Tetrahedron 70 (2014) 4147–4155

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Facile access to cyclooctanoid ring systems via microwave-assisted tandem 6-*exo dig* cyclization–rearrangement sequence

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ARTICLE INFO

*Article history:*
Received 20 January 2014
Received in revised form 26 February 2014
Accepted 28 February 2014
Available online 6 March 2014

ABSTRACT

Appropriately substituted 5-alkyn-1-ol systems bearing a nitrile moiety at the triple bond serve as versatile precursors to a variety of cyclooctenone derivatives via a 'one-pot' base-catalyzed oxyanionic 6-*exo* dig cyclization/Claisen rearrangement sequence under microwave irradiation. It was found that the initially formed cyclic intermediate consists of a mixture of endo and exocyclic isomers, which appear to be in equilibrium under the reaction conditions. However, the only observed products from these reactions are α-cyano-substituted cyclooctenones, derived from the exocyclic dihydrofuran intermediates.



## 1. Introduction

Cyclooctanoid carbocyclic compounds are widespread in nature and many of them exhibit significant biological activity.[1] They have been isolated from various sources, including marine organisms, pathogenic fungi, terrestrial plants, and insects. To date, well over 100 structurally diverse cyclooctanoid natural products with varying degrees of complexity have been identified and characterized.[1] Several representative examples of these are shown in Fig. 1.

Despite their obvious medicinal relevance, efforts to access cyclooctanoid natural products by synthetic means have been slow to emerge primarily because of difficulties associated with the construction of cyclooctane ring systems. As conventional annulation strategies are largely ineffective in this context, most of the methods currently available for the synthesis of eight-membered rings involve various fragmentation reactions of existing polycyclic structures[2,3] and several cycloaddition strategies.[4]

We have recently demonstrated that a variety of cycloheptanoid fused ring systems may be prepared through a known[5] but largely

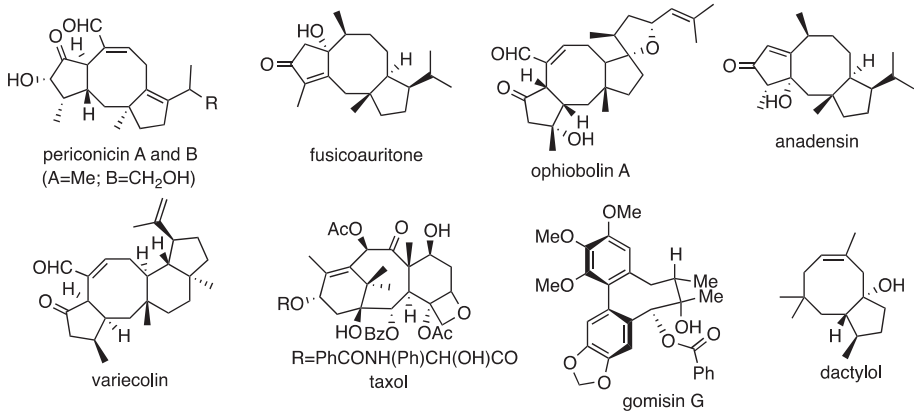


**Fig. 1.** Representative examples of biologically active cyclooctanoid natural products.

ignored tandem reaction sequence that involves a base-catalyzed intramolecular cyclization of appropriately substituted 4-pentyn-1-ols, followed by in situ Claisen rearrangement of the intermediate

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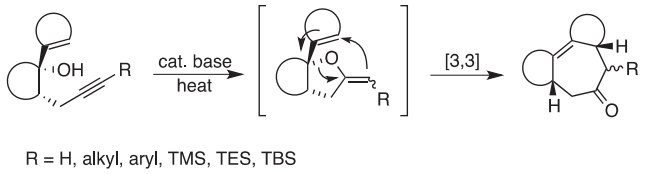
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.089

2-alkylidenetetrahydrofurans (Scheme 1).[6] The reaction was found to be quite general, allowing the rapid construction of mono-, di-, tri-, and tetracyclic carbocyclic structures. Although anionic 5-*exo dig* cyclizations involving oxygen nucleophiles have been known since the early 1950s,[7] these transformations are generally difficult to achieve due to the reversibility and unfavorable equilibria associated with such isomerizations, particularly with unactivated alkynes. In addition, the initially formed exocyclic vinyl ethers are often unstable[8] and isomerize easily to form the corresponding endocyclic derivatives.[9]



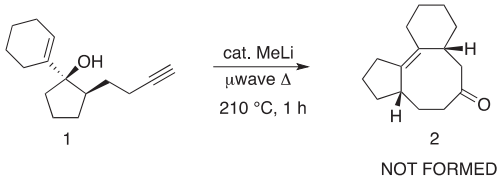

**Scheme 1.** General strategy to cycloheptane-containing polycycles via sequential cyclization/Claisen rearrangement reaction.

These problems may be largely avoided by taking advantage of an appropriately substituted 4-alkyn-1-ol substrate that undergoes cycloisomerization under basic conditions, forming a transient 2-alkylidenetetrahydrofuran species, which rearranges spontaneously via a thermally promoted 3,3-sigmatropic process.[5] It is noteworthy that the initial intramolecular cyclization requires the use of a *catalytic* base that allows for rapid protonation of the intermediate vinyl anion species, and renders the cycloisomerization process irreversible (Scheme 1). Using this strategy as the key ring forming step, the total syntheses of (±)-frondosin C,[10] (−)-frondosin B[11] and the formal synthesis of (±)-frondosin A[12] were recently achieved in our laboratory.

At the outset of the current study, it was envisioned that the methodology successfully developed for the generation of cycloheptanoid structures could also be used for the construction of cyclo*octanoid* ring systems, by simply employing appropriately substituted 5-hexyn-1-ols (instead of 4-pentyl-1-ols) as starting materials.

## 2. Results and discussion

Our initial attempts to employ several homologous 5-hexyn-1-ols as precursors to eight-membered ring containing systems via a base-catalyzed 6-*exo* cyclization/Claisen rearrangement sequence failed completely. For example, treatment of alkynol **1** with a base under microwave irradiation produced no detectable amounts of **2** even after prolonged heating (Scheme 2) and the starting material was recovered quantitatively. The reason for the reaction to fail is almost certainly due to the inability of the 5-alkyn-1-ol **1** to undergo the initial 6-*exo* cyclization. In fact, Paquette et al.[13] and Petasis[14] have previously demonstrated that preformed allyl vinyl ether precursors with terminal exocyclic double bonds, prepared from δ-valerolactone derivatives via the Tebbe[15] or Petasis[14] reactions, are indeed capable of undergoing [3,3]-sigmatropic rearrangements. The failure of the examined 5-alkyn-1-ol system **1** to cyclize is consistent with the observed trend that 6-*exo* isomerizations are generally more sluggish than the corresponding 5-*exo* processes.[16] It was therefore obvious that some degree of initial activation of the triple bond was required in order for the 6-*exo* oxyanionic cyclization to proceed and form the requisite 2-alkylidenetetrahydropyranyl intermediate. Thus, various 5-alkyn-1-ols bearing electron withdrawing ester or nitrile substituents at the triple bond terminus were investigated.

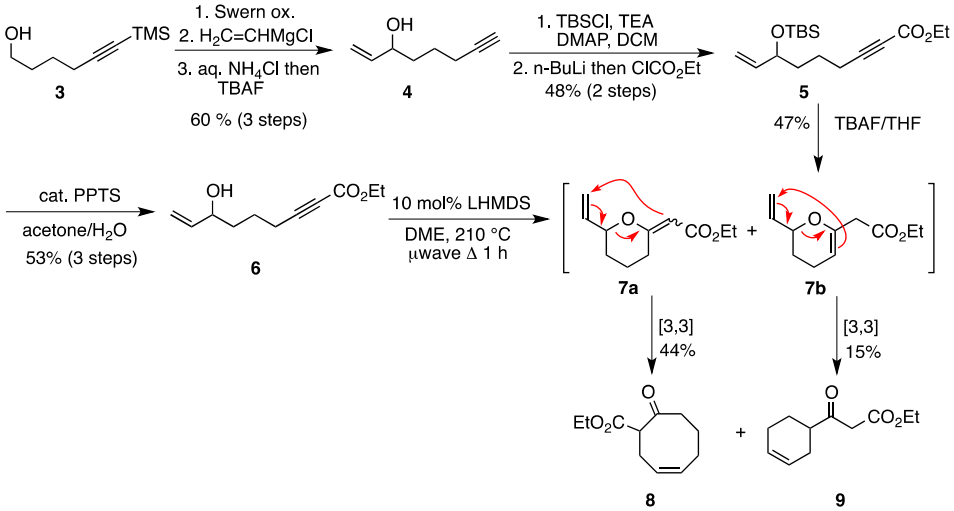



**Scheme 2.** Failed 6-*exo dig* cyclization/Claisen rearrangement reaction.

It should be noted that, although a few strictly oxyanionic 5-*exo dig* cyclizations of this type (oxa-Michael reaction) have been reported in the literature[17] (including by us[18]) the corresponding 6-*exo* cyclizations are almost non-existent.[19] However, activation of triple bonds by transition metal catalysts is more common and various gold catalysts, in particular, have been utilized extensively for intramolecular hydroalkoxylations to generate a THF and THP derivatives via both 5-*exo* and 6-*exo* dig modes of cyclization.[20]

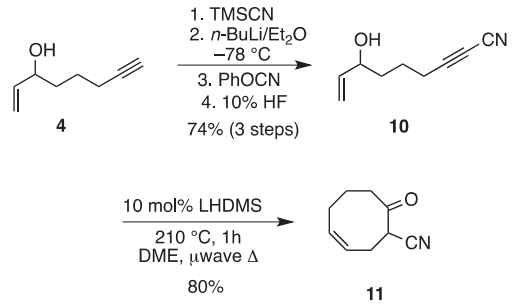
### 2.1. Ester activation

To test the potential of the 6-*exo dig* cyclization/Claisen rearrangement sequence as a route to cyclooctane ring systems, we initially investigated the cyclization of allyl alcohols onto alkynoates. Thus, the carbethoxy derivative **6** was prepared in a straightforward fashion as shown in Scheme 3.

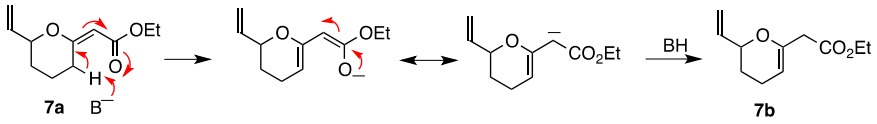



**Scheme 3.** 6-*exo* cyclization/Claisen rearrangement of acetylenic ester **6**.

Upon treatment with catalytic LHDMS (10 mol %) in DME and exposure to microwave irradiation for 1 h, it was found that the desired cyclooctenone **8**[21] was formed in a modest 44% isolated yield along with ca. 15% of an unexpected cyclohexene derivative **9**.[22] This byproduct was presumably formed as a result of an *exo*/*endo* double bond isomerization followed by subsequent 3,3-sigmatropic rearrangement of the resulting allyl vinyl ether **7b**. This isomerization is most likely base-catalyzed, producing a fully conjugated enolate anion intermediate via γ-deprotonation (Scheme 4). In fact, we have observed the formation of both **7a** and **7b** with the endocyclic derivative predominating when **6** was stirred in the presence of catalytic LHDMS even at room temperature. Interestingly, the TBS-protected alcohol **5** was also converted to **7b** upon stirring in the presence of TBAF at room temperature overnight.




**Scheme 5.** 6-*exo* Cyclization/Claisen rearrangement of a cyano derivative.




**Scheme 4.** Possible mechanism for the base-catalyzed *exo*/*endo* isomerization.

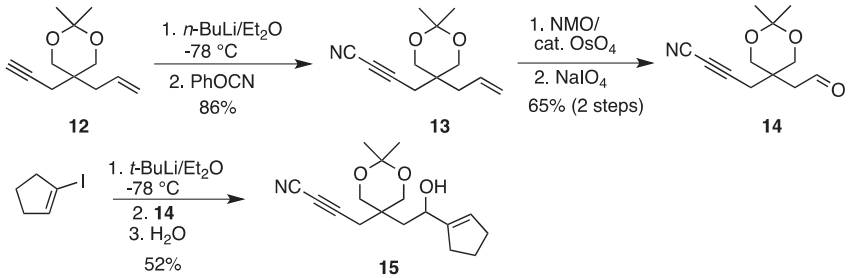
Although similar *exo*/*endo* isomerization reactions involving 2-methylidene tetrahydrofuran derivatives (formed via 5-*exo* dig cyclization) are known to occur under high temperature conditions,[9] we have previously not observed [3,3]-rearrangement reactions involving endocyclic *tetrahydrofuran* intermediates in any of the systems examined. It is reasonable to assume that, in the case of **7b**, the increased flexibility of a six-membered dihydropyran system compared to an analogous five-membered tetrahydrofuran system allows the π-bonds of the allyl vinyl ether system to become proximal enough for this alternative mode of rearrangement to occur. Consistent with our observations, rearrangement of the exocyclic intermediate should be faster because it can proceed through a chair-like transition state while the endocyclic intermediate would need to adopt a boat-like transition state.

It should be noted that **6** also cyclized readily when exposed to catalytic $AuCl_3$ at room temperature,[20b] producing a 1.6 to 1 ratio of *endo* and *exo* isomers, respectively; however, when the reaction mixture was subsequently heated in the microwave oven (in the presence of the Au catalyst), extensive decomposition was observed.

## 2.2. Nitrile activation

In addition to the to ester derivative **6**, analogous cyano-substituted acetylenes were also investigated. Thus, compound **10**, readily prepared from allylic alcohol **4** (Scheme 5), was smoothly converted to the desired cyclooctanone derivative **11** under microwave irradiation in the presence of catalytic base (10 mol % LHMDS) in 80% isolated yield. *Significantly, no products analogous to* ***9*** *were detected in the reaction mixture.*

It is noteworthy that the four-step sequence from alcohol **4**[23] to the corresponding cyano derivative **10** may be performed as a 'one-pot' reaction without the need for isolation of the intermediate products. This process involves transient protection of **4** as a TMS ether with TMSCN under neutral conditions, which enables the selective deprotonation of the terminal acetylene with *n*-BuLi and subsequent cyanylation with PhOCN. Workup with 10% aq HF (or Amberlyst-15) removes the TMS protecting group, affording **10**. Other analogues of **10** were prepared by coupling various vinyllithum reagents, derived from the corresponding vinyl iodides or bromides by low-temperature lithium–halogen exchange, with appropriate acetylenic aldehydes. Systems bearing a cyclic acetal moiety as part of the 5-alkyn-1-ol system were prepared as shown in Scheme 6 starting with the known acetal **12**.[24]

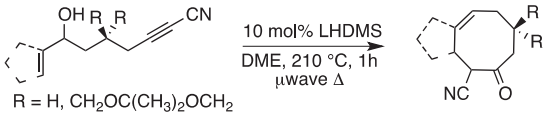


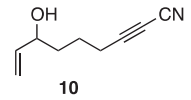
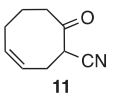
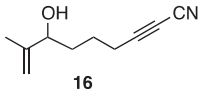
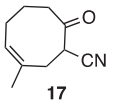
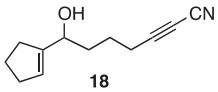
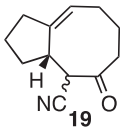
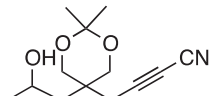
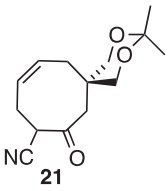
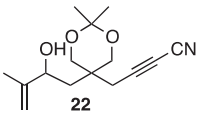
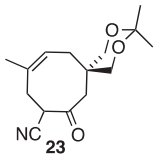
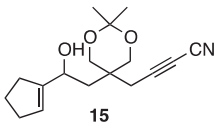
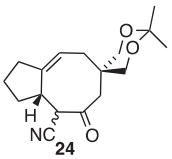

**Scheme 6.** Preparation of acetal-containing 5-alkyn-1-ol systems.

All of the cyano-substituted 5-hexyn-1-ol systems studied so far were found to undergo clean conversion to the desired cyclooctanone derivatives via the 6-*exo* cyclization/Claisen rearrangement process. These experiments demonstrated that fused 5–8 ring systems (Table 1, entries 3 and 6) may also be accessed through this methodology in a straightforward fashion.

It should be emphasized that this chemistry is unique in that it allows the direct formation of cyclooctenone derivatives bearing the versatile α-cyano ketone functionality, which offers ample opportunities for further functionalization and structural diversification. Aside from the many separate functional group

**Table 1**
Preparation of cyclooctanoid ring systems via sequential 6-*exo dig* cyclization/Claisen rearrangement process




| Entry | Allyl alcohol | Product | Yield (%) |
|---|---|---|---|
| 1 |  **10** |  **11** | 80 |
| 2 |  **16** |  **17** | 75 |
| 3 |  **18** |  **19** | 64[a] |
| 4 |  **20** |  **21** | 79 |
| 5 |  **22** |  **23** | 84 |
| 6 |  **15** |  **24** | 78[b] |

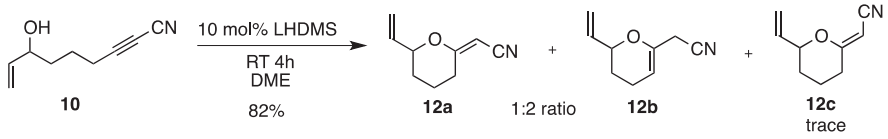
[a] Isolated as a 2.7:1 mixture of diastereomers.
[b] Isolated as a 1:1 mixture of diastereomers.

the reactions at different temperatures followed by careful analysis of the resulting product mixtures. The formation of all four products (**12a**, **12b**, **12c**, **11**) monitored by TLC and the relative abundance of each isomer was determined by NMR analysis (see Experimental section). The $^1$H chemical shift assignments for the *E* and *Z* exocyclic intermediates (**12a** and **12c**) are based on those previously reported for similar systems.[26]

It was also found that compound **10** cyclizes readily even at room temperature when exposed to 10 mol % LHDMS in DME. Under these conditions, **10** underwent a clean cycloisomerization reaction in 4 h to produce a mixture of **12a** and **12b** with only trace amounts of the *Z*-exocyclic isomer **12c** present (Scheme 7). It should be noted that there is no reaction without added base and **10** is stable for extended periods of time when stored at room temperature.

As expected, the formation of the cyclooctenone product **11** is highly temperature dependent as evidenced by a series of experiments conducted in the microwave oven at temperatures ranging from 150 °C to 200 °C. All experiments were conducted in anhydrous DME over a period of 1 h in the presence of 10 mol % LHMDS (1.0 M solution in THF). Thus, at 150 °C, approximately 13% of the product mixture consisted of the cyclooctenone **10**, the balance of the reaction consisting of nearly equal amounts of the *endo* and *exo*-cyclic intermediates **12a** and **12b**. Some isomerization of the *E* and *Z* isomers **12a**/**c** was also observed under these conditions. As temperature was raised, the amount of **11** also increased steadily while concentrations of the cyclized intermediates decreased accordingly. At 190 °C, cyclooctenone **11** and the endocyclic intermediate **12b** made up 72% and 25% of the product mixture, respectively, while only approximately 3% of the (*E*)-exocyclic intermediate **12a** was found to be present. At 200 °C, nearly 86% of **10** had been converted to the desired cyclooctenone **11**, the balance of the reaction consisting of just the endocyclic intermediate **12b**. The ideal temperature for this reaction appears to be 210 °C under which conditions full conversion of **10** to **11** was observed. Since **11** is derived from the exocyclic dihydropyran species **12a** (or **12c**) none of which was present at temperatures at or above 200 °C, it is clear that under these high temperature conditions *endo*/*exo* isomerization involving **12b** serves as a source for the requisite exocyclic species, which then cyclizes rapidly to produce **11**. The results from these experiments are shown graphically in Fig. 2.

We also analyzed reactions that were conducted at 210 °C, monitoring the product composition versus time. It was found that




**Scheme 7.** 6-*exo dig* Cyclization of **10** at room temperature.

manipulations of the ketone carbonyl and cyano groups, there are a number of other possible transformations unique to the α-cyano ketone system that provide access to a variety of functionalized derivatives, including heterocyclic structures.[25]

## 2.3. Rate studies

Although the cyano derivatives investigated thus far appear to undergo clean tandem 6-*exo* cyclization/Claisen rearrangement reactions to afford the expected cyclooctanoid derivatives, closer examination of these processes revealed that both endocyclic dihydropyranyl and tetrahydropyranyl exocyclic species analogous to **7a** and **7b** were intermediates in the reaction. This was confirmed by using compound **10** as a model system and conducting

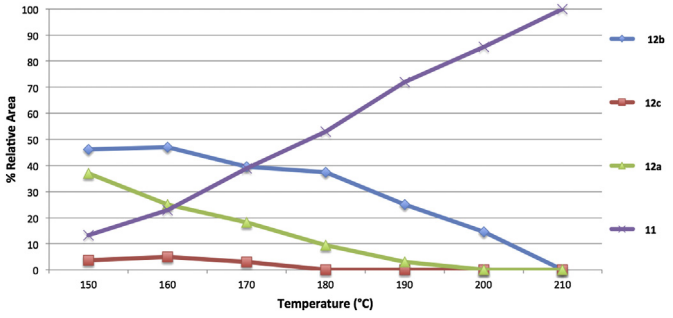



**Fig. 2.** Temperature dependent formation of reaction products upon heating **10** in the presence of catalytic base (LHDMS).

only after 15 min under these conditions, the product mixture consisted of approximately 75% of **11** and 25% **12b**; no exocyclic intermediates (**12a**, **12c**) were observed. After 30 min at 210 °C, more than 90% of the product mixture consisted of **11**; however, full conversion requires 60 min. These results are shown graphically in Fig. 3.

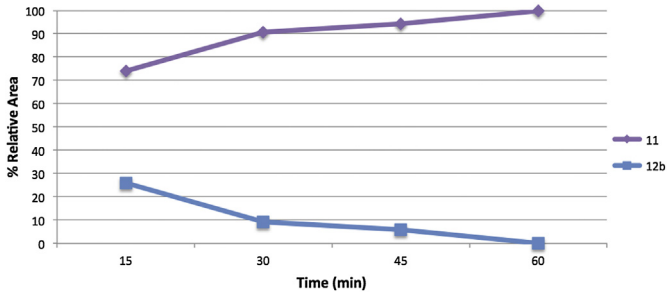



**Fig. 3.** Time dependence of product formation on heating **10** at 210 °C in the presence of catalytic base (LHDMS).

## 3. Conclusion

We have demonstrated that cyano-substituted 5-alkyn-1-ol systems serve as versatile precursors to a variety of cyclooctenone derivatives via a microwave-assisted sequential oxyanionic 6-*exo dig* cyclization/Claisen rearrangement reaction in the presence of catalytic base. It was found that the initially formed cyclic intermediate consists of a mixture of endo and exocyclic isomers, which appear to be in equilibrium under the reaction conditions. Although both the endo and exocyclic intermediates are potentially capable of undergoing 3,3-sigmatropic rearrangements, the only observed products from the reactions investigated so far are α-cyano-substituted cyclooctenones, derived from the exocyclic species. These results demonstrate that isomerization of the endocyclic intermediate to the corresponding exocyclic species is faster than a direct sigmatropic rearrangement, and that the exocyclic intermediate, once formed, rearranges more rapidly provided that enough thermal energy is present.

Slightly different results were obtained when the analogous alkynoate **6** was used as the starting material. In this case, the tandem 6-*exo dig* cyclization/Claisen rearrangement reaction afforded a modest yield of the desired cyclooctenone derivative **8**. In addition, the formation of cyclohexenyl ketoester **9**, derived via competing rearrangement of the endocyclic species **7b**, was also observed under these conditions. The difference in the chemical behavior between the corresponding ester and cyano analogues is not fully understood at this time.

Our future studies will focus on further probing the synthetic utility of the oxyanionic 6-*exo* dig cyclization/Claisen rearrangement sequence as a route to wide variety of cyclooctanoid systems, including natural products. The results from these studies will be reported in due course.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR spectra were obtained using an Agilent DD2-500 NMR (500 MHz) spectrometer. Chemical shifts are reported in units of parts per million (ppm), relative to tetramethylsilane at $\delta$=0.00 ppm. Coupling constants *J* are reported in hertz (Hz).

All microwave experiments were conducted in Biotage Initiator Microwave Synthesizer, equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL or 5 mL microwave vials.

Tetrahydrofuran (THF) and diethyl ether were freshly distilled under $N_2$ from dark blue solutions of sodium benzophenone ketyl. Dimethoxyethane (DME), dichloromethane (DCM), TMSCl, and $Et_3N$ were freshly distilled under $N_2$ from calcium hydride. Bulk solvents were purchased from Fisher or VWR.

All starting reagents were purchased from Sigma–Aldrich, Acros or Strem. The concentrations of solutions of *n*-BuLi, and *t*-BuLi were determined by titrations with *sec*-butyl alcohol using 1,10-phenanthroline as the indicator following the method of Watson and Eastham.[27] All glassware were flame-dried under an inert atmosphere and all reactions were performed under an atmosphere of dry nitrogen.

### 4.2. *tert*-Butyldimethyl(oct-1-en-7-yn-3-yloxy)silane[28]

Alkyne **4**[23] (2.88 g, 23.2 mmol) was dried over molecular sieves in DCM and transferred to a round bottom flask containing DCM (100 mL) at 0 °C. Dry triethylamine (3.92 mL, 28.1 mmol) and a catalytic quantity of DMAP were then added followed by TBSCl (3.89 g, 25.8 mmol). The reaction mixture was allowed to stir overnight while warming to room temperature. The reaction was quenched with $H_2O$ (20 mL) and the layers were separated. The aqueous layer was extracted with DCM (3×30 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. The solution was filtered and solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (pure hexanes) to give 4.10 g of TBS-protected alcohol (74% yield) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.80 (ddd, *J*=17.2, 10.4, 1.2 Hz, 1H), 5.15 (dt, *J*=17.1, 1.2 Hz, 1H), 5.04 (dt, *J*=10.2, 1.3 Hz, 1H), 4.16–4.09 (m, 1H), 2.23–2.15 (m, 2H), 1.94 (t, *J*=2.6 Hz, 1H), 1.64–1.50 (m, 4H), 0.90 (s, 9H), 0.04 (s, 6H), 0.02 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 141.5, 113.8, 84.5, 73.3, 68.3, 37.0, 25.9, 24.1, 18.4, 18.2, -4.4, -4.9.

### 4.3. Ethyl 7-(*tert*-butyldimethylsilyloxy)-8-nonen-2-ynoate (5)

A solution of *tert*-butyldimethyl(1-octen-7-yn-3-yloxy)silane (4.68 g, 19.6 mmol) in THF (80 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M, 14.7 mL, 23.6 mmol) was added dropwise via syringe. The resulting mixture was allowed to stir at this temperature for 30 min. A solution of ethyl chloroformate (8.52 g, 7.47 mL, 78.5 mmol) in 15 mL of THF was then added to the reaction mixture dropwise via cannula. After 1 h, the reaction quenched with 10% HCl (5 mL). The solvent was removed under reduced pressure and the resulting residue was taken up in diethyl ether (25 mL) and $H_2O$ (20 mL), and the layers were separated. The aqueous layer was then extracted with diethyl ether (3×25 mL). The combined ethereal layers were then washed with satd $NaHCO_3$ (25 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and solvent was removed under reduced pressure. The resulting crude oil was purified by column chromatography (3% ethyl acetate in hexanes) to give 3.85 g of the desired ester **13** (63%) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.77 (ddd, *J*=16.1, 10.3, 5.9 Hz, 1H), 5.14 (dt, *J*=17.1, 1.5 Hz, 1H), 5.04 (dt, *J*=10.3, 1.5 Hz, 1H), 4.21 (q, *J*=7.07 Hz, 2H), 4.16–4.10 (m, 1H), 2.37–2.31 (m, 2H), 1.68–1.54 (m, 4H), 1.30 (t, *J*=7.1 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 153.9, 141.2, 114.1, 89.2, 73.3, 73.1, 61.8, 36.9, 25.9, 23.1, 18.7, 18.2, 14.1, −4.4, −4.9. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{30}O_3SiNa$ 333.1862; found 333.1857.

### 4.4. Ethyl 7-hydroxynon-8-en-2-ynoate (6)

Ester **5** (1.20 g, 3.87 mmol) was dissolved in 14 mL of acetone/$H_2O$ (6:1 ratio), a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) was added to the solution, and the reaction mixture was allowed to stir overnight at 50 °C. Solvent was then removed under reduced pressure and the resulting residue was taken up in diethyl ether (15 mL) and $H_2O$ (10 mL). Upon separating layers, the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The remaining crude oil was purified by column chromatography on silica gel (15% EtOAc/hexanes) to give 0.663 g of alcohol **14** (88%) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.87 (ddd, $J$=17.1, 10.2, 6.3 Hz, 1H), 5.25 (dt, $J$=17.1, 1.2 Hz, 1H), 5.14 (dt, $J$=10.2, 1.2 Hz, 1H), 4.21 (q, $J$=7.2 Hz, 2H), 4.16–4.10 (m, 1H), 2.38 (t, $J$=6.1 Hz, 1H), 1.79–1.54 (m, 5H), 1.30 (t, $J$=7.3 Hz, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 153.8, 140.7, 115.1, 88.8, 73.5, 72.6, 61.8, 35.8, 23.4, 18.6, 14.0. HRMS (ESI-TOF) $m/z$ $[M+Na]^+$ calcd for $C_{11}H_{16}O_3Na$ 219.0997; found 219.0995.

### 4.5. Ethyl 2-(2-vinyl-3,4-dihydro-2*H*-pyran-6-yl)ethanoate (7b)

TBS-protected alcohol **5** (0.874 g, 2.82 mmol) was dissolved in THF (5 mL), and TBAF (1.0 M, 2.82 mL, 2.82 mmol) was added to the solution via syringe. The reaction mixture was allowed to stir at room temperature overnight at which point the reaction was judged to be complete by TLC. Solvent was then removed under reduced pressure, and the crude residue was taken up in diethyl ether (10 mL) and $H_2O$ (5 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined ether layers were washed with brine dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The resulting oil was purified by silica column (15% EtOAc/hexanes) to give 0.256 g of **7b** (47%) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.89 (ddd, $J$=17.3, 10.6, 5.6 Hz, 1H), 5.28 (app. d, $J$=17.3 Hz, 1H), 5.14 (app. d, $J$=10.7 Hz, 1H), 4.65 (app. t, $J$=3.5 Hz, 1H), 4.41–4.36 (m, 1H), 4.16 (q, $J$=7.17 Hz, 2H), 3.04 (s, 2H), 2.15–2.06 (m, 1H), 2.06–1.98 (m, 1H), 1.91–1.84 (m, 1H), 1.69–1.60 (m, 1H), 1.26 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 170.6, 147.2, 137.6, 115.5, 98.9, 76.0, 60.7, 40.4, 27.0, 19.6, 14.2. HRMS (ESI-TOF) $m/z$ $[M+Na]^+$ calcd for $C_{11}H_{16}O_3Na$ 219.0997; found 219.0996.

### 4.6. Ethyl 8-oxocyclooct-3-enecarboxylate (8), ethyl 3-(cyclohex-3-enyl)-3-oxopropanoate (9)

Ester **6** (58.0 mg, 0.296 mmol) was dissolved in phenetole (1.5 mL) in a microwave vial and catalytic LHMDS (0.0296 mL, 0.0296 mmol) was added. The mixture was then heated with microwave irradiation at 210 °C for 1 h. At this time, the reaction was judged to be complete by TLC. The reaction mixture was directly purified by column chromatography on silica gel (8% EtOAc/hexanes) to give 25.4 mg of rearranged product **8**[21] (44%) and 8.50 mg of **9**[22] (15%), each as a pale yellow oil. Compound **8**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.79–5.67 (m, 2H), 4.24–4.11 (m, 2H), 3.49–3.43 (m, 1H), 2.91–2.83 (m, 1H), 2.72–2.65 (m, 1H), 2.53–2.46 (m, 1H), 2.41–2.34 (m, 1H), 2.27–2.17 (m, 1H), 2.17–2.09 (m, 1H), 1.78–1.69 (m, 1H), 1.61–1.51 (m, 1H), 1.25 (t, $J$=7.1 Hz, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 208.5, 169.4, 132.4, 127.8, 62.4, 61.3, 39.6, 26.5 25.0, 24.9, 14.1. Compound **9**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 5.69 (m, 2H), 4.19 (q, $J$=7.1 Hz, 2H), 3.51 (s, 2H), 2.77–2.69 (m, 1H), 2.24–2.03 (m, 4H), 1.68–1.54 (m, 2H), 1.28 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 205.4, 167.3, 126.7, 125.0, 61.3, 47.4, 46.8, 26.6, 24.6, 24.4, 14.1.

### 4.7. 7-Hydroxy-8-nonen-2-ynenitrile (10)

Alcohol **4** (0.507 g, 4.08 mmol), dissolved in 2 mL of DCM was dried over activated molecular sieves and then transferred to a 20 mL reaction vial via Teflon cannula. The DCM solvent was then evaporated with the aid of a stream of nitrogen gas, and neat TMSCN (0.486 g, 4.90 mmol) was added via syringe. After 2 h of stirring the reaction was judged to be complete by TLC. The neat solution was then diluted with 6 mL of diethyl ether and nitrogen gas was bubbled through the solution for 15 min to drive off any remaining HCN. The mixture was then cooled to −78 °C and *n*-BuLi was added dropwise (1.6 M, 3.10 mL, 4.90 mmol). After 30 min at this temperature, PhOCN[30] (0.633 g, 5.31 mmol) in 4.0 mL diethyl ether was added dropwise via a syringe. After 30 min of stirring at this temperature the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then diluted with 20 mL of diethyl ether. A solution of 10% NaOH (10 mL) was then added and the biphasic mixture was stirred vigorously for 5 min to remove the phenol byproduct. Layers were separated, and the aqueous layer was extracted with $Et_2O$ (3×10 mL). Aq HF (10%, 5 mL) was then added and the resulting biphasic mixture was stirred rapidly for 30 min, the layers were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined ethereal layers were then washed with water (20 mL), saturated aq $NaHCO_3$, and brine (20 mL), and dried over $MgSO_4$. Filtration and solvent removal under reduced pressure, followed by purification by column chromatography (20% EtOAc/hexanes) gave 445 mg (73%) of the desired product as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.84 (ddd, $J$=17.1, 10.5, 6.1 Hz, 1H), 5.23 (ddd, $J$=17.1, 1.5, 1.0 Hz, 1H), 5.13 (ddd, $J$=10.5 Hz, 1.5, 1.0 Hz, 1H), 4.12 (q, $J$=6.3 Hz, 1H), 2.41 (t, $J$=6.85 Hz, 2H), 1.79–1.59 (m, 5H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 140.5, 115.3, 105.2, 87.1, 72.4, 55.5, 35.5, 23.0, 18.8. HRMS (EI) $m/z$ $[M-H]^+$ calcd for $C_9H_{10}N$ 148.0762; found 148.0761.

### 4.8. 8-Oxo-3-cyclooctenecarbonitrile (11)

Alcohol **10** (0.117 g, 0.783 mmol) was dissolved in DME (2 mL) in a base-washed microwave vial. A solution of LHMDS (1.0 M, 0.0780 mL, 0.0780 mmol) was added via syringe and vial was heated in a microwave reactor for 1 h at 210 °C. Upon cooling, solvent was removed under reduced pressure, and the resulting crude product directly subjected to purification by column chromatography on silica gel (10% EtOAc/hexanes) to afford 93.2 mg (80%) of the desired cyclooctenone product **11** as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.91–5.84 (m, 1H), 5.82–5.76 (m, 1H), 3.68–3.64 (m, 1H), 2.90–2.84 (m, 1H), 2.72–2.61 (m, 2H), 2.55–2.49 (m, 1H), 2.22–2.16 (m, 2H), 1.74–1.66 (m, 2H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 203.1, 134.3, 125.8, 116.5, 48.0, 38.9, 26.2, 26.0, 24.0. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_9H_{12}NO$ 150.0919; found 150.0923.

### 4.9. 4-(5-Allyl-2,2-dimethyl-1,3-dioxan-5-yl)but-2-ynenitrile (13)

To a −78 °C solution of acetal **12** (1.68 g, 8.65 mmol) in an anhydrous diethyl ether (6 mL) was added *n*-BuLi (1.6 M in hexanes, 5.68 mL, 9.10 mmol) dropwise via syringe, and the resulting mixture was allowed to stir for 15 min. A solution of phenyl cyanate (dried over activated molecular sieves) in $Et_2O$ (6 mL) was then added to the reaction mixture dropwise via cannula. The mixture was allowed to stir at −78 °C for 20 min before warming to room temperature. The reaction was quenched with $H_2O$ (20 mL), the layers were separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined ethereal layers were then washed with 10% NaOH (2×20 mL) to remove the phenol

byproduct. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (0%–17.5% EtOAc/hexanes) to give 1.64 g of nitrile **13** (86% yield) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 5.72–5.63 (m, 1H), 5.20–5.14 (m, 2H), 3.72 (d, $J$=12.2 Hz, 2H), 3.54 (d, $J$==12.2 Hz, 2H), 2.68 (s, 2H), 2.08 (d, $J$=7.3 Hz, 2H), 1.42 (s, 3H), 1.40 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 130.7, 120.1, 105.1, 98.5, 84.8, 66.6 (two signals), 57.5, 37.1, 36.5, 27.7, 22.7, 19.6. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; found 220.1340.

### 4.10. 4-(2,2-Dimethyl-5-(2-oxoethyl)-1,3-dioxan-5-yl)but-2-ynenitrile (14)

Nitrile **13** (1.41 g, 6.45 mmol) was dissolved in aq acetone (50 mL, 9:1 acetone to water) along with $OsO_4$ (4% in water, 1.2 mL) and NMO (0.982 g, 8.36 mmol). The reaction mixture was allowed to stir at room temperature for 6 h before quenching with saturated thiosulfate solution. The mixture was then extracted with DCM (3×20 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated to give the crude diol, which was used without purification for the next step. To a rapidly stirred mixture of silica gel (8 g) in DCM (65 mL) was added $NaIO_4$ (0.65 M in $H_2O$, 13.0 mL, 8.44 mmol) followed by the crude diol prepared above in 10 mL DCM. The reaction was judged to be complete by TLC after 10 min, at which point the solution was vacuum filtered and the solids were washed with more DCM. The filtrate was concentrated and the resulting residue was taken up in diethyl ether (50 mL) and $H_2O$ (20 mL). The aqueous layer was separated and extracted with diethyl ether (3×20 mL). The combined ethereal layers were washed with brine and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure, and resulting crude oil was purified by combiflash column chromatography (0–26% gradient of ethyl acetate in hexanes) to give 0.923 g of aldehyde **14** (65% yield over two steps). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.80 (s, 1H), 3.78 (d, $J$=12.2 Hz, 2H), 3.71 (d, $J$=12.2 Hz, 2H), 2.87 (s, 2H), 2.63 (s, 2H), 1.43 (s, 3H), 1.41 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 199.1, 104.8, 98.7, 83.7, 66.1 (two signals), 57.9, 45.6, 35.9, 25.3, 22.7, 21.8. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{12}H_{16}NO_3$ 222.1130; found 222.1129.

### 4.11. 4-(5-(2-Cyclopentenyl-2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-5-yl)but-2-ynenitrile (15)

1-Iodocyclopentene (280 mg, 1.45 mmol) was dissolved in anhydrous diethyl ether (4 mL) and cooled to −78 °C. A solution of *t*-BuLi (1.7 M, 1.70 mL, 2.90 mmol) was then added dropwise via syringe. The resulting mixture was allowed to stir at −78 °C for 10 min before warming to 0 °C for an additional 30 min. The resulting vinyllithium solution was then added dropwise to aldehyde **14** (320 mg, 1.45 mmol) in diethyl ether (6.0 mL) at −78C° over 30 min and the resulting mixture was allowed to stir at this temperature for another 30 min before quenching with methanol (0.5 mL). Upon warming, $H_2O$ (10 mL) was added, as well as additional diethyl ether (20 mL). Layers were separated, and the aqueous layer was extracted with $Et_2O$ (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified via column chromatography on silica gel (49% hexanes, 49% DCM, 2% ethyl acetate) to give 220 mg of the desired allylic alcohol **15** (52%) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.63–5.60 (m, 1H), 4.42 (dd, $J$=8.3, 2.4 Hz, 1H), 3.80 (d, $J$=12.0 Hz, 1H), 3.76 (d, $J$=12.0 Hz, 1H), 3.75 (dd, $J$=11.8, 2.2 Hz, 1H), 3.58 (dd, 12.0, 2.2 Hz, 1H), 3.00 (d, $J$=17.8 Hz, 1H), 2.71 (d, $J$=17.8 Hz, 1H), 2.37–2.24 (m, 4H), 1.90 (quin, $J$=7.3 Hz, 2H), 1.72 (br s, 1H), 1.56–1.46 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 147.3, 125.6, 105.1, 98.4, 85.4, 67.7, 67.6, 66.5, 57.3, 38.4, 36.1, 32.1, 31.3, 27.5, 23.3, 23.1, 19.9. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{17}H_{24}NO_3$ 290.1756; found 290.1755.

### 4.12. 2-Methyl-1-octen-7-yn-3-ol

In a dry round bottom flask, 2-bromopropene (0.735 g, 6.07 mmol) was dissolved in 15 mL anhydrous diethyl ether and cooled to −78 °C. A solution of *t*-BuLi (1.7 M, 7.14 mL, 12.1 mmol) was then added dropwise via a syringe. The resulting mixture was allowed to stir at −78 °C for 15 min before warming to 0 °C for another 15 min to destroy any excess *t*-BuLi. At this point, the solution was cooled to −78 °C and a solution of 6-(trimethylsilyl)-5-hexynal[29] (0.341 g, 2.02 mmol) in 3 mL diethyl ether was added to the reaction mixture dropwise via cannula. After 20 min of stirring at this temperature, the reaction was quenched with saturated $NH_4Cl$ (2 mL) and allowed to warm to room temperature. Distilled water (5 mL) was then added to the mixture and the layers were separated. The aqueous layer was extracted with diethyl ether (3×10 mL), the combined ethereal layers were washed with brine, and dried over $MgSO_4$. The solution was then filtered and concentrated under reduced pressure. The resulting crude residue was then dissolved in THF (4 mL) and catalytic TBAF (1.0M, 0.200 mL, 0.200 mmol) was added via syringe. Upon stirring at room temperature for 15 min, solvent was removed under reduced pressure and the residue was taken up in diethyl ether (10 mL) and $H_2O$ (5 mL). The layers were separated, and the aqueous layer was washed with diethyl ether (3×10 mL). The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude oil by column chromatography on silica gel (8.5% ethyl acetate in hexanes) gave 0.211 g of the desired allylic alcohol (75% yield) as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.95–4.94 (m, 1H), 4.84–4.83 (m, 1H), 4.09 (app. t, $J$=6.1 Hz, 1H), 2.25–2.20 (m, 2H), 1.95 (t, $J$=2.7 Hz, 1H), 1.73 (s, 3H), 1.72–1.42 (m, 5H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 147.4, 111.1, 84.2, 75.4, 68.5, 33.8, 24.5, 18.3, 17.5. HRMS (EI) $m/z$ $[M-H]^+$ calcd for $C_9H_{13}O$ 137.0966; found 137.0967.

### 4.13. 7-Hydroxy-8-methyl-8-nonen-2-ynenitrile (16)

The title compound was prepared from 2-methyl-1-octen-7-yn-3-ol in 76% yield according to the general procedure described for the preparation of **10**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 4.97–4.95 (m, 1H), 4.87 (app. t, $J$=1.5 Hz, 1H), 4.08 (t, $J$=5.6 Hz, 1H), 2.43–2.39 (m, 2H), 1.73 (s, 3H), 1.72–1.53 (m, 5H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 147.0, 111.4, 105.2, 87.0, 75.1, 55.5, 33.5, 23.3, 18.8, 17.6. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{10}H_{14}NO$ 164.1075; found 164.1079.

### 4.14. 3-Methyl-8-oxo-3-cyclooctenecarbonitrile (17)

The title compound was prepared from **16** in 75% yield according the general procedure described for the preparation of **11**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.55 (app td, $J$=8.33, 1.4 Hz, 1H), 3.65–3.61 (m, 1H), 2.84–2.78 (m, 1H), 2.76–2.69 (m, 2H), 2.48–2.42 (m, 1H), 2.18–2.05 (m, 2H), 1.85 (s, 3H), 1.78–1.63 (m, 2H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 202.8, 133.8, 128.2, 117.0, 46.6, 39.1, 30.7, 27.1, 25.2, 23.8. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{10}H_{14}NO$ 164.1075; found 164.1077.

### 4.15. 1-(1-Cyclopentenyl)-5-hexyn-1-ol

The title compound was prepared from 1-iodocyclopentene and 6-(trimethylsilyl)-5-hexynal in 65% yield according to the general

procedure described for the preparation of 2-methyl-1-octen-7-yn-3-ol. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.57–5.59 (m, 1H), 4.26 (t, $J$=6.2 Hz, 1H), 2.20–2.34 (overlapping patterns, 4H), 2.21 (td, $J$=6.7, 2.5 Hz, 2H), 1.93 (t, $J$=2.7 Hz, 1H), 1.87 (quin, $J$=7.4 Hz, 2H), 1.56–1.74 (m, 3H), 1.47–1.56 (m, 2H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 146.9, 125.6, 84.3, 70.8, 68.5, 34.4, 32.1, 31.0, 24.5, 23.3, 18.3. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{11}H_{17}NO$ 165.1279; found 165.1283.

### 4.16. 7-(1-Cyclopentenyl)-7-hydroxyhept-2-ynenitrile (18)

The title compound was prepared from 1-(1-cyclopentenyl)-5-hexyn-1-ol in 65% yield according to the general procedure described for the preparation of **10**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.59–5.61 (m, 1H), 4.20–4.27 (m, 1H), 2.39 (app. t, $J$=6.9 Hz, 2H), 2.22–2.35 (overlapping patterns, 4H), 1.89 (quin, $J$=7.6 Hz, 2H), 1.65–1.75 (m, 2H), 1.59–1.16 (m, 2H), 1.57 (br s, 1H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 146.5, 125.9, 105.2, 87.2, 70.5, 55.5, 34.1, 32.1, 31.1, 23.3, 23.2, 18.8. HRMS (ESI-TOF) $m/z$ $[M+Na]^+$ calcd for $C_{12}H_{15}NONa$ 212.1051; found 212.1050.

### 4.17. Bicyclic cyano ketone 19

The title compound was prepared from **18** as a 2.7:1 mixture of diastereomers in 64% yield according to the general procedure described for the preparation of **11**. Major diastereomer: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.59 (app. t, $J$=8.3 Hz, 1H), 3.36 (d, $J$=11.7 Hz, 1H), 3.06–3.50 (m, 1H), 2.54 (app. t, $J$=6.6 Hz, 2H), 2.24–2.41 (m, 2H), 2.14–2.20 (m, 2H), 1.82–1.92 (m, 2H), 1.66–1.74 (m, 2H), 1.42–1.50 (m, 2H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 203.4, 144.0, 122.8, 117.5, 116.6, 52.7, 40.7, 39.0, 32.4, 32.2, 27.4, 23.3. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{12}H_{16}NO$ 190.1232; found 190.1232.

### 4.18. 4-(5-(2-Hydroxy-3-butenyl)-2,2-dimethyl-1,3-dioxan-5-yl)but-2-ynenitrile (20)

Aldehyde **14** (0.230 g, 1.04 mmol) was dissolved diethyl ether (6 mL) and cooled to −78 °C, and vinyl magnesium chloride (1.6 M, 0.650 ml, 1.04 mmol) was added dropwise. The reaction mixture was allowed to stir for 2 h at −78 °C before being quenched with methanol (0.1 mL). Upon warming to room temperature, 0.5 mL of saturated $K_2CO_3$ was added, the resulting precipitate was filtered, and the filtrate was concentrated under vacuum. The resulting crude product was purified by column chromatography on silica gel (20% EtOAc/hexanes) to give 192 mg (74%) of the desired nitrile **20** as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 5.91–5.84 (ddd, $J$=17.1, 10.2, 5.8 Hz, 1H), 5.25 (dt, $J$=17.10, 1.2 Hz, 1H), 5.13 (dt, $J$=10.2, 1.2 Hz, 1H), 4.32 (app. q, $J$=5.8 Hz, 1H), 3.82–3.74 (overlapping patterns, 3H), 3.60 (dd, $J$=11.7, 1.9 Hz, 1H), 2.99 (d, $J$=17.8 Hz, 1H), 2.72 (d, $J$=17.8 Hz, 1H), 1.71 (br s, 1H), 1.50–1.48 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 141.1, 115.1, 105.1, 98.4, 85.2, 69.6, 67.7, 66.5, 66.1, 39.7, 36.1, 27.2, 23.2, 20.1. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1443; found 250.1452.

### 4.19. 3,3-Dimethyl-8-oxo-2,4-dioxaspiro[5.7]tridec-11-ene-9-carbonitrile (21)

The title compound was prepared in 79% yield from **19** according the general procedure described for the preparation of **11**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.01–5.94 (m, 1H), 5.93–5.86 (m, 1H), 3.76–3.70 (m, 2H), 3.66–3.58 (m, 3H), 2.78–2.66 (m, 3H), 2.47 (d, $J$=12.7 Hz, 1H), 2.28–2.24 (m, 1H), 2.15–2.08 (m, 1H), 1.43 (s, 6H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 200.9, 131.2, 127.4, 116.5, 98.5, 67.5, 67.2, 47.7, 42.9, 36.4, 30.5, 26.4, 24.1, 23.3. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1443; found 250.1442.

### 4.20. 4-(5-(2-Hydroxy-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-yl)but-2-ynenitrile (22)

The title compound was prepared in 46% yield from **14** and 2-bromopropene according to the general procedure described for the preparation **15**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 4.99 (s, 1H), 4.85 (t, $J$=1.5 Hz, 1H), 4.22 (dd, $J$=9.8, 3.0 Hz, 1H), 3.81 (d, $J$=12.0 Hz, 1H), 3.77 (dd, $J$=11.9, 2.0 Hz, 1H), 3.75 (d, $J$=12.0 Hz, 1H), 3.60 (dd, $J$=11.9, 2.0 Hz, 1H), 3.04 (d, $J$=17.6 Hz, 1H), 2.79 (d, $J$=17.6 Hz, 1H), 1.83 (br s, 1H), 1.74 (s, 3H), 1.43–1.52 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 148.0, 110.9, 105.1, 98.4, 85.3, 72.0, 67.8, 66.4, 57.4, 38.2, 36.1, 27.4, 23.0, 19.9, 17.9. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{15}H_{22}NO_3$ 264.1600; found 264.1604.

### 4.21. 3,3,11-Trimethyl-8-oxo-2,4-dioxaspiro[5.7]tridec-11-ene-9-carbonitrile (23)

The title compound was prepared in 84% yield from **22** according the general procedure described for the preparation of **11**. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.54 (app. t, $J$=8.3 Hz, 1H), 3.66–3.71 (m, 2H), 3.55–3.62 (m, 3H), 2.69 (d, $J$=12.3 Hz, 1H), 2.43 (d, $J$=12.3 Hz, 1H), 2.68–2.72 (m, 2H), 2.08–2.16 (m, 1H), 1.98–2.08 (m, 1H), 1.98 (s, 3H), 1.40 (s, 6H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 200.6, 135.6, 124.3, 116.8, 98.5, 67.5, 67.1, 46.5, 43.0, 37.2, 36.6, 31.5, 31.2, 23.9, 23.4. HRMS (ESI-TOF) $m/z$ $[M-CH_3]^+$ calcd for $C_{14}H_{18}NO_3$ 248.1287; found 248.1284.

### 4.22. Bicyclic cyano ketone 24

The title compound was prepared in 78% yield as a 1:1 mixture of diastereomers according the general procedure described for the preparation of **11**. Major diastereomer (after purification by column): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.62 (app. t, $J$=7.8 Hz, 1H), 3.91 (d, $J$=11.7 Hz, 1H), 3.61 (d, $J$=11.7 Hz, 1H), 3.51 (d, $J$=11.7 Hz, 1H), 3.43 (d, $J$=11.8 Hz, 1H), 3.20–3.00 (m, 1H), 2.61 (d, $J$=12.4 Hz, 1H), 2.39 (d, $J$=12.4 Hz, 1H), 2.42–2.25 (m, 2H), 2.19–2.10 (m, 1H), 1.92–1.83 (m, 1H), 1.80–1.72 (m, 1H), 1.69–1.62 (m, 3H), 1.56–1.51 (m, 1H), 1.41 (s, 6H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 201.4, 145.9, 119.7, 116.3, 98.4, 67.6, 67.1, 53.2, 40.8, 36.4, 35.3, 33.1, 32.2, 31.7, 24.6, 23.9, 23.7. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_{17}H_{24}NO_3$ 290.1756; found 290.1755.

### 4.23. Endocyclic dihydropyran (12b), (*E*)-exocyclic tetrahydropyran (12a)

Nitrile **10** (75.5 mg, 0.506 mmol) was dissolved in DME (2.0 mL), and a catalytic amount of LHMDS (1.0 M in THF, 50 μL, 0.0500 mmol) was added. The reaction mixture was allowed to stir at room temperature for 4 h. The solvents were removed and the residue was subjected to purification by column chromatography on silica gel (8% EtOAc/hexanes) to give 20.6 mg of **12a** (27%) and 41.3 mg of **12b** (55%). Compound **12a**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.87 (ddd, $J$=17.6, 10.7, 5.4 Hz, 1H), 5.37 (dt, $J$=17.6, 1.5 Hz, 1H), 5.23 (dt, $J$=10.7, 1.5 Hz, 1H), 4.52–4.56 (m, 1H), 4.33 (t, $J$=1.0 Hz, 1H), 2.37–2.43 (m, 1H), 2.28–2.34 (m, 1H), 1.91–1.97 (m, 1H), 1.78–1.86 (m, 1H), 1.71–1.78 (m, 1H), 1.62–1.71 (m, 1H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$ 173.1, 136.2, 116.8, 116.3, 78.9, 73.8, 28.6, 27.7, 18.5. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_9H_{12}N$ 150.0919; found 150.0917. Compound **12b**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.87 (ddd, $J$=17.6, 10.7 Hz, 5.4 Hz, 1H), 5.29 (dt, $J$=17.1, 1.5 Hz, 1H), 5.19 (dt, $J$=10.7, 1.5 Hz, 1H), 4.85–4.88 (m, 1H), 4.36–4.41 (m, 1H), 3.09 (s, 2H), 1.99–2.14 (m, 2H), 1.86–1.92 (m, 1H), 1.59–1.67 (m, 1H). $^{13}$C NMR (125.6 MHz, $CDCl_3$) $\delta$: 143.4, 136.9, 116.4, 116.0, 98.9, 76.5, 26.8, 23.0, 19.5. HRMS (ESI-TOF) $m/z$ $[M+H]^+$ calcd for $C_9H_{12}N$ 150.0919; found 150.0917.

### 4.24. Rate studies

The rate experiments were conducted by exposing approximately 0.2 M solutions of nitrile **10** in DME to 10 mol % LHMDS and microwave irradiation at various temperatures for 1 h. The experiments were conducted at 150, 160, 170, 180, 190, 200, and 200 °C. The solvents were then removed, diethyl ether was added along with water. The layers were separated, the ethereal layer was dried over $MgSO_4$, filtered, and the ether solvent removed under vacuum. The resulting crude mixtures were then analyzed directly by $^1H$ NMR. The relative amounts of all four possible products of this reaction were determined by integrating the areas of the unique vinyl protons present in each isomeric structure (Fig. 4).

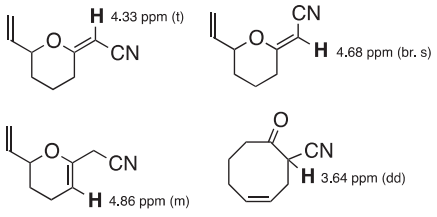



**Fig. 4.** Chemical shifts of the characteristic vinyl protons present in **12a**–**c**, and **11**.


### Acknowledgements

This research was partially supported by grant from the National Institutes of Health (NIGMS). T.V.O. also gratefully acknowledges support from the Hans and Ella McCollum-Vahlteich '21 endowment.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