JOC Article

Highly Selective Synthesis of Bicyclic Quinolizidine Alkaloids and Their Analogues via Double RCM Reaction of *N*-Alkynyl-*N*-(1,ω)-alkadienyl Acrylamides

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The double ring-closing metathesis reaction of *N*-alkynyl-*N*-(1,ω)-alkadienyl acrylamides **1** using first- or second-generation Grubbs' catalyst afforded, in a highly selectively manner, the fused bicyclic quinolizidine alkaloid derivatives and their analogues bearing a 1,3-diene moiety, which may further undergo a Diels−Alder reaction with a dienophile to afford N-containing polycyclic compounds. The excellent selectivity of fused/dumbbell-mode cyclization has been realized by the higher reactivity of the electron-rich C=C bond or carbon−carbon triple bond combined with the lower reactivity of the electron-deficient C=C bond toward metallocarbenes and the thermodynamically more stable nature of fused bicyclic compounds **3** vs dumbbell-type bicyclic compounds **4**.

Introduction

During the past decade, the transition metal-catalyzed metathesis reaction has emerged as one of the most powerful methods in synthetic organic chemistry.[1] The ring-closing metathesis (RCM) reaction has been widely used for the construction of complex cyclic compounds, including natural products. Recently, many applications of double RCM reactions of tetraenes have been explored to provide bicyclic systems[2−4] from acyclic precursors in just "one shot". One formidable challenge in multi-RCM reactions is the selectivity between the combination of multi-RCM reactions of different C=C bonds, which was realized by the unfavorable formation of certain rings in these reported cases.

Fused bicyclic lactams having quinolizidine alkaloid skeletons are commonly observed structural units of many important compounds, which display a broad range of interesting biological activities.[5] For this reason, the construction of fused bicyclic lactam skeletons has attracted much attention among synthetic organic chemists. In our previous study of the double RCM reaction of *N*-alkenyl-*N*-alkadienyl acrylamides, we observed that the selectivity of fused/dumbbell-type products can be controlled by the nature of the catalyst, the electronic/steric effects of the C=C bonds, and the *s*-cis/*s*-trans conformational ratios of the substrates (Scheme 1).[6] In

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SCHEME 1

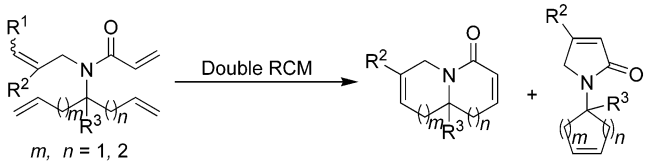
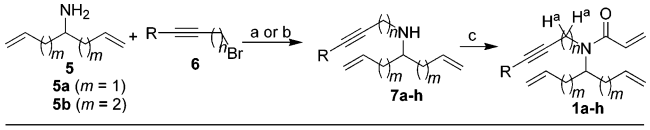


TABLE 1. Synthesis of Trienynes 1[a]



entry	5	6 (R)	reaction conditions	(m, n)	yield (%) of 1 (s-cis:s-trans)
1	**5a**	**6a** (H)	a and c	(1, 1)	72 (**1a**) (43:57)
2	**5a**	**6b** (Me)	a and c	(1, 1)	51 (**1b**) (36:64)
3	**5a**	**6c** (*n*-Pr)	b and c	(1, 1)	41 (**1c**) (40:60)
4	**5a**	**6d** (*n*-C_5H_{11})	a and c	(1, 1)	65 (**1d**) (26:74)
5	**5a**	**6e** ($EtOCH_2$)	b and c	(1, 1)	16 (**1e**) (40:60)
6	**5a**	**6f** (*n*-Bu)	b and c	(1, 2)	57 (**1f**) (47:53)
7	**5b**	**6b** (Me)	b and c	(2, 1)	26 (**1g**) (43:57)
8	**5b**	**6d** (*n*-C_5H_{11})	b and c	(2, 1)	41 (**1h**) (36:64)

[a] Conditions: (a) $CsOH·H_2O$ (1 equiv), 4 Å MS, DMF, 23 °C; (b) K_2CO_3 (2 equiv), DMF, 0 °C−rt; (c) CH_2=CHCOCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, −78 °C−rt.

most cases, the fused bicyclic products were formed highly selectively.

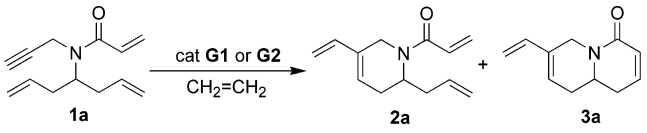
Due to the high reactivity of the C=C bond or C−C triple bond and the low reactivity of an electron-deficient C=C bond,[7] we imagined that in trienynes **1** the first reaction of a metallic carbene complex with the C−C triple bond and the C=C bond may lead to the formation of monocyclic intermediate **2**, which would undergo the second RCM reaction to afford fused bicyclic products **3**. In this paper, we report the successful realization of such a protocol of highly selective double RCM of trienynes **1**, which afforded fused quinolizidine alkaloids and their analogues **3** as the major product (Scheme 2).

Results and Discussion

N-Containing trienynes **1a**−**h**[8] were synthesized from N-propargylation of amine **5**[6] followed by the reaction with acryloyl chloride (Table 1).

To examine the feasibility of this approach, double RCM reaction of trienyne **1a** was investigated under

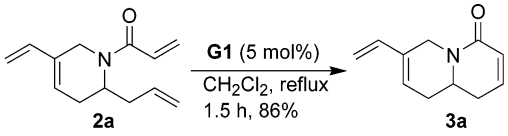
TABLE 2. Double RCM Reaction of 1a Using G1 or G2



entry	catalyst	conditions	time (h)	**2a** (%)	**3a** (%)
1	**G1** (5 mol %)	CH_2Cl_2/reflux	24	22	28
2	**G1** (10 mol %)	toluene/80°C	10	30	18
3[a]	**G2** (5 mol %)	CH_2Cl_2/reflux	13	11	−
4	**G2** (5 mol %)	CH_2Cl_2/reflux	14	−	23
5	**G2** (5 mol %)	toluene/80 °C	4.5	−	17
6	**G1** (5 + 5 mol %)	CH_2Cl_2/reflux	8	19	46
7	**G2** (5 + 5 mol %)	CH_2Cl_2/reflux	8	−	48

[a] Reaction was carried out under Ar.

various conditions (Table 2). The reaction of **1a** under the catalysis of 5 mol % **G1**[9] gave **3a** in a low yield along with monocyclic product **2a** (Table 2, entries 1 and 2), which can be converted to **3a** in 86% yield with 5 mol % **G1** in CH_2Cl_2 for 1.5 h (eq 1). However, when **1a** was treated with 5 mol % **G1** or **G2**[10] in CH_2Cl_2 for 4 h followed by the addition of another portion of 5 mol % **G1** or **G2** with continuous stirring for 4 h, **3a** was isolated in 46 and 48% yields, respectively (Table 2, entries 6 and 7).



(1)

Encouraged by the above results, the double RCM reaction of **1** with an internal C−C triple bond under the catalysis of **G1** or **G2** was investigated (Table 3). We were happy to find that the reaction of **1b** catalyzed by 5 mol % **G1** afforded **3b** in 50% yield (Table 3, entry 1). Furthermore, **G2** was found to be a superior catalyst for the reaction of **1b**−**c** and **1e** in CH_2Cl_2 under reflux to afford **3b**,**c** and **3e** in 53−69% yields, although 2 × 5 mol % **G2** should be applied for a high-yielding conversion of **1e** (Table 3, entries 2−4 and 6). Similar results were obtained for the synthesis of 7,7-bicyclic lactams **3g**,**h** in moderate yields (Table 3, entries 7 and 8). The synthesis of the bicyclic product with two different rings was demonstrated by the treatment of trienyne **1f** with 5 mol % **G2** for 7.5 h to give bicyclic fused lactam **3f** in 62%

SCHEME 2

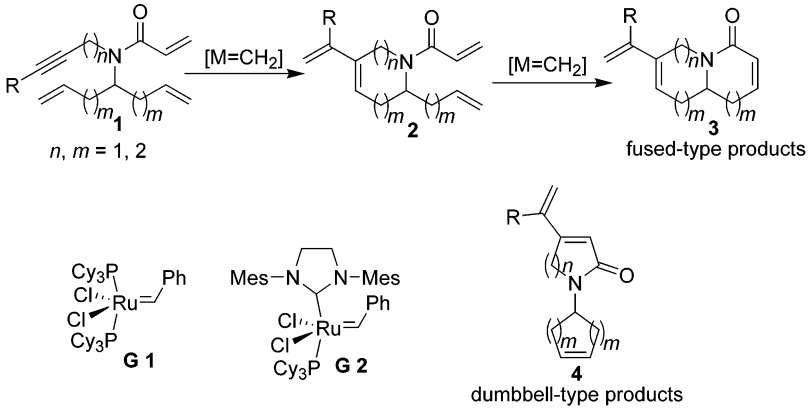
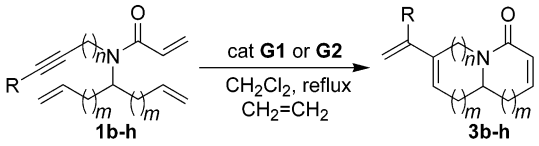


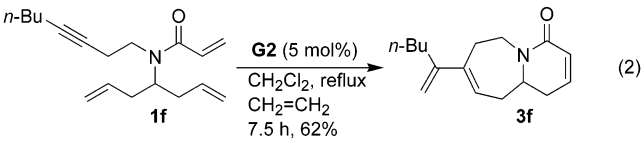
TABLE 3. Double RCM Reaction of 1b−h Using G1 or G2



entry	1 (R)	(*n*, *m*)	catalyst	time (h)	yield (%) of 3
1	**1b** (Me)	(1, 1)	**G1** (5 mol %)	10	50 (**3b**)
2	**1b** (Me)	(1, 1)	**G2** (5 mol %)	11	69 (**3b**)
3	**1c** (*n*-Pr)	(1, 1)	**G2** (5 mol %)	7	67 (**3c**)
4[a]	**1c** (*n*-Pr)	(1, 1)	**G2** (5 mol %)	7	56 (**3c**)
5	**1d** (*n*-C_5H_{11})	(1, 1)	**G2** (5 mol %)	8	75 (**3d**)
6	**1e** ($EtOCH_2$)	(1, 1)	**G2** (5 + 5 mol %)	10	53 (**3e**)
7	**1g** (Me)	(1, 2)	**G2** (5 mol %)	11	47 (**3g**)
8	**1h** (*n*-C_5H_{11})	(1, 2)	**G2** (5 mol %)	7.5	54 (**3h**)

[a] Reaction was carried out under Ar.

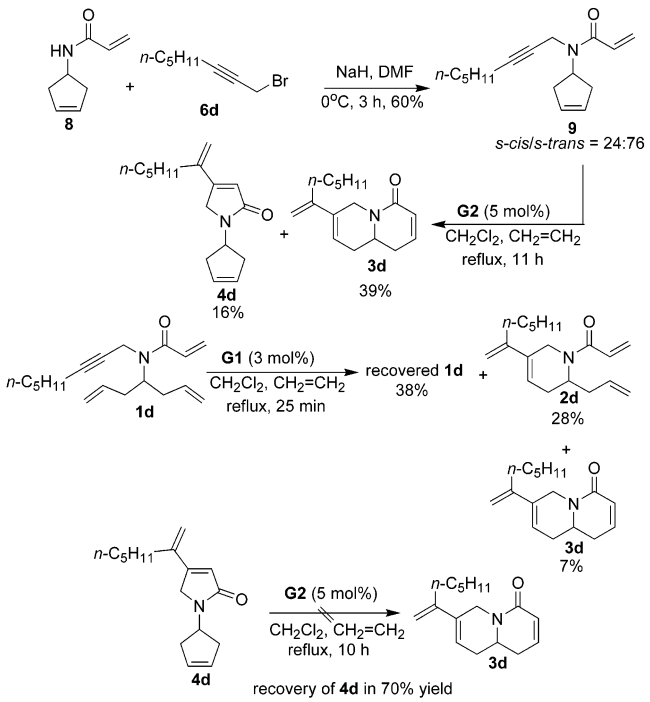
yield (eq 2), indicating that the fused bicyclic product was thermodynamically much more favorable than the dumbbell-type product **4**.[11]



(2)

To study the mechanism, monocyclic compound **9** was prepared from the N-2-alkynylation of **8**.[6] Its treatment with 5 mol % **G2** in CH_2Cl_2 in the presence of $CH_2{=}CH_2$ (1 atm) afforded the fused bicyclic product **3d** (39%) and the dumbbell-type bicycle **4d** (16%), which excluded the possibility of **9** being the intermediate for the double RCM reaction of trienynes **1** (Scheme 3). Judging from the results in eq 1, Table 2, and the results of an incomplete reaction of **1d** with **G1** (Scheme 3), it can be concluded that **2d**-type monocyclic compound is the predominant intermediate for this reaction, which determines the high selectivity for the formation of fused bicyclic products **3**. The results of the ROM/RCM of **9** and RCM reaction of **1d** using **G1** as a catalyst may be speculated by a combination of electronic and conformational factors of **9** and substrates **1**.[8] With the authentic

SCHEME 3



sample of **4d**, we were able to determine the selectivity of fused/dumbbell-type cyclization in the double RCM of **1d** to be >32:1 (**3d** yield, 75%; **4d** yield, 2.3%) by analysis of the ^{1}H NMR spectra for the crude product(s), which is much higher than what was observed in *N*-alkenyl-*N*-(1,ω)-alkadienyl acrylamides.[6] Treatment of isolated pure dumbbell-type product **4d** under the catalysis of **G2** in CH_2Cl_2 did not afford the fused bicyclic product of **3d**, indicating that **3d** was formed directly via the double RCM reaction. The different results for the treatment of **4d** and **9** with **G2** may be explained by the difficulty that the metallic carbene species formed by the ROM of a ring in **4d** would have in interacting with the C=C bond of the second ring.

The intramolecular enyne metathesis is particularly interesting because it can produce cyclic products containing a 1,3-diene moiety, which may undergo further reactions leading to polycyclic compounds.[12] For this, the synthesis of a various of N-containing polycyclic compounds by a Diels−Alder reaction of the cyclized product with a dienophile was studied, and the results are summarized in Table 4. When a solution of **2b−d** and *N*-phenylmaleimide **10a** in toluene was stirred at 60−70°C, the reaction proceeded smoothly to give the tetracyclic compounds **11ba−11da** in good yields. Two stereoisomers were observed in the ^{1}H NMR spectra, the ratio of which ranges from 4:1 to 5.7:1 (Table 4). To determine the stereochemistry of the major isomer, **2c** was treated with **10b** for 1.5 h, which afforded **11cb** as a solid in 76% yield with a distereomeric ratio of 4.3:1. After recrystallization, we obtained its pure major isomer **11cb-1**, the structure of which was unambiguously determined by an

(6) (a) Ma, S.; Ni, B. *Org. Lett*. **2002**, *4*, 639. (b) Ma, S.; Ni, B. *Chem. Eur. J*. **2004**, *10*, 3286.

(7) For a study on the relative reaction rate of olefin substrates with Ru carbenes, see: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484.

(8) Substrates **1a−h** display two different conformers, the ratios of which were determined by their ^{1}H NMR sprectra at room-temperature on the basis of different chemical shifts of protons H[a] in *s*-cis-**1** or *s*-trans-**1**. For the assignment of the ^{1}H NMR signals to *s*-cis/*s*-trans isomers, see: (a) Riggi, I. D.; Gastaldi, S.; Surzur, J. M.; Bertrand, M. P. *J. Org. Chem*. **1992**, *57*, 6118. (b) Stewart, W. E.; Siddall, T. H. *Chem. Rev*. **1970**, *70*, 517. (c) La Planche, L. A.; Rogers, M. T. *J. Am. Chem. Soc*. **1963**, *85*, 3728 and references therein. (d) Oki, M. In *Topics in Stereochemistry: Recent advances in Atropisomerism*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1983; Vol. 14, pp 1−82.

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(11) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.

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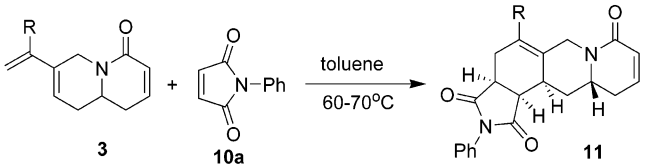
TABLE 4. Diels–Alder Reaction of 3 with *N*-Phenylmaleimide 10a



entry	**3** (R)	(*n*, *m*)	time (h)	yield (%) of **11** (isomeric ratio)
1	**3b** (Me)	(1, 1)	2	84 (**11ba**) (4:1)
2	**3c** (*n*-Pr)	(1, 1)	2	86 (**11ca**) (5.7:1)
3	**3d** (*n*-C_5H_{11})	(1, 1)	3	78 (**11da**) (5.3:1)

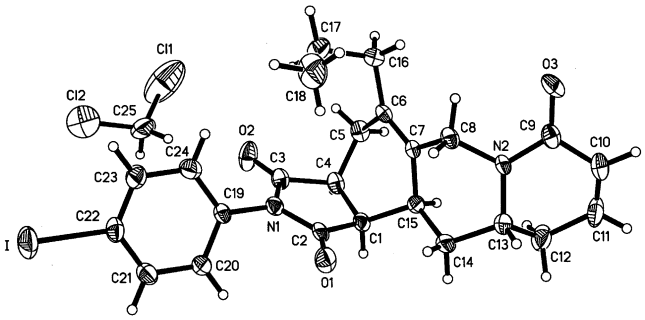
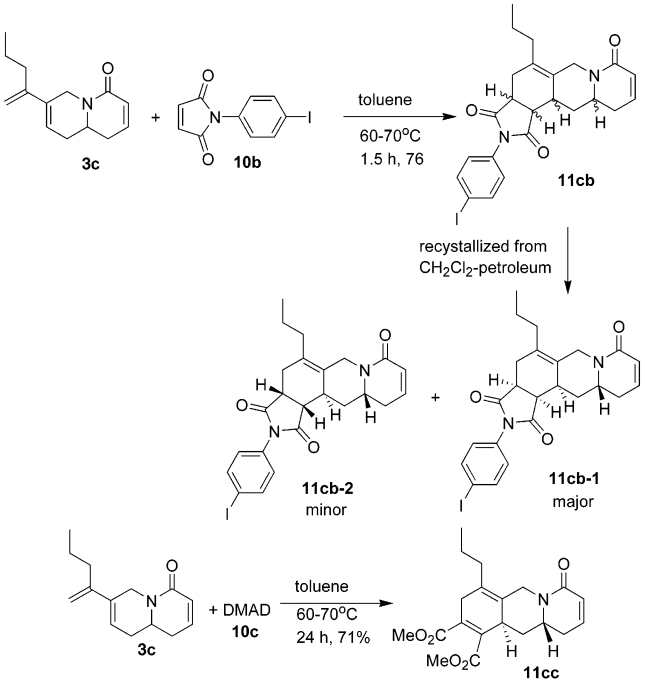


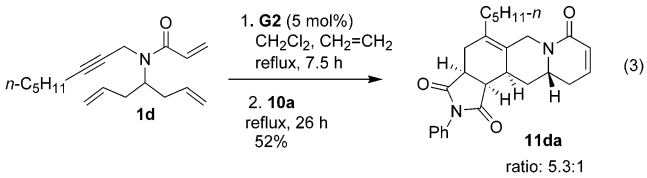
FIGURE 1. ORTEP representation of **11cb-1** with CH_2Cl_2 in the crystal.

SCHEME 4



X-ray diffraction study (Scheme 4, Figure 1).[13] Furthermore, when **2c** was treated with dimethyl acetylenedicarboxylate (DMAD) at 60–70°C for 24 h, the corresponding fused tricyclic product **11cc** was obtained as a single stereoisomer in 71% yield (Scheme 4). The relative stereochemistry of **11cc** was confirmed by the NOE experiment. Depending on the chemistry demonstrated in Scheme 4, we assigned the stereochemistry of the minor stereoisomer of **11cb** to be **11cb-2** (Scheme 4).

Furthermore, one-pot sequential double RCM of trienyne **1**/Diels–Alder reaction was studied. When double RCM reaction of **1d** was carried out under the same conditions as those shown in Table 3 (entry 4) followed by the addition of the dienophile *N*-phenylmaleimide **10a** to the reaction mixture, the product **11da** was obtained in 52% yield after stirring for 26 h under reflux (eq 3).



Conclusion

In summary, we have developed an efficient methodology for the synthesis of the fused-type bicyclic lactams having a 1,3-diene moiety by using ruthenium-catalyzed double RCM reaction of *N*-alkynyl-*N*-(1,ω)-alkadienyl acrylamides **1** in a very high selectivity. It was also demonstrated that the bicyclic lactams **3** are suitable substrates for the preparation of polycyclic quinolizidine and other alkaloid derivatives via further Diels–Alder reactions.

Experimental Section

(1) Synthesis of 1a (Typical Procedure A). To a suspension of activated powdered 4 Å molecular sieves (MS) (1.5 g) in anhydrous DMF (25 mL) was added $CsOH·H_2O$ (908 mg, 5.405 mmol) followed by vigorous stirring for 10 min. After the addition of amine **5a** (600 mg, 5.405 mmol), the reaction mixture was stirred for 30 min followed by the addition of propargyl bromide (772 mg, 6.486 mmol). After 4 h, the mixture was filtered to remove the molecular sieves and the undissolved inorganic salts, rinsed with petroleum ether, quenched with water, extracted with ether, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1 with a few drops of Et_3N) gave **7a** (645 mg, 80%) as a colorless oil, which was used for the next step directly without further characterization.

To a solution of **7a** (645 mg, 4.33 mmol) and Et_3N (0.90 mL, 6.50 mmol) in CH_2Cl_2 (6 mL) was added CH_2=CHCOCl (470 mg, 5.20 mmol) at −78 °C. After the addition, the reaction mixture was warmed to room temperature, quenched with water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ ethyl acetate = 5:1) gave **1a** (794 mg, 72% yield for two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75–6.47 (m, 2H), 5.83–5.60 (m, 3H), 5.20–4.95 (m, 4H), 4.88–4.70 (m, 0.57H), 4.15–3.85 (m, 2.43H), 2.53–2.10 (m, 5H); IR (neat) ν 3302, 2117, 1649, 1613, 1427 cm^{-1}; MS (ESI) *m*/*z* (%) 226.0 (M + Na^+), 204.1 (M + H^+); HRMS (ESI) calcd for $C_{13}H_{17}NONa$ 226.12079, found 226.12092.

(2) Synthesis of 1c (Typical Procedure B). To a solution of **5a** (700 mg, 6.306 mmol) and K_2CO_3 (1.740 g, 12.61 mmol) in DMF (15 mL) was added **6c** (1.015 g, 6.306 mmol) at 0 °C. After the addition, the reaction mixture was stirred for 1 h at 0 °C and then warmed to room temperature. After stirring for 3 h, the reaction mixture was quenched with water (10 mL), extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1 with a small

(13) Crystal data for **22e**-CH_2Cl_2: $C_{25}H_{27}N_2O_3Cl_2I$, M_w = 601.29, orthorhombic, space group *Pbca*, Mo Kα, final *R* indices [$I > 2\sigma(I)$] R_1 = 0.0673, wR_2 = 0.1784, a = 20.9249 (13) Å, b = 9.3581 (6) Å, c = 26.1944 (16) Å, α = 90°, β = 90°, γ = 90°, V = 5129.3 (6) Å^3, T = 293 (2) K, Z = 8, reflections collected/unique: 25 519/4762 (R_{int} = 0.0829), no observation ($I > 2.0\sigma(I)$) 3214, parameters 339, CCDC 218924.

amount of Et_3N) gave **7c** (656 mg, 54%) as a colorless oil, which was used for the next step directly without further characterization.

To a solution of **7c** (656 mg, 3.435) and Et_3N (0.72 mL, 5.153 mmol) in CH_2Cl_2 (12 mL) was added CH_2═CHCOCl (373 mg, 4.121 mmol) at −78 °C. After the addition, the reaction mixture was warmed to room temperature, quenched with water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Evaporation and flash column chromatography on silica gel (petroleum ether/ ethyl acetate = 8:1) gave **1c** (635 mg, 41% yield for two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79−6.44 (m, 1H), 6.41−5.60 (m, 4H), 5.18−4.92 (m, 4H), 4.82−4.68 (m, 0.67H), 4.15−3.80 (m, 2.33H), 2.58−2.20 (m, 4H), 2.18−2.05 (m, 2H), 1.60−1.40 (m, 2H), 1.00−0.80 (m, 3H); IR (neat) ν 2964, 1651, 1614 cm^{-1}; MS (ESI) *m*/*z* (%) 246.2 (M + H$^+$); HRMS (ESI) calcd for $C_{16}H_{23}NONa$ 268.16774, found 268.16730.

(3) Preparation of 3a (Typical Procedure C). To a solution of **1a** (100 mg, 0.493 mmol) in CH_2Cl_2 (10 mL) was added **G2** (21 mg, 5 mol %) under CH_2═CH_2. After the mixture was stirred under reflux for 4 h, another portion of **G2** (21 mg, 5 mol %) was added followed by continuous stirring (4 h); the resulting solution was concentrated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3a** (41 mg, 48%).

(4) Synthesis of 3b (Typical Procedure D). Grubbs' catalyst **G2** (16 mg, 5 mol %) was added to a solution of **1b** (80 mg, 0.369 mmol) in CH_2Cl_2 (7 mL) under an atmosphere of CH_2═CH_2 (1 atm). After the mixture was stirred under reflux for 11 h, the resulting solution was concentrated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3b** (48 mg, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (dt, J = 9.60 and 4.25 Hz, 1H), 5.92−5.80 (m, 2H), 5.00−4.85 (m, 3H), 3.77−3.60 (m, 2H), 2.78−2.60 (m, 1H), 2.58−2.40 (m, 1H), 2.30−2.03 (m, 2H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 140.3, 136.9, 134.7, 124.5, 121.6, 111.0, 50.7, 42.7, 31.6, 28.7, 20.4; IR (neat) ν 3480, 2896, 1671, 1611, 1429, 1257 cm^{-1}; MS (EI) *m*/*z* (%) 190 (M$^+$ + 1, 65.8), 189 (M$^+$, 94.9), 79 (100.0); HRMS (EI) calcd for $C_{12}H_{15}NO$ 189.11537, found 189.11139.

(5) Synthesis of 9. To a suspension of NaH (53 mg, 95% in paraffin oil, 2.10 mmol, 30 min) in DMF (4 mL) was added **8** (240 mg, 1.75 mmol). After the addition, the mixture was stirred for an additional 30 min at room temperature. Then, **6d** (397 mg, 2.10 mmol) was added. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with water, and the mixture was extracted with ether and washed with brine. The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product was further purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give **9** (259 mg, 60%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80−6.50 (m, 1H), 6.46−6.26 (m, 1H), 5.82−5.62 (m, 3H), 5.54−5.35 (m, 0.7H), 4.85−4.65 (m, 0.3H), 4.20−3.80 (m, 2H), 2.80−2.60 (m, 2.5H), 2.58−2.35 (m, 1.5H), 2.22−2.10 (m, 2H), 1.58−1.42 (m, 2H), 1.42−1.22 (m, 4H), 1.00−0.80 (m, 3H); IR (neat) ν 2931, 2858, 1653, 1613 cm^{-1}; MS (ESI) *m*/*z* (%) 246.2 (M + H$^+$); HRMS (ESI) calcd for $C_{16}H_{24}NO$ 246.18579, found 246.18498.

(6) Preparation of 11ba (Typical Procedure E). A solution of **3b** (20 mg, 0.106 mmol) and **10a** (110 mg, 0.636 mmol) in toluene (3 mL) was stirred at 60−70 °C for 2 h. The resulting solution was concentrated and purified by flash column chromatography on silica gel (ethyl acetate) to give **11ba** (32 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.30 (m, 3H), 7.20−7.05 (m, 2H), 6.58−6.45 (m, 1H), 6.00−5.86 (m, 1H), 5.16 (d, J = 16.25 Hz, 0.2 H) and 5.00 (d, J = 16.25 Hz, 0.8H), 4.06−3.90 (m, 1H), 3.60−3.18 (m, 3H), 2.80−1.70 (m, 10H); IR (neat) ν 1708, 1658, 1598 cm^{-1}; MS (EI) *m*/*z* (%) 362 (M$^+$, 86.97), 120 (100.00); HRMS (EI) calcd for $C_{22}H_{22}N_2O_3$ 362.16304, found 362.16588.

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Supporting Information Available: Analytical data for compounds **1**, **2a**,**d**, **3**, **4d**, and **11** and ^{1}H and ^{13}C NMR spectra of those compounds. X-ray data for **1cb-1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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