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Bridgehead vicinal diallylation of norbornene derivatives and extension to propellane derivatives via ring-closing metathesis

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Full Research Paper

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Abstract

Here, we report a simple synthetic strategy to the bridgehead vicinal diallylation of norbornene derivatives. These substrates are useful to generate propellanes via ring-closing metathesis. Single-crystal X-ray diffraction analysis of four compounds led to the realization of configurational correction of earlier reported molecules.

Introduction

The norbornene moiety is a useful template and also a versatile synthon in organic synthesis [1]. The double bond present in the norbornene frame is strained and therefore participates in cycloaddition sequences as a C_2-synthon [2,3]. It was reported that the norbornene system is as strained as cyclopropane or cyclobutane (norbornene, 100 kJ/mol; cyclopropane, 115 kJ/mol; cyclobutane, 110 kJ/mol) [4,5]. Some of the annulated norbornene derivatives undergo retro Diels–Alder (rDA) reactions at ambient temperature in the presence of methylaluminium dichloride and a reactive dienophile [6-8]. Cage compounds with interesting applications have been assembled by a cyclization reaction starting with suitably functionalized norbornene derivatives [9-11]. Moreover, the norbornene unit induces a hairpin-like architecture when it is incorporated into a peptide chain. This property is useful to design norbornene-based ionophores [12]. Due to the strained nature of norbornene systems they are useful precursors for ring-rearrangement metathesis (RRM) [13-21] to generate intricate polycyclics involving non-traditional retrosynthetic routes. Recently, functionalization of unactivated aromatic C–H bonds was achieved by using palladium catalysts and norbornene (Catellani reaction) [22,23]. In view of these applications, the design and synthesis of vicinal diallylnorbornene derivatives is a worthwhile exercise. The double bond present in the allyl group can be further

converted into various other useful functionalities for further synthetic manipulation by adopting the appropriate functional group transformations.

Strategy

Our approach to various propellane derivatives is shown in Figure 1. The target propellane **1** could be assembled from diallyl compound **2** via ring-closing metathesis (RCM) [24-32]. Whereas, the diallyl derivative **2** can be derived from a readily available Diels–Alder (DA) adduct **3** through an allylation sequence.

Results and Discussion

Installation of two C–C bonds to generate quaternary centers in a stereocontrolled manner in a single step is not a trivial exercise. Generally, it was accomplished by radical three-component coupling reactions or Michael-type additions of organocopper reagents starting with conjugated carbonyl compounds [33,34]. But, the resulting alkyl groups are in *trans* orientation. Our journey to propellane **1** synthesis (Figure 1) was commenced with the preparation of known DA adducts **3a**, **3b**, **3aa'** and **3bb'** [35-37]. In this regard, DA adduct **3a** was treated with allyl bromide in the presence of NaH to obtain the corresponding *O*-allylated compound (70%) and *C*-allylated compound **2a** (28%) by using our earlier reported method [38]. Next, diallyl compound **2a** on RCM using Grubbs first generation (G-I) catalyst in CH_2Cl_2 at room temperature (rt) gave the desired propellane derivative **1a** (61%) along with a minor amount of quinone derivative **4** (17%) (Scheme 1). The formation of quinone **4** can be explained on the basis that compound **2a** underwent rDA and RCM in one-pot. Here, the compound **2a** didn't undergo RRM because a metallacyclobutane cannot be formed between the allyl and norbornene double bonds due to structural constraint [39] and moreover, we didn't observe any ring-opening metathesis (ROM) product during RCM reaction. This may be due to the fact that sparging with an inert gas (N_2 or Ar) during RCM process helps to accelerate the loss of ethylene and thus, prevents ROM [39].

Garratt and Hollowood reported that bridgehead functionalization of norbornene derivatives such as *endo*-5-norbornene-2,3-dicarboximide **5** gave bridgehead alkylated compound **6** with retention of configuration (Scheme 2) [40]. Based on this report, we expected the allyl groups introduced via alkylation

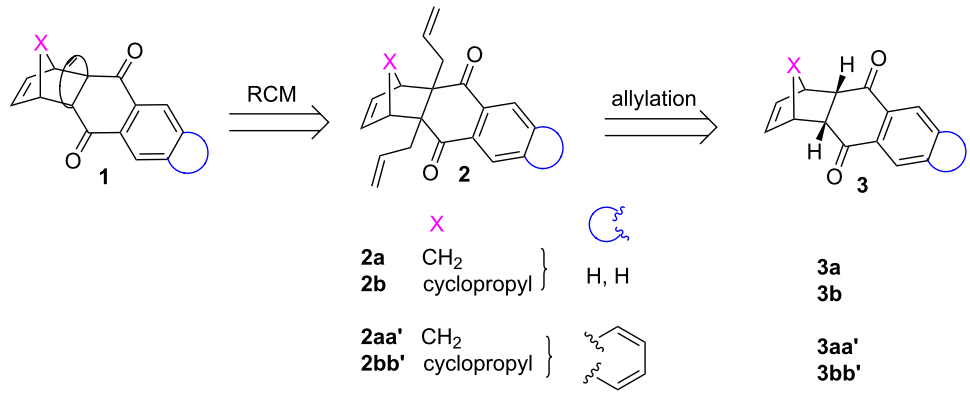
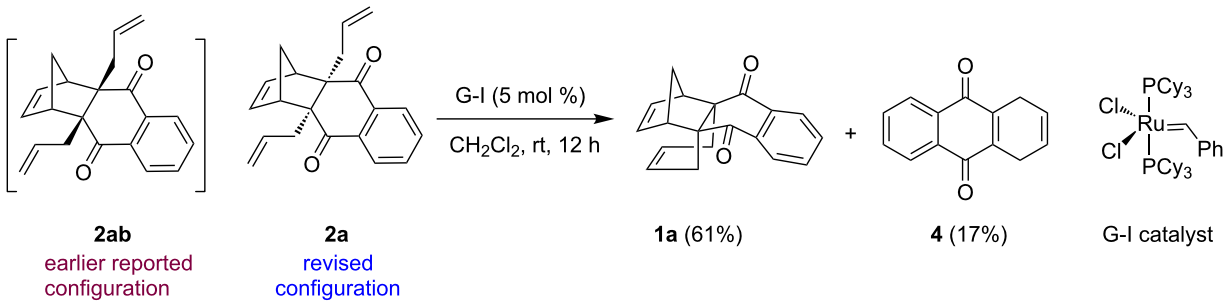
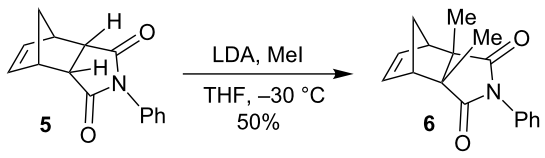


Figure 1: Retrosynthetic approach to propellane derivatives.



Scheme 1: Synthesis of the propellane derivative **1a** via RCM.



Scheme 2: Garratts work on alkylation of norbornene with retention of configuration.

sequence will occupy the *exo* position (see **2ab**) because the bridgehead hydrogens in DA adduct **3a** are in *exo* configuration. Thus, in the final compound **1a** the newly formed 6-membered ring during RCM is supposed to be in the *exo* configuration.

To our surprise, single-crystal X-ray analysis of **1a** revealed that the 6-membered ring (C28–C30–C31–C32–C33–C27) formed via RCM is in *endo* configuration as depicted in Figure 2.

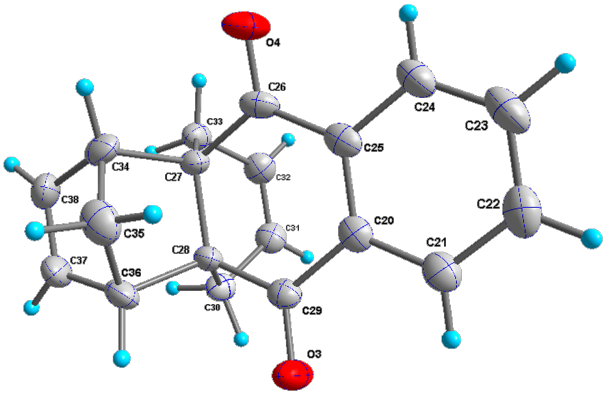


Figure 2: The molecular structure of **1a**, with displacement ellipsoids drawn at the 50% probability level.

At this point, we turned our attention to understand the configurational origin of the allyl groups in **2a**. To understand whether compound **2a** was formed by Claisen rearrangement (CR) of the corresponding *O*-allyl compound or by carbanion mediated *C*-allylation of the DA adduct **3a**, we carried out the alkylation of compound **3a** with *n*-propyl bromide in refluxing THF for 2 h. Here, di-*O*-propyl compound **7** was obtained in 36% yield along with a dehydrogenated compound **8** (20%, Scheme 3). Surprisingly, no *C*-alkylation product was observed from **3a**. This result suggests that the *C*-allyl compound **2a** was formed from the corresponding *O*-allyl compound via CR.

Based on the X-ray structure of **1a** and the above observations, it is clear that the allyl groups in **2a** are in *endo* configuration which can be explained as follows. Since the stereocenters are unaffected during the RCM sequence it is evident that the allyl groups present in **2a** should be in *endo* configuration. To confirm the configuration of the allyl groups, the X-ray structure of previously reported oxa-bowl/propellane hybrid (**15**) [38] was also recorded and it is in agreement with the above findings (Figure 3). These results suggested the revision of earlier reported configuration of allyl groups. More specifically, various compounds (**2ab**, **2aa'b** and **9a–15a**) reported in our previous report [38] need configurational correction and the revised structures (**2aa'** and **9–15**) are included in Table 1.

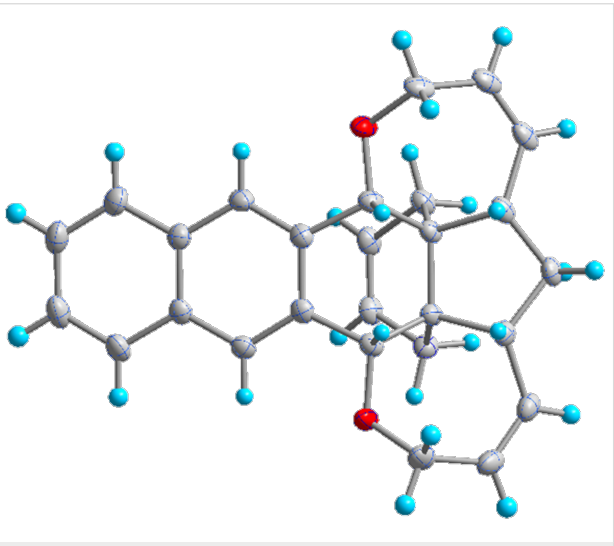
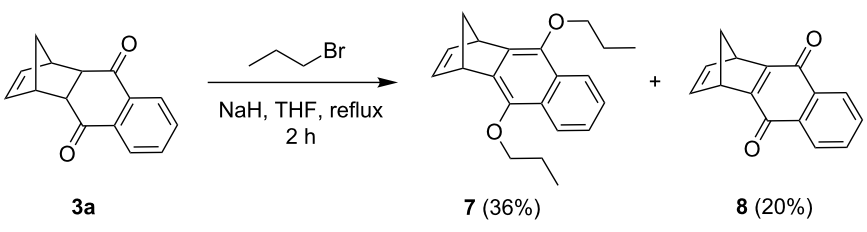


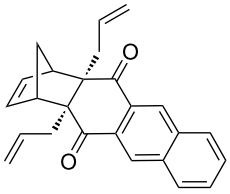
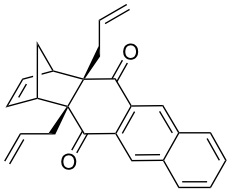
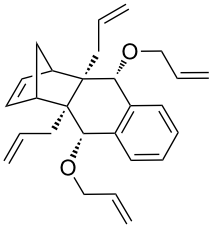
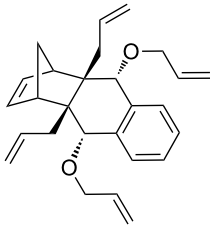
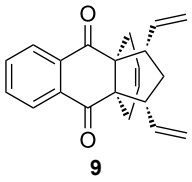
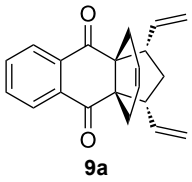
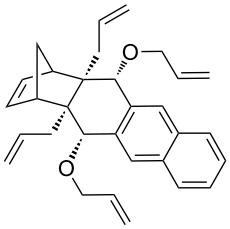
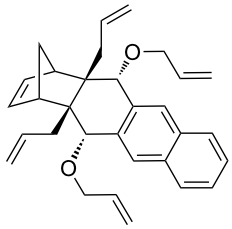
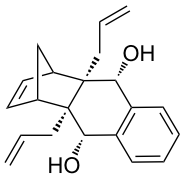
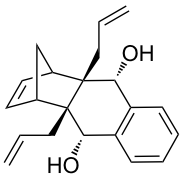
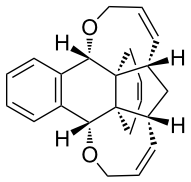
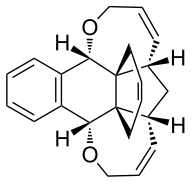
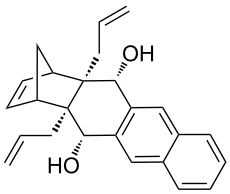
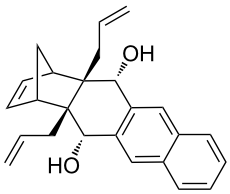
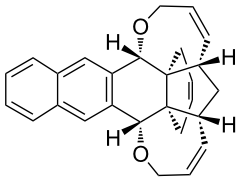
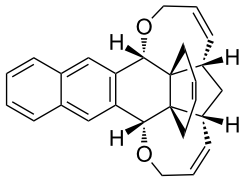
Figure 3: Crystal structure of compound **15** showing 50% displacement ellipsoids.

When the other previously prepared diallyl compound **2aa'** [38] was subjected to RCM using G-I catalyst under similar reaction



Scheme 3: Control experiment carried out to probe the configuration of **2a**.

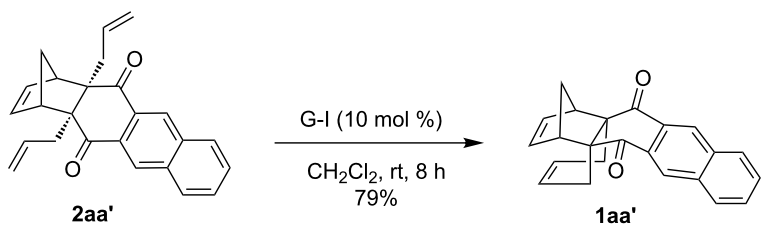
Table 1: Revised structures from our previous work [38] with correct configuration.

Entry	Revised structures	Earlier reported structures (ref. [38])	Entry	Revised structures	Earlier reported structures (ref. [38])
1	 **2aa'**	 **2aa'b**	5	 **12**	 **12a**
2	 **9**	 **9a**	6	 **13**	 **13a**
3	 **10**	 **10a**	7	 **14**	 **14a**
4	 **11**	 **11a**	8	 **15**	 **15a**

conditions the propellane derivative **1aa'** was obtained in 79% yield (Scheme 4).

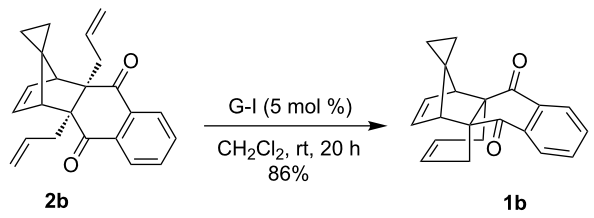
To expand the scope of this strategy, cyclopropyl containing diallyl products **2b** and **2bb'** were also prepared along similar lines starting with the corresponding DA adducts **3b** and **3bb'** [41]. Initially, the diallyl compound **2b** was reacted with G-I catalyst to afford the desired propellane **1b** in 86% yield (Scheme 5). Its structure has been established on the basis of spectroscopic data (^{1}H NMR, ^{13}C NMR and DEPT-135) and was further supported by HRMS data.

In addition, the configuration of **1b** and **2b** were unambiguously determined via single-crystal X-ray diffraction analysis



2aa' **1aa'**

Scheme 4: RCM of the compound **2aa'**.



Scheme 5: RCM approach to the propellane derivative **1b**.

(Figure 4). Based on this data it is clear that the bridgehead allyl groups in the RCM precursor **2b** are in *endo* configuration. Subsequent RCM of diallyl compound **2b** gave the ring-closing product **1b** with retention of the configuration.

Similarly, staring with substrate **2bb'**, another propellane derivative **1bb'** was synthesized using the same catalyst (i.e., G-I) in CH_2Cl_2 at rt. Here, along with the desired propellane **1bb'** (79%) a minor amount of quinone derivative **16** (13%) was also generated due to a one-pot RCM-rDA sequence of **2bb'** which is similar to the substrate **2a** (Scheme 6). Compound **1bb'** was characterized based on the ^1H and ^{13}C NMR, DEPT-135 and further supported by HRMS data. However, spectroscopic data of quinone **16** were identical with the literature values [41].

Conclusion

This methodology was found to be useful to synthesize various propellane derivatives containing a norbornene moiety by employing RCM sequence. Moreover, we have firmly established the configuration of allyl groups at bridgehead position of norbornene derivatives by single-crystal X-ray diffraction analysis. A control experiment with propyl bromide provided an insight into the reaction mechanism that the bridgehead allylation proceeds through enolization, *O*-allylation followed by CR and not via carbanion chemistry. This alternative strategy is useful to introduce vicinal diallyl groups in a *cis* orientation to generate propellane derivatives, which is a different protocol from previously reported methods where the two vicinal alkyl groups are introduced in *trans* orientation. In this study, we have also revised the configuration of our earlier reported molecules containing allyl groups and oxa-bowl/propellane hybrids. Since non-flattened molecules are implicated in biological systems, our results would be useful in drug design [42].

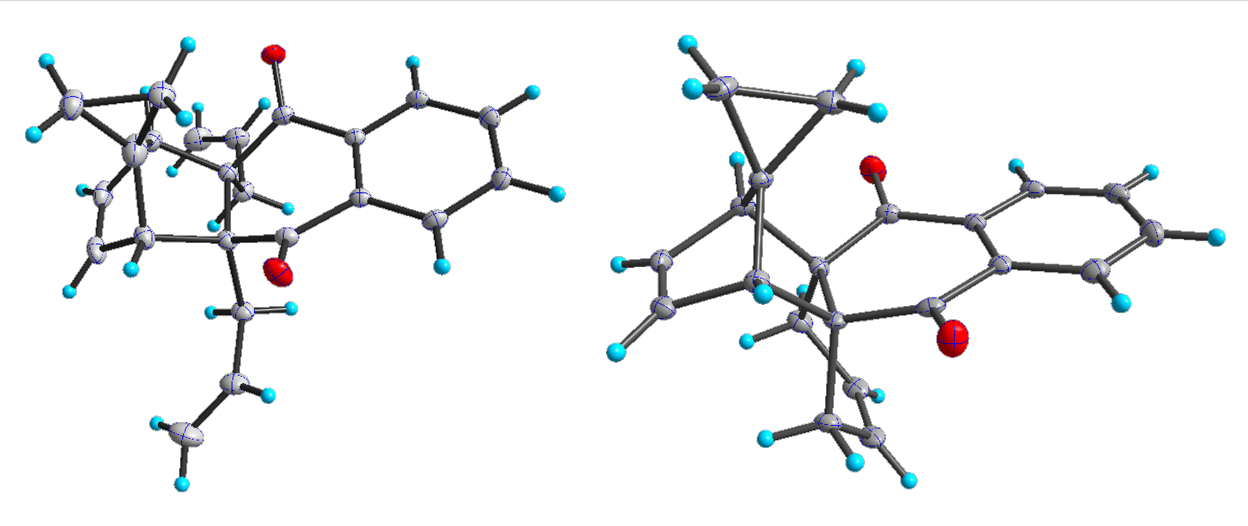
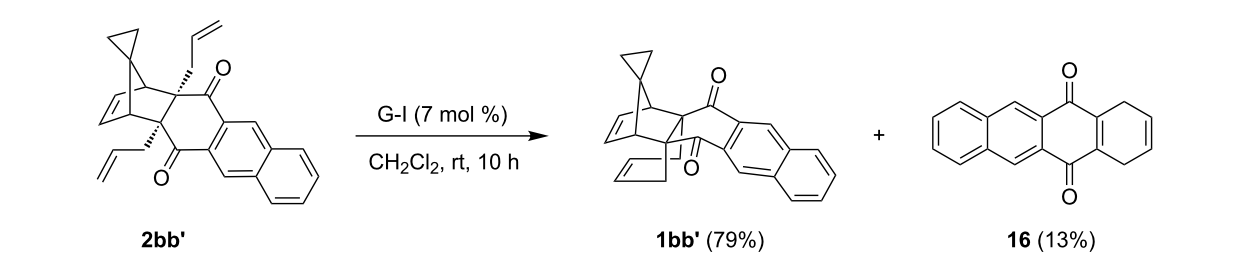


Figure 4: The molecular structures of the compounds **2b** (left) and **1b** (right) showing 30% displacement ellipsoids.



Scheme 6: Construction of the propellane derivative **1bb'** using RCM.

Supporting Information

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 1475412 (**1a**), 1475453 (**1b**), 1475403 (**2b**) and 1451438 (**15**). Copies of the data can be obtained free of charge on application to the Director at CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (FAX: (+44) 1223-336-033; email: deposit@ccdc.cam.ac.uk).

Supporting Information File 1

Experimental procedures, characterization data, copies of ^{1}H & ^{13}C NMR for all new compounds and X-ray data of the compounds **1a**, **1b**, **2b** and **15**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-177-S1.pdf]

Supporting Information File 2

Crystallographic information files of compounds **1a** (CCDC 1475412), **1b** (CCDC 1475453), **2b** (CCDC 1475403) and **15** (CCDC 1451438).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-177-S2.zip]

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