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Chiral 3-hydroxypyrrolidin-2-ones from a Baylis–Hillman adduct: convergent, stereoselective synthesis of a glycosidase inhibitor

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Abstract—The *O*-silyl derivative **4b**, prepared starting from the Baylis–Hillman adduct **4a**, underwent cyclization on treatment with (*S*)-phenylethylamine, to give to an equimolar mixture of the 4,5-*cis*-disubstituted pyrrolidin-2-ones **9** and **10**, exclusively, which after separation by silica gel chromatography were both converted into the 3-hydroxy-4-hydroxymethylpyrrolidine **1** a glycosidase inhibitor.

1. Introduction

In recent years, new approaches to 3-hydroxy-4-hydroxymethyl pyrrolidin-2-ones have been reported, since these products are useful intermediates to bioactive compounds with interesting pharmacological properties.[1] Moreover polyhydroxy pyrrolidin-2-ones can be precursors to polyhydroxy pyrrolidines, that are isosteres of pentoses, the removal of the carbonyl group being a well-established pathway.[2] These latter compounds are inhibitors of glycosidases, enzymes that are present in almost all organisms and are essential in processing oligo- and polysaccharides, glycolipids and glycoproteins,[3] whereas their inhibition allows obesity, diabetes and other metabolic disorders to be controlled.[4] In addition, infection and inflammation can be prevented, since these products block the biogenesis of membrane glycoproteins in fungi, bacteria and viruses.[5] Within this class, compound **1** has been prepared in enantiomerically pure form and displays activity as an inhibitor of glycosidases and could be employed as an antiviral drug (Fig. 1).[6,7]

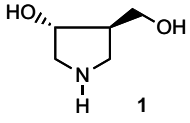

Figure 1.

2. Results and discussion

Recently, 3,4-disubstituted pyrrolidin-2-ones have attracted an increased attention in our group in connection with the design of conformationally restricted analogs of bioactive amino acids.[8] Moreover, 4-hydroxymethyl pyrrolidin-2-ones were employed as intermediates in the synthesis of bioactive nonproteinogenic amino acids.[9] In this context, and as a part of a research program aimed at the synthesis of new peptidonucleic acids, we first devised that the reaction of the anion of the chiral pyrrolidin-2-one **2**[9] with oxaziridine[10,11] or MoOPD[12] could afford the compound **3** suitable to be converted into **1**. However, this product was invariably obtained in very low yield as an erratic diastereomeric mixture whose chromatographic separation was very difficult (Scheme 1).

Thus, we envisaged that compound **1** could be obtained in enantiomerically pure form starting from the Baylis–Hillman adduct **4**.[13–15] However, when **4a** was treated with (*S*)-phenylethylamine,[16] an equimolar mixture of

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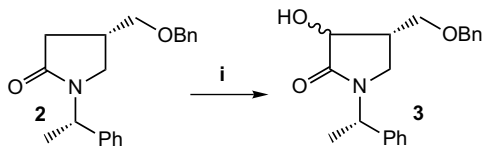
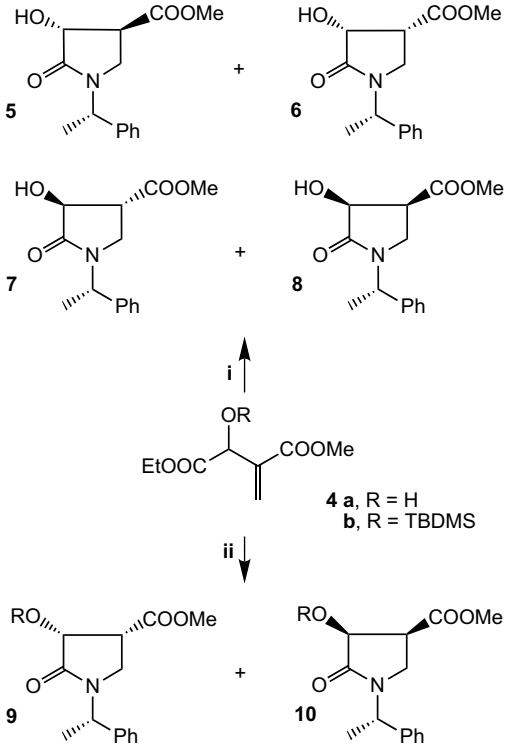


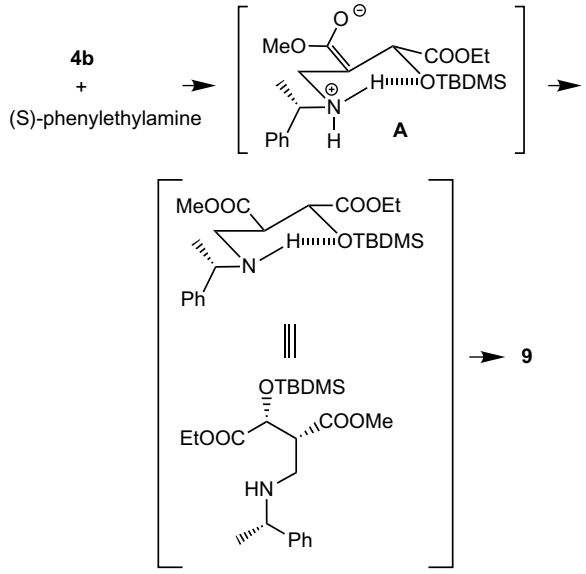
Scheme 1. Reagents and conditions: (i) LiHDMS, THF, −78 °C, then phenyloxaziridine or MoOPD, 10–15% yield as inseparable diastereomeric mixture.

pyrrolidin-2-ones **5**–**8** was obtained and only compound **8** could be separated by silica gel chromatography, the rest being an inseparable mixture of **5**–**7**.[17] Thus, in order to improve the stereoselection of the cyclization, the derivative **4b**, easily prepared starting from **4a**, underwent cyclization with (*S*)-phenylethylamine leading to an equimolar mixture of *cis*-3,4-disubstituted diastereomeric pyrrolidin-2-ones, **9** and **10** (Scheme 2).



Scheme 2. Reagents and conditions: (i) R = H (*S*)-phenylethylamine, MeOH, rt, 20 h, **8** (21% by silica gel chromatography, the rest being an inseparable mixture of compound **5**, **6** and **7**). (ii) R = TBDMS. (a) (*S*)-Phenylethylamine, MeOH, rt, 24 h; (b) refluxing toluene, 4 h, **9** (40%), **10** (38%).

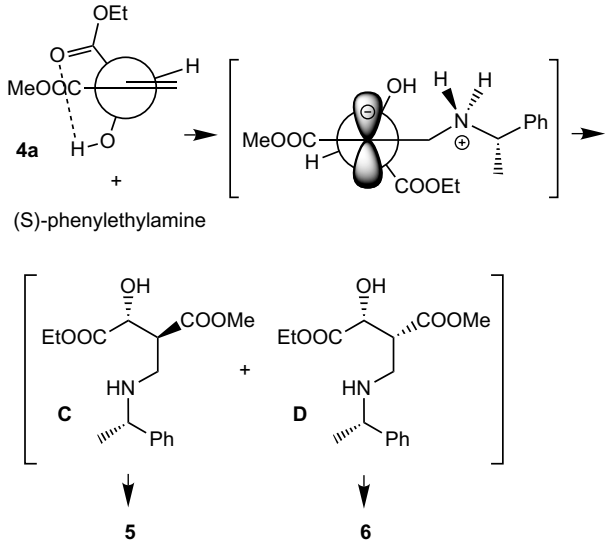
After separation by silica gel chromatography, the configurational assignment of products **9** and **10** was made on the basis of ^{1}H NMR spectral data and supported by NOE experiments.[18] The stereoselective formation of *cis*-isomers **9** and **10** can be explained by inspection of the reaction intermediates, supported by molecular mechanics calculations.[19] In fact, the conjugate addition of (*S*)-phenylethylamine to **4b** seems to be directed by a hydrogen bond involving both the amino group and the oxygen of the silyl ether, leading to a six-membered enolate intermediate. This hypothesis was confirmed by the conformational search performed either in polar and apolar medium for the analogous compound where OMe was changed for OTBDMS.[20] In fact in all the most stable conformers an intramolecular H-bond takes place leading to a chair-like six-membered ring (intermediate **A**), whose protonation gives the more stable di-equatorial substitution pattern (Scheme 3).



Scheme 3.

On the contrary, the conformational search carried out on the adduct **4a** in both polar and apolar medium, evidenced that within 25 kJ/mol stable conformations having an intramolecular H-bond between the hydroxy and the methoxycarbonyl groups are not present. Thus, a six-membered ring cannot arise, probably due to the constrictions of the conjugate planar moiety. Moreover, the most stable conformers of the Baylis–Hillman adduct **4a**[21] in both polar and apolar medium showed an intramolecular H-bond, involving both the hydroxy and the ethoxycarbonyl groups, leading a very stable five-membered ring. This result is in agreement with the absorptions observed in the FT-IR spectra (1732 cm^{-1} for **4a** vs 1740 cm^{-1} for **4b**), that remain unchanged when methanol is changed for chloroform. After conjugate addition, both diastereotopic faces of the enolate anion **B** are similarly hindered as evidenced by three very similar conformers observed within 0.64 kcal/mol.[22,23] Therefore protonation of the enolate anion can occur from both sides, leading to both isomers **5** and **6** (or to **7** and **8**, depending on the configuration at C-2), via the products **C** and **D**, respectively, that were not isolated. This latter process is much faster than formation of hydrogen bond between alcoholic oxygen and ammonium ion, which would constrain the intermediate to a six-membered ring (Scheme 4).

Thus, having both **9** and **10** in hand, a stereoconvergent route was carried out in order to obtain product **1**. In fact, when pyrrolidin-2-one **9** was treated with an equimolar amount of $NaBH_4$ in dry ethanol, the corresponding *trans*-3,4-disubstituted derivative **11** was



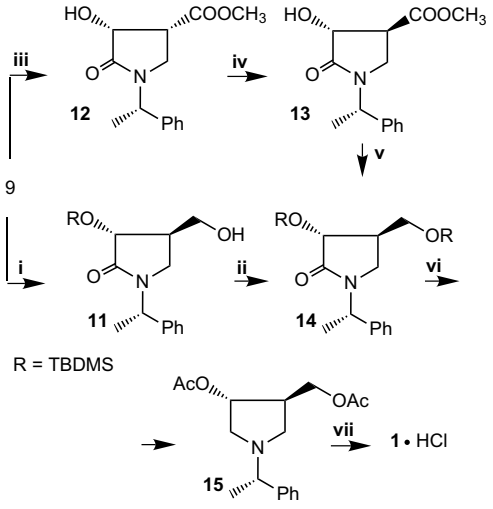
Scheme 4.

obtained in high yield,[24] and the epimerization at C-4, which precedes the reduction step, was ascribed to a small amount of sodium alkoxide in the reaction mixture. The configurational assignment of **11** was performed by means of NOE effects and eventually confirmed by the known specific rotatory power of **1**. In fact, desilylation of the ester **9**, performed with 6 M HCl in methanol, afforded the corresponding *cis*-hydroxy ester **12**, which by treatment with DBU in toluene at 70 °C was quantitatively isomerized to the corresponding *trans*-derivative **13**. Subsequent treatment with $LiAlH_4$ followed by silylation of the raw reaction product gave **14**, which was identical with the compound obtained by silylation of **11**. Deoxygenation and cleavage of the silyl protecting groups, performed with $LiAlH_4$ in refluxing THF,[25] afforded the aminodiol, which was isolated as the corresponding diacetyl derivative **15**.

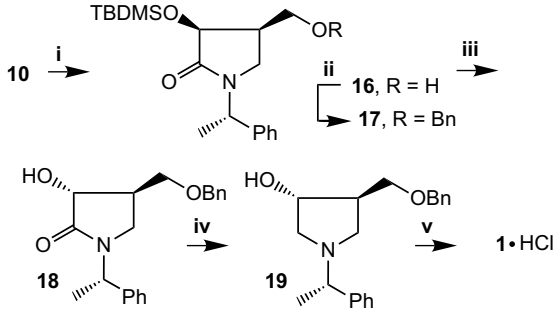
Removal of the phenylethyl group was performed by reaction with chloroethyl chloroformate[26] and eventual treatment of the raw reaction product with 12 M HCl gave **1** as hydrochloride, whose physical and spectral data were identical with those reported in the literature (Scheme 5).

With product **1** in hand, we focused our attention on the synthesis of **1** starting from the pyrrolidin-2-one **10**. At first, compound **10** was converted into the hydroxymethyl derivative **16**, which, after benzylation, gave the benzyloxymethyl derivative **17**. Epimerization at C-3, performed with methanolic KOH, afforded the *trans*-isomer **18** since complete removal of the protecting group TBDMS occurred under reaction conditions. Eventual reduction of the lactam to pyrrolidine, followed by removal of the protecting groups, led to **1** in good yield as the corresponding hydrochloride (Scheme 6).

Next, we explored a simple conversion of compounds **5**–**8**, arising from the cyclization of **4a**, into **1**. Thus, after



Scheme 5. Reagents and conditions: (i) $NaBH_4$, dry ethanol, 0 °C, 12 h, 81%. (ii) TBDMSCl, imidazole, DCM, rt, 5 h, 93%. (iii) 6 M HCl, MeOH, rt, 12 h, 88%. (iv) DBU, toluene, 70 °C, 12 h, 80%. (v) (a) $LiAlH_4$, THF, 0 °C, 2 h; (b) TBDMSCl, imidazole, DCM, rt, 5 h, 78%. (vi) (a) $LiAlH_4$, refluxing THF; (b) AcCl, Et_3N, DMAP, DCM, 0 °C, 2 h, 65%. (vii) (a) Chloroethylchlorocarbonate, DCM, 0 °C, 30 min; (b) refluxing methanol, 40 min; (c) 12 M HCl, MeOH, rt, 1 h, 68%.

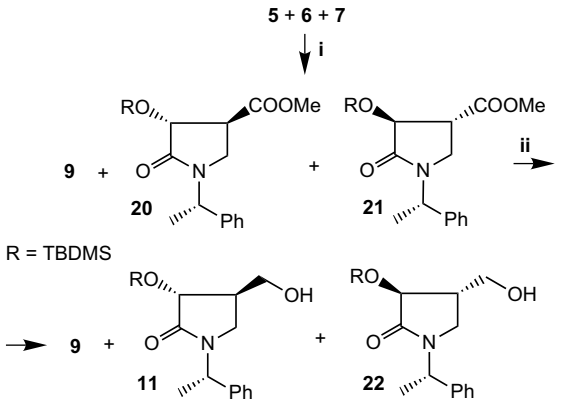


Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C, 80%. (ii) *n*-BuLi, THF, 0 °C, 5 min, then BnBr, refluxing THF, 80%. (iii) KOH, refluxing MeOH–H_2O, 30 h, 58%. (iv) $LiAlH_4$, refluxing THF. (v) (a) $Pd(OH)_2$, 20% on C, H_2; (b) 3 M HCl, 94%.

separation of **8** from the reaction mixture, followed by silylation leading to **10**, the products **5**–**7** were silylated and the mixture, containing **9**, **20** and **21**, was treated with $LiAlH_4$ at 0 °C. Under these conditions, both *trans*-derivatives **20** and **21** were converted into the hydroxymethyl derivatives **11** and **22**, respectively, whereas the ester **9** remained unchanged, and all compounds could be separated by silica gel chromatography (Scheme 7).[27] Therefore, since compounds **9**, **10** and **11** were converted into **1** as described above, the cyclization carried out starting from the adduct **4a** could also be effective for the preparation of **1**, but the sole product **22** proved useless to this goal.

3. Conclusions

An efficient, stereoselective strategy exploiting the Baylis–Hillman adducts **4a** and **4b** allowed chiral 3,4-disub-



Scheme 7. Reagents and conditions: (i) TBDMSCl, imidazole, DCM, rt, 91%. (ii) $LiAlH_4$, THF, 0 °C, 40 min, **9** (18%), **11** (23%), **22** (21%).

stituted γ-lactams and pyrrolidines, which converged to the glycosidase inhibitor **1**, to be prepared. The application of this method to the preparation of new peptidonucleic acids and peptidomimetics is currently underway and results will be reported in due course.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Unless otherwise noted, NMR spectra (200 MHz for ^1H, 50 MHz for ^{13}C, chemical shifts as ppm in the δ scale, coupling constants J in Hz) were recorded at 25 °C in $CDCl_3$ solutions on a Varian Gemini 200 spectrometer. 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). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. EIMS analyses were carried out on a Hewlett–Packard spectrometer model 5890, series II. Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM).

4.2. 1-Ethyl-4-methyl-2-hydroxy-3-methylenebutanedioate 4a

In a one-necked flask (100 mL) ethyl glyoxylate (50% solution in toluene, 20.4 g; 100 mmol), methyl acrylate (8.6 g; 100 mmol) and DABCO (1.0 g; 10 mmol) were added and the mixture was allowed to react for 12 h. The oil was then purified by silica gel chromatography (cyclohexane:ethyl acetate 80:20) to give **4a** (11.8 g; 63% yield) as a colorless oil. IR (neat): 3490, 1732, 1636 cm^{-1}. ^1H NMR: 1.24 (t, 3H, $J = 7.2$), 3.51 (d, 1H, OH, $J = 6.2$), 3.76 (s, 3H), 4.22 (q, 2H, $J = 7.2$), 4.83 (d, 1H, $J = 6.2$), 5.92 (s, 1H), 6.34 (s, 1H); ^{13}C NMR: 14.0, 52.0, 62.2, 71.2, 128.8, 138.1, 165.6,172.2; EIMS: *m/z* 188 (2, M^+), 143 (22), 116 (40), 84 (100). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.01; H, 6.39.

4.3. 1-Ethyl-4-methyl-2-*tert*-butyldimethylsilyloxy-3-methylenebutanedioate 4b

To a solution containing the ester **4a** (2.5 g; 37 mmol) and imidazole (2.5 g; 37 mmol) in DCM (35 mL) at rt, *tert*-butyldimethylchlorosilane (5.6 g; 37 mmol) was added, and the mixture was stirred for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (50 mL), brine (50 mL) was added and the mixture was extracted with ethyl acetate (2 × 100 mL). After drying (Na_2SO_4), the solvent was removed in vacuo and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 90:10), to give the compound **4b** (8.6 g; 95% yield) as a colorless oil. IR (neat): 1740, 1639 cm^{-1}. ^1H NMR: 0.06 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.21 (t, 3H, $J = 7.1$), 3.72 (s, 3H), 4.13 (q, 2H, $J = 7.1$), 5.03 (s, 1H), 6.0 (s, 1H), 6.31 (s, 1H); ^{13}C NMR: −5.4, −5.2, 13.9, 25.5, 51.8, 61.1, 70.1, 125.9, 138.9, 165.8, 170.5. EIMS: *m/z* 288 (2, MH^+-15), 246 (39), 189 (34), 174 (43), 157 (57), 74 (100). Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.56; H, 8.61.

4.4. (3*S*,4*S*,1′*S*)-3-Hydroxy-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one 8

To a solution containing the ester **4a** (3.76 g; 20 mmol) in dry MeOH (20 mL), (*S*)-phenylethylamine (2.4 g; 20 mmol) was added at rt and the mixture was stirred for 20 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (50 mL) that was washed with 3 M HCl. The solvent was dried (Na_2SO_4) and evaporated in vacuo and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 60:40) to give pure pyrrolidin-2-one **8** (1.1 g; 21% yield) as a crystalline solid (mp 73–75 °C), the rest being an inseparable mixture of compounds **5**, **6** and **7**. ^1H NMR: 1.54 (d, 3H, $J = 7.1$), 3.19–3.43 (m, 4H, 3H + OH), 3.59 (s, 3H), 4.58 (d, 1H, $J = 7.9$), 5.49 (q, 1H, $J = 7.1$), 7.20–7.37 (m, 5 ArH); ^{13}C NMR: 16.0, 41.6, 42.9, 49.4, 51.8, 70.8, 127.1, 127.5, 128.3, 138.7, 170.5, 172.3; $[\alpha]_D = -187.9$ (*c* 1.1, $CHCl_3$); EIMS: *m/z* 263 (3, M^+), 246 (4), 221 (8), 187 (21), 134 (16), 121 (19), 106 (70), 70 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.46; N, 5.26.

4.5. (3*R*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one 9 and its (3*S*,4*S*,1′*S*)-isomer 10

To a solution containing the silyl derivative **4b** (6.0 g; 20 mmol) in methanol (50 mL), (*S*)-phenylethylamine (2.4 g; 20 mmol) was added and the mixture was stirred for 24 h at rt. After removal of the solvent, the residue was dissolved in toluene (50 mL) and the solution was refluxed for 4 h. The solvent was then evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) that was washed with 3 M HCl. The solvent was dried (Na_2SO_4) and evaporated in vacuo and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 90:10), to give compound **9** (2.1 g; 40% yield) as a yellow oil. Further elution gave

compound **10** (2.0 g; 38% yield) as a yellow oil. EIMS: *m/z* 378 (1, MH^+), 363 (2), 321 (40), 218 (16), 217 (100), 160 (15), 106 (88). Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.63; H, 8.28; N, 3.71. Found: C, 63.57; H, 8.32; N, 3.66. Compound **9**: ^{1}H NMR: 0.14 (s, 3H), 0.18 (s, 3H), 0.88 (s, 9H), 1.56 (d, 3H, $J = 7.2$), 2.99 (dd, 1H, $J = 7.3$. $J = 9.4$), 3.04–3.16 (m, 1H), 3.87 (s, 3H), 3.69 (dd, 1H, $J = 7.6$, $J = 9.4$), 4.45 (d, 1H, $J = 6.7$), 5.44 (q, 1H, J=7.2), 7.23–7.36 (m, 5 ArH); ^{13}C NMR: −5.6, −4.7, 15.5, 25.5, 41.2, 44.1, 49,3, 51.6, 72.1, 127.0, 127.5, 128.5, 139.5, 169.7, 170.3; $[\alpha]_D = -33.1$ (*c* 8.1, $CHCl_3$). Compound **10**: ^{1}H NMR: 0.13 (s, 3H), 0.17 (s, 3H), 0.84 (s, 9H), 1.53 (d, 3H, $J = 7.1$), 3.14–3.26 (m, 1H), 3.30 (dd, 1H, $J = 9.5$, $J = 9.6$), 3.39 (dd, 1H, $J = 6.8$, $J = 9.6$), 3.63 (s, 3H), 4.47 (d, 1H, $J = 6.4$), 5.45 (q, 1H, $J = 7.1$), 7.25–7.35 (m, 5 ArH); ^{13}C NMR: −5.6, −4.7, 16.2, 25.4, 41.2, 44.3, 48.9, 51.6, 72.1, 126.9, 127.0, 127.4, 128.3, 139.2, 169.6, 170.6; $[\alpha]_D = -148.8$ (*c* 3.0, $CHCl_3$).

4.6. (3*R*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 11

To a solution containing compound **9** (1.13 g; 3 mmol) in dry ethanol (10 mL) $NaBH_4$ (0.48 g; 12 mmol) was added at rt. After 6 h, the reaction mixture was poured in water (30 mL) and extracted with ethyl acetate (3 × 25 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 80:20), to give pure **11** (0.85 g; 81% yield) as a white solid. Mp 84–86 °C. ^{1}H NMR: 0.20 (s, 3H), 0.26 (s, 3H), 0.98 (s, 9H), 1.57 (d, 3H, $J = 7.2$), 2.21 (br s, 1H, OH), 2.31–2.49 (m, 1H), 2.73 (dd, 1H, $J = 8.5$, $J = 9.8$), 3.42 (dd, 1H, $J = 8.1$, $J = 9.8$), 3.63 (dd, 1H, $J = 6.8$, $J = 10.5$), 3.81 (dd, 1H, $J = 4.5$, $J = 10.5$), 4.18 (d, 1H, $J = 8.3$), 5.49 (q, 1H, $J = 7.2$), 7.28–7.43 (m, 5 ArH); ^{13}C NMR: −5.2, −4.1, 16.0, 25.8, 41.4, 44.6, 49.4, 61.9, 73.1, 127.1, 127.5, 128.5, 139.8, 172.5; $[\alpha]_D = -68.7$ (*c* 1.0, $CHCl_3$); EIMS: *m/z* 335 (2, MH^+-15), 293 (81), 150 (16), 122 (13), 106 (100), 70 (74). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.25; H, 8.88; N, 4.08.

4.7. (3*R*,4*R*,1′*S*)-3-Hydroxy-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one 12

To a solution containing compound **9** (2.26 g; 6.0 mmol) in MeOH (15 mL), 6 M HCl (10 mL) was added and the mixture was stirred for 12 h at rt. Then MeOH was partially removed under reduced pressure and the mixture was extracted with ethyl acetate (2 × 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 50:50), to give the compound **12** (1.39 g; 88% yield) as a colorless oil. ^{1}H NMR: 1.60 (d, 3H, $J = 7.3$), 3.04 (dd, 1H, $J = 7.1$, $J = 10.1$), 3.30 (ddd, 1H, $J = 4.1$, $J = 7.1$, $J = 7.8$), 3.53 (br s, 1H, OH), 3.64 (dd, 1H, $J = 4.1$, $J = 10.1$), 3.74 (s, 3H), 4.56 (d, 1H, $J = 7.8$), 5.47 (q, 1H, $J = 7.3$), 7.22–7.42 (m, 5 ArH); ^{13}C NMR: 15.5, 41.8, 42.9, 49.7, 52.0, 70.8, 127.0, 127.7, 128.6, 139.1, 170.5, 171.9; $[\alpha]_D = -72.6$ (*c* 1.1, $CHCl_3$); EIMS: *m/z* 263 (3, M^+), 246 (4), 221 (8), 187 (21), 134 (16), 121 (19), 106 (70), 70 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.81; H, 6.47; N, 5.28.

4.8. (3*R*,4*S*,1′*S*)-3-Hydroxy-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one 13

To a solution containing the ester **12** (1.3 g, 5.0 mmol) in toluene (50 mL), DBU (0.75 g, 5.0 mmol) was added and the mixture was stirred at 70 °C for 12 h. Then ethyl acetate (50 mL) was added and the organic layer was washed with 3 M HCl (15 mL). After drying (Na_2SO_4) and removal of the solvents, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50), to give **13** (1.05 g; 80%) yield as a colorless oil. ^{1}H NMR: 1.56 (d, 3H, $J = 7.1$), 2.12 (br s, 1H, OH), 2.95–3.10 (m, 1H), 3.19 (dd, 1H, $J = 8.5$, $J = 8.5$), 3.54 (dd, 1H, $J = 8.5$, $J = 8.5$), 3.71 (s, 3H), 4.61 (d, 1H, $J = 8.5$), 5.47 (q, 1H, $J = 7.1$), 7.20–7.38 (m, 5 ArH); ^{13}C NMR: 15.8, 41.2, 45.9, 50.0, 52.4, 72.5, 127.0, 127.8, 128.5, 128.6, 128.7, 138.8, 171.7, 172.5; $[\alpha]_D = -27.8$ (*c* 1.0, $CHCl_3$); EIMS: *m/z* 263 (3, M^+), 246 (4), 221 (8), 187 (21), 134 (16), 121 (19), 106 (70), 70 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.47; N, 5.28.

4.9. (3*R*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-*tert*-butyldimethylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 14 from 11

To a solution containing compound **11** (1.05 g; 3.0 mmol) in DCM (20 mL) imidazole (0.2 g; 3.0 mmol) and subsequently *tert*-butyldimethylchlorosilane (0.44 g; 3.0 mmol) were added at rt. After 5 h the mixture was poured in ice water and extracted with ethyl acetate (3 × 30 mL). The solvent was dried (Na_2SO_4) and after evaporation under reduced pressure the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give the compound **14** (1.3 g; 93% yield) as a colorless oil. ^{1}H NMR: −0.07 (s, 3H), −0.03 (s, 3H), 0.15 (s, 3H), 0.22 (s, 3H), 0.78 (s, 9H), 0.92 (s, 9H), 1.53 (d, 3H, $J = 7.1$), 2.18–2.37 (m, 1H), 2.72 (dd, 1H, $J = 8.2$, $J = 9.5$), 3.24 (dd, 1H, $J = 8.6$, $J = 9.5$), 3.61 (d, 2H, $J = 4.3$), 4.24 (d, 1H, $J = 8.1$), 5.47 (q, 1H, $J = 7.1$), 7.18–7.42 (m, 5 ArH); ^{13}C NMR: −5.7, −5.6, −5.2, −4.1, 15.9, 25.7, 25.8, 40.8, 44.3, 49.2, 60.7, 72.1, 127.0, 127.4, 128.5, 140.0, 172.7; $[\alpha]_D = -28.7$ (*c* 1.0, $CHCl_3$); EIMS: *m/z* 464 (1, MH^+), 348 (6), 219 (32), 187 (23), 121 (16), 106 (100). Anal. Calcd for $C_{25}H_{45}NO_3Si_2$: C, 64.74; H, 9.78; N, 3.02. Found: C, 64.69; H, 9.73; N, 3.06.

4.10. (3*R*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-*tert*-butyldimethylsilyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 14 from 13

To a solution containing compound **13** (1.18 g; 4.5 mmol) in dry THF (10 mL), $LiAlH_4$ (0.19 g; 4.5 mmol) was added under stirring at 0 °C and then temperature raised to rt. After 1 h, methanol (1 mL) was added, followed by 3 M HCl (20 mL). The mixture was then extracted with ethyl acetate (3 × 50 mL), the solvent was dried (Na_2SO_4) and removed under

reduced pressure. The residue was dissolved in DCM (20 mL) containing imidazole (0.61 g; 9.0 mmol) and subsequently *tert*-butyldimethylchlorosilane (1.36 g; 9.0 mmol) was added at rt. After 6 h the mixture was poured in ice water and extracted with ethyl acetate (3×50 mL). The solvent was dried (Na_2SO_4) and after evaporation under reduced pressure the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give the compound **14** (1.37 g; 78% yield) as a colorless oil. EIMS: *m/z* 464 (1, MH^+), 348 (6), 219 (32), 187 (23), 121 (16), 106 (100). Anal. Calcd for $C_{25}H_{45}NO_3Si_2$: C, 64.74; H, 9.78; N, 3.02. Found: C, 64.70; H, 9.83; N, 2.98.

4.11. (3*R*,4*R*,1′*S*)-3-Acetoxy-4-acetoxymethyl-1-(1′-phenylethyl)pyrrolidine 15

To a solution containing compound **14** (1.37 g; 3.0 mmol) in dry THF (15 mL), $LiAlH_4$ (0.15 g; 3.5 mmol) was added and the mixture was refluxed for 6 h. Then methanol (1 mL) was added, followed by a saturated solution of Seignette salt (20 mL), and the mixture was eventually extracted with ethyl acetate (3×50 mL). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was dissolved in DCM (10 mL) containing Et_3N (1.78 g; 17 mmol) and DMAP (0.24 g; 2 mmol) and acetyl chloride (1.17 g; 13.5 mmol) was added at rt. After 2 h the mixture was poured in ice water and extracted with ethyl acetate (3×50 mL). The organic layer was separated and dried (Na_2SO_4) and solvents were eventually removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50), to give **15** (0.54 g; 65% yield) as a colorless oil. ^{1}H NMR: 1.35 (d, 3H, $J = 6.5$), 2.02 (s, 3H), 2.05 (s, 3H), 2.12–2.53 (m, 3H), 2.62–2.84 (m, 2H), 3.21 (q, 1H, $J = 6.5$), 4.04 (dd, 1H, $J = 7.0$, $J = 11.0$), 4.16 (dd, 1H, $J = 6.3$, $J = 11.0$), 4.93 (m, 1H), 7.18–7.34 (m, 5 ArH); ^{13}C NMR: 20.8, 21.9, 22.7, 44.1, 54.5, 58.4, 64.5, 65.0, 75.7, 101.4, 127.0, 127.1, 128.3, 144.6, 170.7, 170.8; $[\alpha]_D = -7.4$ (*c* 1.0, $CHCl_3$); EIMS: *m/z* 305 (3, MH^+), 290 (5), 246 (13), 231 (14), 154 (62), 121 (32), 106 (100). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.80; H, 7.56; N, 4.55.

4.12. (3*R*,4*R*)-3-Hydroxy-4-hydroxymethylpyrrolidine hydrochloride 1

To a solution of **15** (0.54 g; 1.75 mmol) in dry DCM (10 mL) chloroethyl chlorocarbonate (0.5 g; 3.5 mmol) was added at 0 °C and after 30 min the solvent was removed under reduced pressure. The residue was dissolved in methanol (5 mL), the solution was refluxed for 40 min and eventually 12 M HCl (1 mL) was added. After 1 h at rt, solvents were evaporated under reduced pressure, the residue was dissolved in H_2O (5 mL) and the aqueous solution was extracted with ethyl acetate (2×10 mL). The organic layers were discarded and water was removed under reduced pressure, to give compound **1** (0.18 g; 68% yield) as a low-melting solid. ^{1}H NMR (D_2O, DSS): 2.43–2.55 (m, 1H), 3.16 (dd, 1H, $J = 5.8$, $J = 12.2$), 3.26 (dd, 1H, $J = 2.7$, $J = 12.6$), 3.43 (dd, 1H, $J = 5.1$, $J = 12.6$), 3.55–3.66 (m, 3H), 4.38–4.43 (m, 1H); ^{13}C NMR (D_2O, DSS): 46.5, 47.8, 52.0, 60.8, 71.8; $[\alpha]_D = +18.3$ (*c* 0.7, CH_3OH) [lit.[6b] +19.0 (*c* 1.0, CH_3OH)]; EIMS (CI): *m/z* 118 (MH^+), 100, 82.

4.13. (3*S*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 16

To a solution containing compound **10** (1.5 g; 4.0 mmol) in dry THF (15 mL), $LiAlH_4$ (0.17 g; 4.0 mmol) was added at 0 °C. After 3 h methanol (1 mL) was added followed by a saturated solution of Seignette salt (20 mL). The mixture was then extracted with ethyl acetate (3×50 mL), the organic layer dried (Na_2SO_4) and eventually removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give the product **16** (1.12 g; 80% yield) as a colorless oil. ^{1}H NMR: 0.19 (s, 3H), 0.22 (s, 3H), 0.91 (s, 9H), 1.48 (d, 3H, $J = 7.1$), 2.41–2.54 (m, 1H), 2.60 (br s, 1H, OH), 2.82 (dd, 1H, $J = 3.7$, $J = 10.1$), 3.25 (dd, 1H, $J = 7.1$, $J = 10.1$), 3.50 (dd, 1H, $J = 5.5$, $J = 11.3$), 3.65 (dd, 1H, $J = 6.5$, $J = 11.3$), 4.48 (d, 1H, $J = 7.4$), 5.42 (q, 1H, $J = 7.1$), 7.23–7.34 (m, 5 ArH); ^{13}C NMR: −5.5, −4.5, 16.0, 25.7, 38.7, 41.8, 49.0, 61.4, 73.5, 126.9, 127.4, 128.4, 139.4, 171.7; $[\alpha]_D = -170.2$ (*c* 1.9, $CHCl_3$); EIMS: *m/z* 335 (2, M^+-15), 293 (54), 189 (82), 150 (11), 106 (100), 82 (67). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.24; H, 8.92; N, 4.06.

4.14. (3*S*,4*R*,1′*S*)-4-Benzyloxymethyl-3-*tert*-butyldimethylsilyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 17

To a solution containing compound **16** (1.12 g; 3.2 mmol), HMPA (2 mL) and triphenylmethane (100 mg) in dry THF (10 mL), *n*-BuLi (1.6 M in hexanes; 2.4 mL) was added at 0 °C. After 10 min benzyl bromide (0.66 g; 3.84 mmol) was added and then the mixture was refluxed for 1 h. The reaction mixture was poured in H_2O (20 mL) and extracted with ethyl acetate (3×40 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 compound **17** (1.12 g; 80% yield) as a colorless oil. ^{1}H NMR: −0.14 (s, 3H), −0.07 (s, 3H), 0.80 (s, 9H), 1.53 (d, 3H, $J = 7.2$), 2.46–2.64 (m, 1H), 2.98 (dd, 1H, $J = 3.9$, $J = 9.9$), 3.21 (dd, 1H, $J = 6.5$, $J = 9.9$), 3.33 (dd, 1H, $J = 9.9$, $J = 10.2$), 3.77 (dd, 1H, $J = 5.5$, $J = 10.2$), 4.17 (d, 1H, $J = 7.0$), 4.89 (ABq, 2H, $J = 12.0$), 5.51 (q, 1H, $J = 7.2$), 7.22–7.43 (m, 10 ArH); ^{13}C NMR: −5.7, −5.6, 16.1, 25.8, 39.5, 41.9, 48.9, 60.0, 76.8, 127.0, 127.4, 127.5, 127.6, 127.8, 128.3, 128.5, 138.0, 139.7, 171.7; $[\alpha]_D = -56.0$ (*c* 1.0, $CHCl_3$); EIMS: *m/z* 383 (19, $MH^+-C_4H_9$), 303 (9), 279 (12), 150 (12), 106 (73), 92 (82), 85 (74), 70 (100). Anal. Calcd for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 71.07; H, 8.42; N, 3.16.

4.15. (3*R*,4*R*,1′*S*)-4-Benzyloxymethyl-3-hydroxy-1-phenylethylpyrrolidin-2-one 18

To a solution of methanol (18 mL) and water (2 mL) containing KOH (1.4 g; 25 mmol), compound **17** (1.12 g; 2.56 mmol) was added, dissolved in methanol

(2 mL). The mixture was refluxed for 30 h and after cooling methanol was partially removed under reduced pressure. After extraction with ethyl acetate (3 × 30 mL), the organic layer was dried (Na_2SO_4) and evaporation carried out under reduced pressure gave a residue, which was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give compound **18** (0.48 g; 58% yield) as a colorless oil. ^{1}H NMR: 1.54 (d, 3H, J = 7.2), 2.05 (br s, 1H, OH), 2.34–2.53 (m, 1H), 2.67 (dd, 1H, J = 7.4, J = 9.8), 3.39 (dd, 1H, J = 8.2, J = 9.8), 3.50 (dd, 1H, J = 6.4, J = 10.8), 3.62 (dd, 1H, J = 5.4, J = 10.8), 3.96 (d, 1H, J = 7.6), 4.96 (ABq, 2H, J = 11.7), 5.48 (q, 1H, J = 7.2), 7.22–7.44 (m, 10 ArH); ^{13}C NMR: 16.0, 41.7, 41.9, 49.3, 62.1, 72.5, 77.6, 127.1, 127.6, 127.8, 128.2, 128.4, 128.5, 128.6, 138.0, 139.7, 172.1; $[\alpha]_D = -35.0$ (c 0.5, $CHCl_3$); EIMS: m/z 326 (4, MH^+), 311 (3), 235 (7), 150 (12), 106 (62), 70 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.77; H, 7.08; N, 4.33.

4.16. (3*R*,4*R*,1′*S*)-4-Benzyloxymethyl-3-hydroxy-1-phenylethylpyrrolidine 19

To a solution containing compound **18** (0.48 g, 1.48 mmol) in dry THF (7 mL), $LiAlH_4$ (60 mg, 1.5 mmol) was added and the mixture was refluxed for 6 h. Then methanol (1 mL) was added, followed by a saturated solution of Seignette salt (20 mL), and the mixture was eventually extracted with ethyl acetate (3 × 30 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 50:50), to give **19** (0.33 g, 71%) as a colorless oil. ^{1}H NMR: 1.39 (d, 3H, J = 6.6), 2.29–2.37 (m, 2H), 2.73 (dd, 1H, J = 6.9, J = 8.9), 2.73–3.02 (m, 2H), 3.20 (br s, 1H, OH), 3.27 (q, 1H, J = 6.6), 3.66 (dd, 1H, J = 4.3, J = 10.3), 3.79 (dd, 1H, J = 4.1, J = 10.3), 4.00 (ddd, 1H, J = 2.0, J = 4.6, J = 6.6), 4.44 (s, 2H), 7.18–7.43 (m, 10 ArH); ^{13}C NMR: 22.6, 46.1, 54.8, 59.7, 65.2, 66.1, 71.2, 81.0, 126.9, 127.1, 127.6, 128.3, 128.4, 138.1, 144.3; $[\alpha]_D = -108.0$ (c 0.3, $CHCl_3$); EIMS: m/z 311 (19, M^+), 249 (4), 173 (5), 123 (64), 106 (100), 78 (71). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.08; H, 8.03; N, 4.46.

4.17. (3*R*,4*R*)-3-Hydroxy-4-hydroxymethylpyrrolidine hydrochloride 1

To a solution containing compound **19** (0.31 g; 1.0 mmol) in CH_3OH (10 mL), $Pd(OH)_2$ (20% on charcoal, 50 mg) was added and the reaction was stirred under H_2 for 4 d. The catalyst was removed by filtration and washed with 3 M HCl (3 mL). The filtrates were combined and evaporated under reduced pressure to give compound **1** (1.44 g; 94%) yield as a low-melting solid. $[\alpha]_D = +18.2$ (c 0.7, CH_3OH) [lit.[7] +19.0 (c 1.0, CH_3OH)]; EIMS (CI): m/z 118 (MH^+), 100, 82.

4.18. (3*S*,4*S*,1′*S*)- 3-*tert*-Butyldimethylsilyloxy-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one 10

Following the same procedure used for preparation of **4b** but starting from compound **8** (1.05 g; 4.0 mmol), the silyl derivative **10** (1.4 g; 94% yield) was obtained as a yellow oil. $[\alpha]_D = -148.6$ (c 3.0, $CHCl_3$).

4.19. (3*R*,4*R*,1′*S*)-3-*tert*-Butyldimethylsilyloxy-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 11 and its (3*S*,4*S*,1′*S*)-isomer 21

To a solution containing the diastereomeric compounds **5**, **6** and **7** (2.37 g; 9.0 mmol overall) in DCM (20 mL), imidazole (0.82 g; 12 mmol) and *tert*-butyldimethylchlorosilane (1.8 g; 12 mmol) were added, and the mixture was stirred for 4 h at rt. Then water (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was dissolved in dry THF (30 mL) and $LiAlH_4$ (0.38 g; 9.0 mmol) was slowly added at 0 °C. After 40 min MeOH (1 mL) was added and subsequently a saturated solution of the Seignette salt (20 mL). The mixture was extracted with ethyl acetate (3 × 30 mL), the solvent dried (Na_2SO_4) and eventually removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 80:20) to give first unchanged **9** (0.56 g; 18% yield) followed by **11** (0.6 g; 23% yield) and **22** (0.66 g; 21% yield). Compound **11**: EIMS: m/z 335 (2, MH^+-15), 293 (81), 150 (16), 122 (13), 106 (100), 70 (74). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.24; H, 8.89; N, 3.96. Compound **22**: white solid. Mp 96–98 °C. ^{1}H NMR: 0.20 (s, 3H), 0.25 (s, 3H), 0.96 (s, 3H), 1.51 (d, 3H, J = 7.1), 2.18–2.36 (m, 1H), 2.89 (br s, 1H, OH), 2.99–3.16 (m, 2H), 3.69 (dd, 1H, J = 6.5, J = 10.6), 3.82 (dd, 1H, J = 4.1, J = 10.6), 4.27 (d, 1H, J = 8.7), 5.44 (q, 1H, J = 7.1), 7.27–7.43 (m, 5 ArH); ^{13}C NMR: −5.1, −4.1, 16.1, 25.8, 41.0, 44.4, 49.2, 61.2, 72.8, 127.0, 127.5, 128.5, 139.6, 172.8; $[\alpha]_D = -180.3$ (c 1.1, $CHCl_3$); EIMS: m/z 335 (2, M^+-15), 293 (74), 150 (11), 106 (100), 70 (67). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.26; H, 8.98; N, 4.05.

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22. AM1 within Hyperchem 5.0-Chemplus 5.2 releases, Hypercube, Gainesville, FL, USA.
23. Selected dihedral angles values for the lowest energy conformer of the anion **B**: (E_n = 0.0 kcal/mol), (C-1)–(C-2)–(C-3)–(CH_2N) = 54.1°; (O-2)–(C-2)–(C-3)–(CH_2N) = −63.0°; (O-2)–(C-2)–(C-3)–(C-4) = 118.5°; (H-2)–(C-2)–(C-3)–(C-4) = −3.8°. Another two similar conformers were also observed: **B-1** (E_n = 0.35 kcal/mol): (C-1)–(C-2)–(C-3)–(CH_2N) = 49.2°; (O-2)–(C-2)–(C-3)–(CH_2N) = −67.9°; (O-2)–(C-2)–(C-3)–(C-4) =112.2°; (H-2)–(C-2)–(C-3)–(C-4) = −9.9°; **B-2** (E_n = 0.67 kcal/mol): (C-1)–(C-2)–(C-3)–(CH_2N) = 59.8°; (O-2)–(C-2)–(C-3)–(CH_2N) = −57.9°; (O-2)–(C-2)–(C-3)–(C-4) = 121.6°; (H-2)–(C-2)–(C-3)–(C-4) = −1.0. The corresponding HOMO frontier electron density at C-2 are, respectively, for **B**: F_r^{HOMO} = 0.717; ε_{HOMO} = −8.13317 eV; $F_r^{HOMO} = 8.70 \times 10^{-2}$; for **B-1**: F_r^{HOMO} = −0.722; ε_{HOMO} = −8.23054 eV; $F_r^{HOMO} = 8.77 \times 10^{-2}$; for **B-2**: F_r^{HOMO} = 0.716; ε_{HOMO} = −8.09239 eV; $F_r^{HOMO} = 8.85 \times 10^{-2}$.
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27. It is worth mentioning however that by raising the temperature or with longer reaction times the selection is lost and also the lactam **9** undergoes reduction.