Organic & Supramolecular Chemistry

Synthesis of Angular Triquinane and [4.3.3]Propellane Derivatives via Ring-Rearrangement Olefin Metathesis

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Herein, a simple and useful approach to angular triquinane and [4.3.3]propellane moieties is described via olefin metathesis starting from *exo* and *endo* Diels-Alder (DA) adducts containing norbornene unit. This approach involves DA reaction, and ring-rearrangement metathesis (RRM) as key steps. Strained norbornene derivatives on allylation at bridgehead position(s) followed by ring-opening metathesis and ring-closing metathesis sequence delivered angular triquinane and also stereochemically different propellane derivatives.

Introduction

Angular triquinanes and [3.3.3]propellanes belongs broadly to polyquinanes which consists of cyclopentane fused rings both in linear and angular fashion.[1] These molecules have several applications in material science, medicinal chemistry and natural product synthesis and found increasing importance with time.[2] Different type of natural products such as modhephene and bukittinggine incorporate propellane skeleton[3] whereas silphinene, (+)-3-oxosilphinene and (+)-l-oxosilphinen-3,5-diol contains angular triquinanes.[4] Some basic triquinanes and propellanes are core units of natural products and they are shown in Figure 1. Due to their structural intricacies and medicinal properties, polyquinanes have attracted the attention of synthetic community and resulted in numerous publications.[5]

It is always a challenging task in organic chemistry to assemble three dimensional structures specially propellanes. Several examples of angular triquinanes have been reported whereas limited number of propellane derivatives are known.[6] Most of those approaches involve elaborate synthetic sequence. In view of our interest in metathesis, we conceived a new approach to angular triquinanes and propellane derivatives involving olefin metathesis as a key step.[7]

To design cyclopentanoids by olefin metathesis,[8] we identified decorated norbornene derivatives with *exo* and *endo* stereochemistry at the ring junction as useful synthons. The retrosynthetic approach to angular triquinane and propellane is shown in Figure 2.

The key steps in our strategy include Diels-Alder (DA) reaction, allylation and ring-rearrangement metathesis (RRM) / ring-opening metathesis (ROM)[9] and ring-closing metathesis (RCM) sequence.

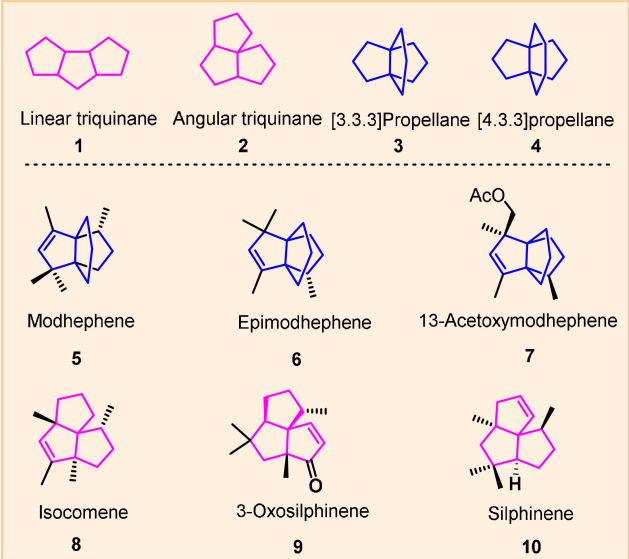

Figure 1. Representive examples of natural products containing angular triquinane and propellane moities as core units.

Results and Discussion

To realize the strategy shown in Figure 2, the known dienophile **13** was prepared by using the reported procedure starting with 2-methyl-1,3-cyclopentanedione **11** (Scheme 1).[10] The dienophile **13** is a useful synthon to prepare the key DA adducts **14** and **15**. The enone **13** on reaction with cyclopentadiene gave two cycloadducts **14** and **15** in 4:1 ratio respectively (Scheme 1).[11] The structures of *endo* and *exo*-adducts were established by NMR spectroscopic and HRMS data and further supported by single crystal X-ray diffraction studies (Figure 3).

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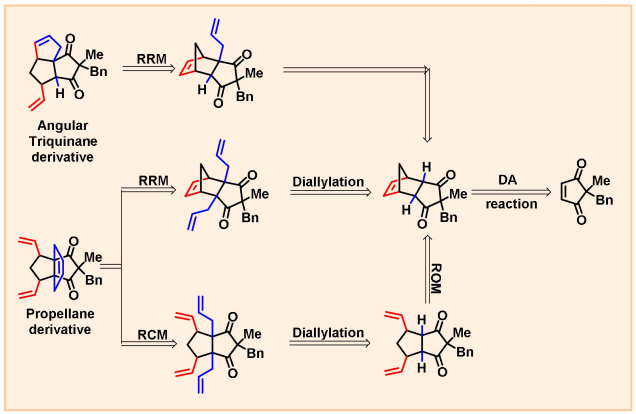
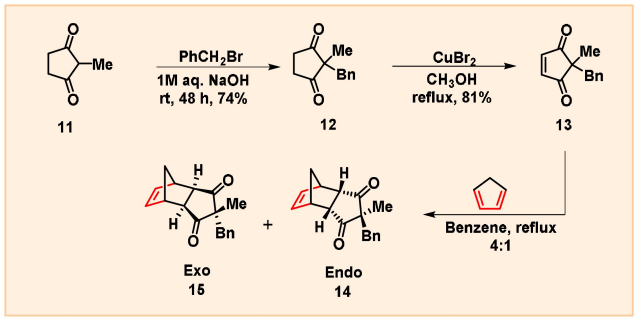


Figure 2. Retrosynthetic strategy to angular triquinane and propellane derivatives.



Scheme 1. Synthesis of Diels-Alder adducts **14** and **15**.

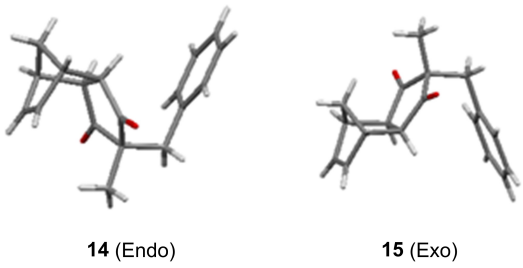
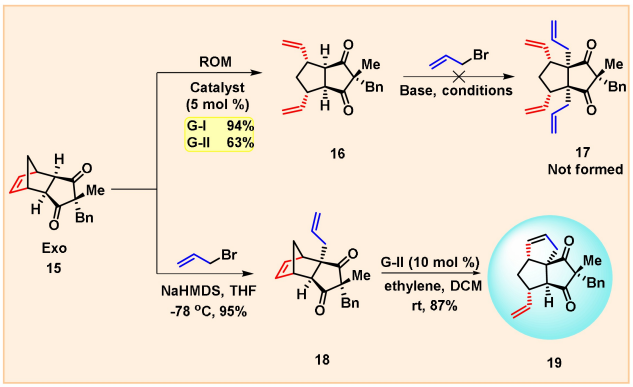


Figure 3. Single-crystal XRD structure of **14** (CCDC 2093701) and **15** (CCDC 2093699).

Having both these isomers **14** and **15** in hand, we first attempted ROM of *exo* isomer **15** using Grubbs (G–I, G-II) catalysts and we realized that the yield of compound **16** is more with G–I catalyst than with G-II catalyst. Diallylation of **16** was attempted using allyl bromide in the presence of different bases such as K_2CO_3, NaHMDS, LiHMDS, LDA, ^tBuOK, NaH and KH under different conditions, but we did not get the diallylated product **17** (Scheme 2). Maybe the presence of two vinyl groups along with the bulky benzyl group (all are below



Scheme 2. Synthesis of angular triquinane derivative **19.**

the plane) in **16** may be responsible for the failure of the diallylation.

So, we considered another route involving the allylation of *exo* isomer **15** via NaHMDS with allyl bromide and we observed only monoallyl product **18**. Based on the literature precedence the stereochemistry of the newly introduced allyl group is retained at the ring junction during alkylation sequence.[6c] Further, single crystal X-ray diffraction studies confirmed this observation (Figure 4). When the mono-allyl derivative **18** was treated with G-II catalyst (10 mol%) under ethylene atmosphere, the angular triquinane **19** was produced in 87% yield (Scheme 2). Based on these facts we attempted diallylation of *exo* isomer **15**. In this regard, the *exo* isomer **15** was subjected to alkylation using KH and allyl bromide at reflux temperature. Fortunately, we found the diallyl product **20** in good yield. Later, the structure and stereochemistry of the compound **20** was confirmed by single crystal X-ray diffraction studies (Figure 4).

When, the diallyl compound **20** was subjected to RRM with G-II catalyst two products were formed, the ring-opened propellane derivative **21** and another norbornene-based propellane **22** (Scheme 3). The good yields of **21** (71%; Table 1, entry 3) and **22** (50%; entry 2) were obtained under optimised reaction conditions.

Along similar lines, the *endo*-isomer also gave diallyl product **23** with KH at reflux temperature. When the compound **23** was subjected to RRM, a chromatographically

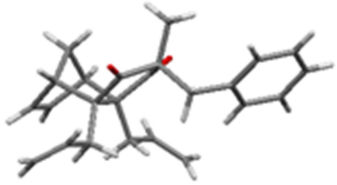


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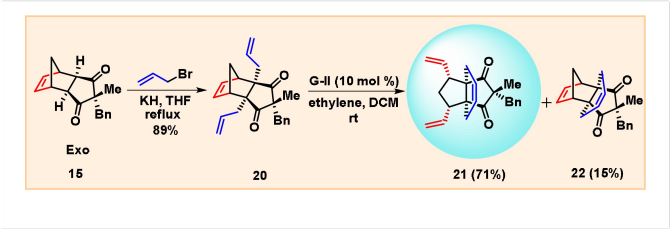
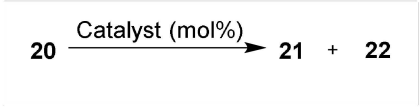
Figure 4. Single-crystal XRD structure of **20** (CCDC 2093692).



Scheme 3. Synthesis of propellane derivatives **21** and **22**.

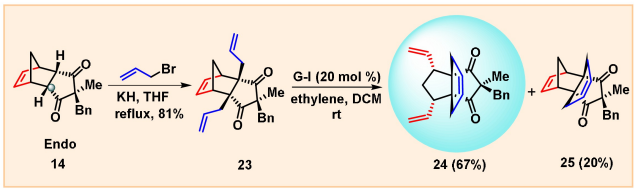
Table 1. Catalyst optimization during RRM[a].



S.No.	Catalyst	mol%	Yield% (21:22)[b]
1.	G-I	10	10:45
2.	G-I	20	25:50
3.	G-II	10	71:15
4.	G-II	20	60:23

[a] All the reactions were carried under ethylene atmosphere in dry DCM for 10 h unless otherwise noted.
[b] Yield of isolated product reported after column chromatography.

separable mixture of products **24** and **25** were obtained (Scheme 4). In this case both the product structures were confirmed by spectroscopic data and further unambiguously established by single crystal X-ray diffraction data (Figure 5). Under optimised conditions, we got good yields of **24** (67%; Table 2, entry 2) and **25** (60%; entry 3).



Scheme 4. Synthesis of propellane derivatives **24** and **25**.

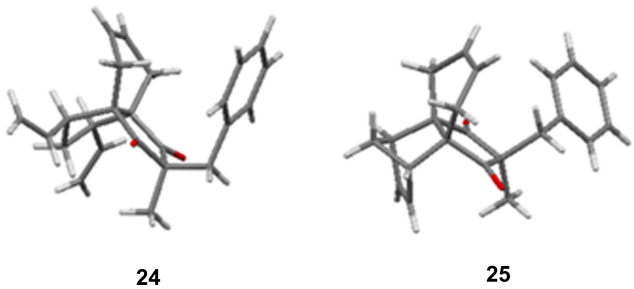
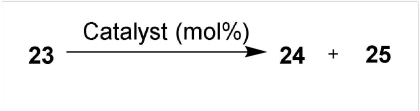


Figure 5. Single-crystal XRD structure of **24** (CCDC 2093688) and **25** (CCDC 2093668).

Table 2. Catalyst optimization during RRM[a].



S.No	Catalyst	mol%	Yield% (24:25)[b]
1.	G-I	10	40:40
2.	G-I	20	67:20
3.	G-II	10	10:60
4.	G-II	20	35:25

[a] All the reactions were carried under ethylene atmosphere in dry DCM for 10 h unless otherwise noted.
[b] Yield of isolated product reported after column chromatography.

Conclusion

In summary, we successfully synthesized angular triquinane derivative **19** and propellane derivatives **21**, **22**, **24** and **25** from both *exo* and *endo* norbornene derivatives. In view of the importance of polyquinanes in medicinal chemistry, the methodology reported here provide a short synthetic sequence to these ring systems via the olefin metathesis as a key step.

Deposition Numbers CCDC 2093701 (for **14**), CCDC 2093699 (for **15**), CCDC 2093692 (for **20**), CCDC 2093688 (for **24**), CCDC 2093668(for **25**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information Summary

All experimental procedures, spectral data (^{1}H NMR, ^{13}C NMR, DEPT-135, HRMS and IR) of all new compounds and X-ray data of **14** (CCDC 2093701), **15** (CCDC 2093699), **20** (CCDC 2093692), **24** (CCDC 2093688), **25** (CCDC 2093668) are provided in supporting information files.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Allylation · Angular triquinane · Cyclopentanoid · Metathesis · Polycyclic · Propellane

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