Stereoselective Synthesis of a Functionalized 2-Oxo-1-azabicyclo[5.3.0]alkane as a Potential Scaffold for Targeted Chemotherapy Strategies

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Abstract: A stereoselective synthesis of functionalized 2-oxo-1-azabicyclo[5.3.0]alkane is presented. Key events of the synthetic sequence were the stereoselective propenylation of an *N*-acyliminium ion and a ring-closing metathesis reaction forming a 7-membered lactam.

Key words: metathesis, ring closure, lactams, bicyclic compounds, asymmetric synthesis, peptides

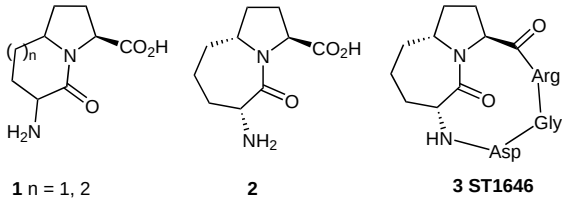

Figure 1

Many physiological processes including cell activation, migration, proliferation and differentiation require direct contact between cells and the extracellular matrix. These interactions are mediated through several different families of CAMs (cell adhesion molecules) including the selectins, the integrins, the cadherins and the immunoglobulins. In particular, integrins are α/β heterodimeric cell surface receptors which play a major role in cell–cell and cell–matrix adhesive interactions[1] and represent the best opportunity of targeting small-molecule antagonists for both therapeutic and diagnostic use in various key diseases.[2] Bicyclo[x.y.0]alkanes **1** have served as scaffolds for the synthesis of integrin antagonists.[3] In particular, we have found that the 2-oxo-1-azabicyclo[5.3.0]alkane (**2**)[4] when incorporated in a cyclic RGD (Arg-Gly-Asp) peptide appears to force the two pharmacophoric groups of Asp and Arg to adopt the correct disposition to interact with the receptors[5] (Figure 1). Compound **3** has shown to be highly active and selective toward the $\alpha_v\beta_3$ integrin which are expressed on the surface of a variety of cell types and are implicated in many pathological processes, such as tumor metastasis, angiogenesis, and osteoporosis.[6] Therefore, **3** could be a potential antitumor drug, and is currently under study in various animal models.

Since the $\alpha_v\beta_3$ integrin is overexpressed by many tumors, ST1646 could also be seen as a tumor-homing peptide and, as such, it could be used to improve the therapeutic index of other cancer chemotherapeutics[7] by selective cell targeting. Thus, our recent efforts have been directed toward the synthesis of functionalised bicyclo[5.3.0]alkane scaffolds bearing appropiate side-chains that can be used to conjugate the most frequently used anticancer drugs to the integrin binders. Although many reports on the synthesis of bicyclic lactams[8,9] can be found in the literature, only a few describe the preparation of azabicyclo[x.y.0]alkanes bearing functionalised side-chains.[10] In the course of our studies on peptide secondary structure mimics we have already synthesized a functionalised 7,5-fused bicyclic lactam using a Horner–Emmons based strategy.[11] However, the number of steps of this approach and the importance of these compounds forced us to investigate new synthetic routes. We now report a stereoselective synthesis based on ring closing metathesis (RCM)[9k] of a 7,5-*trans*-fused bicyclic lactam with a suitably functionalised side-chain.

The starting material for the synthesis was the known 4-allyl pyroglutamic ester **4**[12] (Scheme 1) which, after protecting group manipulation, was converted to the corresponding alcohol **5** via ozonolysis followed by in situ $NaBH_4$ reduction (80% over 3 steps). Hydroxy group protection as the silyl ether (thexyldimethylsilyl chloride, imidazole in DMF) followed by *N*-Boc nitrogen protection using standard conditions afforded the corresponding protected pyroglutamic acid **7** in 92% yield over the two steps. The order of the synthetic sequence was found to be crucial. If the ozonolysis and $NaBH_4$ reduction were performed starting from the *N*-Boc-protected pyroglutamate **8**, an irreversible 'ring switching' to the lactone **9** was observed (Scheme 1).[13]

Selective reduction of the imide **7** to the hemiaminal **11** (Scheme 2) was best performed with lithium triethylborohydride at –78 °C (99%). According to ample literature precedent[14] and to our own experience on similar substrates,[15] the hemiaminal **11** was first converted to the corresponding C5-methoxy derivative **12** by PPTS in MeOH (95%) and then subjected to boron trifluoride mediated 1-

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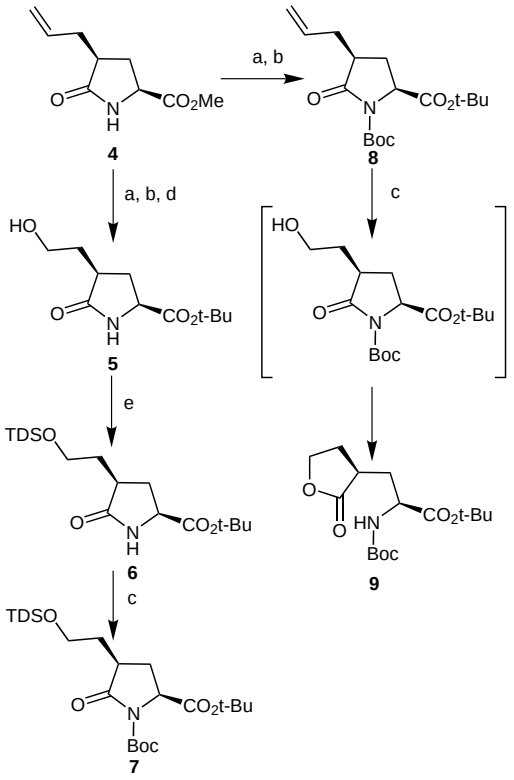
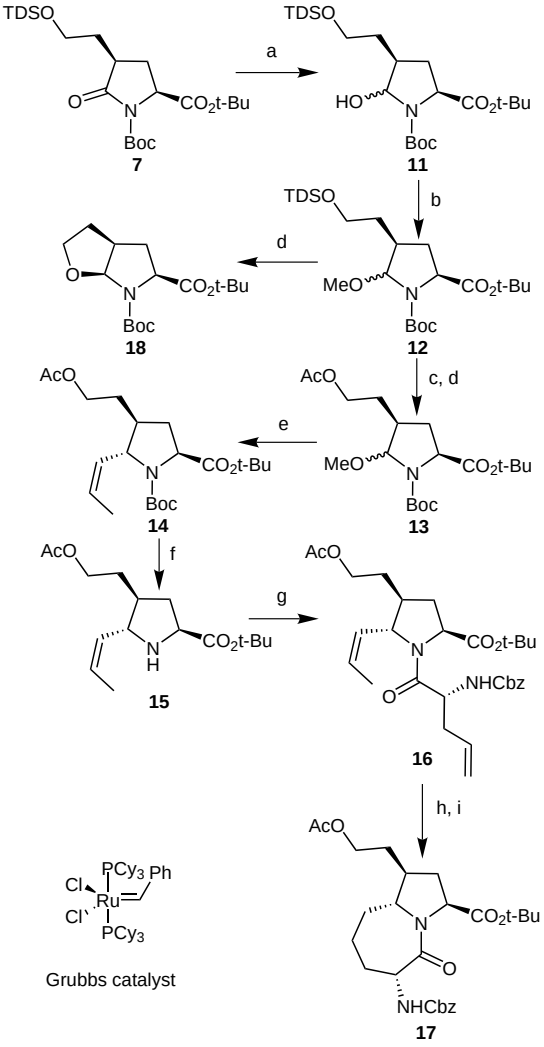


Scheme 1 (a) NaOH, THF, H_2O, quant.; (b) *O*-*tert*-butyl-*N*,*N*-diisopropylisourea, CH_2Cl_2, quant.; (c) Boc_2O, TEA, DMAP, THF, 94%; (d) O_3, MeOH, $NaBH_4$, 80%; (e) TDSCl, imidazole, DMF, 98%.

propenyl cuprate addition as described by McClure et al.[14e] However, the main product observed after cuprate addition was **18** arising by intramolecular nucleophilic attack of the hydroxy group on the intermediate hemiaminal. To avoid oxygen deprotection in the reaction conditions, the protecting group was changed from silyl ether to acetate. The propenyl cuprate addition occurred smoothly on the acetate **13** to yield the 5-propenyl proline **14**, as the only isomer. The product configuration was established by NOE experiments. Selective removal of the *tert*-butoxycarbonyl protecting group from **14** with $HClO_4$ in *t*-BuOAc gave the desired amine **15** (79%).

The coupling of this hindered amine to a racemic mixture of *N*-Cbz allyl glycine proceeded with complete kinetic resolution and afforded **16** as the only isomer in 64% yield using 3.3 equiv of acylating agent. The coupling reaction proceeded equally well by using either the acyl fluoride[16] or the mixed anhydride preactivation methods. The configuration of the amino acid moiety in **16** was not established at this point but was determined by NOE experiment on the final target **17**.

Thus the stage was set for the RCM reaction of the dienyl precursor **16**. The reaction proceeded in 16 h in refluxing CH_2Cl_2 in the presence of 10% of the Grubbs first generation catalyst[17] to give the functionalized bicyclic scaffold in 83% yield. The reduction of the double bond was achieved by $NaBH_4$–$NiCl_2$ in MeOH (80%).[18]



Scheme 2 (a) $LiEt_3BH$, THF, –78 °C, 99%; (b) MeOH, PPTS, 95%; (c) TBAF, THF, 96%; (d) AcCl, Et_3N, CH_2Cl_2, 90%; (e) 1-propenyl bromide, Li, $CuBr{\cdot}Me_2S$, $BF_3{\cdot}Et_2O$, 64%; (f) *t*-BuOAc, $HClO_4$, 0 °C to r.t., 79%; (g) allyl glycine, NMM, isopropyl chloroformate, THF, –30 °C to r.t., 64%; (h) Grubbs catalyst, CH_2Cl_2, 83%; (i) $NaBH_4$–$NiCl_2$, MeOH, 80%.

In summary, we have reported a convenient synthetic route for the preparation of a substituted 2-oxo-1-aza[5.3.0]bicycloalkane based on RCM cyclization. This bicyclic lactam could be used as scaffold for the synthesis of a cyclopentapeptide containing the RGD sequence for targeted chemotherapy strategies.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution as indicated, at 200 (or 300, 400) and 50.3 MHz, respectively. The chemical shift values are given in ppm and the coupling constants *J* in Hz. Optical rotation data were obtained with a Perkin–Elmer model 241 polarimeter. TLC was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out using Macherey–Nagel silica gel 60, 230–400 mesh. Solvents were dried according to standard procedures, and reactions requiring anhyd conditions were performed under nitrogen. Petroleum ether refers to the fraction with bp 40–60 ºC. Solutions containing the final products were dried (Na_2SO_4), filtered, and concentrated under reduced

pressure using a rotary evaporator. Elemental analyses were performed by the staff of the microanalytical laboratory in our department. The (*Z*)-1-lithio-1-propene was prepared from *cis*-1-bromo-1-propene (Aldrich) and lithium powder (high sodium, Aldrich) in Et_2O at –25 °C under an argon atmosphere in ca. 65% yield (based on the bromide).[19] Concentrations of the nearly colorless ethereal solutions of the alkenyllithium were typically ca. 0.7 M as determined by titration.[20] Abbreviations: DMAP, 4-(dimethylamino)pyridine; TBAF tetrabutylammonium fluoride; DMF, *N*,*N*-dimethylformamide; THF tetrahydrofuran; Boc_2O di-*tert*-butyl dicarbonate; TDSCl, thexyldimethylsilyl chloride; PPTS, pyridinium paratoluensulphonate; NMM, *N*-methylmorpholine.

(2*S*,4*R*)-4-Hydroxyethyl-5-oxopyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (5)

A stirred solution of **4** (2.1 g, 9.32 mmol) in MeOH (93 mL) was cooled to –78 °C, whereupon O_3 was bubbled through it (flow rate 30 L/h). After 1.5 h, N_2 was bubbled through the reaction mixture in order to eliminate the excess of O_3. $NaBH_4$ was then added in portions until the ozonide had completely disappeared. The solvent was evaporated under reduced pressure and the residue was redissolved in EtOAc and washed with brine. The organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to yield alcohol **5**.

Yield: 1.8 g (84%); white solid; mp 82–83 °C; $[\alpha]_D^{20}$ –14.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(C*H*$_3$)$_3$], 1.75 (m, 1 H, *H*CHCH$_2$OH), 1.81 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.04 (m, 1 H, *H*CHCH$_2$OH), 2.69 (m, 1 H, CHC=O), 2.72 (m, 1 H, *H*CHCHCOO-*t*-Bu), 3.65 (m, 1 H, HC*H*OH) 3.79 (m, 2 H, HC*H*OH, O*H*), 4.15 (m, 1 H, C*H*COO-*t*-Bu), 5.92 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 179.4, 170.0, 81.8, 60.7, 54.4, 40.0, 33.4, 31.7, 27.3.

MS (FAB): *m*/*z* calcd for $C_{11}H_{19}NO_4$: 229.13; found: 230.

Anal. Calcd for $C_{11}H_{19}NO_4$ (229.13): C, 57.62; H, 8.35; N, 6.11. Found C, 57.70; H, 8.36; N, 6.11.

(2*S*,4*R*)-4-{2-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]ethyl}-5-oxopyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (6)

To a stirred solution of the alcohol **5** (0.708 g, 3.09 mmol), in DMF (4.4 mL), thexyldimethylsilyl chloride (1.82 mL, 9.27 mmol) and imidazole (1.26 g, 18.55 mmol) were added sequentially. After 16 h the solvent was evaporated and the crude was purified by flash chromatography (hexane–EtOAc, 1:1) to yield **6**.

Yield: 1.12 g (98%); colorless oil; $[\alpha]_D^{20}$ +10.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, Si(CH$_3$)$_2$], 0.83–0.90 [m, 12 H, CH$_3$), 1.50 [s, 9 H, C(CH$_3$)$_3$], 1.55 (m, 1 H, *H*CHCH$_2$OSi), 1.63 [m, 1 H, C*H*(CH$_3$)$_2$], 1.90 (m, 1 H, *H*CHCH$_2$OSi), 2.15 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.60 (m 1 H, CHC=O), 2.71 (m, 1 H, *H*CHCHCOO-*t*-Bu), 3.75 (m, 2 H, CH$_2$OSi), 4.12 (m, 1 H, C*H*COO-*t*-Bu), 6.22 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 179.1, 170.8, 60.8, 54.4, 38.7, 34.0, 33.8, 32.1, 27.8, 20.2, 18.4, –3.5, –3.6.

MS (FAB): *m*/*z* calcd for $C_{19}H_{37}NO_4Si$: 371.25; found: 372.

Anal. Calcd for $C_{19}H_{37}NO_4Si$ (371.25): C, 61.41; H, 10.04; N, 3.77. Found: C, 61.51; H, 10.06; N, 3.87.

(2*S*,4*R*)-4-{2-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]ethyl}-5-oxopyrrolidine-1,2-dicarboxylic Acid *tert*-Butyl Ester (7)

To a solution of **6** (0.874 g, 2.35 mmol) in CH_2Cl_2 (4.8 mL) were added Et_3N (0.361mL, 2.59) and a solution of DMAP (0.287 g, 2.35 mmol) and Boc_2O (0.667 g, 3.06 mmol) in CH_2Cl_2 (3 mL). After 3 h, to the reaction mixture was added brine (8 mL) and the organic layers were extracted with CH_2Cl_2. The organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 2:8) to yield **7**.

Yield: 1.04 g (94%); yellow oil.

(2*S*,4*R*)-4-{2-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]ethyl}-5-hydroxypyrrolidine-1,2-dicarboxylic Acid *tert*-Butyl Ester (11)

To a solution of **7** (0.660 g, 1.40 mmol) in anhyd THF (14 mL), $LiEt_3BH$ (1 M in THF; 1.68 mL) was added at –78 °C and the solution was stirred for 50 min, then sat. aq NH_4Cl solution (15 mL) was added. The aq phase was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The crude product, as a yellowish oil, was submitted to the next reaction without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, Si(CH$_3$)$_2$], 0.86 (m, 12 H, CH$_3$), 1.45 [s, 9 H, C(CH$_3$)$_3$], 1.50–2.20 (m, 16 H), 3.60 (m, 2 H, C*H*$_2$OTDS), 4.15 (m, 1 H, C*H*COO-*t*-Bu), 5.25, 5.32 (2 m, 1 H, C*H*OH).

(2*S*,4*R*)-4-{2-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]ethyl}-5-methoxypyrrolidine-1,2-dicarboxylic Acid *tert*-Butyl Ester (12)

To a solution of **11** (0.598 g, 1.26 mmol) in MeOH (14 mL), PPTS (0.453 g, 1.80 mmol) was added. After 12 h, the solvent was evaporated and to the residue was added a phosphate buffer solution (10 mL), the aq phase was extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 1:9) to yield **12**.

Yield: 0.580 g (94%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, Si(CH$_3$)$_2$], 0.86 (m, 12 H, CH$_3$), 1.45 [s, 9 H, C(CH$_3$)$_3$], 1.50–2.35 (m, 15 H), 3.40 (s, 3 H, OCH$_3$), 3.60 (m, 2 H, C*H*$_2$OTDS), 4.10 (m, 1 H, C*H*COO-*t*-Bu), 5.01, 5.10 (2 m, 1 H, C*H*OCH$_3$).

MS (FAB): *m*/*z* calcd for $C_{25}H_{49}NO_6Si$: 487.33; found: 488.

Anal. Calcd for $C_{25}H_{49}NO_6Si$ (487.33): C, 61.56; H, 10.13; N, 2.87. Found: C, 61.68; H, 10.15; N, 2.87.

(2*S*,4*R*)-4-(2-Acetoxyethyl)-5-methoxypyrrolidine-1,2-dicarboxylic Acid *tert*-Butyl Ester (13)

To a solution of **12** (0.170 g, 0.35 mmol) in THF (3.5 mL) was added a solution in THF of TBAF (1 M; 0.450 mL) and the mixture was stirred for 6 h at r.t. To this was added brine (3 mL) and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 1:9) to yield the alcohol.

Yield: 0.115 g (95%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, C(CH$_3$)$_3$], 1.55 [s, 9 H, C(CH$_3$)$_3$], 1.70 (m, 1 H, HC*H*CH$_2$OH), 1.80 (m, 1 H, HC*H*CHCOO-*t*-Bu), 1.90 (m, 1 H, *H*CHCH$_2$OH), 2.15 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.35 (m, 1 H, C*H*CH$_2$CH$_2$OH), 3.40 (s, 3 H, OCH$_3$), 3.70 (m, 2 H, C*H*$_2$OH), 4.15 (m, 1 H, C*H*COO-*t*-Bu), 5.01, 5.10 (2 m, 1 H, C*H*OCH$_3$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.7, 154.4, 88.6, 81.0, 80.7, 63.2, 59.7, 56.7, 40.7, 33.7, 28.6, 28.4, 28.3.

MS (FAB): *m*/*z* calcd for $C_{17}H_{31}NO_6$: 345.22; found: 346.

Anal. Calcd for $C_{17}H_{31}NO_6$ (345.22): C, 59.11; H, 9.05; N, 4.05. Found: C, 59.20; H, 9.06; N, 4.05.

To a solution of the alcohol (0.102 g, 0.30 mmol) in THF (3.0 mL) were added, at 0 °C, Et_3N (0.049 mL, 0.32 mmol) and acetyl chloride (0.023 mL, 0.35 mmol). After 2 h, a buffer phosphate solution (3 mL) was added and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 2:8) to yield **13**.

Yield: 0.098 g (84%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50 [s, 9 H, C(CH_3)$_3$], 1.55 [s, 9 H, C(CH_3)$_3$], 1.70 (m, 1 H, HC*H*CH$_2$OAc), 1.80 (m, 1 H, HC*H*CH-COO-*t*-Bu), 1.90 (m, 1 H, *H*CHCH$_2$OAc), 2.05 (s, 3 H, OCOCH_3), 2.15 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.35 (m, 1 H, C*H*CH$_2$CH$_2$OAc), 3.40 (s, 3 H, OCH_3), 4.10 (m, 2 H, CH_2OAc), 4.15 (m, 1 H, C*H*COO-*t*-Bu), 5.01, 5.10 (2 m, 1 H, C*H*OCH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.7, 171.5, 154.4, 88.6, 81.0, 80.7, 63.2, 59.7, 56.7, 40.7, 33.7, 28.6, 28.4, 28.3, 21.1.

MS (FAB): *m*/*z* calcd for $C_{19}H_{33}NO_7$: 387.23; found: 388.

Anal. Calcd for $C_{19}H_{33}NO_7$ (387.23): C, 58.90; H, 8.58; N, 3.61. Found: C, 59.00; H, 8.60; N, 3.62.

(2*S*,4*R*)-4-(2-Acetoxyethyl)-5-[(*Z*)-propenyl]pyrrolidine-1,2-dicarboxylic Acid *tert*-Butyl Ester (14)

To a vigorously stirred suspension of CuBr·DMS (0.114 g, 0.56 mmol) in anhyd Et_2O (0.5 mL) was added a solution of (*Z*)-1-lithio-1-propene (0.63 M in Et_2O, 0.803 mL) via cannula at –50 °C under an argon atmosphere. The resulting dark brown mixture was stirred for 30 min at –50 °C before being cooled to –78 °C. BF_3·Et_2O (0.074 mL, 0.56 mmol) was then added slowly. After 10 min, a solution of **13** (0.098 g, 0.25 mmol) in anhyd Et_2O (0.450 mL) was then added dropwise via cannula. The black reaction mixture was slowly allowed to warm to r.t. and stirred for 12 h. After this period a mixture of sat. aq NH_4Cl and concd NH_4OH was then added. The mixture was vigorously stirred for 45 min and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 2:8) to yield **14**.

Yield: 0.064 (64%); yellowish oil; $[\alpha]_D^{20}$ +0.11 (*c* 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 1.50 [s, 9 H, C(CH_3)$_3$], 1.58 (m, 1 H, HC*H*CH$_2$OAc), 1.60 (m, 1 H, HC*H*CH-COO-*t*-Bu), 1.70 (m, 3 H, CH=CHCH_3), 1.90 (m, 2 H, *H*CHCH$_2$OAc, *H*CCH$_2$CH$_2$OAc), 2.05 (s, 3 H OCOCH_3), 2.40 (m, 1 H, *H*CHCHCOO-*t*-Bu), 4.10 (m, 2 H, CH_2OAc), 4.20 (m, 1 H, C*H*COO-*t*-Bu), 4.38 (m, 1 H, C*H*CH=CHCH$_3$), 5.30 (m, 1 H, C*H*=CHCH$_3$), 5.60 (m, 1 H, CH=C*H*CH$_3$).

^{13}C NMR (100.6 MHz, HETCOR, $CDCl_3$): δ = 131.5, 124.0, 63.1, 61.0, 60.5, 42.8, 34.3, 34.2, 31.6, 28.7, 28.3, 21.3, 13.7.

MS (FAB): *m*/*z* calcd for $C_{21}H_{35}NO_6$: 397.25; found: 398.

Anal. Calcd for $C_{21}H_{35}NO_6$ (397.25): C, 63.45; H, 8.87; N, 3.52. Found C, 63.60; H, 8.88; N, 3.52.

(2*S*,4*R*)-4-(2-Acetoxyethyl)-5-[(*Z*)-propenyl]pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (15)

To a solution of **14** (0.034 g, 0.09 mmol) in *t*-BuOAc (0.85 mL), at 0 °C, $HClO_4$ (0.077 mL, 0.13 mmol) was added. After 1 h, the reaction was warmed to r.t. and stirred for 4 h, and then Et_3N (0.6 mL) was added. The mixture was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 8:2) to yield **15**.

Yield: 79%; orange oil; $[\alpha]_D^{20}$ –6.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(CH_3)$_3$], 1.52 (m, 1 H, HC*H*CH$_2$OAc), 1.55 (m, 1 H, HC*H*CHCOO-*t*-Bu), 1.76 (m, 3 H, CH=CHCH_3), 1.83 (m, 2 H, *H*CHCH$_2$OAc, *H*CCH$_2$CH$_2$OAc), 2.10 (s, 3 H OCOCH_3), 2.50 (m, 1 H, *H*CHCHCOO-*t*-Bu), 3.2 (s, 1 H, NH), 3.75 (m, 1 H, C*H*CH=CHCH$_3$), 3.90 (m, 1 H, C*H*COO-*t*-Bu), 4.10 (m, 2 H, CH_2OAc), 5.35 (m, 1 H, C*H*=CHCH$_3$), 5.68 (m, 1 H, CH=C*H*CH$_3$).

^{13}C NMR (100.6 MHz, HETCOR, $CDCl_3$): δ = 131.4, 129.0, 63.9, 61.1, 60.0, 43.6, 36.9, 36.6, 31.6, 28.5, 21.6, 13.9.

MS (FAB): *m*/*z* calcd for $C_{16}H_{27}NO_4$: 297.19; found: 298.

Anal. Calcd for $C_{16}H_{27}NO_4$ (297.19): C, 64.62; H, 9.15; N, 4.71. Found C, 64.70; H, 9.16; N, 4.70.

(2*S*,4*R*)-4-(2-Acetoxyethyl)-1-(2-benzyloxycarbonylaminopent-4-enoyl)-5-propenylpyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (16)

To a solution of (±)-*N*-(*Z*)-allylglycine (0.0526 g, 0.211 mmol) in anhyd THF (0.5 mL) was added at –30 °C *N*-methylmorpholine (0.0563 mL, 0.511 mmol) and isobutyl chloroformate (0.0293 mL, 0.224 mmol). After 30 min, **15** (0.019 g, 0.064 mmol) was added, then the reaction mixture was stirred for 12 h. The suspension was filtered on a Celite pad and the solvent was evaporated under reduced pressure. To the crude was added H_2O and the mixture was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 35:65) to yield **16**.

Yield: 0.020 g (61%); yellowish oil; $[\alpha]_D^{20}$ –9.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(CH_3)$_3$], 1.75 (m, 2 H, HC*H*CH$_2$OAc, HC*H*CHCOOBu-*t*), 1.90 (m, 3 H, CH=CHCH_3), 1.95 (m, 1 H, *H*CHCH$_2$OAc), 2.10 (m, 4 H, *H*CCH$_2$CH$_2$OAc, OCH_3), 2.35 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.45 (m, 2 H, CH_2CHNHCbz), 4.10 (m, 2 H, CH_2OAc), 4.32 (m, 1 H, C*H*COO-*t*-Bu), 4.60 (m, 1 H, C*H*NHCbz), 4.75 (m, 1 H, C*H*CH=CHCH$_3$), 5.10 (m, 4 H, CH_2Ph, CH=CH_2), 5.30 (m, 1 H, NH), 5.40 (m, 1 H, C*H*=CHCH$_3$), 5.70 (m, 2 H, C*H*=CH$_2$, CH=C*H*CH$_3$), 7.35 (m, 5 H, aromatics).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.5, 171.0, 170.5, 157.0, 133.4, 131.2, 128.6, 128.1, 127.7, 118.3, 81.4, 66.9, 62.7, 61.3, 60.1, 51.3, 43.9, 33.1, 31.2, 28.0, 21.0, 13.5.

MS (FAB): *m*/*z* calcd for $C_{29}H_{40}N_2O_7$: 528.28; found: 529.

Anal. Calcd for $C_{29}H_{40}N_2O_7$ (528.28): C, 65.89; H, 7.63; N, 5.30. Found C, 66.00; H, 7.64; N, 5.30.

(3*S*,7*S*,8*R*,10*S*)-1-Aza-2-oxo-3-benzyloxycarbonylamino-8-acetoxyethyl-10-carbo-*tert*-butoxybicyclo[5.3.0]decane (17)

To a solution of **16** (0.019 g, 0.0369 mmol) in anhyd CH_2Cl_2 (0.9 mL) under nitrogen was added Grubbs catalyst (0.004 g, 0.005 mmol). After stirring at 40 °C for 60 h, the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (EtOAc–petroleum ether, 35:65) to yield the cyclized product.

Yield: 0.015 g (83%); yellowish oil; $[\alpha]_D^{20}$ –41.1 (*c*1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(CH_3)$_3$], 1.70 (m, 1 H, HC*H*CHCOO-*t*-Bu), 2.04 (m, 1 H, HC*H*CH$_2$OAc), 2.08 (s, 3 H, COCH_3), 2.10 (m, 1 H, *H*CHCH$_2$CH$_2$OAc), 2.20 (m, 1 H, HC*H*CH-NHCbz), 2.40 (m, 1 H, *H*CHCHCOO-*t*-Bu), 2.67 (m, 1 H, *H*CHCH$_2$OAc), 2.70 (m, 1 H, *H*CHCHNHCbz), 4.10 (m, 2 H, CH_2OAc), 4.30 (m, 2 H, C*H*COO-*t*-Bu, C*H*CH=CH), 4.70 (m, 1 H, C*H*NHCbz), 5.10 (m, 2 H, CH_2Ph), 5.50 (m, 1 H, CHCH=C*H*), 5.7 (m, 1 H, CHC*H*=CH), 6.10 (m, 1 H, NH), 7.35 (m, 5 H, aromatics).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.7, 170.2, 155.5, 136.6, 128.7, 128.6, 128.4, 128.2, 128.0, 81.9, 66.9, 62.4, 61.8, 61.3, 51.6, 44.2, 33.2, 32.2, 31.8, 31.1, 28.0, 21.1.

MS (FAB): *m*/*z* calcd for $C_{26}H_{34}N_2O_7$: 486.24; found: 487.

Anal. Calcd for $C_{26}H_{34}N_2O_7$ (486.24): C, 64.18; H, 7.04; N, 5.76. Found C, 64.30; H, 7.05; N, 5.75.

To a solution of the cyclized compound (0.0249 g, 0.051 mmol) in MeOH (0.5 mL) were added $NiCl_2 \cdot 6\ H_2O$ (0.012 g, 0.051 mmol) and $NaBH_4$ (0.01 g, 0.256 mmol). After 1 h, silica gel was added and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether, 4:6) to yield **17**.

Yield: 0.021 g (80%); yellowish oil; $[\alpha]_D^{20}$ –24.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (m, 2 H, *H*CHCH$_2$CH$_2$CHNH), 1.48 [s, 9 H, C(CH$_3$)$_3$], 1.48 (m, 2 H, C*H*$_2$CHNH), 1.70 (m, 1 H, *H*CHCHCOO-*t*-Bu), 1.60–1.80 (m, 2 H, HC*H*CHCOO-*t*-Bu, CH$_3$COCH$_2$*H*CH), 1.80–2.10 (m, 3 H, HC*H*CH$_2$CHNH, CH$_3$COCH$_2$HC*H*, CH$_3$COCH$_2$CH$_2$HC*H*), 2.09 (s, 3 H, COCH$_3$), 2.12 (m, 1 H, *H*CHCH$_2$CHNH), 2.43 (m, 1 H, *H*CH-CHCOO-*t*-Bu), 3.62 (m, 1 H, *H*CCH$_2$CH$_2$OAc), 4.11 (m, 2 H, C*H*$_2$OAc), 4.28 (m, 1 H, C*H*NHCbz), 4.33 (m, 1 H, C*H*COO-*t*-Bu), 5.11 (m, 2 H, C*H*$_2$Ph), 6.28 (m, 1 H, NH), 7.35 (m, 5 H, aromatics).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.2, 171.1, 170.7, 155.5, 136.7, 128.6, 128.1, 81.7, 66.7, 65.0, 62.6, 61.3, 55.0, 43.8, 35.1, 33.0, 32.5, 31.8, 28.1, 27.3, 21.1.

MS (FAB): *m*/*z* calcd for $C_{26}H_{36}N_2O_7$: 488.25; found: 489.

Anal. Calcd for $C_{26}H_{36}N_2O_7$ (488.25): C, 63.92; H, 7.43; N, 5.73. Found C, 63.98; H, 7.44; N, 5.73.

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