Spiro annulation of cage polycycles via Grignard reaction and ring-closing metathesis as key steps

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Full Research Paper

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Abstract
A simple synthetic strategy to \(C_2\)-symmetric bis-spiro-pyrano cage compound 7 involving ring-closing metathesis is reported. The hexacyclic dione 10 was prepared from simple and readily available starting materials such as 1,4-naphthoquinone and cyclopenta diene. The synthesis of an unprecedented octacyclic cage compound through intramolecular Diels–Alder (DA) reaction as a key step is described. The structures of three new cage compounds 7, 12 and 18 were confirmed by single crystal X-ray diffraction studies.

Introduction
Design and synthesis of architecturally intricate cage molecules is a worthwhile challenge. The unique properties associated with the carbocyclic cage frameworks are the main reasons for pursuing their synthesis [1,2]. They are valuable synthons to assemble natural as well as non-natural products [3,4]. In addition, the cage molecules are interesting targets because of their unusual structural features such as the deformation of the ideal C–C bond angles, high degree of symmetry and the enhanced ring strain etc. [5–18].

The structures of a variety of intricate cage systems, for example, snoutane (1) [5], pentaprismane (2) [10], dodecahedrane (3) [11-19], cage crown ether 4 [20], amantadine (5) and pushpakenediol (6) [21] along with the target molecule 7 are shown in Figure 1. Interestingly the amino group containing cage molecule amantadine (5) exhibits antiviral properties [22].

Although, several methods are available for the construction of cage compounds [7,23-33], the synthesis of symmetrical spirocage molecule 7 seems to be a synthetic challenge due to the proximity of the two carbonyl groups in dione 10 which provides a hemiketal with various nucleophiles [34-39]. In view of various applications of cage molecules and the documented difficulties in their synthesis, we conceived a short synthetic
Figure 1: Structures of diverse biologically as well as theoretically interesting molecules.

Figure 2: Retrosynthetic analysis of bis-spiro-pyrano cage compound 7. To this end, the Grignard addition and ring-closing metathesis (RCM) are considered as viable options. The retrosynthetic analysis to the target bis-spiro-cage compound 7 is shown in Figure 2. The target compound 7 could be obtained from O-allylation of the Grignard addition product 11 followed by the two-fold RCM sequence. The required cage dione 10 could be constructed in two steps from readily available starting materials such as 1,4-naphthoquinone (9) and cyclopentadiene (8) [40,41].

Results and Discussion

In connection with the synthesis of new cage molecules, we reported a new approach to the hexacyclic dione 10 and related systems via Claisen rearrangement and RCM as key steps [21,30]. Here, we have prepared the cage dione 10 by the known route involving two atom-economic protocols such as Diels–Alder reaction and [2 + 2] photocycloaddition [42-45] (Scheme 1).

Later, the hexacyclic cage dione 10 was subjected to a Grignard reaction with commercially available allylmagnesium bromide in diethyl ether. Under these conditions, we realized the formation of hemiketal 12 in 84.7% yield instead of the expected diallylated product 11 (Scheme 2). In similar fashion, the cage dione 10 was treated with commercially available vinylmagnesium bromide and the hemiketal 13 [46,47] was obtained in 89.2% yield instead of the desired divinylated compound 14 (Scheme 2). The proximity of the carbonyl groups may be responsible for the formation of hemiketals.

The structures of both these heptacyclic hemiketals 12 and 13 have been confirmed by $^1$H and $^{13}$C NMR spectral data and further supported by HRMS data. Finally their structures have been unambiguously established by single crystal X-ray diffraction studies [48] (Figure 3).

Since our goal was to synthesize the diallylated compound 11, we screened various reaction conditions and finally, we found that the addition of the ethereal solution of the hexacyclic dione
10 to a freshly prepared allyl Grignard reagent at 0 °C gave the expected diallylated compound 11 in 88% yield (Scheme 3). The Grignard reagent at higher concentration (1.0 M solution) exists as a mixture of dimer, trimer and polymeric components. However, the home-made Grignard reagent at low concentration (0.1 M solution) exists mostly in the monomeric form. So, we speculate that the difference in the concentration may be responsible for the formation of diol 11 [49-51]. Alternatively, when the diketone was reacted with an excess amount of Grignard reagent, the carbonyl groups are attacked simultaneously by the Grignard reagent and resulted in the formation of diol 11. When an excess amount of substrate containing carbonyl group was reacted with a limited amount of Grignard reagent, the oxyanion formed by the Grignard reagent attacks the other carbonyl group in a transannular fashion to generate hemiketal derivatives 12 and 13.

Later, the diallyldiol 11 was subjected to an O-allylation sequence under NaH/allyl bromide conditions in DMF to deliver the desired tetraallyl compound 15 (53%) along with the triallyl compound 16 (34.3%) (Scheme 4). Subsequently, the tetraallyl compound 15 was subjected to an RCM sequence with the aid of Grubbs’ first generation catalyst (G-I) in dry CH2Cl2. Surprisingly under these conditions the reaction was found to be sluggish.

Therefore, various other reaction conditions were screened to optimize the yields. Finally, we found that the Grubbs’ first
generation catalyst (G-I) in refluxing toluene gave the desired RCM product 7 in 85% yield. Along similar lines, the triallyl compound 16 gave the RCM product 17 in 66% yield (Scheme 4).

The structures of the annulated cage compounds 7 and 17 have been confirmed by $^1$H and $^{13}$C NMR spectral data and also supported by HRMS data with a molecular weight of 355.16 for 7 and 343.16 for compound 17, respectively. Furthermore, the structure of the bis-spiro pyrano cage compound 7 was confirmed by single crystal X-ray diffraction studies [52] (Figure 4). Fortunately, we observed that the liquid compound 16 kept at room temperature for a long time converted into a solid material. Therefore, we were keen to investigate the reason for this observation. In this context, the $^1$H and $^{13}$C NMR spectra of this compound were again recorded, indicating the occurrence of an intramolecular DA reaction. Later, it was confirmed by single crystal X-ray diffraction studies [53] (Figure 4).

Next, the formation of compound 18 has been confirmed by an independent synthesis. To this end, triallyl compound 16 was subjected to intramolecular DA reaction in refluxing toluene to deliver the DA adduct 18 in 80% yield (Scheme 5).

Surprisingly the related system 19, prepared from 12 did not undergo DA reaction to produce the intramolecular DA adduct 20. Even under prolonged toluene reflux reaction conditions, we did not realize the formation of the required DA product 20 (Scheme 6).

Figure 4: (a) Optimized structure of 18, (b) optimized structure of 7.
Conclusion

In summary, we have demonstrated a new approach to intricate C$_2$-symmetric cage bis-spirocyclic pyran derivative 7 through an allyl Grignard reaction and an RCM sequence. The strategy demonstrated here involves an atom economic process. The synthetic sequence demonstrated here opens up a new route to complex cage targets. Additionally, intramolecular DA reaction opens up a new strategy for the synthesis of highly complex cage compounds that are inaccessible by other routes. Studies to extend the scope of the intramolecular as well as intermolecular DA reaction for the synthesis of interesting cage molecules are in progress.

Supporting Information

Supporting Information File 1
Detailed experimental procedures, characterization data and copies of $^1$H and $^{13}$C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-147-S1.pdf]

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