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Construction of furo[3,4-*c*]pyran skeleton starting from the Baylis–Hillman adducts via the ring-closing metathesis (RCM) reaction of *exo*-methylene tetrahydrofuran

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Abstract—Construction of furo[3,4-*c*]pyran ring skeleton was achieved starting from the Baylis–Hillman adducts. The synthesis was carried out by the successive introduction of propargyl alcohol, radical cyclization, reduction, allylation, and finally ring-closing metathesis reaction.

1. Introduction

Ring-closing metathesis (RCM) reaction is a powerful tool in modern chemistry due to its wide applicability in synthetic organic chemistry.[1–3] By using the RCM reaction tremendous cyclic compounds have been elegantly constructed including carbocyclic and heterocyclic rings.[1–3]

However, RCM reaction between the *exo*-methylene unit of cyclic compound and double bond of the appropriate tether has not been reported much.[4] Barrett and co-workers have reported the example, which dealt with the synthesis of C-19-functionalized 1α-hydroxyvitamin D2 analogues by the RCM reaction of *exo*-methylene compounds.[4a] In their report, they examined silicon and phosphorous tether in the reaction with methylene cyclohexane moiety. Botta and co-workers have used RCM reaction of methylenecyclohexane moiety in their synthesis of Taxuspine X in 20–25% yield.[4b] Fürstner and colleagues reported the successful RCM reaction of methylenecycloalkane derivatives with ruthenium carbene complexes with *N*,*N*-bis(mesityl)imidazole-2-ylidene ligand.[4c] To the best of our knowledge the RCM reaction of *exo*-methylene moiety with the double bond of oxygen atom-containing tether has not been published.

Although RCM reaction could provide very effective routes for the synthesis of a variety of fused heterocyclic compounds,[1–3] the synthesis of furo[3,4-*c*]pyran skeleton using RCM protocol has not been reported. Various furopyran nucleus has been known to constitute an essential part of many biologically important compounds.[5,6] The reported methods for the synthesis of furo[3,4-*c*]pyran nucleus were much limited and used either tungsten-mediated [3+3] cycloaddition of epoxides with tethered alkynes[5a,b] or intramolecular hetero-Diels–Alder reaction.[5c,d,f]

2. Results and discussion

Recently, we have reported the synthesis of 3,4-disubstituted 2,5-dihydrofuran derivatives from the triple bond-containing Baylis–Hillman adducts via radical cyclization and iodolactonization strategy.[7] Meantime we thought that the intermediate, methylene tetrahydrofuran derivative **2a** could be used for the construction of furo[3,4-*c*]pyran skeleton[5,6] of **5a** by using the RCM reaction as shown in Scheme 1.

exo-Methylene tetrahydrofuran **2a** was prepared as previously reported.[7] Reduction of **2a** with $LiAlH_4$ was conducted successfully to give **3a** in 80% yield. Allylation of **3a** was carried out (*t*-BuOK, THF, allyl bromide) to give the requisite starting material **4a** in 81% yield. The RCM reaction of **4a** in the presence of 5 mol% of Grubbs type II catalyst in CH_2Cl_2 at refluxing temperature afforded the desired furo[3,4-*c*]pyran compound **5a** in 92% yield. Although much steric crowdedness could be arisen at the transition state toward the formation of the corresponding intermediate, metallacyclobutane stage (shown in Fig. 1 in a simplified manner),[3d] the desired compound **5a** was synthesized in good yield.[5] In addition, **5a** could be

Keywords: Furo[3,4-*c*]pyran; Baylis–Hillman adducts; *exo*-Methylene tetrahydrofuran; Ring-closing metathesis.
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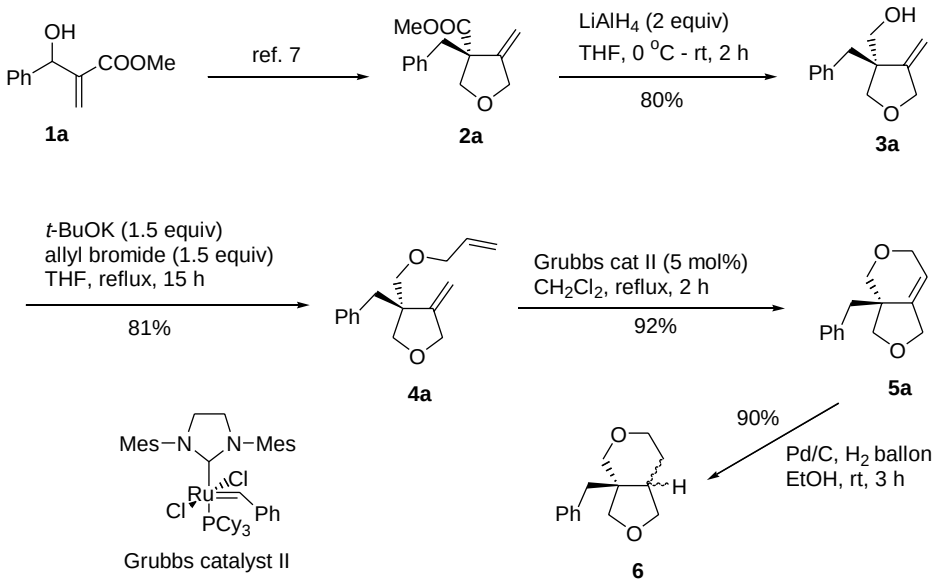


Scheme 1.

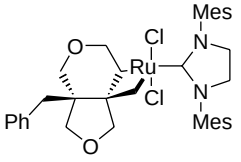
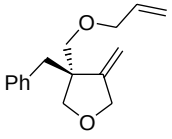
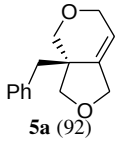
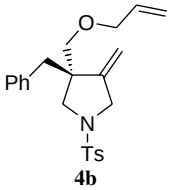
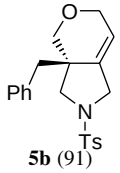
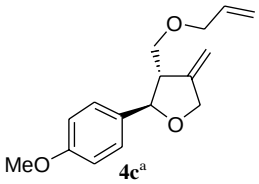
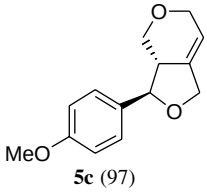
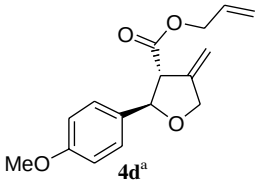
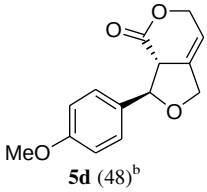


Figure 1. Metallacyclobutane intermediate for **5a**.

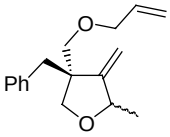
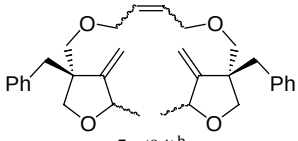
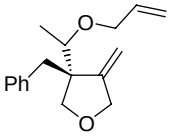
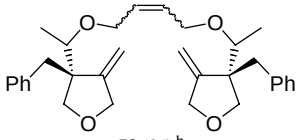
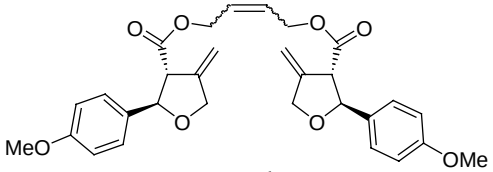
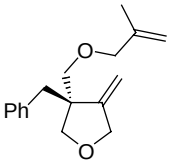
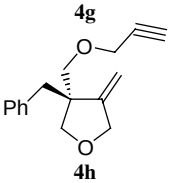
transformed into **6** in 90% yield under catalytic hydrogenation conditions (Pd/C, H_2, EtOH, room temperature, 3 h). We obtained **6** as a single isomer but we did not determine the stereochemistry at this stage. Encouraged by the results we examined the RCM reactions with similar starting materials **4b–h** and the results are summarized in Tables 1 and 2.

Table 1. Successful RCM reaction of *exo*-methylene compounds and Grubbs catalyst

Entry	Substrate	Conditions	Product (%)
1	 **4a**	Cat (5 mol%), 2 h	 **5a** (92)
2	 **4b**	Cat (10 mol%), 80 min	 **5b** (91)
3	 **4c**[a]	Cat (5 mol%), 20 min	 **5c** (97)
4	 **4d**[a]	Cat (5 mol%), 20 min	 **5d** (48)[b]

[a] Pure trans isomer.[9]
[b] Self-metathesis product **5g** was also isolated in 24% yield.

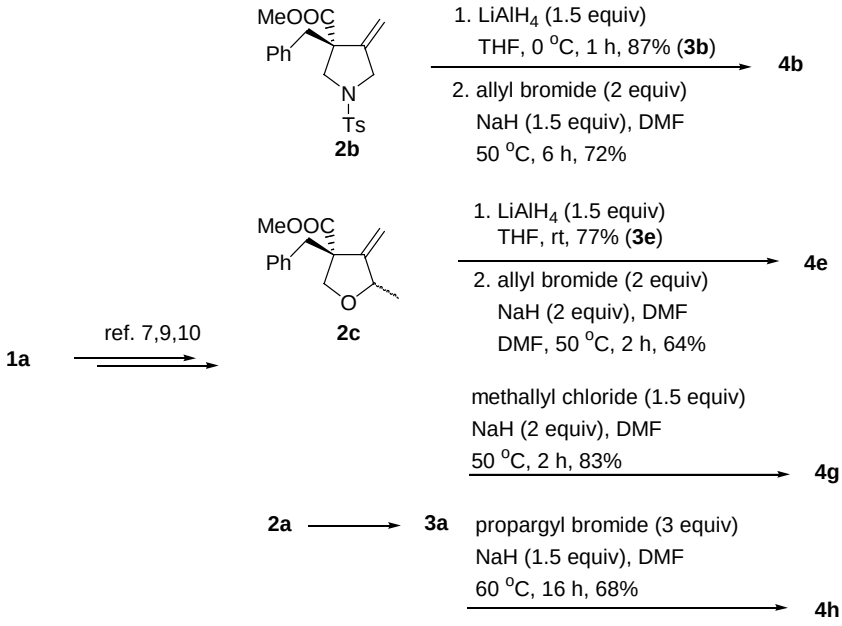
Table 2. Unsuccessful RCM reaction of *exo*-methylene compounds and Grubbs catalyst

Entry	Substrate	Conditions	Product (%)
1	 **4e**[a]	Cat (5 mol%), 12 h	 **5e** (94)[b]
2	 **4f**[a]	Cat (5 mol%), 6 h	 **5f** (85)[b]
3	**4d**	Cat (5 mol%), 1 h	 **5g** (24)[b,c]
4	 **4g**	Cat (10 mol%), 48 h	No reaction
5	 **4h**	Cat (5 mol%), 3 days	**3a** (74)

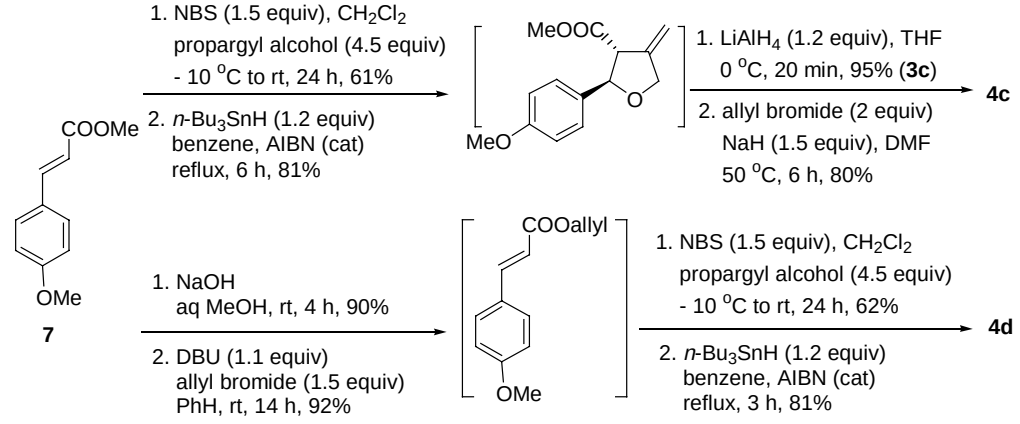
[a] Pure **4e** and **4f** were used, but the stereochemistry is arbitrary.
[b] Pure single isomer was obtained, but we did not assign the stereochemistry.
[c] RCM product **5d** was also isolated in 48% yield.

As shown in Table 1, allyl-substituted starting materials **4b** and **4c** gave the corresponding RCM products **5b** and **5c** successfully in short time in good yields. We could obtain the RCM product **5d**, albeit in low yield, for the allyl ester **4d** (48%, entry 4). In addition, we could isolate the corresponding self-metathesis product **5g** in 24% yield (see also entry 3 in Table 2). Unfortunately, however, we did not obtain the desired RCM products when we used **4e**–**h** as the starting materials as shown in Table 2. The methyl substituent at the 2-position (for **4e**, entry 1) increased the steric crowdedness at the transition state toward RCM product and produced the self-metathesis product **5e**. The situation was same for the allyl ether **4f** (entry 2). For the methallyl-substituted starting material **4g** (entry 4), we failed completely to obtain any product presumably due to the severe steric crowdedness during the reaction progress. As expected, when we compare the differences of reactivity of **4c** and **4e**, the substituent near the metallacyclobutane moiety (like as the methyl group of **4e**) made the RCM reaction difficult, while the substituent far away from the reaction site (like as 4-methoxyphenyl group of **4c**) did not reduce the reactivity toward RCM reaction. For the propargyl ether derivative **4h** (entry 5) we observed the deprotection of propargyl group. Deprotection of propargyl ether moiety has been published recently.[8]

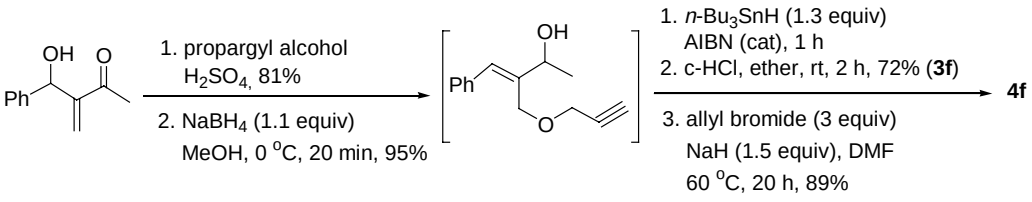
The synthesis of starting materials **4b**–**h** is summarized in Schemes 2–4.[7,9,10] Synthesis of **2a**–**c** was carried out as reported from the corresponding Baylis–Hillman adduct.[7] By following the usual organic laboratory experimental techniques we prepared **4b**, **4e**, **4g**, and **4h** as in Scheme 2 in reasonable yields. Synthesis of **4c** was carried out from methyl 4-methoxycinnamate (**7**) by following bromoetherification with propargyl alcohol (NBS, propargyl alcohol, 61%),[9] radical cyclization (*n*-Bu_3SnH, AIBN, 81%),[9,10] reduction ($LiAlH_4$, 95%), and allylation (allyl bromide, NaH, 80%) as shown in Scheme 3. The compound **4d** was also synthesized from methyl 4-methoxycinnamate by following alkaline hydrolysis (NaOH, 90%), allylation (DBU, allyl bromide, 92%), bromoetherification (NBS, propargyl alcohol, 62%),[9] and radical cyclization (*n*-Bu_3SnH, AIBN, 81%) sequences[9,10] (Scheme 3). Compound **4f** was also synthesized from the Baylis–Hillman adduct of methyl vinyl ketone by following the sequential introduction of propargyl alcohol at the primary position (81%),[7,10] reduction of acetyl group ($NaBH_4$, 95%), radical



Scheme 2.



Scheme 3.



Scheme 4.

cyclization (*n*-Bu_3SnH, AIBN, 72%),[7,10] and allylation (allyl bromide, NaH, 89%) as in Scheme 4.

In summary, we disclosed the first successful RCM reaction of cyclic substrates with *exo*-methylene moiety with the double bond of oxygen atom-containing tether. The steric crowdedness at the metallacyclobutane intermediate stage prohibited the successful RCM reaction in some cases, which afforded the corresponding self-metathesis products. More detailed scope and limitations on the RCM reaction involving *exo*-methylene moiety are currently under study and will be published in due course.

3. Experimental

3.1. General procedure

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in parts per million relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. All

reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

3.2. Synthesis of starting material 2a–c and 3a

Synthesis of the starting materials **2a–c** was carried out according to the reported procedures.[7,9,10] Compound **3a** was prepared from **2a** as follows: to a stirred solution of **2a** (464 mg, 2.0 mmol) in THF (2 mL) was added a solution of $LiAlH_4$ (4 mL, 1 M solution in THF) at 0 °C. The reaction mixture was maintained at room temperature for 2 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 8:2) we obtained **3a** as colorless oil, 327 mg (80%).

3.2.1. Compound 3a. Eighty percentage; a colorless oil; IR (film) 3464, 1662, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (br s, 1H), 2.78 (d, $J=13.5$ Hz, 1H), 2.96 (d, $J=13.5$ Hz, 1H), 3.42–3.56 (m, 2H), 3.70 (d, $J=9.0$ Hz, 1H), 3.84 (d, $J=9.0$ Hz, 1H), 4.28–4.45 (m, 2H), 4.87 (t, $J=2.4$ Hz, 1H), 5.10 (d, $J=2.4$ Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.31, 51.86, 64.89, 72.26, 75.34, 105.05, 126.46, 128.13, 130.17, 137.53, 151.94; ESIMS (*m/z*) 205.1 ($M^+ + H$).

3.3. Synthesis of starting materials 4a–h

Synthesis of **4a** was carried out as follows: To a stirred mixture of **3a** (204 mg, 1.0 mmol) and allyl bromide (182 mg, 1.5 mmol) in dry THF (3 mL) was added *t*-BuOK (168 mg, 1.5 mmol) and heated to reflux for 15 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 95:5) we obtained **4a** as colorless oil, 198 mg (81%). Other compounds **4b**, **4e**, **4g**, and **4h** were synthesized similarly by using the typical experimental procedures (Scheme 2).[7,9,10] The compounds **4c** and **4d** were also prepared from commercial methyl 4-methoxycinnamate by following the typical organic experimental procedures (Scheme 3).[9] Compound **4f** was synthesized from the Baylis–Hillman adduct of methyl vinyl ketone by following the known procedures as in Scheme 4. The spectroscopic data of prepared compounds **4a–h** are as follows. The spectroscopic data of the intermediates (**3b**, **3c**, **3e**, and **3f**) are also reported at the end of this part.

3.3.1. Compound 4a. Eighty-one percentage; a colorless oil; IR (film) 2850, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 2H), 3.22 (d, $J=9.0$ Hz, 1H), 3.28 (d, $J=9.0$ Hz, 1H), 3.75 (d, $J=9.0$ Hz, 1H), 3.84 (d, $J=9.0$ Hz, 1H), 3.97–4.01 (m, 2H), 4.32–4.35 (m, 2H), 4.64 (t, $J=2.4$ Hz, 1H), 4.97 (t, $J=2.4$ Hz, 1H), 5.16–5.34 (m, 2H), 5.87–6.01 (m, 1H), 7.13–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.71, 50.60, 72.14, 72.32, 72.82, 76.61, 105.28, 116.66, 126.22, 127.79, 130.61, 134.78, 137.83, 151.18; ESIMS (*m/z*) 245.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.84; H, 8.18.

3.3.2. Compound 4b. Seventy-two percentage; a colorless oil; IR (film) 2854, 1346, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.82 (s, 2H), 3.09 (d, $J=9.6$ Hz, 1H), 3.12 (d, $J=9.3$ Hz, 1H), 3.18 (d, $J=9.3$ Hz, 1H), 3.26 (d, $J=9.6$ Hz, 1H), 3.81 (t, $J=2.4$ Hz, 2H), 3.92 (dt, $J=5.4$, 1.5 Hz, 2H), 4.67 (t, $J=2.1$ Hz, 1H), 4.97 (t, $J=2.1$ Hz, 1H), 5.12–5.28 (m, 2H), 5.81–5.94 (m, 1H), 7.04–7.27 (m, 5H), 7.30 (d, $J=8.1$ Hz, 2H), 7.65 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.51, 40.16, 50.29, 52.83, 55.79, 72.08, 72.52, 108.30, 116.76, 126.36, 127.84, 127.89, 129.59, 130.51, 132.48, 134.51, 137.12, 143.56, 147.49; ESIMS (*m/z*) 398.2 ($M^+ + H$). Anal. Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85; N, 3.52. Found: C, 69.47; H, 6.94; N, 3.43.

3.3.3. Compound 4c. Eighty percentage; a colorless oil; IR (film) 2839, 1612, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.85–2.90 (m, 1H), 3.54 (d, $J=1.8$ Hz, 1H), 3.57 (d, $J=2.4$ Hz, 1H), 3.80 (s, 3H), 3.96 (dt, $J=5.7$, 1.5 Hz, 2H), 4.41 (dq, $J=13.2$, 2.4 Hz, 1H), 4.57 (dq, $J=13.2$, 2.1 Hz, 1H), 4.78 (d, $J=7.2$ Hz, 1H), 5.02 (q, $J=2.1$ Hz, 1H), 5.08 (q, $J=2.1$ Hz, 1H), 5.13–5.26 (m, 2H), 5.80–5.94 (m, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 7.29 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.59, 55.26, 70.52, 71.24, 72.02, 83.70, 104.89, 113.75, 116.89, 127.68, 133.47, 134.62, 149.34, 159.16; ESIMS (*m/z*) 261.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.67; H, 7.78.

3.3.4. Compound 4d. Eighty-one percentage; a colorless oil; IR (film) 1736, 1612, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49–3.55 (m, 1H), 3.80 (s, 3H), 4.49 (dq, $J=13.2$, 2.4 Hz, 1H), 4.56–4.71 (m, 3H), 5.03–5.34 (m, 5H), 5.83–5.97 (m, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 7.31 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.25, 57.01, 65.70, 71.47, 83.24, 106.47, 113.90, 118.66, 127.50, 131.73, 131.79, 146.47, 159.52, 170.42; ESIMS (*m/z*) 275.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.18; H, 6.54.

3.3.5. Compound 4e. Sixty-four percentage; a colorless oil; IR (film) 2927, 2858, 1099, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, $J=6.3$ Hz, 3H), 2.84 (d, $J=13.2$ Hz, 1H), 2.95 (d, $J=13.2$ Hz, 1H), 3.21 (d, $J=9.0$ Hz, 1H), 3.30 (d, $J=9.0$ Hz, 1H), 3.63 (d, $J=9.0$ Hz, 1H), 3.94–4.00 (m, 3H), 4.38–4.45 (m, 1H), 4.51 (d, $J=2.4$ Hz, 1H), 4.87 (d, $J=2.4$ Hz, 1H), 5.16–5.21 (m, 1H), 5.26–5.34 (m, 1H), 5.87–6.00 (m, 1H), 7.12–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.33, 40.65, 51.25, 72.15, 73.27, 75.19, 78.28, 105.63, 116.69, 126.18, 127.68, 130.91, 134.78, 137.76, 155.73; ESIMS (*m/z*) 259.2 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.95; H, 8.48.

3.3.6. Compound 4f. Eighty-nine percentage; a colorless oil; IR (film) 2985, 1115, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, $J=6.3$ Hz, 3H), 2.92 (d, $J=13.2$ Hz, 1H), 3.03 (d, $J=13.2$ Hz, 1H), 3.45 (q, $J=6.3$ Hz, 1H), 3.75 (d, $J=9.3$ Hz, 1H), 3.86–3.93 (m, 1H), 4.06–4.26 (m, 3H), 4.10 (d, $J=9.3$ Hz, 1H), 4.60 (t, $J=2.3$ Hz, 1H), 5.06 (t, $J=2.0$ Hz, 1H), 5.17–5.22 (m, 1H), 5.31–5.38 (m, 1H), 5.93–6.06 (m, 1H), 7.14–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 40.95, 54.36, 69.93, 72.86, 73.77, 78.70, 105.71, 116.15, 126.14, 127.61, 131.07, 135.28, 137.98,

151.59; ESIMS (*m/z*) 259.2 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.12; H, 8.53.

3.3.7. Compound 4g. Eighty-three percentage; a colorless oil; IR (film) 2850, 1103, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 3H), 2.92 (s, 2H), 3.20 (d, $J=9.3$ Hz, 1H), 3.25 (d, $J=9.3$ Hz, 1H), 3.75 (d, $J=9.0$ Hz, 1H), 3.85 (d, $J=9.0$ Hz, 1H), 3.88 (s, 2H), 4.32 (d, $J=2.1$ Hz, 1H), 4.34 (d, $J=2.1$ Hz, 1H), 4.66 (t, $J=2.4$ Hz, 1H), 4.88–4.91 (m, 1H), 4.96–4.99 (m, 2H), 7.14–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.54, 39.79, 50.61, 72.34, 72.78, 75.18, 76.54, 105.25, 111.90, 126.22, 127.81, 130.61, 137.87, 142.23, 151.24; ESIMS (*m/z*) 259.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.20; H, 8.57.

3.3.8. Compound 4h. Sixty-eight percentage; a colorless oil; IR (film) 2117, 1454, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (t, $J=2.4$ Hz, 1H), 2.87 (d, $J=12.0$ Hz, 1H), 2.92 (d, $J=12.0$ Hz, 1H), 3.33 (d, $J=8.7$ Hz, 1H), 3.39 (d, $J=8.7$ Hz, 1H), 3.76 (q, $J=9.0$ Hz, 1H), 3.84 (q, $J=9.0$ Hz, 1H), 4.18 (d, $J=2.4$ Hz, 2H), 4.33–4.35 (m, 2H), 4.62 (t, $J=2.4$ Hz, 1H), 4.98 (t, $J=2.0$ Hz, 1H), 7.16–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.64, 50.38, 58.48, 72.29, 72.53, 74.54, 76.58, 79.64, 105.52, 126.29, 127.81, 130.71, 137.60, 150.87; ESIMS (*m/z*) 243.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.35; H, 7.58.

3.3.9. Compound 3b. Eighty-seven percentage; a colorless oil; IR (film) 3529, 2924, 1342, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.71 (d, $J=13.5$ Hz, 1H), 2.87 (d, $J=13.5$ Hz, 1H), 3.10 (d, $J=9.9$ Hz, 1H), 3.23 (d, $J=9.9$ Hz, 1H), 3.34–3.49 (m, 2H), 3.79 (dt, $J=14.1$, 2.4 Hz, 1H), 3.87 (dt, $J=14.1$, 2.1 Hz, 1H), 4.85 (t, $J=2.4$ Hz, 1H), 5.09 (t, $J=2.1$ Hz, 1H), 7.08–7.33 (m, 7H), 7.65 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 39.90, 51.57, 52.76, 54.53, 64.58, 108.24, 126.61, 127.81, 128.21, 129.67, 130.21, 132.26, 136.83, 143.74, 148.05. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.41; H, 6.53; N, 3.85.

3.3.10. Compound 3c. Ninety-five percentage; a colorless oil; IR (film) 3529, 3313, 1612, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66 (br s, 1H), 2.73–2.80 (m, 1H), 3.70–3.75 (m, 1H), 3.80 (s, 3H), 3.82–3.88 (m, 1H), 4.38–4.44 (m, 1H), 4.57–4.63 (m, 1H), 4.79 (d, $J=7.4$ Hz, 1H), 5.06 (q, $J=2.4$ Hz, 1H), 5.10 (q, $J=2.1$ Hz, 1H), 6.89 (d, $J=8.7$ Hz, 2H), 7.32 (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.87, 55.26, 61.92, 71.30, 83.18, 104.88, 113.91, 127.70, 133.04, 148.97, 159.33. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.01; H, 7.30.

3.3.11. Compound 3e. Seventy-seven percentage; a colorless oil; IR (film) 3440, 2927, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, $J=6.3$ Hz, 3H), 2.80 (d, $J=13.5$ Hz, 1H), 2.89 (d, $J=13.5$ Hz, 1H), 3.45–3.58 (m, 2H), 3.62 (d, $J=9.0$ Hz, 1H), 3.96 (d, $J=9.0$ Hz, 1H), 4.43–5.0 (m, 1H), 4.77 (d, $J=2.4$ Hz, 1H), 5.01 (d, $J=2.1$ Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.26, 40.55, 52.61, 65.25, 73.00, 78.18, 105.41, 126.46, 128.05, 130.47, 137.47, 156.64. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.19; H, 8.19.

3.3.12. Compound 3f. Eighty-seven percentage; a colorless oil; IR (film) 3440, 2924, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, $J=6.6$ Hz, 3H), 1.99 (d, $J=3.0$ Hz, 1H), 2.85 (d, $J=13.8$ Hz, 1H), 2.98 (d, $J=13.8$ Hz, 1H), 3.78 (d, $J=9.3$ Hz, 1H), 3.84–3.90 (m, 1H), 4.06 (d, $J=9.3$ Hz, 1H), 4.12 (dt, $J=13.5$, 2.8 Hz, 1H), 4.34 (dt, $J=13.5$, 2.1 Hz, 1H), 4.82 (t, $J=2.4$ Hz, 1H), 5.14 (t, $J=2.1$ Hz, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.17, 39.81, 54.14, 72.09, 72.97, 74.60, 105.95, 126.44, 128.01, 130.57, 137.72, 151.14. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.09; H, 8.27.

3.4. The reactions of 4a–h and Grubbs catalyst

To a stirred solution of **4a** (122 mg, 0.5 mmol) was added Grubbs catalyst (21 mg, 5 mol%) and the reaction mixture was heated to reflux for 2 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 85:15) we obtained **5a** as colorless oil, 98 mg (92%). Other entries in Tables 1 and 2 were tried similarly under the similar conditions. The spectroscopic data of prepared compounds are as follows.

3.4.1. Compound 5a. Ninety-two percentage; a colorless oil; IR (film) 2924, 2854, 1103, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.76 (d, $J=13.2$ Hz, 1H), 2.92 (d, $J=13.2$ Hz, 1H), 3.02 (d, $J=10.8$ Hz, 1H), 3.07 (d, $J=8.4$ Hz, 1H), 3.96 (d, $J=8.4$ Hz, 1H), 3.99 (d, $J=10.8$ Hz, 1H), 4.09–4.46 (m, 4H), 5.54–5.58 (m, 1H), 7.19–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.27, 45.87, 64.59, 67.87, 69.06, 72.58, 115.93, 126.32, 128.15, 130.65, 138.11, 141.94; ESIMS (*m/z*) 217.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.58.

3.4.2. Compound 5b. Ninety-one percentage; sticky solid; IR (film) 2924, 2858, 1338, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (d, $J=9.6$ Hz, 1H), 2.44 (s, 3H), 2.71 (d, $J=13.5$ Hz, 1H), 2.87 (d, $J=10.8$ Hz, 1H), 2.89 (d, $J=13.5$ Hz, 1H), 3.53 (d, $J=9.6$ Hz, 1H), 3.69–3.76 (m, 1H), 3.91 (d, $J=10.8$ Hz, 1H), 4.01–4.31 (m, 3H), 5.49–5.52 (m, 1H), 7.13–7.35 (m, 7H), 7.71 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 38.33, 45.16, 50.04, 52.51, 64.78, 67.87, 118.15, 126.52, 127.57, 128.27, 129.71, 130.69, 133.86, 137.21, 138.34, 143.59; ESIMS (*m/z*) 370.1 ($M^+ + H$). Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.21; H, 6.38; N, 3.71.

3.4.3. Compound 5c. Ninety-seven percentage; a colorless oil; IR (film) 1516, 1250, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.73–2.79 (m, 1H), 3.28 (t, $J=10.2$ Hz, 1H), 3.81 (s, 3H), 4.05–4.28 (m, 4H), 4.40–4.47 (m, 1H), 4.64–4.71 (m, 1H), 5.60–5.63 (m, 1H), 6.90 (d, $J=9.0$ Hz, 2H), 7.28 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.31, 55.27, 64.31, 65.89, 66.52, 83.09, 113.96, 116.05, 127.39, 132.17, 138.96, 159.48; ESIMS (*m/z*) 233.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.51; H, 6.79.

3.4.4. Compound 5d. Forty-eight percentage; a colorless oil; IR (film) 1739, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.23–3.29 (m, 1H), 3.81 (s, 3H), 4.48–4.56 (m, 1H), 4.76–4.93 (m, 3H), 5.06 (d, $J=8.7$ Hz, 1H), 5.88–5.93 (m, 1H), 6.91 (d, $J=9.0$ Hz, 2H), 7.48 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.08, 55.28, 68.18, 68.38,

81.22, 112.66, 113.90, 127.73, 131.69, 141.25, 159.51, 169.84; ESIMS (*m*/*z*) 247.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.41; H, 5.76.

3.4.5. Compound 5e. Ninety-four percentage; a colorless oil; IR (film) 2924, 1103, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, $J=6.3$ Hz, 6H), 2.84 (d, $J=13.2$ Hz, 4H), 2.95 (d, $J=13.2$ Hz, 2H), 3.22 (d, $J=9.0$ Hz, 2H), 3.30 (d, $J=9.0$ Hz, 2H), 3.62 (d, $J=9.0$ Hz, 2H), 3.95 (d, $J=9.0$ Hz, 2H), 4.00–4.02 (m, 2H), 4.37–4.44 (m, 2H), 4.50–4.52 (m, 2H), 4.86 (d, $J=2.1$ Hz, 2H), 5.82–5.85 (m, 2H), 7.11–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.33, 40.65, 51.25, 71.16, 73.36, 75.18, 78.28, 105.67, 126.22, 127.70, 129.10, 130.90, 137.73, 155.72; ESIMS (*m*/*z*) 489.3 ($M^+ + H$). Anal. Calcd for $C_{32}H_{40}O_4$: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.37.

3.4.6. Compound 5f. Eighty-five percentage; a colorless oil; IR (film) 2924, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, $J=6.3$ Hz, 6H), 2.92 (d, $J=13.2$ Hz, 2H), 3.03 (d, $J=13.2$ Hz, 2H), 3.48 (q, $J=6.3$ Hz, 2H), 3.74 (d, $J=9.0$ Hz, 2H), 3.92–4.26 (m, 10H), 4.59–4.64 (m, 2H), 5.06 (t, $J=2.1$ Hz, 2H), 5.93 (t, $J=2.7$ Hz, 2H), 7.14–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 40.97, 54.37, 69.06, 72.86, 73.76, 78.83, 105.73, 126.16, 127.63, 129.02, 131.07, 137.95, 151.58; ESIMS (*m*/*z*) 489.3 ($M^+ + H$). Anal. Calcd for $C_{32}H_{40}O_4$: C, 78.65; H, 8.25. Found: C, 78.49; H, 8.11.

3.4.7. Compound 5g. Twenty-four percentage; a colorless oil; IR (film) 1736, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49–3.53 (m, 2H), 3.79 (s, 6H), 4.44–4.51 (m, 2H), 4.56–4.70 (m, 6H), 5.08–5.11 (m, 2H), 5.14–5.19 (m, 4H), 5.79–5.82 (m, 2H), 6.87 (d, $J=8.7$ Hz, 4H), 7.30 (d, $J=8.7$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.25, 56.97, 64.33, 71.46, 83.25, 106.54, 113.92, 127.50, 127.99, 131.69, 146.41, 159.56, 170.34; ESIMS (*m*/*z*) 521.2 ($M^+ + H$). Anal. Calcd for $C_{30}H_{32}O_8$: C, 69.22; H, 6.20. Found: C, 69.10; H, 6.36.

3.5. Synthesis of compound 6

A mixture of **5a** (65 mg, 0.3 mmol) and 5% Pd/C (10 mg) in EtOH (1 mL) was stirred under the atmosphere of H_2 (ballon) at room temperature for 3 h. After filtration, removal of solvent, and column chromatographic purification process (hexanes/EtOAc, 85:15) we obtained **6** as colorless oil, 59 mg (90%).

3.5.1. Compound 6. Ninety percentage; a colorless oil; IR (film) 2924, 2854 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48–1.51 (m, 1H), 1.90–2.02 (m, 1H), 2.16–2.25 (m, 1H), 2.60 (d, $J=13.5$ Hz, 1H), 3.00 (d, $J=13.5$ Hz, 1H), 3.38 (d, $J=12.0$ Hz, 1H), 3.47 (d, $J=9.0$ Hz, 1H), 3.57–3.74 (m, 4H), 3.84 (t, $J=8.4$ Hz, 1H), 4.06 (t, $J=8.4$ Hz, 1H), 7.11–7.14 (m, 2H), 7.19–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.31, 29.63, 39.62, 39.90, 64.41, 68.53, 70.63, 73.76, 126.40, 128.22, 130.00, 137.65; ESIMS (*m*/*z*) 219.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.23.

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