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An In Vitro Investigation into Conformational Aspects of Gabapentin

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Abstract—Conformational analysis of constrained cyclohexane systems was pioneered fifty years ago by Barton and Hassel. We now report an investigation based on a conformational analysis of a number of novel cyclohexane based Gabapentin analogues coupled with their in vitro evaluation at the Gabapentin binding site. These data are used to propose a possible binding conformation for Gabapentin.

Introduction

Conformational analysis of cyclic systems was first brought to light fifty years ago in the pioneering work of Barton and Hassel.[1–3] The principles they described have since been applied to many stereochemical aspects of cyclohexane based systems, including addition of nucleophiles to conformationally constrained cyclohexanones[4–6] and cyclohexylidenecyanoacetates.[7] We have now applied these and other principles to undertake an investigation into the preferred binding conformation of the cyclohexane derivative Gabapentin (Neurontin®) (**1**) for optimal interaction with its binding site.

Gabapentin (**1**) has been introduced as an anticonvulsant agent that is useful as add on therapy in the treatment of epileptic seizures.[8] It has also recently been shown to be a potential treatment for neurogenic pain.[9–11] Gabapentin was originally designed as a lipophilic γ-amino butyric acid (GABA) analogue,[12] but has subsequently been shown not to interact with any of the enzymes on the GABA metabolic pathway, nor does it interact directly with the $GABA_A$ or $GABA_B$ receptors.[13] However, it is able to efficiently cross the blood brain barrier via an L-system amino acid transporter.[14] Gabapentin shows few, if any, toxic side effects at clinically relevant doses.[15] It does, however, possess a relatively short half life, being excreted unchanged, possibly due to its very high water solubility and apparent lack of protein binding in vivo.[16] Recently, it has been shown that Gabapentin binds with high affinity to a novel binding site on the $\alpha_2\delta$ subunit of a calcium channel.[17–19] It is currently proposed that Gabapentin exerts its anticonvulsant and anti-nociceptive actions via interaction with this site, and it is this interaction that the work described here is centred on.

Results and Discussion

The two lowest energy conformations of Gabapentin contain the cyclohexane ring in the chair conformation and have the aminomethyl moiety either axial (**1a**) or equatorial (**1b**). We have recently proposed that, for optimum binding, the aminomethyl should be in the equatorial frame relative to the cyclohexane system as in conformer **1b**.[20] In order to examine this more rigorously we have investigated the conformations of a number of analogues utilising low temperature ^1H NMR techniques.

We synthesised the *cis* and *trans* isomers of (3*R*)-(1-aminomethyl-3-methylcyclohexyl)-acetic acid **2** and **3**, respectively, by the routes outlined previously,[20,21] the key steps being (Scheme 1) the addition of nitromethane to the α,β-unsaturated ester (**4**) and the addition of cyanide to the Knoevenagel adduct (**6**).

It is interesting to note that the direction of addition of the two nucleophiles occur from opposite faces with the nitromethane approaching from the equatorial direction and cyanide approaching from the axial direction, almost exclusively in both cases, as shown by NOE dif-

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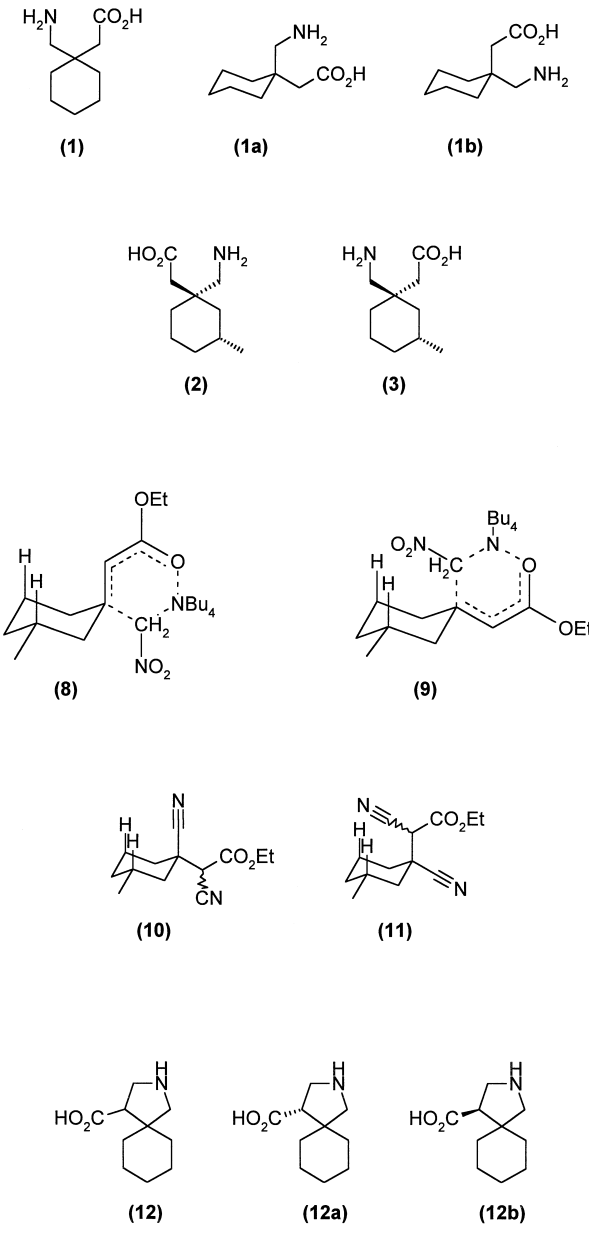
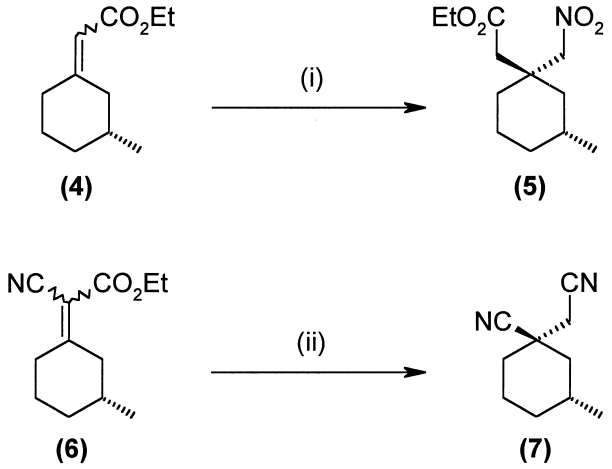




Scheme 1. (i) $MeNO_2$, THF, $Bu_4N^+F^-$, 70°C, 18 h (65%); (ii) KCN, EtOH, H_2O, reflux, 18 h (70%).

ference experiments carried out on the final compounds **2** and **3**. The outcome of the nitromethane addition can be rationalised via the proposed six membered transition states **8** and **9** incorporating the nitromethane anion and the tetrabutylammonium cation.[7] As can be seen, the 1,3 diaxial interactions between the two axial hydrogens on C-3 and C-5 and the axial moiety on C-1 are much more unfavourable for axial attack of nitromethane (transition state **9**) so driving the nitromethane to approach from the equatorial frame.

For the reaction involving potassium cyanide, the potassium cation and cyanide anion are almost completely dissociated in the ethanol solvent.[7] In this case it should also be remembered that the initial product of the addition is the cyanoester **10** or **11** that subsequently undergoes hydrolysis and decarboxylation to give the product. Owing to the dissociation of the potassium and cyanide ions a six membered transition state does not exist so the cyanide simply attacks from the face giving rise to the more thermodynamically stable product. The intermediate **10**, when compared to **11**, has a smaller 1,3-diaxial interaction between the two axial hydrogens on C-3 and C-5 and the axial moiety on C-1. Thus, intermediate **10** is the more thermodynamically stable intermediate so the reaction proceeds through this pathway.

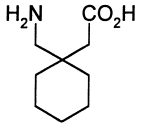
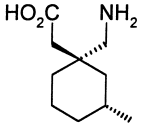
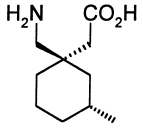
Gabapentin was examined by ^1H NMR in deuteromethanol at room temperature when only a single set of signals is observed owing to the rapid ring flipping at this temperature. On cooling to −80 °C two sets of exocyclic methylene signals were observed in a ratio of 1:2. These signals corresponded to the two conformers **1a** and **1b**, respectively and were assigned as such by comparison of the relative shifts of the two pairs of exocyclic methylene moieties with the corresponding signals from conformationally restricted analogues **2** and **3**. In contrast, both **2** and **3** were shown to exist in single detectable conformations (>99%) at −80 °C, compound **2** being effectively constrained in the conformation with the aminomethyl in the equatorial frame and compound **3** constrained with the aminomethyl axial. Compounds **2** and **3** were examined for binding at the Gabapentin binding site and the results are shown in Table 1. Although both **2** and **3** are expected to undergo ring flipping at room temperature the proportion of any other conformers will be small (<1%) thus making it unlikely that any of these are contributing to the binding affinity observed. The data in Table 1, coupled with the evidence of only a single conformer being accessible at room temperature for compounds **2** and **3**, confirm that the binding conformation of Gabapentin is that with the aminomethyl in the equatorial frame.

Having defined the probable conformation of the cyclohexane ring the investigation was extended to examine the GABA portion of Gabapentin. Here there are a number of low energy conformations accessible. Computer models were built and energy minimised using Sybyl 6.3.[22] The model for Gabapentin was built with the cyclohexane ring in the chair conformation and with the aminomethyl group equatorial. The conformations

of the GABA subunit were then enumerated using a grid search, using 15° increments about bonds α,β (see Fig. 1; the torsion angles were defined by the following atoms: α (1,2,3,4), β (2,3,4,5)); energy minimisation of the other bonds then gives the relative energy of each conformer. The geometry optimisation was effected by minimisation of the molecular mechanics energy (Tripos force field, with Gasteiger–Marsili charges using a distance dependent dielectric constant) by MAXIMIN-II. The geometry optimisation was also used during and after the grid search procedure and energy minimisation was terminated when the rms energy gradient fell below 0.01 kCal/mol/A. Six conformations from the low energy regions were identified and further minimised. The geometry and energy of these conformers are shown in Table 2.

It has been found that a number of lipophilic α-amino acids also bind to the Gabapentin binding site. Thus it is proposed that the amine and acid moieties of Gabapentin should be close enough to each other that they can mimic an α-amino acid; this precludes conformations 3 and 6 in Table 2. Thus four conformations are left for consideration, which fall into two pairs. Conformations 1 and 5 are close to being mirror images and so constitute one pair and conformations 2 and 4 are also close to mirror images so constituting a second pair. In order to further investigate the pair of conformers 2 and 4 a more rigid Gabapentin analogue (**12**) was designed. The (*S*)-enantiomer **12a** closely mimics conformer 2 (Figure 2(a)), whereas the (*R*)-enantiomer **12b** closely mimics the conformer 4 (Figure 2(b)). The models were overlaid by the method of least squares over three pairs of atoms. The racemate **12** was synthesised as its hydrochloride salt by the route outlined in Scheme 2. The two enantiomers could be prepared individually via benzyloxycarbonyl protection (**19**) of the racemic amino acid followed by amide formation

Table 1. $\alpha_2\delta$ subunit binding site affinities for 3-methyl Gabapentin analogues

Compound	Structure	IC_{50}(nM)[a]
Gabapentin (**1**)		140(1)
2		42(6)
3		> 1000

[a]IC_{50} is the concentration (nM) producing half-maximal inhibition of the specific binding of [^{3}H]-Gabapentin to Gabapentin binding sites located on the $\alpha_2\delta$ subunit of a calcium channel. Values shown represent the geometric mean of at least three experiments with the standard error of the mean in parentheses.

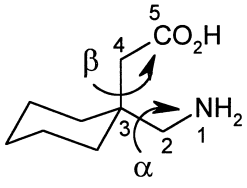
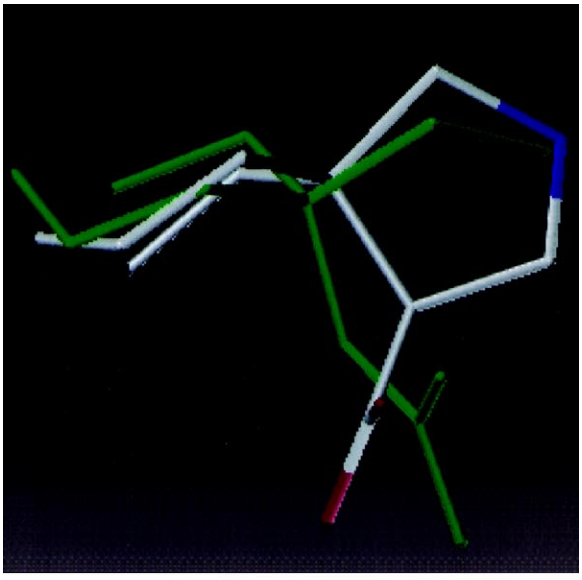
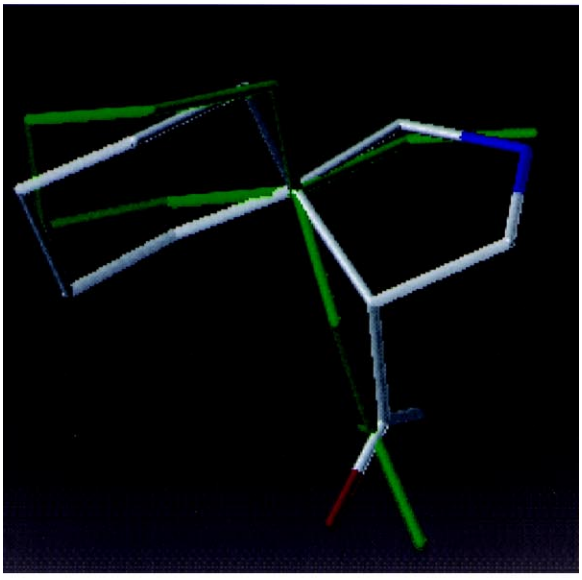


Figure 1. Torsion angles α and β used for the grid search of the GABA subunit of Gabapentin.



(a)



(b)

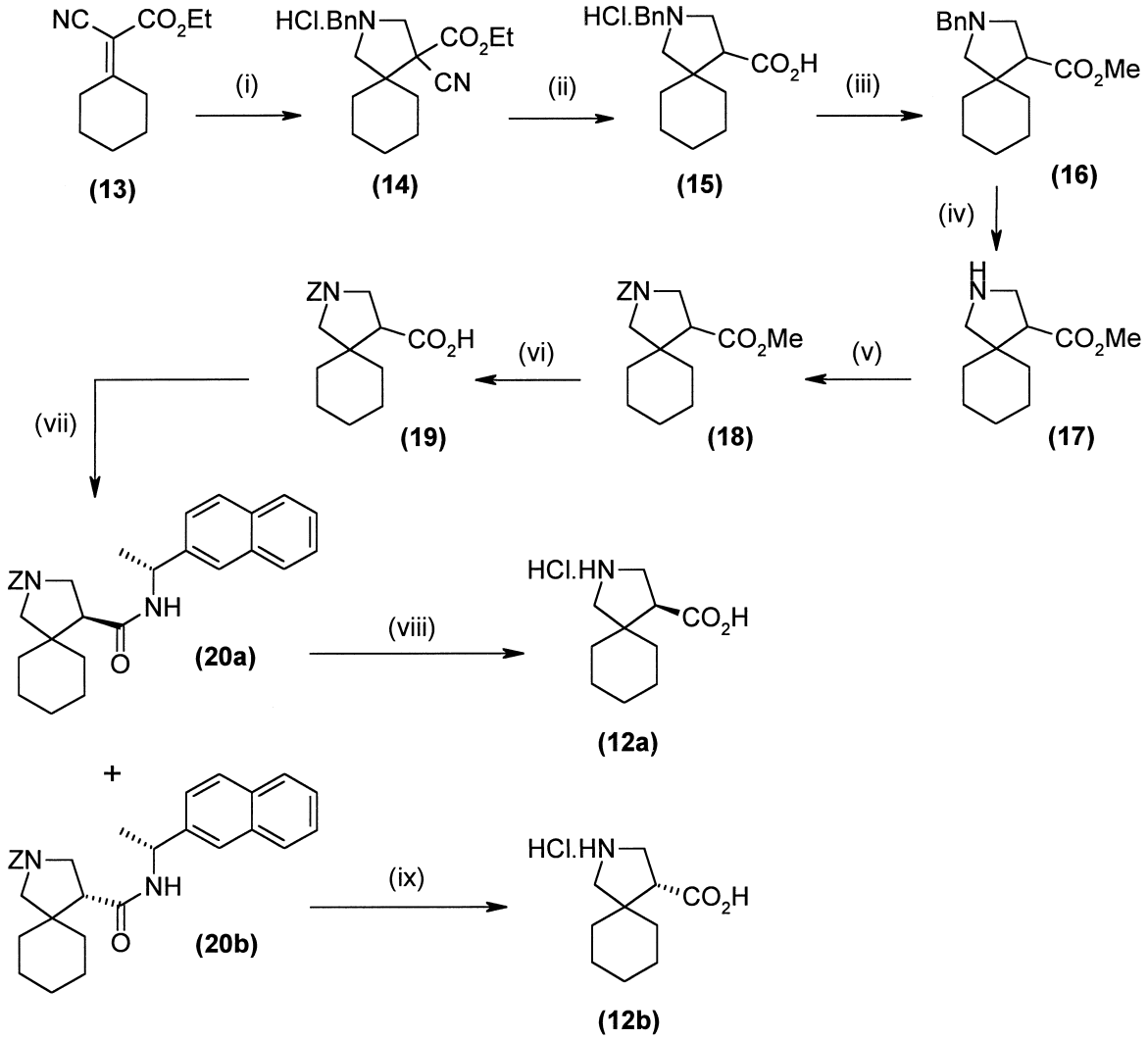
Figure 2. (a) Overlay of Gabapentin conformer 2 (in green) with **12a**; (b) Overlay of Gabapentin conformer 4 (in green) with **12b**.

with (*R*)-(+)-1-(2-Naphthyl)ethylamine to give the two diastereoisomers **20a** and **20b**, which were separable by flash chromatography. To ascertain the absolute stereochemistry of **20a** and **20b**, one of the samples (**20a**) was prepared for X-ray analysis. Crystal structure determination (Fig. 3) showed that **20a** had the absolute configuration of (*R*) at the stereocentre adjacent to the naphthalene ring, as expected, and (*S*) for the centre in the five membered ring. By elimination, the isomer **20b** must have absolute configurations of (*R*) and (*R*), respectively. Hydrolysis of the pure diastereoisomers gave rise to the individual enantiomers **12a** and **12b** with (*S*) and (*R*) configurations, respectively.

The enantiomers **12a** and **12b** were tested for binding at the Gabapentin binding site and gave IC_{50} values of

Table 2. Conformations of the GABA subunit of Gabapentin (**1**)

Conformation	Torsion angles α,β	Molecular mechanics energy kCal/mol	Distance N to CO_2H A
1	−57.2,78.0	3.84	3.03
2	44.6,54.3	2.97	3.23
3	178.3,60.6	5.80	4.43
4	−53.4,−55.5	4.62	3.39
5	69.6,−60.4	5.65	2.91
6	−170,−54.8	5.33	4.40



Bn = $PhCH_2$-, Z = $PhCH_2OCO$-

Scheme 2. (i) $HCl.BnNHCH_2CO_2H$, Et_3N, HCHO, PhH, reflux (82%); (ii) 6 N HCl reflux (94%); (iii) MeOH, HCl, reflux (65%); (iv) $Pd(OH)_2/C$, H_2, MeOH (97%); (v) BnOCOCl, Py, CH_2Cl_2, (88%); (vi) oxane/aq NaOH (89%); (vii) CH_2Cl_2, $(COCl)_2$, $HCONMe_2$ then (*R*)-(+)-1-(2-napthyl)-ethylamine followed by flash chromatography, **20a**: 43%, and **20b**: 39%; (viii) 6 N HCl, THF reflux (73%); (ix) 6 N HCl, THF reflux (78%).

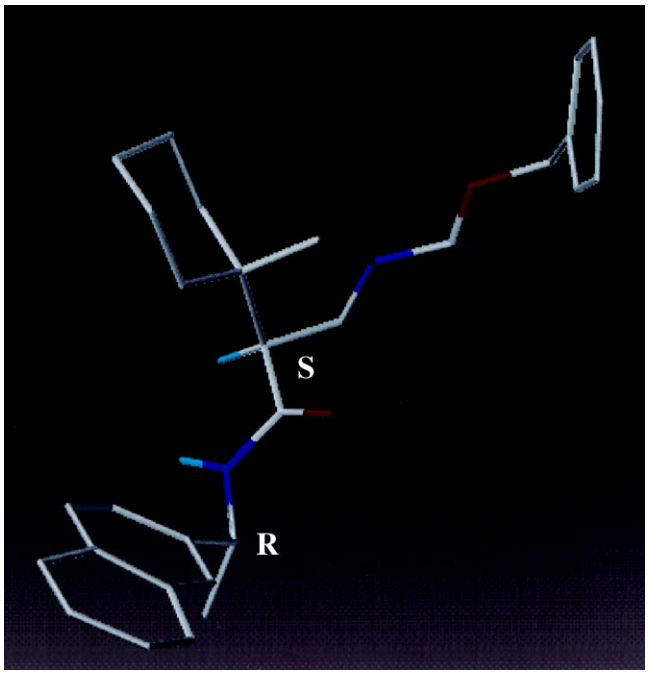


Figure 3. X-ray crystal structure of **20a**.

$>10\,\mu M$ and 120 nM, respectively. These data are consistent with the binding conformation of Gabapentin being close to conformer 4, for good interaction with its binding site on the $\alpha_2\delta$ subunit of a calcium channel.

Conclusion

We have demonstrated, utilising low temperature ^1H NMR techniques of conformationally constrained Gabapentin analogues, that the probable binding conformation of Gabapentin is that with the aminomethyl moiety in the equatorial frame in relation to the cyclohexane ring. The low temperature ^1H NMR of substituted Gabapentin analogues detected only a single conformation in each case, showing other conformations are unlikely to make a contribution to the binding affinity observed. Moreover, a novel Gabapentin analogue with a constrained GABA portion has been used to probe the binding conformation of the GABA moiety of Gabapentin during its interaction with the binding site.

Experimental

Melting points were determined with a Mettler FP80 or a Reichert Thermovar hot-stage apparatus. Proton NMR spectra were recorded on a Varian Unity +400 spectrometer; chemical shifts are recorded in ppm downfield from tetramethylsilane. IR spectra were recorded on a Perkin–Elmer System 2000 Fourier transform spectrophotometer. Mass spectra were recorded with a Finnigan MAT TSQ70 or Fisons VG Trio-2A instrument. Elemental analyses are within ±0.4% of theoretical values and were determined by Medac Ltd., Uxbridge, UK. Normal phase silica gel used for chromatography was Merck no. 9385 (230–400 mesh), and reverse phase silica gel used was Lichroprep RP-18 (230–400 mesh); both were supplied by E. Merck, A.G., Darmstadt, Germany. Anhydrous solvents were purchased in Sureseal™ bottles from Fluka Chemicals Ltd., Glossop, UK. For the X-ray data a colourless rod crystal of (20a) was mounted on a glass fibre with its long axis roughly parallel to the phi axis of the goniometer. Preliminary examination and data collection were performed with Cu K_α radiation ($\lambda = 1.54184$ Å) on an Enraf–Nonius CAD4 computer controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least squares refinement, using the setting angles of 25 reflections in the range $23° < \theta < 43°$, measured by the computer controlled diagonal slit method of centring. The data were collected at 23 °C using the omega scan technique. A total of 3394 reflections were collected, of which 3364 were unique and not systematically absent. The structure was solved by direct methods. Using 277 reflections (minimum E of 1.66) and 3293 relationships, a total of 25 phase sets were produced. A total of 38 atoms were located from an E-map prepared from the phase set with probability statistics. The remaining atoms were located in succeeding difference Fourier transform syntheses.

2-Benzyl-2-aza-spiro[4.5]decane-4-carboxylic acid methyl ester (16). A solution of (13) (4 g; 20.70 mmol), N-Benzylglycine hydrochloride (10.4 g; 51.57 mmol), Triethylamine (7.2 mL; 51.65 mmol) and Paraformaldehyde (5.2 g; 173.30 mmol) in Benzene (120 mL:) was refluxed for 2 h using a Dean–Stark apparatus. After cooling, the reaction mixture was diluted with Toluene (200 mL) and washed with brine. The aqueous phase was extracted with Toluene (3×30 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified over silica-gel chromatography in EtOAc/Heptane (1/3) to give a yellow oil, which was diluted in ether (30 mL) and extracted with 3 N HCl (3×25 mL). The aqueous phase was washed with ether (2×30 mL) and was concentrated under vacuum to give **14** as a white powder (6.20 g; 17.08 mmol), which was used without any further purification. A solution of **14** (6.2 g; 17.08 mmol) in 6 N HCl (120 mL) was refluxed overnight. Evaporating the solvent in vacuo gave 5 g (16.13 mmol; 77% from **13**) of **15** as a pale-yellow solid, which was immediately esterified. Acetyl chloride (5 mL; 70.32 mmol) was slowly added to methanol (100 mL), at 0 °C, under an argon atmosphere. After stirring for 10 min, this solution was transferred to a flask containing **15** (5 g; 16.13 mmol), under an argon atmosphere. The reaction mixture was then stirred at 95 °C for 3 h. After cooling, the methanol was removed in vacuo. The residue was basified with sat. aq Na_2CO_3 and was extracted with ether (3×30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated to give 3 g (10.44 mmol; 50% from **13**) of **16** as a pale-yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.0–1.7 (m, 10H), 2.25 (d, 1H), 2.65–2.9 (m, 4H), 3.6 ([AB]q, 2H), 3.65 (s, 3H, $OC\underline{H}_3$), 7.3 (m, 5H, Ph); MS (ES^+) *m/e*: 288 ($[MH]^+$, 100%).

2-Aza-spiro[4.5]decane-2,4-dicarboxylic acid 2-benzyl ester 4-methyl ester (18). A solution of **16** (3 g; 10.44 mmol) and 10% $Pd(OH)_2/C$ (0.60 g; 20%w/w) in methanol (50 mL) was stirred for 24 h at 40 °C under an atmosphere of dry hydrogen gas. The catalyst was filtered off through a Celite pad and the filtrate was concentrated in vacuo to give 2 g (10.14 mmol; 97%) of **17** as a colourless oil, which was used without any further purification. To a solution of **17** (2 g; 10.14 mmol) in dry Dichloromethane (100 mL) was successively added, at 0 °C, under an argon atmosphere, pyridine (2.04 mL; 25.35 mmol) and benzylchloroformate (2.89 mL; 20.24 mmol). The reaction mixture was then allowed to stir at room temperature for 2 days. The reaction mixture was washed (2×50 mL) with 1 N HCl, dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by silica-gel flash chromatography in ether/heptane (1/1) to give 2.97 g (8.96 mmol; 88%) of **18** as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15–1.7 (m, 10H), 2.8 (m, 1H), 3.3 (m, 1H), 3.45–3.8 (m, 6H), 5.15 ([AB]q, 2H, $PhCH_2$), 7.3 (m, 5H, Ph). MS (ES^+) *m/e*: 332 ($[MH]^+$, 100%).

2-Aza-spiro[4.5]decane-2,4-dicarboxylic acid 2-benzyl ester (19). To a solution of **18** (300 mg; 0.9 mmol) in a mixture dioxane/water (6 mL; 9/1) was added a 2 M solution of NaOH (0.90 mL; 1.8 mmol). The reaction mixture was stirred at 35 °C for 6 h. Solvents were removed in vacuo. The residue was diluted in water (15 mL) and was washed with diethyl ether (3×10 mL). The aqueous phase was acidified with 2 N HCl and was extracted with ethyl acetate (3×15 mL). The ethyl acetate extracts were combined, dried over $MgSO_4$ and concentrated to give 254 mg (0.8 mmol, 89%) of **19** as a colourless gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.2–1.75 (m, 10H), 2.8 (m, 1H), 3.3 (m, 1H), 3.5 to 3.8 (m, 3H), 5.1 (ABq, 2H), 7.3 (m, 5H). MS (ES^+) *m/e*: 318 ($[MH]^+$, 100%).

(4*S*,1′*R*)-4-(1′-Naphthalen-2-yl-ethylcarbamoyl)-2-aza-spiro[4.5]decane-2-carboxylic acid benzyl ester (20a) and (4*R*,1′*R*)-4-(1(-naphthalen-2-yl-ethylcarbamoyl)-2-aza-spiro[4.5]decane-2-carboxylic acid benzyl ester (20b). To a cooled (0 °C) solution of **19** (1.71 g; 5.38 mmol) in dry dichloromethane (35 mL) were successively added, under an argon atmosphere, oxalyl chloride (0.56 mL, 6.42 mmol) and dimethylformamide (20 μL; 0.26 mmol). The reaction mixture was stirred at 0 °C for 30 min and then was allowed to stir at room temperature for 2 h. The solvent was removed in vacuo and the residue was diluted in dry dichloromethane (35 mL). This solution was then added to a solution of (*R*)-(+)-1-(2-naphthyl) ethylamine (1.10 g; 6.42 mmol) and triethylamine (0.90 mL, 6.42 mmol) in dry dichloromethane (50 mL), under an argon atmosphere. The reaction mixture was stirred at room temperature overnight. 2 N HCl (30 mL) was added and the organic and aqueous phases were separated. The organic phase was washed with water (30 mL), dried over $MgSO_4$ and concentrated to give a pale-yellow oil, which was purified over silica-gel chromatography in EtOAc/heptane (1/1) to give 1.1 g (2.34 mmol; 43%) of **20a** and 1.0 g (2.12 mmol; 39%) of **20b** as white solids. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: (**20a**): 1.2–1.65 (m, 13H), 2.4 (m, 1H), 3.35 (d, 1H), 3.5–3.8 (m, 3H), 5.1 (m, 2H), 5.3 (m, 1H), 5.7 (t, 1H), 7.3–7.8 (m, 12H). (**20b**): 1.2–1.65 (m, 13H), 2.4 (m, 1H), 3.25 (d, 1H), 3.5–3.8 (m, 3H), 5.1 (m, 2H), 5.3 (m, 1H), 5.7 (t, 1H), 7.3–7.8 (m, 12H). MS (ES^+) *m/e*: (**20a**) : 471 ($[MH]^+$, 100%); (**20b**): 471 ($[MH]^+$, 100%).

(*S*)-2-Aza-spiro[4.5]decane-4-carboxylic acid hydrochloride (12a). To a solution of **20a** (770 mg; 1.64 mmol) in THF (5 mL) was added 6 N aq HCl (40 mL). The reaction mixture was stirred under reflux overnight. After cooling, the reaction mixture was washed with EtOAc (2×20 mL). The phases were separated and the aqueous phase was concentrated to dryness under vacuum. The crude residue was dissolved in 6 N aqueous HCl (40 mL) and the reaction mixture was stirred under reflux for 60 h. After cooling, the reaction mixture was washed with EtOAc (2×20 mL). The phases were separated and the aqueous phase was concentrated to dryness to leave a solid, which was dissolved in water. Removing water under vacuum led to **12a** as a white powder (263 mg; 1.20 mmol; 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.2–1.8 (m, 10H), 3.1 (t, 1H), 3.4 ([AB]q, 2H), 3.7 (m, 2H). MS (ES^+) *m/e*: 184 ($[MH]^+$, 100%). Microanalysis calculated for $C_{10}H_{17}NO_2$.HCl: C 54.67% H 8.26% Cl 16.14% N 6.37%. Found: C 54.51% H 8.46% Cl 15.96% N 6.22%.

(*R*)-2-Aza-spiro[4.5]decane-4-carboxylic acid hydrochloride (12b). Compound **20b** (553 mg; 1.17 mmol) was converted to 200 mg (0.91 mmol; 78%) of **12b** by the same procedure for **20a** to **12a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.2–1.8 (m, 10H), 3.1 (t, 1H), 3.4 ([AB]q, 2H), 3.7 (m, 2H). MS (ES^+) *m/e*: 184 ($[MH]^+$, 100%). Microanalysis calcd for $C_{10}H_{17}NO_2$.HCl: C 54.67% H 8.26% Cl 16.14% N 6.37%. Found: C 54.48% H 8.42% Cl 15.99% N 6.18%.

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