

A Concise Asymmetric Route to the Bridged Bicyclic Tropane Alkaloid Ferruginine using Enyne Ring Closing Metathesis

Varinder K. Aggarwal,^{} Christopher J. Astle and Mark Rogers-Evans[†]*

School of Chemistry, Bristol University, Cantock's Close, Bristol BS8 1TS, UK.

v.aggarwal@bristol.ac.uk

^{*} Corresponding Author

[†] F. Hoffmann-La Roche Ltd, Pharmaceuticals Division
Lead Generation, PRBC-CI, Bldg 65/416
CH-4070 Basel (Switzerland)

Supporting Information

Infrared spectra were recorded on a Perkin-Elmer 157G FT-IR. Samples were recorded as a thin film.

¹H NMR spectra were recorded at 400 MHz using a Jeol Delta GX instrument.

¹³C NMR spectra were recorded at 100 MHz on a GX400 spectrometer.

Low-resolution electron impact mass spectra (*m/z*) were recorded with a Fisons/VG Autospec System.

Elemental analyses were determined on a Perkin-Elmer 2400 CHN microanalyser.

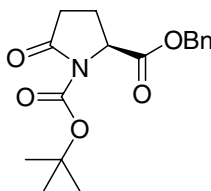
Analytical TLC was performed on Merck Kieselgel 60F₂₅₄ aluminium.

Melting points were determined on a Kholfer hotstage.

The following reagents were used as obtained: L-pyroglutamic acid was obtained from Aldrich; Dess-Martin periodinane was obtained from Lancaster; Grubbs 1st generation catalyst **I** was obtained from Fluka; Grubbs 2nd generation catalyst **II** was obtained from Strem Chemicals. CH₃COCN₂PO(OEt)₂ was prepared as described in the literature.^[1]

Reactions requiring anhydrous conditions were performed in vacuum heat-dried glassware under nitrogen atmospheres. Reaction mixtures were stirred magnetically. The dry solvents MeCN, benzene, toluene, and MeOH were obtained from a sure seal bottle. DCM, THF, Et₂O were obtained from the dry solvent dispenser at the University of Bristol which is built by Anhydrous Engineering and is based on the Grubbs design.^[2]

2-Benzyl 1-*tert*-butyl (2*S*)-5-oxo-1,2-pyrrolidinedicarboxylate (5)^[3]



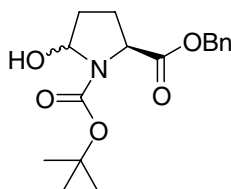
5

To a stirred solution of L-pyroglutamic acid (24 g, 186 mmol) and *N,N*-diisopropylethylamine (38.8 ml, 223 mmol) in CH₂Cl₂ (500 ml) at 0 °C was added benzyl bromide (22.1 ml, 186 mmol), the mixture was heated at reflux for 5 hours, cooled to r.t., and washed with aqueous NaH₂PO_{4(aq)} (2 x 50 ml, 0.2 M). The aqueous layer was extracted with CH₂Cl₂ (3 x 50 ml), and the combined organic layers were washed with brine (25 ml), dried over MgSO₄, filtered and concentrated in *vacuo*. The crude product was then dissolved in a solution of CH₃CN (500 ml) containing 4-dimethylaminopyridine (2.27 g, 18.6 mmol) and di-*tert*-butyl dicarbonate (48.8 g, 223 mmol), and stirred at r.t. for 3 hours. The yellow mixture was washed with NaH₂PO_{4(aq)} (2 x 50 ml, 0.2 M) and brine (25 ml), dried over MgSO₄, filtered, and concentrated in *vacuo* to give a coloured viscous solid. Purification by column chromatography eluting with 40% EtOAc in pet. ether, yielded **5** (37.5 g, 92%) as a colourless crystalline solid;

TLC R_f 0.62 (20% EtOAc in DCM); m.p. 72-73 °C {lit. 69-70 °C,^[3] 57-59 °C,^[4] 72-74 °C^[5]}; [α]_D²⁰ -34.2 (*c* 0.3, CHCl₃) {lit. -37.8 (*c* 1.0, CHCl₃),^[3] -35.0 (*c* 0.98, CHCl₃)^[5]}; IR ν_{max} (neat) / cm⁻¹ 1778, 1739, 1703, 1172, 1154; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 7.39-7.33 (5 H, m, Ph), 5.23 (1 H, d, *J* 12.2 Hz, CH_ACH_BPh), 5.19 (1 H, d, *J* 12.2 Hz, CH_ACH_BPh), 4.65 (1 H, dd, *J* 9.5 and 2.6 Hz, NCH), 2.66-1.98 (4 H, m, CH₂CH₂), 1.42 (9 H, s, OCM₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 173.2, 171.2, 149.3, 135.1, 128.6, 128.7, 128.8, 83.6, 67.4, 59.0, 31.2, 27.9, 21.6; MS *m/z* (EI) 84 (M⁺-CO₂Bn-BOC, 100%), 77 (10%), 65 (15%).

Preparation of compound 6

2-Benzyl 1-*tert*-butyl (2*S*,5*S*)-5-hydroxy-1,2-pyrrolidinedicarboxylate (*cis* - 17)
and **2-Benzyl 1-*tert*-butyl (2*S*,5*R*)-5-hydroxy-1,2-pyrrolidinedicarboxylate (*trans* - 17)**

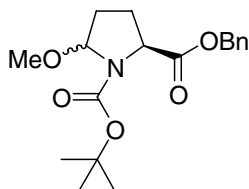


17

To a stirred solution of **5** (16.6 g, 52.2 mmol) in THF (25 ml) at $-78\text{ }^{\circ}\text{C}$ under nitrogen, was added lithiumtriethyl borohydride (62.6 ml, 1.0 M in THF, 62.6 mmol) dropwise over 5 minutes. After 2 hours, the reaction was quenched by the addition of a saturated solution of $\text{NaHCO}_3(\text{aq})$ (10 ml), followed by the addition of Et_2O (20 ml). The aqueous layer was extracted with Et_2O (3 x 30 ml) and the combined organics washed with brine (30 ml), dried over MgSO_4 , filtered and concentrated in *vacuo* to yield light yellow oil. Purification by column chromatography eluting with 20% EtOAc in pet. ether, yielded **17** (14.8 g, 88%) as a clear gum which gave a single peak by GCMS, but was clearly a mixture of two diastereoisomers by ^{13}C and ^1H NMR measured at $100\text{ }^{\circ}\text{C}$ (to eliminate rotomer isomers) in a ratio of 75:25;

TLC R_f 0.42 (40% EtOAc in DCM); IR ν_{max} (neat) / cm^{-1} 3420, 1745, 1688, 1366, 1156; ^1H NMR (400 MHz, d_6 -DMSO, $100\text{ }^{\circ}\text{C}$) δ = 7.39-7.34 (5 H, m, Ph), 5.45-5.41 (1 H, m, CHOH) 5.21-5.15 (2 H, m, CH_2Ar), 4.42 (0.75 H, d, J 9.0 Hz, NCHCO_2Bn), 4.23 (0.25 H, t, J 8.0 Hz, NCHCO_2Bn), 2.49-2.40 (1 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_2$), 2.28-2.05 (1 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_2$), 1.99-1.80 (1 H, m, $\text{CH}_2\text{CH}_\text{A}\text{CH}_\text{B}$), 1.79-1.65 (1 H, m, $\text{CH}_2\text{CH}_\text{A}\text{CH}_\text{B}$), 1.42-1.38 (9 H, m, OCMe_3); ^{13}C NMR (100 MHz, CDCl_3 , $25\text{ }^{\circ}\text{C}$, observed peaks) δ = 172.4, 172.4, 154.2, 154.2, 135.5, 135.5, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 82.4, 82.3, 81.1, 81.0, 66.9, 66.8, 59.5, 59.3, 31.0, 31.0, 28.1, 28.1, 28.0, 27.8; MS m/z (CI) 322 (MH^+ , 13%) 304 ($\text{M}^+ - \text{OH}$, 5%), 204 ($\text{M}^+ - \text{OH} - \text{BOC}$, 15%), 91 (100%); HRMS Found: m/z (CI) 204.1024 $\text{C}_{12}\text{H}_{14}\text{O}_2\text{N}$ requires 204.1024; Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.71; H, 7.51; N, 4.45.

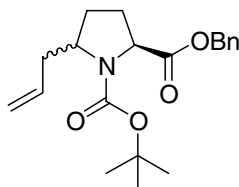
2-Benzyl 1-*tert*-butyl (2*S*,5*S*)-5-methoxy-1,2-pyrrolidinedicarboxylate (*cis* - **6) and 2-benzyl 1-*tert*-butyl (2*S*,5*R*)-5-methoxy-1,2-pyrrolidinedicarboxylate (*trans* - **6**)**



6

To a stirred solution of **17** (1.36 g, 4.24 mmol) in MeOH (25 ml) under nitrogen, was added *p*-toluenesulfonic acid (72 mg, 0.424 mmol). After 5 hours the reaction was quenched with saturated NaHCO_{3(aq)} (10 ml) and then concentrated in *vacuo* to *ca.* 10 ml, followed by the addition of Et₂O (25 ml) and water (25 ml). The aqueous layer was extracted with Et₂O (3 x 20 ml), and the combined organics were dried over MgSO₄, filtered and concentrated in *vacuo* to yield a yellow oil. Purification by column chromatography eluting with 30% EtOAc in pet. ether, yielded **6** (1.39 g, 98%) as a clear oil which appeared to be a single diastereomer by ¹H NMR measured at 100 °C (to eliminate rotamer isomers) but two by ¹³C NMR and two by GCMS; TLC R_f 0.52 (40% EtOAc in pet. ether); IR ν_{max} (neat) / cm⁻¹ 1747, 1701, 1155, 1083; ¹H NMR (400 MHz, *d*₆-DMSO, 100 °C) δ = 7.36-7.33 (5 H, m, Ph), 5.18-5.12 (3 H, m, CH₂Ar and CHOMe), 4.30-4.28 (1 H, m, NCHCO₂Bn), 3.27 (3 H, s, CHOCH₃), 2.34-1.78 (4 H, m, CH₂CH₂), 1.36 (9 H, s, OCM₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C, observed peaks) δ = 172.5, 172.3, 154.0, 153.8, 135.7, 135.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 89.2, 88.2, 80.8, 80.7, 66.4, 66.3, 59.4, 59.1, 56.0, 55.8, 31.2, 30.2, 28.2, 28.1, 27.0, 26.9; MS *m/z* (CI) 304 (MH⁺-OMe, 2%), 204 (MH⁺-OMe-BOC, 10%), 91 (100%); HRMS Found: *m/z* (CI) 304.1544 C₁₂H₁₄O₂N requires 304.1548; Anal. Calcd for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.72; H, 7.83; N, 4.39.

2-Benzyl 1-*tert*-butyl (2*S*,5*R*)-5-allyl-1,2-pyrrolidinedicarboxylate (*cis* - 7) and 2-benzyl 1-*tert*-butyl (2*S*,5*S*)-5-allyl-1,2-pyrrolidinedicarboxylate (*trans* - 7)



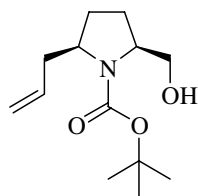
7

To a stirred solution of **6** (203 mg, 0.61 mmol) in Et₂O (25 ml) at –78 °C under nitrogen, was added allyltrimethylsilane (0.436 ml, 2.75 mmol), followed by the dropwise addition of BF₃·Et₂O (77 µl, 0.63 mmol) over 20 minutes. After 2 hours the reaction mixture was allowed to warm to r.t. and left for a further 13 hours. Et₂O (15 ml) and water (20 ml) was then added, the phases were separated, with the aqueous layer being extracted with Et₂O (3 x 20 ml) and the combined organics dried over MgSO₄, filtered and concentrated in *vacuo* to yield a light yellow oil. Purification by column chromatography eluting with 30% EtOAc in pet. ether yielded **7** (196 mg, 93%) as a clear oil which gave two peaks by GCMS, and a mixture of two diastereoisomers by ¹³C and ¹H NMR measured at 100 °C (to eliminate rotomer isomers) in a ratio of 8:2;

TLC R_f 0.6 (30% EtOAc in pet. ether); IR ν_{max} (neat) / cm^{–1} 1747, 1694, 1641; ¹H NMR (400 MHz, *d*₆-DMSO, 100 °C) δ = 7.28-7.23 (5 H, m, Ph), 5.76-5.63 (1 H, m, CH₂=CHCH₂), 5.09-4.89 (4 H, m, CH₂Ph and CH₂CH=CH₂), 4.21-4.16 (1 H, m, NCHCO₂Bn), 3.87-3.78 (0.2 H, m, NCHCH₂CH=CH₂), 3.75 (0.8 H, ddt, *J* 7.4, 3.7 and 3.4 Hz, NCHCH₂CH=CH₂), 2.50-2.40 (1 H, m, CH_ACH_BCH=CH₂), 2.20-2.03 (2 H, m, CH_ACH_BCH=CH₂ and CH_ACH_BCH₂), 1.92-1.72 and 1.66-1.56 (1 H and 2 H, m, CH_ACH_BCH₂), 1.27 (9 H, s, OCM₃); ¹³C NMR (100 MHz, *d*₆-DMSO, 25 °C, observed peaks) δ = 173.0, 172.7, 154.4, 153.7, 135.9, 135.8, 135.4, 135.1, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 117.3, 116.9, 80.0, 79.9, 66.7, 66.6, 60.0, 59.8, 57.6, 57.5, 40.0, 38.3, 28.5, 28.4, 28.2, 28.2, 26.9, 26.9; MS *m/z* (CI) 304 (M⁺–allyl, 23%) 290 (MH⁺–*t*Bu, 2.5%) 246 (MH⁺–BOC, 100%), 204 (M⁺–allyl–BOC, 95%); HRMS Found: *m/z* (CI) 246.1490 C₁₅H₂₀O₂N requires 246.1494; Anal. Calcd for C₂₀H₂₇NO₄: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.75; H, 7.52; N, 4.11.

Should any *N*-BOC deprotection be observed, repeating the second part of the procedure for the preparation of compound **5** ensures a high yield.

***tert*-Butyl (2*R*,5*S*)-2-allyl-5-(hydroxymethyl)-1-pyrrolidinecarboxylate (**18**)**

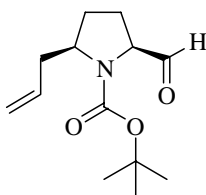


18

To a stirred solution of lithium aluminium hydride (297 mg, 7.84 mmol) in THF (5 ml) at 0 °C was added a solution of **7** (1.06 g, 3.92 mmol, an 8:2 mixture of *cis:trans* diastereomers) in THF (5 ml) dropwise over 10 minutes. After 10 minutes, the reaction was warmed to r.t. and quenched by the sequential addition of water (4 ml), 15% NaOH_(aq) solution (4 ml) and then water (12 ml), the suspension was filtered through Celite, washing with EtOAc (10 ml). The resulting yellow solution was concentrated in *vacuo* to yield a yellow oil. Purification by column chromatography, eluting with 40% EtOAc in pet. ether, allowed separation of the two diastereomers, yielding pure *cis* - **18** (741 mg, 78%) as a clear oil;

TLC R_f 0.40 (40% EtOAc in pet. ether); $[\alpha]_D^{20}$ +6.3 (*c* 0.3, CH₂Cl₂); IR ν_{max} (neat) / cm⁻¹ 3413, 2974, 1663; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 5.81-5.69 (1 H, m, CH₂CH=CH₂), 5.09-5.03 (2 H, m, CH₂CH=CH₂), 4.99 (1 H, br. s, OH), 3.97-3.88 (2 H, m, NCHCH₂CH=CH₂ and NCHCH₂OH), 3.70-3.63 (1 H, m, CH_AH_BOH), 3.58-3.52 (1 H, m, CH_AH_BOH), 2.50-2.45 (1 H, m, CH_AH_BCH=CH₂), 2.28-2.18 (1 H, m, CH_AH_BCH=CH₂), 2.02-1.98 (1 H, m, CH_AH_BCHCH₂OH), 1.91-1.82 (1 H, m, CH_AH_BCH-allyl), 1.74-1.63 (1 H, m, CH_AH_BCH-allyl), 1.61-1.53 (1 H, m, CH_AH_BCHCH₂OH), 1.47 (9 H, s, CMe₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 156.4, 135.0, 117.2, 80.4, 68.1, 61.0, 58.7, 39.7, 28.5, 28.5, 26.8; MS *m/z* (EI) 210 (M⁺-CH₂OH, 18%), 200 (M⁺-allyl, 60%) 154 (M⁺-CH₂OH-*t*Bu, 20%), 100 (M⁺-allyl-BOC, 100%); HRMS Found: *m/z* (EI) 210.1495 C₁₂H₂₀O₂N requires 210.1494; Anal. Calcd for C₁₃H₂₃NO₃: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.61; H, 9.84; N, 5.80.

***tert*-Butyl (2*R*,5*S*)-2-allyl-5-formyl-1-pyrrolidinecarboxylate (**12**)**

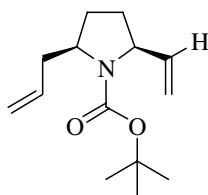


12

To a stirred solution of **18** (420 mg, 1.74 mmol) in water saturated DCM (30 ml), Dess-Martin periodinane (1.55 g, 3.66 mmol) was added and the mixture stirred at r.t. for 30 minutes. An additional portion of water saturated DCM (4 ml) was required to drive the reaction to completion. The reaction mixture was diluted with Et₂O (15 ml), followed by the addition of a solution of sodium thiosulfate (3 g, 19.1 mmol) in 80% saturated solution of NaHCO_{3(aq)} (50 ml). The reaction mixture was stirred rapidly until the solution became clear. The aqueous layer was extracted with Et₂O (2 x 20 ml) and the combined organic layers were washed with NaHCO_{3(aq)} (10 ml), water (10 ml) and brine (10 ml), dried over MgSO₄, filtered and concentrated in *vacuo* to provide a yellow oil. Purification by column chromatography, eluting with 40% EtOAc in pet. ether yielded pure **12** (354 mg, 85%) as a clear oil and as a single diastereomer;

TLC R_f 0.51 (40% EtOAc in pet. ether); $[\alpha]_D^{20}$ -46.2 (*c* 0.2, CH₂Cl₂); IR ν_{max} (neat) / cm⁻¹ 2976, 1736, 1686, 1641; ¹H NMR (400 MHz, *d*₆-DMSO, 100 °C) δ = 9.32 (1 H, s, CHO), 5.81 (1 H, ddt, *J* 17, 10 and 7.5 Hz, CH₂CH=CH₂), 5.07 (1 H, br. d, *J* 17 Hz, CH₂CH=CH_AH_B), 5.04 (1 H, br. d, *J* 10 Hz, CH₂CH=CH_AH_B), 4.03-3.96 (1 H, m, NCHCHO), 3.90-3.78 (1 H, m, NCHCH₂CH=CH₂), 2.48-2.36 (1 H, m, CH_AH_BCH=CH₂), 2.22-2.10 (1H, m, CH_AH_BCH=CH₂), 2.00-1.80 (3 H, m, CH_AH_BCH₂), 1.70-1.64 (1 H, m, CH_AH_BCH₂), 1.40 (9 H, s, CMe₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 200.9, 154.6, 134.0, 117.7, 80.9, 66.0, 58.0, 38.9, 28.4, 25.7, 24.9; MS *m/z* (CI) 184 (MH⁺-^{*t*}Bu, 95%), 154 (M⁺-CHO-^{*t*}Bu, 100%); HRMS Found: *m/z* (CI) 184.0972 C₉H₁₄O₃N requires 184.0974.

***tert*-Butyl (2*R*,5*S*)-2-allyl-5-vinyl-1-pyrrolidinecarboxylate (**10**)**

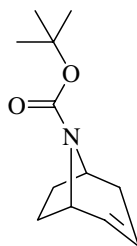


10

To a stirred slurry of methyl triphenylphosphonium bromide (460 mg, 1.29 mmol) in THF (2.5 ml) at r.t. was added dropwise *n*-BuLi (0.86 ml, 1.5 M solution in hexanes, 1.29 mmol) resulting in a bright yellow solution. After two hours, a solution of **12** (154 mg, 0.64 mmol) in THF (2 ml) was added and the reaction mixture was stirred for a further 14 hours. EtOAc (10 ml) was added, the solution was washed with water (10 ml), brine (10 ml), dried over MgSO₄, filtered and concentrated in *vacuo* to provide a yellow oil. Purification by column chromatography, eluting with 20% EtOAc in pet. ether yielded pure **10** (142 mg, 93%) as a clear oil and as a single diastereomer;

TLC R_f 0.57 (20% EtOAc in pet. ether); [α]_D²⁰ +40.7 (*c* 0.2, CH₂Cl₂); IR ν_{max} (neat) / cm⁻¹ 2974, 2341, 1689, 1641; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 5.82-5.71 (2 H, m, CH₂CH=CH₂ and CH₂=CHCHN), 5.15-5.01 (4 H, m, CH₂CH=CH₂ and CH₂=CHCH), 4.27 (1 H, unresolved br. s, NCHCH=CH₂), 3.85 (1 H, unresolved br. s, NCHCH₂CH=CH₂), 2.63 (1 H, unresolved br. s, CH_AH_BCH=CH₂), 2.15-2.10 (1 H, m, CH_AH_BCH=CH₂), 2.05-1.85 (2 H, m, CH₂CH₂), 1.76-1.62 (2 H, m, CH₂CH₂), 1.45 (9 H, s, CMe₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 155.0, 140.1, 135.4, 116.8, 114.0, 79.3, 60.6, 58.3, 39.5, 30.9, 28.5, 28.0; MS *m/z* (EI) 196 (M⁺-allyl, 12%), 140 (M⁺-allyl-^{*t*}Bu, 50%), 57 (100%); HRMS Found: *m/z* (EI) 196.1340 C₁₁H₁₉O₂N requires 196.1338; Anal. Calcd for C₁₄H₂₃NO₂: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.16; H, 9.88; N, 6.00.

(1*S*,5*R*)-*tert*-Butyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (11**)**

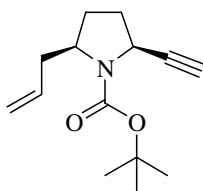


11

To a stirred solution of **10** (42 mg, 0.18 mmol, 0.005 M in benzene), was added 1,3-bis(mesityl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine) ruthenium **II** (15.3 mg, 0.018 mmol). The solution turned yellow upon initial heating, then purple as the mixture was refluxed over 1.5 hours followed by cooling to r.t.. Concentration in *vacuo* provided a black oil. Purification by column chromatography, eluting with 20% EtOAc in pet. ether yielded **11** (36.5 mg, 87%, traces of coloured catalyst impurities) as a slightly impure pale brown oil;

TLC R_f 0.53 (20% EtOAc in pet. ether); $[\alpha]_D^{20}$ -2.2 (c 0.2, CHCl_3) {lit. +3.0 (c 1.0, CHCl_3)^[6]}; IR ν_{max} (neat) / cm^{-1} 2974, 1691, 1635; ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS) δ = 5.99 (1 H, unresolved br. s, NCHCH=CH), 5.55-5.49 (1 H, m, NCHCH=CH), 4.40-4.18 (2 H, m, NCH and NCH), 2.85-2.65 (1 H, m, $\text{CH=CHCH}_\text{A}\text{H}_\text{B}$), 2.22-2.10 (1 H, m, $\text{CH=CHCH}_\text{A}\text{H}_\text{B}$), 1.99-1.60 (4 H, m, CH_2CH_2), 1.45 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, CDCl_3 , 25 °C) δ = 154.2, 133.0, 123.6, 79.2, 53.7, 34.7, 34.0, 29.5, 28.5, 28.4.

***tert*-Butyl (2*R*,5*S*)-2-allyl-5-ethynyl-1-pyrrolidinecarboxylate (**13**)**

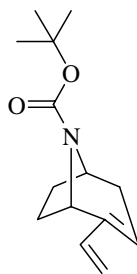


13

To a stirred solution of $\text{CH}_3\text{COCN}_2\text{PO}(\text{OEt})_2$ (1.14 g, 5.92 mmol) in MeOH (10 ml) at r.t. was added K_2CO_3 (1.37 g, 9.88 mmol) resulting in a pale yellow solution. After stirring for 10 minutes, a solution of **12** (1.18 g, 4.94 mmol) in MeOH (5 ml) was added to the reaction mixture, and stirred for 1.5 hours. H_2O (15 ml) was added and the mixture was extracted with Et_2O (3 x 15 ml), the organics were washed with brine (10 ml), dried over Na_2SO_4 , filtered and concentrated in *vacuo* to give a clear oil. Purification by column chromatography, eluting with 30% Et_2O in pet. ether yielded pure **13** (1.08 g, 93%) as a clear oil and as a single diastereomer;

TLC R_f 0.46 (30% Et_2O in pet. ether); $[\alpha]_D^{20}$ -30.5 (c 0.2, CH_2Cl_2); IR ν_{max} (neat) / cm^{-1} 3251, 2976, 1690, 1641; ^1H NMR (400 MHz, CDCl_3 , 25 $^\circ\text{C}$, TMS) δ = 5.79 (1 H, ddt, J 17, 10 and 7 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.12-5.03 (2 H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.51 (1 H, unresolved br. s, $\text{NCHC}\equiv\text{CH}$), 3.83 (1 H, unresolved br. s, $\text{NCHCH}_2\text{CH}=\text{CH}_2$), 2.64 (1 H, unresolved br. s, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}=\text{CH}_2$), 2.31-2.21 (2 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}=\text{CH}_2$ and $\text{C}\equiv\text{CH}$), 2.11-1.81 (4 H, m, CH_2CH_2), 1.50 (9 H, s, CMe_3); ^{13}C NMR (100 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ = 154.1, 135.0, 117.1, 85.1, 79.9, 69.9, 57.8, 48.7, 32.0, 28.5, 28.2; MS m/z (CI) 180 ($\text{MH}_2^+ - \text{tBu}$, 72%), 138 ($\text{MH}^+ - \text{allyl} - \text{tBu}$, 61%), 57 (100%); HRMS Found: m/z (CI) 180.1023 $\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}$ requires 180.1024; Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.25; H, 8.78; N, 6.03.

(1*S*,5*R*)-*tert*-Butyl 2-vinyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (15**)**

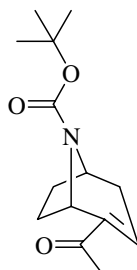


15

To a stirred solution of **13** (70 mg, 0.298 mmol, 0.01 M in CH₂Cl₂) was added bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride **I** (24.5 mg, 0.03 mmol). The solution turned yellow upon initial heating, then purple as the mixture was refluxed over 10 hours followed by cooling to r.t.. Concentration in *vacuo* provided a black oil. Purification by column chromatography, eluting with 20% Et₂O in pet. ether yielded **15** (60.2 mg, 86%, traces of coloured catalyst impurities) as a slightly impure brown oil;

TLC R_f 0.38 (30% Et₂O in pet. ether); [α]_D²⁰ +132.6 (*c* 0.2, CH₂Cl₂); IR ν_{max} (neat) / cm⁻¹ 1695, 1635; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 6.22 (1 H, dd, *J* 17.5 and 11 Hz, CH₂=CH), 5.45 (1 H, unresolved br. s, C=CHCH₂), 5.23-5.10 (1 H, m, CH_AH_B=CH), 4.97 (1 H, d, *J* 11.0 Hz, CH_AH_B=CH), 4.78-4.60 (1 H, m, NCHC=CH), 4.40-4.23 (1 H, m, NCHCH₂CH=C), 2.20-2.11 (1 H, m, NCHCH_ACH_BCH=C), 2.10-1.99 (1 H, m, NCHCH_ACH_BCH=C), 1.94-1.83 (4 H, m, CHCH₂CH₂CH), 1.44 (9 H, s, CMe₃); ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 161.1, 142.7, 135.9, 124.0, 110.9, 79.2, 52.8, 52.5, 34.0, 30.1, 29.7, 28.4; MS *m/z* (CI) 281 (100%), 180 (MH₂⁺-^{*t*}Bu, 25%); HRMS Found: *m/z* (CI) 180.1020 C₁₀H₁₄O₂N requires 180.1024.

(1*S*,5*R*)-*tert*-Butyl 2-acetyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (16**)**



16

To a stirred solution of **15** (37.0 mg, 0.16 mmol) in DMF (2.5 ml) and H₂O (1 ml) was added PdCl₂ (2.8 mg, 0.016 mmol) and CuCl₂ (33 mg, 0.34 mmol). The dark green solution was refluxed for 6 hours then cooled to r.t.. H₂O (10 ml) was added, and the mixture was extracted with Et₂O (3 x 15 ml), the organics were washed with H₂O (3 x 15 ml), brine (10 ml), dried over Na₂SO₄, filtered and concentrated in *vacuo* to give a clear oil. Purification by column chromatography, eluting with 20% Et₂O in pet. ether yielded **16** (32.5 mg, 81%) as a white crystalline solid;

TLC R_f 0.2 (30% Et₂O in pet. ether); m.p. 61-62 °C {lit.^[7] 64-65 °C} [α]_D²⁰ +122.2 (*c* 0.2, CHCl₃) {lit.^[7] +129.1 (*c* 1.00, CHCl₃)}; IR ν_{max} (neat) / cm⁻¹ 1690, 1666; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ = 6.80 (1 H, m, CH₂CH=C), 4.95 (1 H, m, NCHC=CH), 4.32 (1 H, m, NCHCH₂CH=C), 2.90 (1 H, m, CH_AH_BCH=C), 2.27 (3 H, s, C=OMe), 2.17 (1 H, m, CH_AH_BCH=C), 2.05 (2 H, m), 1.86 (1 H, m), 1.58 (1 H, m), 1.43 (9 H, s, CMe₃) {lit.^[7] 6.66 (1 H, m), 4.92 (1 H, d, *J* 5.7 Hz), 4.36 (1 H, m), 2.93 (1 H, m), 2.27 (3 H, s), 2.15 (1 H, m), 2.04 (2 H, m), 1.79 (1 H, dt, *J* 11.8 and 2.4 Hz), 1.55 (1 H, m), 1.43 (9 H, s)}; ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ = 196.9, 154.3, 146.2, 137.6, 80.1, 52.6, 51.8, 35.4, 35.0, 30.3, 28.9, 25.2 {lit.^[7] 196.4, 153.9, 145.5, 137.1, 79.5, 52.0, 51.2, 34.9, 34.6, 29.7, 28.3, 24.8}; MS *m/z* (CI) 209 (MH⁺–C₂H₃O, 12%) 195 (MH⁺–*t*-Bu, 35%), 152 (MH⁺–BOC, 66%).

-
- [1] a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837-1845; b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564; c) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.
- [2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518-1520.
- [3] Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163-2171.
- [4] Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwe, D. *Tetrahedron* **1998**, *54*, 1753.
- [5] August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc.; Perkin Trans 1*, **1996**, 507.
- [6] Lin, R. H.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069-4078.
- [7] Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314-323.