HETEROCYCLES, Vol. 98, No. 1, 2019, pp. 79 - 87. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 12th September, 2018, Accepted, 26th December, 2018, Published online, 31st January, 2019
DOI: 10.3987/COM-18-S(F)81

# RING-OPENING METATHESIS OF *N*-ALKENYL β-LACTAMS†

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†This article is dedicated to Prof. Tohru Fukuyama on the occasion of his 70th birthday.

**Abstract** – We have synthesized a new class of *N*-alkenylated β-lactam derivatives and studied their metathetic behavior. Here, ring-opening metathesis is more favorable than ring-rearrangement metathesis. Molecular modelling studies revealed that the orientation of two olefinic moieties of β-lactam derivatives are far apart and therefore ring-rearrangement metathesis did not occur and ring-opening metathesis is only feasible.

β-Lactam is a small ring heterocycle containing 2-azetidinone moiety and it is found in various natural products and biologically important molecules. β-Lactam moiety has drawn the attention of medicinal chemists due to its presence in a number of medicinally active compounds like antibiotics such as penicillins, cephalosporins, carbapenems and monobactams (Figure 1).[1] Clavulanic acid, tabtoxinine-β-lactam and thienamycin are among selective examples of naturally occurring β-lactam antibiotics (Figure 1).[1b] Clavulanic acid acts as a β-lactamase inhibitor and tabtoxinine-β-lactam inhibits the action of glutamine synthetase (GS). Whereas, thienamycin shows high activity against Gram-positive and Gram-negative bacteria and acts as a bacterial β-lactamase inhibitor. Moreover, the β-lactam framework is a valuable synthon in the design and synthesis of β-amino acids. Due to the importance of the β-lactam analogues several functionalized β-lactams,[2] heterocycle-fused[3] or carbocycle-fused bicyclic β-lactams[4] have been prepared to study their applications in bioorganic chemistry. Beyond its synthetic importance, stereocontrolled synthesis of β-lactam derivatives is considered as a challenging task to organic chemists.[5] Due to these reasons developing new synthetic approaches to this class of molecules is worthy of further investigation.

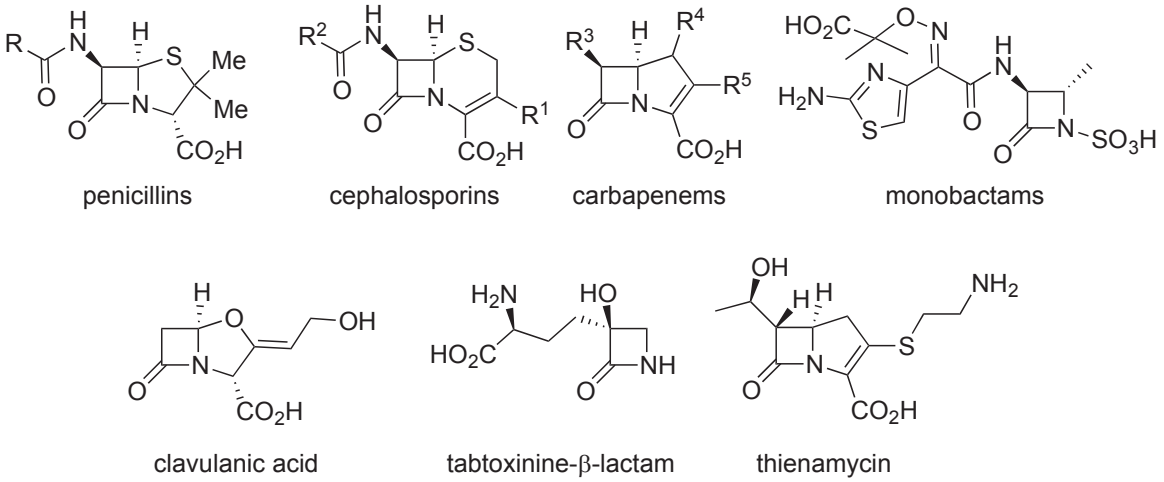



**Figure 1.** Biologically active β-lactam derivatives

Olefin metathesis[6] is an efficient synthetic tool and widely used protocol for the construction of C=C bond containing diverse molecular frameworks. Metathesis strategy is capable of producing stereocontrolled synthesis of complex targets under mild reaction conditions[7] and in this regard, some functionalized β-lactams were also synthesized through metathesis protocol.[8] Previously, ring-opening metathesis (ROM) was applied successfully for the stereocontrolled synthesis of highly functionalized cispentacin (2-aminocyclopentanecarboxylic acid) derivatives.[9] Coe *et al.* successfully utilized ring-closing metathesis (RCM) strategy to synthesize phyllostictine analogue starting with α-methylene-β-lactams.[10] Recently, Fülöp group exploited metathesis strategy to synthesize several β-amino acid derivatives from β-lactams. In this regard, they used several norbornadiene derived β-lactam precursors.[11] In view of our interest in metathesis area, we have synthesized a series of *N*-alkenyl derivatives containing β-lactam unit, which are useful synthons to prepare new and diverse β-lactam derivatives. Structures of various ruthenium catalysts used in our study are shown in Figure 2.

The β-Lactam derivative **2** has been prepared from commercially available norbornadiene **1** in good yield by adopting the known procedure involving chlorosulfonyl isocyanate addition.[12] Later on, it was subjected to *N*-allylation with allyl bromide using NaH at room temperature to produce the *N*-allyl compound **3** in 66% yield (Scheme 1).[13a]

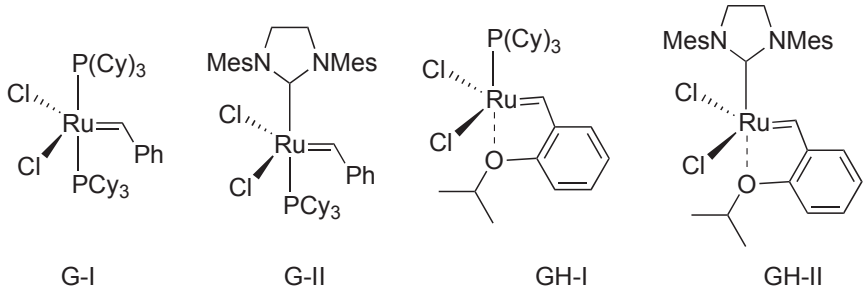
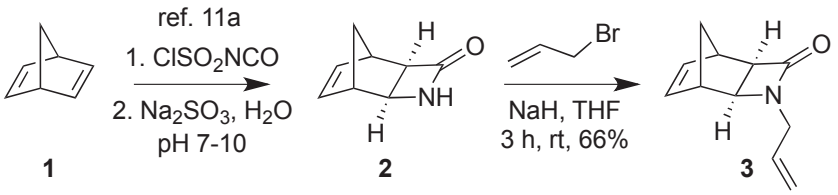


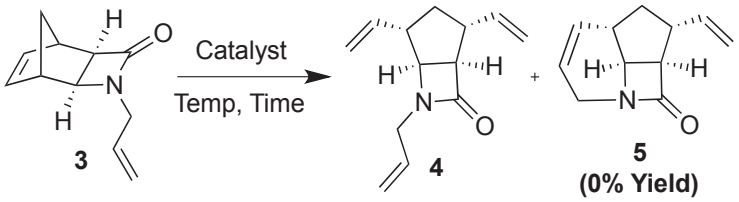

**Figure 2.** Ru-Based catalysts used in the present study




**Scheme 1.** Synthesis of allyl derivative 3

Next, the *N*-allyl derivative **3** was subjected to metathesis using Grubbs first, second generation catalysts (G-I & G-II) and Grubbs-Hoveyda first, second generation catalysts (GH-I & GH-II) under various conditions (Entry 1-5, Table 1). We found that ROM product[13b] **4** was formed in good yields using G-I (Entry 1, Table 1) and G-II catalysts (Entry 2, Table 1) while GH-I (Entry 4, Table 1) and GH-II (Entry 5, Table 1) catalysts gave polymeric products along with poor yields of the ROM product **4**. However, we did not observe ring-rearrangement metathesis (RRM) product **5** during our attempts in metathesis sequence. It may be because of unfavorable orientation of olefinic groups present in the compound **3**.

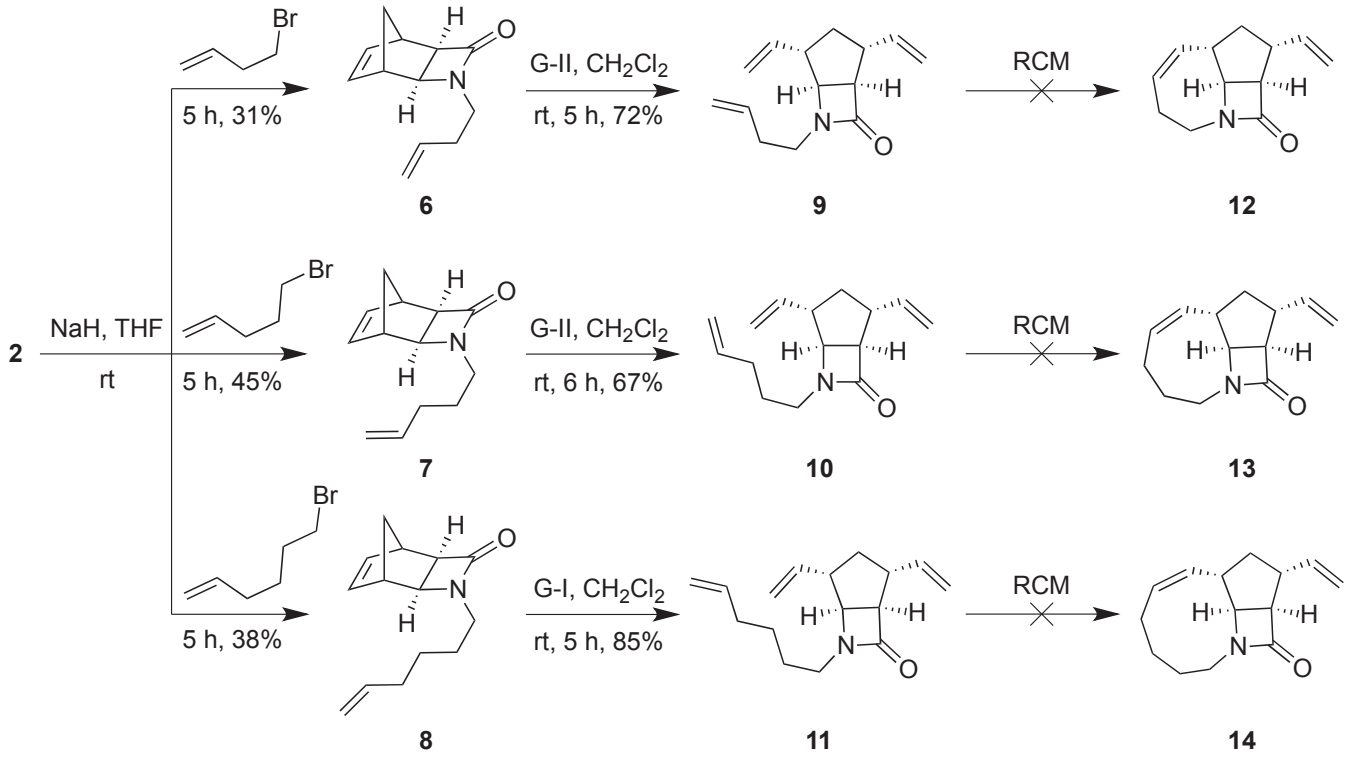
**Table 1.** Reaction conditions used for metathesis of **3**[a]




| Entry | Catalyst[b] | Solvent | Temp (°C) | Time (h) | Yield of 4 (%) |
|---|---|---|---|---|---|
| 1 | G-I | $CH_2Cl_2$ | rt | 4 h | 56 |
| 2 | G-I | PhMe | reflux | 15 h | 74 |
| 3 | G-II | $CH_2Cl_2$ | rt | 12 h | 82 |
| 4 | GH-I | PhMe | reflux | 8 h | 38 |
| 5 | GH-II | $CH_2Cl_2$ | rt | 5 h | 36 |

[a] Reaction was conducted under ethylene atmosphere. [b] 5 mol% catalyst was used during the reaction.

To gain insight, we have synthesized other unsaturated derivatives (**6-8**) bearing 4, 5, and 6 carbon chains on nitrogen and they were further treated with G-I and G-II catalysts under different reaction conditions to generate the corresponding ROM products in good yields (Scheme 2). Later, these ROM derivatives **9-11** were reacted with G-I and G-II catalysts and unfortunately, RCM products **12-14** were not formed. This may be explained on the basis of that our previous study on RCM of cage allyl compounds which indicated that RCM is successful when the distance between allylated carbon atoms is small (1.611 Å). However, the ring-closing metathesis (RCM) product was not feasible when the distance increase to 2.9417 Å.[13c]




**Scheme 2.** *N*-Alkenylation of **2** and the synthesis of their ROM products

To gain insight, we have studied the geometry optimization of *N*-alkenyl derivatives **4**, **9-11** using Gaussian. Gas-phase calculations were carried out at the M062X/6-31G** level of theory and all calculations were carried out using the Gaussian 09 program.[14] The distance between vinyl group and allyl group of **4** is 4.8 Å

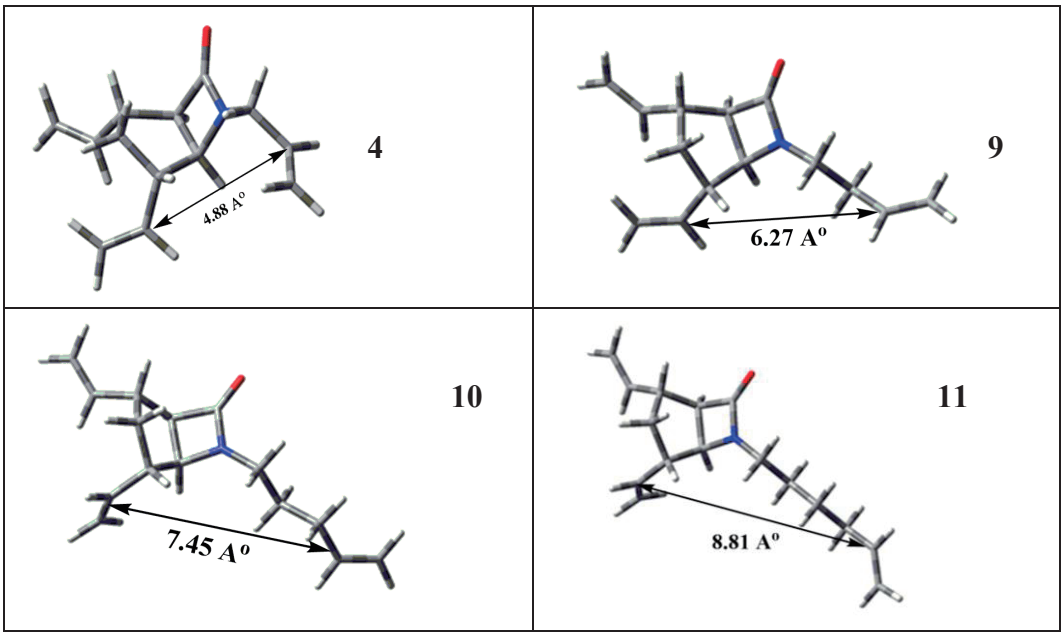



**Figure 3.** Calculated spacial distance between the two olefins based on the optimized geometries

and increases with increasing number of methylenes in *N*-alkenyl chain. These results indicated that two olefinic moieties are far away and the dihedral angle is not favorable for ring-closure. Therefore, these derivatives did not undergo ring-closure to produce tricyclic β-lactam derivatives **12-14** (Figure 3).

In conclusion, we have synthesized a new class of *N*-alkenyl-β-lactam derivatives and also studied their metathetic behaviour. Under metathetic condition, these *N*-alkenyl derivatives underwent ROM instead of RRM and this is because of orientation and distance between *N*-alkenyl olefins is not favorable for cyclization. Further, RCM of ROM derivatives are also unsuccessful due to unfavorable distance of vinylic olefin and *N*-alkenyl olefin moiety. These results were further supported by geometry optimization studies.

## EXPERIMENTAL

All commercially available reagents were used without further purification and the reactions involving air-sensitive catalysts or reagents were performed in degassed solvents. Grubbs (G-I, G-II) and Grubbs-Hoveyda (GH-I, GH-II) catalysts were purchased from Aldrich chemical company. All metathesis reactions were carried out under ethylene atmosphere. The $^{1}$H NMR (400 & 500 MHz) chemical shifts were reported in parts per million (δ) relative to internal standard TMS (7.26 ppm) and the coupling constants J are reported in hertz (Hz). The $^{13}$C NMR (100 & 125 MHz) chemical shifts were referenced to the internal solvent signals (central peak is 77.16 ppm in $CDCl_3$). The high-resolution mass spectrometric (HRMS) measurements were carried out using a Bruker (Maxis Impact) or Micromass Q-ToF spectrometer. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT-IR spectrometer and absorption bands are given in wavenumbers ($cm^{-1}$).

### General Procedure for *N*-Alkylation

To the suspension of NaH (60% in paraffin, 5.0 eq.) freshly washed with dry hexanes (2×) and dried under $N_2$) in dry THF, the compound (1.0 eq.) in dry THF was added under $N_2$ and stirred for 15 min. After being cooled to 0 °C, the alkenyl bromide was added slowly to the reaction mixture and allowed to stir for 3-5 h. After completion of reaction by TLC, the reaction mixture was quenched with ice, extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (2 × 30 mL) and dried over $Na_2SO_4$. After removal of solvent, the crude reaction mixture was purified by column chromatography to yield the desired *N*-alkenyl compound.

### (1*S**,2*S**,5*R**,6*R**)-(±)-3-Allyl-3-azatricyclo[4.2.1.0$^{2,5}$]non-7-en-4-one (3)

Yield: 66% (300 mg as a colourless liquid from 350 mg, 2.59 mmol). $R_f$ = 0.36 (petroleum ether/EtOAc = 7/3). $^{1}$H NMR ($CDCl_3$, 400 MHz): δ = 1.54–1.62 (m, 2H), 2.89 (d, *J* = 6.40 Hz, 2H), 2.94–2.98 (m, 1H), 3.43 (d, *J* = 3.88 Hz, 1H), 3.65 (dd, *J* = 6.72 Hz, *J* = 15.32 Hz, 1H), 3.89 (dd, *J* = 5.96 Hz, *J* = 15.32 Hz, 1H), 5.16 (dd, *J* = 0.97 Hz, *J* = 10.08 Hz, 1H), 5.22 (qd, *J* = 1.50 Hz, *J* = 16.85 Hz, 1H), 5.69–5.81 (m, 1H), 6.04

(dd, $J$ = 3.28 Hz, $J$ = 5.64 Hz, 1H), 6.21 (dd, $J$ = 3.04 Hz, $J$ = 5.64 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): 39.2 (CH), 40.9 ($CH_2$), 41.9 (CH), 43.2 ($CH_2$), 56.7 (CH), 56.9 (CH), 118.6 ($CH_2$), 132.2 (CH), 135.2 (CH), 138.7 (CH), 169.5 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 198.0889, calculated = 198.0881 for $C_{11}H_{13}NO$. IR: 2979, 1740, 1393, 1301, 993, 931, 754, 704.

**(1*S**,2*S**,5*R**,6*R**)-(±)-3-(But-3-en-1-yl)-3-azatricyclo[4.2.1.0$^{2,5}$]non-7-en-4-one (6)**

Yield: 31% (87 mg as a colourless liquid from 200 mg, 1.48 mmol). $R_f$ = 0.38 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.54–1.64 (m, 2H), 2.23–2.36 (m, 2H), 2.91 (brs, 2H), 2.95 (brs, 1H), 3.07–3.15 (m, 1H), 3.34–3.42 (m, 1H), 3.44 (d, $J$ = 3.70 Hz, 1H), 5.03–5.14 (m, 2H), 5.71–5.82 (m, 1H), 6.07 (dd, $J$ = 3.20 Hz, $J$ = 5.50 Hz, 1H), 6.23 (dd, $J$ = 3.20 Hz, $J$ = 5.65 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ = 32.5 ($CH_2$), 39.2 (CH), 39.8 ($CH_2$), 41.0 ($CH_2$), 42.1 (CH), 56.5 (CH), 57.0 (CH), 117.1 ($CH_2$), 135.1 (CH), 138.9 (CH), 169.8 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 212.1047, calculated = 212.1046 for $C_{12}H_{15}NO$. IR: 3011, 2965, 1738, 1375, 1320, 945, 732, 717.

**(1*S**,2*S**,5*R**,6*R**)-(±)-3-(Pent-4-en-1-yl)-3-azatricyclo[4.2.1.0$^{2,5}$]non-7-en-4-one (7)**

Yield: 45% (60 mg as a colourless liquid from 90 mg, 0.66 mmol). $R_f$ = 0.35 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.54–1.70 (m, 4H), 2.03–2.13 (m, 2H), 2.88–2.94 (m, 2H), 2.94–2.98 (m, 1H), 2.99–3.09 (m, 1H), 3.25–3.35 (m, 1H), 3.44 (d, $J$ = 3.84 Hz, 1H), 4.96–5.07 (m, 2H), 5.72–5.84 (m, 1H), 6.08 (dd, $J$ = 3.28 Hz, $J$ = 5.64 Hz, 1H), 6.24 (dd, $J$ = 3.00 Hz, $J$ = 5.64 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 27.4 ($CH_2$), 31.4 ($CH_2$), 39.3 (CH), 40.0 ($CH_2$), 41.1 ($CH_2$), 42.1 (CH), 56.5 (CH), 56.9 (CH), 115.6 ($CH_2$), 135.1 (CH), 137.5 (CH), 138.9 (CH), 169.8 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 226.1202, calculated = 226.1207 for $C_{13}H_{17}NO$. IR: 3004, 2988, 2977, 1741, 1343 1320, 945, 735, 701.

**(1*S**,2*S**,5*R**,6*R**)-(±)-3-(Hex-5-en-1-yl)-3-azatricyclo[4.2.1.0$^{2,5}$]non-7-en-4-one (8)**

Yield: 38% (122 mg as a colourless liquid from 200 mg, 1.5 mmol). $R_f$ = 0.38 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.41 (q, $J$ = 7.38 Hz, 2H), 1.49–1.64 (m, 4H), 2.06 (q, $J$ = 7.10 Hz, 2H), 2.90 (d, $J$ = 6.88 Hz, 2H), 2.92–2.96 (m, 1H), 3.23–3.33 (m, 1H), 3.42 (d, $J$ = 3.80 Hz, 1H), 4.91–5.03 (m, 2H), 5.69–5.82 (m, 1H), 6.07 (dd, $J$ = 3.28 Hz, $J$ = 5.64 Hz, 1H), 6.23 (dd, $J$ = 3.04 Hz, $J$ = 5.60 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 27.5 ($CH_2$), 33.3 ($CH_2$), 39.2 ($CH_2$), 40.3 (CH), 41.1 ($CH_2$), 42.0 ($CH_2$), 56.4 (CH), 56.9 (CH), 115.0 ($CH_2$), 135.1 (CH), 138.3 (CH), 138.9 (CH), 169.8 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 240.1359, calculated = 240.1356 for $C_{14}H_{19}NO$. IR: 2949, 2444, 1739, 880, 770.

**General Procedure for Ring-Opening Metathesis (ROM)**

The solution of compound (1 eq.) in dry $CH_2Cl_2$ (100 mL/mmol) was degassed with $N_2$ gas, followed by ethylene gas for 20 min. Grubb's catalyst (5 mol%) was added to the degassed solution at room temperature under ethylene atmosphere and allowed to stir at room temperature for 5-12 h. After completion of the reaction (monitored by TLC), the crude compound was purified by column chromatography to obtain the desired ROM product.

**(1*R**,2*R**,4*S**,5*S**)-(±)-6-Allyl-2,4-divinyl-6-azabicyclo[3.2.0]heptan-7-one (4)**

Yield: 82% (95 mg as colourless liquid from 95 mg). $R_f$ = 0.39 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 500 MHz): δ = 1.84 (d, *J* = 13.75 Hz, 1H), 2.26–2.34 (m, 1H), 2.76 (t, *J* = 7.27 Hz, 1H), 2.98 (t, *J* = 7.32 Hz, 1H), 3.52 (d, *J* = 3.35 Hz, 1H), 3.59 (dd, *J* = 6.65 Hz, *J* = 15.60 Hz, 1H), 3.91–3.98 (m, 2H), 4.94 (d, *J* = 10.35 Hz, 1H), 5.00 (dd, *J* = 4.90 Hz, *J* = 10.35 Hz, 2H), 5.04 (d, *J* = 10.80 Hz, 1H), 5.17–5.25 (m, 2H), 5.69–5.82 (m, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ = 37.1 (CH), 40.7 (CH), 42.5 (CH), 43.2 ($CH_2$), 60.1 (CH), 63.2 (CH), 114.2 ($CH_2$), 115.4 ($CH_2$), 118.7 ($CH_2$). 132.0 (CH), 139.8 (CH), 141.6 (CH), 168.8 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 226.1204, calculated = 226.1208 for $C_{13}H_{17}NO$. IR: 2934, 1742, 1446, 766.

**(1*R**,2*R**,4*S**,5*S**)-(±)-6-(But-3-en-1-yl)-2,4-divinyl-6-azabicyclo[3.2.0]heptan-7-one (9)**

Yield: 72% (58 mg as a colourless liquid from 70 mg). $R_f$ = 0.41 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.85 (d, *J* = 13.76 Hz, 1H), 2.23–2.37 (m, 4H), 2.75 (t, *J* = 7.16 Hz, 1H), 2.93–3.09 (m, 2H), 3.38–3.47 (m, 1H), 3.50 (d, *J* = 3.60 Hz, 1H), 3.94 (d, *J* = 3.64 Hz, 1H), 4.92–5.17 (m, 6H), 5.70–5.84 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ = 29.5, 29.8, 32.4, 37.3, 39.8, 40.7, 42.7, 60.0, 63.3, 114.2, 115.4, 117.3, 135.1, 140.0, 141.7, 169.1. HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 240.1358, calculated = 240.1362. IR: 2948, 1740, 1433, 795, 764.

**(1*R**,2*R**,4*S**,5*S**)-(±)-6-(Pent-4-en-1-yl)-2,4-divinyl-6-azabicyclo[3.2.0]heptan-7-one (10)**

Yield: 67% (38 mg as a colourless liquid from 50 mg). $R_f$ = 0.40 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 400 MHz): δ = 1.59–1.71 (m, 3H), 1.85 (d, *J* = 13.75 Hz, 1H), 2.09 (q, *J* = 13.75 Hz, 2H), 2.25–2.34 (m, 1H), 2.75 (t, *J* = 7.30 Hz, 1H), 2.89–3.01 (m, 2H), 3.30–3.40 (m, 1H), 3.51 (d, *J* = 3.60 Hz, 1H), 3.92 (d, *J* = 3.60 Hz, 1H), 4.90–5.12 (m, 6H), 5.71–5.85 (m, 3H). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 254.1526, calculated = 254.1521 for $C_{15}H_{21}NO$. IR: 2948, 1741, 1336, 1218, 758.

**(1*R**,2*R**,4*S**,5*S**)-(±)-6-(Pent-4-en-1-yl)-2,4-divinyl-6-azabicyclo[3.2.0]heptan-7-one (11)**

Yield: 85% (96 mg as a colourless liquid from 100 mg). $R_f$ = 0.44 (petroleum ether/EtOAc = 7/3). $^1$H NMR ($CDCl_3$, 500 MHz): 1.40 (p, *J* = 7.51 Hz , 2H), 1.47–1.61 (m, 2H), 1.84 (d, *J* = 13.70 Hz, 1H), 2.06 (q, *J* = 6.98 Hz, 2H), 2.24–2.33 (m, 1H), 2.73 (t, *J* = 7.30 Hz, 1H), 2.88–3.00 (m, 2H), 3.28–3.37 (m, 1H), 3.49 (d, *J* = 2.85 Hz, 1H), 3.90 (d, *J* = 3.40 Hz, 1H), 4.90–5.10 (m, 6H), 5.71–5.83 (m, 3H).$^{13}$C NMR ($CDCl_3$, 125 MHz): δ = 26.4 ($CH_2$), 27.4 ($CH_2$), 33.3 ($CH_2$), 37.2 ($CH_2$), 40.2 (CH), 42.6 (CH), 59.8 (CH), 63.1(CH), 114.1 ($CH_2$), 115.0 ($CH_2$), 115.4 ($CH_2$), 138.3 (CH), 139.9 (CH), 141.7 (CH), 169.0 (C). HRMS (ESI, Q-ToF) *m/z*: found $[M+Na]^+$ = 254.1515, calculated = 254.1516 for $C_{16}H_{23}NO$. IR: 2932, 1475, 1334, 1168, 917, 754.

## ACKNOWLEDGEMENTS

We are thankful to the Department of Science and Technology (EMR/2015/002053), New Delhi and CSIR

(02(0272)/16/EMR-II), New Delhi for financial support. SP thanks UGC, New Delhi for financial support and the awarding of a SRF. SK thanks the DST for the awarding J. C. Bose fellowship (SR/S2/JCB-33/2010). We are also thankful to Praj industries for Pramod Chaudhari Chair Professor (Green Chemistry). SP would like to thank Department of Chemistry, IIT Bombay for computational facility. YD would like to thank DST-SERB, New Delhi [PDF/2016/003115] for 'National Postdoctoral Fellowship'.

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