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Synthesis of a conformationally restricted analog of pregabalin by stereoselective alkylation of a chiral pyrrolidin-2-one

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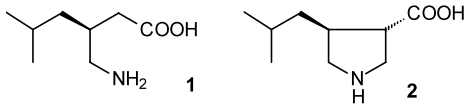
Abstract—The 4-benzyloxymethyl pyrrolidin-2-one, **5**, was alkylated leading to 3,4-*trans*-disubstituted pyrrolidin-2-one **6** in good yield and total diastereoselection, as shown by ^{1}H NMR data and NOE experiments. After reduction of the carbonyl group to give the *trans*-3,4-disubstituted pyrrolidine **7**, and removal of the chiral auxiliary, followed by protection of the nitrogen with *t*-Boc group, the corresponding *N*-protected pyrrolidine, **8** was obtained. The cleavage of the benzyl ether moiety, followed by oxidation of the hydroxy function, gave in good yield the corresponding pyrrolidine carboxylic acid **2**, a restricted analog of pregabalin.

1. Introduction

Pregabalin **1**, a potent anticonvulsant related to the inhibitory neurotransmitter γ-aminobutyric acid, represents a very important drug active in pre-clinical models in treatment of epilepsy and other neuropathologies which displays high affinity for the α2δ component of voltage gated ion channels.[1] In order to investigate the binding properties of pregabalin towards its receptor, the conformationally restricted analog **2** and its enantiomer, *ent*-**2**, were required (Scheme 1).[2]

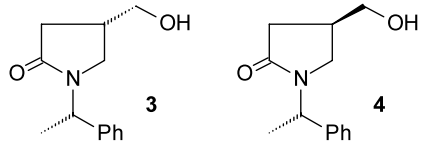
Many strategies have recently been reported in order to prepare 4-substituted 3-pyrrolidine carboxylic acids, since these compounds display an important role in medicinal chemistry, being the heterocyclic nucleus of many biologically active compounds, but good stereochemical control of the products has rarely been attained.[3] Within a project aimed to synthesise conformationally restricted non-proteinogenic amino acids, we considered that appropriate starting materials could be the hydroxymethyl pyrrolidin-2-ones **3** and **4**,[4] whose synthesis was carried out taking advantage of the recently described cyclisation of acyclic malonamides mediated by Mn(III) (Scheme 2).[5]



Scheme 1.

2. Results and discussion

Although alkylation of *N*-benzyl lactams was reported to proceed in poor yield,[6,7] our synthetic approach to compound **2** began with the alkylation of **5**, obtained by reaction of the anion of **3** with benzyl bromide. Deprotonation at C-3, carried out with LiHDMS, followed by treatment with 2-methyl-3-iodopropane, resulted in the formation in good yield of the 3,4-disubstituted derivative **6**, exclusively, whose configuration was established as *trans* on the basis of the NOE between H-3 and C$\underline{H}_2$OBn (8%) (Scheme 3).



Scheme 2.

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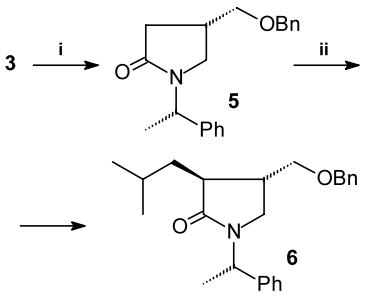


Scheme 3. *Reagents and conditions*: (i) *n*-BuLi THF, HMPA, 0°C, then benzyl bromide, 91%; (ii) LiHDMS, THF, 0°C, then 2-methyl-3-iodopropane, 92%.

With the 3,4-*trans*-disubstituted pyrrolidin-2-one **6** in hand, removal of the carbonyl group, performed by using LAH in refluxing THF, gave the *N*-phenylethyl substituted pyrrolidine, **7**, which underwent nitrogen debenzylation on treatment with chloroethyl chloroformate and the *N*-dealkylated pyrrolidine was directly converted into the corresponding Boc derivative, **8**.[8] The cleavage of the benzyl ether, carried out by hydrogenolysis,[9] afforded the alcohol **9** which underwent oxidation by using the Jones' reagent,[10] leading in good yield to the carboxylic acid. For better purification this compound was directly adsorbed on IRA 900 in the hydroxide form and the carboxylate on polymeric support was treated with iodomethane, to give the ester **10**.[11] Removal of both the Boc and the methyl ester groups, carried out by treating with aqueous HCl, gave the hydrochloride **11** which was eventually converted into the pyrrolidine carboxylic acid **2** by eluting on Dowex 50WX2 resin with 1 M NH_4OH (Scheme 4). It is worth mentioning that the above synthetic sequence, carried out starting from **4**, gave the amino acid *ent*-**2** in good yield, so that both the pregabalin analog, **2**, and its enantiomer, *ent*-**2**, can be available by using the stereoselective alkylation of a chiral pyrrolidin-2-one (Scheme 5). This approach should be useful for the synthesis of a number of 4-substituted pyrrolidine carboxylic acids, compounds which display an interesting biological activity.

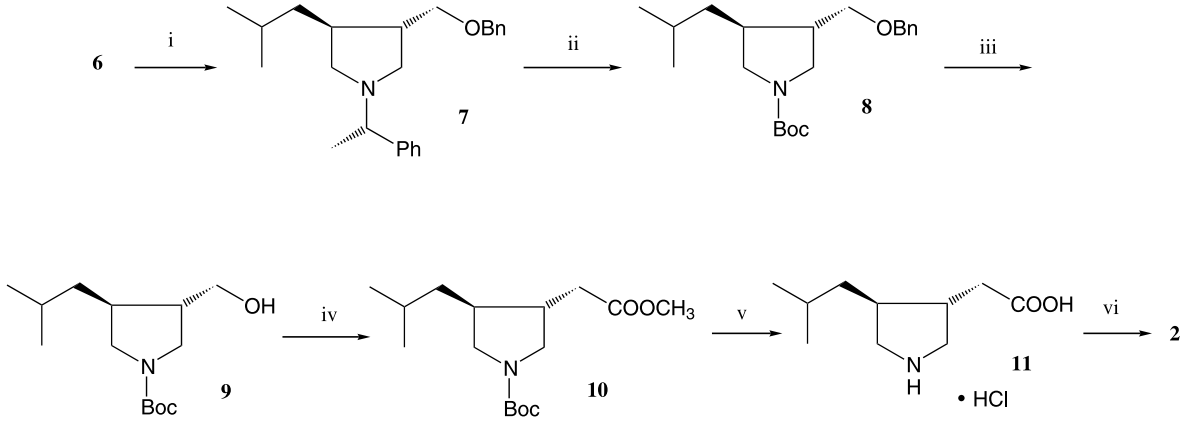
3. Experimental

3.1. General methods and materials

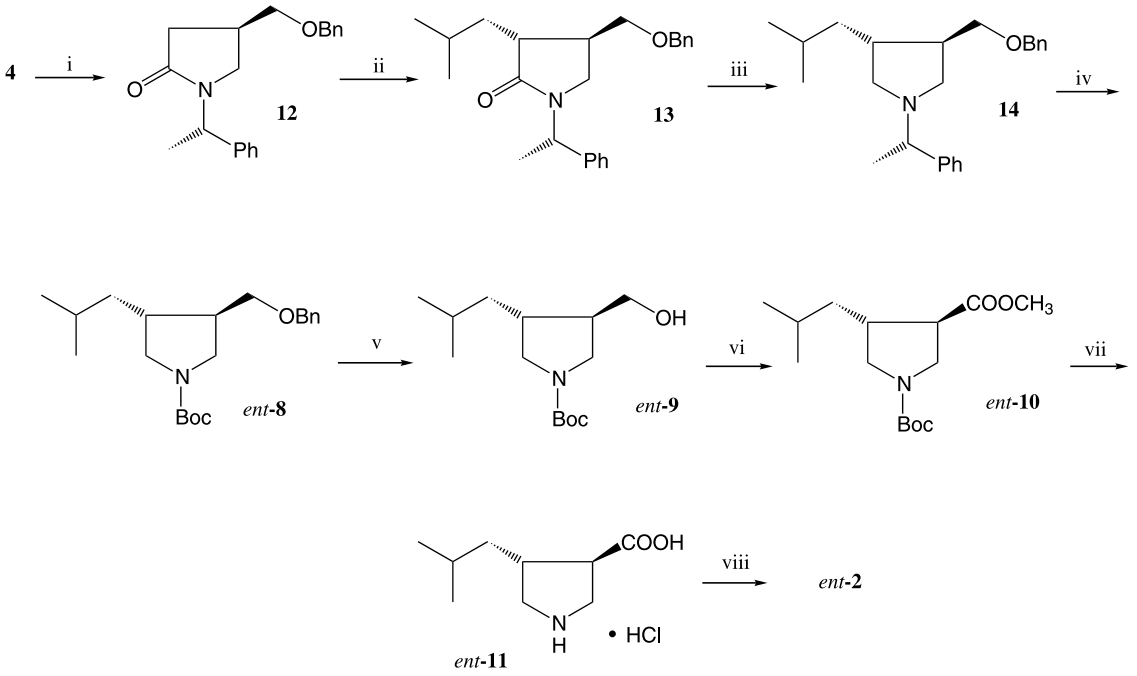
Melting points were measured on a Electrothermal IA 9000 apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20-SX FT-IR spectrophotometer in $CHCl_3$. ^1H and ^{13}C NMR spectra were determined on a Varian Gemini 200 spectrometer in $CDCl_3$ (unless otherwise reported). Chemical shifts are reported in the δ scale and coupling constants (J) values are given in Hz. Diastereomeric purity was determined by GLC analysis by using a Chrompack 9001 gas-chromatograph equipped with a capillary column Chrompack 7720 (50 m×0.25 mm i.d.; stationary phase CP-Sil-5 CB). Specific rotation measurements, $[\alpha]_D$, were recorded at rt on a Perkin–Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). MS analyses were obtained on a Hewlett–Packard spectrometer model 5890, series II. Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM). Tetrahydrofuran was distilled from sodium/benzophenone under an argon atmosphere. (4*S*,1′*S*)-4-Hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one **3** and its diastereomer (4*R*,1′*S*)-**4** were prepared according to Ref. 4.

3.2. (4*S*,1′*S*)-4-Benzyloxymethyl-1-(1′-phenylethyl)-pyrrolidin-2-one 5

To a solution containing pyrrolidin-2-one **3** (2.2 g; 10 mmol), HMPA (2 mL) and triphenylmethane (100 mg) in dry THF (30 mL), *n*-BuLi (2.5 M in hexanes; 4.0 mL) was added at −15°C. After 20 min benzyl bromide (1.7 g; 10 mmol) dissolved in dry THF (10 mL) was added and then the mixture was refluxed for 1 h. The reaction mixture was poured in H_2O (100 mL) and extracted with ethyl acetate (3×100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give compound **5** in 91% yield. Colorless oil. IR ($CHCl_3$): 1665 cm^{-1}; ^1H NMR: 1.48 (d, 3H, $J=7.0$), 2.16–2.32



Scheme 4. *Reagents and conditions*: (i) $LiAlH_4$, refluxing THF, 78%; (ii) $CH_3CH(Cl)OCOCl$, refluxing DCM, refluxing MeOH, then Boc_2O, Et_3N, DMAP, DCM, 76%; (iii) Pd–C 10%, HCOOH, EtOH, 82%. (iii) Jones' reagent, −10°C, then IRA 900 in the hydroxide form, CH_3I, refluxing cyclohexane, 81%; (v) 3 M HCl, rt, 74%; (vi) Dowex 50WX2, 1 M NH_4OH, 64%.



Scheme 5. *Reagents and conditions*: (i) *n*-BuLi THF, HMPA, 0°C, then benzyl bromide, 93%; (ii) LiHDMS, THF, 0°C, then 2-methyl-3-iodopropane, 91%; (iii) $LiAlH_4$, refluxing THF, 77%; (iv) $CH_3CH(Cl)OCOCl$, refluxing DCM, refluxing MeOH, then Boc_2O, Et_3N, DMAP, DCM, 79%; (v) Pd–C 10%, HCOOH, EtOH, 80%; (vi) Jones' reagent, −10°C, then IRA 120 in the hydroxide form, CH_3I, refluxing cyclohexane, 78%; (vii) 3 M HCl, rt 72%; (viii) Dowex 50WX2, 1 M NH_4OH, 62%.

(m, 1H), 2.41–2.64 (m, 2H), 3.08 (dd, 1H, $J=7.2$, $J=9.9$), 3.16 (dd, 1H, $J=5.6$, $J=9.9$), 3.35 (dd, 1H, $J=6.8$, $J=9.1$), 3.45 (dd, 1H, $J=5.4$, $J=9.1$), 4.50 (ABq, 2H, $J=13.2$), 5.48 (q, 1H, $J=7.0$), 7.1–7.45 (m, 10 ArH); ^{13}C NMR: 16.6, 31.9, 35.2, 45.8, 49.4, 127.6, 128.0, 128.2, 128.3, 128.8, 129.0, 129.1, 138.4, 140.6, 173.8; $[\alpha]_D$ −79.4 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 309 (M^+), 294, 105, 91, 77. Anal. calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.58; H, 7.45; N, 4.59.

3.3. (3*S*,4*S*,1′*S*)-4-Benzyloxymethyl-3-(2″-methylprop-1″-yl)-1-(1′-phenylethyl)pyrrolidin-2-one 6

To a solution of pyrrolidin-2-one **5** (3.1 g; 10 mmol) in dry THF (30 mL), LiHMDS (1 M solution in hexanes; 10 mL; 10 mmol) was added dropwise at −15°C under an argon atmosphere. After stirring for 20 min, a solution of 1-iodo-2-methylpropane (1.8 g; 10 mmol) dissolved in dry THF (10 mL) was added at −15°C and the mixture was stirred for a further 2 h. Then the reaction mixture was poured in H_2O (100 mL) and extracted with ethyl acetate (3×100 mL). The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The crude oil was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give the pyrrolidin-2-one **7** in 92% yield as a colourless oil. IR ($CHCl_3$): 1667 cm^{-1}; ^1H NMR: 0.90 (d, 3H, $J=6.3$), 0.92 (d, 3H, $J=6.3$), 1.27 (ddd, 1H, $J=5.2$, $J=8.5$, $J=14.0$), 1.48 (d, 3H, $J=7.1$), 1.61–1.91 (m, 2H), 2.09–2.22 (m, 1H), 2.23–2.36 (m, 1H), 3.01 (dd, 1H, $J=7.6$, $J=9.9$), 3.09 (dd, 1H, $J=5.7$, $J=9.9$), 3.37 (dd, 1H, $J=7.8$, $J=9.1$), 3.49 (dd, 1H, $J=5.0$, $J=9.1$), 4.50 (ABq, 2H, $J=12.0$), 5.47 (q, 1H, $J=7.1$), 7.19–7.42 (m, 10 ArH); ^{13}C NMR: 16.4, 22.4, 23.6, 26.7, 38.7, 40.7, 43.5, 44.4, 49.2, 72.3, 73.7, 127.5, 127.6, 127.8, 128.1, 128.2, 128.9, 129.0, 138.5, 140.8, 176.4; $[\alpha]_D$ −75.2 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 366 (M^++1), 350, 203, 188, 105, 91. Anal. calcd for $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83. Found: C, 78.81; H, 8.49; N, 3.88.

3.4. (3*S*,4*S*,1′*S*)-4-Benzyloxymethyl-3-(2″-methylprop-1″-yl)-1-(1′-phenylethyl)pyrrolidine 7

To a solution containing the pyrrolidin-2-one **6** (3.7 g; 10 mmol) in dry THF (40 mL), $LiAlH_4$ (0.78 g; 20 mmol) was added under an inert atmosphere and the mixture was refluxed for 3 h. Then MeOH (5 mL) and an aqueous saturated NH_4Cl solution (30 mL) were added and the mixture was extracted with ethyl acetate (3×100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give the pyrrolidine **7** in 78% yield as a colourless oil. ^1H NMR: 0.86 (d, 3H, $J=6.5$), 0.87 (d, 3H, $J=6.5$), 1.23–1.35 (m, 2H), 1.35 (d, 3H, $J=6.6$), 1.41–1.59 (m, 1H), 1.78–2.05 (m, 3H), 2.40 (dd, 1H, $J=4.7$, $J=9.4$), 2.53 (dd, 1H, $J=8.0$, $J=9.4$), 2.94 (dd, 1H, $J=6.9$, $J=8.5$), 3.16 (q, 1H, $J=6.6$), 3.31–3.46 (m, 2H), 4.48 (ABq, 2H, $J=12.2$), 7.16–7.41 (m, 10 ArH); ^{13}C NMR: 22.8, 23.8, 27.0, 39.3, 45.2, 57.0, 59.8, 66.2, 73.5, 74.4, 127.2, 127.6, 127.7, 127.9, 128.0, 128.7, 128.8, 139.1, 146.2; $[\alpha]_D$ −38.6 (*c* 0.7, $CHCl_3$); MS (EI): *m*/*z* 352 (M^++1), 336, 309, 204, 105, 91. Anal. calcd for $C_{24}H_{33}NO$: C, 82.00; H, 9.46; N, 3.98. Found: C, 81.93; H, 9.49; N, 3.94.

3.5. (3*S*,4*S*)-3-Benzyloxymethyl-1-(*t*-butoxycarbonyl)-4-(2′-methylprop-1′-yl)pyrrolidine 8

To a solution of **7** (1.8 g; 5 mmol) in DCM (20 mL) chloroethyl chlorocarbonate (1.4 g; 10 mmol) was added at 0°C and after 20 min the solvent was removed under reduced pressure. Then to the residue methanol (40 mL) was added and the solution was refluxed for 30 min. Methanol was removed under reduced pressure and to the residue ethyl acetate (100 mL) and 2 M NaOH (50 mL) were added. After extraction with ethyl acetate (2×100 mL), the organic layer was dried (Na_2SO_4) and eventually the solvent was removed under reduced pressure. The residue was dissolved in DCM (30 mL) containing Et_3N (0.5 g; 5 mmol) and DMAP (0.1 g) and then di-*tert*-butyl dicarbonate (1.1 g; 5 mmol) was added at 0°C. After 4 h, H_2O (20 mL) was added and the mixture extracted with ethyl acetate (2×50 mL). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30) to give **8** in 76% yield as a colourless oil. ^{1}H NMR: 0.87 (d, 3H, $J=6.2$), 0.89 (d, 3H, $J=6.2$), 1.11–1.35 (m, 2H), 1.47 (s, 9H), 1.49–1.62 (m, 1H), 1.88–2.16 (m, 2H), 2.81–3.01 (m, 1H), 3.03–3.25 (m, 1H), 3.30–3.45 (m, 1H), 3.45–3.71 (m, 3H), 4.51 (ABq, 2H, $J=12.2$), 7.24–7.42 (m, 5 ArH); ^{13}C NMR: 22.3, 24.1, 27.1, 29.0, 38.4 (60%), 39.2 (40%), 42.7, 44.5 (40%), 45.4 (60%), 49.5 (40%), 49.9 (60%), 51.9 (60%), 52.2 (40%), 71.4, 73.6, 79.4, 127.9, 128.8, 138.7, 154.9; $[\alpha]_D$ −27.2 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 348 (M^++1), 291, 246, 185, 91, 57. Anal. calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.50; H, 9.51; N, 4.10.

3.6. (3*S*,4*S*)-1-(*t*-Butoxycarbonyl)-3-hydroxymethyl-4-(2′-methylprop-1′-yl)pyrrolidine 9

To a solution containing compound **8** (2.4 g; 7 mmol) and HCOOH (7 mL) in dry ethanol (60 mL) under an argon atmosphere, Pd 10 wt. % on activated carbon (1.4 g) was added and the mixture was stirred for 1 h at rt. After removal of the catalyst by filtration, the organic layer was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The solution was washed with saturated aqueous $NaHCO_3$ (30 mL), the solvent was dried (Na_2SO_4) and removed under reduced pressure gave pure **9** in 82% yield. ^{1}H NMR: 0.88 (d, 3H, $J=6.2$), 0.90 (d, 3H, $J=6.2$), 1.13–1.56 (m, 3H), 1.45 (s, 9H), 1.87–2.08 (m, 2H), 2.77–2.97 (m, 1H), 3.05–3.22 (m, 1H), 3.35–3.88 (m, 4H+OH); ^{13}C NMR: 21.8, 23.5, 26.5, 28.5, 37.5 (50%), 38.1 (50%), 42.2, 46.2 (50%), 47.0 (50%), 48.7 (50%), 49.1 (50%), 51.4 (50%), 51.8 (50%), 63.3, 79.2, 154.6; $[\alpha]_D$ −39.8 (*c* 4.0, $CHCl_3$); MS (EI): *m*/*z* 257 (M^+), 226, 200, 140, 101, 57. Anal. calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.28; H, 10.52; N, 5.51.

3.7. Methyl (3*S*,4*S*)-1-*t*-butoxycarbonyl-4-(2′-methyl prop-1′-yl)-3-pyrrolidinecarboxylate 10

To a solution containing compound **9** (1.0 g; 4 mmol) in acetone (20 mL), the Jones' reagent (1.9 mL) was added at −15°C and the mixture was stirred for 5 min. Then ethyl acetate (20 mL) and subsequently Na_2CO_3 saturated aqueous solution (20 mL) were added at 0°C. After extraction of the aqueous phase with ethyl acetate (50 mL), organics were discarded and the pH of the aqueous layer raised to 2 by slow addition of 1 M HCl under stirring. Then, extraction with ethyl acetate (2×50 mL) followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a residue which was dissolved in methanol (5 mL). This solution was added to a suspension of Amberlite IRA 900 in the hydroxide form (2.0 g) in methanol (10 mL). After 1 h the solvent was filtered off, the polymeric reagent was suspended in cyclohexane (15 mL) and CH_3I (1.8 g; 13 mmol) was added. The mixture was refluxed for 1.5 h, then the resin was removed by filtration and the solvent evaporated under reduced pressure, to give a residue which was purified by silica gel chromatography (cyclohexane:acetate 70:30) affording the ester **10** in 81% overall yield as a colourless oil. IR ($CHCl_3$): 1734, 1711 cm^{-1}; ^{1}H NMR: 0.89 (d, 6H, $J=6.2$), 1.12–1.56 (m, 3H), 1.45 (s, 9H), 2.38–2.54 (m, 1H), 2.54–2.73 (m, 1H), 2.87–2.97 (m, 1H), 3.40–3.52 (m, 1H), 3.55–3.77 (m, 2H), 3.71 (s, 3H); ^{13}C NMR: 21.6, 23.0, 26.2, 26.6, 28.1, 39.5 (70%), 40.1 (30%), 41.8, 48.1 (70%), 49.1 (30%), 50.9, 51.5, 78.9, 153.8, 172.9; $[\alpha]_D$ −38.2 (*c* 3.4, $CHCl_3$); MS (EI): *m*/*z* 285 (M^+), 270, 228, 117. Anal. calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.08; H, 10.02; N, 4.86.

3.8. (3*S*,4*S*)-4-(2′-Methylprop-1′-yl)-3-pyrrolidine carboxylic acid, 2

The ester **10** (0.85 g; 3 mmol) was suspended in 3 M HCl (5.0 mL) and the mixture was stirred for 24 h at rt. Removal of H_2O under reduced pressure gave a solid which was recrystallised from methanol to give (3*S*,4*S*)-4-(2′-methylprop-1′-yl)-3-pyrrolidine carboxylic acid hydrochloride, **11**, in 74% yield. Mp 186–188°C. ^{1}H NMR: 0.87 (m, 6H), 1.28–1.72 (m, 3H), 2.51–2.76 (m, 1H), 2.83–3.15 (m, 2H), 3.45–3.74 (m, 3H). ^{13}C NMR: 24.3, 25.2, 28.9, 43.2, 44.0, 50.1, 51.0, 53.4, 178.8. $[\alpha]_D$ −36.7 (*c* 1.0, H_2O). This product was subjected to ion exchange column (Dowex 50WX2) and eluted with 1 M NH_4OH to give **2** as a white solid (0.33 g; 64% yield). Mp 243–245°C (Lit.[2] 251–254°C); ^{1}H NMR (CD_3OD): 0.79–0.94 (m, 6H), 1.18–1.36 (m, 1H), 1.49–1.66 (m, 2H), 2.38–2.62 (m, 2H), 2.72–2.90 (m, 1H), 3.32–3.53 (m, 3H); ^{13}C NMR (CD_3OD): 21.1, 22.1, 26.3, 40.8, 41.8, 48.4, 50.1, 51.8, 177.5; $[\alpha]_D$ −43.6 (*c* 0.5, MeOH) (Lit.[2] −45.8); MS (CI): *m*/*z* 172 (M^++1). Anal. calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18; Found: 62.93; H, 10.14; N, 8.01.

3.9. (4*R*,1′*S*)-4-Benzyloxymethyl-1-(1′-phenylethyl)-pyrrolidin-2-one 12

This product was prepared in 93% yield from **4** as a colourless oil by the method described for compound **5**. IR ($CHCl_3$): 1671 cm^{-1}; ^{1}H NMR: 1.55 (d, 3H, $J=7.1$), 2.13–2.28 (m, 1H), 2.48–2.67 (m, 2H), 2.83 (dd, 1H, $J=4.2$, $J=9.8$), 3.20 (dd, 1H, $J=7.4$, $J=9.1$), 3.33 (dd, 1H, $J=5.4$, $J=9.1$), 3.43 (dd, 1H, $J=7.7$, $J=9.8$), 4.39

(s, 2H), 5.50 (q, 1H, $J=7.1$), 7.14–7.42 (m, 10 ArH); ^{13}C NMR: 16.6, 31.9, 35.2, 45.7, 49.4, 72.6, 79.8, 127.6, 128.0, 128.1, 128.2, 128.9, 129.0, 129.6, 138.3, 140.6, 173.9; $[\alpha]_D$ −38.4 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 309 (M^+), 294, 105, 91, 77. Anal. calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.60; H, 7.52; N, 4.50.

3.10. (3*R*,4*R*,1′*S*)-4-Benzyloxymethyl-3-(2″-methylprop-1″-yl)-1-(1′-phenylethyl)pyrrolidin-2-one 13

This product was prepared in 91% yield from **12** as a colourless oil by the method described for compound **6**. IR ($CHCl_3$): 1670 cm^{-1}; ^{1}H NMR: 0.91 (d, 3H, $J=6.5$), 0.94 (d, 3H, $J=6.5$), 1.33 (ddd, 1H, $J=5.2$, $J=8.1$, $J=13.3$), 1.51 (d, 3H, $J=7.2$), 1.59–1.91 (m, 2H), 2.20–2.36 (m, 2H), 2.78 (dd, 1H, $J=4.8$, $J=10.0$), 3.20 (dd, 1H, $J=7.8$, J = 9.1), 3.33–3.46 (m, 2H), 4.37 (ABq, 2H, $J=11.9$), 5.49 (q, 1H, $J=7.2$), 7.15–7.41 (m, 10 ArH); ^{13}C NMR: 16.6, 22.4, 23.7, 26.3, 38.6, 40.8, 43.8, 44.3, 49.4, 72.4, 73.7, 127.6, 127.9, 128.1, 128.2, 128.9, 129.0, 138.4, 140.7, 176.6; $[\alpha]_D$ −56.1 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 366 (M^++1), 350, 203, 188, 105, 91. Anal. calcd for $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83. Found: C, 78.83; H, 8.58; N, 3.78.

3.11. (3*R*,4*R*,1′*S*)-4-Benzyloxymethyl-3-(2″-methylprop-1″-yl)-1-(1′-phenylethyl)pyrrolidine, 14

This product was prepared in 77% yield as a colourless oil from **13** by the method described for compound **7**. ^{1}H NMR: 0.82 (d, 6H, $J=6.4$), 1.21–1.32 (m, 1H), 1.34 (d, 3H, $J=6.6$), 1.36–1.54 (m, 1H), 1.65–1.85 (m, 1H), 1.91–2.08 (m, 2H), 2.42–2.56 (m, 1H), 2.63 (dd, 1H, $J=7.5$, $J=9.4$), 2.69 (dd, 1H, $J=4.8$, $J=9.4$), 3.14 (q, 1H, $J=6.6$), 3.39–3.48 (m, 2H), 4.52 (s, 2H), 7.16–7.41 (m, 10 ArH); ^{13}C NMR: 22.9, 23.7, 23.8, 27.0, 39.2, 45.3, 56.7, 60.0, 66.1, 73.5, 74.4, 127.2, 127.7, 128.0, 128.1, 128.7, 128.8, 139.2, 146.4; $[\alpha]_D$ +10.1 (*c* 1, $CHCl_3$); MS (EI): *m*/*z* 352 (M^++1), 336, 309, 204, 105, 91. Anal. calcd for $C_{24}H_{33}NO$: C, 82.00; H, 9.46; N, 3.98. Found: C, 81.95; H, 9.40; N, 4.01.

3.12. (3*R*,4*R*)-3-Benzyloxymethyl-1-(*t*-butoxycarbonyl)-4-(2′-methylprop-1′-yl)pyrrolidine, *ent*-8

This product was prepared in 79% yield from **14** by the method described for compound **8**. $[\alpha]_D$ +26.8 (*c* 0.5, $CHCl_3$).

3.13. (3*R*,4*R*)-1-(*t*-Butoxycarbonyl)-3-hydroxymethyl-4-(2′-methylprop-1′-yl)pyrrolidine, *ent*-9

This product was prepared in 80% yield from *ent*-**8** by the method described for compound **9**. $[\alpha]_D$ +35.8 (*c* 4.6, $CHCl_3$).

3.14. Methyl (3*R*,4*R*)-1-*t*-butoxycarbonyl-4-(2′-methylprop-1′-yl)-3-pyrrolidinecarboxylate, *ent*-10

This product was prepared in 78% yield from *ent*-**9** by the method described for compound **10**. $[\alpha]_D$ +37.5 (*c* 2.0, MeOH).

3.15. (3*R*,4*R*)-4-(2′-Methylprop-1′-yl)-3-pyrrolidine carboxylic acid hydrochloride, *ent*-11

This product was prepared in 72% yield from *ent*-**10** by the method described for compound **11**. $[\alpha]_D$ +36.9 (*c* 1.0, H_2O).

3.16. (3*R*,4*R*)-4-(2′-Methylprop-1′-yl)-3-pyrrolidine carboxylic acid, *ent*-2

This product was prepared in 62% yield from *ent*-**11** by the method described for compound **2**. White solid. Mp 235–237°C (Lit.[2] 236–239°C); $[\alpha]_D$ +43.8 (*c* 0.5, MeOH) (Lit.[2] +44.8).

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