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Rapid Communications

Synthesis of conformationally constrained α-imino acid derivatives *via* ring-closing metathesis

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Conformationally constrained amino acid derivatives are useful in the synthesis of peptidomimetics. Seven-, and eight-membered conformationally constrained α-imino acid derivatives have been prepared *via* RCM (ring-closing metathesis). Interestingly, attempts to achieve the synthesis of nine-membered imino acid derivative resulted in the formation of dimeric, 18-membered macrocyclic bis-α-imino acid derivative.

Keywords: Peptidomemitics, conformationally constrained amino acids, conformationally constrained imino acids, ring-closing metathesis

The conformationally constrained cyclic amino acid derivatives have become important biological targets. In the recent years, the demand for peptide-based drugs has increased to a significant extent[1]. However, the use of peptides as drugs is limited by various factors such as instability towards proteolytic degradation, poor absorption after oral ingestion, rapid excretion through liver and kidneys and undesired effects caused by interaction of the conformationally flexible peptides with various receptors. The peptide modification[2] by incorporation of conformationally constrained amino acids in bioactive peptides and drugs can result in better substrates for structure-activity studies[3].

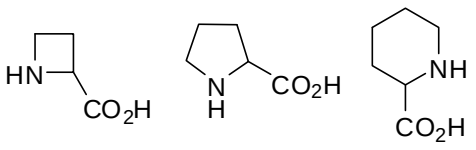
Cyclic $C^{\alpha}N^{\alpha}$ substituted amino acids are generally referred as constrained imino acids and constitute the important class of conformationally constrained amino acids. The replacement of proteinogenic amino acids by cyclic α-imino acid derivatives is well-known strategy for the synthesis of peptidomimetics with diverse pharmacological profiles. Azetidine-2-carboxylic acid **A** and its derivatives are important synthetic targets[4]. Naturally occurring proteinogenic unusual amino acid proline **B** is an integral part of many biologically active peptides and the various approaches are documented for the synthesis of diversely modified proline derivatives[5]. The pipecolic acid **C** moiety is a key structural element of several alkaloids[6], immunosuppressant drugs[7], and enzyme inhibitors[8] (**Figure 1**).

Although, various benzo-fused derivatives of these imino acids such as Tic, Hic, Sic and Nic are reported in the literature[9], the construction of seven-, eight-, and nine-memberd α-imino acid derivatives remain attractive targets for exploration[10]. More specifically, assembling the cyclic eight-, and nine-membered imino acid derivatives appears to be an interesting synthetic exercise. Further, varying the ring size of cyclic imino acids can dramatically alter their properties. As a part of research program, directed towards the synthesis of novel unusual α-amino acid derivatives[11], we focused our attention towards the synthesis of constrained α-imino acid derivatives containing various ring sizes which might subsequently be introduced into peptides assisting in modulating the conformation of polypeptide chains.

Results and Discussion

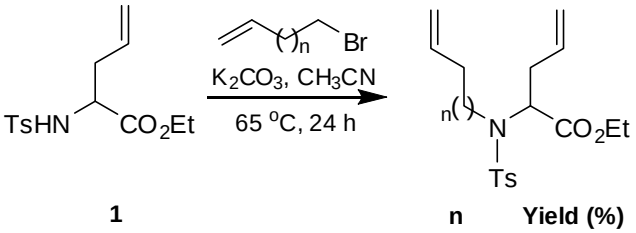
Our strategy for the preparation of constrained α-imino acid derivatives involve the alkylation of amide nitrogen of allyl glycine derivative **1** with various terminally olefinic bromides. Therefore, compound **1** was used as a building block to construct the open chain precursors for the cyclic imino acid derivatives. To realize the strategy, compound **1** was heated at 65ºC with 4-bromo-1-butene and potassium carbonate in dry acetonitrile to obtain compound **2** in 82% yield. Under similar reaction conditions, treatment of 5-bromo-1-pentene and 6-bromo-1-hexene with **1** gave the expected compounds **3** and **4** respectively, in good yield (**Scheme I**).

The well-defined ruthenium carbene complexes **G-I** (Grubbs' 1st generation catalyst)[12] and **G-II** (Grubbs' 2nd generation catalyst)[13] introduced by Grubbs' (**Figure 2**) exhibit an exceptional tolerance towards polar functional groups[14]. We envisioned the synthesis of seven-, eight- and nine-membered cyclic α-imino acid derivatives from the corresponding open chain analogues **2**, **3** and **4** respectively through RCM.



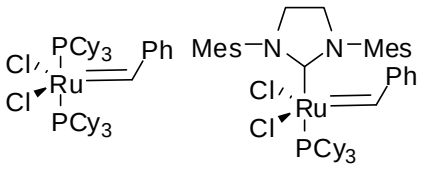
A **B** **C**

Figure 1



	n	Yield (%)
2	1	82
3	2	84
4	3	84

Scheme I

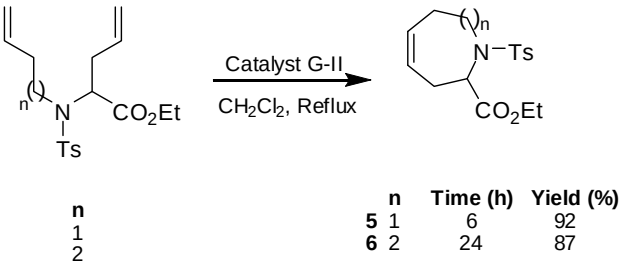


G-I **G-II**

Figure 2

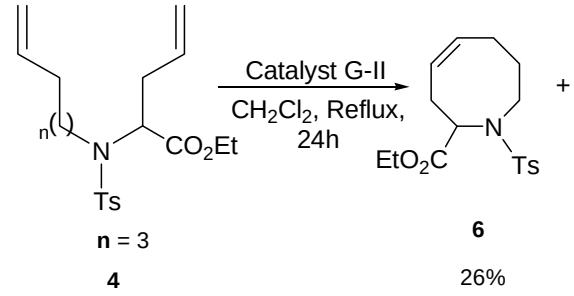
When compound **2** was refluxed with Grubbs' second generation catalyst **G-II** for 6 hr in dry dichloromethane, seven-membered α-imino acid derivative, compound **5** was obtained in 92% yield. In similar manner, compound **3** was subjected to RCM with catalyst **G-II** to compound **6** in 87% yield (**Scheme II**).

To our surprise, when compound **4** was treated with catalyst **G-II**, nine-membered cyclic α-imino acid analogue could not be obtained. In this instance, two products were isolated, and one was found to be a compound **6**. The formation of **6** can be attributed to the isomerization of terminal alkene double bond in substrate **4** followed by RCM[15]. The other product was the isomeric mixture of 18-membered macrocyclic bis-imino acid derivative and the possible structure can be indicated as **7** and/or **8**. Even ^{13}C NMR spectral data couldn't distinguish these two isomers, as both of them are expected to have the same number of peaks in ^{13}C NMR (δ 14.0, 21.6, 26.1, 30.3, 32.6, 33.3, 46.7, 60.5, 61.2, 126.1, 127.6, 129.4, 132.8, 137.1, 143.2, 170.9). The mass spectral data indicated a peak at m/z 703 ($C_{36}H_{50}N_2S_2O_8$+1) which confirmed the formation of dimerized product (**Scheme III**).



	n	Time (h)	Yield (%)
5	1	6	92
6	2	24	87

Scheme II



Scheme III

Although, we were not able to conclude the structure of dimeric product **7** and/or **8**, this observation may be rationalized by assuming that the polar functional groups coordinate to the metal center in one or more intermediates along the RCM pathway and hence favouring the macrocyclization[16].

Conclusion

The synthesis of seven-, and eight-membered cyclic α-imino acid derivatives using a RCM as a key step has been demonstrated. The isomeric mixture of 18-membered macrocyclic bis-imino acid derivative is obtained in an attempted synthesis of nine-

membered analogue. These derivatives may find useful applications in the designing the peptidomemitics.

Experimental Section

Analytical TLC was performed on (10 × 5 cm) glass plate coated with silica gel G or GF 254 (containing 13% $CaSO_4$ as a binder). Visualization of the spots on TLC plate was achieved either by exposure to I_2 vapour or UV light. Column chromatography was performed using silica gel (100-200 mesh) and column was usually eluted with ethyl acetate and petroleum ether (b.p. 60-80ºC) mixture. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectral data were recorded on a Varian VXR 300 and Varian VXR 400 spectrometers using TMS as an internal standard and $CDCl_3$ as solvent. The coupling constants (*J*) are given in hertz (Hz). Mass spectral data was recorded on a Q-TOF micromass machine. Infrared (IR) spectra were recorded on a Nicolet Impact-400 FT IR spectrometer. Solid samples were recorded as KBr wafers and liquid samples were recorded neat. For all the reactions Na_2SO_4 was used as drying agent after work-up.

Allyl glycine derivative **1** (racemic form) was prepared according to the procedure known in the literature[9d]. 4-Bromo-1-butene, 5-bromo-1-pentene, 6-bromo-1-hexene were purchased from Lancaster Chemical Co. (White Lund, U. K.). Second generation Grubbs' catalysts (**G-II**) was purchased from Fluka chemicals (Switzerland).

Preparation of compound 2. To a stirred suspension of finely powdered potassium carbonate (600 mg, 4.35 mmoles) in dry acetonitrile (10 mL) was added compound **1** (65 mg, 0.22 mmole) and 4-bromo-1-butene (58 mg, 0.44 mmole). The resulting heterogeneous mixture was heated at 65ºC for 24 hr under nitrogen. The reaction mixture was cooled and filtered over a short celite pad. The filtrate was concentrated under reduced pressure and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (25 mL × 3). Combined organic layers were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was purified by a silica gel column chromatography. Elution of the column with 5% ethyl acetate/pet. ether mixture gave compound **2** (63 mg, 82%); R_f = 0.42 (hexane–EtOAc, 4:1); IR (neat) ν_{max}: 3078, 2981, 2926, 1737, 1642, 1598, 1494, 1455, 1364, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.10 (3H, t, *J* = 7.2 Hz), 2.31-2.47 (6H, br m) 2.66-2.68 (1H, m) 3.19-3.30 (2H, m) 3.95 (2H, q, *J* = 7.2 Hz) 4.55(1H, dd, *J* = 8 Hz, 6.8 Hz) 5.00-5.17 (4H, m) 5.67-5.78 (2H, m) 7.27 (2H, d, *J* = 8Hz) 7.71 (2H, d, *J* = 8Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.9, 21.5, 34.9, 35.2, 45.4, 59.7, 61.2, 116.9, 118.5, 127.5, 129.4, 133.2, 134.8, 137.1, 143.3, 170.5; Mass (FAB): *m/z* Calcd for $C_{18}H_{25}NSO_4$+Na: 374, Found: 374.

Preparation of compound 3. To a stirred suspension of finely powdered potassium carbonate (370 mg, 2.68 mmoles) in dry acetonitrile (10 mL) was added compound **1** (40 mg, 0.13 mmole) and 5-bromo-1-pentene (39 mg, 0.26 mmole). The resulting heterogeneous mixture was heated at 65ºC for 24 hr under nitrogen. Then, the reaction mixture was cooled and filtered over a short celite pad. The filtrate was concentrated under reduced pressure and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (25 mL × 3). Combined organic layers were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was purified by a silica gel column chromatography. Elution of the column with 5% ethyl acetate/pet. ether mixture gave compound **3** (41 mg, 84%); R_f = 0.44 (hexane–EtOAc, 4:1); IR (neat) ν_{max}: 3080, 2981, 2925, 1734, 1642, 1599, 1494, 1446, 1344, 1162, 1091, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) :δ 1.10 (3H, t, *J* = 7.2 Hz) 1.65-1.68 (1H, m) 1.80-1.85 (1H, m) 1.98-2.03 (2H, m) 2.41-2.44 (4H, m) 2.65-2.69 (1H, m) 3.14-3.23 (2H, m) 3.95 (2H, q, *J* = 7 Hz) 4.55 (1H, dd, *J* = 8.8 Hz, 7 Hz) 4.95-5.16 (4H, m) 5.70-5.78 (2H, m) 7.27 (2H, d, *J* = 8 Hz) 7.71 (2H, d, *J* = 8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ 13.9, 21.5, 29.6, 31.1, 34.9, 45.5, 59.7, 61.1, 115.2, 118.3, 127.5, 129.4, 133.3, 137.3, 137.5, 143.2, 170.5; Mass (FAB): *m/z* Calcd for $C_{19}H_{27}NSO_4$+Na: 388, Found: 388.

Preparation of compound 4. To a stirred suspension of finely powdered potassium carbonate (1.2 g, 8.7 mmoles) in dry acetonitrile (15 mL) was added compound **1** (130 mg, 0.44 mmole) and 6-bromo-1-hexene (143 mg, 0.88 mmole). The resulting heterogeneous mixture was heated at 65°C for 24 hr. Then, the reaction mixture was cooled and filtered over a short celite pad. The filtrate was concentrated under reduced pressure and diluted with water (15 mL). The aqueous layer was extracted with ethyl acetate (25 mL × 3). Combined organic layers were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product, which was purified by a silica gel

column chromatography. Elution of the column with 3% ethyl acetate/pet. ether mixture gave compound **4** (140 mg, 84%); R_f = 0.72 (hexane– EtOAc, 4:1); IR (neat) ν_{max}: 2981, 2925, 1753, 1641, 1494, 1445, 1343, 1162, 1091, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) :δ 1.10 (3H, t, *J* = 7.2 Hz) 1.25-1.37 (2H, m) 1.52-1.76 (2H, m) 1.90-2.06 (2H, m) 2.36-2.47 (4H, m) 2.62-2.72 (1H, m) 3.08-3.27 (2H, m) 3.96 (2H, q, *J* = 7 Hz) 4.54 (1H, dd, *J* = 8.4 Hz, 7.2 Hz) 4.92-5.16 (4H, m) 5.70-5.76 (2H, m) 7.27 (2H, d, *J* = 8.2 Hz) 7.71 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ 14.0, 21.6, 26.4, 30.2, 33.3, 35.0, 46.0, 59.7, 61.2, 114.8, 118.4, 127.6, 129.5, 133.5, 137.5, 138.5, 143.3, 170.7; Mass (FAB) : *m/z* Calcd for $C_{20}H_{29}NSO_4$+Na : 402, Found: 402.

Preparation of compound 5. The solution of compound **2** (52 mg, 0.15 mmole) in dry dichloromethane (10 mL) was degassed with argon for 20 min and Grubbs' second generation catalyst **G-II** (2 mol%, 2.5 mg, 0.0025 mmole) was added under the argon. The reaction mixture was refluxed for 6 hr, cooled to RT and concentrated to dryness under vacuum. The crude compound was purified by silica gel column chromatography. Elution of column with 15% ethyl acetate/pet. ether mixture gave compound **5** (44 mg, 92%); R_f = 0.28 (hexane– EtOAc, 4:1); IR (neat) ν_{max}: 3029, 2902, 2981, 1741, 1598, 1495, 1449, 1334, 1305, 1156, 1095, 1027cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (3H, t, *J* = 7.2 Hz) 2.20-2.57 (6H, m) 2.73-2.80 (1H, m) 3.39-3.46 (1H, m) 3.66-3.72 (1H, m) 3.99-4.11(2H, m) 4.84 (1H, dd, *J* = 7.2Hz, 4Hz) 5.59-5.73 (2H, m) 7.28 (2H, d, *J* = 8 Hz) 7.73 (2H, d, *J* = 8Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ 14.4, 21.6, 30.0, 30.6, 43.5, 58.8, 61.3, 126.0, 127.5, 129.6, 131.8, 137.6, 143.3, 171.0; Mass (FAB) : m/z Calcd for $C_{16}H_{21}NSO_4$+Na : 346, Found: 346.

Preparation of compound 6. The solution of compound **3** (41 mg, 0.10 mmole) in dry dichloromethane (10 mL) was degassed with argon for 20 min and Grubbs' second generation catalyst **G-II** (4 mol%, 3.5mg, 0.004 mmole) was added under the argon. The reaction mixture was refluxed for 24 hr, cooled to RT and concentrated to dryness under vacuum. The crude compound was purified by silica gel column chromatography. Elution of column with 5% ethyl acetate/pet. ether mixture gave compound **6** (33 mg, 87%); R_f = 0.41 (hexane– EtOAc, 4:1); IR (neat): ν_{max} 3024, 2937, 2859, 1738, 1598, 1494, 1449, 1379, 1337,1178, 1160, 1134, 1097cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, t, *J* = 7 Hz) 1.45-1.56 (1H, m) 1.99-2.11 (2H, m) 2.14-2.33 (1H, m) 2.40 (3H, S) 2.51-2.66 (2H, m) 2.96-3.06 (1H, m) 3.63 (1H, dt, *J* = 15.9 Hz, 2.7 Hz) 3.82-4.00 (2H, m) 4.68 (1H, dd, *J* = 7.8 Hz, 4.7 Hz) 5.64-5.72 (1H, m) 5.80-5.89 (1H, m) 7.25 (2H, d, *J* = 8Hz) 7.66 (2H, d, *J* = 8Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) : δ 13.9, 21.5, 24.6, 29.6, 30.1, 45.7, 60.1, 61.1, 125.9, 127.4, 129.3, 133.7, 137.1, 143.1, 170.7; Mass (FAB): *m/*z Calcd for $C_{17}H_{23}NSO_4$+Na: 360, Found: 360.

An attempted RCM of compound 4. The solution of compound **4** (100 mg, 0.26 mmole) in dry dichloromethane (10 mL) was degassed with argon for 20 min and Grubbs second generation catalyst **G-II** (2 mol%, 4 mg, 0.0047 mmole) was added under the argon. The reaction mixture was refluxed for 24 hr, cooled to RT and concentrated to dryness under vacuum. The crude compound was purified by silica gel column chromatography. Elution of column with 10% ethyl acetate/pet. ether mixture gave compound **6** (23 mg, 26 %) and continued elution with 40% ethyl acetate/petroleum ether mixture allowed the isolation of isomeric mixture of compounds **7** and/or **8** (50 mg, 54%); Mixture of isomers of **7** and **8**: R_f = 0.24 (hexane– EtOAc, 4:1); IR (KBr): ν_{max} 2924, 2853, 1736, 1598, 1495, 1465, 1381,1341, 1287, 1161, 1089, 1020, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.03-1.10 (6H, m) 1.24-1.39 (4H, m) 1.59-1.72 (4H, m) 1.97-2.11 (4H, m) 2.35-2.43 (8H, m) 2.45-2.62 (2H, m) 2.97-3.05 (2H, m) 3.28-3.35 (2H, m) 3.82-3.96 (4H, m) 4.45-4.55 (2H, m) 5.41-5.53 (4H, m) 7.24-7.28 (4H, m) 7.65-7.69 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) For major isomer : δ 14.0, 21.6, 26.1, 30.3, 32.6, 33.3, 46.7, 60.5, 61.2, 126.1, 127.6, 129.4, 132.8, 137.1, 143.2, 170.9; Mass (FAB) : *m/z* Calcd for $C_{36}H_{50}N_2S_2O_8$+1: 703, Found: 703.

Abbreviations

DCM, dichloromethane; Et, ethyl; IR, infrared; MHz, mega hertz; mmole, milli mole; M.P., melting point; NMR, nuclear magnetic resonance; FAB, fast atom bombardment; Q-TOF, quadrupole time of flight; RCM, ring closing metathesis; RT, room temperature; Ts, tosyl.

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