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STEREOSELECTIVE SYNTHESIS OF PYRROLIDIN-3-OLS FROM HOMOALLYLAMINES

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Abstract – The reaction of enantiomerically pure *N*-*tert*-butylsulfinyl-homoallylamines **3** (easily prepared by indium mediated allylation of the corresponding *N*-*tert*-butylsulfinylaldimine with allyl bromide) with MCPBA in CH_2Cl_2 at 25 °C leads to epoxysulfonamide derivatives **4** as a *ca.* 1:1 mixture of diastereoisomers. Cyclization of compounds **4** under basic conditions (K_2CO_3 in DMF) affords *cis*- and *trans*-pyrrolidin-3-ols **5** and **6**, respectively.

INTRODUCTION

Homoallylic amines are accessible in an enantiomeric pure form by addition of allyl metal derivatives to imines in the presence of a chiral auxiliary or through a catalytic asymmetric process.[1] These compounds show interest because they are important building blocks in the synthesis of nitrogenated materials.[2] Among chiral auxiliaries, the *N*-sulfinyl group in sulfinimines[3] have been widely studied (Davis proposed the use of *N*-*p*-tolylsulfinimines[4] and more recently J. Ellman developed *N*-*tert*-butyl derivatives[5]) because the nucleophilic additions take place smoothly[6] and the chiral auxiliary can be easily removed under acidic conditions. On the other hand, pyrrolidin-3-ols are versatile nitrogen heterocycles because there are many biologically active compounds bearing this structural array[7] and also because they can be intermediates in the synthesis of other nitrogenated heteroycles.[8] Recently Hodgson *et al.* reported the synthesis of *N*-tosylpyrroldin-3-ols from epoxysulfonamides upon treatment with dimethylsulfoxonium methylide. Starting epoxysulfonamides were prepared by oxidation of allylamine derivatives.[9] In this paper we report on the synthesis of enantiomerically pure pyrrolidin-3-ols by an intramolecular

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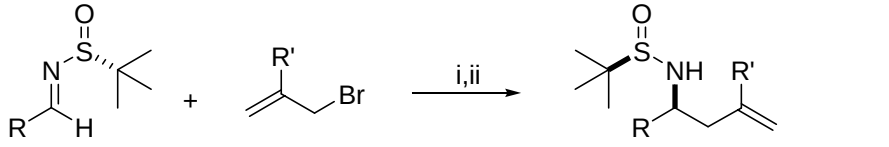
This paper is dedicated to Professor Dr. Ryoji Noyori on occasion of his 70th birthday.

nucleophilic ring opening of the compounds resulting from epoxidation of chiral homoallylamine derivatives.[10]

RESULTS AND DISCUSSION

The reaction of different *N*-*tert*-butylsulfinyl aldimines **1**, which were prepared in high yields from readily available (*R*)- or (*S*)-1,1-dimethylethanesulfinamide[11] and the corresponding aldehyde in dichloromethane at room temperature, with allyl bromides **2** and indium powder in THF at 60 °C affords, after hydrolysis with water, the corresponding *N*-*tert*-butylsulfinylamines **3** with high chemical yields and diastereoselectivities (Scheme 1).[12] Enantiomerically pure compounds **3** were obtained after column chromatography purification (for yields, see Experimental part). A six-membered ring chelation control model has been proposed to explain the high level of stereocontrol.[12] For (*R*)-*N*-*tert*-butylsulfinyl aldimines, the nucleophilic attack takes place in all cases to the *Si* face of the imino group, and logically, to the *Re* face for (*S*)-aldimine derivatives.



1a: R = *i*-Pr
1b: R = $Me(CH_2)_7$
1c: R = $Ph(CH_2)_2$
1d: R = Ph

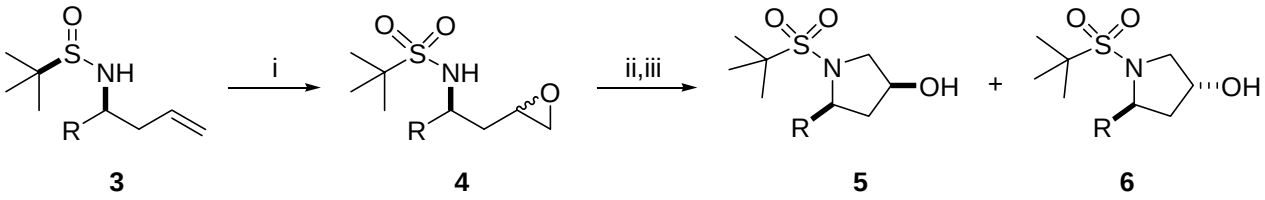
2a: R' = H
2b: R' = Me

3a: R = *i*-Pr, R' = H
3b: R = $Me(CH_2)_7$, R' = H
3c: R = $Ph(CH_2)_2$, R' = H
3d: R = Ph, R' = H
3e: R = Ph, R' = Me

Scheme 1. Reagents and conditions: (i) In, THF, 60 °C, 4 h; (ii) H_2O, 25 °C.

The oxidation of *N*-*tert*-butylsulfinylamines **3** with 3 equivalents of *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature yielded epoxysulfonamide derivatives **4** as a *ca.* 1:1 mixture of diastereoisomers in almost quantitative yields (Scheme 2 and Table 1). The oxidation of sulfinyl to sulfonyl group took place first rapidly. Subsequent epoxydation under these reaction conditions occurred without any stereoselection in spite of the presence of a stereogenic center in the molecule. All attempts to separate diasteroisomers **4** (column chromatography, silica gel, hexane/ethyl acetate) failed. The treatment of the resulting reaction crude with potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 100 °C for 24 hours led with total chemical conversion to a mixture of pyrrolidin-3-ol derivatives **5** and **6**, which in this case were easily separated by column chromatography (Scheme 2 and Table 1). Apparently, pyrrolidin-3-ols **5** (*cis*-isomers) and **6** (*trans*-isomers) are formed through a disfavored 5-*endo*-*tet* ring closure according to Baldwin's rules,[13] instead of a favored 4-*exo*-*tet* process. Probably, the mechanism

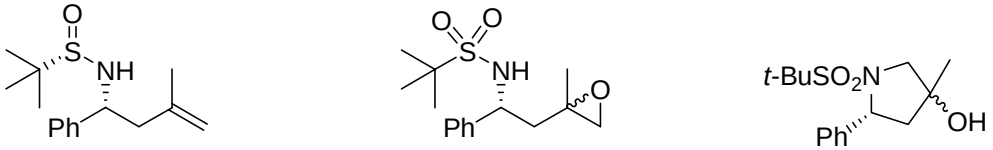
leading to the nitrogen containing five-membered heterocycles **5** and **6** is not so simple, and for that reason, more detailed studies on the mechanism of this process are under progress.



3 **4** **5** **6**

Scheme 2. Reagents and conditions: (i) MCPBA (3 equiv), CH_2Cl_2, 25 °C, 24 h; (ii) K_2CO_3, DMF, 100 °C, 24 h; (iii) H_2O, 25 °C.

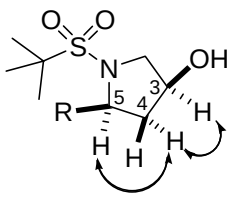
Oxidation of *N-tert*-butylsulfinylamine (R_C,S_S)-**3e**, derived from the indium mediated addition of metallylbromide to the corresponding aldimine under the previously commented reaction conditions, gave epoxysulfonamide derivatives **4i** as a *ca.* 1:1 mixture of diastereoisomers in >95% yield. Treatment of **4i** with potassium carbonate in DMF at 100 °C leads to a mixture of pyrrolidin-3-oles **7** in 81% yield. Unfortunately in this case, it was not possible to separate both diastereoisomers (Chart 1).



(R_C,S_S)-**3e** **4i** **7**

Chart 1

The structure elucidation of compounds **5** and **6** was performed by NMR studies. In Chart 2 NOESY contacts between H-3, H-4α and H-5 in *cis*-pyrrolidin-3-ol derivatives **5** are shown. The solid *cis*-pyrrolidin-3-ol **5g** [R = $Ph(CH)_2$] gave crystals suitable for single crystal X-ray analysis and the obtained structure showed the relative *cis*-configuration[14] and was in total agreement with the NOESY experiments (Chart 2).



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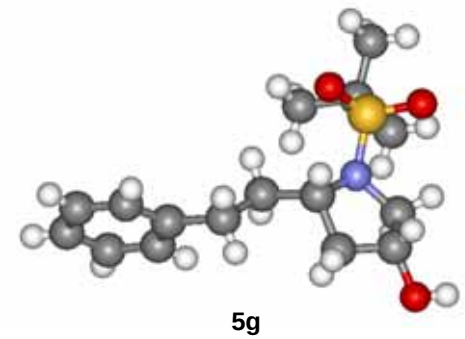
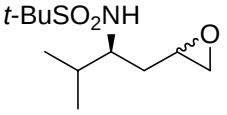
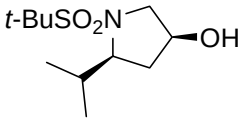
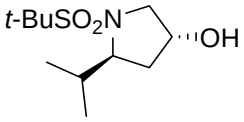
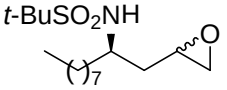
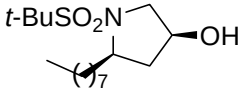
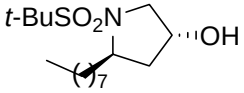
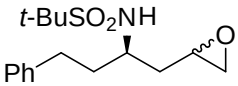
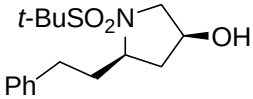
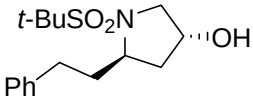
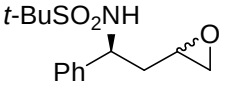
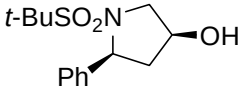
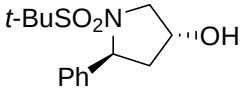
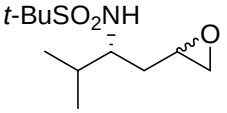
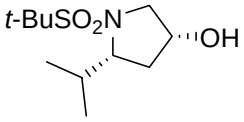
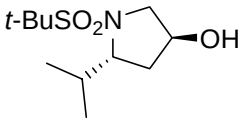
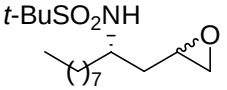
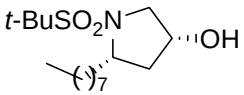
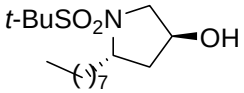
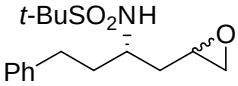
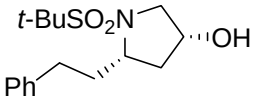
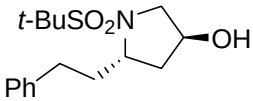
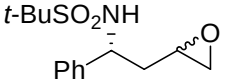
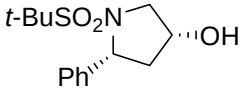
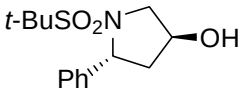


5g

Chart 2

Table 1. Preparation of epoxysulfonamide derivatives **4** and pyrrolidin-3-ols **5** and **6**

	Homoallyl	Epoxysulfonamide **4**[a]			Pyrrolidin-3-ols **5** and **6**[a]		
Entry	amine (**2**)	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
1	(S_C,R_S)-**3a**	**4a**		>95	**5a**		43
					6a		38
2	(R_C,R_S)-**3b**	**4b**		>95	**5b**		44
					6b		37
3	(R_C,R_S)-**3c**	**4c**		>95	**5c**		48
					6c		33
4	(S_C,R_S)-**3d**	**4d**		>95	**5d**		45
					6d		39
5	(R_C,S_S)-**3a**	**4e**		>95	**5e**		40
					6e		36
6	(S_C,S_S)-**3b**	**4f**		>95	**5f**		47
					6f		38
7	(S_C,S_S)-**3c**	**4g**		>95	**5g**		46
					6g		34
8	(R_C,S_S)-**3d**	**4h**		>95	**5h**		43
					6h		38

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [b] Yield based on the starting material **3** (*ca.* 1:1 mixture of diastereoisomers). [c] Yield based on the starting material **4**.

In summary, we have described in this paper a methodology which allows the transformation of epoxysulfonamide derivatives **4** (easily obtained by oxidation of enantiopure *N-tert*-butylsulfinylhomoallylamines **3**) into *cis*- and *trans*-pyrrolidin-3-ols **5** and **6**, respectively upon treatment under basic conditions. Additional studies in this area are currently underway.

EXPERIMENTAL

All reactions were performed in oven dried glassware under argon. All chemicals were commercially available (Acros, Aldrich). *N-tert*-butanesulfinamides (S_S and R_S) were a gift of Medalchemy (>99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). *N-tert*-Butanesulfinyl imines were prepared from freshly distilled aldehydes and *N-tert*-butanesulfinamides (S_S and R_S, >99% ee), following a previously reported procedure[15] with $MgSO_4$ and catalytic PPTS. TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus using open glass capillaries and reported without corrections. HPLC analyses were performed on a JASCO 200-series equipped with a Chiralpak OD-H column. NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using $CDCl_3$ as the solvent and TMS as internal standard. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HRMS (EI) were recorded on a Finnigan MAT 95S.

Preparation of *N-tert*-butylsulfinylhomoallyl amines 3. General procedure.

A mixture of the corresponding *N-tert*-butylsulfinylaldimine **1** (1.0 mmol), allylic bromide **2** (1.2 mmol) and indium powder (1.2 mmol, 0.138 g) in THF (5 mL) was stirred for 4 h at 60 °C. Then, the resulting mixture was hydrolyzed with water (15 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **3**. Yields, physical and spectroscopic data follow.

(3*S*,*R*$_S$)-*N*-*tert*-Butylsulfinyl-2-methylhex-5-en-3-amine [(*S*$_C$,*R*$_S$)-3a]: Yield = 84%; colourless oil; $[\alpha]_D^{22}$ -65 (*c* 0.59, CH_2Cl_2); R_f 0.36 (hexane/EtOAc: 2/1); IR ν (film) 3239, 2957, 2871, 1466, 1388, 1364, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 [6H, d, J = 8.8 Hz, $(CH_3)_2CH$], 1.22 [9H, s, $(CH_3)_3C$], 1.82-1.93 [1H, m, $(CH_3)_2CH$], 2.23-2.43 (2H, m, CH_2), 3.11-3.20 (2H, m, CHNH), 5.13-5.18 (2H, m, CH_2=CH), 5.72-5.86 (1H, m, CH_2=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.3, 22.7 (CH_3), 30.9, 36.9 (CH_2), 55.8 (C), 59.8 (CH), 118.6 (CH_2=CH), 134.7 (CH_2=CH); LRMS (MALDI) *m/z* 310.241 (M+Na), 288.241 (M+H).

(4*R*,*R*$_S$)-*N*-*tert*-Butylsulfinyldodec-1-en-4-amine [(*R*$_C$,*R*$_S$)-3b]: Yield = 91%; colourless oil; $[\alpha]_D^{22}$ -50 (*c* 0.42, CH_2Cl_2); R_f 0.52 (hexane/EtOAc: 2/1); IR ν (film) 3220, 2925, 2854, 1456, 1362, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$), 1.20 [9H, s, $(CH_3)_3C$], 1.26-1.37 (12H, m, 6 × CH_2), 1.45-1.49 (2H, m, CH_2), 2.26-2.45 (2H, m, CH_2), 3.22-3.33 (2H, m, CHNH), 5.12-5.17 (2H, m, C*H*$_2$=CH), 5.71-5.85 (1H, m, CH_2=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6 (CH_3), 25.4, 29.2, 29.4, 29.5, 31.8, 34.9, 40.4 (CH_2), 54.8 (CH), 55.7 (C), 118.8 (*C*H$_2$=CH), 134.2 (CH_2=*C*H); LRMS (MALDI) *m/z* 310.241 (M+Na), 288.241 (M+H).

(3*R*,*R*$_S$)-*N*-*tert*-Butylsulfinyl-1-phenylhex-5-en-3-amine [(*R*$_C$,*R*$_S$)-3c]: Yield = 79%; colourless oil; $[\alpha]_D^{22}$ -44 (*c* 0.68, CH_2Cl_2); R_f 0.33 (hexane/EtOAc: 2/1); IR ν (film) 3237, 3062, 3025, 2926, 2863, 1454, 1363, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 [9H, s, $(CH_3)_3C$], 1.77-1.86 (2H, m, CH_2), 2.38-2.46 (2H, m, CH_2), 2.63-2.73 (2H, m, CH_2), 3.30-3.41 (2H, m, CHNH), 5.14-5.19 (2H, m, C*H*$_2$=CH), 5.71-5.83 (1H, m, CH_2=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (CH_3), 31.8, 36.8, 40.4 (CH_2), 54.5 (CH), 55.8 (C), 119.1 (*C*H$_2$=CH), 125.8, 128.3, 128.4, 133.8, 141.7 (ArC and CH_2=*C*H); LRMS (MALDI) *m/z* 302.173 (M+Na), 280.190 (M+H).

(1*S*,*R*$_S$)-*N*-*tert*-Butylsulfinyl-1-phenylbut-3-en-1-amine [(*S*$_C$,*R*$_S$)-3d]: Yield = 94%; colourless oil; $[\alpha]_D^{22}$ -148 (*c* 0.85, CH_2Cl_2); R_f 0.35 (hexane/EtOAc: 2/1); IR ν (film) 3223, 3064, 3030, 1454, 1363, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 [9H, s, $(CH_3)_3C$], 2.42-2.64 (2H, m, CH_2), 3.70 (1H, br s, NH), 4.45-4.49 (1H, m, C*H*NH), 5.15-5.21 (2H, m, C*H*$_2$=CH), 5.72-5.80 (1H, m, CH_2=C*H*), 7.26-7.34 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.4 (CH_2), 55.6 (C), 57.0 (CH), 119.2 (*C*H$_2$=CH), 127.4, 127.6, 128.4, 134.1, 141.6 (ArC and CH_2=*C*H); LRMS (MALDI) *m/z* 274.197 (M+Na), 252.209 (M+H).

(3*R*,*S*$_S$)-*N*-*tert*-Butylsulfinyl-2-methylhex-5-en-3-amine [(*R*$_C$,*S*$_S$)-3a]: Yield = 82%; Physical and spectroscopic data were found to be the same than for **(*S*$_C$,*R*$_S$)-(3a)**. $[\alpha]_D^{20}$ +77 (c 1.18, CH_2Cl_2).

(4*S*,*S*$_S$)-*N*-*tert*-Butylsulfinyldodec-1-en-4-amine [(*S*$_C$,*S*$_S$)-3b]: Yield = 86%; Physical and spectroscopic data were found to be the same than for **(*R*$_C$,*R*$_S$)-(3b)**. $[\alpha]_D^{20}$ +39 (c 0.51, CH_2Cl_2).

(3*S*,*S*$_S$)-*N*-*tert*-Butylsulfinyl-1-phenylhex-5-en-3-amine [(*S*$_C$,*S*$_S$)-3c]: Yield = 75%; Physical and spectroscopic data were found to be the same than for **(*R*$_C$,*R*$_S$)-(3c)**. $[\alpha]_D^{20}$ +46 (c 0.90, CH_2Cl_2).

(1*R*,*S*$_S$)-*N*-*tert*-Butylsulfinyl-1-phenylbut-3-en-1-amine [(*R*$_C$,*S*$_S$)-3d]: Yield = 90%; physical and spectroscopic data were found to be the same than for **(*S*$_C$,*R*$_S$)-(3d)**. $[\alpha]_D^{20}$ +117 (c 1.18, CH_2Cl_2).

(1*R*,*S*$_S$)-*N*-*tert*-Butylsulfinyl-3-methyl-1-phenylbut-3-en-1-amine [(*R*$_C$,*S*$_S$)-3e]: Yield = 82%; white solid; $[\alpha]_D^{22}$ +168 (*c* 1.02, CH_2Cl_2); mp 80-81 °C (hexane/ CH_2Cl_2); R_f 0.35 (hexane/EtOAc: 2/1); IR ν (KBr) 3294, 3068, 3025, 2868, 1454, 1365, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 [9H, s, $(CH_3)_3C$], 1.79 (3H, s, C*H*$_3$C=CH_2), 2.40-2.44 (2H, m, CH_2), 3.72 (1H, br s, NH), 4.51 (1H, dd, *J* = 9.0,

5.8 Hz, C*H*NH), 4.87 (1H, br s, C*H*H=C), 4.94 (1H, br s, C*H*H=C), 7.26-7.35 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.5 (CH_3), 47.8 (CH_2), 54.3 (CH), 55.5 (C), 114.9 (*C*H_2=CH), 127.4, 127.5, 128.4, 142.0, 142.1 (ArC and CH_2=*C*); LRMS (MALDI) *m/z* 288.151 (M+Na), 266.162 (M+H).

Preparation of *N tert*-butylsulfonylaminoepoxides 4. General procedure.

A mixture of the corresponding *N*-*tert*-butylsulfinylhomoallylamine **3** (1.0 mmol) and *m*-chloroperbenzoic acid (3.0 mmol, 0.518 g) in CH_2Cl_2 (3 mL) was stirred for 24 h at 25 °C. Then, the resulting mixture was hydrolyzed with water (15 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **4** as a 1:1 mixture of distereoisomers. For the next step of the reaction, the reaction crude was used without purification. Yields for compounds **4a-4h** are given in Table and for compound **4i** yield is given in the text. Physical and spectroscopic data follow.

(2*S*,1'*R)-*N*-*tert*-Butylsulfonyl-3-methyl-1-(oxiranyl)butan-2-amine (4a)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ -10 (*c* 1.35, CH_2Cl_2); R_f 0.44 (hexane/EtOAc: 2/1); IR ν (film) 3287, 2963, 2874, 1464, 1366, 1302, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-0.99 [12H, m, 2 × (C*H*$_3$)$_2$CH], 1.41, 1.42 [18H, 2s, 2 × $(CH_3)_3$C], 1.48-1.92 (4H, m, 2 × CH_2), 2.03-2.14 [2H, m, 2 × $(CH_3)_2$C*H*], 2.48-2.49 (1H, m, C*H*HO), 2.54-2.56 (1H, m, C*H*HO), 2.80 (1H, t, *J* = 4.6 Hz, CH*H*O), 2.85 (1H, t, *J* = 4.2 Hz, CH*H*O), 3.04-3.11 (2H, m, 2 × CHO), 3.47-3.59 (2H, m, 2 × C*H*NH), 4.00 (2H, br s, 2 × NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.1, 18.5, 18.6, 24.2, 24.3 (CH_3), 32.4, 32.45 (CH), 34.3, 35.3, 46.6, 47.6 (CH_2), 50.0, 50.1, 58.4, 58.7 (CH), 59.9 (C); LRMS (EI) *m/z* 206 (M^+-*i*-Pr, 16%), 86 (100), 72 (63), 57 (84); HRMS (EI) calcd for $C_8H_{16}NSO_3$ 206.0851, found 206.0831.

(2*R*,1'*R)-*N*-*tert*-Butylsulfonyl-1-(oxiranyl)decan-2-amine (4b)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ -4 (*c* 1.21, CH_2Cl_2); R_f 0.56 (hexane/EtOAc: 2/1); IR ν (film) 3280, 2926, 2855, 1456, 1430, 1304, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 [6H, m, 2 × CH_3), 1.26-1.38 (24H, m, 12 × CH_2), 1.40, 1.41 [18H, 2s, 2 × $(CH_3)_3$C], 1.56-1.68 (6H, m, 3 × CH_2), 1.88-1.99 (2H, m, CH_2), 2.49-2.55 (2H, m, 2 × C*H*HO), 2.79-2.85 (2H, m, 2 × CH*H*O), 3.05-3.09 (2H, m, 2 × CHO), 3.58-3.67 (2H, m, 2 × C*H*NH), 4.10 (1H, d, *J* = 9.2 Hz, NH), 4.18 (1H, d, *J* = 9.6 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_2), 24.2 (CH_3), 25.7, 25.8, 29.1, 29.4, 31.7, 36.2, 36.4, 38.6, 46.6, 47.2 (CH_2), 49.6, 53.8, 53.9 (CH), 59.7, 59.8 (C); LRMS (MALDI) *m/z* 342.206 (M+Na); LRMS (EI) *m/z* 262 (M^+-*t*-Bu, 7%), 206 (23), 142 (100), 86 (78), 57 (70).

(2*R*,1'*R)-*N*-*tert*-Butylsulfonyl-1-(oxiranyl)-4-phenylbutan-2-amine (4c)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ -13 (*c* 0.95, CH_2Cl_2); R_f 0.43 (hexane/EtOAc: 2/1); IR ν (film) 3284, 3069, 3026, 2984, 2930, 1454, 1429, 1303, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38, 1.40 [18H, 2s, 2 ×

$(CH_3)_3C$], 1.73-1.64 (2H, m, 3 × C*H*H), 1.97-2.06 (6H, m, 2 × CH*H*, 2 × CH_2), 2.48-2.55 (2H, m, 2 × C*H*HO), 2.64-2.85 (2H, m, 2 × CH*H*O, $PhCH_2$), 3.06-3.11 (2H, m, 2 × CHO), 3.67-3.74 (2H, m, 2 × C*H*NH), 3.98 (1H, d, *J* = 9.1 Hz, NH), 4.10 (1H, d, *J* = 9.8 Hz, NH), 7.19-7.31 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2 (CH_3), 32.0, 32.2, 37.8, 38.2, 38.4, 38.5, 46.5, 47.2 (CH_2), 49.4, 53.6, 53.7 (CH), 59.8, 59.9 (C), 126.1, 128.3, 128.5, 141.0, 141.1 (ArC); LRMS (EI) *m/z* 311 (M^+, 0.5%), 191 (11), 160 (14), 134 (51), 91 (48), 86 (71), 69 (27), 68 (29), 57 (100); HRMS (EI) calcd for $C_{16}H_{25}NSO_3$ 311.1555, found 311.1605.

(1*S*,1'*R)-*N*-*tert*-Butylsulfonyl-2-(oxiranyl)-1-phenylethanamine (4d)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ -40 (*c* 1.13, CH_2Cl_2); R_f 0.41 (hexane/EtOAc: 2/1); IR ν (film) 3288, 3070, 3029, 2983, 2931, 1455, 1426, 1302, 1127 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28, 1.29 [18H, 2s, 2 × $(CH_3)_3C$], 1.87-1.98 (2H, m, 2 × C*H*H), 1.97-2.06 (2H, m, 2 × CH*H*), 2.08-2.20 (2H, m, 2 × C*H*H), 2.41 (1H, dd, *J* = 4.8, 2.6 Hz, C*H*HO), 2.58 (1H, dd, *J* = 4.8, 2.6 Hz, C*H*HO), 2.71 (1H, t, *J* = 4.5 Hz, CH*H*O), 2.79 (1H, t, *J* = 4.5 Hz, CH*H*O), 2.91-2.95 (2H, m, 2 × CHO), 4.70-4.85 (2H, m, 2 × C*H*NH), 4.96 (1H, d, *J* = 8.7 Hz, NH), 5.14 (1H, d, *J* = 9.2 Hz, NH), 7.28-7.41 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1 (CH_3), 41.5, 42.2, 46.7, 47.1 (CH_2), 49.3, 49.8, 57.0, 57.4 (CH), 59.7, 59.8 (C), 126.1, 126.2, 127.5, 127.7, 128.8, 128.85, 141.4, 141.9 (ArC); LRMS (MALDI) *m/z* 306.166 (M+Na); LRMS (EI) *m/z* 283 (M^+, 1%), 226 (25), 162 (12), 119 (10), 106 (100), 77 (13), 57 (51).

(2*R*,1'*R)-*N*-*tert*-Butylsulfonyl-3-methyl-1-(oxiranyl)butan-2-amine (4e)**: Physical and spectroscopic data were found to be the same than for **(4a)**. $[\alpha]_D^{20}$ +23 (c 2.03, CH_2Cl_2).

(2*S*,1'*R)-*N*-*tert*-Butylsulfonyl-1-(oxiranyl)decan-2-amine (4f)**: Physical and spectroscopic data were found to be the same than for **(4b)**. $[\alpha]_D^{20}$ +3 (c 1.97, CH_2Cl_2).

(2*S*,1'*R)-*N*-*tert*-Butylsulfonyl-1-(oxiranyl)-4-phenylbutan-2-amine (4g)**: Physical and spectroscopic data were found to be the same than for **(4c)**. $[\alpha]_D^{20}$ +12 (c 0.74, CH_2Cl_2).

(1*R*,1'*R)-*N*-*tert*-Butylsulfonyl-2-(oxiranyl)-1-phenylethanamine (4h)**: Physical and spectroscopic data were found to be the same than for **(4d)**. $[\alpha]_D^{20}$ +31 (c 1.13, CH_2Cl_2).

(1*R*,1'*R)-*N*-*tert*-Butylsulfonyl-2-(1-methyloxiranyl)-1-phenylethanamine (4i)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ +3 (*c* 1.00, CH_2Cl_2); R_f 0.48 (hexane/EtOAc: 2/1); IR ν (film) 3286, 3068, 3028, 2984, 2925, 1455, 1422, 1303, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 [18H, s, 2 × $(CH_3)_3C$], 1.32, 1.43 (6H, 2s, 2 × CH_3), 1.95 (1H, dd, *J* = 14.4, 9.1 Hz, C*H*H), 2.06 (2H, dd, *J* = 7.3, 2.2 Hz, 2 × CH*H*), 2.22 (1H, dd, *J* = 14.2, 4.5 Hz, C*H*H), 2.31 (1H, d, *J* = 4.5 Hz, C*H*HO), 2.43 (1H, d, *J* = 4.5 Hz, C*H*HO), 2.68 (1H, d, *J* = 4.2 Hz, CH*H*O), 2.89 (1H, d, *J* = 4.2 Hz, CH*H*O), 4.64-4.80 (2H, m, 2 × C*H*NH), 5.26-5.31 (2H, m, 2 × NH), 7.24-7.38 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.3, 23.9 (CH_3), 45.8, 45.9 (CH_2), 53.3, 54.0 (CH_2), 55.3 , 55.8 (C), 56.1, 56.4 (CH), 59.5 (C), 126.2, 126.6,

127.2, 127.6, 128.6, 128.7, 142.2, 142.4 (ArC); LRMS (MALDI) *m/z* 320.158 (M+Na), 298.055(M+H); LRMS (EI) *m/z* 297 (1%), 226 (14), 176 (15), 159 (11), 135 (10), 106 (100), 91 (13), 77 (11), 57 (52); HRMS (EI) calcd for $C_{11}H_{14}NSO_3$ 240.0695 found 240.0730.

Preparation of *N-tert*-butylsulfonylpyrrolidin-3-ols 5, 6 and 7. General procedure.

A mixture of the reaction crude of the corresponding *N-tert*-butylsulfonylaminoepoxide **4** (1.0 mmol) and K_2CO_3 (3.0 mmol, 0.416 g) in *N*,*N*-dimethylformamide (5 mL) was stirred for 24 h at 100 °C. Then, the resulting mixture was hydrolyzed with water (5 mL), extrated with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **5** and **6**. Compound **7** was obtained as a 1:1 mixture of distereoisomers. Yields for compounds **5** and **6** are given in Table 1 and for compound **7** yield is given in the text. Physical and spectroscopic data follow.

(3*S*,5*S*)-*N-tert*-Butylsulfonyl-5-isopropylpyrrolidin-3-ol (5a): White solid; $[\alpha]_D^{22}$ -33 (*c* 0.83, CH_2Cl_2); mp 92-93 °C (hexane/CH_2Cl_2); R_f 0.55 (hexane/EtOAc: 1/1); IR ν (KBr) 3545-3497 (OH), 2960, 2873, 1465, 1389, 1311, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 6.9 Hz, C*H*$_3$CHCH$_3$), 0.93 (3H, d, *J* = 6.9 Hz, CH$_3$CHC*H*$_3$), 1.37 [9H, s, (CH$_3$)$_3$C], 1.56 (1H, dt, *J* = 12.4, 9.0 Hz, C*H*H), 2.07-2.20 [2H, m, CH*H*, (CH$_3$)$_2$C*H*], 2.42 (1H, br s, OH), 2.80 (1H, dd, *J* = 10.7, 9.1 Hz, C*H*HN), 3.83 (1H, dd, *J* = 10.2, 9.1 Hz, CH*H*N), 4.15-4.34 (2H, m, CHN, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 19.2, 24.4 (CH_3), 30.8 (CH), 32.1, 56.5 (CH_2), 60.4 (C), 62.9, 70.4 (C); LRMS (EI) *m/z* 249 (M^+, 0.1%), 86 (100), 68 (14), 57 (39); HRMS (EI) calcd for $C_8H_{16}NSO_3$ 206.0851, found 206.0837.

(3*R*,5*S*)-*N-tert*-Butylsulfonyl-5-isopropylpyrrolidin-3-ol (6a): White solid; $[\alpha]_D^{22}$ -37 (*c* 0.88, CH_2Cl_2); mp 72-73 °C (hexane/CH_2Cl_2); R_f 0.54 (hexane/EtOAc: 1/1); IR ν (KBr) 3455-3535 (OH), 2963, 2872, 1466, 1384, 1313, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, d, *J* = 6.7 Hz, C*H*$_3$CHCH$_3$), 0.86 (3H, d, *J* = 7.0 Hz, CH$_3$CHC*H*$_3$), 1.40 [9H, s, (CH$_3$)$_3$C], 1.67-1.76 (1H, m, C*H*H), 1.89-1.96 (1H, m, CH*H*), 2.12-2.23 [1H, m, (CH$_3$)$_2$C*H*], 2.53 (1H, br s, OH), 3.11 (1H, dd, *J* = 12.5, 2.8 Hz, C*H*HN), 3.69 (1H, dd, *J* = 12.4, 1.9 Hz, CH*H*N), 4.34-4.45 (2H, m, CHN, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.0, 24.4 (CH_3), 30.4 (CH), 33.4, 58.9 (CH_2), 60.5 (C), 63.4, 71.2 (C); LRMS (EI) *m/z* 249 (M^+, 0.5%), 86 (100), 68 (17), 57 (52); HRMS (EI) calcd for $C_8H_{16}NSO_3$ 206.0851, found 206.0836.

(3*S*,5*R*)-*N-tert*-Butylsulfonyl-5-octylpyrrolidin-3-ol (5b): Colourless oil; $[\alpha]_D^{22}$ -33 (*c* 0.40, CH_2Cl_2); R_f 0.58 (hexane/EtOAc: 1/1); IR ν (film) 3545-3320 (OH), 2962, 2913, 2856, 1464, 1390, 1309, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH$_2$), 1.23-1.32 (12H, m, 6 × CH_2), 1.38 [9H, s, (CH$_3$)$_3$C], 1.46-1.62 (2H, m, 2 × C*H*H), 1.82-1.94 (2H, m, CH*H*, O*H*), 2.27-2.36 (1H, m, CH*H*), 3.00 (1H, dd, *J* = 10.9, 6.8 Hz, C*H*HN), 3.86 (1H, dd, *J* = 10.8, 6.4

Hz, CH*H*N), 4.05-4.14 (1H, m, CHO), 4.36-4.39 (1H, m, CHN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 24.6 (CH_3), 26.0, 29.2, 29.5, 29.55, 31.8, 36.7, 38.8, 56.4 (CH_2), 59.2 (CH), 60.2 (C), 70.9 (CH); LRMS (MALDI) *m/z* 342.235 (M+Na), 320.195(M+H); LRMS (EI) *m/z* 319 (M^+, 0.5%), 206 (31), 142 (11), 86 (100), 68 (13), 57 (55); HRMS (EI) calcd for $C_{16}H_{33}NSO_3$ 319.2181, found 319.2218.

(3*R*,5*R*)-*N*-*tert*-Butylsulfonyl-5-octylpyrrolidin-3-ol (6b): Colourless oil; $[\alpha]_D^{22}$ -29 (*c* 0.49, CH_2Cl_2); R_f 0.52 (hexane/EtOAc: 1/1); IR ν (film) 3520-3340 (OH), 2964, 2915, 2855, 1466, 1390, 1312, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, *J* = 6.7 Hz, C*H*$_3$CH$_2$), 1.23-1.32 (12H, m, 6 × CH_2), 1.40 [9H, s, $(CH_3)_3$C], 1.57-1.66 (2H, m, 2 × C*H*H, O*H*), 1.83-1.87 (1H, m, CH*H*), 2.15-2.22 (1H, m, CH*H*), 3.22 (1H, dd, *J* = 12.1, 2.9 Hz, C*H*HN), 3.67 (1H, dd, *J* = 12.3, 1.7 Hz, CH*H*N), 4.29-4.37 (2H, m, CHN, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 24.5 (CH_3), 25.5, 29.2, 29.5, 29.55, 31.8, 36.3, 40.5, 58.0 (CH_2), 59.1 (CH), 60.1 (C), 71.2 (CH); LRMS (EI) *m/z* 319 (M^+, 1%), 206 (27), 142 (10), 86 (100), 68 (19), 57 (50).

(3*S*,5*R*)-*N*-*tert*-Butylsulfonyl-5-(2-phenylethyl)pyrrolidin-3-ol (5c): White solid; $[\alpha]_D^{22}$ -43 (*c* 0.90, CH_2Cl_2); mp 90-91 °C (hexane/CH_2Cl_2); R_f 0.46 (hexane/EtOAc: 1/1); IR ν (KBr) 3480-3230 (OH), 3068, 3025, 2975, 2875, 1454, 1298, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 [9H, s, $(CH_3)_3$C], 1.63-1.90 (3H, m, CH_2, OH), 2.19-2.38 (2H, m, CH_2), 2.59-2.65 (2H, m, CH_2), 3.04 (1H, dd, *J* = 10.9, 4.3 Hz, C*H*HN), 3.88 (1H, dd, *J* = 10.9, 6.4 Hz, CH*H*N), 4.11-4.21 (1H, m, CHO), 4.39-4.44 (1H, m, CHN), 7.17-7.31 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (CH_3), 32.4, 38.1, 38.9, 56.5 (CH_2), 58.9 (CH), 60.3 (C), 70.9 (CH), 125.9, 128.2, 128.4, 141.3 (ArC); LRMS (EI) *m/z* 311 (M^+, 0.2%), 206 (10), 191 (16), 86 (100), 68 (14), 57 (48); HRMS (EI) calcd for $C_{16}H_{25}NSO_3$ 311.1555, found 311.1582.

(3*R*,5*R*)-*N*-*tert*-Butylsulfonyl-5-(2-phenylethyl)pyrrolidin-3-ol (6c): Colourless oil; $[\alpha]_D^{22}$ -37 (*c* 1.00, CH_2Cl_2); R_f 0.39 (hexane/EtOAc: 1/1); IR ν (film) 3500-3280 (OH), 3069, 3023, 2972, 2877, 1452, 1297, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 [9H, s, $(CH_3)_3$C], 1.63-1.74 (2H, m, CH_2), 2.21-2.31 (3H, m, CH_2, OH), 2.60 (2H, t, *J* = 8.1 Hz, CH_2Ar), 3.26 (1H, dd, *J* = 12.3, 3.0 Hz, C*H*HN), 3.68 (1H, dd, *J* = 12.3, 3.0 Hz, CH*H*N), 4.37-4.45 (2H, m, CHN, CHO), 7.16-7.30 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (CH_3), 31.9, 38.0, 40.6, 58.1 (CH_2), 58.9 (CH), 60.3 (C), 71.1 (CH), 125.9, 128.2, 128.4, 141.3 (ArC); LRMS (EI) *m/z* 311 (M^+, 0.1%), 206 (14), 191 (13), 86 (100), 68 (17), 57 (56); HRMS (EI) calcd for $C_{16}H_{25}NSO_3$ 311.1555, found 311.1580.

(3*S*,5*S*)-*N*-*tert*-Butylsulfonyl-5-phenylpyrrolidin-3-ol (5d): White solid; $[\alpha]_D^{22}$ -45 (*c* 1.10, CH_2Cl_2); mp 113-114 °C (hexane/CH_2Cl_2); R_f 0.50 (hexane/EtOAc: 1/1); IR ν (KBr) 3520-3230 (OH), 3069, 3030, 2975, 2873, 1477, 1364, 1299, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 [9H, s, $(CH_3)_3$C], 1.99-2.17 (1H, m, C*H*H), 2.65-2.74 (1H, m, CH*H*), 3.30 (1H, dd, *J* = 11.1, 6.6 Hz, C*H*HN), 4.13 (1H, dd, *J* = 11.4, 5.0 Hz, CH*H*N), 4.32 (1H, br s, OH), 4.49-4.54 (1H, m, CHO), 5.20 (1H, dd, *J* = 8.3, 6.9 Hz,

CHN), 7.23-7.43 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (CH_3), 43.4, 57.7 (CH_2), 60.5 (C), 62.2, 71.2 (CH), 126.1, 127.5, 128.5, 143.1 (ArC); LRMS (MALDI) *m/z* 306.119 (M+Na); LRMS (EI) *m/z* 283 (M^+, 0.3%), 204 (19), 163 (37), 162 (33), 144 (10), 119 (100), 118 (75), 105 (13), 91 (28), 77 (14), 57 (56).

(3*R*,5*S*)-*N*-*tert*-Butylsulfonyl-5-phenylpyrrolidin-3-ol (6d): White solid; $[\alpha]_D^{22}$ -32 (*c* 1.32, CH_2Cl_2); mp 129-130 °C (hexane/CH_2Cl_2); R_f 0.39 (hexane/EtOAc: 1/1); IR ν (KBr) 3500-3240 (OH), 3072, 3032, 2976, 2929, 2872, 1479, 1365, 1296, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 [9H, s, $(CH_3)_3C$], 2.00-2.11 (1H, m, C*H*H), 2.40 (1H, br s, OH), 2.48-2.56 (1H, m, CH*H*), 3.53 (1H, dd, *J* = 12.3, 3.0 Hz, C*H*HN), 3.95 (1H, dd, *J* = 12.3, 1.3 Hz, CH*H*N), 4.48-4.56 (1H, m, CHO), 5.37 (1H, t, *J* = 8.2 Hz, CHN), 7.23-7.35 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (CH_3), 44.9, 59.4 (CH_2), 60.3 (C), 62.4, 71.4 (CH), 127.2, 127.5, 128.5, 142.9 (ArC); LRMS (MALDI) *m/z* 306.108 (M+Na); LRMS (EI) *m/z* 283 (M^+, 0.3%), 204 (19), 163 (37), 162 (33), 144 (10), 119 (100), 118 (75), 105 (13), 91 (28), 77 (14), 57 (56); HRMS (EI) calcd for $C_{14}H_{21}NSO_3$ 283.1242, found 283.1299.

(3*R*,5*R*)-*N*-*tert*-Butylsulfonyl-5-isopropylpyrrolidin-3-ol (5e): Physical and spectroscopic data were found to be the same than for **(5a)**. $[\alpha]_D^{20}$ +34 (c 0.79, CH_2Cl_2).

(3*S*,5*R*)-*N*-*tert*-Butylsulfonyl-5-isopropylpyrrolidin-3-ol (6e): Physical and spectroscopic data were found to be the same than for **(6a)**. $[\alpha]_D^{20}$ +38 (c 1.26, CH_2Cl_2).

(3*R*,5*S*)-*N*-*tert*-Butylsulfonyl-5-octylpyrrolidin-3-ol (5f): Physical and spectroscopic data were found to be the same than for **(5b)**. $[\alpha]_D^{20}$ +33 (c 1.08, CH_2Cl_2).

(3*S*,5*S*)-*N*-*tert*-Butylsulfonyl-5-octylpyrrolidin-3-ol (6f): Physical and spectroscopic data were found to be the same than for **(6b)**. $[\alpha]_D^{20}$ +35 (c 0.89, CH_2Cl_2).

(3*R*,5*S*)-*N*-*tert*-Butylsulfonyl-5-(2-phenylethyl)pyrrolidin-3-ol (5g): Physical and spectroscopic data were found to be the same than for **(5c)**. $[\alpha]_D^{20}$ +44 (c 0.58, CH_2Cl_2).

(3*S*,5*S*)-*N*-*tert*-Butylsulfonyl-5-(2-phenylethyl)pyrrolidin-3-ol (6g): Physical and spectroscopic data were found to be the same than for **(6c)**. $[\alpha]_D^{20}$ +35 (c 0.89, CH_2Cl_2).

(3*R*,5*R*)-*N*-*tert*-Butylsulfonyl-5-phenylpyrrolidin-3-ol (5h): Physical and spectroscopic data were found to be the same than for **(5d)**. $[\alpha]_D^{20}$ +29 (c 1.00, CH_2Cl_2).

(3*S*,5*R*)-*N*-*tert*-Butylsulfonyl-5-phenylpyrrolidin-3-ol (6h): Physical and spectroscopic data were found to be the same than for **(6d)**. $[\alpha]_D^{20}$ +37 (c 0.32, CH_2Cl_2).

(3*R,5*R*)-*N*-*tert*-Butylsulfonyl-3-methyl-5-phenylpyrrolidin-3-ol (7)**: Diastereomeric mixture; colourless oil; $[\alpha]_D^{22}$ +19 (*c* 1.00, CH_2Cl_2); R_f 0.53 (hexane/EtOAc: 1/1); IR ν (film) 3410-3250 (OH), 3068, 3029, 1455, 1382, 1296, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07, 1.10 [18H, 2s, 2 × $(CH_3)_3C$], 1.44, 1.50 (6H, 2s, 2 × CH_3), 1.91 (1H, dd, *J* = 13.2, 10.0 Hz, C*H*H), 2.14-2.22 (2H, m, C*H*H,

O*H*), 2.37-2.52 (3H, m, 2 × CH*H*, O*H*), 3.41 (2H, dd, *J* = 15.0, 12.0 Hz, 2 × C*H*HN), 3.82-3.87 (2H, m, 2 × CH*H*N), 5.13 (1H, t, *J* = 7.9 Hz, CHN), 5.38 (1H, dd, *J* = 10.0, 7.5 Hz, CHN), 7.24-7.43 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 23.9, 24.0, 25.7 (CH_3), 49.1, 49.9 (CH_2), 60.1, 60.3 (C), 62.2, (CH_2), 62.9, 63.4 (CH), 63.6 (CH_2), 76.5, 77.2 (C), 127.4, 127.5, 127.6, 127.8, 128.4, 128.45, 142.8 (ArC); LRMS (MALDI) *m/z* 320.069 (M+Na); LRMS (EI) *m/z* 297 (M^+, 0.5%), 218 (11), 176 (62), 147 (17), 119 (100), 118 (94), 104 (21), 91 (36), 77 (10), 57 (84); HRMS (EI) calcd for $C_{15}H_{23}NSO_3$ 297.1399 found 297.1436.

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