Terpene Synthesis

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Assembly of Terpenoid Cores by a Simple, Tunable Strategy

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Dedicated to John A. Porco and Jon A. Tunge

Abstract: *Oxygenated, polycyclic terpenoid natural products have important biological activities. Although total synthesis of such terpenes is widely studied, synthetic strategies that allow for controlled placement of oxygen atoms and other functionality remains a challenge. Herein, we present a simple, scalable, and tunable synthetic strategy to assemble terpenoid-like polycycloalkanes from cycloalkanones, malononitrile, and allylic electrophiles, abundantly available reagent classes.*

There are many oxygenated, polycyclic terpenes of medicinal value (Figure 1).[1–9] The terpenoid carbon framework rigidity and the differences in substitution and oxidation patterns result in the rich array of biological activity. Terpenoid synthesis can be achieved with varying degrees of efficiency depending on the target and the synthetic route utilized.[10] From a medicinal chemistry perspective, a tunable synthetic route that relies on operationally simple reactions and uses abundant reagent classes would allow for countless terpenoid natural product analogs to be prepared for biological evaluation.[11]

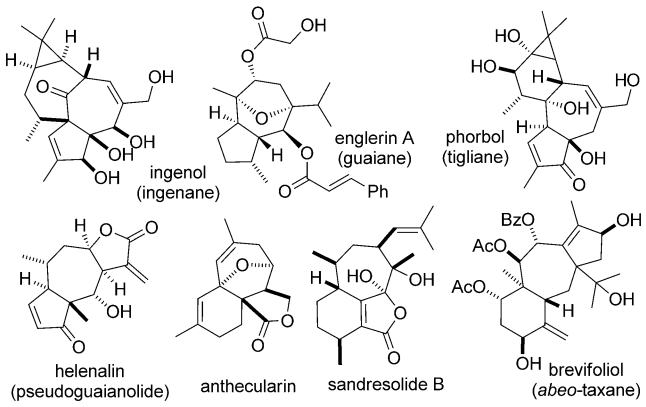
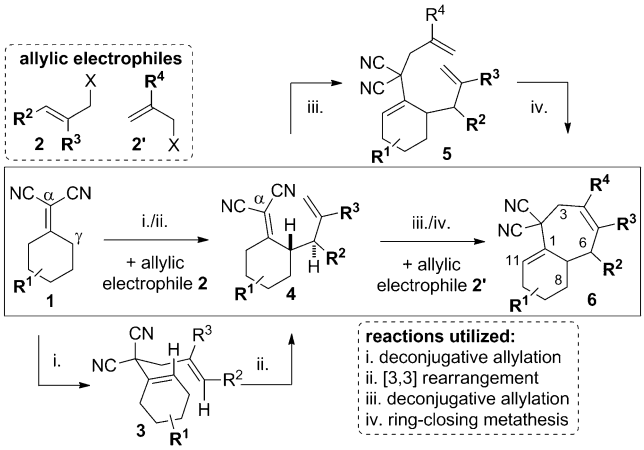


Figure 1. Representative oxygenated terpenoid natural products.

Our goal is to devise an analog-oriented[11] synthetic route to polycyclic terpenoid frameworks where sole carbon sources are abundantly available and the reactions utilized are operationally simple thus allowing for rapid structural tuning. We have envisaged a sequence utilizing ketone-derived Knoevenagel adducts **1**[12] and allylic electrophiles **2/2′** (Scheme 1).[13] Specifically, deconjugative alkylation[13–15] between Knoevenagel adduct **1** and allylic electrophile **2** yields 1,5-dienes **3**, which can undergo a conjugation-driven [3,3] Cope rearrangement to γ-allyl Knoevenagel adduct **4**.[14a,c,d,f,16,17] Repeating the deconjugative alkylation with allylic electrophile **2′** followed by ring-closing metathesis (RCM)[17] yields common terpenoid cores **6** where substitution patterns can be modified by choice of Knoevenagel adduct **1** and allylic electrophiles **2** and **2′**. The chemical transformations are envisioned to be operationally simple: The key C–C fragment couplings proceed via easily generated carbanions prepared from Knoevenagel adducts **1** and **4** (γ-C–H DMSO $pK_a < 10$), the [3,3] rearrangement will proceed under thermal conditions[16,17] and medium-sized ring synthesis by RCM is well precedented using commercial metathesis catalysts.[18]



Scheme 1. Tunable terpenoid synthesis from abundant carbon sources.

The proposed architectures **6** will bear a *gem*-dinitrile functional group at the 2-position. The dinitrile is significant to implementing the proposed route (Scheme 1), but its

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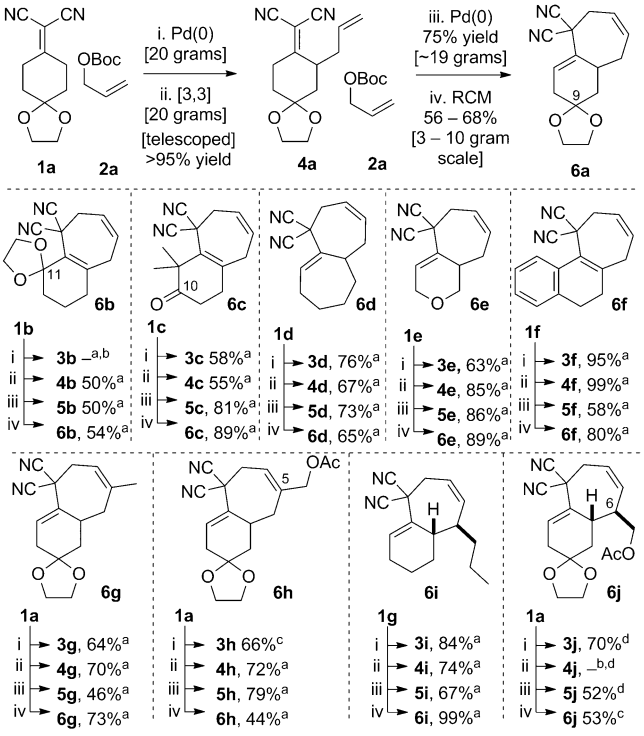
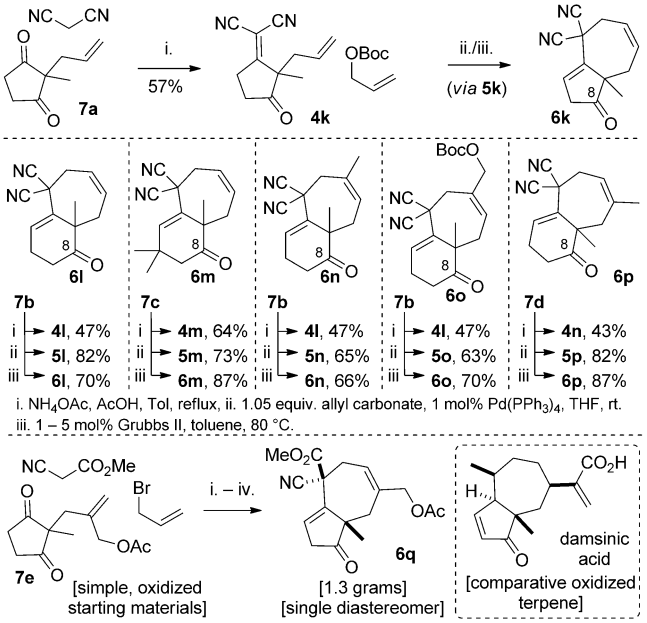
incorporation will also facilitate diversification. Quaternary dinitriles and related functional groups are known to undergo a variety of reactions including decyanation, hydrolysis and other nucleophilic addition reactions.[19] From a medicinal chemistry perspective, a nitrile is sterically small (A value = 0.17), has noted metabolic stability, decreases lipophilicity, and is isosteric to a halogen.[20]

We first examined the scope of the sequence with respect to the different reagent classes (Scheme 2). It is well precedented that alkyl halides can undergo deconjugative alkylation with Knoevenagel adducts,[14] however we ultimately decided to utilize allylic acetates and carbonates due to their bench-stability. As representative conditions, **4a** was prepared by Pd-catalyzed deconjugative allylation with **2a** followed by heating at 150 °C to promote [3,3] rearrangement. The sequence could be telescoped in > 95 % yield over the 2 steps. **6a** was prepared by repeating the deconjugative allylation (via **5a**) followed by ring-closing metathesis. We prepared a series of bicycloalkanes **6b–6j** by varying the starting materials. As we are interested in unique oxidation patterns, we utilized oxygenated Knoevenagel adducts **1a–1c**, and **1e** to yield **6a–6c**, and **6e**. Oxygenated allylic electrophiles translate into unique oxidation patterns about the cycloheptyl ring (**6h**, **6j**). Other cyclic systems could also be prepared (**6d** and **6f**). As a final point, when terminally substituted allylic reagents are utilized for the initial alkylation (e.g. **4i** and **4j**), the allylic transposition results in two new stereocenters diastereoselectively.



i. 1.05 equiv. allyl acetate or carbonate, 0.50 – 1 mol% $Pd(PPh_3)_4$, THF or CH_2Cl_2, rt. ii.140 – 170 °C, toluene, pressure vial, iii. 1.05 equiv. allyl acetate or carbonate, 0.50 – 1 mol% $Pd(PPh_3)_4$, THF or CH_2Cl_2, iv. 1 – 5 mol% Grubbs II, toluene, 80°C. [a] standard scale = 50 – 500 mgs. [b]telescoped, [c] > gram scale reaction [d] 15 – 30 gram scale reaction

Scheme 2. Synthesis of uniquely functionalized and oxygenated bicycloalkanes.

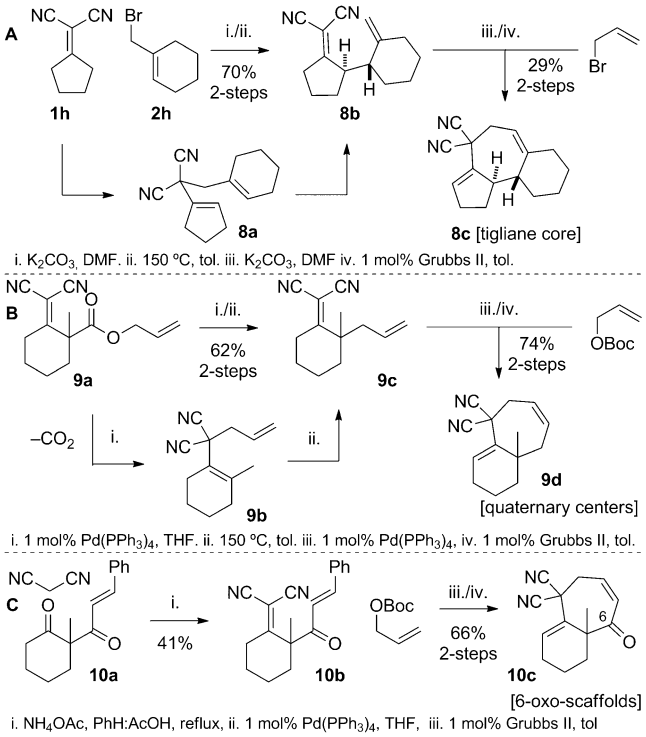


Scheme 3. Synthesis of 8-oxo bicycloalkanes.

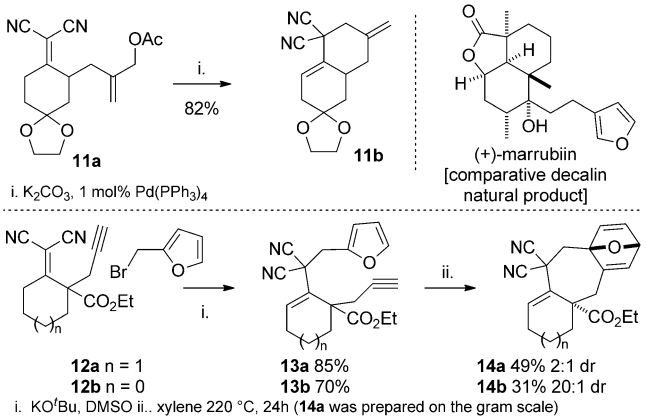
We realized that an additional unique oxidation pattern could be accessed by starting from cyclic, allylated 1,3-diones **7** (Scheme 3). Beginning with **7a**, a Knoevenagel condensation yields γ-allyl Knoevenagel adduct **4k**, which can be processed as previously described by deconjugative allylation then ring-closing metathesis to 8-oxobicycle **6k**. In addition to the 8-keto functional group in the cyclopentenone (**6k**) or hexenone (**6l–6p**), oxygenation and aliphatic substitution can be varied in the cycloheptyl ring resulting in unique bicycloalkanes (**6n–6p**). Furthermore, bicycloalkane **6q** was prepared on the gram-scale. **6q** or related structures may be useful in the synthesis of pseudoguaianolide natural products.

We next examined cyclic allylic electrophile **2h** (Scheme 4 A). We were pleased to find that deconjugative alkylation of **1h** and the cyclic allyl bromide yielded **8a**, which underwent diastereoselective Cope rearrangement to **8b** (two steps, 70 % yield). Repeating the deconjugative allylation followed by ring-closing metathesis yielded the angularly fused tricycloalkane (two steps, 29 % yield). Excitingly, this is a rapid entry into a challenging class of natural products (tigliane and daphnane).

Using a variant of Tunge's decarboxylative allylation[14c,21] we were able to convert **9a** to the 1,5-diene **9b** bearing a tetrasubstituted olefin (Scheme 4 B). It should be pointed out that the decarboxylative method is essential to generating the *more* substituted Knoevenagel adduct's allyl anion as standard deprotonation conditions results in deprotonation from the *less* substituted γ-position (see many of the schemes above). Excitingly, we were able to realize a [3,3] rearrangement to prepare a quaternary center. In this case, the conjugation-driving force allows for a favorable allylic transposition.[17] Using the standard protocol, **9c** was then con-



Scheme 4. Variations on the strategy.



Scheme 5. Other cyclization reactions in lieu of ring-closing metathesis.

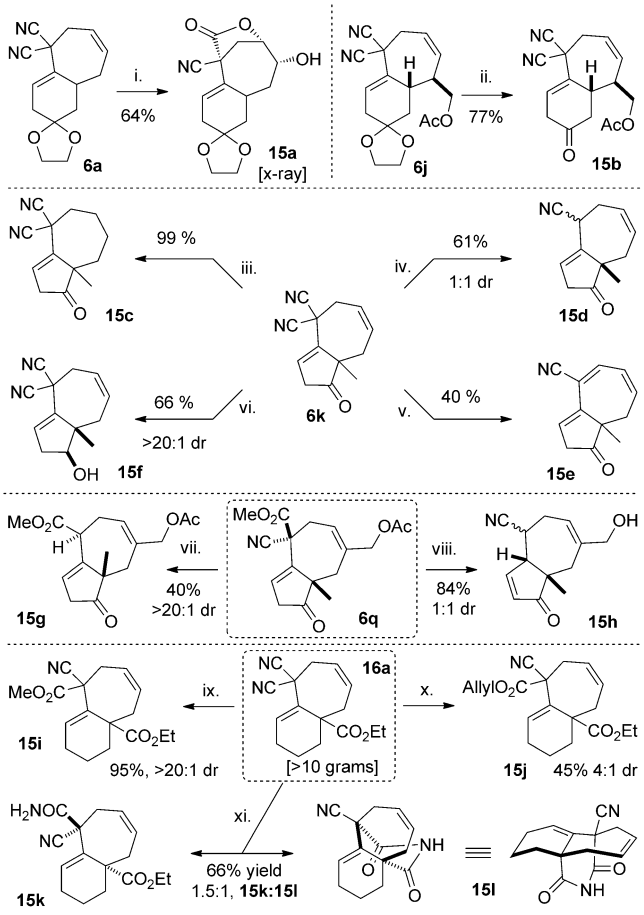
verted to the bicycloalkane **9d** bearing an angular methyl group.

An additional unique oxygenation pattern can be prepared by utilizing exocyclic 1,3-dione **10a** (Scheme 4C). **10a** is prepared from cyclohexanone by Claisen condensation with cinnamoyl chloride, then methylation (K_2CO_3, MeI).[22] **10a** was then subjected to standard Knoevenagel condensation conditions and **10b** was isolated. Interestingly, the molecule contains two ketones but condensation was only observed at the cyclohexanone. The sequence is then completed as previously described to yield a 6-oxygenated scaffold **10c**.

Thus far, we have described sequences terminated by ring-closing metathesis. However, other cyclization reactions can be utilized (Scheme 5). For example, **11a**, prepared by deconjugative α-allylation/[3,3] Cope rearrangement, underwent intramolecular deconjugative α-allylation to yield the decalin **11b**. Though not initially of interest at the outset of our studies, decalin natural products,[23a] such as marrubiin,[23b] may be synthetically viable targets beginning from ketones, malonic acid derivatives, and bis-allylic reagents. γ-Propargyl Knoevenagel adducts **12a–b** were prepared by alkylation then Knoevenagel condensation from their respective commercially available cyclic β-keto esters. Deconjugative alkylation (to **13a–b**) with furfuryl bromide followed by intramolecular Diels–Alder furan (IMDAF) cycloaddition[24] yields the tricyclic frameworks **14a–14b**. Although the cycloaddition yields are modest, this has the potential to be a simple approach to diterpenoid natural product analogs related to icetexane[25] and neodolastane[26] families.

For our final studies, we examined functional group interconversions (Scheme 6). Under Upjohn conditions, the lactone **15a** was isolated as a single diastereomer via dihydroxylation followed by concomitant intramolecular nitrile hydrolysis.[19e] The acetal **6j** could be selectively deprotected.[27] Substrate **6k** underwent a variety of chemoselective transformation in good to excellent yield including hydrogenation, reductive decyanation,[19a,b] dehydrocyanation,[19g,h] and ketone reduction. Building block **6q** also underwent reductive decyanation[19a,b] diastereoselectively yielding substrate **15g** bearing an ester moiety. Alternatively ester hydrolysis and decarboxylation provides access to the mononitrile **15h**.[28] **16a** was prepared by the standard procedure on the 10-gram scale (see the Supporting Information). The nitrile could be converted to the methyl ester **15i** diastereoselectively under simple conditions. We also examined conditions for the synthesis of the allyl ester **15j**, which are precedented to undergo a variety of chemical transformation including decarboxylative protonation (deprotection) and allylation.[21,29,30] Finally, using Dash's simple protocol for nitrile hydrolysis,[19d] amide **15k** and tricyclic imide **15l** were prepared.

In conclusion, we have developed an operationally simple strategy to prepare common terpenoid frameworks from abundant reagent classes. The strategy is tunable over the four-step sequence to yield unique functionalization and oxygenation patterns about the scaffolds. Future directions are four-fold: a) increase the diversity, scope, and complexity of the general strategy, b) use the method in the total synthesis and analog synthesis of specific natural product targets, c) develop asymmetric versions of the strategy, and d) collaboratively explore the biological profiles of the molecules prepared.



i. 3 mol% OsO_4, 1.5 equiv. NMO, in acetone/H_2O, rt, 2h, ii. 10 mol% I_2, acetone, reflux, 12h, iii. 7 %w/w Pd/C, H_2, THF, 4h, iv. 3 equiv. LN (1M in THF), then MeOH/NH_4Cl, -78 °C, 2 min, v. 1.5 equiv. NaH, DMF, 5 min, vi. 1 equiv. $NaBH_4$, MeOH, 0 °C, 15 min., vii. 3 equiv. LN (1M in THF), then MeOH/NH_4Cl, -78 °C, viii. (a) 3 equiv. NaOH, H_2O/MeOH, (b) 10 mol% Cu_2O, MeCN, 80 °C, ix. 5 equiv. K_2CO_3, MeOH, then 2M HCl. x. K_2CO_3, allyl alcohol xi. 3 equiv. KO^{t}Bu, *tert*-amyl alcohol 0 °C

Scheme 6. Examples of functional group interconversion reactions.

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Keywords: [3,3] Cope rearrangement · allylic alkylation · deconjugative alkylation · Knoevenagel adducts · terpene synthesis

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Communications

Terpene Synthesis

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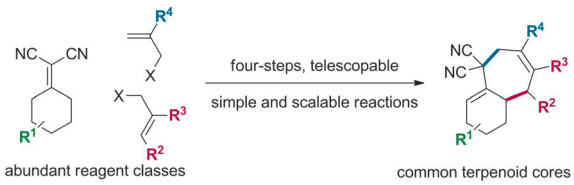

Assembly of Terpenoid Cores by a Simple, Tunable Strategy

How to Cope with a synthesis problem: Total synthesis of oxygenated, polycyclic terpenes is widely studied, although synthetic strategies that allow for controlled placement of oxygen atoms and other functionality remains a challenge. Here presented is a simple, scalable, and tunable synthetic strategy to assemble terpenoid-like polycycloalkanes from cycloalkanones, malononitrile, and allylic electrophiles.