of these *trans*-2,5-

Dedicated to Professor L. Ghosez on the occasion of his sixtieth birthday.

disubstituted pyrrolidines have been reported starting from D- or L-alanine[7], (S)-O-benzylglycidol[8], D-mannitol[9], (2S,5S)-hexanediol[10], or using chiral auxilliaries[11,12].

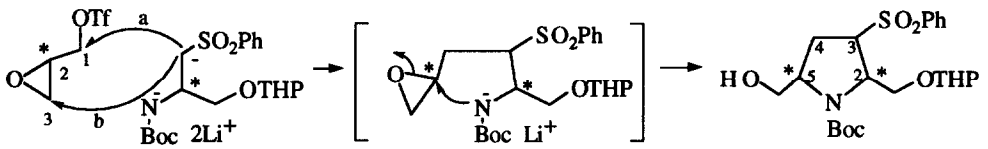
Cis-2,5-disubstituted pyrrolidines of the form C and D have been prepared from L- and D-pyroglutamic acid as key intermediates in the total synthesis of many natural products[13]. In view of the growing interest in the synthesis of conformationally constrained α-amino acids, preparation of C-5 substituted proline with well defined stereochemistry may serve for the construction of a *cis* peptide bond isomer at the proline junction when incorporated into peptides[14]. Although the synthesis of the *cis*-2,5-disubstitued pyrrolidines may seem simpler when compared to the *trans* isomers, development of a general methodology for enantioselective and diastereoselective synthesis of these compounds remains as a formidable challenge.

We describe here a novel method for chirospecific synthesis of any one of the four possible stereoisomers of 2,5-disubstituted pyrrolidines, represented by forms A, B, C, and D in Figure 1. Recently, we have reported a facile synthsesis of (R)- and (S)-C-2-monosubstituted pyrrolidine, piperidine, hexahydroazepine, and azacyclooctane derivatives[15]. This has been accomplished in two or three steps using α,ω-bromochloroalkanes and (2R)- or (2S)-2-t-butoxycarbonylamino-3-phenylsulfonyl-1-(2-tetrahydropyranyloxy)propane, **(R)-1** or **(S)-1**, respectively, which are readily available from L-serine[16] (Schemc 1).



Scheme 1

The above observation has prompted us to investigate the feasibility of expanding the scope of this novel strategy to the asymmetric synthesis of multisubstituted pyrrolidine ring systems and choosing adequate chiral oxiranes as electrophiles. As illustrated in Scheme 2, we anticipated that the sulfonyl carbanion of **1** would react in a regioselective manner at C-1 of glycidyl triflate **2** (*via* path a) to form the epoxide adduct **3**. The intermediate **3** would then undergo cyclization to afford the 2,3,5-trisubstituted pyrrolidine **4** provided that the carbamate anion of **3** would open the epoxide exclusively *via* 5-exo pathway[17,18]. By contrast, there may be a possibility that the sulfonyl carbanion proceeds with the initial epoxide opening (C-3 attack *via* path b) followed by extrusion of the leaving group to afford the C-5-diastereoisomer of **4** through the same intermediate **3** but with opposite stereochemistry at C-5. Be that as it may, we speculated to separate such diastereoisomers at the later stage of the synthesis. This seemed to be an attractive approach to ensure the desired stereochemistry of 2,5-disubstituted pyrrolidine derivatives at the C-2 and C-5 positions since both enantiomers of **1** and **2** are now readily available and in this report we will discuss the results of our findings.

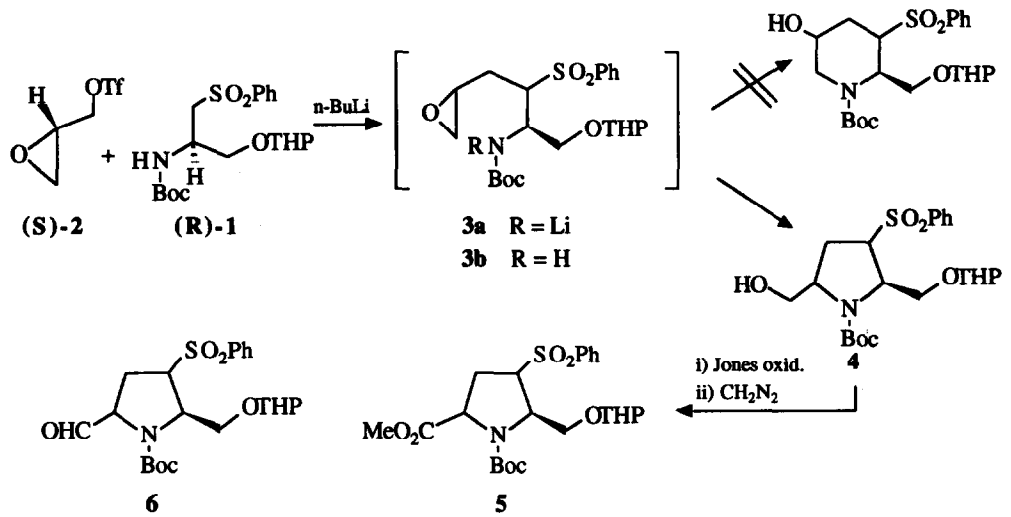


2 Dilithiate of **1** **3** **4**

Scheme 2

RESULTS AND DISCUSSION

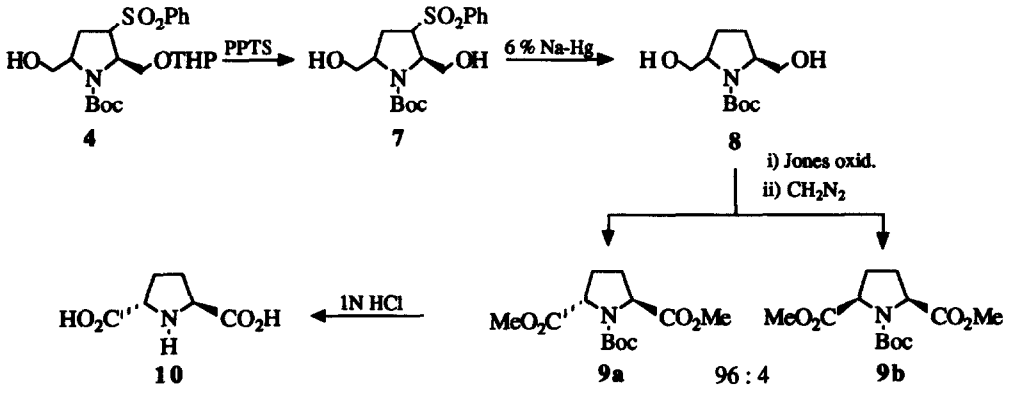
Our initial endeavors commenced with the use of chiral epoxide **(S)-2**[19,20]. Treatment of **(R)-1** with 2 equiv of n-BuLi at -78°C followed by addition of glycidyl triflate **(S)-2** gave the epoxide **3a** within 10 min. This was easily confirmed by developing an aliquot of the reaction mixture at -60°C on TLC. If the reaction was quenched at -60°C after 30 min, we obtained epoxide **3b** in 85 % yield. The epoxide **3b**, which eluted slightly slower than **(R)-1** (EtOAc/ heptane, 1/ 1), completely disappeared when the reaction mixture was allowed to warm gradually to -10°C and stirred at this temperature for 1 h. A new product **4** was observed after quenching the reaction mixture at 0°C and evaporation of the solvent. The residue was purified by flash chromatography to afford **4** in 90% yield together with unreacted **(R)-1** (5%).



Scheme 3

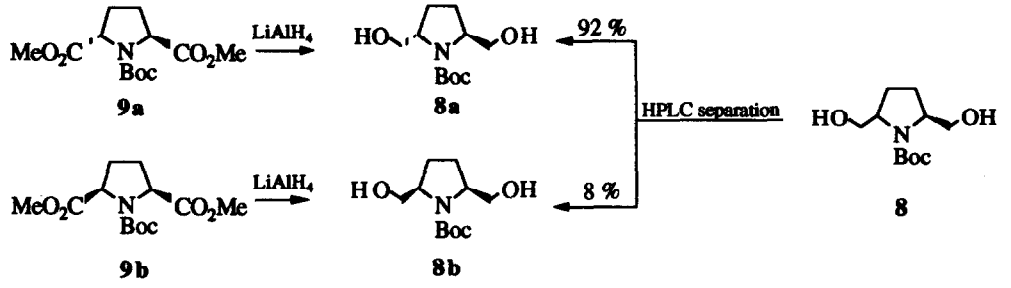
Jones oxidation of the crude **4** and *in situ* treatment with CH_2N_2 gave methyl ester **5** with a very minute quantity of aldehyde **6** from the oxidation reaction, which was later prepared from **4** by Swern oxidation (*vide infra*), and shown not to be a piperidine ketone. This observation clearly demontrates that the carbamate anion **3a** indeed undergoes regiospecific epoxide ring opening in a 5-exo fashion to generate a pyrrolidine ring system. The remaining problem to be solved is the assignment of the correct stereochemistry at C-5 of the resulting pyrrolidine derivative in the above one-pot reaction.

Thus, the alcohol **4** was treated with pyridinium p-toluenesulfonate in EtOH at 50°C to give the diol **7** which was subjected to desulfonylation by 6% Na-Hg. This two step reaction provided diol **8** in 86% overall yield. Jones oxidation of **8** followed by *in situ* treatment with CH_2N_2 afforded the diester as a 96 : 4 mixture of *trans* **9a** and *cis* **9b** diastereomers in 60% yield. The two isomers **9a** and **9b** were easily separated by flash chromatography on silica gel (EtOAc/ heptane, 1/ 4).



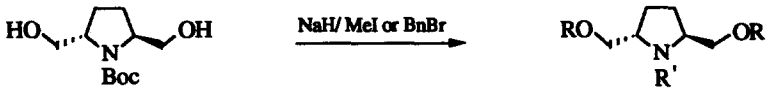
Scheme 4

Acid hydrolysis of **9a** with 1N HCl and purification through ion exchange resin eluting with 1M aqueous pyridine gave (2S,5S) pyrrolidine 2,5-dicarboxylic acid **10**. This dicarboxylic acid is the constituent of the red alga *Schizymenia dubyi*[21]. Overall yield of diacid **10** from **(R)-1** according to our six step reaction sequences was 45% [8,11b,22]. Diesters **9a** and **9b** were separately reduced to **8a** and **8b**, respectively, with $LiAlH_4$ in THF in 85% yield. With *trans* - and *cis* -2,5-dihydroxymethyl pyrrolidine derivatives **8a** and **8b** in hand, a careful analysis of **8** by HPLC was performed to determine the ratio of diastereoisomers of diol **8** obtained from **1-(R)** and **2-(S)**. Indeed, a 92 : 8 mixture of **8a**: **8b** (*trans*: *cis*) diastereoisomers was found.



Scheme 5

Now that preparative HPLC can be used for the purification of crude **8**[23], this is a significantly short and efficient method to prepare diol **8a** in diastereomerically and enantiomerically pure form. Thus, the direct transformation of **8a** to increasingly important chiral auxilliaries **11**[5-12] was performed as shown in Scheme 6.

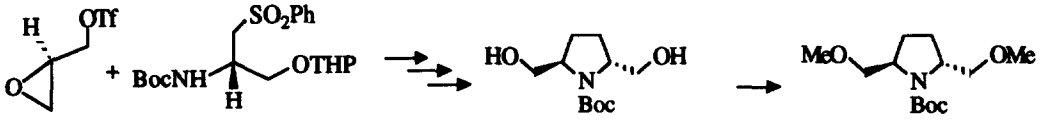


8a

11a R = Me, R' = Boc
11b R = Me, R' = H.HCl
11c R = Bn, R' = Boc

Scheme 6

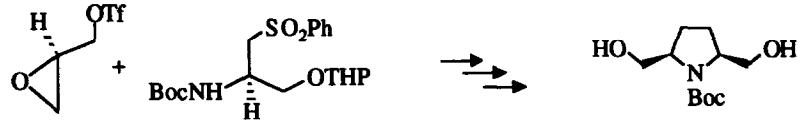
According to the same procedure described for **11a**, its enantiomer **12** was prepared from **(S)-1** and **(R)-2** in 4 steps in 63% overall yield. A HPLC analysis revealed that the ratio of *trans* - and *cis* -2,5-dihydroxymethylpyrrolidine derivatives, the precursor of **12** from epoxide **(R)-2** and **(S)-1**, were almost identical with that of **8**.



(R)-2 **(S)-1** **8c** **12**

Scheme 7

In order to confirm that all three stereoisomers of diol **8** could be synthesized in an enantioselective manner *via* this method, we synthesized **8b** in three steps from easily available epoxide **(R)-2** and **(R)-1**. After deprotection of the THP protected alcohol **4**, reduction of the phenylsulfone functionality and separation by preparative HPLC, the *cis* diastereoisomer **8b** was obtained along with the *trans* isomer in a ratio of approximately 92 to 8, respectively.



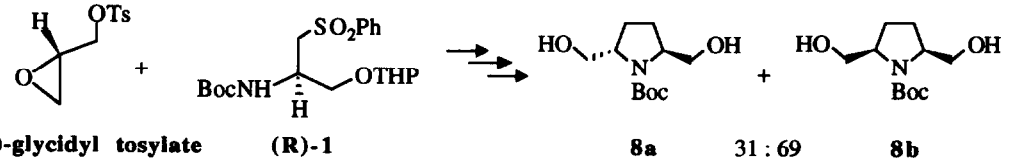
(R)-2 **(R)-1** **8b**

Scheme 8

From these results, it is now concluded that the sulfonyl carbanion of **1** reacts in a regioselective manner (at least 92 %) at C-1 of the homochiral glycidyl triflate **2** (*via* path a) to form the epoxide adduct **3** (see Scheme 2), and that the remaining carbamate anion then undergoes cyclization in a regiospecific manner (*via* 5-exo pathway) to provide the pyrrolidine derivative **4** at around -10°C in "one-pot".

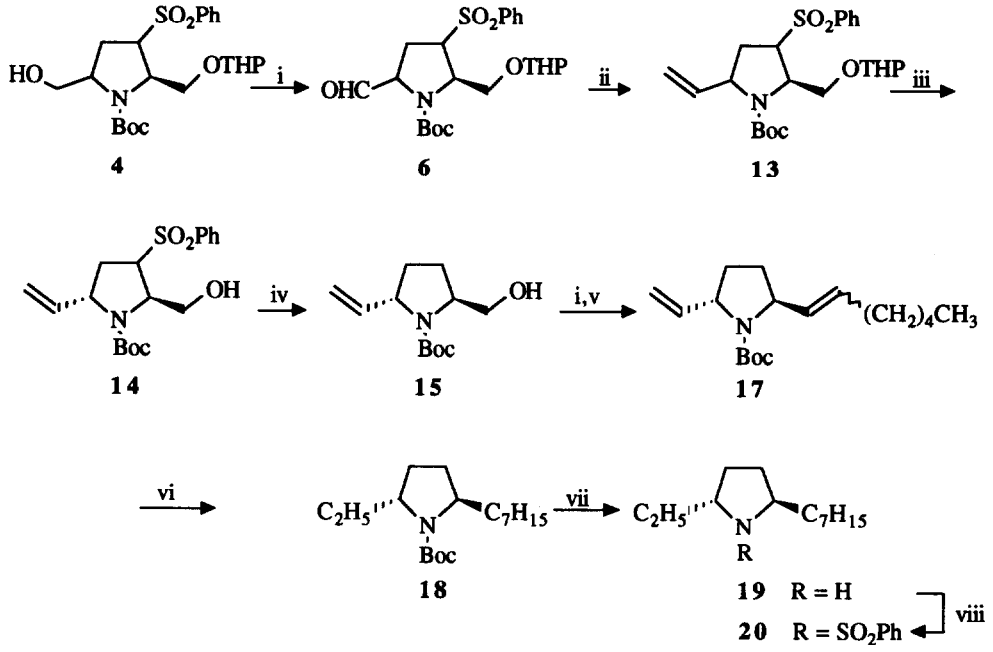
It has been reported that glycidyl tosylate undergoes regiospecific C-3 epoxide opening when treated with organometallic species[17b]. If the same selectivity is observed *via* our method, it would be of great synthetic interest to exploit it. In this context, **(2S)-glycidyl tosylate** was treated with **(R)-1** under the same reaction

conditions described above to afford **4** in 58 % yield together with unreacted **(R)-1** (35 %). Sequential removal of the THP and phenylsulfonyl groups from **4** provided **8** in 85 % overall yield. A HPLC analysis showed that the diol **8** obtained was a 31 : 69 mixture of **8a** : **8b**. Thus, replacement of glycidyl triflate with glycidyl tosylate significantly diminishes the regioselectivity of the sulfonyl carbanion of **1** to the detriment of the diastereomeric purity of final pyrrolidine derivatives.



Scheme 9

Now we turned our interest to the application of this novel methodology to the chirospecific synthesis of *trans*-2,5-dialkylpyrrolidines found in the nature. As illustrated in Scheme 10, our synthetic strategy is straightforward. The transformation of the two alcohol groups (protected and non-protected ones) in the key intermediate **4** into two different alkyl functionalities is to be performed at different stage of the synthesis.



Reagents and conditions: i) $(COCl)_2$/ Me_2SO/ Et_3N, -78°C to 0°C; ii) $CH_3P^+Ph_3Br^-$, - 60°C to rt; iii) 0.1 eq PPTS/EtOH, 50°C; iv) 6 % Na-Hg/ Na_2HPO_4, 0°C; v) $CH_3(CH_2)_5P^+Ph_3Br^-$, -60°C to rt; vi) H_2/ Pd/ C/ MeOH; vii) TFA/ CH_2Cl_2, rt; viii) $PhSO_2Cl$/ 6N NaOH

Scheme 10

The target molecule we have chosen is (2R,5R)-2-heptyl-5-ethylpyrrolidine **19** which is an important component of the venom of the fire ant (*Solenopsis punctaticeps*)[1]. The first asymmetric synthesis of this amine was accomplished in (2S,5S) form[3c], and enantioselective synthesis of the (2R,5R) isomer has also been reported[3d,4a]. Well detailed spectral data described in these previous reports on **19** seemed to be beneficial for an easy assessment of our synthetic methodology.

Thus, Swern oxidation of alcohol **4** gave crude aldehyde **6** which was subjected to Wittig reaction without purification to afford vinyl pyrrolidine **13** in 82 % overall yield after purification by flash chromatography on silica gel (EtOAc/ heptane, 1/ 3). Treatment of **13** with pyridinium p-toluenesulfonate in EtOH at 50°C gave a crystalline residue in quantitative yield. TLC of this residue (EtOAc/ heptane, 2/ 1) revealed the presence of a minute amount of the second product which is slightly less polar than the major product. Purification of the major product was easily effected by repeated recrystallization of the crude product mixture three times to give **14** in 90 % yield. The minor product isolated from the mother liquor by chromatography on silica gel (EtOAc/ heptane, 3/ 1) corresponded to 3 % of the major product by weight. Although we speculated that this minor product might be the C-5 diastereoisomer of **14** from its spectral data, further elaboration on this product was not pursued. The next step was the desulfonylation of **14** by 6 % Na-Hg in anhydrous MeOH at 0°C (90 %) and then repetition of the Swern oxidation-Wittig reaction sequences using n-hexyltriphenylphosphonium bromide to obtain diolefine **17** (77 % yield over two steps) after purification by chromatography on silica gel (EtOAc/ heptane, 1/ 3). Catalytic hydrogenation afforded **18** in quantitative yield which was treated with 50 % trifluoroacetic acid in CH_2Cl_2 at room temperature with subsequent purification by flash chromatography on silica gel ($CHCl_3$/ MeOH, 9/ 1) to afford the final compound **19** in 60 % yield. For further confirmation of the structure of **19** and its stereochemistry, N-phenylsulfonyl derivative **20** was prepared according to the reported procedure[3a]. Comparison of the ^{13}C NMR spectrum obtained from **19** and **20** with those reported in the literature proved useful for the assignment of the correct stereochemistry at C-5. The chemical shifts of the C-2 and C-5 carbons of *trans*-2-heptyl-5-ethylpyrrolidine, to be the values of δ 58.0 and 59.0, 58.2 and 59.8, respectively, were reported by Husson[3c] and Jegham[24]. These two groups have also prepared *cis*-2-heptyl-5-ethylpyrrolidine and reported the chemical shifts of the C-2 and C-5 carbons as δ 59.7 and 61.1, 59.5 and 61.0, respectively. We have found only two peaks at δ 58.18 and 59.71 in the ^{13}C NMR spectrum of **19** and no equivalent peaks of the *cis* isomer in the spectrum of **19**. Furthermore, the ^{13}C spectrum of **20** was proved to be identical with that reported in the literature[3c]. Although the value of $[\alpha]_D$ of **20** was found slightly different from those reported[3c,24], we have thus obtained **19** and **20** as only one diastereoisomer.

In conclusion, we have developed a general method for chirospecific synthesis of any one of the four stereoisomers of symmetrically or unsymmetrically-2,5-disubstituted pyrrolidines. We are currently investigating further application of this novel methodology to the synthesis of other biologically interesting, more complex molecules.

Acknowledgements: We are grateful to Professor P. Potier and Dr. W. R. Nadler for helpful discussion, we also wish to thank Mrs M.-T. Adeline for her collaboration in HPLC studies. Generous gift of L-serine from Ajinomoto Co., Inc.(Tokyo, Japan) is gratefully acknowledged.

EXPERIMENTAL SECTION

Tetrahydrofuran (THF) was distilled under an atmosphere of dry argon from sodium / benzophenone ketyl prior to use. (R)-(+) and (S)-(-) glycidol and (2S)-(+)-glycidyl tosylate were purchased from Aldrich Chemical Co and used as received. All other chemicals were of the highest commercial purity and were used without futher purification. n-Heptane and ethylacetate, used for chromatography were distilled before use. CH_2Cl_2 was distilled from P_2O_5. Flash chromatography was performed on E. Merck Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography (TLC) was carried out on precoated (0.2 mm) Merck silica gel 60 F_{254} plates. Infrared spectra (IR) were obtained in CH_2Cl_2 using a Nicolet 205 (FT) spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ solution (unless indicated otherwise) as solvent using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or WM 400 (400 MHz). ^{13}C NMR were determined on a Bruker AC 200 (50.3 MHz) or a Bruker WM 250 (62.9 MHz) in $CDCl_3$ solution. Chemical shifts are given in ppm downfield from TMS. Mass spectra (MS) were mesured on a AEI, MS-50 (EI spectra) or AEI MS-9 and KRATOS MS-80 (HRMS). Optical rotations were determined in $CHCl_3$, MeOH or EtOH (as indicated) using a Perkin Elmer 243 polarimeter. Elemental analyses were performed by Service de Microanalyse at Institut de Chimie des Substances Naturelles, CNRS, Gif sur Yvette.

(2R)-2-t-Butoxycarbonylamino-3-phenylsulfonyl-5,6-epoxy-1-(2-tetrahydropyranyloxy)-hexane: 3b

A colorless oil. IR: 3150-3620, 2925, 2825, 1710, 1510, 1370, 1325, 1180, 1160, 1040 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.45 (s, 9H), 1.45-1.95 (m, 6H), 2.45 (m, 1H), 2.53 (d, J = 4 Hz, 1H), 2.65 (t, J = 5 Hz, 1H), 2.75 (m, 1H), 3.0 (m, 1H), 3.5 (m, 2H), 3.8 (m, 2H), 4.27 (dd, J = 6, 15 Hz, 1H), 4.48 (dd, J = 6, 15 Hz, 1H), 5.5 (m, 1H), 7.15-7.92 (m, 5H).

(2R)-1-t-Butoxycarbonyl-2-(2-tetrahydropyranyloxy)methyl-3-phenylsulfonyl-5-hydroxymethylpyrrolidine: 4

To a solution of **(R)-1** (2g, 5.01 mmol) in THF (30 mL) was added dropwise n-BuLi (1.6M in hexane) (7.8 mL) at -78°C under argon. The mixture was stirred for 30 min and **(S)-2** (1.34 g, 6.5 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm gradually to 0°C. After stirring for 1 h at 0°C, the solution was concentrated. The residue was dissolved in water and extracted with EtOAc, dried and evaporated to a residue which was flash chromatographed on silica gel eluting with EtOAc/ heptane 1/ 4 to give 1.9 g of **4** (90 % yield) as a colorless oil and 90 mg of **(R)-1**. IR: 2943, 1700, 1445, 1380, 1360, 1300, 1146, 1125, 1070, 1034 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.45 (s, 9H), 1.40-1.80 (m, 6H), 1.90-2.15 (m, 1H), 2.20 -2.40 (m, 1H), 3.25-3.55 (m, 3H), 3.60-4.05 (m, 5H), 4.35-4.60 (m, 2H), 7.50-7.75 (m, 3H), 7.82-7.95 (m, 2H); ^{13}C NMR δ ($CDCl_3$): 19.32, 19.50, 25.07, 28.34, 29.60, 30.10, 30.53 (C_4, C (THP)), 28.34 ($\underline{C}H_3$ Boc), 58.85-68.06 (C_2, C_3, C_5, C_6, C_7, C (THP)), 81.3 (Cq Boc), 99.07, 99.37 (C_t (THP)), 128.66, 129.40 (Ph), 134.09 (Ph), 154.3 ($\underline{C}O$ Boc); Anal. Calcd. for $C_{22}H_{33}NO_7S$: C, 58.01, H, 7.30, N, 3.07, S, 7.03. Found: C, 59.74, H, 7.26, N, 2.97, S, 6.89.

(2R)-1-t-Butoxycarbonyl-(2,5)-bis(hydroxymethyl)-3-phenylsulfonylpyrrolidine: 7

To a solution of **4** (1.4 g, 3.08 mmol) in EtOH (30 mL) was added pyridinium p-toluenesulfonate (77 mg, 0.31 mmol). The solution was stirred for 2 h at 50°C, then concentrated, dissolved in water and extracted with EtOAc. The organic phase was dried and evaporated to give a residue which was chromatographed on silica gel eluting with EtOAc/ heptane 3/ 7 to afford 1.06 g (93% yield) of **7** as a colorless oil. IR: 3420, 2970, 2925, 1680, 1685, 1676, 1673, 1405, 1369, 1300, 1250, 1149, 1080, 1060, 1050 cm^{-1}; ^{13}C NMR δ ($CDCl_3$): 28.22 ($\underline{C}H_3$ Boc), 29.60 (C_4), 60.90 (C_3), 62.77 (C_6, C_7), 64.60 (C_2, C_5), 128.48, 129.34, 134.06, 137.55 (Ph), 154.45 ($\underline{C}O$ Boc).

(2S,5S)-1-t-Butoxycarbonyl-(2,5)-bis(hydroxymethyl)pyrrolidine: 8a
and
(2S,5R)-1-t-Butoxycarbonyl-(2,5)-bis(hydroxymethyl)pyrrolidine: 8b

To a solution of **7** (360 mg, 0.92 mmol) and Na_2HPO_4 (389 mg, 2.73 mmol) in HPLC grade MeOH (15 mL) cooled to 0°C, was added 6% Na-Hg (1.03 g, 2.73 mmol). The mixture was vigorously stirred for 1 h at 0°C. Mercury was removed by decanting the reaction mixture which was evaporated. The residue was dissolved in water and extracted with EtOAc, dried and evaporated to a residue which was subjected to HPLC on silica gel column eluting with propanol-2/ heptane 5/ 95 to give 192 mg and 16 mg of **8a** and **8b**, respectively (93% yield).

8a

A colorless oil. $[\alpha]_D^{20}$ -80° (c 1, MeOH); IR: 3396, 2974, 1669, 1404, 1368, 1248, 1173, 1125, 1050 cm^{-1}; ^{13}C NMR δ ($CDCl_3$): 26.24 (C_3, C_4), 28.33 ($\underline{C}H_3$ Boc), 59.64, 60.11 (C_2, C_5), 62.78, 65.61 (C_6, C_7), 80.44 (Cq Boc), 155.69 ($\underline{C}O$ Boc); Anal. Calcd. for $C_{11}H_{21}NO_4$: C, 57.13, H, 9.15, N, 6.06. Found C, 56.83, H, 8.91, N, 5.98.

8b

A colorless oil. ^{13}C NMR δ ($CDCl_3$): 26.87 (C_3, C_4), 28.46 ($\underline{C}H_3$ Boc), 60.52 (C_2, C_5), 64.40, 65.74 (C_6, C_7), 80.50 (Cq Boc), 156.26 ($\underline{C}O$ Boc); Anal. Calcd. for $C_{11}H_{21}NO_4$: C, 57.13, H, 9.15, N, 6.06. Found: C, 57.03, H, 8.90, N, 5.92.

(2R,5R)-1-t-Butoxycarbonyl-(2,5)-bis(hydroxymethyl)pyrrolidine: 8c

Prepared from **(S)-1** and **(R)-2** according to the procedure described for **8a** and **8b**.
A colorless oil. $[\alpha]_D^{20}$ +79° (c 1.3, MeOH); IR: 3401, 2974, 2933, 1669, 1403, 1368, 1250, 1172, 1125, 1050 cm^{-1}; ^{13}C NMR δ ($CDCl_3$): 26.65, 26.87 (C_3, C_4), 28.49 ($\underline{C}H_3$ Boc), 60.54 (C_2, C_5), 63.40, 66.38 (C_6, C_7), 80.72 (Cq Boc), 156.00 ($\underline{C}O$ Boc); Anal. Calcd. for $C_{11}H_{21}NO_4$: C, 57.13, H, 9.15, N, 6.06. Found: C, 57.19, H, 8.94, N, 5.56.

(2S,5S)-1-t-Butoxycarbonyl-(2,5)-bis(methoxycarbonyl)pyrrolidine: 9a

To a solution of **8a** (200 mg, 0.86 mmol) in acetone (25 mL) was added Jones reagent (955 µL). The mixture was vigorously stirred for 2 h at rt. The solvent was evaporated and the residue was diluted with EtOAc and extracted. The organic layers was dried and evaporated and treated with CH_2N_2 in ether, then evaporated. The residue was chromatographed on silica gel eluting with EtOAc/ heptane 1/ 4 to afford 148 mg of **9a** (60% yield) which was recrystallized from EtOAc-hexane. mp 70-72°C; $[\alpha]_D^{20}$ -72° (c 1, $CHCl_3$); IR: 2970, 1746, 1698, 1392, 1210, 1178, 1162, 1133 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$): 1.45 (s, 9H), 1.95-2.02 (m, 2H), 3.73, 3.74 (2s, 6H), 4.43 (dd, J = 2.0, 8.0 Hz, 1H), 4.55 (dd, J = 2.0, 8.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$): 28.10 ($\underline{C}H_3$ Boc), 28.99 (C_3, C_4), 51.98, 52.12 ($O\underline{C}H_3$), 59.15, 59.40 (C_2, C_5), 80.58 (Cq Boc), 153.39 ($\underline{C}O$ Boc), 172.88, 173.13 ($\underline{C}O$ ester); Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.35, H, 7.37, O, 33.40. Found: C, 54.35, H, 7.23, O, 33.38.

(2S,5R)-1-t-Butoxycarbonyl-(2,5)-bis(methoxycarbonyl)pyrrolidine: 9b

A colorless oil. IR: 2985, 2960, 1762, 1738, 1705, 1440, 1397, 1368, 1295, 1198, 1164, 1130 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$): 1.45 (s, 9H), 2.1-2.25 (m, 4H), 3.8 (s 6H), 4.3 (dd, J = 2.0, 8.0 Hz, 1H), 4.4 (dd, J = 2.0, 8.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$): 28.21 ($\underline{C}H_3$ Boc), 28.77, 29.53 (C_3, C_4), 52.11 ($O\underline{C}H_3$), 59.57, 60.04 (C_2, C_5), 80.76 (Cq Boc), 153.50 ($\underline{C}O$ Boc), 172.17, 172.42 ($\underline{C}O$ ester); Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.35, H, 7.37, N, 4.88. Found: C, 54.44, H, 7.34, N, 4.93.

(2S,5S)-Pyrrrolidine-2,5-dicarboxylic acid: 10

A solution of **9a** (47 mg, 0.202 mmol) was stirred at 100°C in 1N HCl (3 mL) for 2 h. Then the mixture was extracted with EtOAc after cooling to rt. The aqueous layer was concentrated and the residue was fixed on ion exchange resin (type: Dowex 50x8-100), washed sequentially with H_2O and MeOH and eluted with 1M aqueous pyridine to give after evaporation 21 mg of **10** (90% yield). mp > 300°C; $[\alpha]_D^{20}$ -101° (c 1.2, H_2O), {lit. $[\alpha]_D^{31}$ -102° (c 0.983, H_2O)[8], $[\alpha]_D^{20}$ -112° (c 1, H_2O)[21], $[\alpha]_D^{20}$ -107° (c 1.0, H_2O)[22a], $[\alpha]_D$ -104° (c 0.93, H_2O)[22d], $[\alpha]_D$ -110° (c 1, H_2O)[22e]}; ^{13}C NMR δ (MeOD): 25.56, 30.47 (C_3, C_4), 60.93, 62.85 (C_2, C_5), 170.67, 173.62 ($\underline{C}O$ acid).

(2S,5S)-1-t-Butoxycarbonyl-(2,5)-bis(methoxymethyl)pyrrolidine: 11a

To a solution of NaH (47 mg, 60% in oil, 1.17 mmol) in DMF (25 mL) was added, dropwise at 0°C under argon, MeI (98 µL, 1.556 mmol). After 15 min, **8a** (90 mg, 0.389 mmol) was added and the mixture was stirred for 5 h at 0°C. The excess of NaH was destroyed with MeOH and the solution was neutralized with acetic acid, evaporated to dryness and extracted with EtOAc. The organic layer was dried and evaporated and the residue was chromatographed on silica gel eluting with EtOAc/ heptane 1/ 4 to give 82 mg of **11a** (81% yield) as a colorless oil. $[\alpha]_D^{20}$ -89° (c 1.1, EtOH); IR: 2976, 2930, 2894, 2825, 1695, 1457, 1391, 1340, 1300, 1250, 1175, 1125, 1100 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.45 (s, 9H), 1.9 (m, 4H), 3.32 (s, 6H), 3.48 (m, 1H), 3.6 (m, 1H), 3.74 (m, 2H), 3.9 (m, 2H), 3.9 (m, 2H); ^{13}C NMR δ ($CDCl_3$): 25.54, 26.55 (C_3, C_4), 28.44 ($\underline{C}H_3$ Boc),

56.82, 58.86 (C_2, C_5, O<u>C</u>H_3), 71.95, 73.06 (C_6, C_7), 79.35 (Cq Boc), 153.67 (<u>C</u>O Boc); Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.19, H, 9.74, N, 5.40. Found: C, 60.31, H, 9.51, N, 5.47.

Hydrochloride of (2S,5S)-(2,5)-bis(methoxymethyl)pyrrolidine: 11b

A solution of **11a** (47 mg, 0203 mmol) in 1N HCl (2 mL) was stirred at 100°C for 2 h. Then, the solution was extracted with EtOAc after cooling to rt, and the aqueous layer was evaporated to afford 32 mg of **11b** (87% yield). mp 98-100°C; $[\alpha]_D^{20}$ -4° (c 1.07, $CHCl_3$), {lit.[11] $[\alpha]_D^{20}$ -6.4° (c 1.1, $CHCl_3$)}; ^1H NMR δ ($CDCl_3$): 1.5 (s, 9H), 2.0 (m, 4H), 3.3 (s, 6H), 3.5 (m, 2H), 3.7 (m, 2H), 3.92 (m, 2H); ^{13}C NMR δ (MeOD, D_2O): 27.03 (C_3,C_4), 59.48, 60.16 (C_2, C_5), 71.38 (C_7, C_8).

(2S,5S)-1-t-Butoxycarbonyl-(2,5)-bis(benzyloxymethyl)pyrrolidine: 11c

To a solution of NaH (52 mg 60% in oil, 1.3 mmol) in DMF (25 mL) was added dropwise benzyl bromide (206 µL, 1.73 mmol) at 0°C under argon. After 15 min , **8a** (100 mg, 1.43 mmol) was added and the solution was stirred for 5 h at 0°C. The excess of NaH was destroyed and the solution was neutralized with acetic acid, evaporated to dryness and extracted with EtOAc. The organic layer was dried and evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/ heptane 1/ 4 to afford 116 mg of **11c** (65% yield) as a colorless oil. $[\alpha]_D^{20}$ -65° (c 1.3, $CHCl_3$),{lit[8]. $[\alpha]_D^{26}$ -64.24° (c 3.00, $CHCl_3$)}; ^1H NMR δ ($CDCl_3$): 1.45 (s, 9H), 2.0 (m, 4H), 3.3 (t, J = 8.0 Hz, 1H), 3.45 (t, J = 8.0 Hz, 1H), 4.6 (dd, J = 4.0, 10.0 Hz, 1H), 4.7 (dd, J = 4.0, 10.0 Hz, 1H), 4.92 (m, 2H), 4.45 (m, 4H), 7.3 (m, 10H); ^{13}C NMR δ ($CDCl_3$): 25.97, 26.91 (C_3, C_4), 28.51 (<u>C</u>H_3 Boc), 57.22 (C_2, C_5), 70.09, 70.72 (C_6, C_7), 73.24 (<u>C</u>H_2Ph), 79.41 (Cq Boc), 127.50, 128.36 (Ph), 138.46 (Cq ph), 153.77 (<u>C</u>O Boc).

(2R,5R)-1-t-Butoxycarbonyl-(2,5)-bis(methoxymethyl)pyrrolidine: 12

Prepared from **8c** according to the procedure described for **11a**.
A colorless oil. $[\alpha]_D^{20}$ +89° (c 2, EtOH); ^{13}C NMR δ ($CDCl_3$): 27.13 (C_3, C_4), 28.51 (<u>C</u>H_3 Boc), 57.61, 58.93, 58.98 (C_2, C_5, O<u>C</u>H_3), 74.02 (C_6, C_7), 79.4 (Cq Boc), 153.60 (<u>C</u>O Boc); Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.19, H, 9.74, N, 5.40. Found: C, 60.12, H, 9.44, N, 5.25.

(2R)-1-t-Butoxycarbonyl-2-(2-tetrahydropyranyloxy)methyl-3-phenylsulfonyl-5-vinylpyrrolidine: 13

To a solution of oxalyl chloride (0.26 mL, 3.0 mmol) in CH_2Cl_2 (4 mL) was addded dropwise a solution of Me_2SO (0.26 mL, 3.7 mmol) in CH_2Cl_2 (2.0 mL) at -78°C. After stirring for 10 min at -70°C, a solution of **4** (910 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) was added to the mixture. The reaction mixture was stirred at -60°C. After 30 min, triethylamine (0.8 mL, 6.2 mmol) was added to the mixture which was allowed to warm to room temperature and quenched with water. The mixture was diluted with CH_2Cl_2 (10 mL), washed with 20% $KHSO_4$, saturated bicarbonate and brine, then dried, and evaporated to give the crude aldehyde **6**. To a solution of methyltriphenylphosphonuim bromide (785 mg, 2.2 mmol) in THF (40 mL) was added n-BuLi (1.6M in

hexane) (1.37 mL) at -78°C. The reaction mixture was allowed to warm gradually to room temperature, then was cooled to -78°C. A solution of the crude **6** in THF (20 mL) was addded to the mixture which was alllowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched with water at 0°C and extracted with EtOAc, dried and evaporated to a residue which was chromatographed on silica gel eluting with EtOAc/ heptane 1/ 3 to afford 758 mg of **13** (84% yield) as a colorless oil. IR: 3150-3650, 3100, 2950, 2900, 1690, 1390, 1310, 1160, 1140, 1085, 1050 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.35-1.73 (m, 15H), 2.20 (m, 1H), 2.45 (m, 1H) , 3.47 (m, 1H), 3.71 (m, 1H), 3.82 (m, 1H), 4.30 (m, 1H), 4.46 (m, 1H), 4.50 (m, 1H), 5.05 (d, J = 10.0 Hz, 1H), 5.11 (d, J = 17.0 Hz, 1H), 5.92 (m, 1H), 7.62 (dd, J = 8.0 , 8.0 Hz, 2H), 7.70 (dd, J = 8.0 , 8.0 Hz , 1H), 7.78 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$): 19.72, 25.34, 28.46, 30.34, 30.73, 32.74 (C_4, C (THP), $\underline{C}H_3$ Boc), 59.26, 61.32, 61.53, 61.89, 62.74, 65.05, 67.00 (C_2, C_3, C_5, C_8, C (THP)), 80.36 (Cq Boc), 99.55 (C_t (THP)), 114.62 (C_7 (vinyl)), 128.96, 129.41 (Ph), 133.97 (Ph), 138.25, 140.18 (C_6 (vinyl)), 158.52 ($\underline{C}O$ Boc); Anal. Calcd. for $C_{23}H_{33}NO_6S$: C, 61.17, H, 7.36, N, 3.10, S, 7.10. Found: C, 61.07, H, 7.38, N, 3.14, S, 7.20.

(2R)-1-t-Butoxycarbonyl-2-(2-tetrahydropyranyloxy)methyl-3-phenylsulfonyl-5-formylpyrrolidine: 6

A colorless oil. ^{13}C NMR δ ($CDCl_3$): 19.03-19.79, 25.18, 30.24, 30.61 (C_4, C (THP)), 27.95, 28.23, 28.32 ($\underline{C}H_3$ Boc), 57.54-68.21 (C_2, C_3, C_5, C_7, C (THP)), 81.63 (Cq Boc), 97.82, 98.32, 99.62 (C_t (THP)), 128.91, 129.56 (Ph), 134.27, 134.38 (Cq Ph), 151.80, 153.60 ($\underline{C}O$ Boc), 201.93, 202.23 ($\underline{C}O$ aldehyde).

(2R,5S)-1-t-Butoxycarbonyl-2-hydroxymethy-3-phenylsulfonyl-5-vinylpyrrolidine: 14

To a solution of **13** (630 mg, 1.4 mmol) in EtOH (15 mL) was added pyridinium p-toluenesulfonate (35 mg, 0.14 mmol). The solution was stirred for 2 h at 50°C, then concentrated, dissolved in water and extracted with CH_2Cl_2. The organic phase was dried and evaporated to give a solid residue which was crystallized from EtOAc/ heptane. Recrystallization was repeated three times to obtain 460 mg (90% yield) of **14**. mp 147-148°C; IR: 3475, 2987, 2360, 1680, 1310, 1150, 1060 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.43 (s, 9H), 2.22 (m, 1H), 2.42 (m, 1H), 3.53 (m, 1H), 3.67 (m, 1H), 3.82 (m, 1H), 4.28 (m, 1H), 4.41 (m, 1H), 5.05 (d, J = 17.0 Hz, 1H), 5.09 (d, J = 10.0 Hz, 1H), 5.93 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ ($CDCl_3$): 28.38 ($\underline{C}H_3$ Boc), 32.47 (C_4), 60.57, 61.48 (C_2, C_5), 63.39 (C_8), 64.45 (C_3), 80.87 (Cq Boc), 115.00 (C_7 (vinyl)), 128.83, 129.50, 134.15 (Ph), 139.46 (C_6 (vinyl)); Anal. Calcd. for $C_{18}H_{25}NO_5S$: C, 58.53, H, 6.83, N, 3.81, S, 8.72. Found C, 58.86, H, 6.93, N, 3.82, S, 8.43. Isolated minor product, a colorless oil. ^1H NMR δ ($CDCl_3$): 1.43 (s, 9H), 2.03 (m, 1H), 2.60 (m, 1H), 3.50-3.70 (m, 3H), 4.36 (m, 1H), 4.44 (m, 1H), 5.08 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.69 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz, 2H), 7.70 (dd, J = 8.0, 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H).

(2S,5S)-1-t-Butoxycarbonyl-2-hydroxymethyl-5-vinylpyrrolidine: 15

To a solution of **14** (410 mg, 1.12 mmol) and Na_2HPO_4 (470 mg, 3.3 mmol) in HPLC grade MeOH (15 mL) cooled to 0°C, was added 6% Na-Hg (1.25 g, 3.3 mmol). The mixture was vigorously stirred for 1 h at 0°C.

Mercury was removed by decanting the reaction mixture which was evaporated. The residue was dissolved in water and extracted with CH_2Cl_2 dried and evaporated to a residue which was flash chromatographed on silica gel eluting with EtOAc/ heptane 2/ 1 to give 225 mg of **15** (89% yield) as a colorless oil. $[\alpha]_D^{20}$ -27° (c 1.05, $CHCl_3$); IR: 3424, 2977, 1692, 1672, 1398, 1367, 1173, 1124, 1100 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.41 (s, 9H), 1.63 (m, 2H), 2.06 (m, 2H), 3.59 (dd, J = 12.0, 3.0 Hz, 1H), 3.72 (dd, J = 12.0, 7.0 Hz, 1H), 4.07 (m, 1H), 4.30 (m, 1H), 4.99 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 10.0 Hz, 1H), 5.73 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H); ^{13}C NMR δ ($CDCl_3$): 26.14, 30.01 (C_3, C_4), 28.40 ($\underline{C}H_3$ Boc), 59.89, 60.74 (C_2, C_5), 67.36 (C_8), 80.12 (Cq Boc), 113.68 (C_7 (vinyl)), 138.41 (C_6 (vinyl)), 158.52 ($\underline{C}O$ Boc); HRMS Calcd. for $C_{12}H_{21}NO_3$ m/z: 227.1521. Found: 227.1524.

(2S,5S)-1-t-Butoxycarbonyl-2-(1-heptenyl)-5-vinylpyrrolidine: 17

According to the procedure described for **13**.

Treatment of **15** (200 mg, 0.88 mmol) with oxalyl chloride (0.120 mL, 1.32 mmol). Me_2SO (0.13 mL, 1.85 mmol) and triethylamine (0.80 mL, 5.50 mmol) in CH_2Cl_2 (5 mL) affored the crude aldehyde **16**. The Wittig reaction of **16** in THF (10 mL) with n-hexyltriphenylphosphonium bromide (750 mg, 1.75 mmol) and n-BuLi (1.6M in hexane) (1.1 mL, 1.75 mmol) in THF (10 mL). The crude product was purified by chromatography on silica gel eluting with EtOAc/ heptane 1/ 3 to give 200 mg of **17** (77% yield) as an colorless oil. $[\alpha]_D^{20}$ +53° (c 1.05, $CHCl_3$); IR: 3150-3700, 3150, 3010, 2970, 2940, 2880, 2850, 1700, 1450, 1382, 1365, 1320, 1300, 1172, 1150 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.88 (t, J = 6.0 Hz, 3H), 1.20-1.33 (m, 5H), 1.42 (s, 9H), 1.51-1.67 (m, 2H), 1.88-2.20 (m, 5H), 4.38 (m, 1H), 4.56 (m, 1H), 5.06 (m, 2H), 5.33 (m, 2H), 5.75 (m, 1H); ^{13}C NMR δ ($CDCl_3$): 14.05 (CH_3) 22.60, 27.58, 28.57, 29.43, 30.68, 31.40, 31.65 (C_3, C_4, 4x$\underline{C}H_2$, $\underline{C}H_3$ Boc), 54.86, 59.31 (C_2, C_5), 79.12 (Cq Boc), 113.59 (C_7 (vinyl)), 129.15, 130.40, 131.95, 132.66 (C_8, C (olefine)), 138.60 (C_6 (vinyl)), 154.16 ($\underline{C}O$ Boc); HRMS (MH^+) Calcd. for $C_{18}H_{32}NO_2$ 294.2444. Found: 294.2444.

(2R,5R)-1-t-Butoxycarbonyl-2-heptyl-5-ethylpyrrolidine: 18

A solution of **17** (180 mg, 0.61 mmol) in MeOH (10 mL) was stirred in the presence of 10% Pd/ C (20 mg) and hydrogen at atmospheric pressure for 5 h. After removal of the catalyst by filtration through celite, the filtrate was evaporated. The residue was purified by chromatography as described for **17** to yield 170 mg of **18** as an colorless oil (94% yield). $[\alpha]_D^{20}$ -36° (c 1.05, $CHCl_3$). IR : 2963, 2925, 2875, 2860, 1695, 1450, 1390, 1365, 1180, 1110 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.83 (t, J = 6.0 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.13-1.35 (broads, 14H), 1.45 (s, 9H), 1.61 (m, 2H), 1.90 (m, 2H), 3.62 (m, 2H); ^{13}C NMR δ ($CDCl_3$): 10.97 (CH_3), 14.17 (CH_3), 22.76, 26.90, 28.56, 29.46, 29.71, 31.93, 32.94, 34.15 (C_3, C_4, C_6, C_7, C_8, 5x(CH_2)), 28.71 ($\underline{C}H_3$ Boc), 57.88, 59.22 (C_2, C_5), 78.75 (Cq Boc), 153.59 ($\underline{C}O$ Boc); HRMS for $C_{18}H_{35}NO_2$ m/z: 297.2667. Found: 297.2652.

(2R,5R)-2-Heptyl-5-ethylpyrrolidine: 19

To a solution of **18** (150 mg, 0.5 mmol) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 3 h. After evaporation of the acid and the solvent, the residue was dissolved in water and extracted with ether. The aqueous phase was made alkaline with 6N NaOH and extracted with EtOAc (3 x 10 mL). After washing with brine and drying, the residue upon concentration was flash chromatographed on silica gel eluting with 10% MeOH/ $CHCl_3$ to give 60 mg of **19** as an oil (60% yield). $[\alpha]_D^{20}$ -3° (c 1.05, $CHCl_3$) {lit. for the (2S,5S) enantiomer $[\alpha]_D^{20}$ +4° (c 2.0, $CHCl_3$)[3c], $[\alpha]_D^{25}$ -4.4° (c 2.0, $CHCl_3$) for the (2R,5R) enantiomer[3d], $[\alpha]_D^{20}$ -3.6° (c 0.6, $CHCl_3$)[24]}; IR 3330, 2960, 2930, 2850, 1460, 1400, 1375, 1350, 1300, 1200, 1140 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.88 (t, J = 6.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 1.10-1.55 (m, 16H), 1.92 (m, 2H), 2.60 (m, 1H), 3.07 (m, 2H); ^{13}C NMR δ ($CDCl_3$): 1.46 ($\underline{C}H_3$), 14.09 ($\underline{C}H_3$), 22.71, 27.38, 29.35, 29.77, 31.93, 31.98, 32.50, 37.10 (C_3, C_4, C_6, C_7, C_8, 5x(CH_2), 29.93 ($\underline{C}H_3$ Boc), 58.98, 59.71 (C_2, C_5); HRMS for $C_{13}H_{27}N$ m/z: 197.2143. Found: 197.2148. IR and ^{13}C NMR were in complete agreement with those reported in the literature[3c,24].

(2R,5R)-1-Phenylsulfonyl-2-heptyl-5-ethylpyrrolidine: 20

Preparated from **19** (30mg) and phenylsulfonylchloride according to reference[3a]. A colorless oil. $[\alpha]_D^{20}$ -59° (c 1.10, $CHCl_3$) {lit. for the (2S,5S) enantiomer, $[\alpha]_D^{20}$ +62° (c 0.87, $CHCl_3$)[3c], for the (2R,5R) enantiomer $[\alpha]_D^{25}$ -61.4° (c 0.87, $CHCl_3$)[3d]}; IR: 3150-3650, 2957, 2927, 1650, 1464, 1445, 1342, 1225, 1157, 1098, 1071, 1051 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.81 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 6.0 Hz, 3H), 1.05-1.40 (m, 14H), 1.66 (m, 2H), 1.95 (m, 2H), 3.80 (m, 2H), 7.42 (m, 3H), 7.84 (m, 2H); ^{13}C NMR δ ($CDCl_3$): 10.70 ($\underline{C}H_3$), 14.16 (CH_3), 22.74, 26.55, 26.93, 27.66, 28.16, 29.32, 29.55, 31.90, 34.03 (C_3, C_4, C_6, C_7, 5x$\underline{C}H_2$), 61.28, 62.46 (C_2, C_5), 126.95, 128.86, 131.95 (Ph); HRMS for $C_{17}H_{26}NO_2S$ m/z: 308.1684. Found: 308.1689, for $C_{12}H_{16}NO_2S$ m/z 238.0901. Found 238.0902.

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23. HPLC conditions For the determination of the ratio of the *trans* **8a** and the *cis* **8b** : column , Novapack Si 4μ; column size, 3.9 x 150 mm; eluent, heptane/ propanol-2 95/ 5; flow rate, 2 mL/ min; detector, Refractometer R 410 (Waters); retention time, **8b** (*cis*) 5.06 min, **8a** (*trans*) 8.54 min. For Preparative HPLC: silica gel column , column size, 25 x 10 cm; flow rate, 10 mL/ min ; eluent; heptane/ propanol-2, 92/ 8.
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