A Journal of the Gesellschaft Deutscher Chemiker

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201703186
Angew. Chem. 10.1002/ange.201703186

Link to VoR: http://dx.doi.org/10.1002/anie.201703186
http://dx.doi.org/10.1002/ange.201703186

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10.1002/anie.201703186

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An Enyne Cope Rearrangement Enables Polycycloalkane Synthesis from Abundant Starting Materials by a Simple Strategy

Sarah K. Scott,[a] and Alexander J. Grenning*[a]

Dedication ((optional))

Abstract: Cyclohexanone-derived Knoevenagel adducts (cyclohexylidenemalononitriles) and two different propargyl electrophiles serve as carbon sources for assembling diverse 6/7/5 tricycloalkanes, a common terpenoid framework. The sequence involves three unique reactions: (i.) deconjugative propargylation, (ii.) one-pot enyne Cope rearrangement/deconjugative propargylation, and (iii.) allenic-Pauson-Khand reaction.

Simplifying access to complex terpenoid scaffolds for application in the drug discovery process is a major goal of modern organic chemistry.[1] For example, natural product analogs can be accessed by (a) semisynthesis,[2] (b) "total" or *de novo* synthesis,[3] and by (c) diversity-oriented synthesis.[4] Efforts in our laboratory are aimed at identifying combinations of abundant starting materials and simple reaction sequences that can be used to tunably and scalably assemble common terpenoid cores.[5] This way, diverse scaffolds can be prepared and derivatized for biological evaluation.

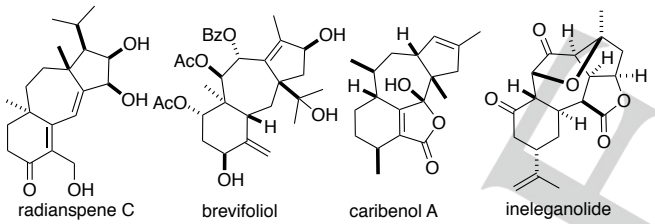
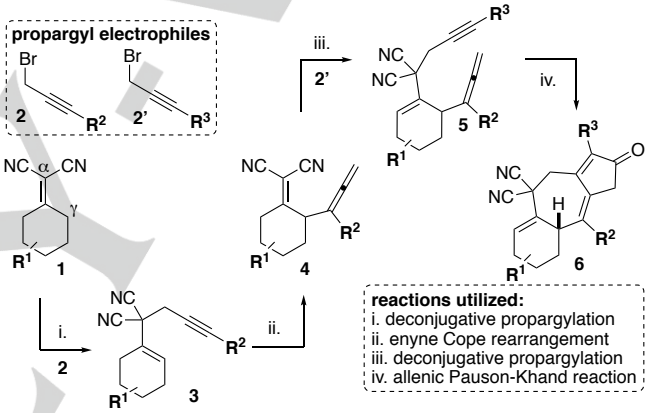


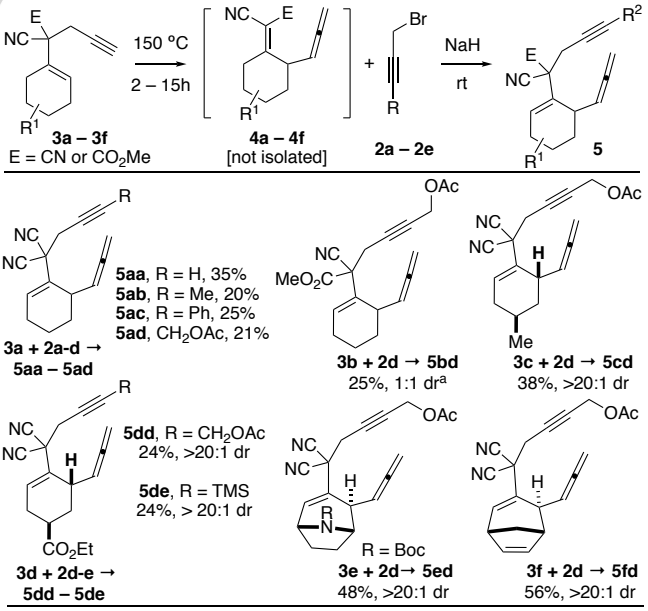
Figure 1. Representative 6/7/5 tricycloalkane terpenes.

Inspired by synthetically challenging[6] and bioactive[7] 6/7/5 tricyclic terpenoid natural products (Figure 1), we devised the following reaction sequence to tunably assemble their cores decorated with numerous functional groups (Scheme 1): deconjugative α-alkylation[8] of Knoevenagel adduct **1** with propargyl bromide **2** prepares the 1,5-enyne **3**. Enyne Cope rearrangement[9] results in γ-allenyl Knoevenagel adduct **4** and repeating the deconjugative α-propargylation step affords the 1,7-allenyne **5**. Finally, allenic-Pauson-Khand reaction[6f,k,10,11] yields the target cores from abundant carbon sources.

This synthetic hypothesis has several notable features. First, it employs only abundant starting materials (ketones + malononitrile = Knoevenagel adducts; propargyl electrophiles). Second, the coupling reactions (deconjugative α-alkylation) are operationally simple due to the ease of Knoevenagel adduct anion generation (γ-C–H pKa < 10).[12] The strategy also necessitates the exploration of a rare 1,5-enyne Cope rearrangement;[9] this reaction is known (three isolated examples[9a-c]) and computationally examined,[9d] but has little to no application in synthesis.[13] However, the related propargyl enol ether Claisen counterpart is more established and utilized.[14] The final feature is the use of the allenic-Pauson-Khand reaction (PKR). When preparing hydroazulenes by PKR, it is essential that the "alkene" coupling partner be an allene.[6f,k,10,11]



Scheme 1. The strategy for assembling 6/7/5 scaffolds.



standard protocol: 300 mg – 2 g of 1,5-enyne substrate **3a – 3f**, toluene (0.1 M), 150 °C, then swap toluene for THF (0.5 M), add NaH (1.1 equiv.) and propargyl bromide derivative (1.5 equiv.), rt. [a] reaction ran at 170 °C.

Scheme 2. Scope of 1,7-allenyne synthesis.

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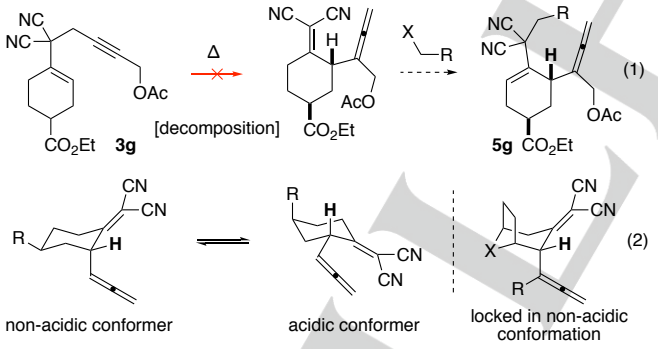
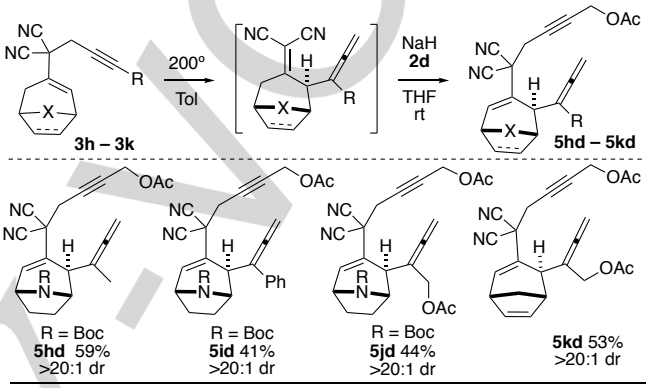
Supporting information for this article is given via a link at the end of the document.

To begin our studies, 1,5-enynes **3a – 3f** bearing a terminal alkyne were prepared by deconjugative propargylation. We were pleased to find that the 1,5-enyne Cope rearrangement went forward at 150 °C in toluene in screw-cap pressure flasks (Scheme 2). It was most practical and efficient to perform a telescoped sequence where the γ-allenyl Knoevenagel adducts generated *in situ* were directly treated with NaH and a 1° propargyl bromide derivative to yield the 1,7-allenynes **5** (20% – 56% yields of 1,7-allenynes **5** from 1,5-dienes **3**). Reported in Scheme 2 are two-step yields, averaging 45% – 75% yield per step, where inexpensive and abundant starting materials are converted into synthetically useful 1,7-allenyes. Notably, the procedure is scalable and reproducible; the sequence was routinely examined on the 300 mg – 2 gram scale. Through the sequence, cyclohexenyl substitution is altered by choice of cycloalkanone starting material and alkyne substitution is varied by choice of propargyl bromide starting material. Furthermore, cyclohexenyl substitution renders the Cope rearrangement diastereoselective (>20:1 dr). Finally, bicyclic 1,7-allenynes **5ed** and **5fd** could be accessed from tropinone (**3e**) and the (4+3) adduct (**3f**) of cyclopentadiene and trichloroacetone.

We next examined the Cope rearrangement of 1,5-enynes **3g – 3k** bearing an internal alkyne (eq. 1 and Scheme 3). Unfortunately, internal alkyne substrates such as **3g** required higher temperatures (200 °C) to rearrange, which resulted in decomposition (eq. 1). However, the bridged bicyclic substrates **3h – 3k** underwent an efficient Cope rearrangement and the desired allenynes could be isolated in good yields over the telescoped sequence. We suspect that the increased stability of the bicyclic allenynes (Scheme 3) *vs*. monocyclic allenes (Scheme 2) is a result of a locked, non-acidic conformation (eq. 2).

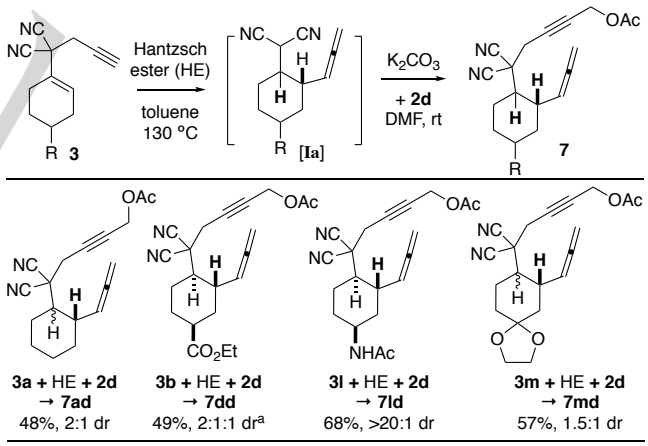


Although the enyne [3,3] rearrangement/deconjugative alkylation sequence is reproducible and scalable (ranging from 300 mg – 2 g), we wished to find ways of improving the overall efficiency, as yields in the 20 – 35% range would likely limit the utility of the transformation. We suspect that observed yields are a result of significant decomposition by isomerization enabled by the high acidity of the γ-C–H (eq. 2).[9c] Thus, an enyne-[3,3] rearrangement/alkylidene reduction/alkylation sequence was examined to prepare similar scaffolds (Scheme 4). Fortunately, Hantzsch ester was a selective and mild reductant of the alkylidenemalononitrile moiety. Thus, heating a mixture of 1,5-enyne **3** and Hantzsch ester at 130 °C results in allenyl malononitriles [**Ia**], which could be directly alkylated with propargyl bromide **2d** yielding allenynes **7** in a significantly higher yield compared to the original protocol (Scheme 2). Furthermore, the new method allows for increased scope: enynes **3l** and **3m** decompose under thermal, Hantzsch ester-free conditions. The addition of Hantzsch ester to the thermal transformation results in a [3,3] rearrangement then rapid consumption of the unstable alkylidene thus avoiding decomposition. Generally speaking, the alkylidene reduction step is non-diastereoselective unless the core contains an additional stereocenter, as was the case for the acetamide-containing substrate (**7ld**).



(i.) standard protocol: ~300 mg of 1,5-enyne substrate **3h – 3k**, toluene (0.1 M), 200 °C, then swap toluene for THF (0.5 M), add NaH (1.1 equiv.) and propargyl bromide derivative **2d** (1.5 equiv.), rt.

Scheme 3. Cope Rearrangement of 1,5-enynes bearing an internal alkyne.

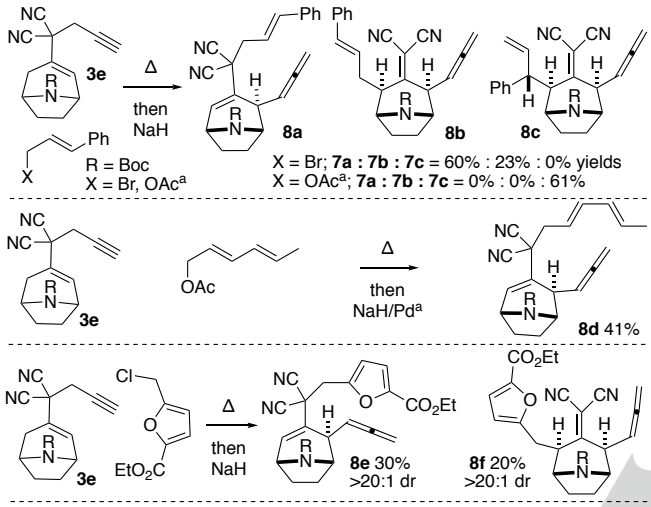


(i.) standard protocol: 100 mg of 1,5-enyne substrate, Hantzsch ester (2 equiv.), toluene (0.1 M), 140 °C, then swap toluene for DMF (0.5 M), add K_2CO_3 (3 equiv.) and propargyl bromide derivative **2d** (2 equiv.), rt. [a] major diastereomer shown

Scheme 4. Allenyne synthesis by enyne-[3,3] rearrangement/reduction/propargylation

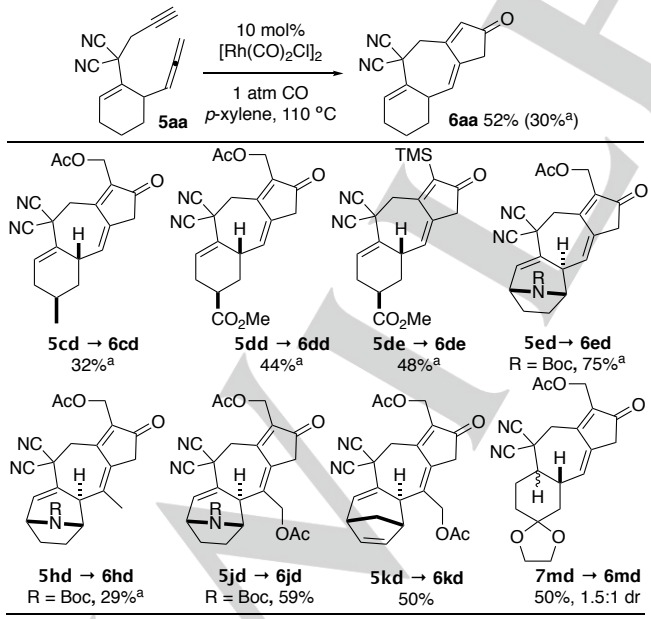
Allenes are generally useful for intramolecular cycloisomerization.[15] As such, other functionalized electrophiles were examined to prepare diverse allene/tethered-π substrates (Scheme 5). Enyne Cope rearrangement/allylation with cinnamyl bromide resulted in separable products **8a** and **8b** in

60% and 23% yields, respectively. Enyne Cope rearrangement/Pd-catalyzed allylation with cinnamyl acetate intriguingly resulted in diastereo-, γ-, and branch-selective allylation in good yield (product **8c**[16]). Additionally, enyne Cope rearrangement/Pd-catalyzed allylation with sorbyl acetate resulted exclusively in linear-selective deconjugative α-allylation (**8d**). Finally, enyne-Cope rearrangement/alkylation with a furan-containing electrophile resulted in a separable mixture of deconjugative α-alkylation product **8e** and γ-alkylated product **8f**.



(i.) standard protocol: 300 mg **3e**, toluene (0.1 M), 150 ºC, then swap toluene for THF (0.5 M), add NaH (1.1 equiv) and alkyl halide derivative (1.5 equiv.). [a] 5 mol% $Pd(PPh_3)_4$

Scheme 5. Other allene/tethered π-systems prepared.

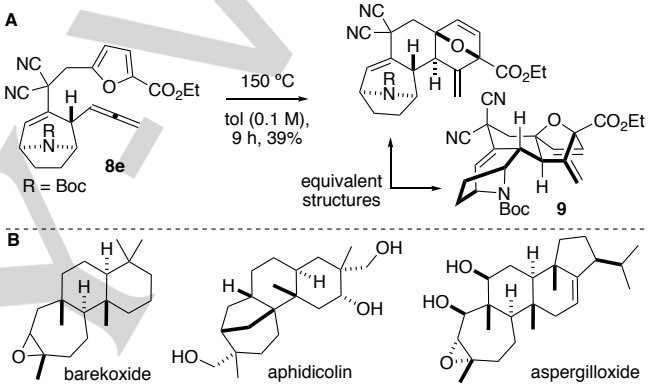


50 – 400 mg of allenyne **5**, 1 atm CO, 10 mol% $[Rh(CO)_2Cl]_2$, *p*-xylene (0.005 M), 110 ºC. [a] tol (0.01 M) *in lieu* of *p*-xylene, 5 mol% $[Rh(CO)_2Cl]_2$, 90 ºC

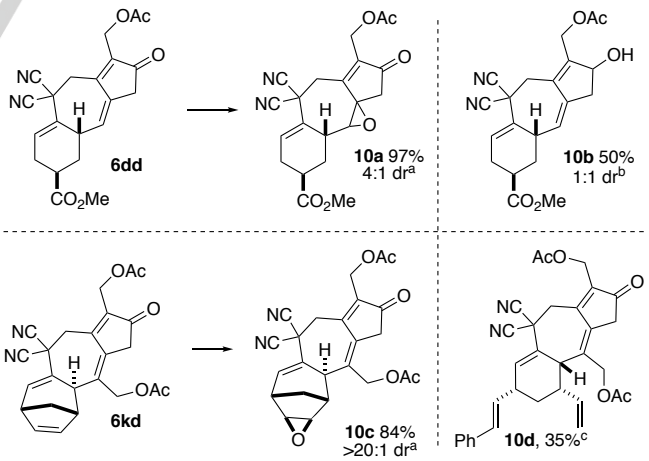
Scheme 6. Synthesis of 6/7/5 tricycloalkane frameworks.

Using the allenic-Pauson-Khand reaction,[6f,k,10,11] the 1,7-allenynes were converted into their respective 6/7/5 tricycloalkane cores **6** without incident by the standard literature protocol developed and applied by Brummond and others (Scheme 6).[6f,k,10,11] The cores are highly complex and diverse, considering the sequence is four steps from abundant starting materials.

We also examined the furan-containing allene **8e** for intramolecular Diels-Alder furan (IMDAF) reactivity (Scheme 7A).[17] We were pleased to find that thermal conditions could convert **8e** to the functionally dense polycycloalkane **9** in 39% yield. **9** contains a 6/6/7 tricycloalkane framework, two-heteroatomic bridges, and numerous other functional groups and was prepared in four steps from inexpensive commercial materials. Notably, there are terpenoid natural products that bear a related tricycloalkane ring system (Scheme 7B).[18]



Scheme 7. A. An intramolecular Diels-Alder furan reaction. **B.** Related 6/6/7 tricycloalkane natural products.



[a] ~ 1.5 equiv. *m*CPBA, DCM (0.1 M), 0 ºC – rt [b] 2 equiv. $NaBH_4$, MeOH (0.5 M) 0 ºC. [c] 3 equiv. styrene, ethylene (1 atm), 3 mol% Grubbs II, 60 ºC

Scheme 8. Functional group interconversion reactions.

As final experiments, we examined preliminary functional group interconversion reactions on the scaffolds (Scheme 8). The most reactive olefin toward epoxidation was the γ,δ-olefin

on the conjugated dienone for substrate **6dd** yielding product **10a**. For the more strained scaffold **6kd**, the bicyclo[3.2.1]octene was most reactive yielding **10c**. Also, the ketone could be reduced using $NaBH_4$ to prepare **10b**. Finally, ring-opening/cross metathesis could be performed on the bicyclo[3.2.1]octene core yielding **10d**.

In conclusion, we have examined a new route to 6/7/5 tricycloalkane frameworks. The sequence hinged on the development of poorly understood 3,3-dicyano-1,5-enyne Cope rearrangement. We have developed conditions and outlined current understanding and limitation for this transformation. Per the inspiration of the route, we examined the synthesis of diverse linear 6/7/5 tricycloalkanes and also prepared a highly complex 6/6/7 tricycloalkane, all in four steps from cycloalkanone, malononitrile, and two different propargyl-, allyl-, and/or furan-containing electrophiles. Future directions include target and analog synthesis, rendering the strategy asymmetric, and further examination of the enyne Cope rearrangement to identify many previously inaccessible allenes for processing into polycycloalkane architectures by ring-forming reactions (e.g. Diels-Alder and cycloisomerization).

Experimental Section

See the supporting information for detailed experimental procedures, characterization data, and spectral reprints

Acknowledgements

We thank the College of Liberal Arts and Sciences and the Department of Chemistry at the University of Florida for start-up funds.

Keywords: Knoevenagel Adducts • 1,5-enyne Cope rearrangement • allenic Pauson-Khand reaction • terpenoid natural products

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10.1002/anie.201703186

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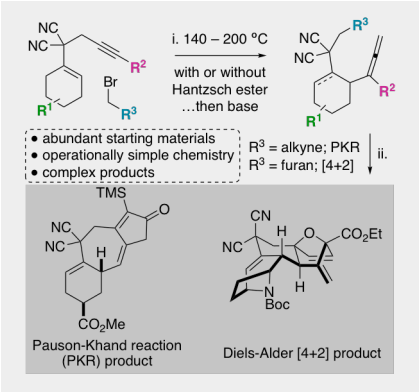

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