

Approaches to a Synthesis of α -Kainic acid

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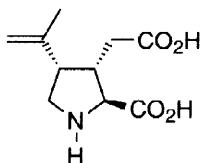
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Abstract: A formal synthesis of (–)- α -kainic acid was achieved from L-pyroglutamic acid. The C-4 substituent of the pyrrolidine ring was introduced by using a ketyl radical cyclization on an ene carbamate. © 1999 Elsevier Science Ltd. All rights reserved.

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

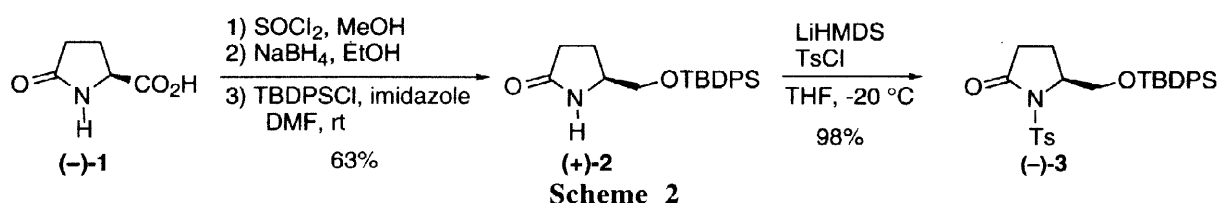
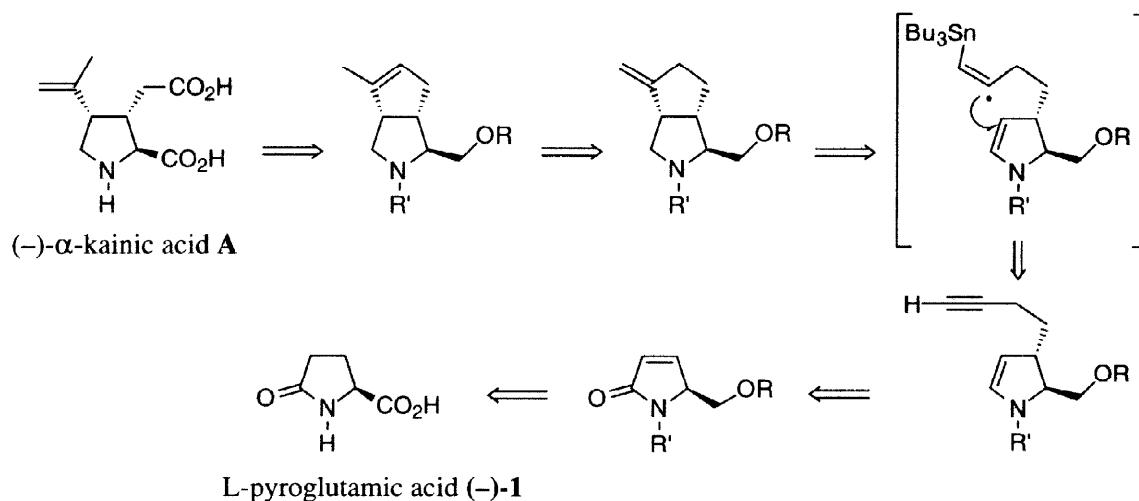
Because of its biological importance as well as its synthetic interest, several enantiocontrolled syntheses have been disclosed. Oppolzer's synthesis of (–)- α -kainic acid relying on an intramolecular ene reaction stands as the first and, as yet remains, the most efficient approach in terms of the number of steps and overall yield.⁴ In other approaches, intramolecular Pauson-Khand reaction,^{5–8} tandem Michael reactions,⁹ thiazolium¹⁰ or azomethine¹¹ ylide cycloadditions, Diels-Alder addition,¹² retro Diels-Alder reaction of keto dicyclopentadiene,¹³ palladium induced cyclization,¹⁴ aldol condensation¹⁵ or enolate Claisen rearrangement¹⁶ 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.

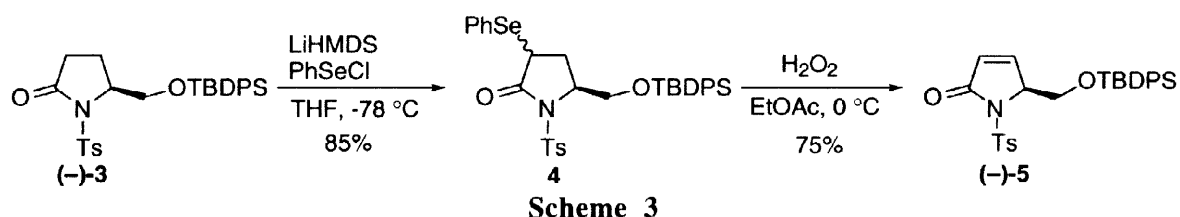
L-Pyroglutamic acid (–)-**1** was transformed into the protected amido-alcohol (+)-**2** [m.p = 70 °C, $[\alpha]_D^{20} + 57.1$ (c 0.25, THF)]^{28,29} in 3 steps with an overall yield of 63% (Scheme 2). Compound (+)-**2** was

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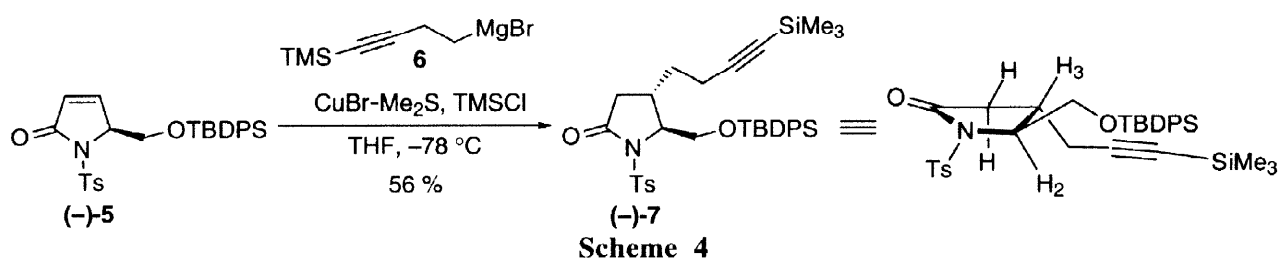
tosylated to afford the corresponding sulfonamide (–)-**3**³⁰ in the presence of LiHMDS, followed by addition of *p*-toluenesulfonyl chloride (yield: 98%).



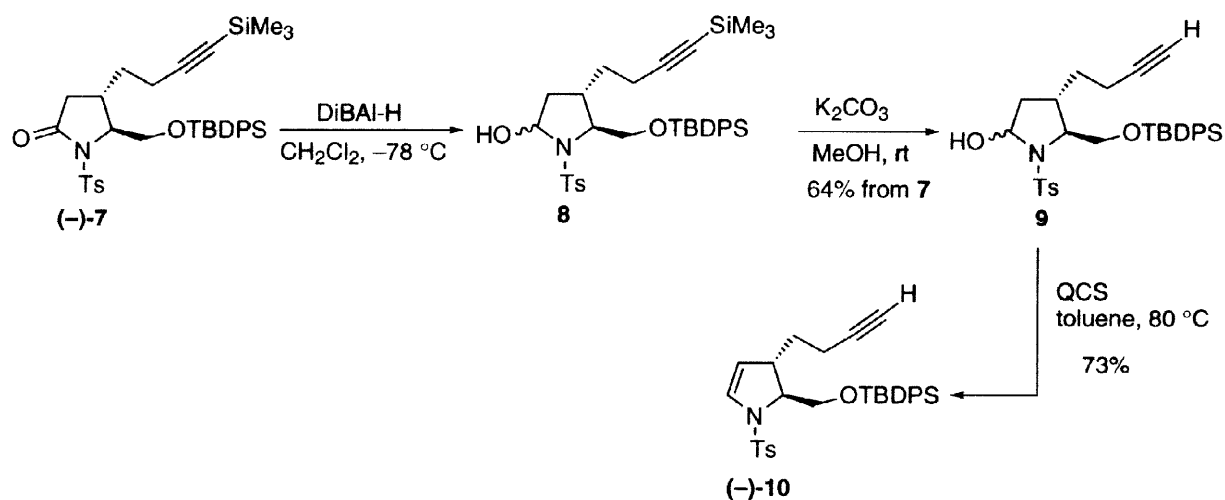
In order to introduce the butynyl side chain at C-3, the obtained tosylamide (–)-**3** was transformed into the corresponding enamide (–)-**5**³⁰ via phenylselenylation (LiHMDS, 1 equiv.; PhSeCl, 1 equiv.; –78 °C; 85% yield) and subsequent oxidation with H₂O₂ in ethyl acetate (yield: 75%) (Scheme 3).



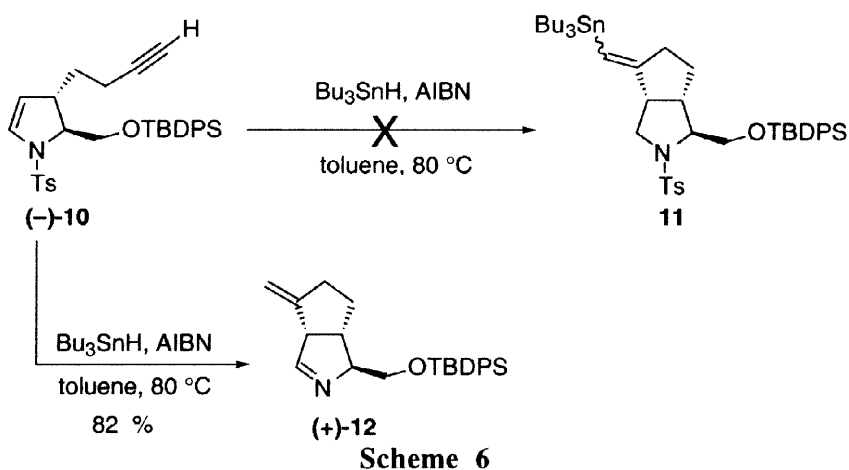
Conjugate addition of the organocupromagnesium derivative **6**, prepared from the corresponding bromide,³¹ in the presence of TMSCl on (–)-**5** furnished the expected C-3 alkylated pyrrolidone (–)-**7** in 56% yield (Scheme 4). The conjugate addition is diastereoselective. The ¹H NMR spectrum of (–)-**7**, shows that the coupling constant between H-2 and H-3 is equal to zero, implying that the dihedral angle between 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



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).



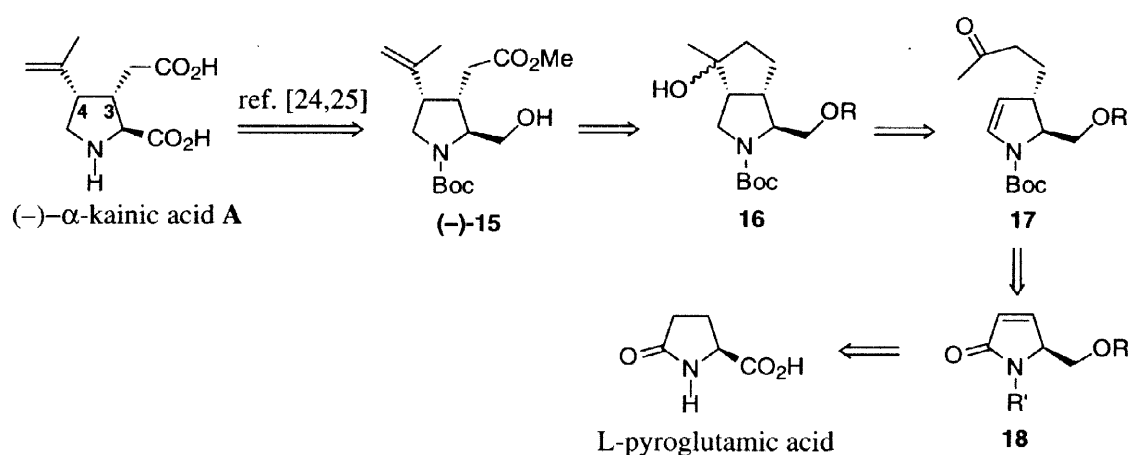
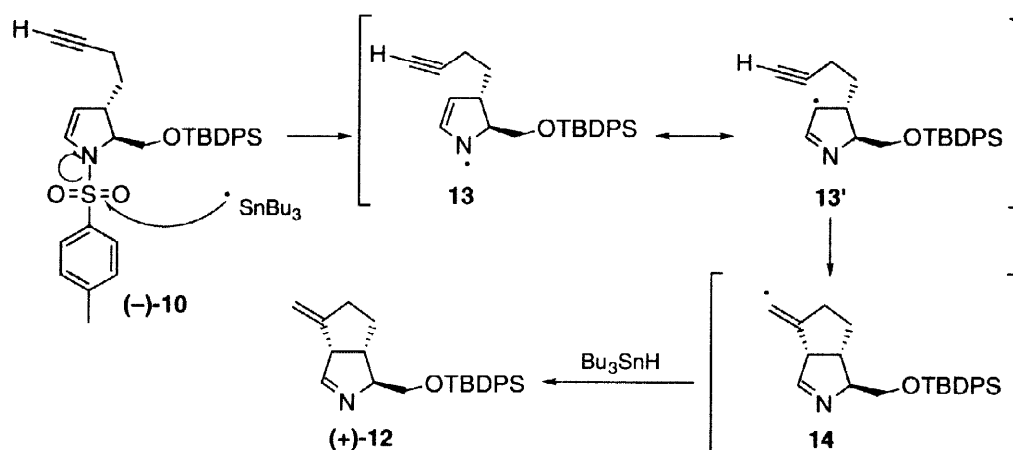
Treatment of (–)-**10** with *n*-Bu₃SnH in the presence of a catalytic amount of AIBN at 80 °C in toluene did not lead to the expected product **11** but to the unsaturated bicyclic enamine (+)-**12**. We have to point out that the two *exo*-methylene hydrogen atoms are visible in the ¹H NMR spectrum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



The obtainment of (+)-**12** can be explained by the attack of the tri-*n*-butylstannyl radical onto the tosyl group³⁴ of (–)-**10**. This implies the formation of the ene-aminy radical **13** ↔ **13'**. A 5-*exo*-dig cyclization³⁵ 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

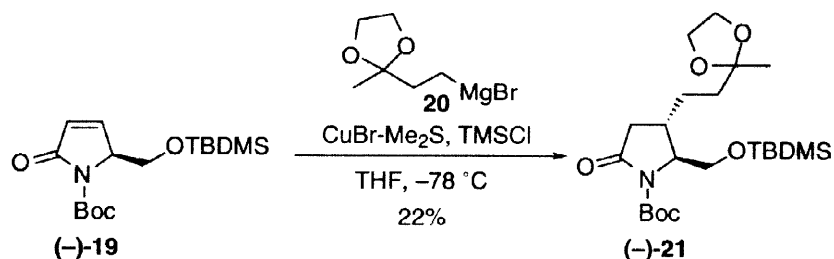
(-)- α -kainic acid was planned from intermediate **17** according to the following retrosynthetic scheme (Scheme 8). The synthesis of intermediate **17** was envisaged by applying a conjugate addition of an organocupromagnesium derivative on intermediate **18**.



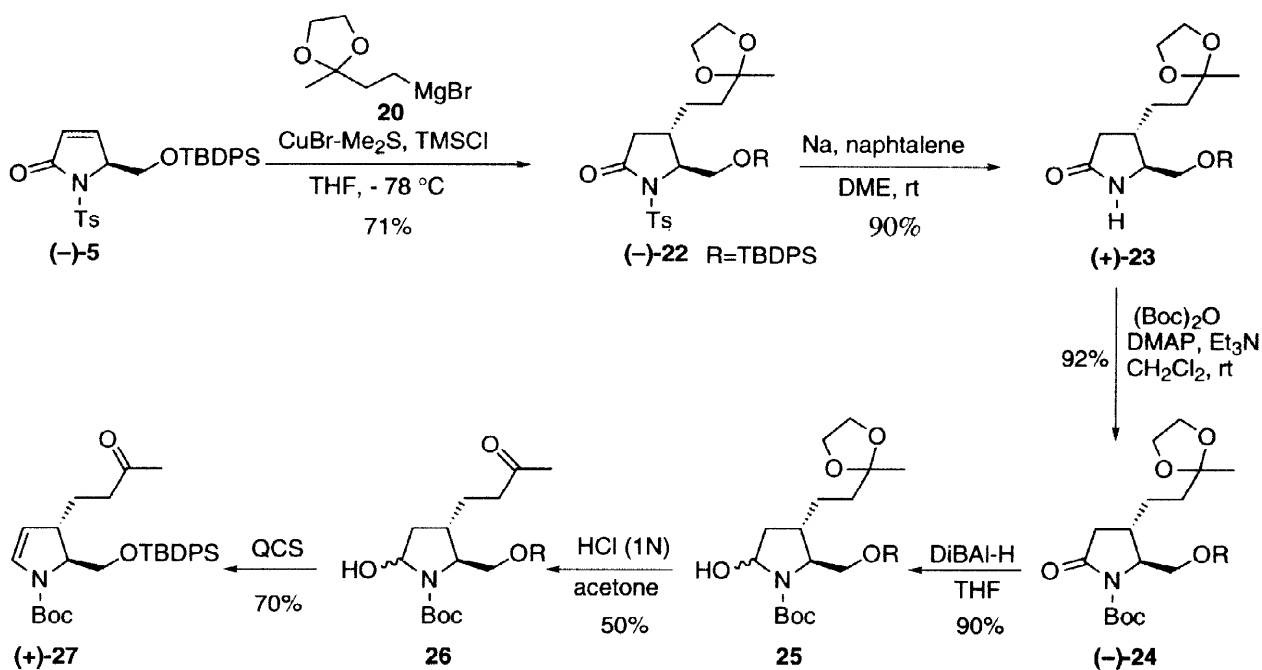
The synthesis of the precursor (-)-**21** was achieved by conjugate addition of the organocupromagnesium derivative **20**^{36–38} on (-)-**19**,³⁹ in the presence of TMSCl which furnished the expected C-3 alkylated pyrrolidone (-)-**21** in poor yield (< 25%) (Scheme 9). In contrast, when the addition 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, H₂O-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 Et₃N (10 equiv.) at 254 nm in CH₃CN (10⁻²M).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 SmI₂ 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

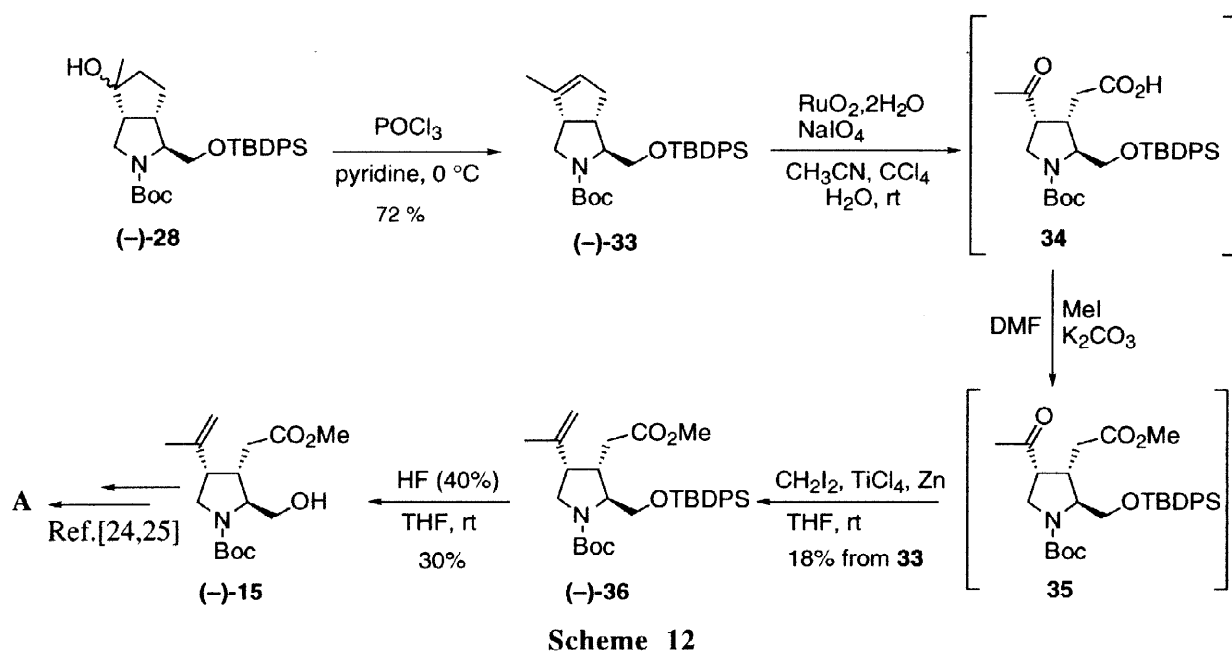
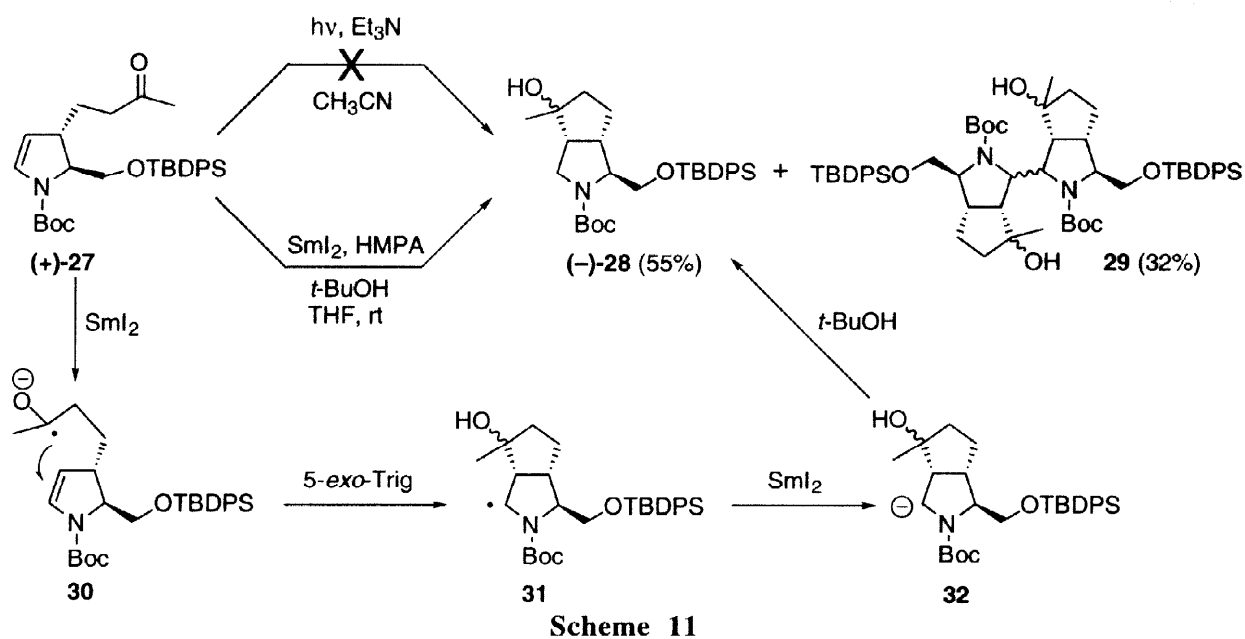


Scheme 10

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 $\text{RuO}_2\text{-NaIO}_4$ 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 THF¹⁶ (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-pyrroglutamic 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.



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 F254) 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.

(+)-(5S)-5-[[*tert*-Butyldiphenylsilyloxy]methyl]pyrrolidin-2-one (2). To a solution of (+)-(5S)-5-(hydroxymethyl)pyrrolidin-2-one⁴³ (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 ($\text{M}^+ - t\text{-Bu}$, 100), 218 (51), 199 (14), 181 (11), 84 (13).

(–)-(5S)-5-[[*tert*-Butyldiphenylsilyloxy]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 ($\text{M}^+ - t\text{-Bu}$, 100), 353 (17), 218 (26), 181 (11), 155 (28), 135 (12).

(3SR,5S)-5-[[*tert*-Butyldiphenylsilyloxy]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 1 h 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).

(-)-(5S)-5-[[*tert*-Butyldiphenylsilyloxy]methyl]-1-tosyl-1,5-dihydro-2H-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% H₂O₂ 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 Et₂O (150 mL) and the organic layer was washed successively with water (50 mL), brine (20 mL) and a saturated aqueous NaHCO₃ (100 mL). After drying over MgSO₄, the solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (Et₂O/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); [α]_D²⁰ = -107.7 (*c* 1.11, EtOH); IR (KBr) 1735 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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).

(-)-(4S,5S)-5-[[*tert*-Butyldiphenylsilyloxy]methyl]-1-tosyl-4-[4-(trimethylsilyl)but-3-ynyl]pyrrolidin-2-one (7). To a solution of CuBr·Me₂S (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-yne³¹ (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 NH₄Cl solution (5 mL). The aqueous layer was extracted with Et₂O (2 × 10 mL) and the combined organic phases were dried over MgSO₄ 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); [α]_D²⁰ = -53.7 (*c* 0.5 THF); IR (neat) 2180, 1735 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₁H₃₆NO₄SSi (M⁺-*t*-Bu) 574.1903, found 574.1901.

(2SR,4S,5S)-5-[[*tert*-Butyldiphenylsilyloxy]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 CH₂Cl₂ (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 NH₄Cl solution (5 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL) and the combined organic phases were dried over MgSO₄ 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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-H₂O, 100), 290 (82), 273, (88), 135 (80), 91 (50).

(2SR,4S,5S)-5-[[*tert*-Butyldiphenylsilyloxy]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).

(–)-(2S,3S)-5-[[*tert*-Butyldiphenylsilyl]oxy]methyl]-4-but-3-ynyl-1-tosyl-2,3-dihydro-1H-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).

(+)-(1S,3aS,6aS)-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).

(4S,5S)-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 $CuBr \cdot Me_2S$ (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-dioxolane³⁶ (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 ($\text{M}^+ - \text{CH}_3$, 2), 370 (10), 330 (78), 286 (33), 150 (42), 87 (100), 57 (62); HRMS calcd for $\text{C}_{18}\text{H}_{32}\text{NO}_5\text{Si}$ ($\text{M}^+ - t\text{-BuO}$) 370.2049, found 370.2050.

(-)-(4S,5S)-5-[[*tert*-Butyldiphenylsilyloxy]methyl]-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-tosylpyrrolidin-2-one (22). To a solution of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (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-dioxolane³⁶ (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} ; ^1H 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 ($\text{M}^+ - \text{CH}_3$, 2), 564 ($\text{M}^+ - t\text{-Bu}$, 100), 353 (22), 199 (36), 155 (50), 135 (33); HRMS calcd for $\text{C}_{30}\text{H}_{34}\text{NO}_6\text{SSi}$ ($\text{M}^+ - t\text{-Bu}$) 564.1876, found 564.1877.

(+)-(4S,5S)-5-[[*tert*-Butyldiphenylsilyloxy]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) $3212, 1695\text{ cm}^{-1}$; ^1H 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 ($\text{M}^+ - \text{CH}_3$, 8), 410 ($\text{M}^+ - t\text{-Bu}$, 100), 332 (60), 306 (27), 199 (47), 181 (30), 168 (14), 162 (15), 150 (62); HRMS calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_4\text{Si}$ ($\text{M}^+ - \text{CH}_3$) 452.2257, found 452.2256.

(-)-(4S,5S)-1-(*tert*-Butoxycarbonyl)-5-[[*tert*-butyldiphenylsilyloxy]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, CH₂Cl₂); IR (neat) 1790, 1753, 1715 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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⁺–C₉H₁₇O₂, 100), 348 (12), 332 (58), 306 (28), 207 (21), 199 (32), 181 (21), 162 (15), 150 (33), 135 (14); HRMS calcd for C₂₃H₂₈NO₄Si (M⁺–C₉H₁₇O₂) 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 NH₄Cl solution (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL) and the combined organic phases were dried over MgSO₄ and filtered. The solvent was removed *in vacuo* to afford an oil which was purified by flash column chromatography on silica gel (CH₂Cl₂/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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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⁺–H₂O, 4), 496 (M⁺–C₄H₉O, 4), 451 (10), 438 (20), 394 (79), 349 (18), 290 (28), 87 (65), 57 (100); HRMS calcd for C₂₃H₃₈NO₅Si (M⁺–C₄H₉O) 496.2519, found 496.2518; Anal. Calcd for C₃₂H₄₇NO₆Si: 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-hydroxy-pyrrolidin-3-yl)butan-2-one (26). To a solution of **25** (4 g, 7.03 mmol, 1 equiv) in acetone (70 mL) and H₂O (20 mL) at room temperature, was added HCl (1 M, 20 mL). After 6 h at room temperature, the reaction mixture was neutralized with NaHCO₃ until pH~7. The organic phases were dried over MgSO₄, 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 (CDCl₃, 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); ¹³C NMR (CDCl₃) (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 (CDCl₃, 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); ¹³C NMR (CDCl₃) (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 C₂₁H₂₄NO₂Si (M⁺–Boc–*t*-Bu–H₂O) 350.1576, found 350.1574; Anal. Calcd for C₃₀H₄₃NO₅Si: 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, K₂CO₃ (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 $\text{C}_{30}\text{H}_{41}\text{NO}_4\text{Si}$ (M^+) 507.2805, found 507.2804.

(1S,3aS,6aS)-2-(tert-Butoxycarbonyl)-1-[[tert-butyl(diphenylsilyl)oxy]methyl]-4-methyl-octahydrocyclopenta[c]pyrrol-4-ol (28) and **(1,1',3S,3'S,3aS,3a'S,6aS,6a'S)-2,2'-bis(tert-butoxycarbonyl)-3,3'-bis[[tert-butyl-dimethylsilyl]oxy]methyl-4,4'-dimethyl-hexadecahydro-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 ($\text{M}^+ - t\text{-BuO}$, 5), 396 (100), 283 (23), 199 (95), 184 (63), 57 (56); HRMS calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_3\text{Si}$ ($\text{M}^+ - t\text{-BuO}$) 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 ($\text{M}^+ + \text{H}$), 918 ($\text{M}^+ + \text{H} - \text{CH}_2=\text{C}(\text{CH}_3)_2 - \text{CO}_2$), 900 ($\text{M}^+ + \text{H} - \text{CH}_2=\text{C}(\text{CH}_3)_2 - \text{CO}_2 - \text{H}_2\text{O}$), 862 ($\text{M}^+ + \text{H} - 2 \times (\text{CH}_2=\text{C}(\text{CH}_3)_2) - \text{CO}_2$), 844 ($\text{M}^+ + \text{H} - 2 \times (\text{CH}_2=\text{C}(\text{CH}_3)_2) - \text{CO}_2 - \text{H}_2\text{O}$), 818 ($\text{M}^+ + \text{H} - 2 \times (\text{CH}_2=\text{C}(\text{CH}_3)_2) - 2 \times \text{CO}_2$).

(-)-(1S,3aS,6aS)-2-(tert-Butoxycarbonyl)-1-[[tert-butyl(diphenylsilyl)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, 1.84 mmol, 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} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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(2S,3S,4R)-1-(tert-butoxycarbonyl)-2-[[tert-butyl-diphenylsilyl]-oxy]methyl-4-isopropenylpyrrolidine-3-acetate (36). A mixture of $\text{RuO}_2 \cdot \text{H}_2\text{O}$ (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 later, 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} ; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 ($\text{M}^+ - \text{C}_4\text{H}_9$), 438 (42), 393 (31), 378 (78), 122 (64), 57 (100). HRMS calcd for $\text{C}_{28}\text{H}_{36}\text{NO}_5\text{Si}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 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} ; $^1\text{H NMR}$ (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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