Synthesis of spiro-pyridopyridine analogues by Grubbs' catalyst mediated alkene and enyne metathesis reaction†

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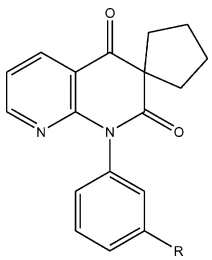
A practical synthesis of spiro-naphthyridinone derivatives is described by the combination of the Claisen rearrangement and ring-closing metathesis/ring-closing enyne metathesis process. The RCM or RCEM proceeded smoothly in the presence of Grubbs' first generation catalyst at room temperature under a nitrogen atmosphere.

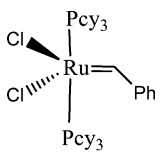
Of the six isomeric pyridopyridines, 1,8-naphthyridine derivatives have received considerable attention in the last 15 years. This class of compounds has attracted considerable attention primarily due to the presence of a 1,8-naphthyridine skeleton in many compounds which have been isolated from natural substances and exhibit various biological activities. Substituted naphthyridines are used for combating exo- and endo-parasites in agriculture and in cattle breeding, as preservatives and ingredients of cutting fluids, and also as ligands in analytical chemistry.[1] Compounds in these classes exhibit fungicidal activity against phytopathogenic fungi and some of these patent drugs are used for the treatment of memory loss, aging and Alzheimer's disease and also as antiallergic agents.[2] In particular, naphthyridines and spiro-naphthyridinones are useful for suppressing the immune response and in the treatment of autoimmune and other immune disorders.[3] Compound **1a** had an ED50 of 0.13 mg topically in the arachidonic acid mouse ear test, a measure of its utility in the treatment of hyperproliferative skin diseases.[4] Compound **1b** was used to treat arachidonic acid induced edema by 82% in comparison to a non-treated control. An ointment was prepared for these diseases, which contained compound **1** with benzyl alcohol, mineral oil and white petroleum base.[5]



1a R = H
1b R = Cl

The synthetic procedure for the patent compound **1** is quite complicated. They were synthesized from a complex starting material, ethyl 2-[(3,4-dichlorophenyl)amino]-3-pyridinecarboxylate. A mixture of ethyl 2-[(3,4-dichlorophenyl)amino]-3-pyridinecarboxylate, γ-valerolactone, and $KOCMe_3$ was heated at 110 °C for 5 h to afford substituted hydroxynaphthyridinone. Finally the hydroxynaphthyridin-2(1*H*)-one was heated with Eaton's reagent to give the corresponding spiro-naphthyridinone **1**.[4]

Our strategy is based on the tandem Claisen rearrangement and RCM/RCEM protocol. Recently ring closing metathesis[6] and ring closing enyne metathesis[7] has been proved to be highly effective for the synthesis of different ring compounds from acyclic diene or dienyne precursors. RCM is very high yielding, easier to perform and tolerant of a wide variety of functional groups. In the RCM process, the ring-closed products lack the number of carbon atoms but the RCEM has its advantage in that it is an atom economical reaction. This success hinges on the development of a well-defined catalyst such as Grubbs' catalyst **A**[8] and its functional group tolerance. Hence it appeared to us that the combination of a Claisen rearrangement and RCM/RCEM could be a synthetic strategy to prepare various spiro-naphthyridinone analogues. Herein we wish to report our results. The retro-synthetic analysis of the title compound **1** is summarized in Scheme 1.



A

Compounds **2**, **3**, **4** and **5** were prepared according to our previously published procedure.[9] The *O*,*C*-dialkylated products **5** in refluxing chlorobenzene for 3 h afforded the corresponding *C*,*C*-dialkylated product **6** in 90% yield (Scheme 2). Also a simple alkylation of compound **2** with allyl bromide (2 equivalents) in refluxing dry acetone in the presence of anhydrous K_2CO_3 for about 40 h afforded *C*,*C*-diallylated product (20–22%) (**6**) along with the *O*,*C*-diallylated product (**5**) (Scheme 3).

Initially we have focused our attention on the synthesis of spiro-annulated heterocyclic products *via* the ring closing metathesis process. To test this premise, a dichloromethane solution of the compound **6a** and Grubbs' catalysts **A** (10 mol %) was stirred at room temperature under a nitrogen atmosphere for 7 h. Usual workup of the reaction mixture afforded the corresponding spiro-derivative **7a** in 92% yield (Scheme 4). Similarly **7b** was obtained from **6b** in 90% yield.

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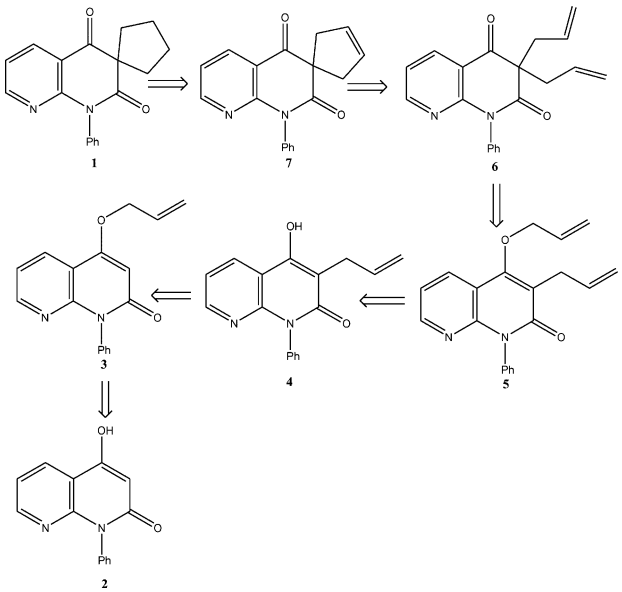
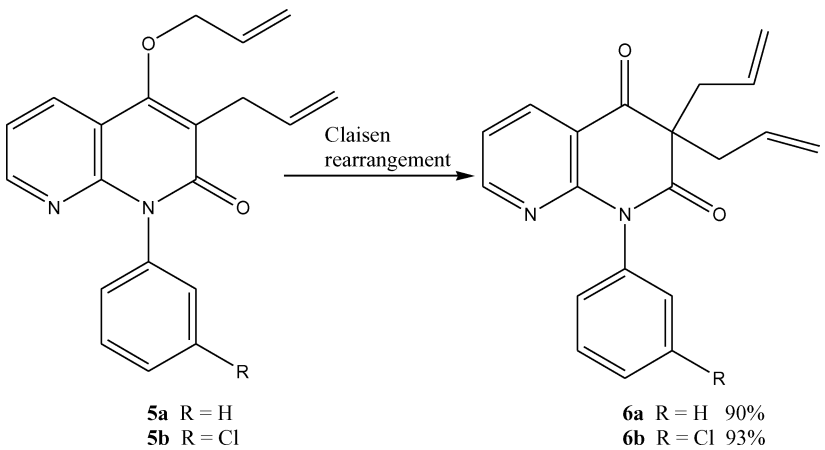
† Electronic supplementary information (ESI) available: Mass spectrum of **7a** and ^{1}H NMR of **7a** and **10a**. See DOI: 10.1039/b603125k



Scheme 1

The spiroheterocycles **7a,b** were characterized from their elemental analyses and spectroscopic data. Compound **7a** showed a two-proton singlet at δ5.64 indicating the presence of two olefinic protons and two non-equivalent doublets at δ3.08–3.12 (two protons) and δ3.16–3.20 (two protons) indicating the methylene protons in the five-membered ring. Encouraged by the results of the RCM of dienes **6a,b**, we undertook a study of the synthesis of substituted spiro-derivatives *via* the ring closing enyne metathesis. Synthesis of the RCEM precursors is depicted in Scheme 5. Straightforward alkylation of compound **4** with 2 equivalents of propargyl bromide/1-aryloxy-4-chlorobut-2-yne **8a–d** in refluxing acetone for 7–8 h afforded the corresponding *C*,*C*-dienyne derivatives **9a–d** in 30–40% yield along with *O*,*C*-dialkylated products. The desired dienynes **9a–d** were easily separated by column chromatography over silica gel using 9 : 1 petroleum ether–ethyl acetate as eluant.

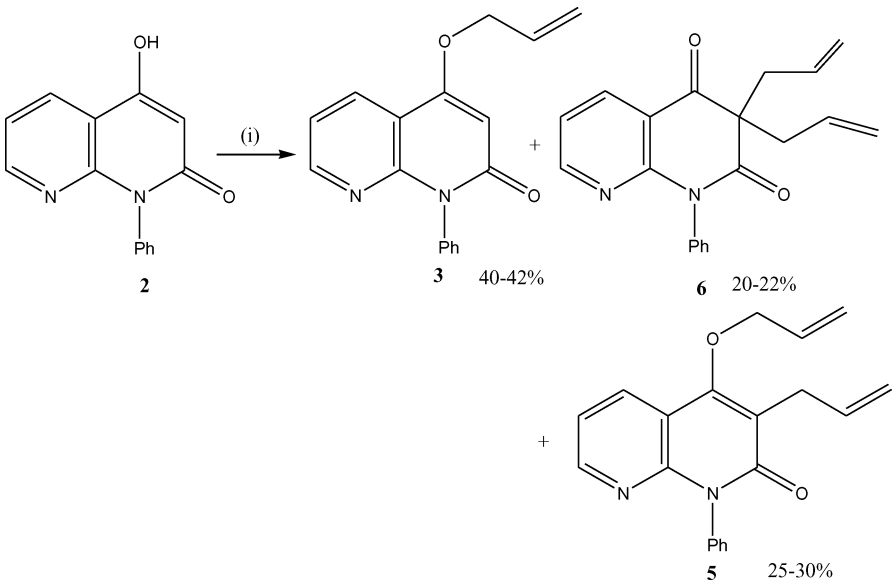
The analogous substituted spiro-naphthyridinone derivatives **10a–d** were prepared by conventional RCEM procedure. When a dichloromethane solution of **9a** and the Grubbs' catalyst **A** was stirred at room temperature for 4 h under a nitrogen atmosphere, the desired vinyl substituted **10a** was obtained in 85% yield.



5a R = H
5b R = Cl

6a R = H 90%
6b R = Cl 93%

Scheme 2



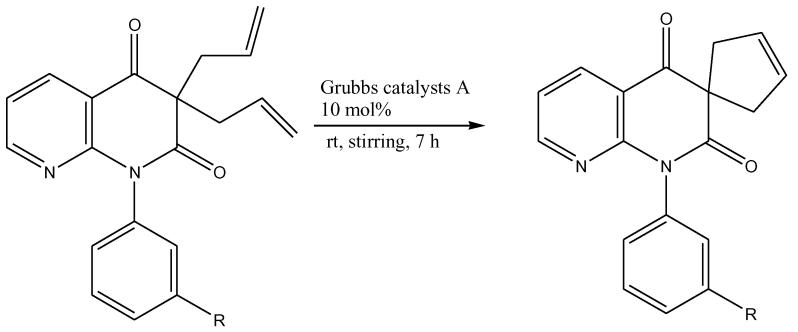
2

3 40-42%

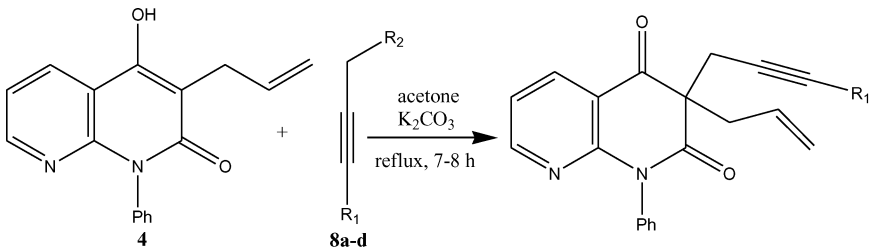
6 20-22%

5 25-30%

Scheme 3 Reagents and reaction conditions: (i) Dry acetone, K_2CO_3, allyl bromide (2 equiv.), reflux, 40 h.

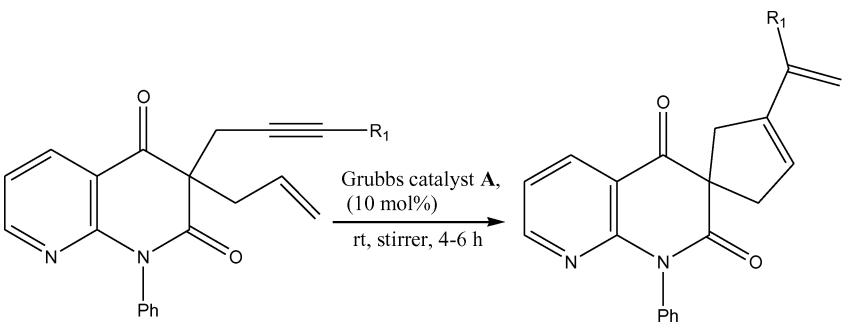


Scheme 4



	R_1	R_2	Yield(%)
9a	H	Br	30
9b	$-CH_2-O-C_6H_4CH_3$	Cl	32
9c	$-CH_2-O-C_6H_4Cl$	Cl	38
9d	$-CH_2-O-C_6H_3Cl_2$	Cl	40

Scheme 5



	R_1	Yield(%)
10a	H	85
10b	$-CH_2-O-C_6H_4CH_3$	92
10c	$-CH_2-O-C_6H_4Cl$	96
10d	$-CH_2-O-C_6H_3Cl_2$	93

Scheme 6

Similarly other spiroheterocycles **10b–d** were obtained in 92–96% yield from **9b–d** (Scheme 6).

Thus we have demonstrated a synthetic strategy for the preparation of spiro-naphthyridinone derivatives *via* the RCM and RCEM protocol. The biological activity of the compound **1** is well known and recently, it has been used as a drug for hyperproliferative skin diseases. Hence its analogous derivatives (substituted or unsubstituted) may be potentially bioactive compounds. Our RCM/RCEM protocol for the synthesis of target molecules is facile and the yield of the products is excellent. Therefore, we believe that our procedure is superior to the previously reported one.

Experimental

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (400 MHz) and ^{13}C NMR (125.7 MHz) spectra were recorded on AVANCE-400 and Bruker DPX-500 spectrometers in $CDCl_3$ (chemical shifts in δ) with TMS as internal standard. Elemental analyses and mass spectra were recorded on a Leco 932 CHNS analyzer and on a JEOL JMS-600 instrument respectively. ^1H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata, Bose Institute, Kolkata and Chembiotek Research International, Kolkata. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60–80 °C. The 1-aryloxy-4-chlorobut-2-ynes **8a–d** were prepared according to the published procedure.[10]

General procedure for the preparation of compounds 6a,b

Compounds **5a,b** (300 mg) were refluxed in chlorobenzene (4 ml) for 3 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. Chlorobenzene was eluted out with petroleum ether. When the column was eluted with 10% ethyl acetate–petroleum ether, compounds **6a,b** were obtained in 90–93% yield.

Compound 6a. Yield: 90%; white crystalline solid; mp 108–110 °C; IR (KBr) ν_{max}: 2923, 1698, 1668, 1585 cm^{-1}; UV (EtOH) λ_{max}: 333, 262, 224 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.82–2.83 (d, $J = 6.4$ Hz, 4H, $-CH_2-$), 5.01–5.03 (d, $J = 9.6$ Hz, 2H, $=CH_2$), 5.09–5.14 (d, $J = 17.2$ Hz, 2H, $=CH_2$), 5.59–5.70 (m, 2H, –CH=), 7.05–7.23 (m, 3H, ArH), 7.42–7.45 (t, $J = 7.6$ Hz, 1H, ArH), 7.49–7.52 (t, $J = 7.6$ Hz, 2H, ArH), 8.25–8.27 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H, ArH), 8.38–8.40 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H, ArH), MS: $m/z =$ 318 (M^+); Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66; N, 8.80%. Found: C, 75.68; H, 5.84; N, 8.66%.

Compound 6b. Yield: 93%; white crystalline solid; mp 108–110 °C; IR (KBr) ν_{max}: 2923, 1698, 1668, 1585 cm^{-1}; UV (EtOH) λ_{max}: 333, 262, 224 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.83–2.84 (d, $J = 6.4$ Hz, 4H, $-CH_2-$), 5.01–5.03 (d, $J = 9.6$ Hz, 2H, $=CH_2$), 5.11–5.15 (d, $J = 17.2$ Hz, 2H, $=CH_2$), 5.59–5.71 (m, 2H, –CH=), 7.07–7.25 (m, 2H, ArH), 7.43–7.47 (t, $J = 7.6$ Hz, 1H, ArH), 7.49–7.52 (t, $J = 7.6$ Hz, 2H, ArH), 8.26–8.28 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H, ArH), 8.38–8.40 (dd, $J = 1.6$ Hz, 4.8 Hz, 1H, ArH), MS: $m/z =$ 354, 352 (M^+); Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.82; N, 7.94%. Found: C, 68.30; H, 4.96; N, 8.11%.

General procedure for the preparation of compounds 9a–d

A mixture of 3-allyl-4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**4**) (2 mmol), 2 equivalents of propargyl bromide/1-aryloxy-4-chlorobut-2-yne **8a–d** and anhydrous K_2CO_3 (2 g) was refluxed in dry acetone (60 ml) for 7–8 h. The reaction mixture was cooled and filtered. Removal of solvent from the filtrate gave a gummy mass. This was subjected to column chromatography over silica gel. Elution of the column with petroleum ether–ethyl acetate (9 : 1) furnished compounds **9a–d**.

Compound 9a. Yield: 30%; white crystalline solid; mp 135–137 °C; IR (KBr) ν_{max}: 3285, 3267, 2921, 1702, 1668, 1586, 1435, 1358 cm^{-1}; UV (EtOH) λ_{max}: 333, 263, 227 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.91–1.92 (t, $J = 2.3$ Hz, 1H), 2.76–2.78 (d, $J = 7.3$ Hz, 2H, $-CH_2$), 2.93 (d, $J = 1.9$ Hz, 2H, $-CH_2$), 5.05–5.08 (d, $J = 10.1$ Hz, 1H, $=CH_2$), 5.12–5.17 (d, $J = 16.6$ Hz, 1H, $=CH_2$), 5.60–5.66 (m, 1H, –CH=), 7.09–7.13 (dd, $J = 4.7$ Hz, 7.5 Hz, 1H, ArH), 7.21–7.25 (m, 2H, ArH), 7.45–7.48 (t, $J = 7.2$ Hz, 1H, ArH), 7.52–7.56 (t, $J = 7.2$ Hz, 2H, ArH), 8.31–8.33 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H, ArH), 8.43–8.45 (dd, $J = 1.6$ Hz, 4.5 Hz, 1H, ArH); MS: $m/z = 316$ (M^+); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86%. Found: C, 75.76; H, 4.85; N, 9.09%.

Compound 9b. Yield: 32%; white crystalline solid; mp 94–96 °C; IR (KBr) ν_{max}: 2922, 1698, 1668, 1586 cm^{-1}; UV (EtOH) λ_{max}: 335, 264, 225 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.19 (s, 3H, $-CH_3$), 2.73–2.75 (d, $J = 7.3$ Hz, 2H, $-CH_2$), 2.95 (s, 2H, $-CH_2$), 4.37–4.41 (d, $J = 15.6$ Hz, 1H), 4.45–4.49 (d, $J = 15.6$ Hz, 1H), 5.03–5.05 (d, $J = 10$ Hz, 1H, $=CH_2$), 5.10–5.14 (d, $J = 17$ Hz, 1H, $=CH_2$), 5.55–5.63 (m, 1H, =CH–), 6.60–6.62 (d, $J = 8.4$ Hz, 2H, ArH), 6.86–6.88 (d, $J = 8.2$ Hz, 2H, ArH), 7.04–7.07 (m, 3H, ArH), 7.42–7.48 (m, 3H, ArH), 8.23–8.25 (dd, $J = 1.6$ Hz, 7.6 Hz, 1H, ArH), 8.38–8.40 (dd, $J = 1.6$ Hz, 4.5 Hz, 1H, ArH); MS: $m/z =$ 436 (M^+); Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.06; H, 5.50; N, 6.42%. Found: C, 77.26; H, 5.69; N, 6.20%.

Compound 9c. Yield: 38%; white crystalline solid; mp 90–92 °C; IR (KBr) ν_{max}: 2921, 1698, 1668, 1585 cm^{-1}; UV (EtOH) λ_{max}: 335, 264, 223 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.71–2.73 (d, $J = 7.3$ Hz, 2H, $-CH_2$), 2.96 (s, 2H, $-CH_2$), 4.39–4.43 (d, $J = 15.8$ Hz, 1H), 4.50–4.54 (d, $J = 15.8$ Hz, 1H), 5.03–5.05 (d, $J = 10.1$ Hz, 1H, $=CH_2$), 5.10–5.14 (d, $J = 16.8$ Hz, 1H, $=CH_2$), 5.55–5.62 (m, 1H, =CH–), 6.63–6.65 (d, $J = 8.8$ Hz, 2H, ArH), 6.98–7.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.05–7.09 (m, 3H, ArH), 7.44–7.52 (m, 3H, ArH), 8.29–8.32 (dd, $J = 1.2$ Hz, 7.4 Hz, 1H, ArH), 8.44–8.45 (d, $J = 2.9$ Hz, 1H, ArH) MS: $m/z = 458$, 456 (M^+); Anal. Calcd for $C_{27}H_{21}ClN_2O_3$: C, 70.97; H, 4.60; N, 6.13%. Found: C, 70.73; H, 4.76; N, 6.34%.

Compound 9d. Yield: 40%; colorless solid; mp 101–103 °C; IR (KBr) ν_{max}: 2921, 1696, 1668, 1584 cm^{-1}; UV (EtOH) λ_{max}: 333, 264, 221 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.71–2.73 (d, $J = 7.3$ Hz, 2H, $-CH_2$), 2.94 (s, 2H, $-CH_2$), 4.38–4.42 (d, $J = 15.8$ Hz, 1H), 4.52–4.56 (d, $J = 15.8$ Hz, 1H), 5.01–5.03 (d, $J = 10.1$ Hz, 1H, $=CH_2$), 5.10–5.14 (d, $J = 16.8$ Hz, 1H, $=CH_2$), 5.55–5.63 (m, 1H, –CH=), 6.66–6.68 (d, $J = 8.8$ Hz, 2H, ArH), 6.98–7.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.05–7.11 (m, 3H, ArH), 7.44–7.57 (m, 2H, ArH), 8.24–8.26 (dd, $J = 1.2$ Hz, 7.4 Hz, 1H, ArH), 8.41–8.43 (d, $J = 2.9$ Hz, 1H, ArH); MS: $m/z = 494$, 492, 490 (M^+); Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_3$: C, 65.98; H, 4.07; N, 5.70%. Found: C, 66.18; H, 4.28; N, 5.93%.

Typical procedure for ring closing metathesis reaction for the preparation of compounds 7 and 10

To a solution of substrate **6a** (50 mg, 0.158 mmol) in dry degassed CH_2Cl_2 (8 ml) under N_2 was added catalyst **A** (10 mol%, 13 mg)

and the reaction was stirred at room temperature for 4 h. After the removal of the solvent, the residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 4 : 1) to give **7a** in 92% yield. The diene **6b** and dienynes **9a–d** were treated in a similar manner to give the corresponding cyclized products **7b** and **10a–d** in excellent yield.

Compound 7a. Yield: 92%; white solid; mp 230–232 °C; IR (KBr) ν_{max}: 2925, 1708, 1671, 1584 cm^{-1}; UV (EtOH) λ_{max}: 326, 261, 219 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.08–3.12 (d, J = 15.5 Hz, 2H, $-CH_2$), 3.16–3.20 (d, J = 15.5 Hz, 2H, $-CH_2$), 5.64 (s, 2H, –CH=CH–), 7.09–7.12 (m, 1H, ArH), 7.21–7.24 (m, 2H, ArH), 7.43–7.47 (t, J = 7.3 Hz, 1H, ArH), 7.51–7.55 (t, J = 7.3 Hz, 2H, ArH), 8.28–8.31 (dd, J = 1.3 Hz, 7.6 Hz, 1H, ArH), 8.43–8.44 (dd, J = 1.3 Hz, 4.3 Hz, 1H, ArH); MS: m/z = 290 (M^+); Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65%. Found: C, 74.67; H, 5.05; N, 9.82%.

Compound 7b. Yield: 90%; white solid; mp 221–223 °C; IR (KBr) ν_{max}: 2923, 1706, 1674, 1583 cm^{-1}; UV (EtOH) λ_{max}: 325, 261, 217 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.08–3.12 (d, J = 15.4 Hz, 2H, $-CH_2$), 3.15–3.19 (d, J = 15.5 Hz, 2H, $-CH_2$), 5.65 (s, 2H, –CH=CH–), 7.12–7.15 (m, 2H, ArH), 7.23 (s, 1H, ArH), 7.42–7.48 (m, 2H, ArH), 8.29–8.31 (dd, J = 1.5 Hz, 7.6 Hz, 1H, ArH), 8.43–8.44 (dd, J = 1.5 Hz, 4.5 Hz, 1H, ArH); MS: m/z = 326, 324 (M^+); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.56; H, 4.00; N, 8.62%. Found: C, 66.75; H, 4.21; N, 8.87%.

Compund 10a. Yield: 85%; white crystalline solid; mp 182–184 °C; IR (KBr) ν_{max}: 2918, 1709, 1675, 1583 cm^{-1}; UV (EtOH) λ_{max}: 316, 263, 223 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.14–3.28 (m, 4H, $-CH_2$), 5.04–5.12 (m, 2H, $=CH_2$), 5.60 (s, 1H, =CH), 6.48–6.55 (dd, J = 10.7 Hz, 17.4 Hz, 1H, =CH–), 7.10–7.13 (dd, J = 4.8 Hz, 7.4 Hz, 1H, ArH), 7.21–7.24 (m, 2H, ArH), 7.44–7.47 (t, J = 7.3 Hz, 1H, ArH), 7.51–7.55 (t, J = 7.3 Hz, 2H, ArH), 8.28–8.31 (dd, J = 1.4 Hz, 7.6 Hz, 1H, ArH), 8.43–8.45 (dd, J = 1.4 Hz, 4.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 125.7 MHz): 40.6, 42.7, 62.9, 115.4, 115.7, 119.5, 126.3, 128.9, 129.2, 129.9, 132.5, 137.2, 137.4, 139.8, 154.6, 155.5, 174.0, 194.5, MS: m/z = 316 (M^+); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86%. Found: C, 76.16; H, 5.26; N, 8.62%.

Compound 10b. Yield: 92%; colorless solid; mp 152–154 °C; IR (KBr) ν_{max}: 2921, 1714, 1678, 1582 cm^{-1}; UV (EtOH) λ_{max}: 356, 265, 224 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, $-CH_3$), 3.20–3.39 (m, 4H, $-CH_2$), 4.68 (s, 2H, $-OCH_2$), 5.13 (s, 1H, =CH), 5.34 (s, 1H, =CH), 5.72 (s, 1H, =CH), 6.80–6.83 (d, J = 8.4 Hz, 2H, ArH), 7.05–7.07 (d, J = 8.2 Hz, 2H, ArH), 7.11–7.14 (dd, J = 4.8 Hz, 7.4 Hz, 1H, ArH), 7.22–7.25 (m, 2H, ArH), 7.44–7.48 (t, J = 7.2 Hz, 1H, ArH), 7.52–7.55 (t, J = 7.2 Hz, 2H, ArH), 8.29–8.31 (dd, J = 1.4 Hz, 7.5 Hz, 1H, ArH), 8.44–8.45 (dd, J = 1.4 Hz, 4.4 Hz, 1H, ArH);^{13}C NMR ($CDCl_3$, 125.7 MHz): 20.8, 42.4, 43.3, 62.3, 69.4, 115.1, 115.2, 115.5, 119.6, 123.3, 129.0, 129.2, 130.0, 130.2, 130.6, 137.2, 137.4, 137.8, 138.6, 154.6, 155.5, 156.9, 173.9, 194.4; MS: m/z = 436 (M^+); Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.06; H, 5.50; N, 6.42%. Found: C, 77.31; H, 5.71; N, 6.28%.

Compound 10c. Yield: 96%; white solid; mp 146–148 °C; IR (KBr) ν_{max}: 2917, 1715, 1680, 1582 cm^{-1}; UV (EtOH) λ_{max}: 320, 261, 225 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.21–3.39 (m, 4H, $-CH_2$), 4.68 (s, 2H, $-OCH_2$), 5.15 (s, 1H, $=CH_2$), 5.32 (s, 1H, $=CH_2$), 5.70 (s, 1H, =CH–), 6.83–6.85 (d, J = 8.8 Hz, 2H, ArH), 7.11–7.14 (dd, J = 4.8 Hz, 7.5 Hz, 1H, ArH), 7.20–7.25 (m, 4H, ArH), 7.44–7.47 (t, J = 7.3 Hz, 1H, ArH), 7.52–7.56 (t, J = 7.3 Hz, 2H, ArH), 8.29–8.32 (dd, J = 1.5 Hz, 7.6 Hz, 1H, ArH), 8.44–8.45 (dd, J = 1.5 Hz, 4.5 Hz, 1H, ArH); MS: m/z = 458, 456 (M^+); Anal. Calcd for $C_{27}H_{21}ClN_2O_3$: C, 70.97; H, 4.60; N, 6.13%. Found: C, 71.15; H, 4.81; N, 5.89%.

Compound 10d. Yield: 93%; white crystalline solid; mp 162–164 °C; IR (KBr) ν_{max}: 2921, 1713, 1683, 1585 cm^{-1}; UV (EtOH) λ_{max}: 322, 261, 221 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.21–3.38 (m, 4H, $-CH_2$), 4.68 (s, 2H, $-OCH_2$), 5.14 (s, 1H, $=CH_2$), 5.30 (s, 1H, $=CH_2$), 5.70 (s, 1H, =CH–), 6.82–6.84 (d, J = 8.8 Hz, 2H, ArH), 7.10–7.13 (dd, J = 4.8 Hz, 7.5 Hz, 1H, ArH), 7.22–7.27 (m, 4H, ArH), 7.40–7.46 (t, J = 7.3 Hz, 1H, ArH), 7.51–7.55 (t, J = 7.3 Hz, 2H, ArH), 8.29–8.31 (dd, J = 1.5 Hz, 7.6 Hz, 1H, ArH), 8.44–8.46 (dd, J = 1.5 Hz, 4.5 Hz, 1H, ArH); MS: m/z = 494, 492, 490 (M^+); Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_3$: C, 65.98; H, 4.07; N, 5.70%. Found: C, 65.75; H, 4.25; N, 5.91%.

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