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## SYNTHETIC APPROACH TO OXA-CAGE SYSTEMS VIA RING-CLOSING METATHESIS<sup>†</sup>

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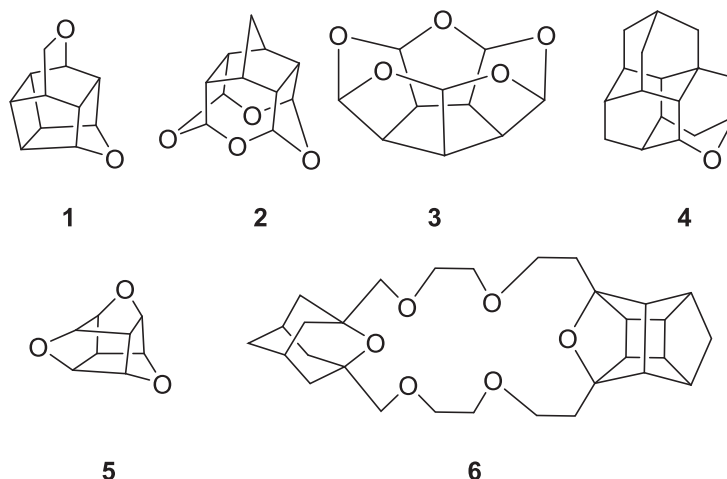
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**Abstract** – Here, we report a new synthetic approach to oxa-cage systems by employing RCM as a key step. These cage systems were assembled starting with easily accessible starting materials by adopting a three-step sequence involving the Grignard addition, allylation followed by RCM.

### INTRODUCTION

Since 1970's, research on cage molecules has increased gradually.<sup>1,2</sup> Recently, the emphasis has been shifted towards the development of efficient synthetic strategies to cage molecules with the aim of producing materials suitable as solid propellants. In view of their applications in diverse areas of chemistry such as synthesis of natural products,<sup>3</sup> medicinal chemistry,<sup>4</sup> pharmaceutical applications, design of new strategies to these molecules is highly desirable activity.<sup>5</sup> Additionally, cage systems serve as useful candidates in high energy materials,<sup>6</sup> polymers,<sup>7</sup> thermostable oils,<sup>8</sup> supramolecular chemistry,<sup>9</sup> and in proposing various ligands suitable for chelation with selected metal ions.<sup>10</sup> Due to the rigidity associated with their compact skeletons, synthesis of these molecules has become a worthwhile challenge. Moreover, these molecules possess an unusual strain energy and also show deviation from normal C–C bond angles and consequently they tend to undergo unusual molecular rearrangements.<sup>11</sup> Therefore, considerable interest has been directed in studying acid catalyzed rearrangement of cage propellanes.<sup>12</sup> Moreover, Lewis acid mediated rearrangement offers a unique opportunity to assemble unusual cage systems. Several reports are available for the synthesis of oxa-cage molecules (**1-6**).<sup>13</sup> As part of our ongoing research program aimed at designing intricate molecules based on metathesis,<sup>14</sup> here, we conceived ring-closing metathesis (RCM) approach to generate highly functionalized oxa-cage systems. In this regard, we identified cage diones **8-10** as useful starting materials.

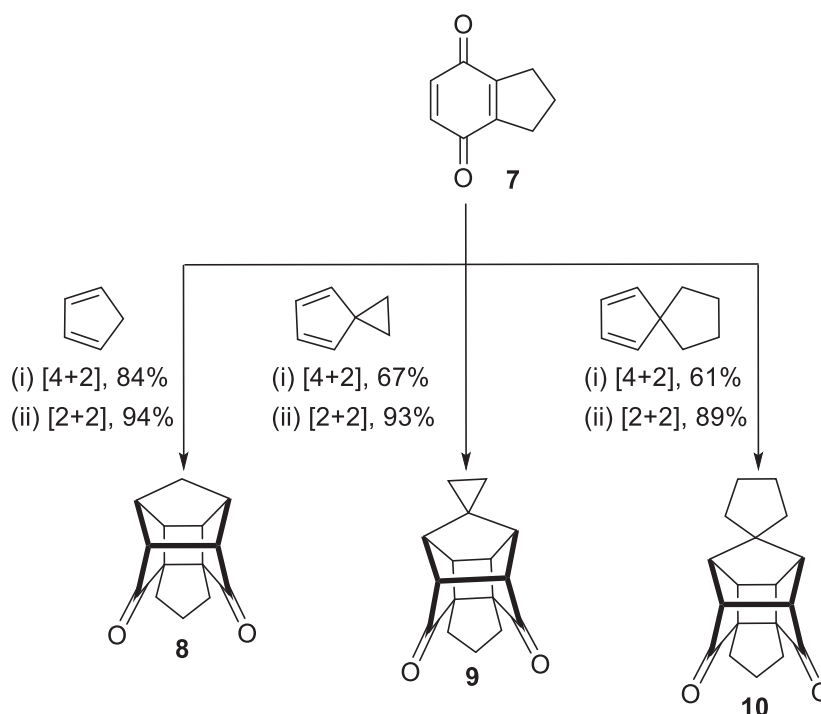
<sup>†</sup> Dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th Birthday



**Figure 1.** Various oxygen containing caged molecules **1-6**

## RESULTS AND DISCUSSION

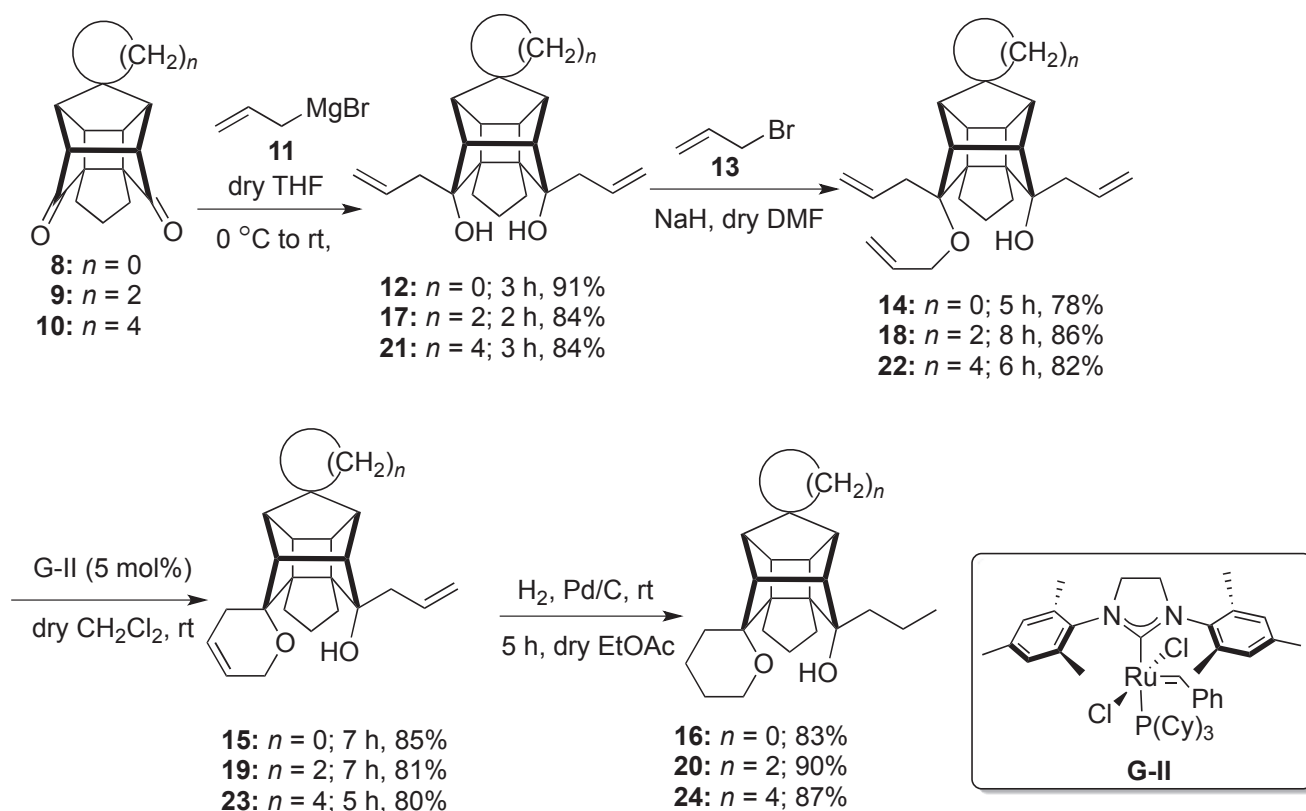
In view of our interest in designing new strategies for the construction of different cage molecules, we chose various building blocks **8-10**<sup>15</sup> useful for assembling oxa-cage systems. These precursors were prepared from the annulated quinone derivative **7**<sup>16</sup> by adopting a two-step synthetic sequence involving [4+2] reaction using suitable diene partners followed by [2+2] cycloaddition reaction as key steps.



**Scheme 1.** Preparation of cage systems **8**, **9**, and **10**

Initially, we assembled the known cage systems **8**, **9**, and **10** via a Diels–Alder reaction with an appropriate diene partners followed by [2+2] cycloaddition of the resulting cycloadduct (Scheme 1). To build the

oxygen containing cage systems with spiro linkage, the cage dione **8** was treated with allylmagnesium bromide **11** in dry THF at 0 °C to room temperature for 3 h to deliver the expected diol **12** (91%). Next, the diol was subjected to allylation using 8 equivalents of allyl bromide (**13**) in the presence of NaH (8 equivalents) in dry DMF for 5 h to afford the mono-*O*-allyl product **14** (78%). Further, to realize the di-*O*-allylation we used a large amount of allyl bromide and NaH, then the reaction mixture was stirred for extended period (*i.e.*, 2 days). Even under forcing reaction conditions, we did not observe the formation of di-*O*-allyl product. Next, exposure of the triallyl compound **14** to the metathesis catalyst, G-II, furnished the unsaturated cyclized ether **15** (85%). Subsequently, reduction of the cyclized product **15** was accomplished with H<sub>2</sub>, Pd/C to deliver the saturated oxa-cage system **16** in 83% yield (Scheme 2; *n* = 0). Structures of these compounds **12**, **14**, **15**, and **16** were determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR spectral data and further supported by HRMS information. Finally, the structure and stereochemistry of hydroxyl groups present in compound **12** was unambiguously established by single-crystal X-ray diffraction studies<sup>17</sup> (Figure 2).

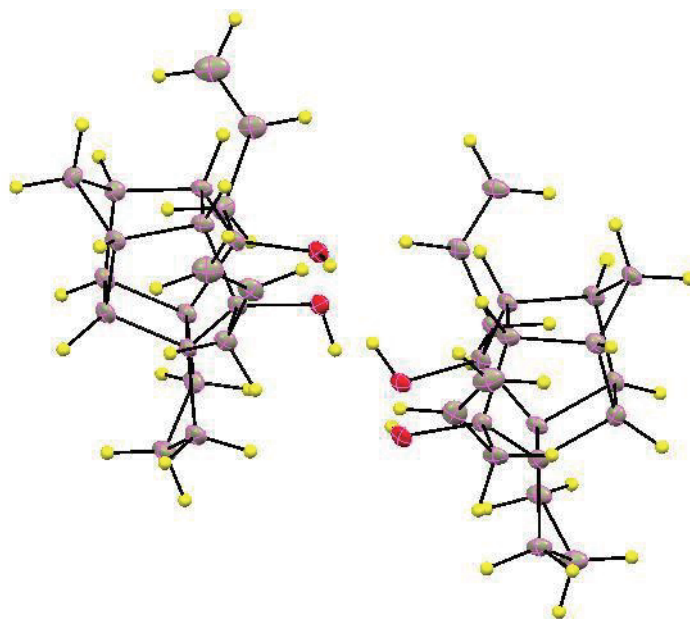


**Scheme 2.** Synthesis of oxa-cage systems **16**, **20**, and **24**

Along similar lines, the cyclopropane bearing cage dione **9** was treated with Grignard reagent **11** to provide the expected diol **17** (84%). Later, allylation of the diol **17** furnished the mono-*O*-allyl product **18** (86%). Next, triallyl compound **18** was subjected to the metathesis sequence with G-II catalyst to deliver the

cyclized product **19** (81%). Finally, reduction of the metathesis product with the aid of H<sub>2</sub>, Pd/C led to the formation of the saturated oxa-cage system **20** in 90% yield (Scheme 2; *n* = 2). Structure of these compounds **17**, **18**, **19**, and **20** were determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR spectral values and further supported by HRMS data.

Similarly, treatment of the cage dione **10** with Grignard reagent **11** produced the diol **21** (84%). The mono-*O*-allylated product **22** (82%) was obtained via allylation of diol **21** using allyl bromide **13** in the presence of NaH. Later, the triallyl compound **22** was subjected to metathesis with G-II catalyst to deliver the ring closure product **23** (80%), which on subsequent reduction with H<sub>2</sub>, Pd/C produced the oxa-cage system **24** in 87% yield (Scheme 2; *n* = 4). Structure of the compounds **21**, **22**, **23**, and **24** were determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR values and further supported by HRMS spectroscopic data. It is worth mentioning that during the course of allylation sequence with an excess amount of allyl bromide **13** (or excess amount of NaH) and longer reaction time was not useful to realize the diallylation of compound **21**. It may be due to the steric hindrance associated with the triallyl compound **22**.



**12** (CCDC 1825224)

**Figure 2.** A view of the molecular structure **12**, showing 20% probability displacement ellipsoids

We have demonstrated a simple and an efficient three-step synthetic sequence to assemble highly functionalized oxa-cage systems such as **16**, **20** and **24** starting with cage diones **8-10** as key precursors. Here, we employed Grignard addition, allylation and RCM as key steps. Feasibility of RCM protocol to construct oxa-cage systems bearing cyclopropane and cyclopentane rings was realized.

## EXPERIMENTAL

### General Experimental Details

All the required reagents, chemicals and solvents were purchased from the commercial suppliers and used as without any further purification. Analytical TLC was performed on (10 × 5) glass plates coated with Acme's silica gel (GF-254) containing 13% calcium sulfate as a binder. All the reactions were monitored by TLC using suitable solvent system and visualization was done under UV light, exposure to iodine vapour and by dipping in to a solution of KMnO<sub>4</sub>. Dry reactions were performed in oven dried glassware under nitrogen atmosphere by using standard syringe-septum techniques. Acme's silica gel (100-200 mesh size) and neutral alumina was used for column chromatography and solvents were concentrated under vacuo on rotary evaporator. Benzene and DCM were distilled from P<sub>2</sub>O<sub>5</sub> or CaH<sub>2</sub> and EtOAc was dried by using K<sub>2</sub>CO<sub>3</sub>.

IR spectra were collected on a Nicolet Impact-400 FTIR spectrometer and samples were prepared as a thin film between CsCl plates by dissolving the compound in DCM and CHCl<sub>3</sub> and then evaporating the solvent. <sup>1</sup>H NMR (400 and 500 MHz), <sup>13</sup>C NMR, <sup>13</sup>C-APT NMR, DEPT 135 NMR (100 and 125 MHz) spectra were recorded on Bruker spectrometer and samples were prepared in CDCl<sub>3</sub> solvent. The chemical shifts are reported in parts per million (ppm) on delta scale with TMS as an internal standard and values for the coupling constants (*J*) are given in Hz. The standard abbreviations for <sup>1</sup>H NMR spin couplings are given as s, d, t, q, dd, dt, td, and m for singlet, doublet, triplet, quartet, doublet of doublet, doublet of triplet, triplet of doublet and multiplet respectively. High-resolution mass spectra (HRMS) were recorded in a positive ion electrospray ionization (ESI). All melting points were recorded on Veego VMP-CMP melting point apparatus and are uncorrected. All reported yields are isolated yields of the products after column purification. X-Ray data were recorded on diffractometer equipped with graphite monochromatic Mo K $\alpha$  radiation and structure was solved by direct methods shelxl-97 and refined by full-matrix least-squares against F<sup>2</sup> using shelxl-97 software.

### General Procedure for Allyl Grignard Addition to Cage Diones **8**, **9** and **10**

To a freshly prepared allylmagnesium bromide solution in dry Et<sub>2</sub>O was added to the cage diones **8**, **9** and **10** in dry Et<sub>2</sub>O (200 mg, 0.93 mmol for **8** or 150 mg, 0.62 mmol for **9** or 100 mg, 0.37 mmol for **10**) by dropwise addition over a period of 10 min under continuous flow of nitrogen at room temperature. After conclusion of the reaction (3 h for **8**, 2 h for **9** and 3 h for **10**, reaction progress monitored by TLC monitoring, the reaction mixture was quenched with saturated aq. NH<sub>4</sub>Cl solution at 0 °C, and the resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated under vacuum and the resulting crude residue was subjected to silica gel column chromatography (10 to 15% EtOAc/petroleum ether as an eluent) to afford pure **12** as a colorless crystalline solid, **17** and **21** as a colorless liquid.

**Compound 12 (cage diol):** Colorless crystalline solid; mp 165-167 °C; Yield: 255 mg (91%); IR (neat,  $\text{cm}^{-1}$ ): 3184, 2954, 2866, 1639, 1457, 1281, 1159, 1078, 1042, 1000;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.98-5.90 (m, 2H), 5.27 (s, 2H), 5.12-5.08 (m, 4H), 2.34 (d,  $J = 1.4$  Hz, 2H), 2.21-2.16 (m, 4H), 2.07 (dd,  $J = 13.9, 7.9$  Hz, 2H), 1.99 (d,  $J = 2.2$  Hz, 2H), 1.94-1.89 (m, 1H), 1.76-1.46 (m, 6H), 1.07 (d,  $J = 10.6$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  133.8, 117.9, 76.7, 57.3, 49.7, 43.2, 42.8, 42.0, 34.3, 28.5, 25.2 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{20}\text{H}_{26}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 321.1825; found: 321.1823.

**Compound 17 (cage diol):** Colorless liquid; Yield 172 mg (84%); IR (neat,  $\text{cm}^{-1}$ ): 3228, 2936, 2233, 1628, 1412, 1223, 1163, 1053, 916;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.97-5.87 (m, 2H), 5.27 (s, 2H), 5.11-5.04 (m, 4H), 2.44 (d,  $J = 1.4$  Hz, 2H), 2.18-2.13 (m, 4H), 2.03-1.90 (m, 3H), 1.76-1.46 (m, 7H), 0.50-0.47 (m, 2H), 0.33-0.29 (m, 2H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  133.8, 118.1, 77.5, 57.6, 50.5, 49.6, 43.3, 42.0, 30.7, 28.8, 25.4, 5.2, 4.7 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{22}\text{H}_{28}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 347.1982; found: 347.1981.

**Compound 21 (cage diol):** Colorless liquid; Yield 110 mg (84%); IR (neat,  $\text{cm}^{-1}$ ): 3228, 2936, 2233, 1628, 1412, 1223, 1163, 1053, 916;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.98-5.87 (m, 2H), 5.13-5.06 (m, 4H), 2.35 (d,  $J = 1.6$  Hz, 2H), 2.18-2.09 (m, 4H), 2.05-1.99 (m, 2H), 1.94-1.89 (m, 3H), 1.74-1.63 (m, 1H), 1.60-1.42 (m, 10H), 1.22 (t,  $J = 7.0$  Hz, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  133.8, 118.1, 77.5, 56.8, 56.2, 51.9, 49.7, 43.0, 42.0, 32.2, 30.1, 28.7, 25.9, 25.6, 25.3 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{24}\text{H}_{32}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 375.2295; found: 375.2292.

#### General Procedure for Synthesis of RCM Precursors 14, 18, and 22

To a suspension of sodium hydride (2.2-5.3 mmol, 8 equiv) in anhydrous DMF (5-10 mL) was added to cage diols **12**, **17** and **21** (0.28-0.67 mmol, 1 equiv) under nitrogen at 0 °C. Then the reaction mixture was stirred for 15 min at room temperature. Later on, allyl bromide (2.2-5.3 mmol, 8 equiv) was added and then stirring was continued for 5-8 h. At the end of the reaction (TLC analysis), the crude reaction mixture was quenched with saturated aq.  $\text{NH}_4\text{Cl}$  and the resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure and the resulting crude residue was subjected to silica gel column chromatography using 2-3% EtOAc/PE as an eluent to afford pure **14**, **18**, and **22** respectively, as colorless liquids.

**Compound 14:** Colorless liquid; prepared from compound **12** (200 mg, 0.67 mmol); Yield: 178 mg (78%); IR (neat,  $\text{cm}^{-1}$ ): 3369, 3076, 2950, 2625, 2449, 1644, 1456, 1302, 1105, 928, 850;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.34 (d,  $J = 2.2$  Hz, 1H), 6.08-5.79 (m, 3H), 5.26 (dq,  $J = 16.9, 1.8$  Hz, 1H), 5.13 (dq,  $J = 10.4, 1.5$  Hz, 1H), 5.09-5.01 (m, 4H), 4.01 (dt,  $J = 5.6, 1.4$  Hz, 1H), 3.98 (dt,  $J = 5.7, 1.3$  Hz, 1H), 2.45-2.15 (m, 7H), 2.02-1.88 (m, 4H), 1.70-1.56 (m, 4H), 1.50-1.44 (m, 2H), 1.10 (dt,  $J = 10.6, 1.5$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  135.2, 134.6, 133.5, 117.4, 116.9, 116.2, 82.9, 66.0, 58.4, 58.2,

50.5, 48.7, 44.0, 43.3, 43.1, 42.7, 42.2, 39.9, 34.6, 30.2, 28.4, 25.3 ppm; HRMS (ESI):  $m/z$  calcd for  $C_{23}H_{30}NaO_2 [M+Na]^+$ : 361.2138; found: 361.2136.

**Compound 18:** Colorless liquid; prepared from compound **17** (150 mg, 0.46 mmol); Yield: 145 mg (86%); IR (neat,  $cm^{-1}$ ): 3234, 2952, 1438, 1218, 1057;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  6.35 (d,  $J = 2.2$  Hz, 1H), 6.05-5.79 (m, 3H), 5.26 (d,  $J = 1.5$  Hz, 1H), 5.12 (d,  $J = 1.1$  Hz, 1H), 5.05-4.95 (m, 4H), 4.13 (dt,  $J = 11.8, 5.1$  Hz, 1H), 4.03 (dt,  $J = 11.7, 5.5$  Hz, 1H), 2.62-2.59 (m, 1H), 2.41-2.13 (m, 6H), 1.91-1.83 (m, 2H), 1.70-1.58 (m, 6H), 1.48-1.44 (m, 1H), 0.52-0.45 (m, 2H), 0.36-0.29 (m, 2H) ppm;  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  135.1, 134.5, 133.5, 117.4, 116.9, 116.1, 82.7, 76.7, 65.9, 58.5, 58.2, 51.2, 50.3, 49.3, 49.2, 43.5, 43.0, 41.9, 39.6, 30.8, 30.2, 28.4, 25.4, 5.1, 4.8 ppm; HRMS (ESI):  $m/z$  calcd for  $C_{25}H_{32}NaO_2 [M+Na]^+$ : 387.2295; found: 387.2299.

**Compound 22:** Colorless liquid; prepared from compound **21** (100 mg, 0.28 mmol); Yield: 92 mg (82%); IR (neat,  $cm^{-1}$ ): 3383, 3077, 2952, 2861, 1635, 1446, 1334, 1217, 1168, 997, 915;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  6.34 (d,  $J = 2.1$  Hz, 1H), 6.04-5.79 (m, 3H), 5.25 (dt,  $J = 16.9, 1.6$  Hz, 1H), 5.12 (dt,  $J = 10.4, 1.4$  Hz, 1H), 5.05-5.00 (m, 4H), 4.13 (dt,  $J = 5.3, 1.4$  Hz, 1H), 4.00 (dt,  $J = 6.2, 1.2$  Hz, 1H), 2.53-2.50 (m, 1H), 2.38-2.26 (m, 3H), 2.22 (dd,  $J = 14.2, 5.1$  Hz, 1H), 2.10-2.04 (m, 2H), 1.91-1.84 (m, 4H), 1.70-1.43 (m, 11H), 1.27-1.19 (m, 2H) ppm;  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  135.1, 134.6, 133.5, 117.4, 116.8, 116.1, 82.9, 65.9, 57.8, 57.6, 56.2, 52.5, 51.6, 50.4, 48.5, 43.4, 42.8, 42.0, 39.8, 32.2, 30.3, 30.2, 28.5, 26.0, 25.7, 25.3 ppm; HRMS (ESI):  $m/z$  calcd for  $C_{27}H_{36}KO_2 [M+K]^+$ : 431.2347; found: 431.2344.

### General Procedure for Synthesis of Compounds **15**, **19**, and **23** via RCM Sequence

To a stirred solution of compounds **14**, **18**, and **22** such as RCM precursors (0.20-0.44 mmol, 1 equiv) in anhydrous DCM (10 mL) was degassed with nitrogen for 10 min was added G-II catalyst (5 mol%). Then the reaction mixture was stirred at room temperature for 5-7 h. After completion of the reaction (reaction progress monitored by TLC), then the solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography using 3-5% EtOAc/PE as an eluent to give ring closure products **15**, **19** and **23** as colorless liquids.

**Compound 15:** Colorless liquid; prepared from compound **14** (150 mg, 0.44 mmol); Yield: 117 mg (85%); IR (neat,  $cm^{-1}$ ): 3328, 2955, 2857, 1440, 1374, 1267, 1182, 1072, 909;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  6.63 (d,  $J = 1.8$  Hz, 1H), 6.08-5.79 (m, 1H), 5.81-5.76 (m, 1H), 5.68-5.63 (m, 1H), 5.10-5.04 (m, 2H), 4.27-4.24 (m, 2H), 2.53 (ddd,  $J = 8.6, 3.8, 1.6$  Hz, 1H), 2.38-2.32 (m, 2H), 2.29-2.22 (m, 3H), 2.03-1.89 (m, 5H), 1.71-1.65 (m, 1H), 1.62-1.48 (m, 5H), 1.09 (dt,  $J = 10.6, 1.6$  Hz, 1H) ppm;  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  135.1, 124.1, 123.9, 116.4, 79.4, 64.8, 58.1, 56.8, 50.3, 46.3, 44.4, 43.3, 43.1, 42.8, 42.2, 34.5, 31.2, 29.7, 28.7, 25.3 ppm; HRMS (ESI):  $m/z$  calcd for  $C_{21}H_{27}O_2 [M+H]^+$ : 311.2006; found: 311.2005.

**Compound 19:** Colorless liquid; prepared from compound **18** (120 mg, 0.32 mmol); Yield: 90 mg (81%); IR (neat,  $\text{cm}^{-1}$ ): 3284, 2952, 2864, 1432, 1075, 920;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.65 (d,  $J = 1.8$  Hz, 1H), 6.04-5.93 (m, 1H), 5.77-5.72 (m, 1H), 5.66-5.63 (m, 1H), 5.02 (td,  $J = 8.9, 1.2$  Hz, 2H), 4.32-4.21 (m, 2H), 2.75 (ddd,  $J = 8.4, 3.8, 1.5$  Hz, 1H), 2.45 (ddd,  $J = 8.8, 3.6, 1.6$  Hz, 1H), 2.25-2.14 (m, 4H), 1.93-1.80 (m, 3H), 1.73-1.58 (m, 5H), 1.55-1.47 (m, 2H), 0.50-0.44 (m, 2H), 0.34-0.27 (m, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  135.0, 124.1, 123.8, 116.4, 79.3, 64.8, 58.1, 57.0, 51.0, 50.7, 49.3, 46.7, 43.6, 43.1, 42.0, 30.9, 30.7, 29.6, 28.8, 25.3, 5.1, 4.8 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{28}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 359.1982; found: 359.1986.

**Compound 23:** Colorless liquid; prepared from compound **22** (80 mg, 0.20 mmol); Yield: 61 mg (80%); IR (neat,  $\text{cm}^{-1}$ ): 3218, 2938, 2369, 1437, 1219, 1020, 915;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.64 (d,  $J = 1.9$  Hz, 1H), 6.05-5.95 (m, 1H), 5.80-5.74 (m, 1H), 5.65 (dd,  $J = 10.1, 2.6$  Hz, 1H), 5.07-5.02 (m, 2H), 4.31-4.20 (m, 2H), 2.66 (ddd,  $J = 8.3, 3.8, 1.7$  Hz, 1H), 2.37 (ddd,  $J = 8.2, 3.8, 1.8$  Hz, 1H), 2.26-2.19 (m, 2H), 2.13-2.05 (m, 2H), 1.97-1.86 (m, 5H), 1.72-1.46 (m, 11H), 1.25-1.19 (m, 2H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  135.0, 124.1, 123.8, 116.3, 79.4, 64.7, 57.4, 56.3, 56.2, 52.9, 51.6, 50.2, 45.9, 43.4, 42.9, 42.1, 32.1, 31.0, 30.2, 29.7, 28.8, 25.9, 25.7, 25.2 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{25}\text{H}_{32}\text{KO}_2$   $[\text{M}+\text{K}]^+$ : 403.2034; found: 403.2038.

### General Procedure for Synthesis of **16**, **20** and **24** via Catalytic Hydrogenation

To a stirred solution of RCM products **15**, **19** and **23** (0.20-0.32 mmol, 1 equiv) in dry EtOAc (5 mL), 10 mol% (8-10 mg) Pd/C was added. Then the resulting reaction mixture was stirred at room temperature for 4-5 h under hydrogen atmosphere (1 atm). After completion of the reaction by TLC evident, the reaction mixture was filtered through Celite pad and washed with EtOAc (10 mL). The combined washings and filtrate was evaporated under vacuum and the resulting crude residue was purified by silica gel column chromatography using 4-7% EtOAc/PE as an eluent to afford the hydrogenated products **16**, **20** and **24** as color liquids.

**Compound 16:** Colorless liquid; prepared from compound **15** (100 mg, 0.32 mmol); Yield: 84 mg (83%); IR (neat,  $\text{cm}^{-1}$ ): 3313, 2955, 2870, 1451, 1277, 1086, 1042;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.63 (d,  $J = 2.2$  Hz, 1H), 3.86-3.83 (m, 1H), 3.75-3.70 (m, 1H), 2.78-2.76 (m, 1H), 2.29-2.25 (m, 3H), 1.99-1.86 (m, 3H), 1.68-1.62 (m, 5H), 1.57-1.46 (m, 8H), 1.44-1.30 (m, 2H), 1.25-1.81 (m, 1H), 1.08 (d,  $J = 10.5$  Hz, 1H), 0.89 (t,  $J = 7.2$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  81.0, 76.6, 65.2, 58.2, 57.4, 50.0, 44.2, 43.6, 43.48, 43.43, 42.2, 39.9, 34.5, 31.3, 29.0, 28.7, 25.8, 25.3, 19.0, 15.8, 15.1 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{30}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 337.2138; found: 337.2137.

**Compound 20:** Colorless liquid; prepared from compound **19** (75 mg, 0.22 mmol); Yield: 69 mg (90%); IR (neat,  $\text{cm}^{-1}$ ): 3230, 2949, 2355, 1640, 1491, 1268, 1227, 1154, 1129, 914;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.65 (d,  $J = 2.0$  Hz, 1H), 3.86-3.84 (m, 1H), 3.78-3.73 (m, 1H), 3.02-3.00 (m, 1H), 2.48-2.46

(m, 1H), 2.16-2.12 (m, 2H), 1.89-1.85 (m, 1H), 1.66-1.52 (m, 9H), 1.50-1.42 (m, 5H), 1.35-1.26 (m, 2H), 1.14-1.08 (m, 1H), 0.86 (t,  $J = 7.0$  Hz, 3H), 0.53-0.47 (m, 2H), 0.35-0.29 (m, 2H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  80.9, 76.5, 65.2, 58.3, 57.5, 50.6, 50.4, 49.5, 44.2, 43.8, 42.6, 39.6, 31.0, 30.7, 29.1, 28.8, 25.7, 25.3, 18.9, 15.7, 15.1, 5.2, 4.8 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{32}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 363.2295; found: 363.2294.

**Compound 24:** Colorless liquid; prepared from compound **23** (75 mg, 0.20 mmol); Yield: 66 mg (87%); IR (neat,  $\text{cm}^{-1}$ ): 3379, 3077, 3013, 2945, 2857, 1639, 1446, 1337, 1215, 1185, 1169, 1047, 998, 912;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.77 (s, 1H), 3.86-3.83 (m, 1H), 3.76-3.72 (m, 1H), 2.92-2.90 (m, 1H), 2.40-2.38 (m, 1H), 2.08-2.01 (m, 2H), 1.90-1.82 (m, 3H), 1.70-1.50 (m, 12H), 1.49-1.43 (m, 5H), 1.41-1.11 (m, 6H), 1.88 (t,  $J = 7.0$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  81.1, 76.8, 65.1, 57.6, 56.7, 56.1, 52.8, 51.9, 49.8, 43.6, 43.3, 42.4, 39.7, 32.2, 31.2, 30.3, 29.1, 28.8, 26.0, 25.8, 25.7, 25.2, 18.9, 15.7, 15.1 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{25}\text{H}_{36}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$ : 391.2607; found: 391.2603.

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17. CCDC-**1825224** (**12**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). ORTEP of product **12**, please see the SI file.