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TETRAHEDRON

Approaches to a Synthesis of α-Kainic acid

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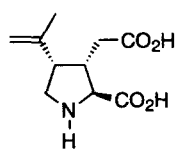
Abstract: A formal synthesis of (–)-α-kainic acid was achieved from L-pyroglutamic acid. The C-4 substituent of the pyrrolidine ring was introduced by using a ketyl radical cyclization on an ene carbamate.

Keywords: asymmetric synthesis, cyclization, kainoids, radicals and radical reaction.

α-Kainic acid **A**, first isolated in 1953 from the marine alga *Digenea simplex*,[1] is the parent member of the kainoids displaying potent anthelmintic properties and neurotransmitting activity[2,3] in the central nervous system. Among these properties, the neuroexcitatory activity is attributed to their *trans* C-2/C-3 : *cis* C-3/C-4 structure and the functionality at the C-4 center beside the 2-carboxy and 3-carboxymethyl functionalities.



(–)-α-kainic acid **A**

Figure 1

Because of its biological importance as well as its synthetic interest, several enantiocontrolled syntheses have been disclosed. Oppolzer's synthesis of (–)-α-kainic acid relying on an intramolecular ene reaction stands as the first and, as yet remains, the most efficient approach in terms of the number of steps and overall yield.[4] In other approaches, intramolecular Pauson-Khand reaction,[5–8] tandem Michael reactions,[9] thiazolium[10] or azomethine[11] ylide cycloadditions, Diels-Alder addition,[12] retro Diels-Alder reaction of keto dicyclopentadiene,[13] palladium induced cyclization,[14] aldol condensation[15] or enolate Claisen rearrangement[16] have been used. More recently, syntheses of several kainoids using free radical cyclization reaction have been presented.[17–26] We report here two approaches to (–)-α-kainic acid via bicyclic compound using both an intramolecular radical cyclization of a vinyl radical and an intramolecular radical cyclization of a ketyl radical.[27]

The synthesis of (–)-α-kainic acid from L-pyroglutamic acid using an unsaturated vinyl radical was planned according to the following retrosynthetic scheme (Scheme 1). The generation of the desired vinyl radical was envisaged by the addition of *n*-Bu3SnH on the acetylenic functionality.

L-Pyroglutamic acid **(–)-1** was transformed into the protected amido-alcohol **(+)-2** [m.p = 70 °C, $[\alpha]_D^{20}$ + 57.1 (*c* 0.25, THF)][28,29] in 3 steps with an overall yield of 63% (Scheme 2). Compound **(+)-2** was

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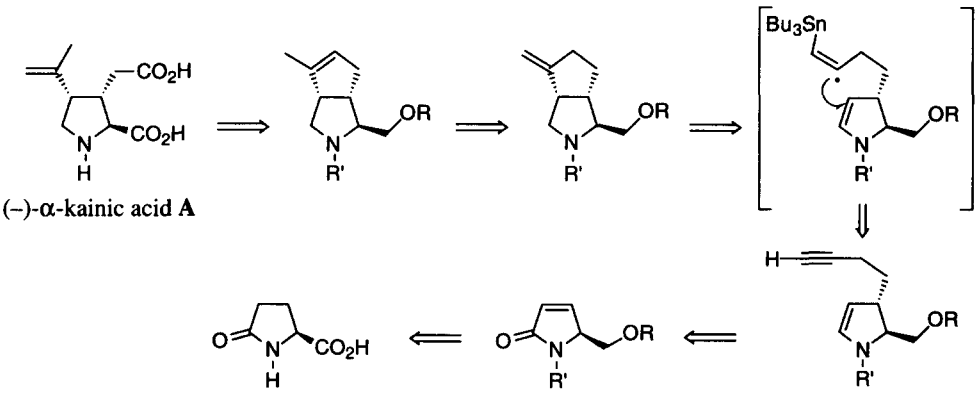
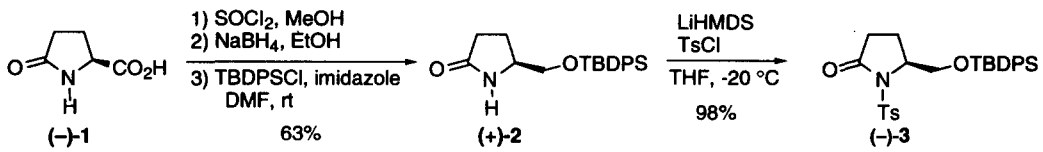
tosylated to afford the corresponding sulfonamide (–)-3[30] in the presence of LiHMDS, followed by addition of *p*-toluenesulfonyl chloride (yield: 98%).



(–)-α-kainic acid **A**

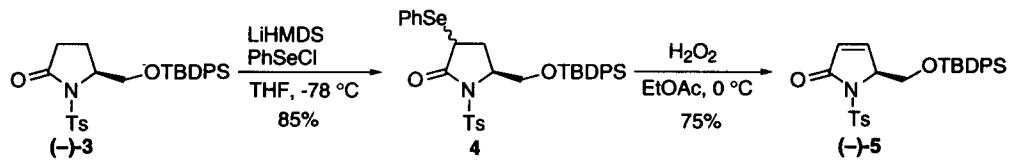
L-pyroglutamic acid (–)-**1**

Scheme 1



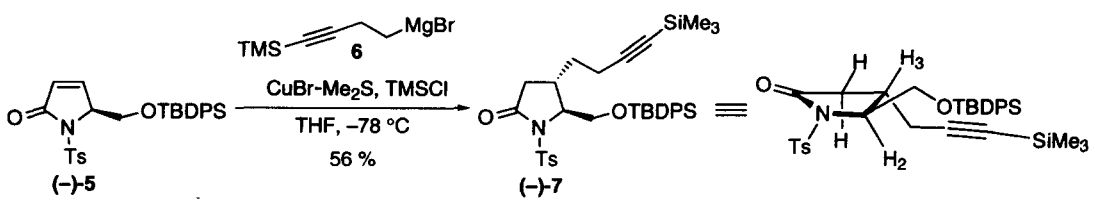
Scheme 2

In order to introduce the butynyl side chain at C-3, the obtained tosylamide (–)-**3** was transformed into the corresponding enamide (–)-**5**[30] via phenylselenylation (LiHMDS, 1 equiv.; PhSeCl, 1 equiv.; - 78 °C; 85% yield) and subsequent oxidation with H_2O_2 in ethyl acetate (yield: 75%) (Scheme 3).



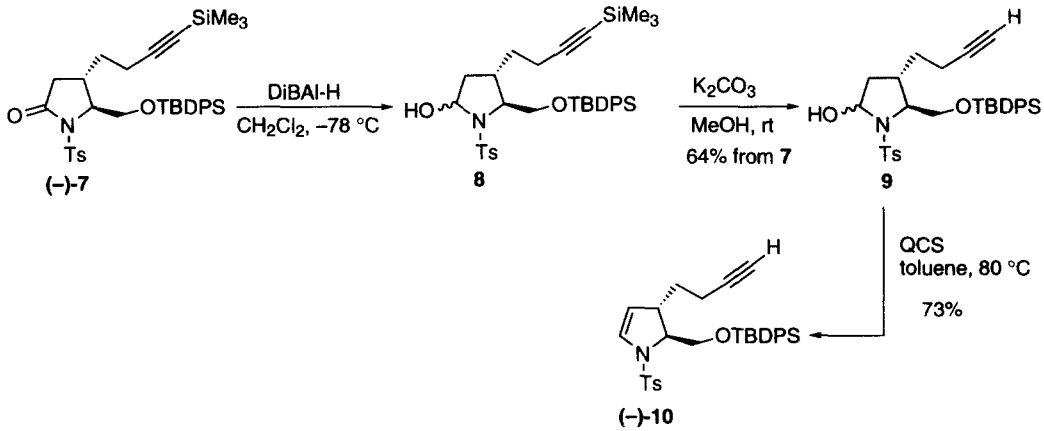
Scheme 3

Conjugate addition of the organocupromagnesium derivative **6**, prepared from the corresponding bromide,[31] in the presence of TMSCl on (–)-**5** furnished the expected C-3 alkylated pyrrolidone (–)-**7** in 56% yield (Scheme 4). The conjugate addition is diastereoselective. The ^{1}H NMR spectrum of (–)-**7**, shows that the coupling constant between H-2 and H-3 is equal to zero, implying that the dihedral angle betwen H-2 and H-3 is near 90°, and is related to a relative *trans* stereochemistry between the two side-chains at C-2 and C-3.[32]



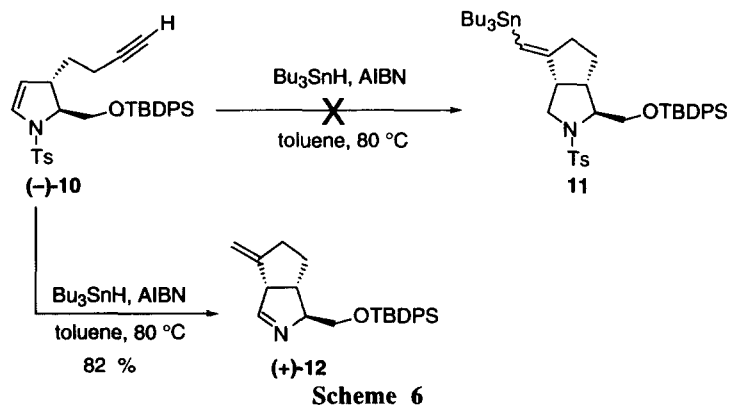
Scheme 4

The enetosylamide (–)-**10** required as a precursor of the vinyl radical was prepared by reduction of the tosylamide (–)-**7** by DiBAl-H followed by deprotection of the acetylenic functionality by using K_2CO_3 in MeOH. The overall yield for the two steps was 64%. Dehydration of the corresponding hydroxytosylamide **9** by using quinolinium camphorsulfonate (QCS)[33] in toluene for 10 min at 80 °C afforded the enetosylamide (–)-**10** in 73% (Scheme 5).



Scheme 5

Treatment of (–)-**10** with *n*-Bu3SnH in the presence of a catalytic amount of AIBN at 80 °C in toluene did not lead to the expected product **11** but to the unsaturated bicyclic enamine (+)-**12**. We have to point out that the two *exo*-methylenic hydrogen atoms are visible in the ^1H NMR spectrum of the crude reaction mixture. This observation excludes a destannylation reaction during the purification of the reaction mixture on silica gel (Scheme 6).

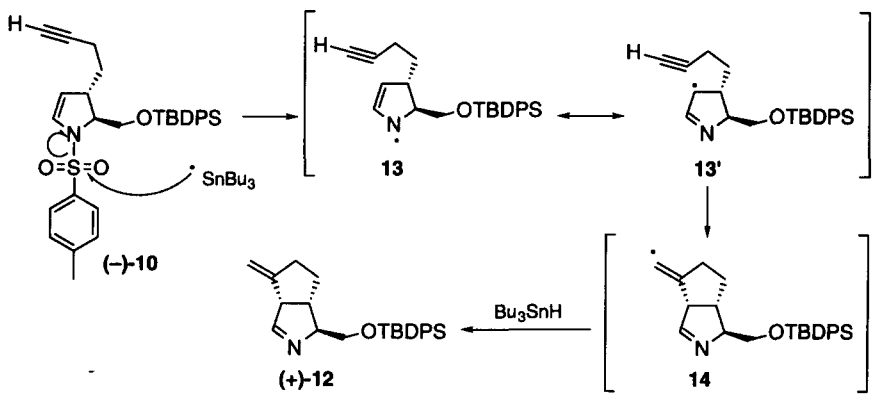


Scheme 6

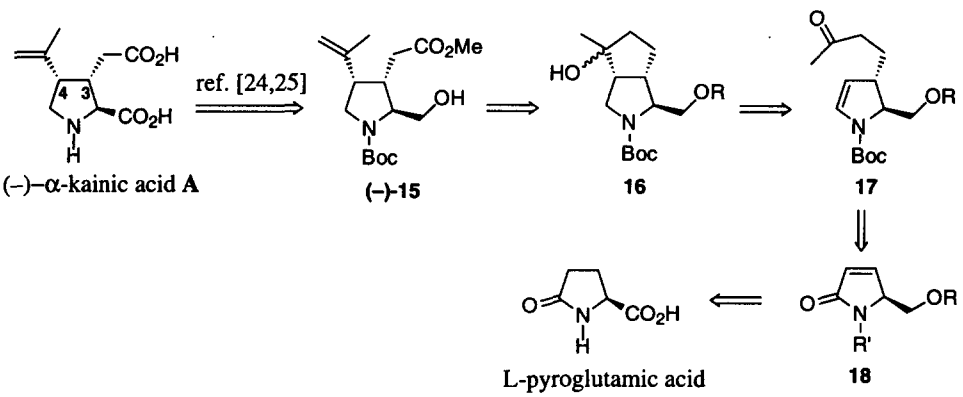
The obtainment of (+)-**12** can be explained by the attack of the tri-*n*-butylstannyl radical onto the tosyl group[34] of (–)-**10**. This implies the formation of the ene-aminyl radical **13**↔**13'**. A 5-*exo*-dig cyclization[35] takes place and produces radical intermediate **14** which, after reduction, affords the observed bicyclic imine (+)-**12** (Scheme 7).

A second possibility to obtain a bicyclic compound **16**, a precursor of (–)-α-kainic acid, is the use of an intramolecular radical cyclization of a ketyl radical issued from an unsaturated ketone **17**. The access to

(–)-α-kainic acid was planned from intermediate **17** according to the following retrosynthetic scheme (Scheme 8). The synthesis of intermediate **17** was envisaged by applying a conjugate addition of an organocupromagnesium derivative on intermediate **18**.



Scheme 7

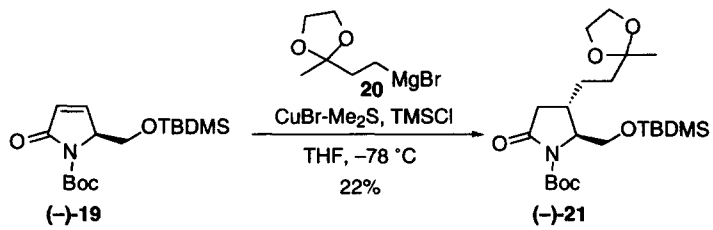


Scheme 8

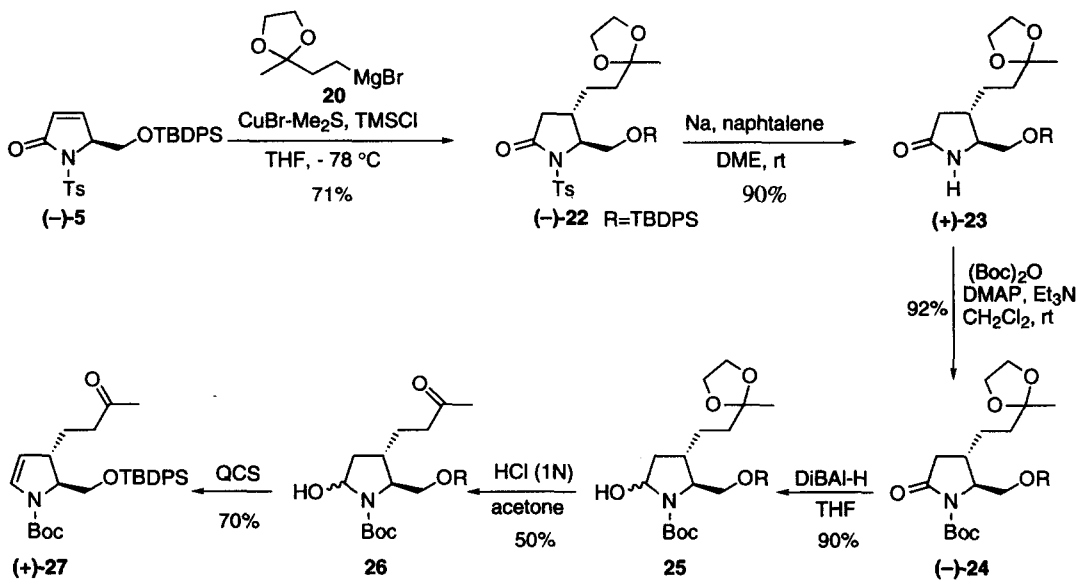
The synthesis of the precursor **(–)-21** was achieved by conjugate addition of the organocupromagnesium derivative **20**[36–38] on **(–)-19**,[39] in the presence of TMSCl which furnished the expected C-3 alkylated pyrrolidone **(–)-21** in poor yield (< 25%) (Scheme 9). In contrast, when the addition was carried on with tosylamide **(–)-5** the yield of the alkylated pyrrolidone **(–)-22** was 71%. Desulfonation of **(–)-22** by Na naphthalenide,[40] followed by *tert*-butoxycarbonylation [$(Boc)_2O$], afforded the carbamate **(–)-24** with an overall yield of 83%. The required enecarbamate **(+)-27** for the radical cyclization was prepared by reduction of amide **(–)-24** by DiBAl-H (90%) followed by deprotection of the ketone (HCl, H_2O-acetone) and dehydration of the corresponding hydroxycarbamate **26** by quinolinium camphorsulfonate (QCS). The overall yield for the two steps was 35% (Scheme 10).

The ketyl radical cyclization was attempted on irradiation of ketone **(+)-27** in the presence of Et_3N (10 equiv.) at 254 nm in CH_3CN (10^{-2}M).[41] Under these conditions no product of cyclization could be detected by GC-MS or by ^1H NMR. However when the ketyl radical was generated on treatment of **(+)-27** with SmI_2 in THF in the presence of HMPA (20 equiv.) and t-BuOH (3 equiv.),[42] bicyclic amine **(–)-28** was isolated in 55% yield together with **29**, the product of pinacolic coupling (32%). Under these conditions, the ketyl radical attacks the enamine in a 5-*exo*-trig process to produce intermediate radical **31**. This radical can be reduced to the

organosamarium derivative **32** by a second electron transfer. Intermediate **32** is then protonated by *t*-butanol with generation of the azabicyclic compound (–)-**28**. The configuration of the tertiary alcohol moiety could not be determined (Scheme 11).



Scheme 9

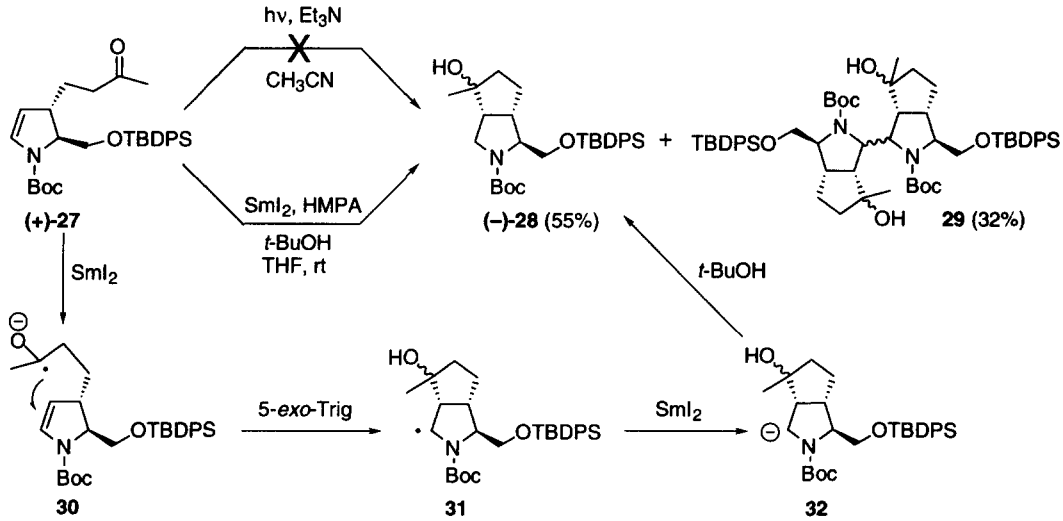


Scheme 10

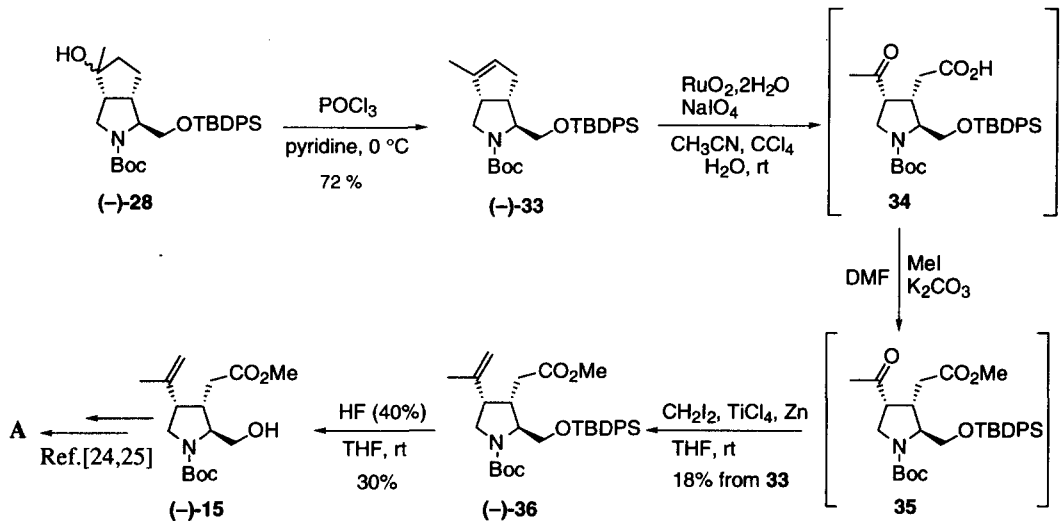
Transformation of the bicyclic system (–)-**28** into (–)-**15** was achieved in 5 steps. Treatment of the tertiary alcohol (–)-**28** with $POCl_3$ in pyridine afforded alkene (–)-**33** (72% yield). This compound was then treated with RuO_2-$NaIO_4$ to produce ketocarboxylic acid **34** that was treated directly with CH_3I in the presence of K_2CO_3 to produce **35**, the methylenation (CH_2I_2, $TiCl_4$, Zn^{10}) of which gave (–)-**36**. No purification was attempted with compound **35** in order to avoid its epimerisation at C-4. Finally, the known precursor (–)-**15**[24,25] of the (–)-α-kainic acid was obtained on treating (–)-**36** with a solution of HF (40 %) in THF[16] (yield > 30%) (Scheme 12).

Since the *trans*, *cis*-trisubstituted pyrrolidine (–)-**15** has been converted into (–)-α-kainic acid **A** without difficulty,[24,25] the present transformation of L-pyroglutamic acid (–)-**1** into (–)-**15** (18 steps) constitutes a new formal synthesis of this natural product.

Our work demonstrates that *cis*-3,4-disubstituted pyrrolidines can be obtained with high stereoselectivity employing a 5-*exo*-trig radical induced cyclization either from an enetosylate or from δ,ε-unsaturated ketones.



Scheme 11



Scheme 12

EXPERIMENTAL SECTION

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. – THF was distilled from Na benzophenone ketyl immediately prior to use. – CH_2Cl_2 and Et_3N were distilled from calcium hydride under argon. – Moisture sensitive reactions were conducted in oven-dried glassware under an argon atmosphere. – Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230-400 mesh). – Melting points are uncorrected. – IR: Perkin-Elmer 298. – Optical rotations: Perkin-Elmer 241MC polarimeter. – Elemental analyses: Service Régional de Microanalyse de l'Université P. et M. Curie. – HRMS: Centre de Spectrochimie Organique de l'Université P. et M. Curie. – NMR: Bruker AC 300

spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at $\delta = 7.27$ for ^1H and to $CDCl_3$ at $\delta = 77.1$ for ^{13}C. – MS: Mass spectra were obtained by GC/MS with electron impact ionization on a 5971 Hewlett Packard instrument at 70 eV; only selected ions are reported.

(+)-(5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}pyrrolidin-2-one (2). To a solution of (+)-(5*S*)-5-(hydroxymethyl)pyrrolidin-2-one[43] (5.1 g, 44.4 mmol, 1.0 equiv) in DMF (16 mL) at room temperature was added TBDMSCl (14.9 g, 54.3 mmol, 1.2 equiv), then imidazole (7.6 g, 112 mmol, 2.5 equiv). After 24 h at room temperature, Et_2O (200 mL) was added and the organic layer was washed successively with a 10% citric acid solution (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and water (100 mL), dried over $MgSO_4$, and the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc) to give **2** (15.6 g, 44.2 mmol, 99% yield) as a colorless solid: mp 70–74 °C; R_f 0.45 (EtOAc/cyclohexane 60/40); $[\alpha]_D^{20} = +57.1$ (*c* 0.25, THF); IR (KBr) 3200, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.70–1.83 (m, 1H), 2.20–2.21 (m, 1H), 2.30–2.36 (m, 2H), 3.52–3.65 (m, 2H), 3.76–3.84 (m, 1H), 6.5 (broad s, 1H), 7.36–7.47 (m, 6H), 7.64–7.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 178.1 (s), 135.4 (d), 135.3 (d), 132.9 (s), 132.8 (s), 129.8 (d), 129.7 (d), 127.7 (d), 127.6 (d), 67.1 (t), 55.5 (d), 29.7 (t), 26.6 (q), 22.7 (t), 19.0 (s); EI MS *m/z* (relative intensity) 296 (M^+–*t*-Bu, 100), 218 (51), 199 (14), 181 (11), 84 (13).

(–)-(5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-tosylpyrrolidin-2-one (3). To a stirred solution of HMDS (15.9 mL, 75.6 mmol, 1 equiv) in THF (250 mL) at –20 °C, a 2.5 M solution of *n*-butyllithium in hexane (33.2 mL, 83.0 mmol, 1.1 equiv) was added dropwise. After 5 min, a solution of amide **2** (26.7 g, 75.6 mmol, 1 equiv) in THF (50 mL) was added dropwise followed, after 1 h, by the addition of a solution of TsCl (17.3 g, 90.8 mmol, 1.2 equiv) in THF (25 mL). The reaction mixture was allowed to warm slowly to room temperature. After 1 h at room temperature, the mixture was poured into a saturated NH_4Cl solution (50 mL) and extracted with Et_2O (2 × 100 mL). The combined organic phases were neutralized with a saturated $NaHCO_3$ solution until pH~7, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30/70) to give **3** (37.5 g, 73.9 mmol, 98% yield) as a white solid. R_f 0.31 (EtOAc/cyclohexane 20/80); $[\alpha]_D^{20} = -19.8$ (*c* 1.1, CH_2Cl_2); IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.95–2.37 (m, 3H), 2.38 (s, 3H), 2.63–2.72 (m, 1H), 3.80–3.85 (m, 1H), 4.06–4.11 (m, 1H), 4.43–4.46 (m, 1H), 7.20–7.22 (m, 2H), 7.38–7.41 (m, 6H), 7.61–7.64 (m, 4H), 7.91–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.9 (s), 144.7 (s), 136.0 (s), 135.5 (d), 135.4 (d), 132.7 (s), 132.3 (s), 129.9 (d), 129.8 (d), 129.4 (d), 128.0 (d), 127.8 (d), 127.7 (d), 65.7 (t), 60.6 (d), 31.5 (t), 26.7 (q), 22.4 (t), 21.4 (q), 19.0 (s); EI MS *m/z* (relative intensity) 450 (M^+– *t*-Bu, 100), 353 (17), 218 (26), 181 (11), 155 (28), 135 (12).

(3*SR*,5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-3-(phenylseleno)-1-tosyl-pyrrolidin-2-one (4). To a stirred solution of HMDS (4.35 mL, 20.6 mmol, 1.1 equiv) in THF (30 ml) at –78 °C, a 2.5 M solution of *n*-butyllithium in hexane (9.0 mL, 22.5 mmol, 1.2 equiv) was added dropwise and after 15 min a solution of tosylamide **3** (9.51 g, 18.75 mmol, 1 equiv) in THF (10 mL) was added dropwise. After 2 h, a solution of PhSeCl (4.67 g, 24.4 mmol, 1.3 equiv) in THF (20 mL) was added. After 1h at –78 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was poured into a saturated aqueous NH_4Cl solution (25 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (eluting with a gradient of 0–30% of EtOAc/cyclohexane) to give an inseparable mixture (ratio 70/30 according to ^1H NMR) of isomers **4** (10.5 g, 15.5 mmol, 85% yield) as a yellow oil. R_f 0.51 (EtOAc/cyclohexane 20/80); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 6.3 H), 1.06 (s, 2.7 H), 2.14–2.25 (m, 1H), 2.33–2.44 (m, 4H), 3.77–3.81 (m, 1H), 4.10–4.29 (m, 3H), 7.16–7.98 (m, 19H).

(–)-(5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (5). To a stirred solution of **4** (7.7 g, 11.6 mmol, 1 equiv) in EtOAc (140 ml) at 0 °C, was added a 30% H_2O_2 solution (6.1 mL). After 15 min, the solution was allowed to warm to room temperature and stirred for an additional 15 min. To the reaction mixture was added Et_2O (150 mL) and the organic layer was washed successively with water (50 mL), brine (20 mL) and a saturated aqueous $NaHCO_3$ (100 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (Et_2O/cyclohexane 40/60) to give **5** (4.4 g, 8.7 mmol, 75% yield) as a yellow amorphous solid. R_f 0.30 (EtOAc/cyclohexane 30/70); $[\alpha]_D^{20}$ = - 107.7 (*c* 1.11, EtOH); IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H), 2.37 (s, 3H), 4.07 (dd, *J* = 5.8 and 10.3 Hz, 1H), 4.24 (dd, J = 2.9 and 10.3 Hz, 1H), 4.79–4.82 (m, 1H), 6.00–6.03 (m, 1H), 7.08–7.11 (m, 1H), 7.22–7.26 (m, 2H), 7.37–7.46 (m, 6H), 7.59–7.62 (m, 4H), 7.90–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.0 (s), 150.8 (d), 144.8 (s), 144.7 (s), 135.5 (d), 135.4 (d), 132.5 (s), 132.4 (s), 130.0 (d), 129.9 (d), 129.8 (d), 129.4 (d), 127.8 (d), 127.7 (d), 126.2 (d), 65.1 (d), 62.9 (t), 26.7 (q), 21.4 (q), 19.0 (s).

(–)-(4*S*,5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-tosyl-4-[4-(trimethylsilyl)but-3-ynyl]pyrrolidin-2-one (7). To a solution of CuBr·Me_2S (0.43 g, 2.05 mmol, 0.6 equiv) in THF (4 mL) at –78 °C, a solution of **6** was added dropwise, freshly prepared from Mg (1.49 g, 62.2 mmol, 18 equiv.) and 4-bromo-1-(trimethylsilyl)but-1-yne[31] (4.5 g, 20.7 mmol, 6 equiv) in THF (40 mL). After 10 min, TMSCl (0.88 mL, 6.9 mmol, 2 equiv) was added, followed by the addition of a solution of **5** (1.74 g, 3.45 mmol, 1 equiv) in THF (15 ml). After 15 min at –78 °C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 20/80) to give **7** (1.22 g, 1.93 mmol, 56% yield) as a colourless oil. R_f 0.48 (EtOAc/cyclohexane 15/85); $[\alpha]_D^{20}$ = –53.7 (*c* 0.5 THF); IR (neat) 2180, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (s, 9H), 1.04 (s, 9H), 1.41–1.65 (m, 2H), 2.03 (dd, *J* = 1.1 and 17.6 Hz, 1H), 2.20–2.22 (m, 1H), 2.38–2.42 (m, 5H), 2.90 (dd, *J* = 8.4 and 17.6 Hz, 1H), 3.87 (dd, *J* = 2.7 and 11.2 Hz, 1H), 3.97 (dd, *J* = 4.7 and 11.2 Hz, 1H), 4.12–4.17 (m, 1H), 7.23–7.27 (m, 2H), 7.37–7.47 (m, 6H), 7.58–7.64 (m, 4H), 7.85–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.2 (s), 144.8 (s), 135.6 (s), 135.5 (d), 135.5 (d), 132.7 (s), 132.3 (s), 130.0 (d), 129.9 (d), 129.4 (d), 128.1 (d), 127.8 (d), 127.7 (d), 105.2 (s), 85.8 (s), 65.8 (t), 65.5 (d), 37.6 (t), 34.4 (d), 33.2 (t), 26.8 (q), 21.6 (q), 19.1 (s), 17.4 (t), 0.00 (q); EI MS *m/z* (relative intensity) 574 (M^+–*t*-Bu, 100), 353 (14), 197 (14), 155 (21), 91 (74); HRMS calcd for $C_{31}H_{36}NO_4SSi$ (M^+–*t*-Bu) 574.1903, found 574.1901.

(2*SR*,4*S*,5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl-1-tosyl-4-[4-(trimethylsilyl)but-3-ynyl]pyrrolidin-2-ol (8). To a stirred solution of **7** (0.94 g, 1.5 mmol, 1.0 equiv) in CH_2Cl_2 (14 ml) at –78 °C, an 1 M solution of DiBAl-H in hexane (1.8 mL, 1.78 mmol, 1.2 equiv) was added dropwise. After 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30/70) to give **8** (0.80 g, 1.27 mmol, 85% yield) as a colourless oil. R_f 0.48 (EtOAc/cyclohexane 15/85); IR (neat) 3550–3400, 2180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 9H), 0.83–0.91 (m, 2H), 1.07 (s, 9H), 1.16–1.29 (m, 1H), 1.36–1.45 (m, 1H), 1.95–2.05 (m, 2H), 2.43–2.47 (m, 4H), 3.26–3.37 (m, 2H), 3.77–3.82 (m, 2H), 5.38–5.42 (m, 1H), 7.27–7.30 (m, 2H), 7.40–7.47 (m, 6H), 7.61-7.78 (m, 6H) ^{13}C NMR ($CDCl_3$) δ 143.6 (s), 135.7 (d), 135.6 (d), 132.9 (s), 132.6 (s), 129.8 (d), 129.6 (d), 127.8 (d), 127.7 (d), 127 .0 (d), 105.9 (s), 84.8 (s), 84.5 (d), 65.8 (d), 65.1 (t), 38.5 (t), 38.1 (d), 32.5 (t), 26.8 (q), 21.5 (q), 18.1 (t), 0.0 (q); EI MS *m/z* (relative intensity) 600 (3), 558 (M^+–*t*-Bu–H_2O, 100), 290 (82), 273, (88), 135 (80), 91 (50).

(2*SR*,4*S*,5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-but-3-ynyl-1-tosylpyrrolidin-2-ol (9). To a stirred solution of **8** (0.82 g, 1.3 mmol, 1.0 equiv) in MeOH (4 ml) at room temperature, was added

K_2CO_3 (0.2 g, 1.42 mmol, 1.1 equiv). After 15 h at room temperature, the reaction mixture was neutralized with an aqueous HCl solution (1 M). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 15/85) to give **9** (0.52 g, 0.94 mmol, 72% yield) as a colourless oil. R*f* 0.48 (EtOAc/cyclohexane 15/85); IR (neat) 3600–3350, 3300, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.16 (m, 11H), 1.20–1.31 (m, 1H), 1.38–1.47 (m, 1H), 1.88–2.03 (m, 2H), 2.06 (s, 1H), 2.42 (s, 3H), 2.52–2.59 (m, 1H), 3.31–3.36 (m, 2H), 3.80–3.82 (m, 1H), 5.38–5.43 (m, 1H), 7.27–7.30 (m, 2H), 7.37–7.63 (m, 8H), 7.63–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 143.6 (s), 135.6 (d), 135.5 (d), 132.8 (s), 132.6 (s), 129.7 (d), 127.6 (d), 127.5 (d), 127.0 (d), 126.9 (d), 84.5 (d), 83.0 (d), 68.8 (s), 65.6 (d), 64.9 (t), 38.3 (t), 37.5 (d), 32.2 (t), 26.7 (q), 21.3 (q), 19.0 (s), 16.6 (t); EI MS *m/z* (relative intensity) 330 (M^+–*t*-Bu–H_2O–Ts–H, 2), 292 (4), 273 (18), 199 (19), 155 (25), 135 (70), 91 (100).

(–)-(2*S*,3*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-but-3-ynyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (10). A mixture of **9** (0.48 g, 0.85 mmol, 1.0 equiv) and QCS (0.05 g, 0.12 mmol, 0.15 equiv.) in toluene (30 mL) was warmed to 80 °C for 10 min, then K_2CO_3 (0.5 g) was added. The reaction mixture was cooled to room temperature and filtered. The organic solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (eluting with a gradient of 0–15% of EtOAc/cyclohexane) to give **10** (0.34 g, 0.62 mmol, 73% yield) as a colourless oil. R*f* 0.37 (EtOAc/cyclohexane 15/85); $[\alpha]_D^{20}$ = –217.0 (*c* 2.65, EtOH); IR (neat) 3300, 1600 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.44–0.69 (m, 2H), 0.77 (s, 9H), 1.51–1.61 (m, 2H), 2.00–2.02 (m, 1H), 2.13 (s, 3H), 2.68–2.75 (m, 1H), 3.14–3.19 (m, 1H), 3.46–3.52 (m, 1H), 3.59–3.64 (m, 1H), 4.93–4.95 (m, 1H), 6.03–6.08 (m, 1H), 7.13–7.20 (m, 8H), 7.33–7.36 (m, 2H), 7.43–7.47 (m, 4H); ^{13}C NMR (acetone-d_6) δ 144.7 (s), 136.1 (d), 136.0 (d), 133.8 (s), 133.6 (s), 130.5 (d), 130.4 (d), 130.3 (d), 130.1 (d), 128.4 (d,), 128.3 (d), 128.2 (d), 116.1 (d), 83.8 (d), 69.7 (s), 66.4 (t), 65.7 (d), 46.1 (d), 35.0 (t), 26.9 (q), 21.1 (q), 19.4 (s), 15.4 (t).

(+)-(1*S*,3a*S*,6a*S*)-1-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-methylidene-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrrole (12). To a stirred solution of **10** (0.31 g, 0.57 mmol, 1 equiv) in toluene (85 mL) were added AIBN (0.01 g) and *n*-Bu_3SnH (0.17 mL, 0.62 mmol, 1.1 equiv) at 80 °C. After 1 h at 80 °C, the reaction mixture was cooled to room temperature and the organic solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 20/80) to give **12** (0.18 g, 0.47 mmol, 82% yield) as a colourless oil. R*f* 0.42 (EtOAc/cyclohexane 30/70); $[\alpha]_D^{20}$ = +167.6 (*c* 1.02, CH_2Cl_2); IR (neat) 1615, 1425, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.26–1.51 (m, 1H), 1.94 (dq, *J* = 7.9 and 12.5 Hz, 1H), 2.18–2.27 (m, 2H), 2.76–2.85 (m, 1H), 3.73 (dd, *J* = 4.7 and 9.9 Hz, 1H), 3.80 (d, *J* = 8.46 Hz, 1H), 3.91 (dd, J = 3.6 and 9.9 Hz, 1H), 3.96–4.00 (m, 1H), 4.91–5.03 (m, 2H), 7.36–7.44 (m, 7H), 7.66–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.5 (s), 149.8 (s), 135.5 (d), 135.4 (d), 133.5 (s), 133.2 (s), 129.5 (d), 129.4 (d), 127.6 (d), 127.5 (d), 106.9 (t), 82.4 (d), 65.9 (t), 61.0 (d), 42.6 (d), 32.6 (t), 31.9 (t), 26.7 (q), 19.1 (s); EI MS *m/z* (relative intensity) 389 (M^+, 2), 374 (10), 332 (100), 304 (4), 240 (10), 199 (12), 181 (13), 162 (15), 135 (12), 93 (29).

(4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolidin-2-one (21). To a solution of CuBr·Me_2S (0.08 g, 0.4 mmol, 0.2 equiv) in THF (1 mL) at –78 °C, a solution of **20**, freshly prepared from Mg (1 g, 42 mmol, 21 equiv) and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[36] (2.73 g, 14 mmol, 7 equiv) in THF (28 mL) was added dropwise. After 20 min at –78 °C, TMSCl (0.51 mL, 4 mmol, 2 equiv) was added, followed by the addition of a solution of **19**[39] (0.65 g, 2 mmol, 1 equiv) in THF (2 ml) dropwise. The reaction mixture was allowed to warm slowly to room temperature and quenched with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 20/80) to give **21** (0.2 g, 0.44 mmol, 22% yield) as a colourless oil. R*f* 0.44 (EtOAc/cyclohexane 20/80); $[\alpha]_D^{20}$ = –29.5 (*c* 2.61 THF); IR (neat) 1785, 1750, 1705 cm^{-1}; ^1H NMR ($CDCl_3$)

δ –0.05 (s, 3H), –0.04 (s, 3H), 0.78 (s, 9H), 1.21 (s, 3H), 1.25–1.37 (m, 2H), 1.45 (s, 9H), 1.46–1.59 (m, 2H), 1.98–2.15 (m, 2H), 2.77 (dd, J = 9.2 and 17.6 Hz, 1H), 3.59 (dd, J =1.8 and 10.3 Hz, 1H), 3.61–3.62 (m, 1H), 3.79–3.89 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 74.0 (s), 149.5 (s), 109.3 (s), 82.5 (s), 64.4 (t), 64.3 (d), 63.7 (t), 38.5 (t), 36.2 (t), 33.2 (d), 29.3 (t), 27.8 (q), 25.5 (q), 23.6 (q), 17.9 (s), –5.7 (q); EI MS *m/z* (relative intensity) 428 (M^+–CH_3, 2), 370 (10), 330 (78), 286 (33), 150 (42), 87 (100), 57 (62); HRMS calcd for $C_{18}H_{32}NO_5Si$ (M^+–*t*-BuO) 370.2049, found 370.2050.

(–)-(4*S*,5*S*)-5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-tosylpyrrolidin-2-one (22). To a solution of CuBr·Me_2S (1.63 g, 7.9 mmol, 0.7 equiv) in THF (16 mL) at –78 °C was added dropwise a solution of **20**, freshly prepared from Mg (5.72 g, 238 mmol, 21 equiv.) and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[36] (15.5 g, 79.4 mmol, 7 equiv) in THF (140 mL). After 10 min at –78 °C, TMSCl (2.88 mL, 22.7 mmol, 2 equiv) was added, followed by the addition of a solution of **5** (5.7 g, 11.3 mmol, 1 equiv) in THF (25 ml). After 10 min at –78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (4 × 50 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (eluting with a gradient of 10–30% of EtOAc/cyclohexane) to give **22** (4.98 g, 8 mmol, 71% yield) as a colourless oil. R_f 0.38 (EtOAc/cyclohexane 30/70); $[\alpha]_D^{20}$ = –16.8 (*c* 1.95 THF); IR (neat) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.23 (s, 3H), 1.30–1.37 (m, 2H), 1.54–1.59 (m, 2H), 1.99 (d, J = 17.6 Hz, 1H), 2.20–2.28 (m, 1H), 2.42 (s, 3H), 2.84 (dd, J = 17.6 and 8.4 Hz, 1H), 3.82–3.92 (m, 5H), 3.96–4.01 (m, 1H), 4.05–4.08 (m, 1H), 7.24–7.27 (m, 2H), 7.37–7.45 (m, 6H), 7.6–7.64 (m, 4H), 7.87–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4 (s), 144.7 (s), 135.7 (s,), 135.5 (d), 135.4 (d), 133.5 (s), 132.7 (s), 129.4 (d), 128.0 (d), 127.8 (d), 127.7 (d), 109.2 (s), 65.9 (d), 64.5 (t), 64.4 (t), 64.3 (t), 37.7 (t), 36.0 (t), 34.7 (d), 28.9 (t), 26.7 (q), 23.7 (q), 21.5 (q), 19.0 (s); EI MS *m/z* (relative intensity) 606 (M^+–CH_3, 2), 564 (M^+–*t*-Bu, 100), 353 (22), 199 (36), 155 (50), 135 (33); HRMS calcd for $C_{30}H_{34}NO_6SSi$ (M^+–*t*-Bu) 564.1876, found 564.1877.

(+)-(4*S*,5*S*)5-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolidin-2-one (23). To a stirred solution of naphthalene (8.6 g, 67.8 mmol, 6 equiv) in DME (60 mL) was added Na (1.5 g, 67.8 mmol, 6 equiv) at room temperature. After activation by sonication for 10 min, the green solution was stirred 2 h at room temperature. A solution of **22** (5 g, 8.1 mmol, 1 equiv) in DME (60 mL) was added dropwise to the previously prepared Na naphthalenide solution at 0 °C. After 10 min, the reaction mixture was hydrolyzed with an aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (elution was achieved with a gradient of 50–100% of EtOAc/cyclohexane) to give **23** (3.4 g, 7.3 mmol, 90% yield) as a colourless oil. R_f 0.2 (EtOAc); $[\alpha]_D^{20}$ = +211 (*c* 1.4 THF); IR (neat) 3212, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.27 (s, 3H), 1.44–1.60 (m, 4H), 1.97–2.06 (m, 2H), 2.50 (dd, J = 19.1 and 11 Hz, 1H), 3.39–3.44 (m, 1H), 3.49–3.55 (m, 1H), 3.64–3.69 (m, 1H), 3.85–3.94 (m, 4H), 5.91 (s, 1H), 7.37–7.45 (m, 6H), 7.62–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.4 (s), 135.4 (d), 135.3 (d), 132.8 (s), 129.8 (d), 127.7 (d), 129.7 (d), 109.4 (s), 66.8 (t), 64.5 (t), 64.4 (t), 61.4 (d), 36.7 (t), 36.4 (t), 36.2 (d), 28.8 (t), 26.6 (q), 23.6 (q), 19.0 (s); EI MS *m/z* (relative intensity) 452 (M^+-CH_3, 8), 410 (M^+-t-Bu, 100), 332 (60), 306 (27), 199 (47), 181 (30), 168 (14), 162 (15), 150 (62); HRMS calcd for $C_{26}H_{34}NO_4Si$ (M^+–CH_3) 452.2257, found 452.2256.

(–)-(4*S*,5*S*)1-(*tert*-Butoxycarbonyl)-5-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolidin-2-one (24). To a solution of **23** (3.42 g, 7.3 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at room temperature was added di-*tert*-butyl dicarbonate (3.2 g, 14.6 mmol, 2 equiv), DMAP (0.89 g, 7.3 mmol, 1 equiv) and Et_3N (2 mL, 14.6 mmol, 2 equiv). After 24 h at room temperature, Et_2O (100 mL) was added and the organic layer was washed with 1 M HCl (15 mL). The organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc) to give **24** (3.9 g, 6.88 mmol, 95% yield) as a colourless oil. R_f 0.3

(EtOAc/cyclohexane 30/70); $[\alpha]_D^{20} = -19.2$ (*c* 2.4, CH_2Cl_2); IR (neat) 1790, 1753, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.31 (s, 3H), 1.45 (s, 9H), 1.47–1.71 (m, 4H), 2.16 (dd, *J* = 1.8 and 17.6 Hz, 1H), 2.25–2.32 (m, 1H), 2.93 (dd, *J* = 8.8 and 17.6 Hz, 1H), 3.67–3.73 (m, 1H), 3.85–3.98 (m, 6H), 7.35–7.45 (m, 6H), 7.58–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.4 (s), 149.8 (s), 135.4 (d), 135.3 (d), 132.9 (s), 132.5 (s), 129.7 (d), 127.6 (d), 127.7 (d), 109.4 (s), 82.6 (s), 64.6 (t), 64.5 (t), 64.4 (t), 64.3 (d), 36.7 (t), 36.4 (t), 33.3 (d), 29.4 (t), 27.8 (q), 26.6 (q), 23.7 (q), 19.0 (s); EI MS *m/z* (relative intensity) 453 (6), 410 (M^+–$C_9H_{17}O_2$, 100), 348 (12), 332 (58), 306 (28), 207 (21), 199 (32), 181 (21), 162 (15), 150 (33), 135 (14); HRMS calcd for $C_{23}H_{28}NO_4Si$ (M^+–$C_9H_{17}O_2$) 410.1787, found 410.1787.

(2*SR*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolidin-2-ol (25). To a solution of **24** (4.1 g, 7.3 mmol, 1 equiv) in THF (20 ml) at –78 °C, an 1 M solution of DiBAl-H in hexane (9.5 mL, 9.5 mmol, 1.3 equiv) was added dropwise. After 2 h at –78 °C, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc 80/20) to give an inseparable mixture (ratio 64/36 according to ^1H NMR) of isomers **25** (3.7 g, 6.5 mmol, 90% yield) as a colourless oil. R_f 0.3 (EtOAc/cyclohexane 30/70); IR (neat) 3440, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3.24H), 1.07 (s, 5.76H), 1.31–1.35 (m, 11H), 1.44–1.52 (m, 6H), 1.62–1.74 (m, 2H), 3.50–3.72 (m, 3H), 3.90-3.95 (m, 4H), 5.45–5.55 (m, 1H), 7.36–7.43 (m, 6H), 7.63–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.2 (s), 135.4 (d), 135.3 (d), 132.9 (s), 129.6 (d), 129.5 (d), 127.6 (d), 127.5 (d), 109.5 (s), 81.9 (d), 80.0 (s), 65.6 (t), 64.5 (t), 64.3 (t), 63.9 (d), 38.4 (d), 37.7 (t), 37.3 (t), 28.7 (t), 28.1 (q), 26.7 (q), 23.7 (q), 19. 0 (s); EI MS *m/z* (relative intensity) 551 (M^+–H_2O, 4), 496 (M^+–C_4H_9O, 4), 451 (10), 438 (20), 394 (79), 349 (18), 290 (28), 87 (65), 57 (100); HRMS calcd for $C_{23}H_{38}NO_5Si$ (M^+–C_4H_9O) 496.2519, found 496.2518; Anal. Calcd for $C_{32}H_{47}NO_6Si$: C, 67.48; H, 8.26; N, 2.46. Found C, 67.43; H, 8.19; N, 2.42.

4-((2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-5-hydroxypyrrolidin-3-yl)butan-2-one (26). To a solution of **25** (4 g, 7.03 mmol, 1 equiv) in acetone (70 mL) and H_2O (20 mL) at room temperature, was added HCl (1 M, 20 mL). After 6 h at room temperature, the reaction mixture was neutralized with $NaHCO_3$ until pH~7. The organic phases were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (eluting with a gradient of 10–100% of EtOAc/cyclohexane) to give an inseparable mixture (ratio 64/36 according to ^1H NMR) of isomers **26** (1.8 g, 3.4 mmol, 50% yield) as a colourless oil. R_f 0.25 (EtOAc/cyclohexane 30/70); IR (neat) 3440, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) (major isomer) δ 1.05–1.08 (m, 9H), 1.34–1.41 (m, 9H), 1.42–1.58 (m, 3H), 1.62–1.73 (m, 1H), 1.87–1.99 (m, 1H), 2.07–2.14 (m, 3H), 2.20–2.31 (m, 1H), 2.43–2.57 (m, 1H), 3.42–3.57 (m, 1H), 3.66–3.84 (m, 2H), 5.36–5.45 (m, 1H), 7.34–7.39 (m, 6H), 7.60–7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) (major isomer) δ 207.7 (s), 154.2 (s), 135.4 (d), 132.9 (s), 132.8 (s), 129.7 (d), 127.6 (d), 81.8 (d), 80.2 (s), 63.8 (d), 63.7 (t), 41.7 (t), 37.9 (d), 37.5 (t), 29.7 (q), 28.1 (q), 27.6 (t), 26.7 (q), 20.9 (s); ^1H NMR ($CDCl_3$, doubling due to amide rotamers) (minor isomer) δ 1.01–1.11 (m, 9H), 1.32–1.37 (m, 5H), 1.48–1.59 (m, 6H), 1.65–1.74 (m, 1H), 1.90–2.05 (m, 1H), 2.10–2.14 (m, 3H), 2.36–2.53 (m, 3H), 3.46–3.72 (m, 3H), 5.43–5.53 (m, 1H), 7.36–7.44 (m, 6H), 7.60–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$) (minor isomer) δ 208.1 (s), 154.7 (s), 135.3 (d), 133.1 (s), 133.0 (s), 129.6 (d), 127.6 (d), 82.7 (d), 80.2 (s), 64.6 (d), 64.1 (t), 42.0 (t), 39.2 (d), 35.3 (t), 29.6 (q), 29.0 (t), 28.2 (q), 26.7 (q), 19.0 (s); HRMS calcd for $C_{21}H_{24}NO_2Si$ (M^+–Boc– *t*-Bu–H_2O) 350.1576, found 350.1574; Anal. Calcd for $C_{30}H_{43}NO_5Si$: C, 68.57; H, 8.19; N, 2.66. Found C, 68.37; H, 8.33; N, 2.58.

(+)-4-(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-2,3-dihydro-1*H*-pyrrol-3-yl)butan-2-one (27). A mixture of **26** (0.12 g, 0.21 mmol, 1.0 equiv) and QCS (12.7 mg, 0.03 mmol, 0.15 equiv.) in toluene (5 mL) was warmed to 80 °C. After 10 min, K_2CO_3 (0.3 g) was

added. The reaction mixture was cooled to room temperature and filtered. The organic solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (eluting with a gradient of 0–10% of EtOAc/cyclohexane) to give **27** (76 mg, 0.15 mmol, 70% yield) as a colourless oil. R*f* 0.56 (EtOAc/cyclohexane 60/40); $[\alpha]_D^{20}$ = +36.2 (*c* 0.58, THF); IR (neat) 1695, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.07 (s, 9H), 1.34 and 1.46 (2 s, 9H), 1.69–1.76 (m, 2H), 2.12 (s, 3H), 2.46-2.51 (m, 2H), 2.90–3.04 (m, 1H), 3.79–3.90 (m, 3H), 4.89–4.98 (m, 1H), 6.43–6.56 (m, 1H), 7.37–7.41 (m, 6H), 7.63–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 208.2 (s), 151.6 (s), 151.2 (s), 135.4 (d), 133.3 (d), 133.1 (d), 129.6 (d), 129.5 (d), 127.5 (d), 110.1 (d), 80.2 (s), 80.0 (s), 64.5 (t), 63.5 (t), 63.2 (t), 63.1 (d), 45.6 (d), 44.5 (d), 40.4 (t), 29.7 (q), 29.0 (t), 28.9 (q), 28.2 (q), 28.1 (q), 26.6 (q), 19.2 (s); EI MS *m/z* (relative intensity) 507 (M^+, 5), 434 (9), 394 (28), 350 (90), 292 (25), 199 (36), 138 (48), 80 (55), 57 (100); HRMS calcd for $C_{30}H_{41}NO_4Si$ (M^+) 507.2805, found 507.2804.

(1*S*,3a*S*,6a*S*)-2-(*tert*-Butoxycarbonyl)-1-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-4-methyl-octahydrocyclopenta[*c*]pyrrol-4-ol (28) and **(1,1',3*S*,3'*S*,3a*S*,3a'*S*,6a*S*,6a'*S*)-2,2'-bis(*tert*-butoxycarbonyl)-3,3'-bis{[(*tert*-butyl-dimethylsilyl)oxy]methyl}-4,4'-dimethyl-hexadeca-hydro-1,1'-bi[cyclopenta[*c*]-pyrrole]-6,6'-diol (29).** To a stirred suspension of Sm (0.75 g, 4.95 mmol, 2.8 equiv) in THF (50 mL) at room temperature was added CH_2I_2 (0.36 mL, 4.25 mmol, 2.5 equiv). After 2 h at room temperature, HMPA (6.16 mL, 35.4 mmol, 20 equiv) was added and the reaction mixture was stirred for an additional 15 min. A mixture of *t*-BuOH (0.5 mL, 5.31 mmol, 3 equiv) and **27** (0.9 g, 1.77 mmol, 1 equiv) in THF (10 mL) was added dropwise. After 15 min at room temperature, the reaction mixture was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (elution was achieved with a gradient of 20–100% of EtOAc/cyclohexane) to give **28** (0.5 g, 0.97 mmol, 55% yield) as a colourless oil and **29** (0.57 g, 0.56 mmol, 32% yield) as a colourless oil.

Analytical data of 28: R*f* 0.35 (EtOAc/cyclohexane 30/70); $[\alpha]_D^{20}$ = –7.3 (*c* 1.84, CH_2Cl_2); IR (neat) 3420, 1690, 1660 cm^{-1}; ^1H NMR (toluene-d_8 at 90 °C) δ 1.09 (s, 3H), 1.15 (s, 9H), 1.32–1.61 (m, 12H), 2.05–2.16 (m, 1H), 2.38 (dd, *J* = 6.3 and 15.7 Hz, 1H), 2.93–3.01 (m, 1H), 3.32 (dd, *J* = 6.3 and 11.7 Hz, 1H), 3.39 (dd, *J* = 9.0 and 11.7 Hz, 1H), 3.71–3.77 (m, 1H), 3.80–3.85 (m, 2H), 7.22–7.26 (m, 6H), 7.27–7.76 (m, 4H); ^{13}C NMR (toluene-d_8 at 90 °C) δ 154.1 (s), 135.4 (d), 133.4 (s), 129.5 (d), 127.5 (d), 82.0 (s), 79.1 (s), 66.2 (d), 65.1 (t), 53.7 (d), 48.6 (t), 45.4 (d), 38.1 (t), 30.0 (t), 28.3 (q), 26.7 (q), 24.4 (q), 19.0 (s); EI MS *m/z* (relative intensity) 436 (M^+–*t*-BuO, 5), 396 (100), 283 (23), 199 (95), 184 (63), 57 (56); HRMS calcd for $C_{26}H_{34}NO_3Si$ (M^+–*t*-BuO) 436.2308, found 436.2307.

Analytical data of 29: R*f* 0.14 (EtOAc/cyclohexane 30/70); IR (neat) 3420, 1690, 1660 cm^{-1}; ^1H NMR (toluene-d_8 at 90 °C) δ 1.13 (s, 3H), 1.19 (s, 9H), 1.26 (s, 9H), 1.51–1.69 (m, 3H), 2.13–2.23 (m, 1H), 2.27–2.30 (m,1H), 2.99–3.07 (m, 1H), 3.75–3.81 (m, 1H), 4.03 (s, 1H), 4.11–4.17 (m, 1H), 4.22–4.25 (m, 1H), 7.19–7.26 (m, 6H), 7.77–7.82 (m, 4H); ^{13}C NMR (toluene-d_8 at 90 °C) δ 25.0 (q), 27.6 (q), 28.7 (q), 31.5 (t), 42.3 (t), 47.6 (d), 58.3 (d), 64.5 (d), 68.7 (t), 69.5 (d), 79.2 (s), 81.0 (s), 128.0 (d), 128.1 (d), 129.8 (d), 129.9 (d), 135.1 (s), 135.3 (s), 136.2 (d), 136.3 (d), 155.2 (s). MS (FAB$^+$) *m/z*: 1018 (M^+ + H), 918 (M^+ + H – CH_2=$C(CH_3)_2$ – CO_2), 900 (M^+ + H – CH_2=$C(CH_3)_2$ – CO_2 – H_2O), 862 (M^+ + H – 2 × (CH_2=$C(CH_3)_2$) – CO_2), 844 (M^+ + H – 2 × (CH_2=$C(CH_3)_2$) – CO_2 – H_2O), 818 (M^+ + H – 2 × (CH_2=$C(CH_3)_2$) – 2 × CO_2).

(–)-(1*S*,3a*S*,6a*S*)-2-(*tert*-Butoxycarbonyl)-1-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-4-methyl-1,2,3,3a,6,6a-hexahydrocyclopenta[*c*]pyrrole (33). To a stirred solution of **28** (0.37 g, 0.73 mmol, 1 equiv) in pyridine (6 mL) at 0 °C, was added $POCl_3$ (0.17 mL, 1.84mmol, 2.5 equiv). After 2 h at 0 °C, Et_2O (20 mL) was added and the organic layer was washed successively with a saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phases were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane

10/90) to give **33** (0.26 g, 0.52 mmol, 72% yield) as a colourless oil. R*f* 0.65 (EtOAc/cyclohexane 30/70); $[\alpha]_D^{20} = -18.3$ (*c* 1.8, CH_2Cl_2); IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.05 (s, 9H), 1.15–1.54 (m, 9H), 1.66–1.73 (m, 3H), 2.18–2.30 (m, 1H), 2.51–2.72 (m, 1H), 2.91–3.15 (m, 2H), 3.35–3.95 (m, 5H), 4.30–5.32 (m, 1H), 7.35–7.45 (m, 6H), 7.60-7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.0 (s), 140.7 (s), 135.4 (d), 135.3 (d), 133.4 (s), 129.5 (d), 127.5 (d), 124.3 (d), 78.8 (s), 65.2 (t), 64.2(d), 51.7 (d), 49.1 (t), 45.1 (d), 39.2 (t), 28.3 (q), 26.7 (q), 19.1 (s), 15.1 (q).

(–)-Methyl(2*S*,3*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-2-{[(*tert*-butyldiphenylsilyl)-oxy]methyl}-4-isopropenylpyrrolidine-3-acetate (36). A mixture of $RuO_2 \cdot H_2O$ (13.8 mg, 0.1 mmol, 0.2 equiv) and $NaIO_4$ (0.46 g, 2.1 mmol, 4.1 equiv) in CH_3CN (1 mL) and CCl_4 (1 mL) was vigorously stirred at room temperature for 15 min. To this mixture was added a solution of **33** (0.26 g, 0.52 mmol, 1 equiv) in CH_3CN (0.5 mL) and CCl_4 (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then partitioned between ether (5 mL) and H_2O (5 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude carboxylic acid **34** was dissolved in DMF (2 mL) and treated sequentially with K_2CO_3 (0.1 g, 0.78 mmol, 1.5 equiv) and CH_3I (0.065 mL, 1.04 mmol, 2 equiv) at room temperature. After 2 h at room temperature, Et_2O (3 mL) was added and the reaction mixture was washed with 1 M HCl (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was dissolved in pentane (5 mL) and the solvent was removed *in vacuo* to give **35** as an oil which was used without further purification.

To a stirred suspension of Zn (0.3 g, 4.64 mmol, 12 equiv) and CH_2I_2 (0.2 g, 0.77 mmol, 2 equiv) in THF (2 mL) was added $TiCl_4$ (0.77 mL, 0.77 mmol, 2 equiv) at room temperature. After 2 h, a solution of **35** (0.21 g, 0.38 mmol, 1 equiv) in THF (2 mL) was added and 24 h latter, Et_2O (5 mL) was added and the organic phase was washed with 0.1 M HCl (3 mL), dried over $MgSO_4$ filtered and concentrated *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (cyclohexane) to give **36** (51 mg, 0.09 mmol, 18% yield from **33**) as a colourless oil. R*f* 0.30 (cyclohexane); $[\alpha]_D^{20} = -26.3$ (*c* 0.4, CH_2Cl_2); IR (neat) 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.07 (s, 9H), 1.27–1.35 (m, 9H), 1.72–1.76 (m, 3H), 2.12–2.49 (m, 2H), 2.77–3.19 (m, 2H), 3.40–3.81 (m, 8H), 4.67–4.94 (m, 2H), 7.37–7.44 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.0 (s), 22.4 (q), 26.7 (q), 28.3 (q), 32.8 (t), 38.6 (d), 44.7 (d), 47.9 (t), 51.4 (q), 63.2 (d), 68.0 (t), 79.4 (s), 112.3 (t), 127.5 (d), 128.6 (d), 133.1 (s), 133.2 (s), 135.4 (d), 141.7 (s), 154.1 (s), 172.9 (s); EI MS *m/z* (relative intensity) 494 (M^+–C_4H_9), 438 (42), 393 (31), 378 (78), 122 (64), 57 (100). HRMS calcd for $C_{28}H_{36}NO_5Si$ (M^+–C_4H_9) 494.2362, found: 494.2361.

(–)-Methyl(2S,3S,4R)-1-(tert-butoxycarbonyl)-2-(hydroxymethyl)-4-isopropenyl-pyrrolidine-3-acetate (15). To a stirred solution of **36** (0.014 g, 0.025 mmol) in THF (1 mL) was added dropwise a solution 40% HF (0.5 mL) at room temperature. After 20 min at room temperature, K_2CO_3 was added until pH~7 and the reaction mixture was extracted with ether (3 × 7 mL). The organic phases were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 50/50) to give **15** (0.0024 g, 0.007 mmol, 30% yield) as a colourless oil. R*f* 0.35 (EtOAc/cyclohexane 50/50); $[\alpha]_D^{20} = -35$ (*c* 0.2, $CHCl_3$) {ref.[25] $[\alpha]_D^{20} = -38$ (*c* 0.2, $CHCl_3$)}; IR (neat) 3421, 1737, 1690, 1674, 1403 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.71 (s, 3H), 2.17–2.37 (m, 2H), 2.46-2.53 (m, 1H), 2.90–2.97 (m, 1H), 3.48 (d, *J* = 7.7 Hz, 2H), 3.58–3.82 (m, 6H), 4.67–4.69 (m, 1H), 4.89–4.93 (m, 1H).

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