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Topologically driven tandem radical cyclization-based strategy for the synthesis of oxa- and aza-cages

Santosh J. Gharpure *, Suheel K. Porwal

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India

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ABSTRACT

Tandem radical cyclization-based strategy for the synthesis of oxa- and aza-cage compounds is described. The aryl iodides **1** and *N*-tosyl propargylated amine **8** lead to oxa- and aza-cages, respectively, after two tandem 5-*exo*-*trig* radical cyclizations. The alcohols **11** on reaction with $^{n}Bu_3SnH$ and AIBN give rise to the oxa-cages **14** bearing the tributyltin moiety after three tandem 5-*exo*-*trig* cyclizations. On the other hand, reaction of the propargyl ether **16** under similar conditions furnishes the oxa-cage **17** by a 5-*exo*-*trig*, 4-*exo*-*trig*, 5-*exo*-*trig* tandem radical cyclization sequence.

1. Introduction

Over the past several years, synthesis of strained organic molecules has attracted considerable attention.[1] Majority of the early efforts in this area were directed toward the synthesis of carbacycles. Subsequent studies on heteroatom-substituted bowls and cages demonstrated that these molecules are interesting targets. Not only are these molecules esthetically pleasing but also in many a case they are 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 possess hydrophobic and hydrophilic surfaces. These molecules were implicated for their 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).[2] These findings have provided further impetus particularly for the synthesis of oxa- and aza-bowls and cages.[3]

Majority of the work reported on the oxa-bowls and cages 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.[4] In addition to these studies, there are other strategies which have been described in the literature for the synthesis of oxa-cages and these include intramolecular alkene-oxirane photocycloaddition,[5] transannular cyclization of suitable compounds,[6] tandem cyclization,[7] dehydration of diols with proper stereochemistry,[8] by base-promoted rearrangement[9] and intramolecular etherification of an alkene bond with organoselenium reagents.[10] Even though a variety of methods are reported for the synthesis of oxa- and aza-bowls and cages, tandem radical cyclization-based strategies[11] are not commonly found in this area. Herein, we describe a novel strategy for the construction of oxa- and aza-cages employing tandem radical cyclizations which is driven by the topology of these molecules. This strategy also allows for the incorporation of tributyltin moiety in the oxa-cage structure which could be potentially exploited for further functionalization.

2. Result and discussion

In continuation of our interest on using vinylogous carbonates in the synthesis of cyclic ethers,[12] we have developed an efficient strategy for the stereoselective synthesis of unsymmetrical dioxa-cage compounds containing ether linkages employing a 6-*exo*-*trig* alkyl radical cyclization to vinylogous carbonates. We also established that in the cases where there is a possibility of competing 5-*exo*-*trig* cyclization, the mono oxa-cage compounds are formed exclusively rather than the corresponding dioxa-cage com-

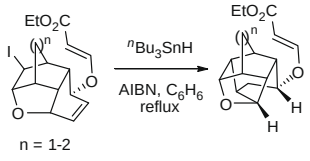

Figure 1. Unusual formation of the oxa-cage.

* Corresponding author. Tel.: +91 44 22574228; fax: +91 44 22574202.
E-mail address: sjgharpure@iitm.ac.in (S.J. Gharpure).

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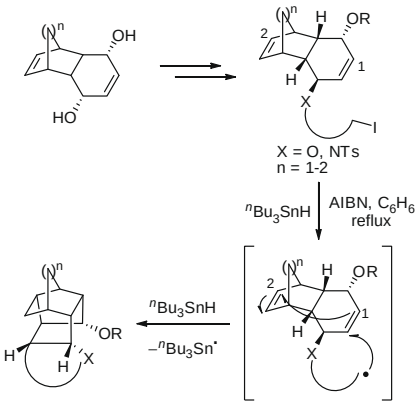


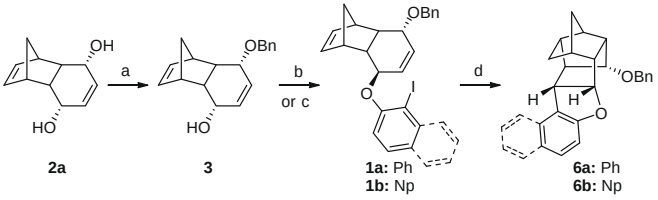
Figure 2. New strategy for the synthesis of the oxa- and aza-cages.

pounds (Fig. 1). Based on this example, we envisioned that a radical generated at C-1 would undergo a 5-*exo-trig* cyclization to form a bond between C-1 and C-2 followed by a subsequent reduction leading to the cage compound (Fig. 2).

The generation of the radical at C-1 in turn could be achieved by tethering an appropriate radical precursor such as iodide on oxygen or nitrogen. The required substrates could be synthesized starting from the known diols obtained from Diels–Alder adducts of cyclic dienes and benzoquinone. This strategy would then essentially involve two topologically driven tandem 5-*exo-trig* radical cyclizations leading to the formation of oxa- and aza-cages.

We envisioned that the iodides **1a–b** would be useful precursors to test the feasibility of the hypothesis. Their synthesis is outlined in Scheme 1. Monoprotection of the hydroxyl group of the diol **2a** using NaH and benzyl bromide furnished the alcohol **3**. The reaction of the alcohol **3** with DIAD, triphenylphosphine, and 2-iodophenol (**4**) generated the iodide **1a**. On the other hand, Mitsunobu inversion of the hydroxyl group in the alcohol **3** using 1-iodo-2-naphthol (**5**) generated the iodide **1b** in good yield (Scheme 1). Having the requisite iodide precursors in hand, we turned our attention to test the feasibility of the proposed radical cyclization. Thus, a slow addition of a solution of tributyltin hydride and AIBN in benzene to a refluxing solution of the iodide **1a** and AIBN in benzene, gratifyingly yielded the expected oxa-cage compound **6a** in good yield. The structure of the oxa-cage **6a** was established with the help of spectroscopic analysis.[13] Further, the stereochemistry was unambiguously confirmed by single crystal X-ray diffraction studies (Fig. 3).[14] The reaction of the iodide **1b** was uneventful furnishing the oxa-cage **6b** in 64% yield.

We argued that incorporation of the nitrogen atom in the cage, would give rise to aza-cages and expand the scope of this strategy. Thus, Mitsunobu inversion of the alcohol **3** using *N*-tosyl propargyl amine (**7**) furnished the dienyne **8** (Scheme 2). The dienyne **8** was then subjected to standard radical conditions using tributyltin hydride and AIBN. The addition of the tributyltin radical to alkyne lead to the formation of vinyl radical, which underwent a 5-*exo-trig* cyclization followed by another 5-*exo-trig* cyclization to furnish a mixture of the vinyl tin derivatives **9**. Treatment of the stanane **9** with acetic acid in methanol for three days resulted in the olefin **10** after proto-destanylation. These examples demonstrated that it is indeed possible to make use of the topology of these Diels–Alder adducts for the synthesis of the oxa- and aza-cage compounds.



Scheme 1. Reagents, conditions, and yields: (a) NaH, BnBr, DMF, 0 °C–rt, 12 h, 55%; (b) 2-iodophenol (**4**), Ph$_3$P, DIAD, THF, rt, 4 h, 68%; (c) 1-iodo-2-naphthol (**5**), Ph$_3$P, DIAD, THF, rt, 4 h, 58%; (d) ^{n}Bu$_3$SnH, AIBN, C$_6$H$_6$, reflux, 3 h, 70% (for **6a**), 64% (for **6b**).

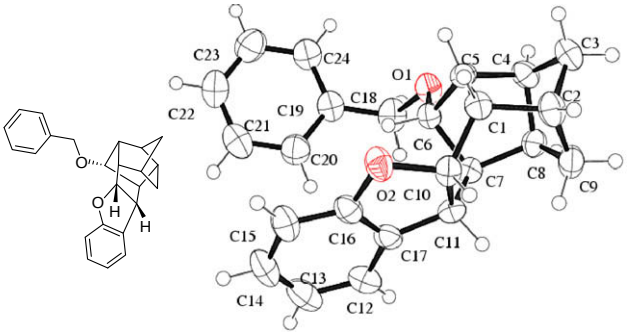
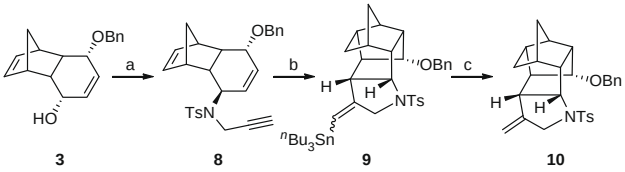


Figure 3. ORTEP diagram of the oxa-cage **6a**.



Scheme 2. Reagents, conditions, and yields: (a) *N*-tosyl propargyl amine (**7**), Ph$_3$P, DIAD, THF, rt, 4 h, 69%; (b) ^{n}Bu$_3$SnH, AIBN, C$_6$H$_6$, reflux, 3 h, 75%; (c) AcOH, MeOH, rt, 3 days, 82%.

The synthesis of this aza-cage **9** prompted us to further ponder if the vinylstanane can also be used as the radical acceptor so as to lead to the third 5-*exo-trig* cyclization. Clearly, the reason why this otherwise facile 5-*exo-trig* radical cyclization is not taking place here is because of the molecular topology—during the Mitsunobu inversion the stereochemistry at the carbon bearing nitrogen was inverted. We argued that if this inversion is avoided, the radical intermediate generated after the first two cyclizations would undergo third 5-*exo-trig* cyclization to generate a tributytin-bearing cage compound. The logical precursor then would be the alkyne **11** which would undergo intermolecular addition of the tributyltin radical generating a vinyl radical. The intramolecular addition of this vinyl radical to olefin in 5-*exo-trig* fashion would lead to the radical intermediate **12** (Fig. 4). Further 5-*exo-trig* cyclization of **12** would give rise to

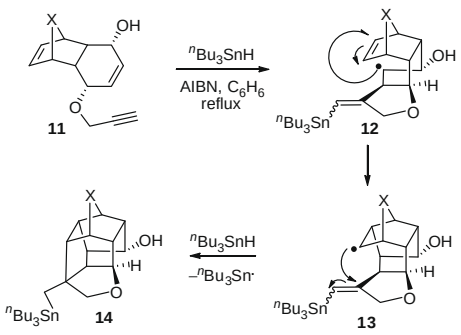


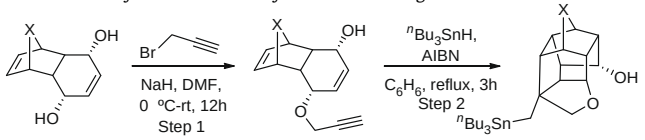
Figure 4. Tandem radical cyclization for the synthesis of oxa-cages.

a new radical **13**. Finally, this radical intermediate **13** would lead to the oxa-cage **14** after third 5-*exo-trig* cyclization followed by subsequent reduction with tributyltin hydride.

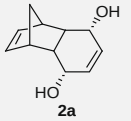
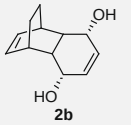
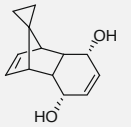
To test the feasibility of this hypothesis, synthesis of the propargylated alcohol **11a** (X = CH_2) was undertaken. Thus, treatment of the diol **2a** with NaH and propargyl bromide furnished the mono-propargylated alcohol **11a**. The alcohol **11a** was directly used in the radical cyclization reaction. Gratifyingly, a slow addition of a solution of tributyltin hydride and AIBN in benzene to a refluxing solution of the alkyne **11a** and AIBN in benzene furnished the oxa-cage **14a** after three successive 5-*exo-trig* radical cyclization reactions (Table 1, entry 1). To establish the generality of this protocol the alcohols **11b–c** were synthesised from the corresponding diols **2b–c**. The treatment of the alcohols **11b–c** under standard radical conditions leads to the formation of the stanyl oxa-cages **14b–c**, respectively, in good yields (Table 1, entries 2 and 3). To our knowledge, these are the first examples of the oxa-cages which contain tributylstanyl moiety.

Finally, we envisioned that replacing one of the 5-*exo-trig* cyclization steps by a 4-*exo-trig* cyclization would be challenging and highlight the utility of this protocol further by introducing a four-membered ring in the oxa-cage. To this end, the known[15] alcohol **15** was converted to its propargyl ether derivative **16**. We were delighted to see that reaction of the ether **16** with tributyltin hydride and AIBN in refluxing benzene indeed furnished the oxa-cage **17** albeit in lower yield compared to earlier cases (Scheme 3). However, given the difficulties associated with the four-membered ring formations, it is remarkable that this product forms at all. We believe that this is possible due to the topology of the molecules which restricts the conformational flexibility of the radical generated after the first 5-*exo-trig* cyclization thereby facilitating the 4-*exo-trig* cyclization.[16] The radical thus generated subsequently undergoes the third cyclization—this time a 5-*exo-trig* cyclization leading to the formation of the oxa-cage **17**.

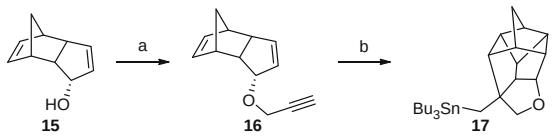
Table 1
Tandem radical cyclization for the synthesis of oxa-cages



2 **11** **14**

Entry	Diol	Yield[a] (%)		Oxa-cage product
		Step 1	Step 2	
1	 **2a**	58	72	 **14a**
2	 **2b**	55	65	 **14b**
3	 **2c**	57	68	 **14c**

[a] Yield refers to chromatographically purified material.



15 **16** **17**

Scheme 3. Reagents, conditions, and yields: (a) NaH, propargyl bromide, DMF, 0 °C–rt, 12 h, 65%; (b) ^{n}Bu$_3$SnH, AIBN, C$_6$H$_6$, reflux, 3 h, 35%.

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-cages after three tandem 5-*exo-trig* cyclizations. The strain involved in these molecules can be beneficially used in the construction of oxa-cages bearing a four-membered ring. These are the first examples of oxa-cages which also incorporate the tributylstanyl moiety which could be further used in functionalizing these oxa-cages.

4. Representative experimental procedure

To a stirred, refluxing solution of the alcohol **11a** (102.0 mg, 0.47 mmol) and AIBN (16.0 mg, 0.1 mmol) in dry benzene (15 ml) was added a solution of ^{n}Bu$_3$SnH (254 μl, 0.944 mmol) and AIBN (16.0 mg, 0.1 mmol) in dry benzene (15 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 (1:4) as eluent furnished the oxa-cage **14a** (172.0 mg, 72%) as a colorless oil.

Acknowledgments

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13. All the compounds exhibited spectral data consistent with their structures. Melting point, IR, NMR, (^{1}H and ^{13}C) and HRMS spectral data for some of the compounds are as follows: Oxa-cage **6a**: Mp 168–170 °C. IR (neat): 3001, 2938, 2869, 1592, 1474, 1456, 1365, 1228, 1072, 1052, 956, 943, 869, 750, 734, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.10 (m, 5H), 7.05–6.95 (m, 2H), 6.89 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.68 (dd, J = 9.2, 2.0 Hz, 1H), 4.19 (AB, J = 12.0 Hz, 1H), 4.11 (AB, J = 12.0 Hz, 1H), 3.71 (dd, J = 9.2, 2.0 Hz, 1H), 3.47 (d, J = 0.8 Hz, 1H), 2.89 (br s, 1H), 2.65–2.60 (m, 1H), 2.45–2.35 (m, 2H), 2.35–2.25 (m, 1H), 2.21 (br s, 1H), 1.75 (ABX, J = 12.8, 0.0 Hz, 1H), 1.64 (AB, J = 10.3 Hz, 1H), 1.36 (AB, J = 10.3 Hz, 1H), 1.32 (ABX, J = 12.8, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 159.35 (C), 138.93 (C), 131.51 (C), 128.39 (CH), 128.28 (2 × CH), 127.79 (2 × CH), 127.30 (CH), 124.15 (CH), 120.68 (CH), 109.34 (CH), 84.47 (CH), 79.18 (CH), 69.50 (CH_2), 47.91 (CH), 47.83 (CH), 47.46 (CH), 46.33 (CH), 44.20 (CH), 38.45 (CH_2), 38.05 (CH), 35.85 (CH), 33.26 (CH_2). HRMS (ESI, M+Na$^+$): calcd for $C_{24}H_{24}O_2Na$: 367.1674; found 367.1669. Aza-cage **10**: IR (neat): 2941, 2870, 1598, 1494, 1454, 1352, 1337, 1305 1160, 1091, 1043, 1024, 1014, 906, 814, 727 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 7.62 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.35–7.20 (m, 5H), 5.02 (d, J = 2.0 Hz, 1H), 4.95 (d, J = 2.0 Hz, 1H), 4.43 (AB, J = 12.4 Hz, 1H), 4.39 (AB, J = 12.4 Hz, 1H), 4.04 (AB, J = 14.4 Hz, 1H), 3.79 (s, 1H), 3.64 (AB, J = 14.4 Hz, 1H), 3.27 (AB, J = 9.2 Hz, 1H), 3.15–3.05 (m, 2H), 2.82 (br s, 1H), 2.44 (s, 3H), 2.31 (br s, 3H), 2.14 (br s, 1H), 1.60–1.50 (m, 2H), 1.30–1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 147.62 (C), 143.80 (C), 139.35 (C), 129.80 (2 × CH), 128.40 (2 × CH), 128.09 (2 × CH), 127.59 (2 × CH), 127.45 (CH), 106.48 (CH_2), 80.12 (CH), 69.50 (CH_2), 61.67 (CH), 54.87 (CH_2), 49.16 (CH), 47.61(CH), 47.25 (CH), 46.62 (CH), 43.42 (CH), 39.54 (CH), 38.09 (CH_2), 35.58 (CH), 33.75 (CH_2), 21.67 (CH_3). HRMS (ESI, M+H$^+$): calcd for $C_{28}H_{32}NO_3S$ 462.2103; found 462.2115. Oxa-cage **14a**: IR (neat): 3406, 2952, 2921, 2868, 1462, 1376, 1340, 1290, 1067, 1043, 993, 919, 874, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20–4.05 (m, 2H), 3.84 (AB, J = 7.7 Hz, 1H), 3.48 (AB, J = 7.7 Hz, 1H), 2.79 (q, J = 7.0 Hz, 1H), 2.65 (br s, 1H), 2.47 (dt, J = 7.3, 2.4 Hz, 1H), 2.25 (t, J = 6.8 Hz, 1H), 2.20–2.15 (m, 2H), 2.15–2.05 (m, 1H), 1.85–1.80 (m, 1H), 1.62 (br s, 1H), 1.55–1.25 (m, 14H), 1.06 (AB, J = 13.2 Hz, 1H), 0.89 (t, J = 7.3 Hz, 9H), 0.85–0.75 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 76.60 (CH_2), 76.42 (CH), 74.15 (CH), 57.55 (CH), 56.30 (CH), 54.32 (C), 48.28 (CH), 47.84 (CH), 47.03 (CH), 44.71 (CH), 42.94 (CH), 40.96 (CH), 37.75 (CH_2), 29.33 (3 × CH_2), 27.54 (3 × CH_2), 15.96 (CH_2), 13.81 (3 × CH_3), 10.16 (3 × CH_2). HRMS (ESI, M+H$^+$): calcd for $C_{26}H_{43}O_2Sn$ 507.2285, found 507.2283. Oxa-cage **17**: IR (neat): 2953, 2922, 2853, 1463, 1376, 1336, 1072, 1064, 1042, 954, 938, 881, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 (dd, J = 7.1, 5.2 Hz, 1H), 4.16 (AB, J = 8.0 Hz, 1H), 3.68 (AB, J = 8.0 Hz, 1H), 2.88 (qn, J = 5.7 Hz, 1H), 2.70–2.60 (m, 2H), 2.60–2.55 (m, 1H), 2.51 (br s, 1H), 2.35–2.25 (m, 2H), 2.04 (br s, 1H) 1.50–1.35 (m, 8H), 1.35–1.25 (m, 6H), 0.95 (AB, J = 13.2 Hz, 1H), 0.88 (t, J = 7.2 Hz, 9H), 0.85–0.75 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 88.97 (CH), 79.39 (CH_2), 59.23 (C), 58.68 (CH), 57.68 (CH), 51.42 (CH), 47.64 (CH), 44.63 (CH), 42.06 (CH), 41.68 (CH_2), 40.45 (CH), 36.50 (CH), 29.34 (3 × CH_2), 27.54 (3 × CH_2), 17.46 (CH_2), 13.81 (3 × CH_3), 10.17 (3 × CH_2). HRMS (ESI, M+H$^+$): calcd for $C_{25}H_{43}OSn$ 479.2336, found 479.2327.
14. Crystal data for Oxa-cage **6a**: formula: $C_{24}H_{24}O_2$; unit cell parameters: a 6.0096(5) b 16.600(2) c 17.666(2); space group $P212121$; CCDC No. 747002. CCDC 747002 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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