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# Tandem radical cyclization-based strategy for the synthesis of oxa- and aza-cages: a case of fragmentation versus cyclization

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## ABSTRACT

A new strategy for the synthesis of oxa- and aza-cage compounds based on tandem radical cyclizations is described. The iodides **1** lead to oxa-cages **3** after two tandem radical cyclizations. The ester **10aa** on reaction with *n*-Bu<sub>3</sub>SnH and AIBN gives rise to the oxa-cage **12aa** after two tandem 5-*exo-trig* cyclizations. On the other hand, reaction of the ketones **17aa** and **21** under similar conditions furnished the oxa-cages **20aa** and **23**, respectively, via a double 5-*exo-trig* tandem radical cyclization followed by fragmentation.

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## 1. Introduction

Synthesis of strained organic molecules has been a topic of interest amongst synthetic and theoretical chemists over the past several years.<sup>1</sup> Whereas majority of the early efforts in this area were directed toward the synthesis of carbocycles, recent studies are focused on new synthetic strategies toward heteroatom-substituted bowls and cages. The synthesis of heteroatom-substituted cages is interesting on two counts viz. (i) these molecules are aesthetically pleasing and allow for testing new reactions for their synthesis as these are strained molecules and (ii) in many a cases they were thought to be more useful than their carbon analogues as they could function as ligands for chelation with metal ions and could potentially be used for transporting metal ions across the bilayers as they possessed hydrophobic and hydrophilic surfaces.<sup>2</sup> These molecules were suggested to have interesting pharmacological properties as well in the treatment of diseases ranging from Parkinson's and Alzheimer's disease to anti-viral agents against influenza and the immunodeficiency virus (HIV).<sup>3</sup> As a result, this area of the synthesis of oxa- and aza-bowls and cages continues to flourish.<sup>4</sup>

Amongst the various synthetic strategies developed for the synthesis of the oxa-bowls and cages, majority dealt with syntheses of acetal/ketal containing oxa-cage compounds which were obtained by ozonolysis of Diels–Alder adducts followed by treatment with suitable acid.<sup>5</sup> There are several other strategies which have been used for the synthesis of oxa-cages—some prominent ones include intramolecular alkene-oxirane photocycloaddition,<sup>6</sup> transannular cyclization of suitable compounds,<sup>7</sup> tandem cyclization,<sup>8</sup> dehydration of diols with proper stereochemistry,<sup>9</sup> by base promoted rearrangement<sup>10</sup>, and intramolecular etherification of an alkene bond with organoselenium reagents.<sup>11</sup> Surprisingly, radical-based strat-

egies<sup>12</sup> were not commonly available for the synthesis of oxa- and aza-bowls and cages until we described the first such report on the synthesis of oxa-cages using alkyl radical cyclization to vinylogous carbonates.<sup>13</sup> Herein, we describe a new strategy for the construction of oxa- and aza-cages employing tandem radical cyclizations. Further, we demonstrate that if the cyclization is attempted on ketones or olefins without stabilizing groups, fragmentation reactions take place leading to the new types of oxa-cages.

## 2. Result and discussion

In continuation of our interest on using vinylogous carbonates in the synthesis of cyclic ethers,<sup>14</sup> we have developed an efficient strategy for the stereoselective synthesis of asymmetric dioxo-cage compounds containing ether linkages employing a 6-*exo-trig* alkyl radical cyclization to vinylogous carbonates.<sup>13a</sup> We also established that in the cases where there is possibility of competing 5-*exo-trig* cyclization, the mono oxa-cage compounds are formed exclusively rather than the corresponding dioxo-cage compounds (Fig. 1).

We reasoned that the radical generated at C3 after the first 5-*exo-trig* cyclization (i.e., after C1–C2 bond formation) does not cyclize on the vinylogous carbonate moiety as it would be a 4-*exo-trig* cyclization reaction which is normally a difficult cyclization. Based

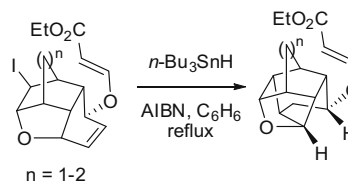
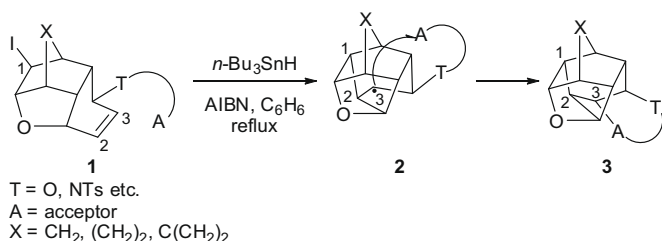


Figure 1. Unusual formation of the oxa-cage.

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**Figure 2.** Tandem radical cyclization for the synthesis of the oxa- and aza-cages.

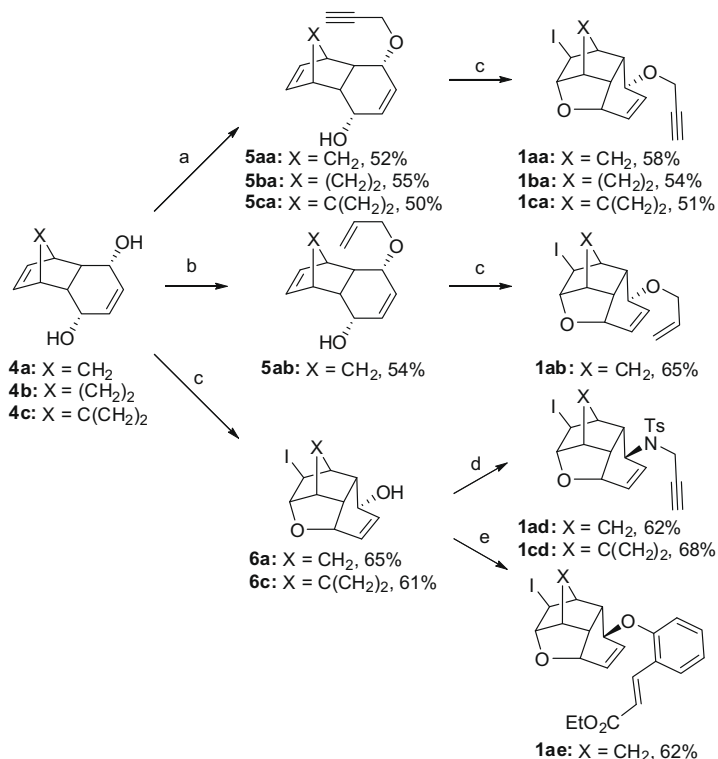
on this example, we envisioned that if vinylogous carbonate moiety is substituted by appropriate acceptor A tethered on the cyclohexene ring then the radical formed at C3 after the first 5-*exo-trig* cyclization would undergo another tandem radical cyclization on the acceptor A followed by subsequent reduction to generate a new type of cage compound (Fig. 2).

To test the feasibility of this hypothesis, synthesis of the requisite iodide precursors **1** was undertaken. Their synthesis is outlined in Scheme 1. Thus, mono-propargylation of the diols **4a–c** using NaH and propargyl bromide furnished the alcohols **5aa–ca** in moderate yields. On the other hand mono-allylation of the diol **4a** using NaH and allyl bromide gave the alcohol **5ab**. Iodoetherification of the alcohols **5aa–ca** and **5ab** using iodine and aq NaHCO<sub>3</sub> yielded the corresponding iodides **1aa–ca** and **1ab**, respectively. For the synthesis of the iodides **1ad**, **1cd**, and **1ae**, a slightly different method was used. Iodoetherification of the diols **4a** and **4c** generated the alcohols **6a** and **6c**, respectively, in good yields. The reaction of the alcohols **6a** and **6c** with DIAD, triphenylphosphine, and *N*-tosyl propargyl amine (**7**) furnished the iodides **1ad** and **1cd**, respectively. On the other hand, Mitsunobu inversion of the alcohol **6a** using ethyl *o*-hydroxycinnamate (**8**) yielded the iodide **1ae**.

Having the iodides **1** in hand, we turned our attention to the targeted radical cyclization reaction for the synthesis of oxa-cage compounds **3**. The results of this study are summarized in Table 1.

In the initial experiment, to a refluxing solution of the iodide **1aa** and AIBN in benzene was added dropwise a solution of *n*-Bu<sub>3</sub>SnH and AIBN in benzene. Gratifyingly, the oxa-cage compound **3aa** was obtained in good yields via a 5-*exo-trig*, 5-*exo-dig* tandem radical cyclization. Repetition of the same reaction on the iodides **1ba** and **1ca** furnished the corresponding oxa-cage derivatives **3ba** and **3ca** in comparable yields suggesting that a change in the bridging group does not affect the efficiency of the reaction.<sup>15</sup> The structure of the oxa-cages **3** was established based on their spectral data.<sup>16</sup> Interestingly, the cyclopropane moiety in the iodide **3ca** was not affected under the conditions employed. In an effort to expand the scope of the acceptor moiety, the reaction was carried out on the iodide **1ab** which contains an olefin as acceptor for second radical cyclization step. The reaction was found to work equally well leading to the formation of the oxa-cage **3ab** via two 5-*exo-trig* tandem radical cyclizations in good yields as a ca. 3:1 mixture of diastereomers at the methyl group bearing carbon. In a similar manner, the method could be used for the synthesis of the aza-cages **3ad** and **3cd** with comparable efficiency. The iodide **1ae** which involved a tandem 5-*exo-trig*, 6-*exo-trig* radical cyclization also underwent smooth reaction giving a ca. 3:1 diastereomeric mixture of oxa-cage **3ae** in good yields establishing the generality of this protocol.

The  $\alpha$ -alkylidene  $\gamma$ -butyrolactone moiety which is present in many biologically important natural products could be installed in these oxa-cages. The oxa-cage **3aa** was chosen as a representative example. Thus, reaction of the oxa-cage **3aa** with pyridinium dichromate (PDC) in refluxing dichloromethane furnished the desired  $\alpha$ -methylene  $\gamma$ -butyrolactones **9aa** in moderate yield (Scheme 2). Further efforts are underway to test its biological activity.



**Scheme 1.** Reagents and conditions: (a) NaH, propargyl bromide, DMF, 0 °C to rt, 12 h; (b) NaH, allyl bromide, DMF, 0 °C to rt, 12 h; (c) I<sub>2</sub>, aq NaHCO<sub>3</sub>, THF/H<sub>2</sub>O (3:1), 0 °C to rt, 1 h; (d) *N*-tosyl propargyl amine (**7**), Ph<sub>3</sub>P, DIAD, THF, rt, 4 h; (e) ethyl *o*-hydroxycinnamate (**8**), Ph<sub>3</sub>P, DIAD, THF, rt, 4 h.

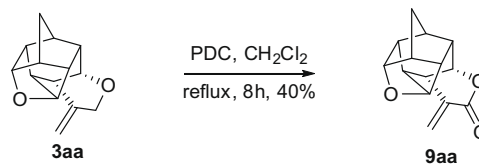
**Table 1**  
Tandem radical cyclization for the synthesis of oxa-cages

Entry	Iodide	Yield <sup>a</sup> (%)	dr	Oxa-cage product
1		70	—	
2		69	—	
3		65	—	
4		84	3:1 <sup>b</sup>	
5		68	—	
6		62	—	
7		72	3:1 <sup>b</sup>	

<sup>a</sup> Yield refers to chromatographically purified material.

<sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture.

Based on the topology of these molecules we reasoned that if the radical on C1 cyclizes to C2, it might be possible to generate a radical at C2 and cyclize to C1 (Fig. 3). For this approach to be successful, the acceptor should be substituted by the radical precursor so that the tethered radical would cyclize on the C3 generating a radical at C2 which in turn will undergo a 5-*exo-trig* cyclization furnishing the oxa-cage. The generation of the initial radical could be achieved by having an appropriate radical precursor



**Scheme 2.** Synthesis of the oxa-cage **9aa** bearing  $\alpha$ -methylene  $\gamma$ -butyrolactone moiety.

such as iodide tethered on oxygen or nitrogen of the six-membered ring. This strategy would then essentially involve two topologically driven tandem radical cyclizations leading to the formation of oxa- and aza-cages.

We envisioned that the iodides **10aa** and **10aa'** would be useful precursors to test the feasibility of the hypothesis. Monoprotection of the hydroxyl group of the diol **4a** using acetic anhydride and triethyl amine in the presence of catalytic *N,N*-dimethylaminopyridine (DMAP) furnished the alcohol **13a**. Mitsunobu inversion of the hydroxyl group in alcohol **13a** using 2-iodophenol (**14**), DIAD, and triphenyl phosphine generated the iodide **15aa** in good yield (Scheme 3). Deprotection of the acetate group in the iodide **15aa** using aq NaOH in methanol at room temperature furnished alcohol **16aa** in good yield. Hydroxyetherification of the alcohol **16aa** using *m*-CPBA followed by PCC oxidation furnished the ketone **17aa** in good yield. Horner–Wadsworth–Emmons modification of the Wittig olefination on the ketone **17aa** gave the iodide **10aa** in good yield. On the other hand, Wittig methylenation of the ketone **17aa** furnished the iodide **10aa'**.

Having the requisite iodides **10aa** and **10aa'** in hand, their reaction under standard radical conditions was studied. The iodide **10aa** when subjected to the standard radical cyclization condition gave the expected oxa-cage compound **12aa** in good yield via two tandem 5-*exo-trig* cyclizations (Scheme 4). Interestingly, reaction of the iodide **10aa'** under identical conditions furnished the oxa-cage **18aa'**. Its formation can be explained by initial two tandem 5-*exo-trig* cyclizations generating the radical intermediate **19aa'** followed by the fragmentation, as the electron-withdrawing group which can stabilize the radical is absent. Moreover, the fragmentation process, besides releasing strain, also generates a more stable alkoxy substituted radical which subsequently undergoes reduction.<sup>17</sup>

At this juncture, we were curious to explore the possibility of using carbonyl group of the ketone **17aa** as the radical acceptor. We reasoned that there is a good chance that the second step of the tandem radical cyclization on the ketone would generate an alkoxy radical which will lead to fragmentation rather than the tertiary alcohol product, in a similar fashion to the iodide **10aa'**. Thus, the ketone **17aa** was reacted with *n*-Bu<sub>3</sub>SnH and AIBN in refluxing benzene. The reaction indeed led to fragmentation product **20aa** in good yields (Scheme 5). The structure of the ketone **20aa** was unambiguously confirmed by carrying out single crystal X-ray diffraction studies (Fig. 4).<sup>18</sup> Interestingly, ozonolysis of the olefin **18aa'** followed by reductive workup also generated the same ketone **20aa** thus unambiguously ascertaining the structure of the olefin **18aa'**.

Finally, the generality of this fragmentation reaction was established by carrying out similar reactions on the alkynes **21**. Thus, reaction of the alcohols **5aa** and **5ba** with *m*-CPBA furnished the cyclized alcohols **22aa** and **22ba** which upon oxidation using PCC gave the corresponding ketone precursors **21aa** and **21ba** (Scheme 6). Treatment of the ketones **21aa** and **21ba** with *n*-Bu<sub>3</sub>SnH and AIBN in refluxing benzene followed by proto-destany-

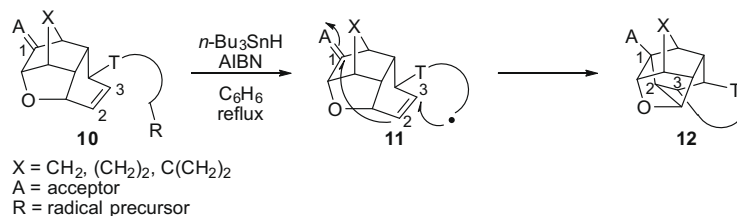
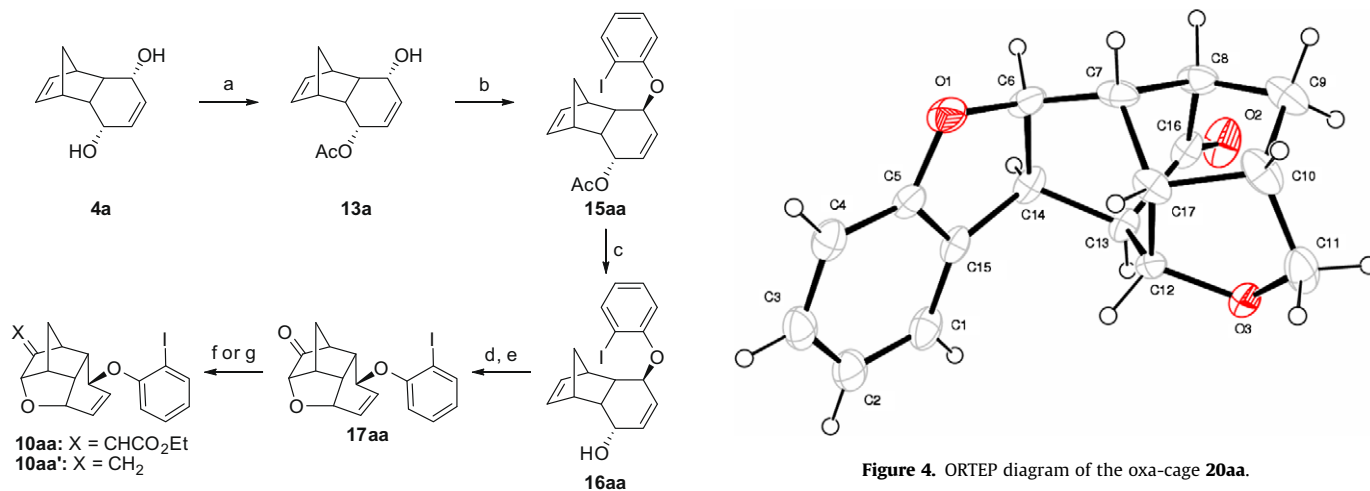
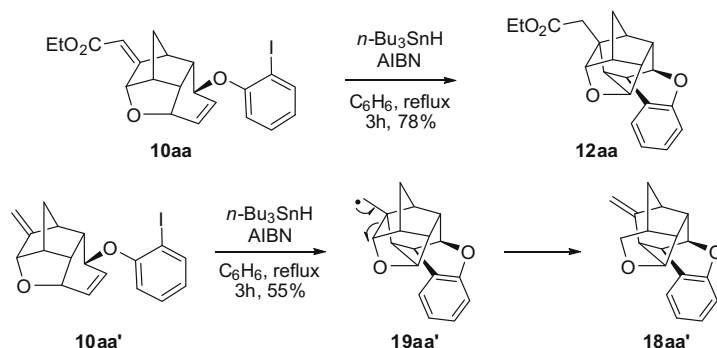


Figure 3. A new strategy for the synthesis of the oxa- and aza-cages.

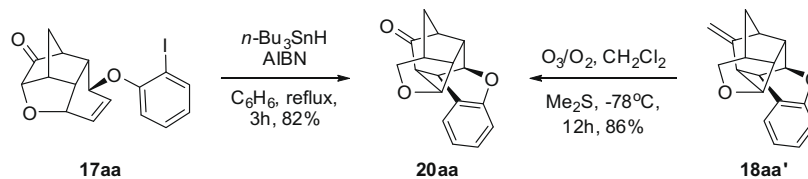
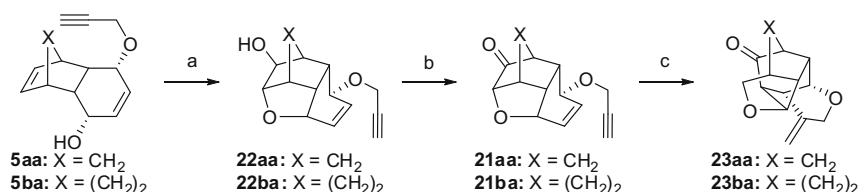
Figure 4. ORTEP diagram of the oxa-cage **20aa**.

**Scheme 3.** Reagents and conditions: (a) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, THF (1:1), 0 °C to rt, 12 h, 58%; (b) 2-iodophenol (**14**), PPh<sub>3</sub>, DIAD, THF, rt, 6 h, 67%; (c) 5% aq NaOH, MeOH, rt, 3 h, 74%; (d) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 24 h, 84%; (e) PCC, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS, rt, 3 h, 68%; (f) triethyl phosphonoacetate, NaH, THF, 0 °C to rt, 4 h, 88%; (g) Ph<sub>3</sub>P<sup>+</sup>CH<sub>3</sub>I<sup>-</sup>, *t*-BuOK, THF, 0 °C to rt, 12 h, 82%.

lation using silica indeed furnished the fragmentation products **23aa** and **23ba**, respectively, in good overall yields thus establishing the generality of this fragmentation reaction.



Scheme 4. Tandem radical reaction: cyclization versus fragmentation.

Scheme 5. Synthesis of the oxa-cage **20aa** by fragmentation reaction.

**Scheme 6.** Reagents and conditions: (a) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 24 h, 62% (**22aa**), 58% (**22ba**); (b) PCC, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å mol sieves, rt, 3 h, 50% (**21aa**), 55% (**21ba**); (c) (i) *n*-Bu<sub>3</sub>SnH, AIBN, C<sub>6</sub>H<sub>6</sub>, reflux, 3 h; (ii) SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 68% (**23aa**), 63% (**23ba**) (over two steps).

### 3. Conclusions

In conclusion, we have developed a tandem radical cyclization-based strategy for the construction of novel oxa- and aza-cage systems. We have shown that the molecular topology plays an important role allowing for the construction of the oxa- and aza-cages after two tandem 5-*exo-trig* or 5-*exo-trig*, 5-*exo-dig* or 5-*exo-trig*, 6-*exo-trig* cyclizations. Further, we have demonstrated that the nature of the acceptor moiety plays an important role in dictating the outcome of cyclization reaction versus fragmentation reaction and that the fragmentation reaction after the initial two tandem 5-*exo-trig* cyclizations generates a new type of oxa- and aza-cage compounds.

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- Representative experimental procedure*: To a stirred, refluxing solution of the iodide **1ba** (90.0 mg, 0.25 mmol) and AIBN (8.5 mg, 0.05 mmol) in dry benzene (15 mL) was added a solution of *n*-Bu<sub>3</sub>SnH (136  $\mu$ L, 0.51 mmol) and AIBN (8.5 mg, 0.05 mmol) in dry benzene (10 mL) over a period of 2 h under nitrogen atmosphere. The reaction mixture was further refluxed till completion (ca. 3 h, TLC control). It was then cooled and the solvent was removed under reduced pressure. Purification of the residue by silica gel column chromatography using ethyl acetate/hexanes (1:15) as eluent furnished the oxa-cage **3ba** (40.0 mg, 69%) as a white solid.
- All the compounds exhibited spectral data consistent with their structures. Melting point, IR, NMR (<sup>1</sup>H and <sup>13</sup>C), and HRMS spectral data for some of the compounds are as follows: Oxa-cage **3ba**: IR (neat) 3075, 2930, 2859, 1669, 1464, 1446, 1416, 1355, 1294, 1181, 1137, 1087, 1058, 1044, 1008, 1030, 1016, 970, 962, 951, 909, 885, 863, 811, 798, 760, 729, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.97–4.94 (m, 1H), 4.88 (q, *J* = 2.4 Hz, 1H), 4.45–4.30 (m, 4H), 4.23 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.01 (ddd, *J* = 9.6, 3.2, 1.6 Hz, 1H), 2.27 (ddd, *J* = 7.2, 4.4, 3.2 Hz, 1H), 2.08 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.05–1.90 (m, 2H), 1.80–1.75 (m, 1H), 1.75–1.60 (m, 3H), 1.55–1.40 (m, 1H), 1.30–1.15 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  150.54 (C), 103.22 (CH<sub>2</sub>), 79.49 (CH), 79.38 (CH), 78.84 (CH), 72.70 (CH<sub>2</sub>), 43.24 (CH), 42.04 (CH), 37.90 (CH), 37.56 (CH), 36.89 (CH), 35.37 (CH), 24.18 (CH), 22.50 (CH<sub>2</sub>), 17.10 (CH<sub>2</sub>); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>15</sub>H<sub>19</sub>O<sub>2</sub> 231.1385, found 231.1389. Oxa-cage **3ad**: IR (neat) 2979, 2880, 1598, 1456, 1366, 1344, 1317, 1268, 1162, 1093, 1042, 1014, 1004, 986, 959, 910, 840, 817, 780, 759, 735, 709 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.05 (q, *J* = 2.0 Hz, 1H), 4.98 (q, *J* = 2.0 Hz, 1H), 4.60–4.57 (m, 1H), 4.29 (br s, 1H), 4.12 (dq, *J* = 12.4, 2.0 Hz, 1H), 3.57 (dt, *J* = 14.0, 2.0 Hz, 1H), 3.35 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.79 (d, *J* = 8.8 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.44 (s, 3H), 2.32 (t, *J* = 5.6 Hz, 1H), 2.01 (q, *J* = 5.2 Hz, 1H), 2.00–1.90 (m, 1H), 1.68 (dt, *J* = 6.4, 2.0 Hz, 1H), 1.51 (ABX, *J* = 10.4, 1.6 Hz, 1H), 1.38 (ABX, *J* = 10.4, 0.0 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  146.36 (C), 144.01 (C), 132.01 (C), 129.84 (2  $\times$  CH), 128.20 (2  $\times$  CH), 108.46 (CH<sub>2</sub>), 85.46 (CH), 76.68 (CH), 57.53 (CH), 54.23 (CH<sub>2</sub>), 47.90 (CH), 46.47 (CH), 43.70 (CH), 38.98 (CH), 38.02 (2  $\times$  CH), 37.61 (CH), 31.95 (CH<sub>2</sub>), 21.72 (CH<sub>3</sub>); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub> 370.1477, found 370.1481. Oxa-cage **12aa**: IR (neat) 2981, 1728, 1596, 1477, 1461, 1368, 1313, 1229, 1200, 1181, 1148, 1059, 1015, 1003, 946, 914, 749 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.17 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.93 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.48 (br s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.87 (br s, 1H), 3.41 (d, *J* = 9.0 Hz, 1H), 2.52 (br s, 1H), 2.45 (AB, *J* = 13.7 Hz, 1H), 2.41 (AB, *J* = 13.7 Hz, 1H), 2.35 (q, *J* = 5.6 Hz, 1H), 2.17 (t, *J* = 5.8 Hz, 1H), 2.06 (br s, 1H), 1.70 (br s, 1H), 1.65 (AB, *J* = 10.6 Hz, 1H), 1.36 (AB, *J* = 10.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  171.59 (C), 159.90 (C), 129.39 (C), 128.68 (CH), 125.11 (CH), 120.78 (CH), 109.40 (CH), 89.82 (CH), 80.00 (CH), 77.48 (CH), 60.72 (CH<sub>2</sub>), 50.29 (CH), 48.59 (CH), 45.53 (CH), 43.03 (CH), 42.92 (CH), 39.35 (CH<sub>2</sub>), 37.00 (CH), 37.00 (C), 31.11 (CH<sub>2</sub>), 14.47 (CH<sub>3</sub>); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>21</sub>H<sub>23</sub>O<sub>4</sub> 339.1596; found 339.1591. Oxa-cage **20aa**: mp 216–218 °C; IR (neat) 2956, 2930, 2906, 2864, 1727, 1596, 1478, 1461, 1232, 1168, 1072, 1016, 929, 856, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.20–7.10 (m, 2H), 6.88 (td, *J* = 7.3, 0.7 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.13 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.90–3.80 (m, 2H), 3.60 (ABX, *J* = 8.7, 0.0 Hz, 1H), 3.56 (ABX, *J* = 8.7, 4.0 Hz, 1H), 2.94 (t, *J* = 3.4 Hz, 1H), 2.95–2.85 (m, 2H), 2.85–2.75 (m, 1H), 2.65–2.55 (m, 1H), 2.38 (ddd, *J* = 13.8, 10.4, 8.0 Hz, 1H), 1.49 (dd, *J* = 13.8, 2.5 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  214.29 (C), 159.39 (C), 129.42 (CH), 125.27 (C), 125.27 (CH), 121.14 (CH), 109.63 (CH), 79.13 (CH), 73.97 (CH), 73.21 (CH<sub>2</sub>), 51.28 (CH), 50.03 (CH), 46.72 (CH), 41.87 (2  $\times$  CH), 41.71 (CH), 36.05 (CH<sub>2</sub>); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>O<sub>3</sub> 269.1178, found 269.1175. Oxa-cage **18aa**: IR (neat) 2930, 2856, 1598, 1506, 1478, 1460, 1352, 1236, 1176, 1082, 1046, 1016, 988, 964, 949, 913, 852, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.05 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.98 (s, 1H), 4.86 (s, 1H), 3.76 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.65 (dd, *J* = 10.6, 4.2 Hz, 1H), 3.65–3.60 (m, 2H), 2.79 (t, *J* = 3.5 Hz, 1H), 2.75–2.60 (m, 3H), 2.54 (q, *J* = 4.0 Hz, 1H), 2.35 (ddd, *J* = 12.9, 10.3, 6.5 Hz, 1H), 1.33 (dd, *J* = 12.9, 2.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  159.61 (C), 151.82 (C), 128.73 (CH), 127.14 (C), 125.34 (CH), 120.60 (CH), 110.90 (CH<sub>2</sub>), 109.32 (CH), 80.89 (CH), 76.42 (CH), 74.08 (CH<sub>2</sub>), 45.27 (CH), 45.20 (CH), 43.95 (CH), 42.02 (2  $\times$  CH), 41.93 (CH<sub>2</sub>), 41.88 (CH); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>18</sub>H<sub>19</sub>O<sub>2</sub> 267.1385, found 267.1386. Oxa-cage **23aa**: mp 142–144 °C; IR (neat) 2957, 2933, 2903, 2864, 2818, 1721, 1668, 1360, 1265, 1209, 1198, 1157, 1079, 1035, 966, 940, 928, 901, 884, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.11 (q, *J* = 2.0 Hz, 1H), 5.06 (q, *J* = 2.0 Hz, 1H), 4.43 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.32 (ABX, *J* = 12.6, 1.6 Hz, 1H), 4.25–4.15 (m, 2H), 3.76 (ABX, *J* = 8.7, 3.7 Hz, 1H), 3.69 (ABX, *J* = 8.7, 0.0 Hz, 1H), 3.00–2.90 (m, 1H), 2.85–2.75 (m, 2H), 2.75 (q, *J* = 4.0 Hz, 1H), 2.70 (t, *J* = 3.1 Hz, 1H), 2.67 (t, *J* = 4.2 Hz, 1H), 2.30–2.20 (m, 1H), 1.42 (dd, *J* = 13.4, 1.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, DEPT)  $\delta$  213.94 (C), 147.26 (C), 107.39 (CH<sub>2</sub>), 77.48 (CH), 76.96 (CH), 74.75 (CH<sub>2</sub>), 72.22 (CH<sub>2</sub>), 53.41 (CH), 49.40 (CH), 46.05 (CH), 44.52 (CH), 43.76 (CH), 41.85 (CH), 35.38 (CH<sub>2</sub>); HRMS (ESI, M+H<sup>+</sup>) *m/z* calcd for C<sub>14</sub>H<sub>17</sub>O<sub>3</sub> 233.1178, found 233.1183.
- For some selected examples for fragmentation reactions using radicals, see: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, 108, 8102; (b) Nishida, A.

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18. Crystal data for oxa-cage **20aa**: Formula: C<sub>17</sub>H<sub>16</sub>O<sub>3</sub>; unit cell parameters: *a* 22.783(3) *b* 6.4262(8) *c* 19.301(2)  $\beta$  116.444(5) space group C2/c; CCDC No. 770582. CCDC 770582 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).