

Supplementary data for article:

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Study of the intramolecular Heck reaction: Synthesis of the Bicyclic Core of Corialstonidine

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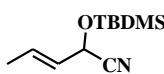
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1. General

The NMR spectra were recorded on a Bruker Avance III (500 MHz) spectrometer. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as the internal standard. Deuteriochloroform was used as a solvent, unless otherwise stated. Mass spectral data were recorded using Agilent MSD TOF spectrometer coupled with Agilent 1200 HPLC. IR spectra were recorded on IR Termo Scientific NICOLET iS10 (4950) spectrometer. Flash chromatography employed silica gel 60 (230-400 mesh) while thin layer chromatography was carried out using alumina plates with 0.25mm silica layer (Kieselgel 60 F₂₅₄, Merck).

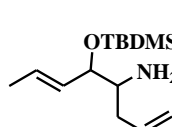
2. Procedures

2.1 (*E*)-(2-*tert*-Butyldimethylsilyloxy)pent-3-enitrile (**3**)¹⁻³

 A solution of KCN (4.64 g, 71 mmol) and AcOH (4.46 mL, 78 mmol) in MeOH (38 mL) was added dropwise during 50 min to a solution of croton aldehyde (4.0 g, 57 mmol) in CH₂Cl₂ (190.0 mL) at 0° C under nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and stirred for additional 2h. The mixture was then partitioned between ether (380 mL) and a 4:1 mixture of brine and saturated aqueous sodium bicarbonate solution (380 mL). The aqueous layer was extracted with ether (3x120 mL) and the combined organic layers were washed with a 4:1 mixture of brine and saturated aqueous sodium bicarbonate solution (2 × 380 mL). The organic layer was dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The crude cyanohydrin, used without further purification, was added to a solution of imidazole (4.46 g, 66 mmol) and *tert*-butyl-dimethylsilyl chloride (7.08 g, 47 mmol) in dry DMF (88 mL) at 0° C. The resulting mixture was stirred for 16h allowing to reach room temperature and then poured into H₂O (80 mL). The water layer was extracted with ether (3x50 mL), the extract washed with brine (30 mL), dried (Na₂SO₄) and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 97:3 v/v petroleum ether-ether) to afford the product (3.73 g, 60%) as a colorless liquid. Spectral data are identical to those previously reported in the literature.³

¹H NMR (500 MHz, CDCl₃) δ = 0.15, 0.17 (2s, 6H, 2CH₃, TBDMS), 0.92 (s, 9H, C(CH₃)₃), 1.76 (dt, 3H, $J=6.5\text{Hz}$, $J=2.5\text{Hz}$, CH₃), 4.88-4.91 (m, 1H, CH(OTBDMS)), 5.52-5.57 (m, 1H, CH₃CH=CH), 5.92-5.99 (m, 1H, CH₃CH=CH). ¹³C NMR (125 MHz, CDCl₃) δ = -5.1, -5.0, 17.4, 18.1, 25.5, 62.6, 118.8, 126.3, 130.8. m/z (EI) 211.1 (M⁺-1), 196.1, 154.1, 127.1, 113.1, 99.0

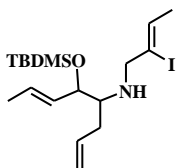
2.2 (*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-amino-octa-1,6-dien (**4**)⁴

 *O*-TBDMS cyanohydrin (2.82 g, 13.4 mmol) was dissolved in dry ether (134.0 mL) and to this solution a solution of Grignard reagent (prepared from allyl bromide, 2.42 g, 20 mmol, and Mg, 0.58 g in 75 mL ether) was

added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1h, cooled to -20° C and quenched with dry MeOH (22.3 mL). After a few minutes the mixture was cooled to -80° C and NaBH₄ (1.27 g, 33.5 mmol) was added. The reaction mixture was slowly warmed to room temperature, then stirred for additional 2 h and poured into water (100 mL). The organic layer was separated and the water layer extracted with ether (3x100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 7:3 v/v petroleum ether-ether saturated with NH₃) to furnish the product (2.03 g, 56%) as light yellow oil.

IR ν_{max} : 2955, 2857, 1252, 970. **¹H NMR (500 MHz, CDCl₃)** δ = 0.00, 0.03 (2s, 6H, 2CH₃, TBDMS), 0.87 (s, 9H, C(CH₃)₃), 1.24 (brs, 2H, NH₂), 1.69-1.70 (m, 3H, CH₃), 1.91-1.97 (m, 1H, CH(NH₂)-CH₂), 2.26-2.31 (m, 1H, CH(NH₂)-CH₂), 2.72 (dt, $J=9.0\text{Hz}$, $J=4.5\text{Hz}$, 1H, CH(NH₂)), 3.88-3.90 (m, 1H, CH(OTBDMS)), 5.04-5.10 (m, 2H, CH₂=CH), 5.38-5.43 (m, 1H, CH₃CH=CH), 5.56-5.65 (m, 1H, CH₃CH=CH), 5.75-5.84 (m, 1H, CH₂=CHCH₂). **¹³C NMR (125 MHz, CDCl₃)** δ = -4.9, -4.1, 17.7, 18.1, 25.8, 37.6, 55.8, 77.3, 117.0, 128.0, 130.9, 136.2. **m/z (EI)** 254.2 (M⁺-1), 214.2, 198.2, 185.2, 156.1, 113.1 **HRMS (ESI)**: calculated for C₁₄H₂₉NOSi (M+H)⁺ 256.20912 found 256.20995

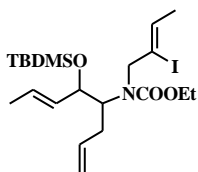
2.3 2(E)-5-(tert-Butyldimethylsilyloxy)-4-[(Z)-2-iodobut-2-enylamino]octa-1,6-dien (5)^{5,6}



To a mixture of amine **4** (1.94g, 7.61 mmol) and activated 4Å molecular sieves (2.15 g) in THF/DMF (26 mL, v:v:1:1) (Z)-2-iodobutenyl bromide (2.0 g, 7.61 mmol) in THF (29 mL) was added followed by Cs₂CO₃ (2.8 g, 8.4 mmol) at 0° C. The reaction mixture was then first warmed to room temperature and then heated at 85 °C (oil bath temperature) for 16 h. The mixture was then diluted with water (10 mL) and extracted with ether (3x60 mL). The combined ethereal layers were washed with water (3x10 mL), brine (20 mL) and dried (Na₂SO₄). The solid was separated by filtration, the solvent removed under reduced pressure and the residue was purified by flash chromatography (SiO₂, 95:5 v/v petroleum ether-ether) to afford the product (2.44 g 74%) as light yellow oil.

IR ν_{max} : 2927, 2855, 1251, 799. **¹H NMR (500 MHz, CDCl₃)** δ = 0.01, 0.04 (2s, 6H, 2CH₃, TBDMS), 0.89 (s, 9H, C(CH₃)₃), 1.72 (dd, $J=6.5\text{Hz}$, $J=1\text{Hz}$, 3H, CH₃CH=CH), 1.77 (dd, $J=6.0\text{Hz}$, $J=0.5\text{Hz}$, 3H, CH₃CH=C(I)), 2.11-2.25 (m, 2H, CH₂=CHCH₂), 2.56-2.59 (m, 1H, CH₂CHNH), 3.52 (brs, 2H, CH₂NH), 4.03-4.05 (m, 1H, CH(OTBDMS)), 5.03-5.09 (m, 2H, CH₂=CHCH₂), 5.45-5.50 (m, 1H, CH₃CH=CH), 5.57-5.63 (m, 1H, CH₃CH=CH), 5.80-5.86 (m, 2H, CH₃CH=C(I), CH₂=CHCH₂). **¹³C NMR (125 MHz, CDCl₃)** δ = -4.9, -3.2, 17.8, 18.2, 21.7, 26.0, 34.6, 59.2, 59.8, 75.5, 111.3, 116.7, 127.9, 131.1, 131.5, 136.0. **m/z (EI)** 420.1 (M⁺-15), 378.1, 336.0, 250.0, 180.9, 156.1. **HRMS (ESI)**: calculated for C₁₈H₃₄INOSi (M+H)⁺ 436.15271 found 436.15419

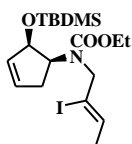
2.4 Ethyl (*E*)-5-*tert*-butyldimethylsilyloxyocta-1,6-dien-4-yl-(*Z*)-2-iodobut-2-enylcarbamate (**6**)⁷



A solution of amine **5** (1.91 g, 4.4 mmol) in anhydrous THF (35 mL) was added under nitrogen atmosphere to a suspension of NaH (60%, 0.21g, 5.3 mmol) in THF (13 mL) at -20° C. After being stirred for 20 minutes to this mixture a solution of ClCOOEt (0.62 mL, 6.6 mmol) in THF (4 mL) was added and the reaction mixture was stirred overnight allowing to reach room temperature. The reaction mixture was quenched with H₂O (35 mL) and extracted with Et₂O (3x50 mL). The combined organic extracts were dried (Na₂SO₄), the solid separated by filtration and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 95/5 v/v petroleum ether-ether) to afford the product (1.92 g, 86 %) as light yellow oil.

IR ν_{\max} : 2928, 2856, 1701, 799, 774. **¹H NMR (500 MHz, CDCl₃)** δ = -0.07, 0.04 (2s, 6H, 2CH₃, TBDMS), 0.88 (s, 9H, C(CH₃)₃), 1.19-1.30 (m, 3H, COOCH₂CH₃), 1.66 (d, J =6.5Hz, 3H, CH₃CH=C(I)), 1.75 (d, J =6.5Hz, 3H, CH₃CH=C(I)), 2.31-2.57 (m, 2H, CH₂=CHCH₂), 3.50 (m, 1H, NCH₂CH(I)), 4.02-4.34 (m, 5H, COOCH₂CH₃, CH(OTBDMS)CHNCH₂), 4.97-5.04 (m, 2H, CH₂=CHCH₂), 5.32-5.40 (m, 1H, CH₃CH=CH), 5.50-5.59 (m, 1H, CH₃CH=CH), 5.74-5.79 (m, 2H, CH₃CH=C(I), CH₂=CHCH₂). **¹³C NMR (125 MHz, CDCl₃)** δ = -4.7, -3.9, 14.7, 17.7, 17.8(2C), 18.1, 21.5, 21.6, 25.9, 33.2, 58.8, 61.1, 61.4, 62.9, 63.5, 75.3, 75.7, 104.9, 105.4, 116.4, 116.5, 127.6, 127.9, 128.0, 130.6, 131.7, 132.2, 132.4, 136.4, 136.6, 156.2, 156.8. **m/z (EI)** 492.2(M⁺-15), 450.1, 322.0, 294.1, 250.0, 185.1. **HRMS (ESI):** calculated for C₂₁H₃₈INO₃Si (M+Na)⁺ 530.15578 found 530.15521

2.5 Ethyl 2-*tert*-butyldimethylsilyloxycyclopent-3-enyl-(*Z*)-2-iodobut-2-enylcarbamate (**7**)⁴

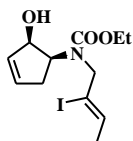


To a solution of triene **6** (1.80 g, 3.5 mmol) in CH₂Cl₂ (305 mL), Grubbs catalyst I (0.088 g, 0.10 mmol) was added and the mixture was stirred at room temperature for 16h. The reaction mixture was filtered through Celite and solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 9:1 v/v petroleum ether-ether) to afford the product (1.60 g, 98%) as light brown oil.

IR ν_{\max} : 2928, 2856, 1700, 1250, 773. **¹H NMR (500 MHz, CDCl₃)** δ = 0.02, 0.05, 0.06 (3s, 6H, 2CH₃, TBDMS), 0.88, 0.89 (2s, 9H, C(CH₃)₃), 1.21-1.30 (m, 3H, COOCH₂CH₃), 1.77-1.80 (m, 3H, CH₃CH=C(I)), 2.41-2.49 (m, 2H, CH₂CHN), 3.89-3.93 (m, 1H, NCH₂CH(I)), 4.12-4.19 (m, 2H, COOCH₂CH₃), 4.40-4.75 (m, 3H, NCH₂CH(I), CH(OTBDMS), CH(NCOOEt)), 5.63-5.92 (m, 3H, CH=CH, CH₃CH=C(I)). **¹³C NMR (125 MHz, CDCl₃)** δ = -5.0, -4.9(2C), -4.8, 14.7(2C), 18.0, 18.1, 21.5, 21.6, 25.8, 33.6, 34.3, 56.7, 57.0, 57.1, 57.7, 61.4, 61.6, 75.0, 75.3, 107.0, 107.2, 127.0, 127.2, 131.5, 131.6, 132.0, 132.2, 132.9, 133.0, 156.7, 156.8. **m/z (EI)** 450.2(M⁺-29), 408.1, 362.0,

338.2, 252.1, 206.1. **HRMS (ESI):** calculated for $C_{18}H_{32}INO_3Si$ 488.10883 found 488.10699

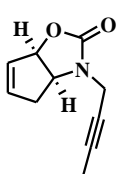
2.6 Ethyl 2-hydroxycyclopent-3-enyl-(Z)-2-iodobut-2-enylcarbamate (**8**)⁸



$PdCl_2(CH_3CN)_2$ (0.039 g, 0.15 mmol) was added to a solution of **7** (1.40 g, 3 mmol) in acetone (15 mL) and water (271 μ L). The reaction mixture was refluxed for 6 h, allowed to reach room temperature and then diluted with ether (150 mL) and washed with water (3x10 mL). The organic layer was dried (Na_2SO_4), the solid separated by filtration and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , 1:1 v/v petroleum ether-ether) to afford the product (0.88 g, 84%) as light yellow oil.

IR ν_{max} : 3242, 1674, 1413, 1249, 772. **1H NMR (500 MHz, $CDCl_3$)** δ = 1.26 (t, $J=7$ Hz, 3H, $COOCH_2CH_3$), 1.81 (dt, $J=6.5$ Hz, $J=1.5$ Hz, 3H, $CH_3CH=C(I)$), 2.45-2.51 (m, 1H, CH_2CHN), 2.95 (brs, 1H, CH_2CHN), 3.98 (brs, 1H, CHN), 4.14-4.27 (m, 4H, $N(COOCH_2CH_3)CH_2$), 4.65-4.68 (m, 1H, $CH(OH)$), 5.88-5.91 (m, 2H, $CH_3CH=C(I)$, $CH=CHCH(OH)$), 5.96-5.97 (m, 1H, $CH=CHCH_2$). **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 14.6, 21.7, 29.7, 34.5, 40.4, 53.4, 59.0, 60.1, 61.8, 65.3, 76.0, 105.7, 130.6, 132.0, 132.4, 133.1, 157.6. **m/z (EI)** 333.1(M^+-18), 270, 224.2, 178.1, 134.1, 114.1. **HRMS (ESI):** calculated for $C_{12}H_{18}INO_3$ ($M+H$)⁺ 352.04041 found 352.03920

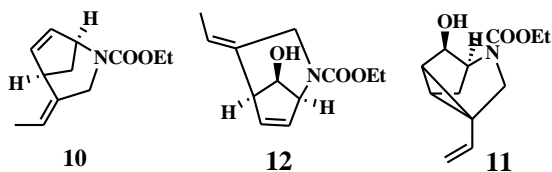
2.7 3-(But-2-ynyl)-3a,4-dihydro-3H-cyclopenta[d]oxazol-2(6aH)-one (**9**)⁹



A solution of **8** (0.038 g, 0.11 mmol) and TBAF (0.54 mL, 1.0 M in THF, 0.54 mmol) in dry THF (1.1 mL) was stirred under nitrogen atmosphere at room temperature. Progress of the reaction was monitored by TLC (petroleum ether:ether:dichloromethane 7/3/1). Upon completion, ether (30 mL) and water (5 mL) were added and the organic layer was separated and dried (Na_2SO_4). The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2 , 8:2 v/v petroleum ether-ether) to afford the product (0.014 g, 75%) as colorless oil.

IR ν_{max} : 2922, 1735, 1410, 1031, 708. **1H NMR (500 MHz, $CDCl_3$)** δ = 1.83 (t, $J=2.5$ Hz, 3H, CH_3), 2.61-2.63 (m, 2H, CH_2CH), 3.74 (dq, $J=17$ Hz, $J=2.5$ Hz, 1H, NCH_2), 4.30 (dq, $J=17$ Hz, $J=2.5$ Hz, 1H, NCH_2), 4.49-4.52 (m, 1H, CHN), 5.43-5.45 (m, 1H, $CHOCO$), 5.85-5.88 (m, 1H, $CH=CHCH_2$), 6.05-6.08 (m, 1H, $CH=CHCH_2$). **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 3.4, 32.9, 37.1, 56.3, 72.3, 80.9, 82.8, 128.4, 135.3, 156.8. **m/z (EI)** 177.1 (M^+), 162.0, 148.1, 132.1, 112.0, 91.1. **HRMS (ESI):** calculated for $C_{10}H_{11}NO_2$ ($M+H$)⁺ 178.08626 found 178.08623

2.8 Cyclisation of allylalcohol **8**¹⁰



A mixture of compound **8** (0.1 g, 0.28 mmol), Pd(OAc)₂ (6.4 mg, 0.028 mmol), PPh₃ (14.9 mg, 0.056 mmol), Et₃N (0.08 mL, 0.57 mmol) in toluene (29 mL) was refluxed under nitrogen atmosphere for 16h. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM (50 mL), washed with water (10 mL), dried (Na₂SO₄) and filtered. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography (SiO₂, 6:4:1 v/v/v petroleum ether-ether-dichloromethane) to afford **10** (0.006 g, 9%) and **12** (0.030 g, 47%) as light yellow oils. Further elution (5:5:1 v/v/v petroleum ether- ether-dichloromethane) afforded **11** (0.010 g, 15%) as light yellow oil.

(4E)-Ethyl 4-ethylidene-2-aza-bicyclo[3.2.1]oct-6-ene-2-carboxylate (**10**)

IR ν_{\max} : 1698, 1415, 1379, 1110. **¹H NMR (500 MHz, DMSO)** δ = 1.17 (m, 3H, COOCH₂CH₃), 1.69 (d, J =7Hz, 3H, CH₃CH=C), 2.39-2.46 (m, 1H, CH₂CHN), 2.62-2.69 (m, 1H, CH₂CHN), 3.73-3.79 (m, 1H, N(COOEt)CH₂), 3.93-4.02 (m, 4H, N(COOCH₂CH₃)CH₂, CH=CHCHCH₂), 4.39 (m, 1H, CH(NCOOEt)), 5.39-5.43 (m, 1H, CH₃CH=C), 5.54-5.55 (m, 1H, CH=CHCH(N)), 5.71-5.73 (m, 1H, CH=CHCH(N)). **¹³C NMR (125 MHz, DMSO)** δ = 13.9, 14.7, 40.3, 41.1, 50.0, 50.4, 50.8, 51.7, 59.6, 60.2, 60.3, 115.9, 116.0, 128.7, 128.8, 129.6, 129.7, 129.8, 131.4, 131.5, 137.4, 138.0, 153.8. **m/z (EI)** 207.1 (M⁺), 192, 178, 162.1, 134.1, 120.1. **HRMS (ESI)**: calculated for C₁₂H₁₇NO₂ (M+H)⁺ 208.13321 found 208.13359

Ethyl-4-aza-6-hydroxy-2-vinyl-tricyclo[3.2.1.0^{2.7}]octane-4-carboxylate (**11**)

IR ν_{\max} : 3408, 1678, 1435, 1329, 1111. **¹H NMR (500 MHz, CDCl₃)** δ = 1.24-1.30 (m, 3H, COOCH₂CH₃), 1.55 (brs, 1H, CHCHC), 1.62-1.63 (m, 1H, CHCHC), 1.82 and 2.35 (s+brd, 1H, OH), 2.04 (m, 2H, CHCH₂CH(N)), 3.75 (t, J =13.5Hz, 1H, N(COOEt)CH₂), 3.88-3.92 (m, 1H, N(COOEt)CH₂), 4.13-4.21 (m, 3H, CH(NCOOCH₂CH₃)), 4.40-4.47 (m, 1H, CH(OH)), 4.87-4.96 (m, 2H, CH₂=CHC), 5.36-5.44 (m, 1H, CH₂=CHC). **¹³C NMR (125 MHz, CDCl₃)** δ = 14.6, 14.7, 22.8, 22.9, 23.9, 27.7, 27.9, 28.8, 28.9, 41.5, 51.4, 51.9, 61.4, 73.2, 73.3, 111.2, 111.4, 140.1, 140.2, 155.9, 156.5. **m/z (EI)** 223.1 (M⁺), 208.1, 195.1, 179.1, 166.1, 150.1 **HRMS (ESI)**: calculated for C₁₂H₁₇NO₃ (M+H)⁺ 224.12812 found 224.12847

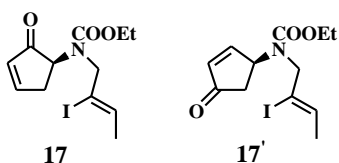
(4Z)-Ethyl-2-aza-4-ethylidene-8-hydroxy-bicyclo[3.2.1]oct-6-ene (**12**)

IR ν_{\max} : 2917, 1680, 1423, 728. **¹H NMR (500 MHz, CDCl₃)** δ = 1.28 (m, 3H, COOCH₂CH₃), 1.66-1.71 (m, 3H, CH₃CH=C), 2.09-2.19 (m, 1H, OH), 2.95-2.96 (m, 1H,

CHCH(OH)), 3.47-3.50 (m, 1H, N(COOEt)CH₂), 4.03 (brs, 1H, CH(OH)), 4.13-4.18 (m, 2H, CH₂CH₃), 4.57-4.59 (m, 1H, N(COOEt)CHH), 4.76 (brs, 1H, CH(NCOOEt)), 5.43-5.46 (m, 1H, CH₃CH=C), 5.94-6.00 (m, 1H, CH=CHC(N)), 6.17-6.18 (m, 1H, CH=CHC(N)). ¹³C NMR (125 MHz, CDCl₃) δ=12.8, 13.0, 13.8, 14.6, 14.7, 30.3, 40.5, 44.8, 52.4, 58.0, 61.1, 61.5, 61.6, 73.2, 73.6, 127.8, 129.3, 129.5, 136.1, 136.9, 156.4. m/z (EI) 223.0 (M⁺), 194.0, 181.0, 167.0, 153.0, 134.0. HRMS (ESI): calculated for C₁₂H₁₇NO₃ (M+H)⁺ 224.12812 found 224.12844

2.9 Ethyl (Z)-2-iodobut-2-enyl-2-oxocyclopent-3-enylcarbamate (**17**) and ethyl (Z)-2-iodobut-2-enyl-4-oxocyclopent-2-enylcarbamate (**17'**)¹¹

Swern oxidation^{11,12}



A solution of dimethyl sulfoxide (0.3g, 0.27 mL, 3.73 mmol) in CH₂Cl₂ (13 mL) was cooled to -74° C and then treated with oxalyl chloride (0.15 mL, 1.78 mmol) in one portion. The reaction mixture was stirred for 45 min and a solution of alcohol **8** (0.57 g, 1.62 mmol) in DCM (3.7 mL) was then added dropwise via cannula. The resulting cloudy mixture was stirred at -74° C for 1 h and then Et₃N (0.82 g, 1.12 mL, 8.1 mmol) was added dropwise. The resulting cloudy mixture was maintained at -74° C for 10 min and then allowed to warm to room temperature. The reaction mixture was diluted with ether (120 mL) and washed with hydrochloric acid (35 mL, 0.1 M), water (35 mL), and brine (35 mL). The organic layer was dried (Na₂SO₄), the solid separated by filtration and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂ impregnated with AgNO₃,¹² 6.5:2.5:1 v/v/v petroleum ether-ether-dichloromethane) to afford the products **17** (0.226 g, 40%) and **17'** (0.17 g, 30%) as light yellow oils.

Dess-Martin oxidation¹³

Alcohol **8** (1.0 g, 2.85 mmol) was dissolved in H₂O-saturated CH₂Cl₂ (94 mL). Dess-Martin reagent (2.17 g, 5.13 mmol) was added and the reaction mixture was vigorously stirred at room temperature. Progress of the reaction was monitored by TLC (petroleum ether-ether-dichloromethane 6.5:2.5:1). Upon completion, the reaction mixture was diluted with 10% Na₂S₂O₃-saturated aqueous NaHCO₃ (30 mL 1:1). Organic layer was separated and the aqueous layer was extracted with ether (2x50 mL). The combined organic layers were washed with H₂O (10 mL), brine (10 mL) and dried (Na₂SO₄). The solid was separated by filtration and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 6.5:2.5:1 v/v/v petroleum ether- ether-dichloromethane) to afford product **17** (0.736 g, 74%) as light yellow oil.

PDC oxidation^{12,14}

To a solution of alcohol **8** (0.3 g, 0.85 mmol) in CH₂Cl₂ (50 mL), PDC (0.627 g, 1.71 mmol) was added under nitrogen atmosphere. The mixture was stirred at room temperature for 6 h and then filtered, the solid was washed with CH₂Cl₂ (50 mL), and the combined organic layers dried (Na₂SO₄). The solvent was then evaporated under reduced pressure and the crude residue was purified by flash chromatography (SiO₂ impregnated with AgNO₃,¹² 6.5:2.5:1 v/v/v petroleum ether- ether-dichloromethane) to afford products **17** (0.23 g, 77%) and **17'** (0.015g, 5%) as light yellow oils.

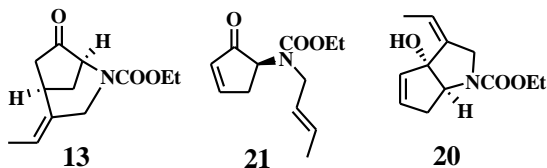
Ethyl (Z)-2-iodobut-2-enyl-2-oxocyclopent-3-enylcarbamate (**17**)

IR ν_{\max} : 1694, 1445, 1238, 757. **¹H NMR (500 MHz, CDCl₃)** δ = 1.12, 1.27 (2t, J =7Hz, 3H, CH₂CH₃), 1.80 (d, J =7Hz, 3H, CH₃CH=C(I)), 2.85-3.02 (m, 2H, CH₂CHN), 3.57-3.59 (m, 1H, CH(NCOOEt)), 4.06-4.17 (m, 3H, N(COOCH₂CH₃)CH₂), 4.54 and 4.65 (d+d, J =16Hz, 1H, NCH₂CH(I)), 5.97-6.05 (m, 1H, CH₃CH=C(I)), 6.22-6.27 (m, 1H, CH=CHC(O)), 7.58-7.59 (m, 1H, CH=CHC(O)). **¹³C NMR (125 MHz, CDCl₃)** δ = 14.2, 14.6, 21.7, 35.0, 36.1, 59.8, 60.5(2C), 60.8, 62.0, 105.2, 105.5, 132.4, 132.7, 133.1, 133.5, 155.0, 155.3, 160.5, 160.8, 204.9, 205.1. **m/z (EI)** 349.0 (M⁺), 268.0, 222.1, 194.1, 176.1, 150.1. **HRMS (ESI)**: calculated for C₁₂H₁₆INO₃ (M+H)⁺ 350.02476 found 350.02464.

Ethyl (Z)-2-iodobut-2-enyl-4-oxocyclopent-2-enylcarbamate (**17'**)

IR ν_{\max} : 1976, 1694, 1232, 729. **¹H NMR (500 MHz, CDCl₃)** δ = 1.25 (m, 3H, CH₂CH₃), 1.79 (d, J =6.5Hz, 3H, CH₃CH=C(I)), 2.47 (dd, J =18.5Hz, J =3Hz, 1H, CH₂CO), 2.70 (dd, J =18.5Hz, J =7Hz, 1H, CH₂CO), 4.09-4.20 (m, 4H, CHN(COOCH₂CH₃)CH₂), 4.86-5.13 (m, 1H, NCHHCH(I)), 5.84 (brs, 1H, CH₃CH=C(I)), 6.25-6.26 (m, 1H, CH=CHC(O)), 7.56 (dd, J =6.0Hz, J =2.5Hz, 1H, CH=CHC(O)). **¹³C NMR (125 MHz, CDCl₃)** δ = 14.4, 21.6, 30.3, 39.8, 40.6, 56.2, 57.0, 57.7, 60.4, 60.5, 61.9, 62.0, 105.8, 131.8, 132.3, 132.6, 133.0, 133.4, 135.1, 135.3, 155.7, 160.8, 162.3, 206.0. **m/z (EI)** 348.9 (M⁺), 222.1, 194.0, 168.0, 150.1, 114.0. **HRMS (ESI)**: calculated for C₁₂H₁₆INO₃ (M+H)⁺ 350.02476 found 350.02457

2.10 Cyclisation of ketone **17** via intramolecular reductive Heck reaction¹⁵



A mixture of compound **17** (0.301 g, 0.862 mmol), Pd(OAc)₂ (0.019 g, 0.086 mmol), PPh₃ (0.045 g, 0.172 mmol), Et₃N (1.5 mL, 10.3 mmol) in DMF (86 mL) was heated at 120 °C (oil bath

temperature) for 18h. The reaction mixture was then cooled to room temperature, diluted with ether (100 mL) and washed with water (3×20 mL). Organic layer was separated and washed with brine (25 mL) and dried (Na₂SO₄). The solid was separated by filtration and the solvent was evaporated under reduced pressure. The residue purified by flash chromatography (SiO₂, 7:2:1 v/v/v petroleum ether-ether-dichloromethane) to afford the

product **13** (0.057 g, 30%). Further elution (6:3:1 v/v/v petroleum ether-ether-dichloromethane) afforded the products **21** (0.029 g, 15%) and **20** (0.019 g, 10%) as light yellow oils.

(4E) Ethyl-4-ethylidene-7-oxo-2-aza-bicyclo[3.2.1]octane-2-carboxylate (13)

IR ν_{\max} :1694, 1293, 1151, 730. **¹H NMR (500 MHz, CDCl₃)** δ =1.27 (t, J =7.3Hz, 3H, CH₂CH₃), 1.65 (d, J =7Hz, 3H, CH₃CH=C), 1.97-2.13 (m, 3H, CH₂CHCH₂CH(N)), 2.37-2.42 (m, 1H, CH₂C(O)), 3.56-3.57 (m, 1H, CH₂CHC), 3.86 (brd, 1H, J =15Hz, N(COOEt)CH₂), 4.14-4.19 (m, 3H, N(COOCH₂CH₃)CH₂), 4.38-4.57 (m, 1H, CH(NCOOEt)), 5.38-5.39 (m, 1H, CH₃CH=C). **¹³C NMR (125 MHz, CDCl₃)** δ =12.4, 14.4, 14.6, 15.2, 32.8, 34.2, 42.6, 46.4, 46.8, 53.4, 57.4, 57.6, 61.8, 61.9, 65.8, 119.3, 132.7, 135.3, 155.0, 213.8, 214.4. **m/z (EI)** 223.1 (M⁺), 195.1, 180.1, 167.1, 152.1, 140.0. **HRMS (ESI)**: calculated for C₁₂H₁₇NO₃ (M+H)⁺ 224.12812 found 224.12779.

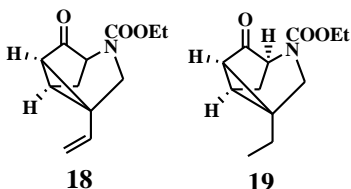
(3Z) Ethyl 3-ethylidene-3,3a,6,6a-tetrahydro-3a-hydroxycyclopenta[b]pyrrole-1(2H)-carboxylate (20)

IR ν_{\max} : 3385, 1675, 1422, 1118. **¹H NMR (500 MHz, CDCl₃)** δ =1.26 (t, J =7Hz, 3H, CH₂CH₃), 1.89 (dt, J =7.5Hz, J =2Hz, 3H, CH₃CH=C), 2.27-2.43 (m, 2H, CH₂CH(N), OH), 2.96-2.97 (m, 1H, CH₂CH(N)), 4.00-4.03 (brd, J =15.5Hz, 1H, N(COOEt)CH₂), 4.12-4.15 (m, 2H, CH₂CH₃), 4.28-4.29 (m, 2H, CH(NCOOEt)CH₂), 5.53 (brs, 1H, CH₃CH=C), 5.85-5.87(m, 2H, CH=CH). **¹³C NMR (125 MHz, CDCl₃)** δ =13.8, 14.7, 30.3, 39.1, 39.8, 51.7, 51.9, 61.1, 61.9, 70.1, 70.4, 92.0, 92.7, 120.3, 125.5, 131.5, 132.9, 133.1, 133.4, 138.0, 139.1, 139.5, 154.9, 160.5, 160.8. **m/z (EI)** 223.1 (M⁺), 205.1, 194.0, 177.1, 160.1, 142.1. **HRMS (ESI)**: calculated for C₁₂H₁₇NO₃ (M+H)⁺ 224.12812 found 224.12790. **HRMS (ESI)**: calculated for C₁₂H₁₇NO₃ (M-H₂O)⁺ 205.10973 found 205.11055.

Ethyl (E) but-2-enyl-2-oxocyclopent-3-enylcarbamate (21)

IR ν_{\max} :1694, 1422, 1230, 769. **¹H NMR (500 MHz, CDCl₃)** δ =1.21 (m, 3H, CH₂CH₃), 1.70 (dd, J =6.5Hz, J =1Hz, 3H, CH₃CH=C), 2.70-2.95 (m, 2H, CH₂CHN), 3.72-4.13 (m, 5H, CHN(COOCH₂CH₃)CH₂), 5.45-5.50 (m, 1H, CH₃CH=CH), 5.62-5.65 (m, 1H, CH₃CH=CH), 6.23-6.26 (m, 1H, CH=CHC(O)), 7.60 (brs, 1H, CH=CHC(O)). **¹³C NMR (125 MHz, CDCl₃)** δ =14.2, 14.4, 14.5, 17.7, 24.3, 30.3, 33.6, 34.6, 35.6, 49.7, 50.6, 50.8, 59.2, 60.2, 61.6, 61.9, 125.5, 126.4, 126.8, 126.9, 128.6, 129.0, 129.5, 132.6, 132.9, 153.4, 154.9, 155.4, 160.1, 160.4, 203.8, 205.1, 205.3. **m/z (EI)** 223.1 (M⁺), 168.1, 154.1, 142.1, 124.1, 112.1. **HRMS (ESI)**: calculated for C₁₂H₁₇NO₃ (M+H)⁺ 224.12812 found 224.12815

2.11 Cyclisation of ketone **17** via intramolecular reductive Heck reaction with HCOONa¹⁶



To a solution of compound **17** (0.03 g, 0.086 mmol) in DMF (2 mL) was added the Pd₂(dba)₃ (1.5 mg, 0.002 mmol) and HCOONa (0.012 g, 0.172 mmol) under nitrogen atmosphere. The mixture was heated at 120° C (oil bath temperature) for 18h and then allowed to cool to room temperature. The resulting reaction mixture was diluted with ether (30 mL) and washed with water (3x5 mL). Organic layer was washed with brine (5 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (SiO₂, 7:3 v/v petroleum ether-ether) to afford the product as light yellow oil (9.5 mg, 50%) as inseparable mixture of **18** and **19**.

Ethyl-4-aza-2-vinyl-tricyclo[3.2.1.0^{2,7}]octan-6-one (**18**) and ethyl-4-aza-2-ethyl-tricyclo[3.2.1.0^{2,7}]octan-6-one (**19**)

¹H NMR (500 MHz, CDCl₃) δ = 0.99 (t, J=7.5Hz, 3H, CH₃CH₂C (**19**)), 1.25-1.27 (m, 6H, CH₂CH₃ from ethyl ester (**18**, **19**)), 1.45-1.52 (m, 2H, CH₃CH₂C), 1.80-1.81 (m, 1H, CHCHC(O) (**19**)), 2.03-2.14 (m, 3H, CHCHCH₂ (**18**), CHCHCH₂ (**19**)), 2.20-2.29 (m, 3H, CHCHCH₂ (**18**), CHCHCH₂ (**19**)), 2.39-2.41 (m, 1H, CHCHCH₂ (**18**)), 3.66-3.74 (m, 2H, N(COOEt)CH₂ (**19**)), 3.84-3.93 (m, 2H, N(COOEt)CH₂ (**18**)), 4.06-4.27 (m, 6H, CHN(COOCH₂CH₃) (**18**), CHN(COOCH₂CH₃) (**19**)), 5.07-5.14 (m, 2H, CH₂=CHC (**18**)), 5.44-5.52 (m, 1H, CH₂=CHC (**18**)). ¹³C NMR (125 MHz, CDCl₃) δ = 10.6, 14.5, 14.7, 28.1, 28.2(2C), 29.7, 29.9(2C), 30.0, 30.3, 32.9, 33.1, 34.5, 34.7, 36.5, 36.7, 37.0, 41.5, 42.6, 53.1, 53.3, 53.9, 54.1, 61.7, 61.8, 114.3, 114.4, 125.5, 136.7, 136.8, 154.1, 154.2, 154.3, 203.9, 204.2, 205.2, 205.4. m/z (EI) 221.1 (M⁺), 193.1, 176.1, 164.0, 148.1, 132.0 (**18**). m/z (EI) 223.1 (M⁺), 194.1, 178.1, 166.1, 150.1, 138.0 (**19**).

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