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Target Specific Tactics in Olefin Metathesis: Synthetic Approach to *cis-syn-cis*-Triquinanes and -Propellanes

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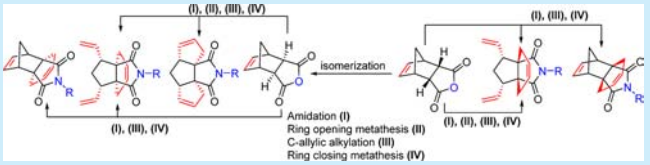
Supporting Information

ABSTRACT: A concise and simple synthetic approach to *cis-syn-cis*-triquinanes and -propellanes has been demonstrated via olefin metathesis starting with *exo*-nadic anhydride. This approach involves a ring-opening and ring-closing metathesis sequence of norbornene derivatives using Grubb's catalyst. Early-stage diallylation of norbornene derivatives is demonstrated followed by ring-closing metathesis that delivers propellanes exclusively. Surprisingly, ring-opening metathesis, late-stage diallylation, followed by ring-closing metathesis delivers triquinane as well as propellane derivatives.



Cyclopentanoid synthesis appears to be a never-ending challenge because a wide range of biological properties are associated with compounds containing cyclopentanoid unit(s).[1] For example, the synthesis of prostaglandins[2] started in the 1960s is still drawing the attention of synthetic chemists due to their medicinal importance and the need to produce them via efficient and green methods. Polyquinanes consist of fused five-membered rings in a linear as well as angular fashion. Linear triquinanes are further divided into two types based on their stereochemistry at the ring junction, such as *cis-anti-cis*-**1** and *cis-syn-cis*-**5**. C_{11}-Triquinanes with *cis-anti-cis* fusion were found to be core structural units in many bioactive natural products like coriolin,[3] whereas compounds containing *cis-syn-cis* stereochemistry with folded forms serve as critical building blocks in designing several complex non-natural products such as peristylanes and dodecahedrane (Figure 1).[4] Occasionally, suitably functionalized *cis-syn-cis* tricyclopentanoids can be isomerized[3c] to *cis-anti-cis* isomers at high temperature. Additionally, triquinane frameworks can be categorized as linear-,[3a,5] angular-,[6] and propellane-type[7] systems. Linear triquinane derivatives with the *cis-anti-cis* configuration were isolated from plant, microbial, and marine sources with interesting biological activities such as antibacterial and antitumor.[3a]

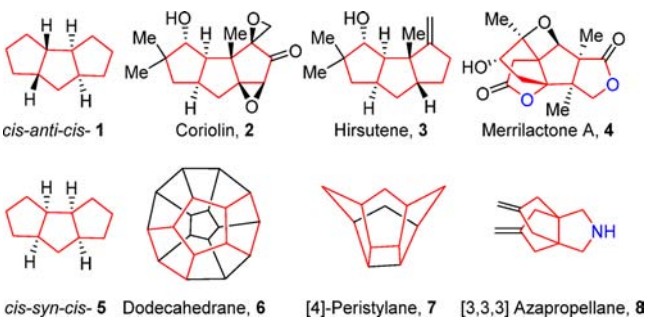


Figure 1. Natural and non-natural products containing cyclopentanoid moiety.

In 1966, Comer and Trotter reported the first triquinane-based natural product hirsutic acid, isolated from basidimycetes *Stereum hirsutum*, and confirmed its structure by a single-crystal X-ray diffraction analysis.[8] Among these triquinane motifs, we plan to design new strategies to linear triquinanes and propellanes by a combined usage of ring-opening metathesis (ROM) and ring-closing metathesis (RCM) strategy. Selected methods reported for synthesis of triquinanes are metal mediated C−C bond cleavage,[4e] Weiss−Cook condensation,[9] cascade radical cyclization,[5c] cycloadditions,[10] photothermal metathesis,[3c] and oxa-di-π-methane rearrangement,[11] etc. In view of our long-term interest in olefin metathesis,[12] we conceived a new synthetic approach to tricyclopentanoid system based on ring-rearrangement metathesis[13] (RRM) as a key step.

We plan to use Diels−Alder (DA) adducts derived from cyclopentadiene and maleic anhydride as a starting material. To generate stereochemical diversity in the final products one can use *exo* as well as *endo* DA adducts. Since bis(triquinanes)[11] are biologically active and pharmaceutically important building blocks, this methodology has been extended toward the synthesis of bis(triquinane) derivatives.

Our approach to linear triquinane derivatives such as **15** begins with *endo*-nadic anhydride **9**, easily prepared by a DA reaction between cyclopentadiene and maleic anhydride at 0 °C. Later, the anhydride **9** was heated at 180 °C for 24 h to furnish *exo*-nadic anhydride **10**.[14] Next, we attempted diallylation of *exo*-DA adduct **10** under different reaction conditions (NaH/allyl bromide and LiHMDS/allyl bromide at different temperatures), but unfortunately, we were unable to obtain the desired product **11** (Scheme 1).

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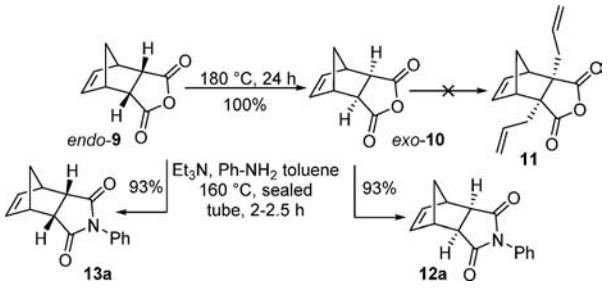
Scheme 1. Allyation of *exo*-Nadic Anhydride



exo-*N*-Phenyl derivative **12a** was subjected to ring-junction alkylation with methyl iodide with retention of stereochemistry,[15] the *exo*-nadic anhydride **10** was reacted with aniline in the presence of Et_3N in toluene at 160 °C (sealed tube) to deliver the *N*-phenyl derivative **12a** (93%). Along a similar line, derivative **13a** was prepared (Scheme 1). Later, **12a** reacted with allyl bromide in the presence of NaHMDS (1 M solution in THF) produced the diallyl compound **14** (77%), a suitable precursor for RRM. At this point, we note that our approach departed from previous routes[16] to triquinane synthesis as our key synthon contains vicinal allyl groups at norbornene ring junction, introduced by taking advantage of carbanion chemistry. When the diallyl compound **14** was subjected to RRM in the presence of Grubb's first-generation (G-I) catalyst in dry CH_2Cl_2 the propellane derivatives **16a** and **17** were obtained in 60% and 37% yields, respectively.

The stereochemistry of propellane derivative **17**[19] has been confirmed by a single-crystal X-ray diffraction analysis, which clearly establishes that the stereochemistry has been retained at the ring junction during allylation (Figure 2). Unfortunately, the desired RRM product **15a** was not realized by this route (Scheme 2).

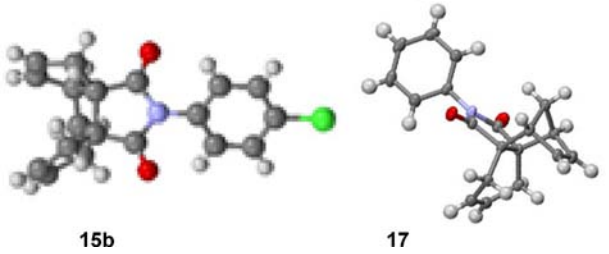
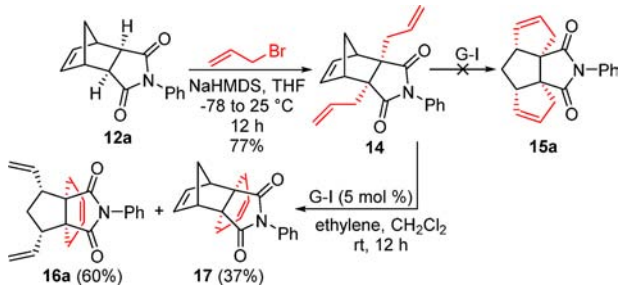


Figure 2. ORTEP diagram of triquinane **15b** and propellane **17**.

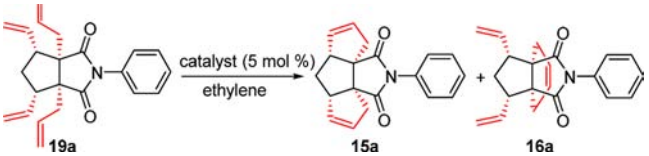
Scheme 2. Synthesis of *endo*-Propellanes 16a and 17 by Olefin Metathesis



Formation of tricyclic propellane **16a** clearly indicated that the tetraolefin **19a** may be a better precursor to deliver the triquinane derivative **15a**. Therefore, we attempted to assemble the triquinane **15a** starting with the norbornene derivative **12a**. In this regard, initially, compound **12a** was subjected to ROM in the presence of ethylene using G-I catalyst to afford **18a** in 93% yield. Further, vicinal C-allylation of **18a** at the ring junction was carried out with allyl bromide in the presence of NaHMDS (1 M solution in THF) to deliver the diallyl derivative **19a** in 75% yield.

Finally, RCM of **19a** was carried out with a variety of catalysts (see the Supporting Information) under different reaction conditions (Table 1). We found that G-II catalyst (Table 1, entry 3) in CH_2Cl_2 is a better choice to generate the triquinane derivative **15a** (91%), which also gave minor amount of propellane **16a** (8%).

Table 1. Catalyst Screening



entry	catalyst	solvent	temp/time (h)	**15a**:**16a**[a] (%)
1	G-I	CH_2Cl_2	rt/12	53:47
2	G-I	toluene	reflux/15	25:22
3	G-II	CH_2Cl_2	rt/16	91:08
4	G-II	toluene	reflux/16	85:06
5	GH-I	CH_2Cl_2	rt/13.5	50:33
6	GH-I	toluene	reflux/14	18:28
7	GH-II	CH_2Cl_2	rt/14	80:17
8	GH-II	toluene	reflux/12	42:30
9	M73 SIMe	CH_2Cl_2	rt/10	43:33
10	M853 SIPr	CH_2Cl_2	rt/12	50:36
11	M71-I	CH_2Cl_2	rt/12	31:18
12	M71 SIPr	CH_2Cl_2	rt/12	44:28
13	M71 SIMes	CH_2Cl_2	rt/12	25:22

[a]Isolated yields. Structures of catalysts used in the screening are provided in the Supporting Information

Along similar lines, triquinanes **15b–d** and propallene derivatives **16b–d** were synthesized via the RCM sequence (Scheme 3). The gross structure and stereochemistry of the triquinane derivative **15b**[19] have been established by single-crystal X-ray diffraction data (Figure 2).

Armed with the success of the triquinane synthesis, next we extended this strategy to bis(triquinane) derivatives starting with *exo*-nadic anhydride **10**. In this context, 4,4′-diaminodiphenylmethane **20** was treated with *exo*-nadic anhydride **10** in the presence of Et_3N in toluene at 160 °C (sealed tube) to deliver the compound **21** (96%).

Later, ROM was carried out with dimeric compound **21** with the aid of G-I catalyst to afford the ring-opening compound **22** in 94% yield. The tetraallyl compound **23** was obtained from **22** by treatment with NaHMDS (1 M solution in THF) in the presence of allyl bromide at low temperature. Then, the tetraallyl derivative **23** was subjected to RCM with G-II catalyst in CH_2Cl_2 to afford bis(triquinane) **24**, triquinane–propellane **25**, and bis(propellane) **26** derivative in 35%, 37%, and 22% yields, respectively (Scheme 4).

Similarly, we attempted the synthesis of triquinane derivative **30** by this method (Scheme 5). In this context, compound **13a** was treated with G-I catalyst in anhydrous CH_2Cl_2 to give ring-

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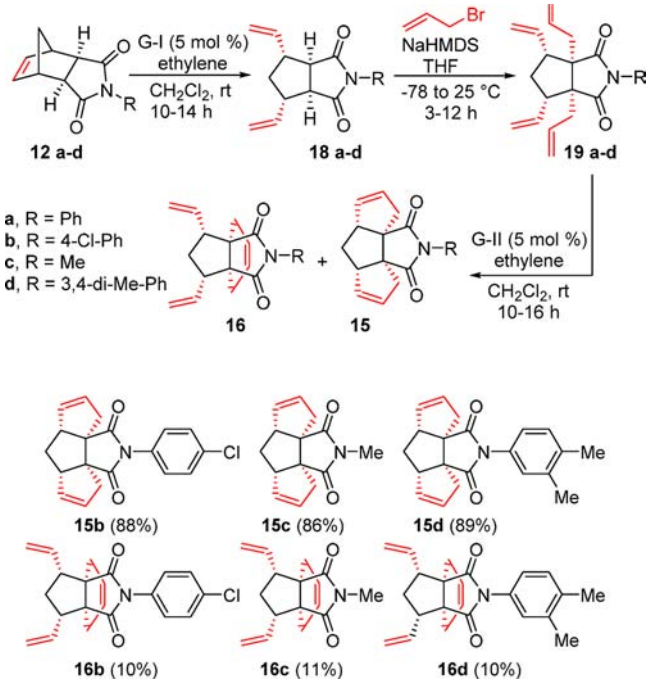
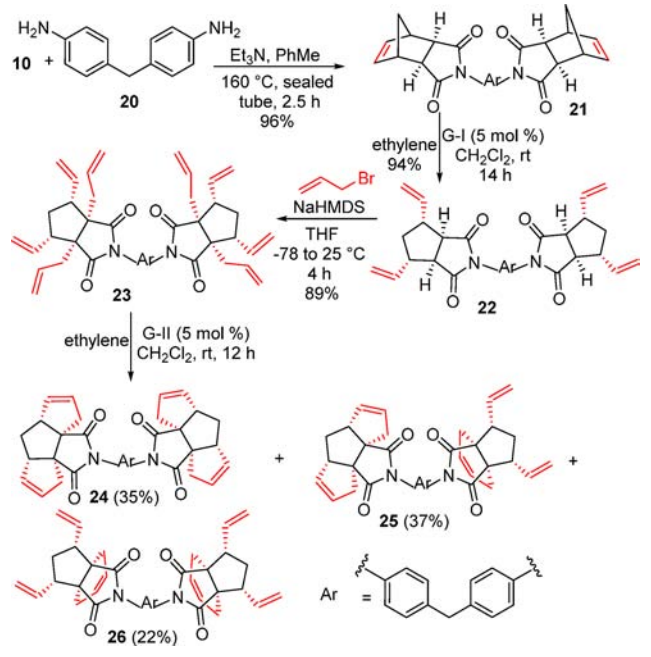
Scheme 3. Synthesis of Triquinanes and Propellanes by ROM−RCM Sequence



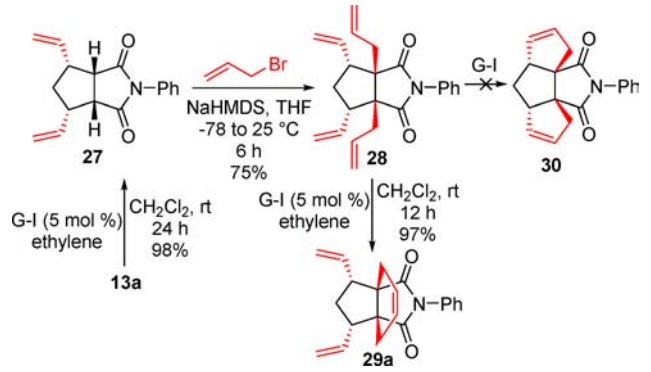
Scheme 4. Synthesis of Bis(triquinane) Derivatives and Propellanes via Olefin Metathesis



opening product **27** in 98% yield. Next, it was subjected to C-allylation in the presence of NaHMDS (1 M solution in THF) to afford **28** with allyl bromide at −78 °C with retention of configuration at the ring junction. Later, the diallyl compound **28** was treated with G-I catalyst to deliver the propellane derivative **29a** in 97% yield (Scheme 5).

In the case of G-II, we obtained a similar yield of propellane **29a**. Unfortunately, we were unable to obtain the triquinane derivative **30** by the sequence-regulated metathesis. It may be

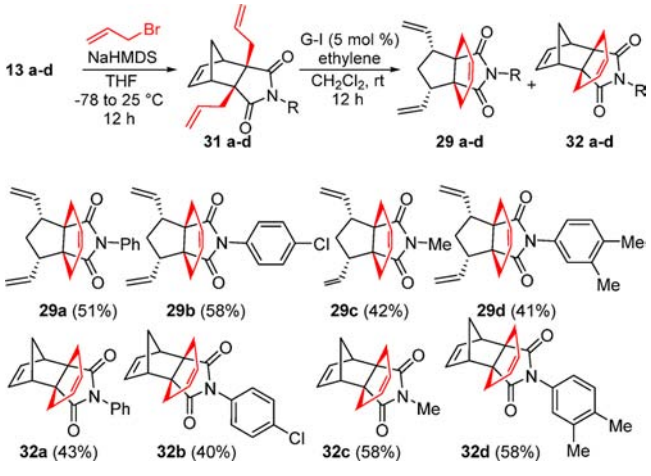
Scheme 5. Synthesis of Propellane by ROM/RCM Sequence



because with a *cis*-bicyclo[3.3.0]octane system the trans stereochemistry at the ring junction is not favorable.

Further, the diallyl norbornene derivative **31a** has been used in a metathesis sequence to generate stereochemical diversity in propellane derivatives. Allylation of **13a** was carried out with allyl bromide in the presence of NaHMDS (1 M solution in THF) at low temperature afford diallyl derivatives **31a** in 77% yield. Subsequently, the compound **31a** was subjected to metathesis using G-I catalyst (5 mol %) to deliver propellane derivatives **29a** (51%) and **32a** (43%). It is worth mentioning that similar propellane derivatives exhibit activity against H1N1 anti-influenza A virus (Figure 1).[17] Hence, this strategy has been extended to propellane derivatives **29b−d** and **32b−d**, which were synthesized starting with diallyl derivatives **31b−d** in good yield (Scheme 6).

Scheme 6. Synthesis of *exo*-Propellanes by RCM



In summary, we have demonstrated a new synthetic strategy to access *cis-syn-cis*-triquinanes by application of ROM, C-allylation, and RCM as key steps. More importantly, we have shown that norbornene system **14** with bridgehead allyl groups at the vicinal position gave propellane derivatives **16a** and **17**, whereas diquinane systems **19a−d** containing bridgehead allyl groups and vinyl groups at the 1,3 position of cyclopentane gave the corresponding *cis-syn-cis*-triquinanes **15a−d** along with propellane derivatives. Our strategy is devoid of functional group interconversion and unproductive redox manipulations and thus embraces the step economy. These tactical refinements clearly indicate that the sequence of olefin metathesis and allylation is critical in norbornene systems to determine the

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outcome of the end product structure. We believe that demonstration of this strategy adds a new tactic in designing polycyclic and propellanes in a diversity-oriented[18] manner. We have also synthesized 15 stereochemically diverse propellane derivatives, which is not possible by conventional routes. Since the nonflattened three-dimensional[17] molecular shape is implicated in medicinal chemistry, our results are of interest in drug design.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00537.

X-ray data for **15b** (CIF)

X-ray data for **17** (CIF)

Experimental procedures, spectral data of new compounds, and structures of catalysts used in screening in Table 1 (PDF)

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Notes

The authors declare no competing financial interest.

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(19) CCDC nos. 1448823 (**15b**) and 1449096 (**17**) contain the supplementary crystallographic data for this paper. The 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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