New Diastereoselective Route to 2-Substituted *cis*-(2*S*,5*S*)- and *trans*-(2*S*,5*R*)-5-Alkylpyrrolidines as Indolizidine and Pyrrolizidine Scaffolds

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A new and short stereoselective route to the synthesis of enantiopure *cis*-2,5-disubstituted pyrrolidines as indolizidine or pyrrolizidine scaffolds has been developed. The method, which uses (*S*)-pyroglutamic acid as a chiral starting material, is based on the ring opening of *N*-protected γ-lactams by alkyl phenyl sulfone carbanions, followed by desulfonylation and reductive amination of alkyl γ-amino ketones. The diastereoselectivity depends on the substitution of the starting γ-lactams, and on the alkyl group of the phenyl sulfone. Total *cis* diastereoselectivity was observed in the formation of *tert*-butyl 5-alkylprolinates.

Introduction

Pyrrolidines are very important constituents in many living organisms,[1,2] present in plants and several animals either themselves, or as components of more complex alkaloids. Among them, several indolizidines and pyrrolizidines bearing alkyl chains in the position α to the nitrogen exert control and protective functions against other living organisms, and are biologically significant.[3] Of the examples shown in Figure 1, the 3,5-dialkylindolizidine monomorine I (**1**) is a trail pheromone of the Pharaoh ant *Monomorium pharaonis* L.,[4] whereas indolizidine (−)-223AB (**2**) is a constituent of the poison frog *Dendrobates histrionicus*.[5] Notably, its less widespread *cis*-3,5-dialkylated analogue **3** has been isolated both from amphibians and from the *Solenopsis Diplorhoptrum* worker ant.[6] Pyrrolizidine alkaloids such as (−)-xenovenine (**4**) have been found in the venom of ants belonging to the same *Solenopsis* genus[7] or to *Monomorium* species.[8]

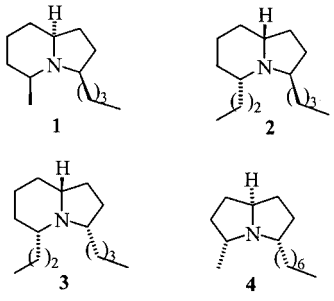
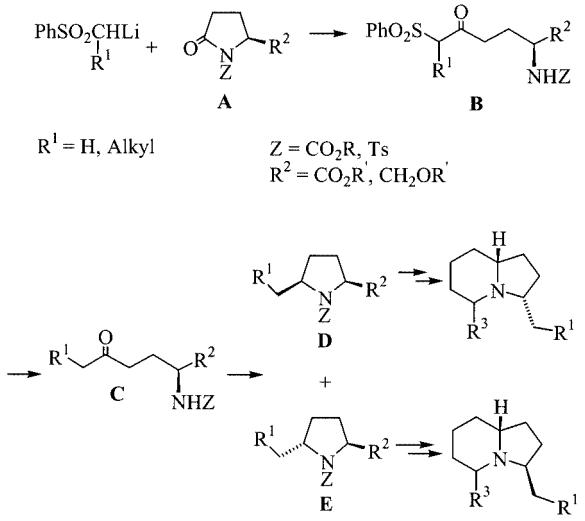


Figure 1. Some examples of naturally occurring 3,5-dialkylindolizidines and pyrrolizidines

Among the strategies to synthesize these bicyclic alkaloids so far developed, cyclization steps of conveniently 2,5-disubstituted pyrrolidines[9] are well documented.[10−15] A new synthetic route to 5-alkylprolinols starting from either of the available enantiomers of pyroglutamic acid, as outlined in the general Scheme 1, is therefore described here. This route, illustrated with the (2*S*) enantiomers used in this work, involves ring opening of the derived 2-substituted *N*-(alkoxycarbonyl)pyrrolidinones (**A**) with the anions of alkyl phenyl sulfones (here methyl and decyl phenyl sulfones), followed by desulfonylation of the resulting β-keto sulfones **B** and subsequent cyclization of **C** by reductive amination.



Scheme 1. General scheme for the synthesis of 2,5-disubstituted pyrrolidines as indolizidine scaffolds

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Indeed, the *cis* (**D**, R^2 = CH_2OH) or *trans* (**E**, R^2 = CH_2OH) 5-alkyl-2-(hydroxymethyl)pyrrolidines could be excellent intermediates in the synthesis of indolizidines and pyrrolizidines related to **1**−**4**, natural or not, since the hydroxymethyl group can be converted into appropriate functions for formation of the bicyclic skeletons.[11−15] This approach is of special interest, due to the relative rarity of synthetic routes to 2,5-*cis* configurations in pyrrolidine substituents in the literature.[11,15,16]

Results and Discussion

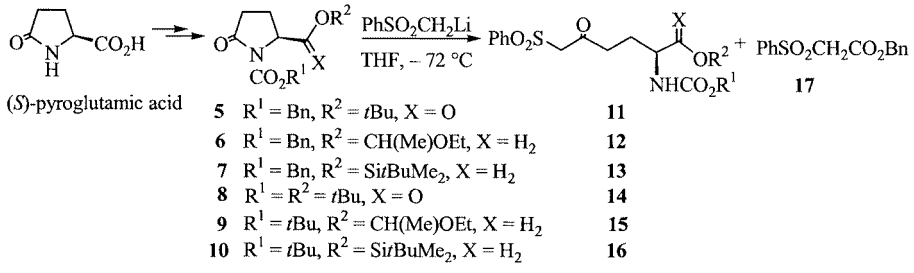
The first key step is based on the fact that the presence of *N*-protecting alkoxycarbonyl (or sulfonyl) groups is well known to enhance considerably the electrophilic character of lactam carbonyl groups, due to their electron-withdrawing aptitude.[17−19] With respect to carbon nucleophilic additions, ring openings of such pyrrolidinones with Grignard reagents or aryllithium are well demonstrated.[19] However, only a few examples accounted for the reactivity of alkyl phenyl sulfone anions in nucleophilic addition to activated β-,[20] γ-[21] and δ-lactam carbonyls.[22] We therefore recently reported[23] reactions between deprotonated methyl phenyl sulfone and several functionalised *N*-(alkoxycarbonyl)pyrrolidinones derived from (*S*)-pyroglutamic acid, and the use of one of the resulting β-keto sulfones in the synthesis of *tert*-butyl *cis*-5-alkylprolinates. Here we complete these preliminary results, showing that the β-keto sulfones constitute useful intermediates in the synthesis of *cis*-5-alkyl-2-(hydroxymethyl)pyrrolidines.

The ring-opening reactions (Scheme 2) were carried out by employing $PhSO_2Me$/*n*BuLi as nucleophilic agent[24] in anhydrous THF at −72 °C.

Some assays were conducted with *tert*-butyl *N*-(benzyloxycarbonyl)pyroglutamate (**5**)[25] in order to determine the ratio of the carbanion needed for an efficient conversion. On going from the use of one equivalent of the sulfone carbanion to the use of two equivalents the yield of the β-keto sulfone **11** increased as expected, (49 to 74%, respectively). This is probably due to the fact that the generated β-keto sulfone is more acidic and can reprotonate the lithio(phenylsulfonyl)methane,[20,26] but no evidence for lactam opening by a carbanion of the resulting β-keto sulfone was found. Unlike in the reported additions to esters,[27] the use of methyl phenyl sulfone dilithium was shown to be less efficient in our case, producing a more complex mixture. Further results obtained with monolithiated methyl phenyl sulfone and other protected γ-lactams **6** to **10**[28] derived from (*S*)-pyroglutaminol are summarized in Table 1.

Some benzyl (phenylsulfonyl)acetate (**17**) was formed in the reactions of **5**−**7,** through monocarbanion attack of the *N*-benzyloxycarbonyl groups (Entries 1−3). This partial *N*-protecting group displacement was completely avoided with the sterically hindered derivatives **8**−**10**. Thus, protection with *N*-Boc groups, much less amenable to nucleophilic attack, resulted in improved yields of the corresponding β-keto sulfones (Table 1, cf. Entries 1 and 4, 2 and 5, 3 and 6).

Because of the presence of ester functions at C-2, racemization could occur with derivatives **5** and **8**. For this reason, it was important to evaluate the enantiopurity of the derived β-keto sulfones, principally of compound **11**, which was used further in the synthesis of *cis*-2,5-disubstituted pyrrolidines. Two independent methods were employed in order to determine the enantiomeric excess of **11**. ^1H NMR spectra in the presence of [Eu(hfc)$_3$] as chiral shift reagent and chiral HPLC, with comparison with the corresponding racemate synthesized in the same way, indicated the absence

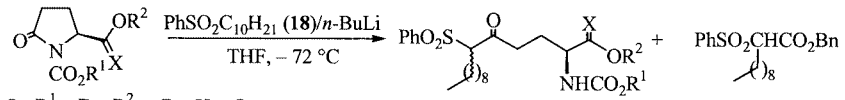


Scheme 2. Ring opening of *N*-alkoxycarbonyl-γ-lactams by lithio(phenylsulfonyl)methane

Table 1. Ring opening of *N*-alkoxycarbonyl-γ-lactams by lithio(phenylsulfonyl)methane (THF, −72 °C)

Entry	Lactam	R^1	R^2	X	β-Keto sulfone (%)	$PhSO_2CH_2CO_2R^1$ (%)
1	**5**	Bn	*t*Bu	O	**11** (74)	**17** (21)
2	**6**	Bn	EVE[a]	H_2	**12** (58)	**17** (25)
3	**7**	Bn	TBS	H_2	**13** (62)	**17** (18)
4	**8**	*t*Bu	*t*Bu	O	**14** (95)	not observed
5	**9**	*t*Bu	EVE	H_2	**15** (84)	not observed
6	**10**	*t*Bu	TBS	H_2	**16** (90)	not observed

[a] EVE = CH(Me)OEt.



5 R^1 = Bn, R^2 = *t*Bu, X = O — **19**
6 R^1 = Bn, R^2 = CH(Me)OEt, X = H_2 — **20**
7 R^1 = Bn, R^2 = Si*t*BuMe$_2$, X = H_2 — **21**
8 R^1 = R^2 = *t*Bu, X = O — **22**
9 R^1 = *t*Bu, R^2 = CH(Me)OEt, X = H_2 — **23**
10 R^1 = *t*Bu, R^2 = Si*t*BuMe$_2$, X = H_2 — **24**

25

Scheme 3. Ring opening of *N*-alkoxycarbonyl-γ-lactams by lithio(phenylsulfonyl)decane

of racemization [*ee* > 95% (^{1}H NMR), *ee* 99% (chiral HPLC)].[29a]

We next turned our attention towards the preparation of β-keto sulfones substituted with long alkyl chains, as models for the introduction of the alkyl substituents present in the alkaloids **1**−**4**. With the phenylsulfonyl methyl ketones **11** to **16** in hand, *C*-alkylations with alkyl halides could be envisioned for this purpose, but these reactions could be complicated by *O*-alkylations, as previously observed with β-keto sulfoxides.[30] Consequently, the opening of *N*-alkoxycarbonyl-γ-lactams with the monolithiated carbanion of decyl phenyl sulfone **18**[31] was investigated as an example that might be extendable to other long alkyl chains. The sulfone **18** was prepared in high yield (91%) by alkylation of methyl phenyl sulfone with 1-bromononane in THF at low temperature. It was used to open the lactams **5** to **10**, by the same procedure as used for methyl phenyl sulfone, and afforded β-keto sulfones **19** to **24** as diastereomeric mixtures (Scheme 3). The results are summarized in Table 2.

Table 2. Ring opening of *N*-alkoxycarbonyl-γ-lactams by lithio(phenylsulfonyl)decane (THF, −72 °C)

Entry	Lactam	β-Keto sulfone (%)	$PhSO_2CH(R)CO_2R^1$ R = C_9H_{19} (%)
1	**5**	**19** (69)	**25** (7)
2	**6**	**20** (58)	**25** (7)
3	**7**	**21** (50)	**25** (10)
4	**8**	**22** (72)	–
5	**9**	**23** (75)	–
6	**10**	**24** (74)	–

The *N*-protecting group displacement of *N*-(benzyloxycarbonyl)-γ-lactams **5**−**7** to afford **25** was minimized with decyl phenyl sulfone, but the yields of the ketones are to some extent lower than in the case of methyl phenyl sulfone. This could be due to the difference in acidity between these two sulfones,[32] to steric factors or to a retroaddition process, since appreciable quantities of starting lactams were recovered, even when the conversion seemed complete by TLC analysis of the reaction mixture.

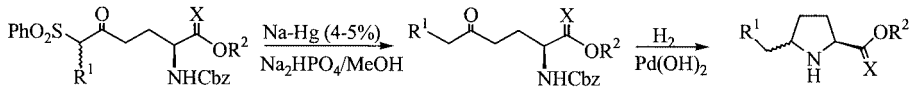
Hydrogenation of 2-substituted Δ^1-pyrroline intermediates is known to afford *cis*-2,5-disubstituted pyrrolidines,[16,33] particularly *cis*-5-alkylprolinates.[34] Thus, in order to develop a stereoselective and efficient route to *cis*-2,5-disubstituted pyrrolidines, the sulfones **11**−**13** and **19**−**21** were desulfonylated with 4−5% sodium amalgam in MeOH at room temperature, giving rise to the corresponding alkyl ketones **26**−**31** in moderate to high yields. Subsequent reductive amination of these ketones under *N*-deprotection conditions (H_2, 1 atm), with $Pd(OH)_2$ as catalyst, afforded the corresponding pyrrolidines **32**−**37** in high yields (Table 3, Scheme 4).

In the reaction affording *tert*-butyl 5-alkylprolinates, the absence of racemization during desulfonylation with sodium amalgam was verified by chiral HPLC of **26** (*ee* 98.5%).[29b] As expected, the reductive aminations of the *tert*-butyl esters **26** and **29** were found to be completely stereoselective, giving rise exclusively to the *cis*-5-disubstituted prolinates **32** and **35**, in 91 and 93% yields, respectively. However, the generally high stereoselectivity in the formation of disubstituted pyrrolidines by reductive amination under hydrogen[33,35] was not observed in the cases of the 2-hydroxymethyl derivatives **27**, **28** and **30**, which produced mixtures, the *cis* diastereomers always being the major ones (Table 4).

The compositions of the mixtures depend on the alkyl groups on the ketones (CH_2R^1), better stereoselectivity being found in the case of 5-decylpyrrolidines [R^1 = $(CH_2)_8Me$] than in the case of 5-methylpyrrolidines (R^1 =

Table 3. Desulfonylation of β-keto sulfones followed by reductive amination

Entry	Sulfone (1 equiv.)	Equiv. Na/equiv. Na_2HPO_4	Time (min)	Ketone yield (%)	$H_2/Pd(OH)_2$ time (h)	Pyrrolidine yield (%)
1	**11**	3.1−5.0	75	**26** (58)	5	**32** (91)
2	**12**	2.7−5.0	45	**27** (63)	6	**33** (76)
3	**13**	3.0−5.2	50	**28** (65)	6	**34** (86)
4	**19**	2.9−4.2	75	**29** (85)	5	**35** (93)
5	**20**	3.0−4.0	75	**30** (92)	6	**36** (68)
6	**21**	3.0−4.0	75	**31** (92)	6	**37** (84)



11 R^1 = H, R^2 = *t*Bu, X = O
12 R^1 = H, R^2 = CH(Me)OEt, X = H_2
13 R^1 = H, R^2 = Si*t*BuMe$_2$, X = H_2
19 R^1 = $(CH_2)_8CH_3$, R^2 = *t*Bu, X = O
20 R^1 = $(CH_2)_8CH_3$, R^2 = CH(Me)OEt, X = H_2
21 R^1 = $(CH_2)_8CH_3$, R^2 = Si*t*BuMe$_2$, X = H_2

26 R^1 = H, R^2 = *t*Bu, X = O — **32**
27 R^1 = H, R^2 = CH(Me)OEt, X = H_2 — **33**
28 R^1 = H, R^2 = Si*t*BuMe$_2$, X = H_2 — **34**
29 R^1 = $(CH_2)_8CH_3$, R^2 = *t*Bu, X = O — **35**
30 R^1 = $(CH_2)_8CH_3$, R^2 = CH(Me)OEt, X = H_2 — **36**
31 R^1 = $(CH_2)_8CH_3$, R^2 = Si*t*BuMe$_2$, X = H_2 — **37**

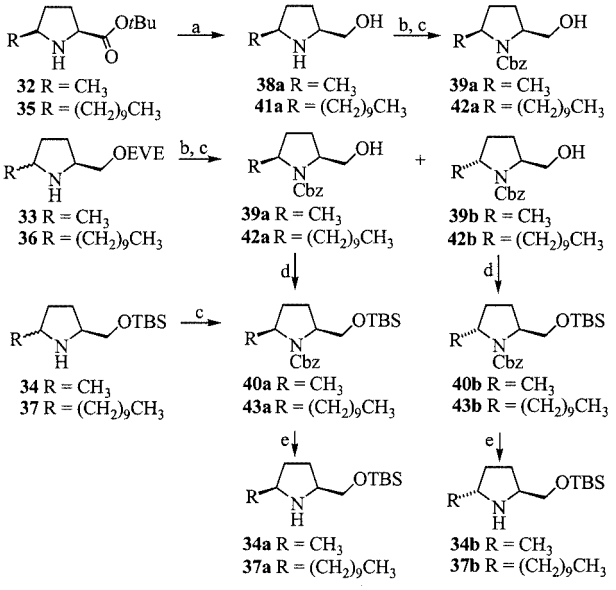
Scheme 4. Desulfonylation of β-keto sulfones followed by reductive amination

Table 4. Diastereoselectivity in the reductive amination step

Entry	Alkyl ketone	X	R^1	R^2	2,5-Dialkylpyrrolidine (*cis*/*trans* %)
1	**26**	O	H	*t*Bu	**32** (98:0)
2	**27**	H_2	H	EVE	**33** (57:43)
3	**28**	H_2	H	TBS	**34** (76:24)
4	**29**	O	$(CH_2)_8Me$	*t*Bu	**35** (> 98:0)
5	**30**	H_2	$(CH_2)_8Me$	EVE	**36** (71:29)
6	**31**	H_2	$CH_2)_8Me$	TBS	**37** (95:5)

H; cf. Entries 2 and 5 and Entries 3 and 6). The stereoselectivity also depends on the substituents at C-2. Steric factors can explain the minor stereoselectivity encountered with the compounds **27** and **30**, in which the flexibility of the extended 1-ethoxyethoxymethyl group at C-2 (CH_2OEVE) might favour the exposure of the more hindered face, allowing the insertion of H_2.

The diastereoselectivity in the formation of 5-methylpyrrolidines was directly evaluated by NMR, because the separation of the diastereomers was difficult. In order to ascertain the configurations deduced from ^{1}H and ^{13}C NMR spectroscopic data,[12a,36] several chemical correlations were carried out, as reported below (Scheme 5).



Reagents: a): $LiAlH_4$, THF; b): H_3O^+, Cl^-; c): Na_2CO_3/CbzCl, CH_2Cl_2-H_2O; d): TBSCl, CH_2Cl_2-DMF; e): H_2/$Pd(OH)_2$, MeOH.

Scheme 5. Chemical correlations between the 2,5-disubstituted pyrrolidines

LAH reduction of the ester **32** exclusively afforded the previously described *cis* primary alcohol **38a**.[15a] This polar compound was rather difficult to handle and readily carbonated due to its basic character, and so was converted into the *N*-benzyloxycarbonyl derivative **39a**. On the other hand, the mixture of diastereomers **33** was *O*-deprotected by acid hydrolysis and transformed into the separable *N*-benzylcarbamates *cis*-**39a** and *trans*-**39b**. It is noteworthy that long reaction times were needed in order to avoid kinetic effects in the formation of these carbamates.[37] The compound **39b**[13] and its enantiomer *ent*-**39b**[14] [absolute configuration (2*R*,5*S*)] have been already described by two groups, but opposite signs of optical rotation have been successively reported in the two cases. This controversy is now resolved, *ent*-**39b** being dextrorotatory.[14a] The configurations of **39a** and **39b** thus being fully established, each diastereomer was protected, as the *tert*-butyldimethylsilyl derivatives **40a** and **40b**, respectively, and these were *N*-deprotected to give **34a** and **34b** (Scheme 5) for comparison with the same compounds resulting from reductive amination of **28**.

The 5-decylpyrrolidines **35**−**37** were correlated according to the same scheme. In the ^{1}H NMR of Cbz derivatives **39** and **42**, the methylene signals of the benzyl groups corroborate previous observations[36] and indicate the relative 2,5 configurations of these pyrrolidines, with good agreement between **42a** and **39a** and between **42b** and **39b**. The methylene protons of the *tert*-butyldimethylsilyloxymethyl groups in **34** and **37** also show very different patterns in the *cis* (**a**) and *trans* (**b**) diastereomers and are indicative of their relative 2,5 configurations. However, as none of 5-decyl-pyrrolidines was known, the configuration of **41a** was ascertained by a single-crystal X-ray analysis of its hydrobromide. Figure 2 gives an overview of the molecule. The chemical correlations achieved from the alcohol **42a** and from its C-5 epimer **42b**, according to the Scheme 5, allowed confirmation of the composition of the diastereomer mixture given for **36** and **37**.

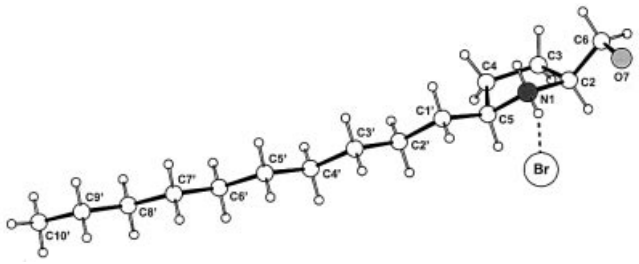


Figure 2. X-ray structure analysis of **41a** hydrobromide: ORTEP drawing of one molecule of the unit cell.

Conclusion

In conclusion, the opening of *N*-(alkoxycarbonyl)pyrrolidinones derived from (*S*)-pyroglutamic acid with lithiated alkyl phenyl sulfones afforded functionalized acyclic β-keto sulfones in good yields. These synthetic intermediates could be useful, particularly in the diastereoselective preparation of *cis*-2,5-disubstituted pyrrolidines. The stereoselectivity increased when large nucleophiles were employed to open the lactam ring and when conformationally restricted substituents were present. Thus, *cis*-5-alkyl prolinates were obtained with complete diastereoselectivity in only three steps, starting from the easily available (*S*)-*tert*-butyl pyroglutamate, and carbamates derived from pyroglutaminol gave better results when *O*-protected with TBS than with the flexible 1-ethoxyethyl group. Synthetic precursors of indolizidine and pyrrolizidine alkaloids could be obtained in this way and the addition of more complex phenyl sulfones can be also envisioned.

Experimental Section

General: Melting points were determined with a Büchi B-540 apparatus and were uncorrected. Optical rotations were measured with a Jasco P-1010 polarimeter and the concentrations were given in g/100 mL. IR spectra (film, $CHCl_3$) were recorded with a Perkin−Elmer Spectrum BX (FT) instrument. ^{1}H NMR spectra ($CDCl_3$, $CHCl_3$ δ = 7.26 ppm) were obtained with a Bruker AM-300 machine. ^{13}C NMR spectra were also recorded with the AM-300 (75.0 MHz, $CDCl_3$ centred at 77.0 ppm). Mass spectra and high-resolution mass spectra were measured with Navigator (ESI), Micromass LC-TOF or Automass Thermo-Finnigan spectrometers. Chromatography was performed on silica gel (SDS, 230−400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 +366). "Usual workup" means that the organic layer was dried with magnesium sulfate and filtered and the solvents were evaporated under vacuum

***tert*-Butyl (2*S*)-2-[(Benzyloxycarbonyl)amino]-5-oxo-6-(phenylsulfonyl)hexanoate (11):** *n*BuLi (1.6 M solution in hexanes, 1.20 mL, 1.92 mmol) was added to a solution of methyl phenyl sulfone (311 mg, 1.99 mmol) in dry THF (6.0 mL), stirred at −72 °C under argon. After the mixture had been stirred at −72 °C for 0.5 h, a solution of lactam **5** (316 mg, 0.99 mmol) in THF (4.0 mL) was added dropwise. The mixture was stirred at the same temperature for 1.75 h, and a saturated aqueous solution of NH_4Cl (5 mL) was then added. The cooling bath was removed, water (10 mL) was added, and the products were extracted with CH_2Cl_2. The residue obtained after usual workup was purified by chromatography (eluent: heptane/Et_2O/MeOH, 50:50:1, v/v) to give benzyl (phenylsulfonyl)acetate (**17**) (61 mg, 21%), recovered methyl phenyl sulfone (134 mg, 43%) and the keto sulfone **11** (347 mg, 74%) as a colourless, thick oil. $[\alpha]_D^{23} = -5.8$ (c = 1.40, $CHCl_3$). IR: $\tilde{\nu}$ = 3366, 2979, 2935, 1722, 1523, 1449, 1369, 1323, 1154, 1052 cm^{-1}. ^{1}H NMR: δ = 7.86 (d, J = 8.1 Hz, 2 H, SO_2Ph), 7.66 (dd, 1 H, SO_2Ph), 7.55 (dd, $J \approx J'$ = 7.0 Hz, 2 H, SO_2Ph), 7.34 (m, 5 H, CH_2Ph), 5.38 (br. d, J = 7.5 Hz, 1 H, NH), 5.08 (2d, J = 12.1 Hz, 2 H, PhCH_2), 4.19 (m, 1 H, 2-H), 4.11 (s, 2 H, 6-H_2), 2.78 (m, 2 H, 4-H_2), 2.15 (m, 1 H, 3-Ha), 1.82 (m, 1 H, 3-Hb), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 197.02 (CO), 170.76 (CO_2), 155.99 (NCO_2), 138.66 (qC, Ar), 136.19 (qC, Ar), 134.23, 129.29, 128.48, 128.18, 128.05 (CH, Ar), 82.60 (qC, *t*Bu), 66.93, 66.84, (PhCH_2, C-6), 53.28 (C-2), 40.06 (C-4), 27.88 (CH_3, *t*Bu), 26.46 (C-3) ppm. MS (ESI): *m*/*z* (%) = 514 (20) $[M + K]^+$, 498 (100) $[M + Na]^+$, 467, 458, 442, 339. HRMS (ESI): $C_{24}H_{29}NO_7SNa^+$ $[MNa]^+$: 498.1562; found 498.1545.

The racemate (±)-**11** was synthesized in the same way in order to evaluate the enantiomeric excess. The ^{1}H NMR spectrum of (±)-**11** in $CDCl_3$ (0.025 mmol/mL) in the presence of $[Eu(hfc)_3]$ as chiral shift reagent (0.0015 mmol/mL) showed splitting of several signals (PhCH_2, 2-H, 6-H_2). No splitting of these signals was detected with **11** under the same conditions, indicating an *ee* > 95%; for chiral HPLC conditions, see ref.[29].

The β-keto sulfones **12**−**16** and **19**−**24** were prepared by the same procedure.

Benzyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxo-5-(phenylsulfonyl)-pentylcarbamate (12): Starting lactam: 0.45 mmol, yield 58% of a colourless oil (two diastereomers, owing to the stereogenic centre in the ethoxyethoxy group), after purification by chromatography (eluent heptane/Et_2O/MeOH, 40:60:1, v/v). $[\alpha]_D^{23} = -20.8$ (c = 0.72, $CHCl_3$). IR: $\tilde{\nu}$ = 3369, 2979, 2931, 1719, 1527, 1448, 1322, 1239, 1150, 1136 cm^{-1}. ^{1}H NMR: δ = 7.87 (d, 2 H, SO_2Ph), 7.67 (dd, 1 H, SO_2Ph), 7.56 (dd, J = 7.9, J' = 7.3 Hz, 2 H, SO_2Ph), 7.35 (m, 5 H, CH_2Ph), 5.16 (br. d, J = 8.9 Hz, 0.5 H, NH), 5.08 (2d, J = 12.4 Hz, 2 H, PhCH_2), 5.03 (br. d, J = 8.9 Hz, 0.5 H, NH), 4.65 (2 q, 1 H, OCHO), 4.11 (s, 2 H, 5-H_2), 3.73 (m, 1 H, 1-H), 3.58 (m, 2 H, OCH_2), 3.44 (m, 2 H, OCH_2), 2.76 (br. m, $J \approx J'$ = 6.8 Hz, 2 H, 3-H_2), 1.79 (m, 2 H, 2-H_2), 1.27 (d, J = 5.3 Hz, 3 H, CHCH_3), 1.18 (t, J = 7.0 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 197.70 (CO), 156.26 (NCO_2), 138.76 (qC, Ar), 136.44 (qC, Ar), 134.16, 129.25, 128.50, 128.19, 128.13, 128.02 (CH, Ar), 99.99, 99.70 (OCHO), 67.15, 66.83, 66.74, 66.70 (PhCH_2, C-5), 65.77 (OCH_2), 61.39, 61.13 (OCH_2), 49.99, 49.96 (C-1), 40.80 (C-3), 25.86 (C-2), 19.65, 19.58 (CHCH_3), 15.20, 15.16 (CH_2CH_3) ppm. MS (ESI): *m*/*z* (%) = 516 (30) $[M + K]^+$, 500 (100) $[M + Na]^+$.

Benzyl (1*S*)-1-[(1-*tert*-Butyldimethylsilyl)oxymethyl]-4-oxo-5-(phenylsulfonyl)pentylcarbamate (13): Starting lactam: 0.12 mmol, yield 62% of a colourless, thick oil, after chromatography (eluent: CH_2Cl_2). $[\alpha]_D^{23} = -30.8$ (c = 0.50, $CHCl_3$). IR: $\tilde{\nu}$ = 3370, 2953, 2930, 2857, 1718, 1524, 1448, 1323, 1253, 1153, 838 cm^{-1}. ^{1}H NMR: δ = 7.87 (d, J = 7.7 Hz, 2 H, SO_2Ph), 7.66 (dd, 1 H, SO_2Ph), 7.55 (dd, $J \approx J'$ = 7.2 Hz, 2 H, SO_2Ph), 7.34 (m, 5 H, CH_2Ph), 5.07 (2d, J = 12.6 Hz, 2 H, PhCH_2), 4.96 (br. d, J = 8.1 Hz, 1 H, NH), 4.11 (s, 2 H, 5-H_2), 3.59 (m, 3 H, OCH_2, 1-H), 2.74 (m, 2 H, 3-H_2), 1.76 (m, 2 H, 2-H_2), 0.87 (s, 9 H, *t*Bu), 0.03 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 197.78 (CO), 156.28 (NCO_2), 138.77 (qC, Ar), 136.49 (qC, Ar), 134.16, 129.25, 128.50, 128.21, 128.13, 128.05 (CH, Ar), 66.87, 66.68 (PhCH_2, C-5), 65.04 (OCH_2), 51.42 (C-1), 40.81 (C-3), 25.81 (CH_3, *t*Bu), 25.47 (C-2), 18.21 (qC,

*t*Bu), −5.56 ($SiMe_2$) ppm. MS (ESI): *m/z* (%) = 558 (20) $[M + K]^+$, 542 (100) $[M + Na]^+$, 540.

***tert*-Butyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-oxo-6-(phenylsulfonyl)hexanoate (14):** Starting lactam: 2.0 mmol, 95% as colourless crystals, after chromatography (eluent: heptane/Et_2O/MeOH, 50:50:1, v/v). M.p. 101−102 °C. $[\alpha]_D^{22} = -2.1$ (*c* = 0.69, $CHCl_3$). IR: $\tilde{\nu}$ = 3380, 2979, 2933, 1718, 1449, 1368, 1323, 1251, 1154 cm^{-1}. ^1H NMR: δ = 7.87 (d, *J* = 8.3 Hz, 2 H, SO_2Ph), 7.67 (dd, 1 H, SO_2Ph), 7.56 (dd, *J* ≈ *J′* = 6.8 Hz, 2 H, SO_2Ph), 5.09 (br. d, *J* = 6.8 Hz, 1 H, NH), 4.17 (2d, *J* = 12.1 Hz, 2 H, 6-H_2), 4.10 (m, 1 H, 2-H), 2.79 (m, 2 H, 4-H_2), 2.11 (m, 1 H, 3-Ha), 1.78 (m, 1 H, 3-Hb), 1.44 (s, 9 H, *t*Bu), 1.42 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 197.10 (CO), 171.15 (CO_2), 155.51 (NCO_2), 138.70 (qC, Ar), 134.24, 129.31, 128.20 (CH, Ar), 82.34 (qC, *t*Bu), 79.84 (qC, *t*Bu), 66.98 (C-6), 52.84 (C-2), 40.16 (C-4), 28.24 (CH_3, *t*Bu), 27.91 (CH_3, *t*Bu), 26.65 (C-3) ppm. MS (ESI): *m/z* (%) = 480 (20) $[M + K]^+$, 464 (100) $[M + Na]^+$, 442 $[MH]^+$, 408, 349. $C_{21}H_{31}NO_7S$ (441.53): calcd. C 57.12, H 7.08, N 3.17, S 7.26; found C 57.16, H 7.01, N 3.02, S 6.96.

***tert*-Butyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxo-5-(phenylsulfonyl)-pentylcarbamate (15):** Starting lactam: 0.20 mmol, 84% as colourless crystals (two diastereomers), after chromatography (eluent: heptane/Et_2O/MeOH, 60:40:1). M.p. 60−63 °C. $[\alpha]_D^{23} = -24.8$ (*c* = 0.50, $CHCl_3$). IR: $\tilde{\nu}$ = 3379, 2978, 2932, 1711, 1516, 1448, 1323, 1247, 1155 cm^{-1}. ^1H NMR: δ = 7.88 (d, *J* = 8.1 Hz, 2 H, SO_2Ph), 7.67 (dd, 1 H, SO_2Ph), 7.56 (dd, *J* ≈ *J′* = 7.5 Hz, 2 H, SO_2Ph), 4.89 (br. d, *J* = 8.3 Hz, 0.5 H, NH), 4.75 (br. d, *J* = 8.7 Hz, 0.5 H, NH), 4.64 (m, 1 H, OCHO), 4.18 (2 d, *J* = 13.8 Hz, 2 H, 5-H_2), 3.52, 3.45 (2 m, 5 H, 2 OCH_2, 1-H), 2.77 (m, 2 H, 3-H_2), 1.78 (2 m, 2 H, 2-H_2), 1.42 (s, 9 H, *t*Bu), 1.27 (d, *J* = 5.3 Hz, 3 H, $CHCH_3$), 1.18 (2 t, *J* = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 197.81, 197.78 (CO), 155.80 (NCO_2), 138.80 (qC, Ar), 134.18, 129.28, 128.23 (CH, Ar), 100.09, 99.71 (OCHO), 79.34, 79.29 (qC, *t*Bu), 67.54, 67.01, 66.92 (C-5, OCH_2), 61.43, 61.13 (OCH_2), 49.33, 49.26 (C-1), 40.85 (C-3), 28.33 (CH_3, *t*Bu), 26.06 (C-2), 19.71, 19.62 ($CHCH_3$), 15.22, 15.18 (CH_2CH_3) ppm. MS (ESI): *m/z* (%) = 482 (15) $[M + K]^+$, 466 (100) $[M + Na]^+$, 410. $C_{21}H_{33}NO_7S$ (443.55): calcd. C 56.86, H 7.50, N 3.16, S 7.23; found C 57.07, H 7.52, N 3.01, S 7.02.

***tert*-Butyl (1*S*)-1-[(*tert*-Butyldimethylsilyl)oxymethyl]-4-oxo-5-(phenylsulfonyl)pentylcarbamate (16):** Starting lactam: 0.10 mmol, 90% as colourless crystals, after chromatography (eluent: CH_2Cl_2). M.p. 74−76 °C. $[\alpha]_D^{23} = -33.7$ (*c* = 0.60, $CHCl_3$). IR: $\tilde{\nu}$ = 3388, 2930, 2857, 1709, 1499, 1448, 1391, 1323, 1252, 1156, 1112, 838 cm^{-1}. ^1H NMR: δ = 7.89 (d, *J* = 8.1 Hz, 2 H, SO_2Ph), 7.67 (dd, 1 H, SO_2Ph), 7.57 (dd, *J* = 7.2 Hz, 2 H, SO_2Ph), 4.67 (br. d, *J* = 8.0 Hz, 1 H, NH), 4.19 (2 d, *J* = 13.5 Hz, 2 H, 5-H_2), 3.55 (m, 3 H, OCH_2, 5-H), 2.77 (m, 2 H, 3-H_2), 1.80 (m, 1 H, 2-Ha), 1.67 (m, 1 H, 2-Hb), 1.43 (s, 9 H, CO_2*t*Bu), 0.88 (s, 9 H, Si*t*Bu), 0.04 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 197.90 (CO), 155.88 (NCO_2), 138.81 (qC, Ar), 134.18, 129.28, 128.25 (CH, Ar), 79.32 (qC, CO_2*t*Bu), 67.05 (C-5), 65.16 (OCH_2), 50.77 (C-1), 40.87 (C-3), 28.36 (CH_3, CO_2*t*Bu), 25.84 (CH_3, Si*t*Bu), 25.68 (C-2), 18.25 (qC, Si*t*Bu), −5.53 ($SiMe_2$) ppm. MS (ESI): *m/z* (%) = 524 (15) $[M + K]^+$, 508 (100) $[M + Na]^+$. $C_{23}H_{39}NO_6SSi$ (485.68): calcd. C 56.87, H 8.09, N 2.88, S 6.60; found C 56.87, H 8.07, N 2.75, S 6.51.

***tert*-Butyl (2*S*)-2-[(Benzyloxycarbonyl)amino]-5-oxo-6-(phenylsulfonyl)pentadecanoate (19):** Starting lactam: 0.98 mmol, yield 69% of a colourless oil (two diastereomers), after chromatography (eluent: heptane/Et_2O, 2:1). $[\alpha]_D^{23} = +2.92$ (*c* = 1.45, $CHCl_3$). IR: $\tilde{\nu}$ = 3368, 2927, 2856, 1721, 1523, 1449, 1369, 1310, 1153 cm^{-1}. ^1H NMR: δ = 7.75 (m, 2 H, SO_2Ph), 7.66 (br. dd, 1 H, SO_2Ph), 7.53 (2dd, *J* = 7.9, *J′* = 7.3 Hz, 2 H, SO_2Ph), 7.36 (m, 5 H, CH_2Ph), 5.35 (br. d, 1 H, NH), 5.11 (br. s, 2 H, $PhCH_2$), 4.24 (m, 1 H, 2-H), 4.05 (m, 1 H, 6-H), 2.98 (m, 1 H, 4-Ha), 2.61 (m, 1 H, 4-Hb), 2.14 (m, 1 H), 1.90 (m, 1 H), 1.83 (m, 2 H, 7-H_2), 1.47 (s, 9 H, *t*Bu), 1.18 [m, 14 H, $(CH_2)_7$], 0.86 (br. t, *J* = 6.6 Hz, 3 H, 15-H_3) ppm. ^{13}C NMR: δ = 201.48, 201.45 (CO), 170.85 (CO_2), 155.89 (NCO_2), 136.35, 136.21 (qC, Ar), 134.25, 129.35, 129.05, 129.03, 128.52, 128.17, 128.08 (CH, Ar), 82.61, 82.57 (qC, *t*Bu), 75.19, 75.13 (C-6), 66.97 ($PhCH_2$), 53.56, 53.46 (C-2), 41.01 (C-4), 31.77, 29.33, 29.17, 29.14, 29.06 (CH_2), 27.94 (CH_3, *t*Bu), 27.06, 26.86, 26.45, 26.25, 22.60 (CH_2), 14.06 (C-15) ppm. MS (ESI): *m/z* (%) = 640 (60) $[M + K]^+$, 624 (100) $[M + Na]^+$.

Benzyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxo-5-(phenylsulfonyl)-tetradecylcarbamate (20): Starting lactam: 0.77 mmol, yield 58% of a crystalline solid (four diastereomers), after chromatography (eluent heptane/Et_2O, 2:1). M.p. 47−49 °C. IR: $\tilde{\nu}$ = 3369, 2927, 2856, 1718, 1526, 1448, 1310, 1236, 1146, 1083 cm^{-1}. ^1H NMR: δ = 7.76 (br. d, 2 H, SO_2Ph), 7.66 (m, 1 H, SO_2Ph), 7.53 (m, 2 H, SO_2Ph), 7.35 (m, 5 H, CH_2Ph), 5.10 (m, 2.5 H, $PhCH_2$, NH), 4.99 (br. d, *J* = 9.2 Hz, 0.5 H, NH), 4.66 (br. q, 1 H, CHO), 4.06 (br. s, 1 H, 5-H), 3.77 (m, 1 H, 1-H), 3.59, 3.45 (2 m, 4 H, 2 OCH_2), 2.97 (m, 1 H, 3-Ha), 2.61 (m, 1 H, 3-Hb), 1.83 (m, 4 H, 2-H_2, 6-H_2), 1.28 (d, *J* = 5.3 Hz, 3 H, $CHCH_3$), 1.18 [m, 17 H, $(CH_2)_7$, CH_2CH_3], 0.86 (t, *J* = 6.6 Hz, 3 H, 14-H_3) ppm. ^{13}C NMR: δ = 202.07, 202.04 (CO), 156.08 (NCO_2), 136.50, 136.47 (qC, Ar), 134.20, 134.18, 129.39, 129.00, 128.50, 128.09, 128.02 (CH, Ar), 99.99, 99.74 (OCHO), 75.17, 75.06 (C-5), 67.12, 66.96, 66.78, 66.70 ($PhCH_2$, OCH_2), 61.38, 61.15 (OCH_2), 50.53, 50.42, 50.29, 50.19 (C-1), 42.03, 41.92 (C-3), 31.78, 29.35, 29.20, 29.17, 29.15, 29.07, 27.15, 27.10, 26.87, 26.85, 25.89, 25.84, 25.59, 22.61 (CH_2), 19.70, 19.63 ($CHCH_3$), 15.25, 15.22 (CH_2CH_3), 14.06 (C-14) ppm. MS (ESI): *m/z* (%) = 642 (15) $[M + K]^+$, 624 (100) $[M + Na]^+$, 439. $C_{33}H_{49}NO_7S$ (603.80): calcd. C 65.64, H 8.18, N 2.32, S 5.31; found C 65.64, H 7.97, N 2.26, S 5.12.

Benzyl (1*S*)-1-[(1-*tert*-Butyldimethylsilyl)oxymethyl]-4-oxo-5-(phenylsulfonyl)tetradecylcarbamate (21): Starting lactam: 1.19 mmol, yield 56% of a colourless oil (two diastereomers), after chromatography (eluent: CH_2Cl_2). IR: $\tilde{\nu}$ = 3438, 3375, 2954, 2928, 2856, 1720, 1511, 1466, 1448, 1310, 1253, 1148, 838 cm^{-1}. ^1H NMR: δ = 7.75 (m, 2 H, SO_2Ph), 7.66 (m, 1 H, SO_2Ph), 7.54 (2dd, *J* = 7.3, *J′* = 7.0 Hz, 2 H, SO_2Ph), 7.35 (m, 5 H, CH_2Ph), 5.10 (br. s, 2 H, $PhCH_2$), 4.93 (br. s, 1 H, NH), 4.07 (br. dd, *J* = 11.3, *J′* = 7.0 Hz, 1 H, 5-H), 3.66 (m, 1 H, 1-H), 3.62 (m, OCH_2), 2.95 (m, 1 H, 3-Ha), 2.61 (m, 1 H, 3-Hb), 1.83 (m, 4 H, 2-H_2, 6-H_2), 1.19 [m, 14 H, $(CH_2)_7$], 0.88 (m, 12 H, *t*Bu, 14-H_3), 0.04 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 202.15, 202.12 (CO), 155.14, 155.09 (NCO_2), 136.47 (qC, Ar), 134.20, 129.39, 128.99, 128.52, 128.50, 128.10, 128.05 (CH, Ar), 75.16, 75.05 (C-5), 66.67 ($PhCH_2$), 64.99, 64.86 (OCH_2), 51.88, 51.65 (C-1), 42.05, 41.90 (C-3), 31.79, 29.35, 29.17, 29.15, 29.07, 27.10, 26.88, 26.84 (CH_2), 25.84 (CH_3, *t*Bu), 25.44, 25.15, 22.61 (CH_2), 18.24 (qC, *t*Bu), 14.06 (C-14), −5.53 ($SiMe_2$) ppm. MS (ESI): *m/z* (%) = 684 (22) $[M + K]^+$, 668 (100) $[M + Na]^+$.

***tert*-Butyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino-5-oxo-6-(phenylsulfonyl)pentadecanoate (22):** Starting lactam: 0.37 mmol, yield 72% of a colourless oil (two diastereomers), after chromatography (eluent: CH_2Cl_2). $[\alpha]_D^{25} = +2.0$ (*c* = 0.74, $CHCl_3$). IR: $\tilde{\nu}$ = 3381, 2928, 2856, 1715, 1504, 1448, 1367, 1320, 1310, 1251, 1153 cm^{-1}. ^1H NMR: δ = 7.76 (m, 2 H, SO_2Ph), 7.68 (dd, 1 H, SO_2Ph), 7.56 (dd, *J* = 7.9, *J′* = 7.7 Hz, 2 H, SO_2Ph), 5.06 (br. s, 1 H, NH), 4.14 (br. s, 1 H, 2-H), 4.06 (m, 1 H, 6-H), 2.98 (m, 1 H, 4-Ha), 2.63 (m, 1 H, 4-Hb), 2.09 (m, 1 H, 3-Ha), 1.89 (m, 1 H, 3-Hb), 1.83 (m, 2 H,

7-H_2), 1.47 (s, 9 H, *t*Bu), 1.44 (2 s, 9 H, *t*Bu), 1.20 [m, 14 H, $(CH_2)_7$], 0.86 (t, J = 6.6 Hz, 3 H, 15-H_3) ppm. ^{13}C NMR: δ = 201.56, 201.50 (CO), 171.27 (CO_2), 155.47 (NCO_2), 136.43 (qC, Ar), 134.25, 129.35, 129.04 (CH, Ar), 82.31, 82.27 (qC, *t*Bu), 79.83 (qC, *t*Bu), 75.22 (C-6), 53.19, 53.02 (C-2), 41.09 (C-4), 31.75, 29.33, 29.20, 29.13, 29.07 (CH_2), 28.29 (CH_3, *t*Bu), 27.96 (CH_3, *t*Bu), 27.05, 26.87, 26.62, 26.31 (CH_2), 14.05 (C-15) ppm. MS (EI): *m*/*z* (%) = 568 [MH^+, weak], 512, 466, 456, 412, 394, 366, 207, 57 (100).

***tert*-Butyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxo-5-(phenylsulfonyl)-tetradecylcarbamate (23):** Starting lactam: 0.14 mmol, yield 75% of a colourless oil (four diastereomers), after chromatography (eluent: CH_2Cl_2). IR: ṽ = 3383, 2927, 2856, 1713, 1448, 1309, 1148, 1083 cm^{-1}. ^{1}H NMR: δ = 7.76 (m, 2 H, SO_2Ph), 7.67 (dd, 1 H, SO_2Ph), 7.55 (dd, J = 7.7, J' = 7.3 Hz, 2 H, SO_2Ph), 4.82, 4.72 (2 br. d, J = 8.7 Hz, 1 H, NH), 4.67 (m, 1 H, OCHO), 4.07 (dd, J = 14.5, J' = 7.2 Hz, 1 H, 5-H), 3.65, 3.44 (2 m, 5 H, 2 OCH_2, 1-H), 2.97 (m, 1 H, 3-Ha), 2.63 (m, 1 H, 3-Hb), 1.82 (m, 4 H, 2-H_2, 6-H_2), 1.44, 1.43 (2 s, 9 H, *t*Bu), 1.29 (d, J = 5.5 Hz, 3 H, CHCH_3), 1.19 [m, 17 H, $(CH_2)_7$, CH_2CH_3], 0.86 (t, J = 6.6 Hz, 3 H, 14-H_3) ppm. ^{13}C NMR: δ = 202.14, 202.09 (CO), 155.73, 155.64 (NCO_2), 136.50 (qC, Ar), 134.20, 129.39, 129.01 (CH, Ar), 100.05, 99.71 (CHO), 79.30 (qC, *t*Bu), 75.20, 75.10 (C-5), 67.51, 67.27, 66.95, 66.71 (OCH_2), 61.36, 61.13 (OCH_2), 49.86, 49.72, 49.55, 49.47 (C-1), 42.04, 41.90 (C-3), 31.77, 29.34, 29.23, 29.14, 29.08 (CH_2), 28.36 (CH_3, *t*Bu), 27.16, 27.07, 26.86, 25.99, 25.69, 22.60 (CH_2), 19.76, 19.65 (CHCH_3), 15.26, 15.24 (CH_2CH_3), 14.05 (C-14) ppm.

***tert*-Butyl (1*S*)-1-[(1-*tert*-Butyldimethylsilyl)oxymethyl]-4-oxo-5-(phenylsulfonyl)tetradecylcarbamate (24):** Starting lactam: 0.12 mmol, yield 74% of a colourless oil (two diastereomers), after chromatography (eluent: CH_2Cl_2). IR: ṽ = 3448, 3390, 2955, 2927, 2856, 1716, 1498, 1447, 1365, 1320, 1309, 1251, 1172, 1151, 837 cm^{-1}. ^{1}H NMR: δ = 7.77 (br. d, 2 H, SO_2Ph), 7.67 (br. dd, 1 H, SO_2Ph), 7.55 (dd, J = 7.7, J' = 7.3 Hz, 2 H, SO_2Ph), 4.65 (br. s, 1 H, NH), 4.09 (dd, J = 14.1, J' = 7.0 Hz, 1 H, 5-H), 3.58 (m, 3 H, OCH_2, 1-H), 2.95 (m, 1 H, 3-Ha), 2.62 (m, 1 H, 3-Hb), 1.81 (m, 4 H, 2-H_2, 6-H_2), 1.44, 1.43 (2 s, 9 H, CO_2*t*Bu), 1.19 [m, 14 H, $(CH_2)_7$], 0.89 (s, 9 H, Si*t*Bu), 0.86 (t, J = 7.0 Hz, 3 H, 14-H_3), 0.05, 0.04 (2 s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 202.23, 202.18 (CO), 155.70, 155.65 (NCO_2), 136.52, 136.47 (qC, Ar), 134.18, 129.38, 128.98 (CH, Ar), 79.23 (qC, CO_2*t*Bu), 75.19, 75.08 (C-5), 65.13, 64.96 (OCH_2), 51.26, 50.96 (C-1), 42.06, 41.88 (C-3), 31.76, 29.34, 29.22, 29.16, 29.13, 29.07, 29.06 (CH_2), 28.37 (CH_3, CO_2*t*Bu), 27.14, 27.06, 26.86 (CH_2), 25.86 (CH_3, Si*t*Bu), 25.58, 25.23, 22.60 (CH_2), 18.26 (qC, Si*t*Bu), 14.05 (C-14), −5.48 (SiMe), −5.52 (SiMe) ppm. MS (EI): *m*/*z* (%) = 612 [$(MH)^+$, weak], 538, 498, 454, 366, 116 (100).

***tert*-Butyl (2*S*)-2-[(Benzyloxycarbonyl)amino]-5-oxohexanoate (26):** Sodium amalgam (4−5%, 840 mg, 1.64 mmol) and Na_2HPO_4 (379 mg, 2.67 mmol) were added under argon to a solution of β-keto sulfone **11** (254 mg, 0.534 mmol) in dry MeOH (5.0 mL). The solution was stirred vigorously for 75 min at room temp., and CH_2Cl_2 (10 mL) and water (5 mL) were then added. The aqueous phase was extracted three times with CH_2Cl_2, and after usual workup, the residue was purified by chromatography (eluent: heptane/Et_2O/MeOH, 50:50:1) to give the methylketone **26** (103 mg, 58%) as a colourless oil, together with recovered starting material (54 mg, 21%). Compound **26**: $[\alpha]_D^{23}$ = +6.7 (c = 0.45, $CHCl_3$). IR: ṽ = 3343, 2978, 2932, 1731, 1714, 1531, 1455, 1369, 1225, 1154, 1059 cm^{-1}. ^{1}H NMR: δ = 7.35 (m, 5 H, Ph), 5.35 (br. d, J = 7.7 Hz, 1 H, NH), 5.10 (2d, J = 11.9 Hz, 2 H, PhCH_2), 4.22 (m, 1 H, 2-H), 2.51 (m, 2 H, 4-H_2), 2.13 (m, 4 H, masked 3-Ha, 6-H_3), 1.86 (m, 1 H, 3-Hb), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 207.53 (CO), 171.10 (CO_2), 155.97 (NCO_2), 136.26 (qC, Ar), 128.51, 128.17, 128.10 (CH, Ar), 82.39 (qC, *t*Bu), 66.93 (PhCH_2), 53.81 (C-2), 39.28 (C-4), 29.98 (C-6), 27.95 (CH_3, *t*Bu), 26.73 (C-3) ppm. MS (ESI): *m*/*z* (%) = 358 (59) [M + Na]$^+$, 302 (100), 227. HRMS (ESI): $C_{18}H_{25}NO_5Na$ [MNa]$^+$: 358.1586; found 358.1605.

The ketones **27**, **28**, and **29**−**31** were prepared in the same manner.

Benzyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxopentylcarbamate (27): Starting keto sulfone: 0.80 mmol, 63% as an oil (two diastereomers), after chromatography (eluent: heptane/Et_2O/MeOH, 50:75:1). $[\alpha]_D^{23}$ = −15.3 (c = 0.67, $CHCl_3$). IR: ṽ = 3333, 2978, 2934, 1715, 1530, 1240, 1135, 1083, 1060 cm^{-1}. ^{1}H NMR: δ = 7.35 (m, 5 H, Ph), 5.09 (br. s, 1 H, PhCH, + 0.5 H, masked NH), 5.07 (br. d, J = 9.0 Hz, 0.5 H, NH), 4.79 (2 q, J = 5.3 Hz, 0.5 H, OCHO), 4.65 (2 q, J = 5.3 Hz, 0.5 H, OCHO), 4.61, 4.48 (2 d, J = 11.9 Hz, 1 H, PhCH), 3.76 (m, 1 H, 1-H), 3.58, 3.45 (2 m, 4 H, 2 OCH_2), 2.50 (m, 2 H, 3-H_2), 2.10 (2 s, 3 H, 5-H_3), 1.81 (m, 2 H, 2-H_2), 1.35, 1.27 (2 d, J = 5.3 Hz, 3 H, CHCH_3), 1.17 (t, J = 7.0 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 208.28 (CO), 156.14 (NCO_2), 137.99, 137.95, 136.47 (qC, Ar), 128.45, 128.37, 128.06, 128.02, 127.99, 127.56 (CH, Ar), 99.92, 99.67, 99.49, 99.35 (OCHO), 67.66, 67.39, 67.14, 66.86, 66.61 (PhCH_2, OCH_2), 61.30, 61.03 (OCH_2), 50.61, 50.53 (C-1), 40.05 (C-3), 29.94 (C-5), 26.10 (C-2), 19.65, 19.58, 19.51 (CHCH_3), 15.20, 15.17 (CH_2CH_3) ppm. MS (EI): *m*/*z* (%) = 338 (0.25) [MH]$^+$, 292, 248, 234, 190, 156, 134, 107, 91 (100).

Benzyl (1*S*)-[1-(*tert*-Butyldimethylsilyl)oxymethyl]-4-oxopentylcarbamate (28): Starting keto sulfone: 0.29 mmol, yield 65% of a colourless oil, after chromatography (eluent: heptane/Et_2O/MeOH, 50:50:1. $[\alpha]_D^{23}$ = −24.7 (c = 0.60, $CHCl_3$). IR: ṽ = 3343, 3336, 2955, 2930, 2857, 1716, 1530, 1252, 837 cm^{-1}. ^{1}H NMR: δ = 7.36 (m, 5 H, Ph), 5.10 (2d, J = 12.1 Hz, 2 H, PhCH_2), 4.45 (br. d, J = 7.9 Hz, 1 H, NH), 3.66 (m, 1 H, 1-H), 3.62 (br. s, 2 H, OCH_2), 2.51 (m, 2 H, 3-H_2), 2.12 (s, 3 H, 5-H_3), 1.80 (m, 2 H, 2-H_2), 0.87 (s, 9 H, *t*Bu), 0.04 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 208.41 (CO), 156.18 (NCO_2), 136.55 (qC, Ar), 128.48, 128.07, 128.04 (CH, Ar), 66.60, 65.11 (PhCH_2, OCH_2), 52.03 (C-1), 40.09 (C-3), 29.97 (C-5), 25.82 (CH_3, *t*Bu), 25.73 (C-2), 18.22 (qC, *t*Bu), − 5.54 ($SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 418 (82) [M + K]$^+$, 403, 402 (100) [M + Na]$^+$, 390.

***tert*-Butyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-oxopentadecanoate (29):** Starting keto sulfone: 0.47 mmol, yield 85% of a colourless oil, after chromatography (eluent: heptane/Et_2O, 2:1). $[\alpha]_D^{23}$ = +5.6 (c = 1.43, $CHCl_3$). IR: ṽ = 3347, 2926, 2855, 1718, 1524, 1455, 1368, 1252, 1223, 1156 cm^{-1}. ^{1}H NMR: δ = 7.34 (m, 5 H, Ph), 5.36 (br. d, J = 8.0 Hz, 1 H, NH), 5.09 (2 d, J = 12.6 Hz, 2 H, PhCH_2), 4.21 (m, $J \approx J'$ = 8.1, J'' = 4.9 Hz, 1 H, 2-H), 2.46 (m, 2 H, 4-H_2), 2.36 (dd, $J \approx J' \approx$ 7.4 Hz, 2 H, 6-H_2), 2.11 (m, 1 H, 3-Ha), 1.87 (m, 1 H, 3-Hb), 1.53 (m, 2 H, 7-H_2), 1.45 (br. s, 9 H, *t*Bu), 1.25 [br. s, 14 H, $(CH_2)_7$], 0.87 (br. t, J = 7.0 Hz, 3 H, 15-H_3) ppm. ^{13}C NMR: δ = 210.00 (CO), 171.13 (CO_2), 155.94 (NCO_2), 136.26 (qC, Ar), 128.47, 128.11, 128.05 (CH, Ar), 82.27 (qC, *t*Bu), 66.87 (PhCH_2), 53.87 (C-2), 42.89, 38.30 (C-4, C-6), 31.84, 29.52, 29.43, 29.36, 29.27, 29.17 [$(CH_2)_6$], 27.92 (CH_3, *t*Bu), 26.66 (C-3), 23.77, 22.63 [$(CH_2)_2$], 14.06 (C-15) ppm. MS (ESI): *m*/*z* (%) = 500 (12) [M + K]$^+$, 484 (100) [M + Na]$^+$, 428.

Benzyl (1*S*)-1-[(1-Ethoxyethoxy)methyl]-4-oxotetradecylcarbamate (30): Starting keto sulfone: 0.42 mmol, yield 92% of a white, crystalline solid (two diastereomers), after chromatography (eluent: heptane/Et_2O, 2:1). M.p. 59−61 °C. $[\alpha]_D^{24}$ = −13.3 (c = 0.60, $CHCl_3$). IR: ṽ = 3316, 2923, 2851, 1703 (sh), 1691, 1545, 1061 cm^{-1}. ^{1}H NMR: δ = 7.34 (m, 5 H, Ph), 5.08 (br. s, 2 H, PhCH_2

+ 0.5 H, masked NH), 4.99 (br. d, 0.5 H, NH), 4.65 (q, J = 5.4 Hz, 1 H, OCHO), 3.73 (m, 1 H, 1-H), 3.57, 3.43 (2 m, 4 H, 2 OCH_2), 2.46 (m, 2 H, 3-H_2), 2.36 (dd, $J \approx J' \approx$ 7.4 Hz, 2 H, 5-H_2), 1.81 (m, 2 H, 2-H_2), 1.52 (m, 2 H, 6-H_2), 1.26 (d, 3 H, CHCH_3), 1.24 [m, 14 H, $(CH_2)_7$], 1.17 (2 t, J = 7.1 Hz, 3 H, CH_2CH_3), 0.87 (t, J = 7.0 Hz, 3 H, 14-H_3) ppm. ^{13}C NMR: δ = 210.82 (CO), 156.14 (NCO_2), 136.54 (qC, Ar), 128.46, 128.06, 128.04, 127.98 (CH, Ar), 99.90, 99.66 (OCHO), 67.11, 66.88, 66.57 (PhCH_2, OCH_2), 61.28, 60.99 (OCH_2), 50.75, 50.68 (C-1), 42.91, 39.18 (C-3, C-5), 31.85, 29.53, 29.44, 29.38, 29.27, 29.20 (CH_2), 26.08 (C-2), 23.80, 22.63 (CH_2), 19.66, 19.59 (CHCH_3), 15.22, 15.20 (CH_2CH_3), 14.07 (C-14) ppm. MS (ESI): m/z (%) = 486 (92) $[M + Na]^+$, 413 (100), 393, 360. $C_{27}H_{45}NO_5$ (463.64): calcd. C 69.94, H 9.78, N 3.02; found C 70.05, H 9.81, N 2.79.

Benzyl (1*S*)-1-[(1-*tert*-Butyldimethylsilyl)oxymethyl]-4-oxotetradecylcarbamate (31): Starting keto sulfone: 0.60 mmol, yield 92% of a colourless oil, after chromatography (eluent: heptane/Et_2O, 3:1). $[\alpha]_D^{23}$ = −19.5 (c = 1.29, $CHCl_3$). IR: $\tilde{\nu}$ = 3443, 3342, 2927, 2856, 1714, 1527, 1465, 1252, 837 cm^{-1}. ^{1}H NMR: δ = 7.34 (m, 5 H, Ph), 5.08 (2d, J = 12.5 Hz, 2 H, PhCH_2), 4.95 (br. d, J = 8.6 Hz, 1 H, NH), 3.64 (m, 1 H, 1-H), 3.61 (br. s, 2 H, OCH_2), 2.46 (m, 2 H, 3-H_2), 2.36 (dd, $J \approx J' \approx$ 7.3 Hz, 2 H, 5-H_2), 1.78 (m, 2 H, 2-H_2), 1.52 (m, 2 H, 6-H_2), 1.25 [m, 14 H, $(CH_2)_7$], 0.88 (m, 12 H, tBu, 14-H_3), 0.03 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 210.84 (CO), 156.14 (NCO_2), 136.55 (qC, Ar), 128.44, 128.02, 127.98 (CH, Ar), 66.54, 65.12 (PhCH_2, OCH_2), 52.16 (C-1), 42.89, 39.17 (C-3, C-5), 31.83, 29.52, 29.42, 29.36, 29.25, 29.18 [$(CH_2)_6$], 25.80 (CH_3, tBu), 25.64 (C-2), 23.79, 22.62 [$(CH_2)_2$], 18.20 (qC, tBu), 14.06 (C-14), −5.56 ($SiMe_2$) ppm. MS (ESI): m/z (%) = 529 (15) $[MH + Na]^+$, 528 (100) $[M + Na]^+$.

***tert*-Butyl (2*S*, 5*S*)-5-Methylprolinate (32):** $Pd(OH)_2$ (50 mg) was added to a solution of methylketone **26** (220 mg, 0.657 mmol) in dry MeOH (10 mL). The mixture was stirred under H_2 (1 atm) at room temp. for 6 h and filtered, and the catalyst was washed several times with MeOH. The solution was evaporated to dryness. The residue was percolated through silica gel (eluent: heptane/EtOAc/Et_3N 50:50:few drops) to give pure pyrrolidine **32** (110.5 mg, 91%) as a colourless oil. $[\alpha]_D^{23}$ = −11.8 (c = 0.74). IR: $\tilde{\nu}$ = 3432, 3339, 3294, 2966, 2932, 2873, 1727, 1458, 1368, 1228, 1159 cm^{-1}. ^{1}H NMR: δ = 3.64 (dd, J = 9.0, J' = 5.1 Hz, 1 H, 2-H), 3.14 (m, 1 H, H-5), 2.41 (br. s, 1 H, NH), 2.07 (m, 1 H, 3-Ha), 1.87 (m, 2 H, 3-Hb, 4-Ha), 1.45 (s, 9 H, tBu), 1.21 (d + m, J = 6.4 Hz, 4 H, CH_3, 4-Hb) ppm. ^{13}C NMR: δ = 174.48 (CO_2), 81.08 (qC, tBu), 60.91 (C-2), 55.56 (C-5), 33.54, 31.10 (C-3, C-4), 28.00 (CH_3, tBu), 20.50 (CH_3) ppm. MS (ESI): m/z (%) = 208 (25) $[M + Na]^+$, 187, 186 (100) $[MH]^+$, 130. HRMS (ESI): $C_{10}H_{20}NO_2$ (MH^+, 186.1494); found 186.1508.

***cis*- and *trans*-(2*S*)-2-[(1-Ethoxyethoxy)methyl]-5-methylpyrrolidines (33):** Yield 89% of a semi-solid gum (four diastereomers), after percolation on silica gel (eluent: EtOAc/MeOH/NH_4OH, 10:1:0.1 to 5:1/0.1). IR: $\tilde{\nu}$ = 3403, 2974, 2934, 1382, 1136, 1088, 1057 cm^{-1}. ^{1}H NMR: δ = 5.76 (br. s, 1 H, NH), 4.73, 4.68 (2 m, 1 H, OCHO), 3.78−3.27 (3 m, 6 H, 2-H, 5-H, 2 OCH_2), 2.03, 1.93, 1.68, 1.50 (4 m, 4 H, 3-H_2, 4-H_2), 1.32 (4 d, 6 H, 2 CHCH_3), 1.18 (2 t, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 100.39, 100.07, 100.04, 99.93 (OCHO), 67.82, 66.99, 66.54, 66.46 (OCH_2), 61.64, 61.42, 61.18, 61.14 (OCH_2), 58.63, 58.60, 57.51, 57.46 (C-2), 55.30, 55.26, 54.87, 54.79 (C-5), 33.11, 33.07, 32.58, 32.49 and 27.71, 27.69, 27.58, 27.42 (C-4, C-3), 19.98, 19.85, 19.76, 19.69, 19.38, 19.30 (2 CHCH_3), 15.29, 15.27, 15.25 (CH_2CH_3) ppm. MS (ESI): m/z (%) = 210 (32) $[M + Na]^+$, 188 (100) $[MH]^+$, 142, 116. HRMS (ESI): $C_{10}H_{22}NO_2$ $[MH^+]$: 188.1645; found 188.1599.

***cis*- and *trans*-(2*S*)-2-[(*tert*-Butylsilyloxy)methyl]-5-methylpyrrolidines (34):** Yield 86% of a semi-solid gum (two diastereomers, *cis*/*trans* 76:24), after chromatography (eluent: EtOAc/MeOH/NH_4OH, 9:1:0.1). IR: $\tilde{\nu}$ = 3306, 2956, 2930, 2858, 1254, 1105, 837, 777 cm^{-1}. ^{1}H NMR: δ = 3.66 (dd, J = 10.0, J' = 4.7 Hz, 0.76 H, OCHa, *cis*), 3.56 (dd, J' = 5.0 Hz, 0.76 H, OCHb, *cis*), 3.51 (br. d, 0.48 H, OCH_2, *trans*), 3.37 (m, 0.24 H, 2-H, *trans*), 3.27 (m, 0.24 H, 5-H, *trans*), 3.16 (m, 2-H, 5-H, *cis*), 2.87 (br. s, 1 H, NH), 1.88, 1.74 (2m, 2 H), 1.59 (m, 0.76 H, *cis*), 1.47 (m, 0.24 H, *trans*), 1.29 (m, 0.24 H, *trans*), 1.25 (m, 0.76 H, *cis*), 1.18 (d, J = 6.3 Hz, CHCH_3, *cis*), 1.15 (d, J = 6.3 Hz, CHCH_3, *trans*), 0.88 (br. s, 9 H, tBu), 0.04 (br. s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 65.98, 65.75 (OCH_2), 60.48, 59.14 (C-2), 54.85, 52.98 (C-5), 33.82, 33.58 and 27.87, 27.83 (C-4, C-3), 25.86 (CH_3, tBu), 21.49, 21.06 (CHCH_3), 18.24 (qC, tBu), −5.37 (SiMe), −5.43 (SiMe) ppm. MS (ESI): m/z (%) = 230 (100) $[MH]^+$, 214.

***tert*-Butyl (2*S*,5*S*)-5-Decylprolinate (35):** Yield 93% of a colourless oil. $[\alpha]_D^{23}$ = −12.8 (c = 0.54, $CHCl_3$). IR: $\tilde{\nu}$ = 3341, 3292, 2957, 2925, 2854, 1729, 1459, 1367, 1226, 1158 cm^{-1}. ^{1}H NMR: δ = 3.60 (dd, J = 9.0, J' = 5.3 Hz, 1 H, 2-H), 2.96 (m, 1 H, 5-H), 2.04 (m, 1 H, 3-Ha), 1.94 (br. s, 1 H, NH), 1.83 (m, 2 H, 3-Hb, 4-Ha), 1.54 (m, 1′-Ha), 1.44 (s, 10 H, tBu + 1′-Hb), 1.24 [m, 16 H, $(CH_2)_8$], 1.18 (m, 1 H, 4-Hb), 0.86 (t, J = 6.8 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 174.69 (CO_2), 80.86 (qC, tBu), 60.68, 60.36 (C-2, C-5), 35.90, 31.87, 31.83, 30.72, 29.75, 29.58, 29.30 (C-3, C-4, $(CH_2)_n$], 28.00 (CH_3, tBu), 27.42, 22.65 (2 CH_2), 14.08 (CH_3) ppm. MS (ESI): m/z (%) = 528, 312 (100) $[MH]^+$, 256. HRMS (ESI): $C_{19}H_{38}NO_2$ $[MH]^+$: 312.2902; found 312.2940.

***cis*- and *trans*-(2*S*)-5-Decyl-2-[(1-ethoxy)ethoxymethyl]pyrrolidines (36):** 68%, as an oil (four diastereomers), after chromatography (eluent: heptane/Et_2O/MeOH/Et_3N, 50:50:1:few drops to 40:20:1:few drops). IR: $\tilde{\nu}$ = 3347, 2924, 2855, 1461, 1380, 1135 cm^{-1}. ^{1}H NMR: δ = 4.66 (m, 1 H, OCHO), 3.62, 3.43, 3.30, 3.20, 3.05, 2.93 (6 m, 6 H, 2 OCH_2, 2-H, 5-H), 1.96 (br. s, 1 H, NH), 1.89, 1.79 (2 m, 2 H, 3-Ha, 4-Ha), 1.41, 1.31 (2 m, 3 H, 3-Hb, 4-Hb, 1′-Ha), 1.27 (d, J = 5.4 Hz, 3 H, CHCH_3), 1.22 [m, 17 H, 1′-Hb, $(CH_2)_8$], 1.16 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 0.84 (t, J = 6.9 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 99.91, 99.75, 99.58, 99.50 (OCHO), 69.40, 68.67, 68.51, 68.27 (OCH_2), 61.08, 60.97, 60.91 (OCH_2), 59.47, 59.38, 58.15, 58.11, 57.72, 57.61, 57.00, 56.93 (C-2, C-5), 36.78, 36.58, 31.90, 31.88, 31.83, 31.11, 31.01, 29.77, 29.74, 29.55, 29.26, 28.23, 28.19, 27.70, 27.48, 27.45, 27.29, 22.61 (C-3, C-4, $(CH_2)_n$], 19.80, 19.75, 19.71 (CHCH_3), 15.23 (OCH_2CH_3), 14.04 (CH_2CH_3) ppm. MS (ESI): m/z (%) = 336 (22) $[M + Na]^+$, 314 (10) $[MH]^+$, 268, 243, 242 (100), 224.

***cis*- and *trans*-(2*S*)-2-[(*tert*-Butylsilyloxy)methyl]-5-decylpyrrolidines (37):** Yield 84% of a colourless oil (two diastereomers *cis*/*trans*, 94:6). $[\alpha]_D^{22}$ = +2.7 (c = 0.82, $CHCl_3$). IR: $\tilde{\nu}$ = 3351, 3306, 2955, 2926, 2855, 1464, 1253, 1092, 837, 776 cm^{-1}. ^{1}H NMR: δ = 3.61 (dd, J = 9.9, J' = 4.7 Hz, 0.94 H, OCHa, *cis*), 3.53 (dd, J' = 5.1 Hz, 0.94 H, OCHb, *cis*), 3.46 (d, J = 6.0 Hz, 0.12 H, OCH_2, *trans*), 3.28 (m, 0.06 H, 2-H, *trans*), 3.12 (m, 0.94 H, 2-H, *cis*), 3.04 (m, 0.06 H, 5-H, *trans*), 2.95 (m, 0.94 H, 5-H, *cis*), 1.81 (m, 2 H, NH, 4-Ha), 1.71 (m, 1 H, 3-Ha), 1.49 (m, 1 H, 3-Hb), 1.24 (m, 19 H, 4-Hb, $(CH_2)_9$], 0.88 (s, 9 H, tBu), 0.86 (t, J = 7.0 Hz, 3 H, CH_3), 0.04 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 66.13, 66.08 (OCH_2), 60.15, 59.67 (C-2, C-5, *cis*), 58.98, 57.52 (C-2, C-5, *trans*), 36.95 (C-4, *trans*), 36.60 (C-4, *cis*), 31.99, 31.88, 31.70, 29.84, 29.80, 29.59, 29.31, 27.58, 27.44, 27.39 [C-3, $(CH_2)_8$], 25.90 (CH_3, tBu), 22.65 (CH_2), 18.28 (qC, tBu), 14.09 (CH_2CH_3), −5.37 (SiMe), −5.39 (SiMe) ppm. MS (ESI): m/z (%) = 356 (67) $[MH]^+$, 224

(100). HRMS (ESI): $C_{21}H_{46}NOSi$ [MH^+]: 356.3349; found 356.3389.

(2*S*,5*S*)-2-(Hydroxymethyl)-5-methylpyrrolidine (38a): $LiAlH_4$ (25 mg) was added to a solution of the pyrrolidine **32** (92 mg, 0.50 mmol) in dry THF (4 mL), and the mixture was heated at reflux for 2.5 h. After the mixture was cooled, diethyl ether saturated with water (2 mL) and finally several drops of water were added, and the solution was filtered, the solid was washed several times with THF/MeOH (1:1), and the solution was evaporated to dryness under reduced pressure. The residue was purified by chromatography (eluent: CH_2Cl_2/MeOH/NH_4OH, 5:1:0.1) to give the pyrrolidine **38a** (35 mg, 62%, not optimized) as a thick, colourless oil that spontaneously transformed into its carbonate. Data for the base: $[\alpha]_D^{23}$ = +12.7 (*c* = 0.7, EtOH), ref.: $[\alpha]_D^{25}$ = +8.8 (*c* = 0.40, EtOH).[15a] IR: $\tilde{\nu}$ = 3307, 2960, 2928, 2872, 1410 cm^{-1}. ^1H NMR ($CDCl_3$ + ε D_2O/NaOD): δ = 4.69 (br. s, 1 H, NH), 3.56 (dd, *J* = 10.3, *J*′ = 3.8 Hz, 1 H, OCHa), 3.35 (dd, *J*′ = 5.8 Hz, 1 H, OCHb), 3.30 (masked m, 1 H, 2-H), 3.22 (m, 1 H, 5-H), 1.82 (m, 2 H, 3-Ha, 4-Ha), 1.57 (m, 1 H, 3-Hb), 1.29 (m, 1 H, 4-Hb), 1.13 (d, *J* = 6.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$ + ε of D_2O/NaOD): δ = 65.16 (OCH_2), 58.95 (C-2), 54.32 (C-5), 33.35, 27.71 (C-4, C-3), 21.81 (CH_3) ppm.

***O*-Deprotection of 33: *cis*- and *trans*-(2*S*)-2-(Hydroxymethyl)-5-methylpyrrolidines (38):** The mixture of *cis*- and *trans*-(2*S*)-2-[(1-ethoxyethoxy)methyl]-5-methylpyrrolidines (**33**, 50.0 mg, 0.267 mmol) was treated with HCl (1 N, 0.3 mL) in THF (2.7 mL) for 3 h at room temp. The solution was then concentrated under reduced pressure to provide the pyrrolidine **38** hydrochlorides (30.0 mg, 74%) as a pale yellow oil. ^1H NMR of the bases ($CDCl_3$ + ε D_2O/NaOD) allowed the accurate evaluation of the *cis*/*trans* ratio as 57:43.

(2*S*,5*S*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)-5-methylpyrrolidine (39a): Na_2CO_3 (21 mg, 0.198 mmol) and benzyl chloroformate (15 μL, 0.105 mmol) were added with vigorous stirring to **38a** as the hydrochloride (15.0 mg, 0.099 mmol) in a mixture of CH_2Cl_2 (1 mL) and H_2O (0.3 mL). After 2.5 h, CH_2Cl_2 (2 mL) and water (2 mL) were added, the aqueous phase was extracted with CH_2Cl_2, and, after usual workup, the residue was purified by preparative TLC (eluent: heptane/Et_2O, 1:1, v/v) to give the *N*-benzyloxycarbonyl derivative **39a** (20.0 mg, 81%) as an oil. $[\alpha]_D^{23}$ = −7.5 (*c* = 1.92, $CHCl_3$). IR: $\tilde{\nu}$ = 3429, 2967, 2877, 1694, 1682, 1412, 1353, 1300, 1098 cm^{-1}. ^1H NMR: δ = 7.36 (m, 5 H, Ph), 5.15 (2d, *J* = 12.3 Hz, 2 H, PhCH_2), 4.61 (br. s, 1 H, OH), 4.05 (m, 1 H, H-5), 3.99 (m, 1 H, H-2), 3.71 (br. d, 1 H, OCHa), 3.59 (dd, *J* = 11.2, *J*′ = 7.2 Hz, 1 H, OCHb), 1.97 (m, 2 H, 3-Ha, 4-Hb), 1.71 (m, 1 H, 3-Hb), 1.58 (m, 1 H, 4-Hb), 1.18 (br. d, *J* = 5.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 157.38 (NCO_2), 136.45 (qC, Ar), 128.50, 128.04, 127.86 (CH, Ar), 68.20, 67.24 (Ph*C*H_2, OCH_2), 61.99 (C-2), 54.85 (C-5), 31.31, 26.75 (C-4, C-3), 21.43 (CH_3) ppm. MS (EI): *m*/*z* (%) = 249 (1.1) [$M]^+$, 218, 174, 91 (100).

***cis*- and *trans*-(2*S*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)-5-methylpyrrolidine (39):** The mixture of the pyrrolidines **38** (as hydrochlorides) obtained by *O*-deprotection of pyrrolidines **33** (see above), was converted into the *N*-Cbz derivatives as described for pure **38a** (with a longer reaction time to avoid kinetic effects in the formation of these carbamates)[37] to give the mixture of diastereomers **39** (42 mg, 86%) as a colourless oil. The diastereomers were separated by chromatography (eluent: heptane/EtOAc, 3:2, v/v) to provide first the *cis* diastereoisomer **39a** (data described above) and then the *trans* isomer **39b** as a colourless oil. $[\alpha]_D^{23}$ = −45.3 (*c* = 0.70, $CHCl_3$) [ref. $[\alpha]_D^{23}$ = −45.8 (*c* = 3.895, $CHCl_3$),[13a] *ent*-**39b**: $[\alpha]_D^{23}$ = +43.8 (*c* = 0.40, $CHCl_3$).[14a] In both cases the opposite signs were successively reported in further papers by the same groups.[13b,14b]

(2*S*,5*S*)-*N*-(Benzyloxycarbonyl)-2-[(*tert*-butyldimethylsilyloxy)-methyl]-5-methylpyrrolidine (40a): The *cis* diastereomer **39a** (14 mg, 0.056 mmol) was treated with imidazole (9.0 mg, 0.132 mmol) and *tert*-butyldimethylsilyl chloride (10.0 mg, 0.066 mmol) in a mixture of CH_2Cl_2 (0.8 mL) and dry DMF (0.2 mL) at room temp. After 15 h, diethyl ether (1 mL) was added, the solution was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (eluent: heptane/Et_2O, 2:1, v/v) to afford **40a** (16 mg, 80%) as a colourless oil. $[\alpha]_D^{24}$ = −28.6 (*c* = 1.51, $CHCl_3$). IR: $\tilde{\nu}$ = 2956, 2930, 2857, 1703, 1405, 1352, 1094, 837, 775 cm^{-1}. ^1H NMR: δ = 7.35 (m, 5 H, Ph), 5.12 (br. s, 2 H, PhCH_2), 3.91 (m, 2 H, 2-H, 5-H), 3.71, 3.46 (2 br. m, 2 H, OCH_2), 1.98 (m, 2 H, 3-Ha, 4-Hb), 1.86 (m, 1 H, 3-Hb), 1.61 (m, 1 H, 4-Hb), 1.22 (br. d, 3 H, CH_3), 0.87 (s, 9 H, *t*Bu), 0.04, 0.01 (2 br. s, 6 H, $SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 402 (20) [M + K]$^+$, 386 (100) [M + Na]$^+$, 364 (56) [MH]$^+$, 320, 256.

(2*S*,5*R*)-*N*-(Benzyloxycarbonyl)-2-[(*tert*-butyldimethylsilyloxy)-methyl]-5-methylpyrrolidine (40b): The *trans* diastereomer **39b** (14 mg, 0.056 mmol) was transformed exactly as described above into **40b** (17 mg, 85%), as an oil. $[\alpha]_D^{24}$ = −53.3 (*c* = 1.63, $CHCl_3$). IR: $\tilde{\nu}$ = 2955, 2930, 2857, 1703, 1406, 1353, 1090, 836, 776 cm^{-1}. ^1H NMR (two conformers): δ = 7.35 (m, 5 H, Ph), 5.15, 5.07 (2 dd, 2 H, PhCH_2), 3.98, 3.92, 3.84 (3 m, 2 H, 5-H, 2-H), 3.75 (dd, *J* = 9.9, *J*′ = 3.0 Hz, OCHa, conformer 1), 3.64 (dd, *J*′ = 3.6 Hz, OCHb, conformer 1), 3.63 (dd, *J* = 9.7 Hz, OCHa, conformer 2), 3.36 (dd, *J*′ = 8.1 Hz, OCHb, conformer 2), 2.21−1.89 (m, 3 H, 3-H_2, 4-Ha), 1.47 (m, 1 H, 4-Hb), 1.20, 1.13 (2 d, *J* ≈ 6 Hz, 3 H, CH_3), 0.88, 0.84 (2 s, 9 H, *t*Bu), 0.04, 0.02 (2 s, 3 H, SiMe), −0.07 (s, 3 H, SiMe) ppm. MS (ESI): *m*/*z* (%) = 386 (100) [M + Na]$^+$, 364 (20) [MH]$^+$, 286, 256.

(2*S*,5*S*)-2-[(*tert*-Butylsilyl)oxymethyl]-5-methylpyrrolidine (34a): $Pd(OH)_2$ (4 mg) was added to a solution of **40a** (15 mg, 0.041 mmol) in dry MeOH (1.5 mL). The solution was stirred for 4 h under H_2 (1 atm), the catalyst was filtered off and washed several times with MeOH, and the solution was evaporated under reduced pressure. The residue was purified by chromatography (eluent: EtOAc/MeOH/NH_4OH, 5:1:0.1, v/v) to give the pure pyrrolidine **34a** (7 mg, 74%) as a colourless oil. $[\alpha]_D^{24}$ = +2.6 (*c* = 0.61, $CHCl_3$). IR: $\tilde{\nu}$ = 3306, 2956, 2929, 2858, 1472, 1462, 1255, 1107, 836, 776 cm^{-1}. ^1H NMR: δ = 3.65 (dd, *J* = 10.0, *J*′ = 4.6 Hz, 1 H, OCHa), 3.55 (dd, *J*′ = 5.0 Hz, 1 H, OCHb), 3.15 (m, 2 H, 2-H, 5-H), 1.91 (br. s, 1 H, NH), 1.82, 1.73 (2 m, 2 H, 4-Ha, 3-Ha), 1.56 (m, 1 H, 3-Hb), 1.25 (m, 1 H, 4-Hb), 1.15 (d, *J* = 6.2 Hz, 3 H, CHCH_3), 0.89 (s, 9 H, *t*Bu), 0.05 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 65.90 (OCH_2), 60.54 (C-2), 54.88 (C-5), 33.66, 27.92 (C-4, C-3), 25.91 (CH_3, *t*Bu), 21.19 (CH*C*H_3), 18.30 (qC, *t*Bu), −5.38 ($SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 252 (3) [M + Na]$^+$, 231 (100) [$MH_2]^+$.

(2*S*,5*R*)-2-[(*tert*-Butylsilyloxy)methyl]-5-methylpyrrolidine (34b): Compound **40b** (16 mg, 0.303 mmol) was *N*-deprotected exactly as described above, affording pyrrolidine **34b** (8 mg, 84%) as a colourless oil. $[\alpha]_D^{24}$ = +1.6 (*c* = 0.60, $CHCl_3$). IR: $\tilde{\nu}$ = 3344, 3306, 2957, 2929, 2857, 1471, 1463, 1255, 1096, 837, 775 cm^{-1}. ^1H NMR: δ = 3.49 (d, 2 H, OCH_2), 3.36 (m, 1 H, 2-H), 3.25 (m, 1 H, 5-H), 2.03 (br. s, 1 H, NH), 1.93, 1.90 (2 m, 2 H, 3-Ha, 4-Hb), 1.45 (m, 1 H, 3-Hb), 1.30 (m, 1 H, 4-Hb), 1.12 (d, *J* = 6.2 Hz, 3 H, CHCH_3), 0.89 (s, 9 H, *t*Bu), 0.05 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 66.19 (OCH_2), 59.19 (C-2), 52.87 (C-5), 33.92, 27.98 (C-4, C-3), 25.93

(CH_3, *t*Bu), 21.72 ($CHCH_3$), 18.31 (qC, *t*Bu), −5.34 ($SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 252 (12) $[M + Na]^+$, 231 (100) $[MH_2]^+$.

X-ray Crystal Structure Analysis of (2*S*,5*S*)-5-Decyl-2-(hydroxymethyl)pyrrolidine Hydrobromide (41a hydrobromide): (2*S*,5*S*)-5-Decyl-2-(hydroxymethyl)pyrrolidine (**41a**, see below) in methanol solution was treated dropwise with a dilute methanolic solution of HBr until pH 2−3. After evaporation to dryness, the residue was crystallised in acetone to give the hydrobromide as colourless crystals. M.p. 86 °C.

Crystallographic Data: Fragile, colourless crystal of 0.025 × 0.05 × 0.50 mm. $(C_{15}H_{32}NO)^+ Br^-$, M_w = 322.33. The compound crystallizes in the monoclinic system, space group $P2_1$, Z = 4: four molecules in the unit cell, of parameters: a = 9.607(9), b = 7.664(7), c = 23.602(22) Å, β = 91.54(3)°. V = 1737 Å^3, $d_{calcd.}$ = 1.232 g·cm^{-3}, F(000) = 688, λ(Mo-K_α) = 0.71073 Å, μ = 2.36 mm^{-1} (absorption corrections without effect). Data were measured with a Nonius−Kappa CCD area-detector diffractometer, by use of graphite-monochromated Mo-K_α radiation, in phi scans, up to θ = 27.4°. A full sphere of 29056 data was collected, affording 13668 monoclinic reflections, of which 7067 were unique (R_{int} = 0.086). 4833 of these reflections were considered as observed having $F_o \geq 4\,\sigma(F_o)$. The structure was solved by direct methods with the aid of the program SHELXS-86 and refined anisotropically by full-matrix, least-squares, based upon unique F^2 with the aid of the SHELXL-93 program.[38] The hydrogen atoms, not located, were calculated at theoretical positions (except for those of the hydroxy groups), and assigned an isotropic displacement parameter equivalent to 1.10 that of the bonded atom. Thus, refinement of 327 parameters converged to $R_1(F)$ = 0.1222 for the 4833 observed reflections and $wR2(F^2)$ = 0.2774 for all the unique data with a goodness-of-fit factor S of 1.141. The residual electron density was found between −0.86 and 1.774 e·Å^{-3} near the bromine ions (1.37 Å), probably due to the absorption. The two molecules of the asymmetric unit are nearly the same, linked together by a hydrogen bond of 2.856 Å through their hydroxy groups. This study confirmed the stereochemistry (*S*) at carbon atoms C2 and C5, with the orientation (*cis*) of the substituents at these atoms and the absolute configuration, deduced from the differences between the Bijvoët pairs induced by the anomalous diffraction of bromine atoms. CCDC-213180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

(2*S*,5*S*)-*N*-(Benzyloxycarbonyl)-5-decyl-2-(hydroxymethyl)-pyrrolidine (42a):

a) From *tert*-Butyl (2*S*,5*S*)-5-Decylprolinate (35): $LiAlH_4$ reduction of the *tert*-butyl ester **35** (125 mg, 0.401 mmol), as described for **32**, afforded (2*S*,5*S*)-5-decyl-2-(hydroxymethyl)pyrrolidine (**41a**) converted to its hydrochloride (83 mg, 75%), which was treated with Na_2CO_3 and benzyl chloroformate in CH_2Cl_2/H_2O (3:1) as described for **38a**, to give the *N*-Cbz derivative **42a** (93 mg, 84%) as a colourless oil. $[\alpha]_D^{23}$ = +5.1 (*c* = 0.40, $CHCl_3$). IR: ṽ = 3428, 2954, 2925, 2854, 1698, 1678, 1455, 1413, 1355, 1111 cm^{-1}. ^{1}H NMR: δ = 7.35 (m, 5 H, Ph), 5.15 (2 d, *J* = 12.3 Hz, 2 H, PhCH_2), 4.64 (br. s, 1 H, OH), 4.00 (m, 1 H, 2-H), 3.92 (m, 1 H, 5-H), 3.70 (br. d, 1 H, OCHa), 3.57 (dd, *J* = 10.4, *J′* = 7.7 Hz, 1 H, OCHb), 1.99 (m, 1 H, 3-Ha), 1.86 (m, 1 H, 4-Hb), 1.63 (m, 3 H, 3-Hb, 4-Hb,1′-Ha), 1.23 [2 m, 17 H, 1′-Hb, $(CH_2)_8$], 0.88 (br. t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 157.58 (NCO_2), 136.38 (qC, Ar), 128.47, 128.04, 127.90 (CH, Ar), 68.24, 67.22 (PhCH_2, OCH_2), 61.70, 59.30 (C-2, C-5), 35.27, 31.87, 29.56, 29.52, 29.47, 29.30, 28.89 [C-3, C-4, $(CH_2)_6$], 26.76, 26.40, 22.65 [$(CH_2)_3$], 14.09 (CH_3) ppm. HRMS (ESI): $C_{23}H_{37}NO_3Na$ [MNa^+] 398.2671, found 398.2681.

b) From *cis*- and *trans*-(2*S*)-5-Decyl-2-[(1-ethoxyethoxy)methyl]pyrrolidines (36): The mixture of pyrrolidines **36** (74 mg, 0.236 mmol) was *O*-deprotected with 0.25 N HCl in THF and treated with Na_2CO_3 and benzyl chloroformate as described for the mixture **33**, for 5 h. After usual workup, the residue was purified by chromatography (eluent: heptane/Et_2O, 2:1 v/v) to give first the (2*S*,5*S*) diastereomer **42a** [60 mg; all the data are identical with those described above, MS(ESI): *m*/*z* (%) = 414 $[M + K]^+$, 398 (100) $[M + Na]^+$, 376 $[MH]^+$, 332, 242], and then (2*S*,5*R*)-**42b** (24 mg, oil), in a 97% yield for both compounds:

(2*S*,5*R*)-*N*-(Benzyloxycarbonyl)-5-decyl-2-(hydroxymethyl)-pyrrolidine (42b): $[\alpha]_D^{23}$ = −40.0 (*c* = 1.52, $CHCl_3$). IR: ṽ = 3429, 2924, 2854, 1701, 1677, 1454, 1411, 1355, 1110 cm^{-1}. ^{1}H NMR: δ = 7.35 (m, 5 H, Ph), 5.19, 5.09 (2 d, *J* = 12.3 Hz, 2 H, PhCH_2), 4.05 (m, 1 H, 2-H), 3.83 (ddd, *J* = 9.0, *J′* = 8.2, *J″* = 2.4 Hz, 1 H, 5-H), 3.71 (m, 1 H, OCHa), 3.63 (m, 1 H, OCHb), 2.04 (m, 1 H, 3-Ha), 1.92 (m, 1 H, 4-Ha), 1.66 (m, 3 H, 3-Hb, 4-Hb, 1′-H), 1.27, 1.19 [2 m, 17 H, 1′-Hb, $(CH_2)_8$], 0.88 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 156.65 (NCO_2), 136.45 (qC, Ar), 128.47, 128.02, 127.93 (CH, Ar), 67.24, 67.14 (PhCH_2, OCH_2), 60.31, 59.04 (C-2, C-5), 33.58, 31.89, 29.57, 29.51, 29.41, 29.32, 28.15 (C-3, C-4, $(CH_2)_6$], 26.67, 26.43, 22.67 ($(CH_2)_3$], 14.11 (CH_3) ppm. MS (ESI): *m*/*z* (%) = 414 (13) $[M + K]^+$, 398 (100) $[M + Na]^+$, 376 $[MH]^+$, 332, 268.

(2*S*,5*S*)-*N*-(Benzyloxycarbonyl)-2-[(*tert*-butyldimethylsilyloxy)-methyl]-5-decylpyrrolidine (43a): Compound **42a** (23 mg, 0.061 mmol) was *O*-silylated as indicated for **39a**. The crude product was purified by preparative TLC (eluent: heptane/Et_2O, 2:1, v/v) to afford **43a** (26 mg, 87%) as a colourless oil. $[\alpha]_D^{24}$ = −11.9 (*c* = 1.00, $CHCl_3$). IR: ṽ = 2955, 2927, 2855, 1704, 1464, 1406, 1097, 836 cm^{-1}. ^{1}H NMR (two conformers): δ = 7.34 (m, 5 H, Ph), 5.12 (s, 2 H, PhCH_2), 3.89 (m, 1 H, 2-H), 3.81 (m, 1 H, 5-H), 3.71, 3.44 (2 m, 2 H, OCH_2), 1.94, 1.88 (2 m, 3 H, 3-H_2, 4-Ha), 1.65 (m, 1 H, 4-Hb), 1.25 [m, 18 H, $(CH_2)_9$], 0.88 (t, *J* = 6.5 Hz + s, 12 H, CH_3, *t*Bu), 0.03, 0.00 (2 br. s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 155.32 (NCO_2), 136.97 (qC, Ar), 128.38, 127.94, 127.78 (CH, Ar), 66.53 (PhCH_2), 64.31, 63.49 (OCH_2), 60.18, 59.64, 59.39, 58.71 (C-2, C-5), 35.36, 35.15, 31.89, 29.60, 29.32, 26.31 [C-3, C-4, $(CH_2)_8$], 25.90 (CH_3, *t*Bu), 22.67 (CH_2), 18.27 (qC, *t*Bu), 14.10 (CH_3), −5.40 (SiMe), −5.46 (SiMe) ppm. MS (ESI): *m*/*z* (%) = 528 (42) $[M + K]^+$, 512 (100) $[M + Na]^+$, 490 $[MH]^+$.

(2*S*,5*R*)-*N*-(Benzyloxycarbonyl)-2-[(*tert*-butyldimethylsilyloxy)-methyl]-5-decylpyrrolidine (43b): The *trans* diastereomer **42b** (13 mg, 0.037 mmol) was silylated exactly as described above, giving rise to **43b** (11 mg, 65%) as a colourless oil. $[\alpha]_D^{23}$ = −50.3 (*c* = 0.50, $CHCl_3$). IR: ṽ = 2954, 2926, 2855, 1702, 1406, 1100, 836 cm^{-1}. ^{1}H NMR: δ = 7.34 (m, 5 H, Ph), 5.19, 5.07 (2 dd, 2 H, PhCH_2), 3.89, 3.77 (2 m, 5-H, 2-H, OCHa, conformer 1), 3.64 (m, 1 H, OCHb , conformer 1, OCHa, conformer 2), 3.35 (dd, *J* = 9.6, *J′* = 8.1 Hz, OCHb, conformer 2), 2.10−1.80 (m, 3 H, 3-H_2, 4-Ha), 1.61 (m, 1 H, 4-Hb), 1.25, 1.23 [2 m, 18 H, $(CH_2)_9$], 0.87, 0.83 (2 s, 12 H, CH_3, *t*Bu), 0.04, 0.02 (2 s, 3 H, SiMe) −0.07 (s, 3 H, SiMe) ppm. ^{13}C NMR: δ = 154.45, 154.14 (NCO_2), 136.98, 136.86 (qC, Ar), 128.45, 128.37, 128.22, 127.93, 127.82, 127.78 (CH, Ar), 66.51, 66.42 (PhCH_2), 63.15, 62.39 (OCH_2), 59.05, 58.89, 58.55, 58.37 (C-2, C-5), 34.05, 32.60, 31.91, 30.30, 29.68, 29.60, 29.50,

29.33, 27.85, 26.69, 26.62, 26.48, 25.93 (C-3, C-4, $(CH_2)_n$], 25.88, 25.84 (CH_3, *t*Bu), 25.42, 22.68 (CH_2), 18.19 (qC, *t*Bu), 14.12 (CH_3), −5.41, −5.44, −5.49, −5.51 ($SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 512 (100) $[M + Na]^+$, 427.

Compounds 43 from 37: Na_2CO_3 (59 mg, 0.577 mmol) and CbzCl (41 μL, 0.287 mmol) were added to a solution of the pyrrolidine mixture **37** (90 mg, 0.253 mmol) in CH_2Cl_2 (4 mL)/H_2O (1 mL) and the mixture was vigorously stirred for 5 h. After usual workup, the residue was purified by preparative TLC (eluent: heptane/Et_2O, 2:1 v/v) to afford first pyrrolidine **43b** (5 mg), and then **43a** (100 mg) in 83% yield for both diastereomers, all data being identical, respectively, with those described above.

(2*S*,5*S*)-2-[(*tert*-Butylsilyloxy)methyl]-5-decylpyrrolidine (37a): $Pd(OH)_2$ (5 mg) was added to a solution of **43a** (26 mg, 0.053 mmol) in dry MeOH (1.5 mL). The solution was stirred for 3 h under H_2 (1 atm), filtered, with washing several times with MeOH, and concentrated under reduced pressure. The residue was purified by chromatography (eluent: heptane/Et_2O/MeOH/NEt_3, 10:10:1:drops, v/v) to give the pure pyrrolidine **37a** (15 mg, 79%). Oil. $[\alpha]_D^{24} = +2.5$ (*c* = 0.61, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2955, 2926, 2855, 1463, 1254, 1092, 837, 776 cm^{-1}. ^1H NMR: δ = 3.62 (dd, *J* = 9.9, *J*′ = 4.7 Hz, 1 H, OCHa), 3.54 (dd, *J*′ = 5.2 Hz, 1 H, OCHb), 3.13 (m, 1 H, 2-H), 2.95 (m, 1 H, 5-H), 1.88 (br. s, 1 H, NH), 1.85, 1.71 (2 m, 2 H, 4-Ha, 3-Ha), 1.50 (m, 1 H, 3-Hb), 1.30 (masked m, 3 H, 4-Hb, 1′-H_2), 1.25 [m, 16 H, $(CH_2)_8$], 0.89 (s, 9 H, *t*Bu), 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.04 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 66.04 (OCH_2), 60.16 (C-2), 59.70 (C-5), 36.59, 31.89, 31.72, 29.85, 29.60, 29.33, 27.45, 27.44 (C-3, C-4, $(CH_2)_8$], 25.92 (CH_3, *t*Bu), 22.67 (CH_2), 18.30 (qC, *t*Bu), 14.10 (CH_3), −5.37 ($SiMe_2$) ppm. MS (ESI): *m*/*z* (%) = 357 (100) $[MH_2]^+$, 356 $[MH]^+$, 224.

(2*S*,5*R*)-2-[(*tert*-Butylsilyloxy)methyl]-5-decylpyrrolidine (37b): Compound **43b** (11 mg, 0.022 mmol) afforded pyrrolidine **37b** (7 mg, 88%) exactly as described above. Oil. $[\alpha]_D^{24} = +3.7$ (*c* = 0.77, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3350, 2955, 2926, 2855, 1463, 1255, 1096, 837, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.47 (d, *J* = 5.9 Hz, 2 H, OCH_2), 3.30 (m, 1 H, 2-H), 3.06 (m, 1 H, 5-H), 1.90 (m, 4 H, NH, 4-Ha, 3-H_2), 1.41 (m, 1 H, 4-Hb), 1.25 [m, 18 H, $(CH_2)_9$], 0.89 (s, 9 H, *t*Bu), 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.05 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR: δ = 66.10 (OCH_2), 59.00 (C-2), 57.57 (C-5), 36.88, 31.98, 31.90, 29.81, 29.62, 29.33, 27.58, 27.39 (C-3, C-4, $(CH_2)_8$], 25.93 (*t*Bu), 22.67 (CH_2), 18.30 (qC, *t*Bu), 14.11 (CH_3), −5.30 (SiMe), −5.34 (SiMe) ppm. MS (ESI): *m*/*z* (%) = 356 (100) $[MH]^+$, 224.

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