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A STEREOSELECTIVE APPROACH TO BOTH 3,4-*TRANS*-DISUBSTITUTED PYRROLIDIN-2-ONES AND PYRROLIDINES. A CONVENIENT SYNTHESIS OF (3*R*,4*R*)-4-BENZYL-3-PYRROLIDINECARBOXYLIC ACID

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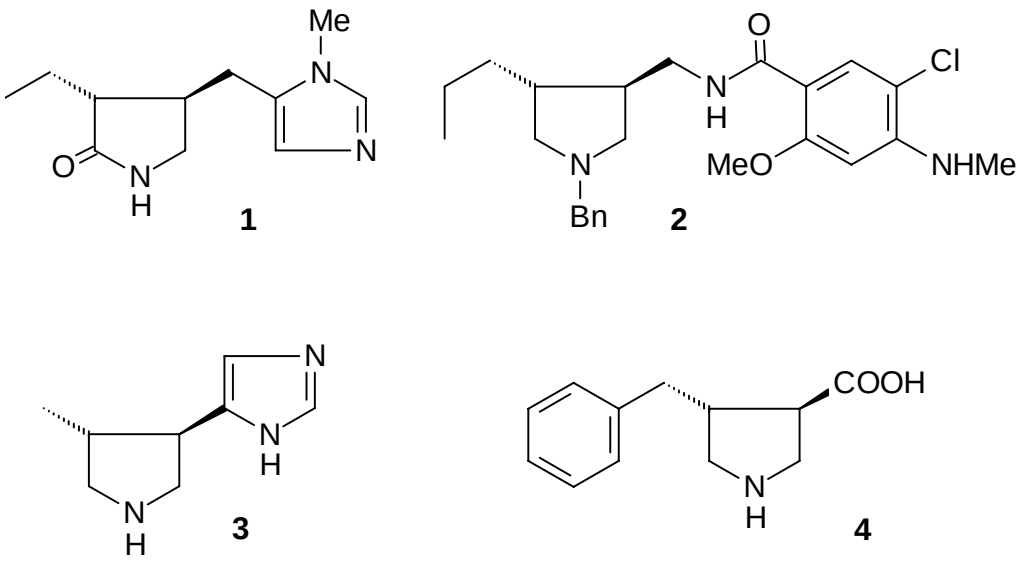
Abstract – Chiral 4-alkyloxymethyl- and silyloxymethylpyrrolidin-2-ones, **(10a-c)**, underwent alkylation to give the corresponding 3,4-*trans*-disubstituted pyrrolidin-2-ones, **(11a-g)**, in good yield and total stereoselection, as shown by ^{1}H NMR spectral data and n.O.e. experiments. Moreover compounds **(11a-c)** were converted into the corresponding 3,4-*trans*-disubstituted pyrrolidines, **(12a-c)**. Removal of the chiral auxiliary from **12a**, followed by protection of the nitrogen with *t*-Boc group, led to the corresponding derivative **(13)**. Cleavage of the benzyl ether and subsequent oxidation of the hydroxy function afforded (3*R*,4*R*)-4-benzyl-3-pyrrolidinecarboxylic acid **(4)**.

INTRODUCTION

Chiral 3,4-*trans*-disubstituted pyrrolidin-2-ones and pyrrolidines were shown to exhibit a broad spectrum of pharmacological activities. Thus, pilolactam **(1)** is effective in oftalmology, [1] compound Sch 50971, **(2)**, acts as H_3 agonist, [2] the amide **(3)** showed an interesting dopamine receptor binding activity [3] and an analogue of the endogeneous peptide PLG (Pro-Leu-Gly-NH_2) in which Pro is changed with *trans*-4-benzyl-3-pyrrolidinecarboxylic acid, **(4)**, resulted metabolically more stable than the parent tripeptide in treatment of both the Parkinson disease and schizofrenia (Scheme 1). [4] In addition, several enantiopure 1,3,4-substituted pyrrolidines were prepared and used as auxiliaries for a lot of important

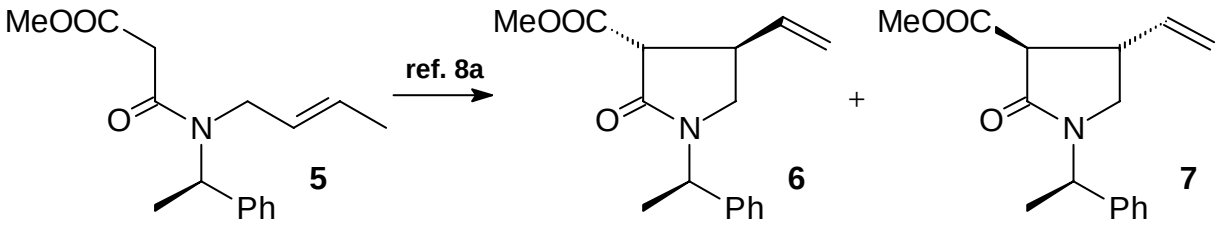
transformations. [5] Therefore, the development of methods for the stereoselective synthesis of 3,4-disubstituted pyrrolidin-2-ones, which can be precursors of 3,4-disubstituted pyrrolidines, is of growing interest. [6,7]



Scheme 1

RESULTS AND DISCUSSION

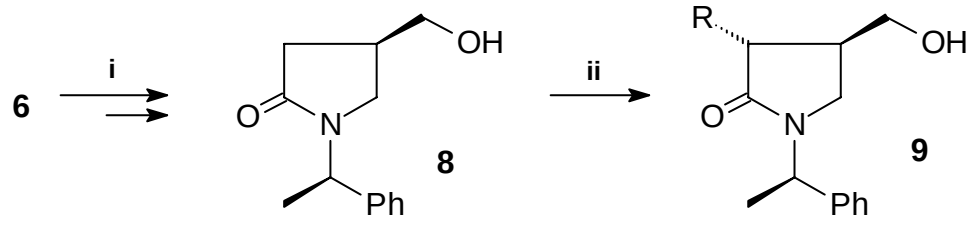
Within a project directed towards the synthesis of conformationally restricted non proteinogenic amino acids active at the CNS level, [8] we devised that enantiomerically pure 4,5-*trans*-disubstituted pyrrolidin-2-ones could arise from pyrrolidin-2-ones **(6)** and **(7)** we already obtained by cyclisation of the chiral malonamide (**5**) mediated by Mn(III) (Scheme 2). [8c]



Scheme 2

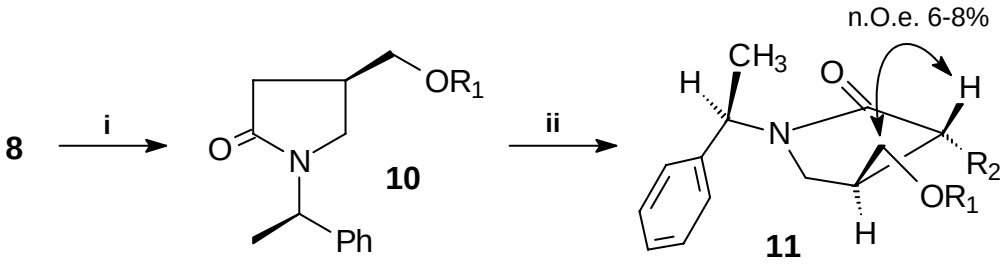
Thus, pyrrolidin-2-one **(6)** was easily converted into the corresponding 4-hydroxymethyl derivative **(8)**, [8c] but alkylation carried out with n-BuLi in THF, followed by addition of the appropriate alkyl halide, proceeded in low yield, to give **9**, probably due to the low solubility of the dianion. On the other hand,

when HMPA was employed in order to completely dissolve the dianion, substantial amounts of the *O*-alkylation product were isolated from the reaction mixture (Scheme 3).



Scheme 3. ***Reagents and conditions*****: i.** See ref. 9. **ii.** n-BuLi (2 equiv), THF, HMPA, 0°C (**a.** R = $C_6H_5CH_2$, 51%; **b.** R = C_2H_5, 48%; **c.** R = $C_6H_5CH_2OCH_2$, 44%).

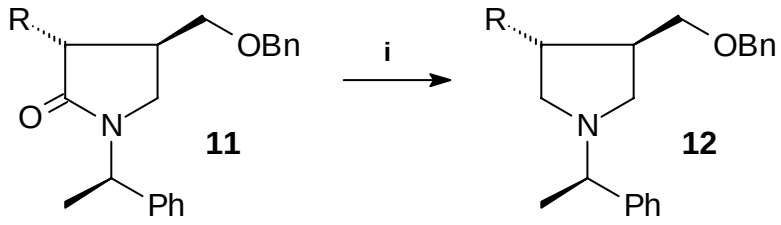
However, when 4-hydroxymethyl derivative **(8)** was converted into the corresponding benzyl, tetrahydropyranyl or TBDMS ethers **(10)** respectively, the alkylation proceeded in high yield and total stereoselection to give 3,4-disubstituted pyrrolidin-2-ones **(11)**, the *trans*-isomer being the sole product isolated from the reaction mixture, whose configuration was assigned on the basis of n.O.e. experiments (Scheme 4). The stereochemical outcome of the reaction leading to 3,4-*trans*-disubstituted compounds **(11)**, exclusively, can be ascribed to the effect of the substituent at C-4. In fact, by steric hindrance the alkylating reagent is biased to attack the enolate anion of **10** only from the opposite side with respect to this substituent.



Scheme 4. ***Reagents and conditions*****. i.** For **10a** (R_1 = Bn): n-BuLi, THF, HMPA, then BnBr, 91%. For **10b** (R_1 = THP): H 15, DHP, DCM, 81%. For **10c** (R_1 =TBDMS): NaH, THF, then TBDMSCl, 78%. **ii.** n-BuLi, THF, 0°C. **a.** $R_1 = R_2$ = Bn, 87%; **b.** R_1 = Bn, R_2 = Et, 91%; **c.** R_1 = Bn, $R_2 = BnOCH_2$, 67% ; **d.** R_1 = THP, $R_2 = BnOCH_2$, 71%; **e.** R_1 = THP, R_2 = COOMe, 68%; **f.** R_1 = THP, R_2 = *t*-$BuCOOCH_2$, 66%; **g.** R_1 = TBDMS, R_2 = n-Pr, 85%.

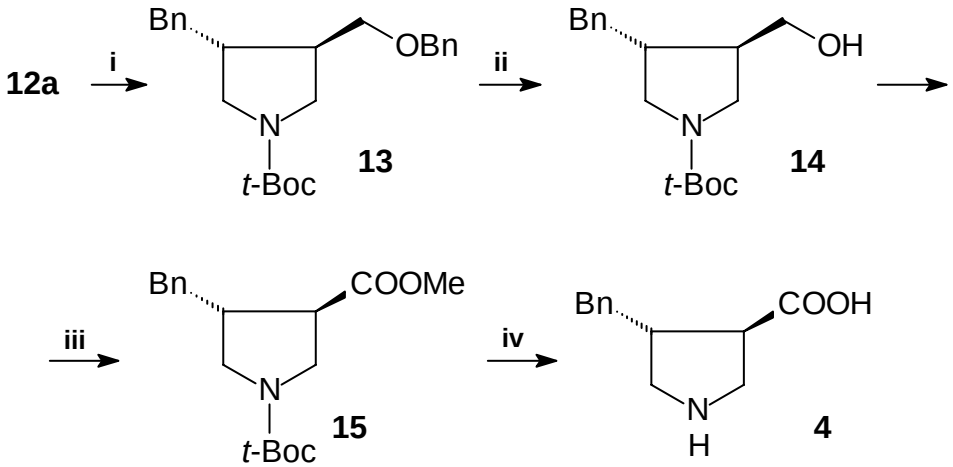
Since the reduction of pyrrolidin-2-ones to the corresponding pyrrolidines is of interest in both natural products and synthetic chemistry, [7] the pyrrolidin-2-ones **(11a-c)** were converted into the corresponding

pyrrolidines **(12a-c)** by treatment with LAH in refluxing THF (Scheme 5).



Scheme 5. ***Reagents and conditions*****. i.** LAH, refluxing THF. **a.** R = Bn, 78%; **b.** R = Et, 76%; **c.** R = $BnOCH_2$, 78%.

The usefulness of this approach to chiral 3,4-*trans*-disubstituted pyrrolidines was proven by the synthesis of the bioactive non proteinogenic amino acid (3*R*,4*R*)-**(4)**.[4] Thus, starting from **12a**, the chiral phenylethyl group was removed by using chloroethyl chloroformate in methanol, [10] to give the corresponding pyrrolidine which was directly converted into the corresponding *t*-Boc derivative **(13)**. The cleavage of the benzyl ether, performed by catalytic transfer hydrogenation in HCOOH, [11] gave the alcohol **(14)**, and subsequent oxidation, carried out by using the Jones' reagent at low temperature, led to the carboxylic acid, which without isolation was converted into its methyl ester **(15)** by using CH_2N_2. Eventually, removal of both the *t*-Boc and the methyl ester groups, carried out by treating with aqueous HCl, followed by elution on Dowex 50WX2, allowed to obtain the (3*R*,4*R*)-4-benzyl-3-pyrrolidinecarboxylic acid **(4)** (Scheme 6). [13]



Scheme 6. ***Reagents and conditions*****: i.** MeCH(Cl)OCOCl, refluxing DCM, refluxing MeOH, then Boc_2O, Et_3N, DMAP, DCM, 71% yield. **ii.** 10% Pd-C, HCOOH, EtOH, 82% yield. **iii.** Jones' reagent, then CH_2N_2, 83% yield. **iv.** a. 3 M HCl, rt,. b. Dowex 50WX2, 1 M NH_4OH as eluant, 50% overall yield.

EXPERIMENTAL

IR spectra were recorded on FT-IR Fourier Nicolet 20-SX spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Varian Gemini 200 spectrometer at 200 and 50.3 MHz for ^{1}H and ^{13}C, respectively, in $CDCl_3$ unless otherwise reported. Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Diastereomeric purity was determined by g.l.c. analysis by using a Chrompack 9001 gas-chromatograph equipped with a capillary column Chrompack 7720 (50 m x 0.25 mm i.d.; stationary phase CP-Sil-5 CB). Optical rotations, $[\alpha]_D$, were recorded at room temperature on a Perkin-Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). MS spectral 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. Compound **(8)** was obtained according ref. 9.

General procedure for the alkylation of pyrrolidin-2-one (8).

To a solution of pyrrolidin-2-one **(8)** (2.2 g; 10 mmol) in dry THF (30 mL) n-BuLi (2.5 M in hexanes; 8 mL; 20 mmol) was added under argon at -15 °C and the mixture was stirred for 20 min. Then a solution of the appropriate halide (10 mmol) dissolved in dry THF (10 mL) was added. After 1 h H_2O (100 mL) was added and the mixture extracted with ethyl acetate (3 x 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 70:30) to give pure compounds **(9a-c).**

(3*R*,4*R*,1′*R*)-3-Benzyl-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (9a)

Starting from **8** and benzyl bromide, **9a** (1.6 g; 51% yield) was obtained as a colorless oil. IR ($CHCl_3$): 3350, 1665 cm^{-1}; ^{1}H NMR: 1.50 (d, 3H, *J* = 7.1), 1.71 (br s, 1H, OH), 2.13 (m, 1H), 2.62 (ddd, 1H, *J* = 4.6, *J* = 7.6, *J* = 8.0), 2.75 - 2.93 (m, 2H), 3.06 (dd, 1H, *J* = 6.6, *J* =13.7), 3.17 (dd, 1H, *J* = 4.5, *J* = 13.7), 3.32 (dd, 1H, *J* = 7.2, *J* = 10.5), 3.41 (dd, 1H, *J* = 5.3, *J* = 10.5), 5.48 (q, 1H, *J* = 7.1), 7.14 - 7.38 (m, 10 ArH); ^{13}C NMR: 16.6, 36.5, 36.9, 44.2, 46.7, 49.6, 64.2, 126.9, 127.0, 127.5, 127.6, 127.8, 128.0, 128.1, 129.0, 129.8, 129.9, 139.3, 140.4, 175.3; $[\alpha]_D$ +73.7° (c 0.5, $CHCl_3$). 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, 77.59; H, 7.45; N, 4.58.

(3*R*,4*R*,1′*R*)-3-Ethyl-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (9b)

Starting from **8** and ethyl iodide, **9b** (1.2 g; 48% yield) was obtained as a colorless oil. IR ($CHCl_3$): 3345, 1668 cm^{-1}; ^{1}H NMR: 0.94 (t, 3H, *J* = 7.3), 1.50 (d, 3H, *J* = 7.1), 1.54 - 1.86 (m, 2H), 2.04 (br s, 1H, OH), 2.11 - 2.31 (m, 2H), 3.02 (dd, 1H, *J* = 7.9, *J* = 9.8), 3.13 (dd, 1H, *J* = 5.8, *J* = 9.8), 3.55 (dd, 1H, *J* = 7.2, *J* = 10.4), 3.69 (dd, 1H, *J* = 4.9, *J* = 10.4), 5.47 (q, 1H, *J* = 7.1), 7.21 - 7.42 (m, 5 ArH); ^{13}C NMR: 11.5, 16.5,

23.9, 39.1, 44.3, 46.4, 49.3, 65.1, 127.5, 127.6, 127.9, 129.0, 140.6, 176.0; $[\alpha]_D$ +68.4° (c 0.5, $CHCl_3$); MS (EI): *m/z* 247 (M^+), 232, 105, 91, 77. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.79; H, 8.52; N, 6.39.

(3*R*,4*R*,1′*R*)-3-Benzyloxymethyl-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (9c)

Starting from **8** and benzyl chloromethyl ether, **9c** (1.5 g; 43% yield) was obtained as a colorless oil. IR ($CHCl_3$): 3345, 1670 cm^{-1}; ^1H NMR: 1.51 (d, 3H, *J* = 7.1), 2.25 - 2.47 (m, 1H), 2.62 (ddd, 1H, *J* = 11.7, *J* = 8.3, *J* = 3.5), 2.95 (dd, 1H, *J* = 7.8, *J* = 9.6), 3.06 (dd, 1H, *J* = 8.7, *J* = 9.6), 3.32 (br s, 1H, OH), 3.55 - 3.69 (m, 3H), 3.96 (dd, 1H, *J* = 9.2, *J* = 3.5), 5.47 (q, 1H, *J* = 7.1), 7.19 - 7.41 (m, 10 ArH); ^{13}C NMR: 16.6, 40.8, 43.6, 48.5, 49.6, 65.1, 70.9, 74.1, 127.4, 127.9, 128.3, 128.4, 128.9, 129.0, 129.1, 137.9, 140.3, 173.1; $[\alpha]_D$ +85.9° (c 1, $CHCl_3$); MS (EI): *m/z* 339 (M^+), 324, 233, 202, 188, 172, 105, 91, 77. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.25; H, 7.36; N, 4.08.

(4*R*,1′*R*)-4-Benzyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (10a)

To a solution containing pyrrolidin-2-one **(8)** (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 x 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 **10a** (2.8 g; 91% yield) as a colorless oil. IR ($CHCl_3$): 3347, 1665 cm^{-1}; ^1H NMR: 1.48 (d, 3H, *J* = 7.0), 2.16 - 2.32 (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.

(4*R*,1′*R*)-1-Phenylethyl-4-tetrahydropyranyloxymethylpyrrolidin-2-one (10b).

To a solution containing the pyrrolidin-2-one **(8)** (2.2 g; 10 mmol) and dihydropyran (1.68 g; 20 mmol) in ethyl acetate (50 mL) resin 15 (3.0 g) was added and the mixture was stirred for 3 h at 0 °C. Then the resin was filtered off, the solvent removed under reduced pressure and the residue purified by silica gel chromatography (cyclohexane:ethyl acetate 30:70) to give **10b** (2.5 g; 81% yield) as a colorless oil (equimolar diastereomeric mixture). IR ($CHCl_3$): 1665 cm^{-1}; ^1H NMR: 1.52 (d, 3H, *J* = 7.1), 1.53 - 1.96 (m, 6H), 2.18 - 2.38 (m, 1H), 2.42 - 2.64 (m, 2H), 3.01 - 3.22 (m, 2H), 3.24 - 3.41 (m, 1H), 3.43 - 3.56 (m, 1H,

3.63 - 3.86 (m, 2H), 4.57 (m, 1H), 5.49 (q, 1H, *J* = 7.1), 7.22 - 7.41 (m, 5 ArH); ^{13}C NMR: 16.5, 19.9, 25.8, 30.9, 31.6 (50%), 31.7 (50%), 35.2, 45.8 (50%), 45.9 (50%), 49.3, 62.8, 69.9, 99.4 (50%), 99.6 (50%), 127.5, 127.9, 129.0, 140.5, 173.8 (50%), 173.9 (50%). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.19; H, 8.27; N, 4.59.

(4*R*,1′*R*)-4-*t*-Butyldimethylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (10c)

In a three-necked flask under argon atmosphere NaH (480 mg; 50% in mineral oil; 10 mmol) was suspended in pentane (20 mL) under stirring and after 10 min the solvent was removed by decanting. Then dry THF (30 mL) was added, followed by a solution of compound **(8)** (2.2 g; 10 mmol) dissolved in dry THF (15 mL). After 15 min a solution containing TBDMSCl (1.5 g; 10 mmol) in dry THF (5 mL) was added at 0 °C and the reaction mixture was stirred at rt for 6 h. The clear solution was poured in H_2O-ice and extracted with ethyl acetate (3 x 50 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 70:30) to give **10c** (2.6 g; 78% yield) as a colorless oil. IR ($CHCl_3$): 1667 cm^{-1}; ^{1}H NMR: 0.03 (s, 6H), 0.86 (s, 9H), 1.51 (d, 3H, *J* = 7.2), 2.19 - 2.54 (m, 3H), 3.01 (dd, 1H, *J* = 7.9, *J* = 9.7), 3.16 (dd, 1H, *J* = 3.7, *J* = 9.7), 3.50 (dd, 1H, *J* = 6.1, *J* = 10.1), 3.56 (dd, 1H, *J* = 5.1, *J* = 10.1), 5.49 (q, 1H, *J* = 7.2), 7.21 - 7.39 (m, 5 ArH); ^{13}C NMR: -5.0, -4.9, 16.6, 18.7, 26.3, 33.7, 34.7, 45.1, 49.3, 65.1, 127.6, 127.9, 129.0, 140.7, 174.0; $[\alpha]_D$ +55.7° (c 5, $CHCl_3$); MS (EI): *m/z* 333 (M^+), 318, 214, 105, 77, 57. Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 69.38; H, 9.41; N, 4.17.

General procedure for the alkylation of pyrrolidin-2-ones (10a-c).

To a solution of pyrrolidin-2-ones **(10a-c)** (10 mmol) in dry THF (30 mL), n-BuLi (2.5 M solution in hexanes; 4.0 mL; 10 mmol) was added dropwise at - 15 °C under argon atmosphere. After stirring for 20 min, a solution of the appropriate halide (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 x 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 pure pyrrolidin-2-ones **(11a-g)**.

(3*R*,4*R*,1′*R*)-3-Benzyl-4-benzyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (11a)

Starting from **10a** and benzyl bromide, **11a** (3.1 g; 78% yield) was obtained as a colorless oil. IR ($CHCl_3$): 1664 cm^{-1}; ^{1}H NMR: 1.48 (d, 3H, *J* = 7.0), 2.15 - 2.35 (m, 1H), 2.67 (ddd, 1H, *J* = 4.6, *J* = 7.5, *J* = 12.2), 4.37 (ABq, 2H, *J* = 12.4), 5.51 (q, 1H, *J* = 7.0), 7.13 - 7.43 (m, 15 ArH); ^{13}C NMR: 16.6, 35.6, 37.1, 44.5, 46.9, 49.4, 71.8, 73.6, 126.9, 127.4, 127.8, 128.1, 128.2, 128.9, 129.9, 138.5, 139.3, 140.6, 175.0; $[\alpha]_D$

+34.2° (c 1, $CHCl_3$); MS (EI): *m/z* 399 (M^+), 384, 307, 158, 77. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.11; H, 7.28; N, 3.47.

(3*R*,4*R*,1′*R*)-4-Benzyloxymethyl-3-ethyl-1-(1′-phenylethyl)pyrrolidin-2-one (11b)

Starting from **10a** and ethyl iodide, **11b** (2.6 g; 76% yield) was obtained as a colorless oil. IR ($CHCl_3$): 1660 cm^{-1}; ^1H NMR: 0.96 (t, 3H, *J* = 7.0), 1.49 (d, 3H, *J* = 7.1), 1.51 - 1.75 (m, 2H), 2.16 - 2.32 (m, 2H), 3.10 (dd, 1H, *J* = 7.9, *J* = 9.9), 3.09 (dd, 1H, *J* = 6.1, *J* = 9.9), 3.38 (dd, 1H, *J* = 7.5, *J* = 9.1), 3.51 (dd, 1H, *J* = 4.7, *J* = 9.1), 4.50 (ABq, 2H, *J* = 12.2), 5.49 (q, 1H, *J* = 7.1), 7.21 - 7.34 (m, 10 ArH); ^{13}C NMR: 11.5, 16.4, 23.8, 27.4, 37.2, 44.6, 46.7, 49.2, 72.6, 73.7, 127.5, 127.8, 128.1, 128.2, 128.9, 138.5, 140.8, 175.8; $[\alpha]_D$ +98.9° (c 1, $CHCl_3$); MS (EI): *m/z* 337 (M^+), 322, 158, 77. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30, H, 8.06; N, 4.15. Found: C, 78.24; H, 8.01; N, 4.11.

(3*R*,4*R*,1′*R*)-3,4-Dibenzyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (11c)

Starting from **10a** and chloromethyl benzyl ether, **11c** (2.9 g; 67%) was obtained as a colorless oil. IR ($CHCl_3$): 1660 cm^{-1}; ^1H NMR: 1.54 (d, 3H, *J* = 7.1), 2.55 - 2.75 (m, 2H), 3.07 - 3.21 (m, 2H), 3.46 (dd, 1H, *J* = 6.9, *J* = 9.1), 3.57 (dd, 1H, *J* = 5.0, *J* = 9.1), 3.76 (dd, 1H, *J* = 3.2, *J* = 9.4), 3.90 (dd, 1H, *J* = 4.0, *J* = 9.4), 4.55 (ABq, 2 x 2H, *J* = 12.5), 5.55 (q, 1H, *J* = 7.1), 7.11 - 7.45 (m, 15 ArH); ^{13}C NMR: 16.7, 35.7, 44.8, 46.8, 49.4, 70.2, 72.3, 73.7, 73.8, 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 138.5, 138.9, 140.5, 173.8; $[\alpha]_D$ +80.5° (c 1, $CHCl_3$); MS (EI): *m/z* 429 (M^+) 414, 352, 338, 214, 157, 91, 77. Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.23; H, 7.24; N, 3.22.

(3*R*,4*R*,1′*R*)-3-Benzyloxymethyl-1-phenylethyl-4-tetrahydropyranyloxymethylpyrrolidin-2-one (11d)

Starting from **10b** and chloromethyl benzyl ether, **11d** (3.0 g; 71%) was obtained as a colorless oil (equimolar diastereomeric mixture). IR ($CHCl_3$): 1665 cm^{-1}; ^1H NMR: 1.44 - 1.81 (m, 6H), 1.55 (d, 3H, *J* = 7.2), 2.35 - 2.64 (m, 2H), 2.91 - 3.21 (m, 3H), 3.28 - 3.54 (m, 3H), 3.58 - 3.91 (m, 4H), 4.51 (ABq, 2H, *J* = 12.5), 4.56 (m, 1H), 5.54 (q, 1H, *J* = 7.2), 7.15 - 7.42 (m, 10 ArH); ^{13}C NMR: 16.5, 19.9, 25.8, 30.9, 31.6 (50%), 31.7 (50%), 35.2, 45.8 (50%), 45.9 (50%), 49.3, 62.8, 69.9, 99.4 (50%), 99.6 (50%),127.5, 127.9, 129.0, 140.5,173.8 (50%), 173.9 (50%). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.65; N, 3.31. Found: C. 73.66; H, 7.59; N, 3.26.

(3*R*,4*R*,1′*R*)-3-Methoxycarbonyl-1-phenylethyl-4-tetrahydropyranyloxymethylpyrrolidin-2-one (11e)

Starting from **10b** and methyl chloroformate, **11e** was obtained (2.4 g; 68%) as a colorless oil (equimolar diastereomeric mixture). IR ($CHCl_3$): 1665 cm^{-1}; ^1H NMR: 1.41 - 1.88 (m, 6H), 1.53 (d, 3H, *J* = 7.1), 2.75 - 3.01 (m, 1H), 3.06 - 3.22 (m, 2H), 3.31 - 3,59 (m, 3H), 3.65 - 3.90 (m, 2H), 3.78 (s, 3H), 4.57 (m, 1H), 5.45 (q, 1H, *J* = 7.1); ^{13}C NMR: 16.4 (50%), 16.6 (50%), 19.7, 25.8, 30.8, 36.5 (50%), 36.6 (50%), 44.2 (50%), 44.4 (50%), 49.9, 52.7 (50%), 53.1 (50%), 62.6 (50%), 62.7 (50%), 68.1 (50%), 68.4 (50%), 78.2, 99.3 (50%), 99.6 (50%), 127.4, 127.8, 128.0, 129.1, 140.0, 169.2. Anal. Calcd for $C_{20}H_{20}NO_5$: C, 67.79; H, 5.69; N, 3.95. Found: C, 67.83; H, 5.62; N, 3.91.

(3*R*,4*R*,1′*R*)-1-(1′-Phenylethyl)-3-pivaloyloxymethyl-4-tetrahydropyranyloxymethylpyrrolidin-2-one (11f)

Starting from **10b** and chloromethyl pivalate, **11f** was obtained (2.6 g; 66%) as a colorless oil (equimolar diastereomeric mixture). IR ($CHCl_3$): 1736, 1668 cm^{-1}; ^1H NMR: 1.28 (s, 9H), 1.35 - 1.91 (m, 6H), 1.51 (d, 3H, *J* = 7.1), 2.59 - 2.78 (m, 1H), 2.96 - 3.10 (m, 1H), 3.12 - 3.35 (m, 3H), 3.41 - 3.56 (m, 1H), 3.62 - 3.74 (m, 3H), 4.05 (dd, 1H, *J* = 4.9, *J* = 8,9), 4.56 (m, 1H), 5.41 (q, 1H, *J* = 7.1), 7.18 - 7.41 (m, 5 ArH); ^{13}C NMR: 16.7, 19.8 (50%), 20.0 (50%), 25.8, 26.2, 26.3, 30.9, 37.5 (50%), 37.6 (50%), 44.6 (50%), 44.8 (50%), 45.6, 49.6, 53.2 (50%), 53.6 (50%), 62.8 (50%), 63.0 (50%), 68.4 (50%), 68.9 (50%), 99.5 (50%), 99.6 (50%); 127.4, 127.9, 129.0,140.0 (50%), 140.1 (50%), 171.0 (50%), 171.1 (50%). Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.39; H, 8.19; N, 3.43.

(3*R*,4*R*,1′*R*)-4-*t*-Butyldimethylsilyloxymethyl-1-(1′-phenylethyl)-3-propylpyrrolidin-2-one (11g)

Starting from **10c** and propyl iodide, **11g** (3.3 g; 87%) was obtained as a colorless oil. IR ($CHCl_3$): 1667 cm^{-1}; ^1H NMR: 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.89 (t, 3H, *J* = 6.9), 1.28 - 1.51 (m, 3H), 1.48 (d, 3H, *J* = 7.0), 1.61 - 1.81 (m, 1H), 1.99 - 2.14 (m, 1H), 2.22 - 2.34 (m, 1H), 2.92 (dd, 1H, *J* = 8.1, *J* = 9.8), 3.06 (dd, 1H, *J* = 5.7, *J* = 9.8), 3.50 (dd, 1H, *J* = 6.4, *J* = 10.0), 3.57 (dd, 1H, *J* = 5.2, *J* = 10.0), 5.48 (q, 1H, J = 7.0), 7.18 - 7.34 (m, 5 ArH); ^{13}C NMR: -5.2, -5.1, 14.4, 16.2, 18.4, 20.3, 26.1, 27.2, 33.2, 39.6, 43.3, 44.5, 48.9, 64.6, 127.1, 127.5, 128.7, 140.6, 175.8; $[\alpha]_D$ +100.4° (c 5, $CHCl_3$); MS (EI): *m/z* 376 (M^+ + 1), 360, 318, 214, 188, 105, 91, 77, 57. Anal. Calcd for $C_{22}H_{37}NO_2Si$: C, 70.35, H, 9.93; N, 3.73. Found: C, 70.29; H, 9.89; N, 3.76.

General procedure for preparation of pyrrolidines (12a-c).

To a solution containing pyrrolidin-2-ones (**11a-c)** (10 mmol) in dry THF (40 mL), $LiAlH_4$ (0.78 g; 20 mmol) was added under inert atmosphere and the mixture was refluxed for 3 h. Then MeOH (5 mL) and aqueous saturated NH_4Cl solution(30 mL) were subsequently added and the mixture was extracted with ethyl acetate (3 x 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 pyrrolidines (**12a-c)** as colorless oils.

(3*R*,4*R*,1′*R*)-3-Benzyl-4-benzyloxymethyl-1-(1′-phenylethyl)pyrrolidine (12a)

Starting from **11a**, **12a** (3.0 g; 78%) was obtained as a colorless oil. ^{1}H NMR: 1.51 (d, 3H, *J* = 6.7), 2.15 - 2.38 (m, 2H), 2.47 (dd, 1H, *J* = 6.9, *J* = 9.9), 2.61 - 2.75 (m, 2H), 2.82 (dd, 1H, *J* = 6.1, *J* = 13.5), 2.99 (dd, 1H, *J* = 6.7, *J* = 9.9), 3.15 (dd, 1H, *J* = 7.6, *J* = 9.9), 3.28 (d, 2H, *J* = 5.5), 3.58 (q, 1H, *J* = 6.7), 4.40 (ABq, 2H, *J* = 12.3), 7.09 - 7.42 (m, 15 ArH); ^{13}C NMR: 23.2, 40.5, 42.2, 43.8, 56.0, 57.9, 65.9, 72.4, 73.5, 126.6, 128.1, 128.2, 128.4, 128.9, 129.1, 129.3, 138.8, 140.7, 141.9; $[\alpha]_D$ +26.0° (c 1, $CHCl_3$); MS (EI): *m/z* 386 (M^+ +1), 371, 370, 279, 188, 107, 91, 77. Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.10; N, 3.63. Found: C, 84.05; H, 8.04; N, 3.58.

(3*R*,4*R*,1′*R*)-4-Benzyloxymethyl-3-ethyl-1-(1′-phenylethyl)pyrrolidine (12b)

Starting from **11b**, **12b** (2.5 g; 76%) was obtained as a colorless oil. ^{1}H NMR: 0.88 (t, 3H, *J* = 7.3), 1.37 (d, 3H, *J* = 6.6), 1.41 - 1.58 (m, 2H), 1.60 - 1.78 (m, 1H), 1.95 - 2.12 (m, 2H), 2.40 (dd, 1H, *J* = 4.8, *J* = 9.2), 2.58 (dd, 1H, *J* = 9.2, *J* = 9.2), 2.92 (dd, 1H, *J* = 8.0, *J* = 8.0), 3.17 (q, 1H, *J* = 7.3), 3.38 (dd, 1H, *J* = 8.8, *J* = 9.0), 3.44 (dd, 1H, *J* = 6.1, *J* =9.0), 4.50 (ABq, 2H, *J* = 12.1), 7.18 - 7.45 (m, 10 ArH); ^{13}C NMR: 13.1, 23.8, 28.4, 43.3, 44.4, 57.2, 59.3, 66.2, 73.5, 74.5, 127.2, 127.6, 127.9, 128.0, 128.7, 128.8, 139.1; $[\alpha]_D$ +36.3° (c 0.9, $CHCl_3$); MS (EI): *m/z* 324 (M^+ +1), 309, 308, 232, 203, 188, 105, 91, 77. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.61; H, 8.98; N, 4.29.

(3*R*,4*R*,1′*R*)-3,4-Dibenzyloxymethyl-1-(1′-phenylethyl)pyrrolidine (12c)

Starting from **11c**, **12c** (3.2 g; 78%) was obtained as a colorless oil. ^{1}H NMR: 1.37 (d, 3H, *J* = 6.4), 2.04 - 2.25 (m, 2H), 2.31 (dd, 2H, *J* = 5.1, *J* = 9.1), 2.76 (dd, 2H, *J* = 7.2, *J* = 9.1), 3.19 (q, 1H, *J* = 6.4), 3.42 (dd, 2H, *J* = 8.8, *J* = 8.9), 3.50 (dd, 2H, *J* = 5.8, *J* = 8.9), 4.51 (ABq, 4H, *J* = 12.4), 7.18 - 7.43 (m, 15 ArH); ^{13}C NMR: 23.7, 41.7, 56.8, 66.0, 73.5, 74.1, 127.3, 127.6, 127.9, 128.7, 128.0, 139.1; $[\alpha]_D$ +37.6° (c 0.5, $CHCl_3$); MS: *m/z* 416 (M^+ +1), 400, 309, 294, 203, 158, 91, 77. Anal. Calcd for $C_{28}H_{33}NO_2$: C, 80.93; H, 8.00; N, 3.37. Found: C, 80.88; H, 7.94; N, 3.33.

(3*R*,4*R*)-4-Benzyl-3-benzyloxymethyl-1-*t*-butoxycarbonylpyrrolidine (13)

To a solution of **12a** (1.9 g; 5 mmol) in dichloromethane (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 presssure and to the residue ethyl acetate (100 mL) and 2 M NaOH (50 mL) were added.

After extraction with ethyl acetate (2 x 100 mL), the organic layer was dried (Na_2SO_4) and then 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-*t*-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 x 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 **13** (1.4 g; 71%) as a colorless oil. IR ($CHCl_3$): 1708 cm^{-1}; ^1H NMR: 1.44 (s, 9H), 2.12 - 2.39 (m, 2H), 2.56 (dd, 1H, *J* = 8.5, *J* = 13.6), 2.86 (dd, 1H, *J* = 5.1, *J* = 13.6), 2.95 - 3.12 (m, 1H), 3.12 - 3.27 (m, 1H), 3.30 - 3.71 (m, 4H), 4.47 (s, 2H), 7.11 - 7.44 (m, 10 ArH); ^{13}C NMR: 29.0, 39.3, 42.2 (60%), 42.8 (40%), 43.6 (40%), 44.4 (60%), 49.2 (40%), 49.8 (60%), 51.5, 71.5, 73.6, 79.6, 126.7, 128.0, 128.1, 128.9, 129.2, 129.3, 138.7, 140.4, 155.0; $[\alpha]_D$ +13.9° (c 1.2, $CHCl_3$); MS (EI): *m/z* 381 (M^+), 366, 280, 219, 129, 91, 57. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.48; H, 8.09; N, 3.75.

(3*R*,4*R*)-4-Benzyl-1-*t*-butoxycarbonyl-3-hydroxymethylpyrrolidine (14)

To a solution containing compound (**13**) (2.0 g; 5.3 mmol) and HCOOH (6 mL) in dry ethanol (50 mL) under argon atmosphere, 10 wt. % Pd on activated carbon (1.3 g) was added and the mixture was stirred for 1 h at rt. Then the catalyst was filtered off, the organic layer was removed under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). After washing with an aqueous $NaHCO_3$ saturated solution (30 mL), the solvent was dried (Na_2SO_4) and evaporation under reduced pressure gave the compound **(14)** (1.3 g; 82%) as an oil which was used without further purification. IR ($CHCl_3$): 1708 cm^{-1}; ^1H NMR: 1.44 (s, 9H), 1.66 (br s, 1 H, OH), 2.03 - 2.21 (m, 1H), 2.21 - 2.42 (m, 1H), 2.59 (dd, 1H, *J* = 8.3, *J* = 13.7), 2.84 (dd, 1H, *J* = 5.9, *J* = 13.7), 2.95 - 3.29 (m, 2H), 3.31 - 3.73 (m, 4H), 7.11 - 7.36 (m, 5 ArH); ^{13}C NMR: 28.5, 38.8, 41.2 (50%), 41.7 (50%), 45.6 (50%), 46.0 (50%), 48.0 (50%), 48.9 (50%), 50.9, 79.2, 126.2, 128.4, 128.5, 128.6, 128.7, 139.8, 154.6 (50%), 160.7 (50%); $[\alpha]_D$ +14.1° (c 4.6, $CHCl_3$); MS (EI): *m/z* 291 (M^+), 260, 234, 177, 91, 57. Anal. Calcd for $C_{17}H_{25}NO_3$. C, 70.07; H, 8.65; N, 4.81. Found: 70.03; H, 8.68; N, 4.77.

Methyl (3*R*,4*R*)-4-Benzyl-1-*t*-butoxycarbonyl-3-pyrrolidinecarboxylate (15)

To a solution containing compound **(14)** (1.0 g; 3.4 mmol) in acetone (18 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 saturated aqueous Na_2CO_3 solution (15 mL) were added at 0 °C. After extraction of the aqueous phase with ethyl acetate (50 mL), organics were discarded and pH of the aqueous layer raised to 2 by slow addition of 1 M HCl under stirring. Then, extraction with ethyl acetate (2 x 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 treated with an ethereal solution of CH_2N_2 in ether until nitrogen evolution ceased and the solvent was evaporated under reduced pressure, to give a residue which was purified by silica gel chromatography (cyclohexane:acetate 70:30) affording the ester **(15)** (0.9 g; 83% yield) as a colorless oil. IR ($CHCl_3$): 1743, 1708 cm^{-1}; ^1H NMR: 1.44 (s, 9H), 2.55 - 2.95 (m, 4H), 2.95 - 3.14 (m, 1H), 3.38 - 3.60 (m, 2H), 3.63 (s, 3H), 3.63 - 3.81 (m, 1H), 7.11 - 7.36 (m, 5 ArH); ^{13}C NMR: 27.9, 37.9, 42.5 (60%), 43.1 (40%), 46.9 (40%), 47.7, 48.1 (60%), 50.0, 51.3, 78.8, 125.9, 127.9, 128.2, 128.4, 138.4, 153.5, 172.4; $[\alpha]_D$ +20.4° (c 2.7, $CHCl_3$); MS (EI): *m/z* 319 (M^+), 304, 288, 234, 108, 91, 77. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: 67.63; H, 7.86; N, 4.43.

(3*R*,4*R*)-4-Benzyl-3-pyrrolidinecarboxylic acid (4)

The compound **(15)** (0.53 g; 1.7 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 the corresponding hydrochloride as a white solid [mp 181-183 °C; ^1H NMR (D_2O): 2.78 - 3.21 (m, 5H), 3.39 - 3.72 (m, 3H), 7.21 - 7.46 (m, 5 ArH); ^{13}C NMR (D_2O): 40.0, 46.3, 49.9, 50.1, 52.6, 129.9, 131.8, 132.0, 141.4, 178.1; $[\alpha]_D$ 8.3 (c 1, H_2O)]. This product, dissolved in H_2O, was subjected to ion exchange column (Dowex 50WX2, elution with 1 M NH_4OH) to give the corresponding amino acid **(4)** as a white solid (0.18 g; 50%), mp 241-243 °C (decomp); ^1H NMR (CD_3OD): 2.52 - 2.87 (m, 3H), 2.91 - 3.16 (m, 2H), 3.18 - 3.34 (m, 1H), 3.43 - 3.53 (m, 2H), 7.12 - 7.33 (m, 5 ArH); ^{13}C NMR (CD_3OD): 39.4, 45.9, 49.6, 50.9, 51.9, 127.9, 130.0, 130.2, 130.3, 140.8, 178.3; $[\alpha]_D$ +40.1° (c 1.1, MeOH); MS (CI): *m/z* 206 (M^+ +1), 114, 91, 77. Anal. Calcd for $C_{12}H_{15}NO_2$. C, 70.22; H, 7.37, N, 6.82. Found: 70.14; H, 7.28; N, 6.95.

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13. It is worth mentioning that good results were observed also when the (4*S*,1′*R*)-4-hydroxymethyl

derivative **(I)**, easily obtained starting from **7** according ref. 9, was converted into the corresponding benzyl ether **(II)** and subsequent alkylation reaction led to **IIIa,b** in good yield, thus allowing to prepare the diastereomers of compounds (**11)**. (**i.** n-Buli, THF, then BnBr, 91% **ii**. n-BuLi, THF, 0°C. Then, for **IIIa,** BnBr, R = Bn, 91% and, for **IIIb**, EtI, R = Et, 87%).