Tetrahedron 67 (2011) 9890–9898

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

A [4+4] annulation strategy for the synthesis of eight-membered carbocycles based on intramolecular cycloadditions of conjugated enynes

Julia M. Robinson, Sami F. Tlais, Jennie Fong, Rick L. Danheiser *

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

ARTICLE INFO

Article history:
Received 7 August 2011
Received in revised form 8 September 2011
Accepted 9 September 2011
Available online 14 September 2011

Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

Keywords:
Conjugated enynes
Eight-membered rings
Cycloaddition
Electrocyclic ring opening
Cyclooctatrienones

ABSTRACT

A [4+4] annulation strategy for the synthesis of eight-membered carbocycles is reported that proceeds via a cascade involving two pericyclic processes. In the first step, the [4+2] cycloaddition of a conjugated enyne with an electron-deficient cyclobutene generates a strained six-membered cyclic allene that isomerizes to the corresponding 1,3-cyclohexadiene. In the second step, this bicyclo[4.2.0]octa-2,4-diene intermediate undergoes thermal or acid-promoted 6-electron electrocyclic ring opening to furnish a 2,4,6-cyclooctatrienone. The latter transformation represents the first example of the promotion of 6-electron electrocyclic ring opening reactions by acid.

1. Introduction

[4+2] Cycloadditions of conjugated enynes[1,2] generate six-membered carbocycles that incorporate an additional element of unsaturation relative to the cycloadducts produced in conventional Diels–Alder reactions. When alkynes are employed as 'enynophiles', the cyclic allenes[3] initially produced isomerize to form benzenoid aromatic compounds (Scheme 1).[4] This version of the enyne cycloaddition provides an attractive alternative to benzannulations based on Diels–Alder reactions of specially designed *diene* substrates, such as α-pyrones. In enyne cycloadditions where alkenes are employed as enynophiles, conjugated cyclohexadienes are generated that potentially can undergo in situ rearrangement leading to the formation of other useful cyclic systems. Herein we describe the application of this latter approach in a new [4+4] annulation strategy for the synthesis of eight-membered carbocyclic compounds.

Eight-membered carbocyclic rings are key features in the structures of several important classes of bioactive natural products and are relatively difficult to access using conventional methodology.[5] Scheme 2 outlines our new [4+4] annulation strategy[6–8] for the synthesis of eight-membered rings. Intramolecular [4+2] cycloaddition of a conjugated enyne with a cyclobutene derivative generates a cyclic allene of general type **3** that is expected to rapidly isomerize via either proton or hydrogen atom transfer pathways to afford the bicyclo[4.2.0]-2,4-octadiene intermediate **4**. Electrocyclic ring opening[9] then produces the desired eight-membered ring containing system. In principle, the conversion of enyne cycloaddition substrate **1** to cyclooctatriene **2** should be possible in a single synthetic operation as a cascade ('domino') reaction process.[10] Although the thermal interconversion of bicyclo[4.2.0]-2,4-octadienes and 1,3,5-cyclooctatrienes is an equilibrium process that often favors the bicyclic system, in this case we expected to be able to direct the reaction to favor the desired eight-membered ring isomer through the appropriate choice of substituents (vide infra).

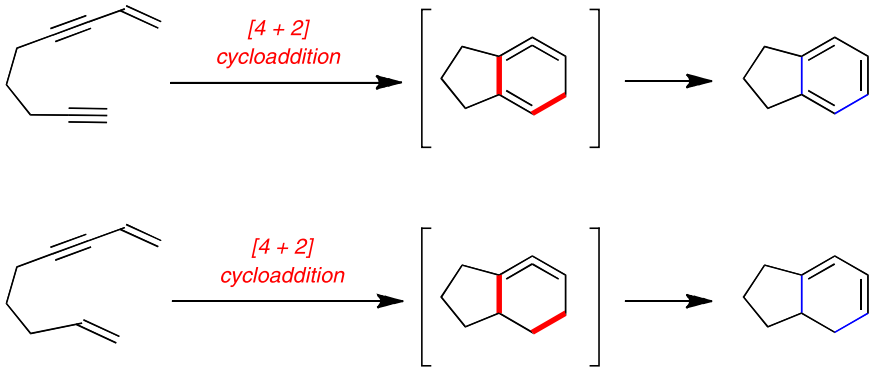
2. Results and discussion

2.1. [4+4] Annulation with cyclobutenones

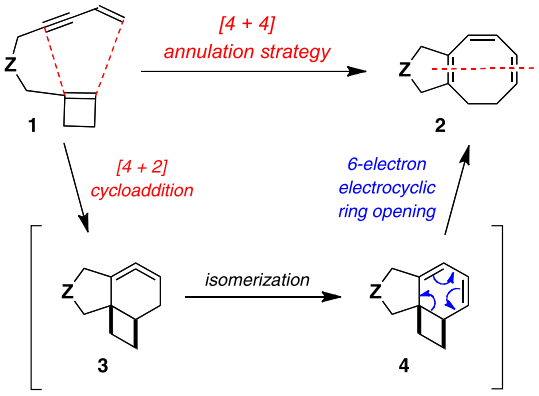
As in the case of Diels–Alder reactions and dipolar cycloadditions, the [4+2] cycloaddition of conjugated enynes proceeds with the greatest facility when electron-deficient π bonds are employed as reaction partners.[1,2] We began our investigation of the proposed [4+4] annulation strategy by examining the cycloaddition of enyne **7** in which a cyclobutenone[11] serves as the enynophile component. Eq. 1 outlines the synthesis of cyclobutenone **7**, which features the

* Corresponding author. E-mail address: danheisr@mit.edu (R.L. Danheiser).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.031

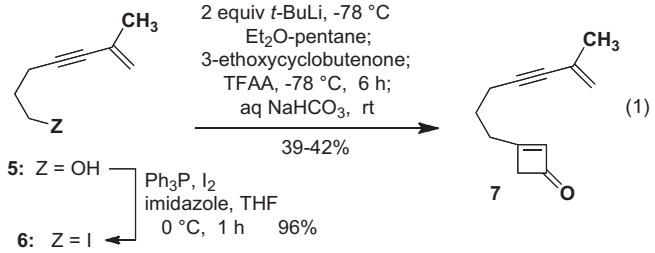


Scheme 1. [4+2] Cycloadditions of conjugated enynes.

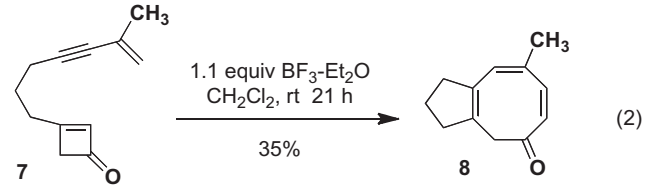


Scheme 2. [4+4] Annulation strategy for the synthesis of eight-membered carbocycles.

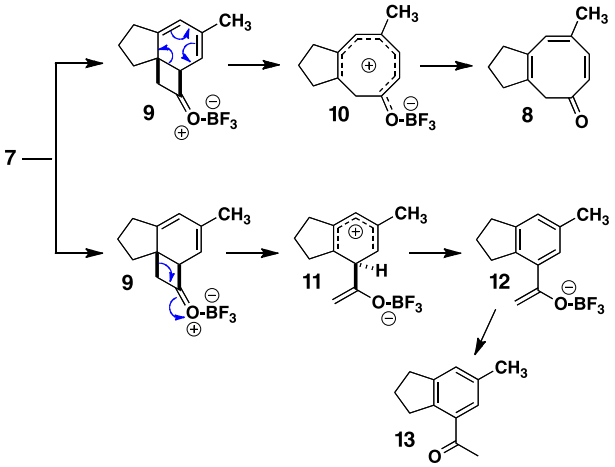
reaction of 3-ethoxycyclobutenone[12] with an organolithium compound prepared beginning from the known enynyl alcohol **5**.[13,14]



Cyclobutenones undergo 4-electron electrocyclic ring opening to form vinylketenes at elevated temperature,[15] so we initially examined the [4+2] enyne cycloaddition of **7** in the presence of Lewis and Brønsted acids[2a] in the hope of achieving the desired transformation at rt or below. In the event, exposure of cyclobutenone **7** to MsOH or Lewis acids, such as $TiCl_4$, $AlCl_3$, and Me_2AlCl produced complex mixtures, but we were pleased to find that reaction with BF_3-etherate at rt gave the desired cyclooctatrienone **8**[16] in 35% yield (Eq. 2).

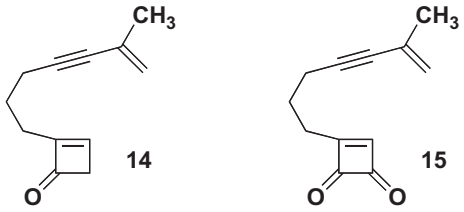


Under these and related conditions, an aromatic ketone byproduct was also isolated in comparable amounts that was identified as the indan derivative **13**. For example, reaction of **7** with 1.4 equiv of BF_3-etherate at 50 °C for 4 h afforded a mixture of cyclooctatrienone **8** (30%) and indan **13** (36%). Scheme 3 outlines a plausible mechanism for the formation of these two major products of the reaction. The electrocyclic cleavage of bicyclo [4.2.0]-2,4-octadienes usually requires elevated temperatures, typically in the range 60–100 °C. In many cases an equilibrium mixture of bicyclooctadiene and cyclooctatriene is observed, with the ratio dependent on the nature of the substituents.[17] In the case of the ketone–Lewis acid complex **9**, we expected the ring opening to proceed under unusually mild conditions and to greatly favor **10** due to the increased delocalization of positive charge in the product of electrocyclic opening. Note that the transformation of **9** to **10** can also be viewed as a variant of the well known cyclobutyl to homoallyl carbocation rearrangement. In a similar fashion, the formation of the aromatic ketone byproduct **13** could be proceeding via cyclobutyl carbocation rearrangement involving the alternate C2–C3 bond of the four-membered ring to generate the delocalized pentadienyl cation intermediate **11**.



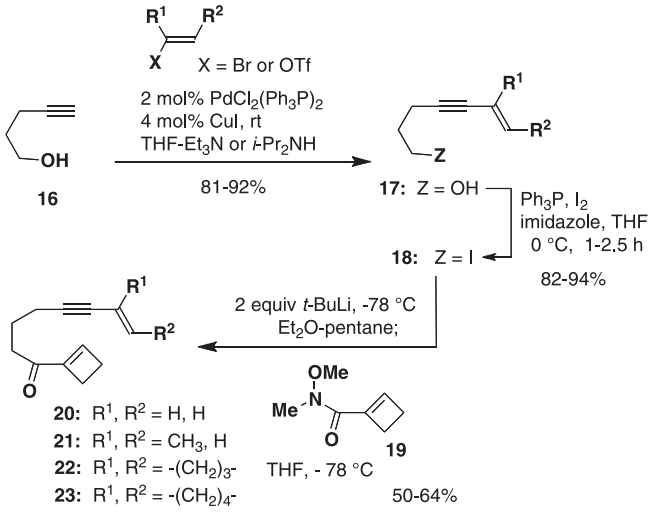
Scheme 3. Mechanism for the formation of [4+4] product **8** and byproduct **13**.

Two other cyclobutenone cycloaddition substrates (**14** and **15**) were next prepared and subjected to treatment with both Lewis and Brønsted acids under a variety of conditions. None of the desired [4+4] annulation products were detected in these reactions, which either returned unreacted starting material or led to the formation of complex mixtures of uncharacterizable products. We therefore next turned our attention to systems in which the carbonyl activating group is positioned exocyclic with respect to the cyclobutene ring. It was our expectation that these substrates would not be subject to the unproductive mode of fragmentation observed in the reactions of cyclobutenones, and might therefore undergo the desired [4+4] annulation more efficiently and in good yield.



2.2. [4+4] Annulation with acylcyclobutenes

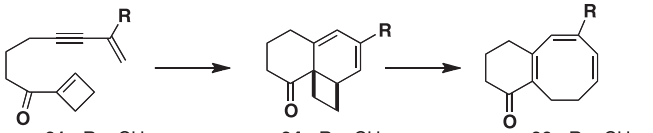
Scheme 4 outlines our syntheses of acylcyclobutene cycloaddition substrates **20**–**23**, which are based on an application of the Weinreb ketone synthesis.[18,19] The requisite cyclobutenyl Weinreb amide building block (**19**) was prepared from cyclobutenecarboxylic acid[20] in 79% yield by treatment with oxalyl chloride (cat. DMF, CH_2Cl_2, rt, 1 h) followed by addition of 1.1 equiv of *N*,*O*-dimethylhydroxylamine hydrochloride and 2.2 equiv of Et_3N (rt, 1 h).



Scheme 4. Synthesis of acylcyclobutene cycloaddition substrates.

The [4+4] annulation with acylcyclobutene **21** was examined first. No reaction of this substrate was observed upon heating at 110 °C, while at higher temperatures the desired cyclooctatriene **26** was observed to form, but only as one component in a complex mixture of products. In the presence of BF_3-etherate only a small amount of **26** was detected upon reaction at −55 °C, and at higher temperatures significant polymerization took place. However, exposure of cyclobutenyl ketone **21** to 1 equiv of MsOH at −78 °C led to a relatively clean reaction to afford the desired intermediate tricyclic ketone **24**. This compound could not be purified without partial decomposition, and therefore was best carried on in the electrocyclic ring opening step without prior purification.

In some trials the treatment of **21** with MsOH at −78 °C led to incomplete cycloaddition, and reaction at higher temperature resulted in the formation of numerous byproducts. After some experimentation, a more reproducible protocol was developed utilizing reaction with 2,4,6-triisopropylbenzenesulfonic acid ('$TIPPSO_3H$')[21] at 0 °C. Thus, exposure of **21** to the action of 0.5 equiv of $TIPPSO_3H$ in dichloromethane at 0 °C for 2 h cleanly furnished the desired tricyclic ketone **24** in good yield (Scheme 5). Other acids, such as TsOH, camphorsulfonic acid, and trifluoroacetic acid were not effective promoters of the enyne cycloaddition and led to either sluggish reaction, or decomposition at higher temperatures. Interestingly, the related enyne substrate **20** was found to react slowly in the presence of $TIPPSO_3H$, and in this case the optimal protocol for the [4+2] cycloaddition involves reaction with MsOH at −30 to −15 °C.

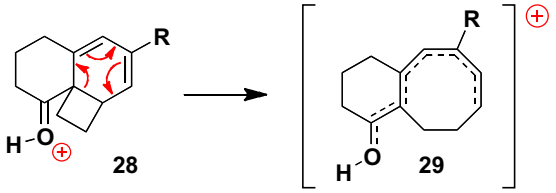


			overall yield
R = Me	1 equiv MsOH CH_2Cl_2, -78 °C, 4 h	CH_2Cl_2, 70 °C, 5 h	69%
R = Me	0.5 equiv $TIPPSO_3H$ CH_2Cl_2, 0 °C, 2 h	CH_2Cl_2, 90 °C, 20 h	78%
R = Me	0.5 equiv $TIPPSO_3H$ CH_2Cl_2, 0 °C, 2 h (TIPP = $(i\text{-Pr})_3C_6H_2$)	2 equiv CSA CH_2Cl_2, 50 °C, 17 h	61%
R = H	1 equiv MsOH, CH_2Cl_2 -30 to -15 °C, 2.5 h	2 equiv CSA CH_2Cl_2, 100 °C, 15 h	55%
		10 equiv $CaCO_3$ CH_2Cl_2, 100 °C, 13 h	NR

Scheme 5. [4+4] Annulations of acylcyclobutenes **24** and **25**.

Thermolysis of unpurified tricyclic ketone **24** at 90–95 °C overnight brought about the desired 6-electron electrocyclic opening reaction affording the cyclooctatriene **26** in 78% overall yield from **21** after purification by column chromatography. Surprisingly, some samples of **21** underwent rearrangement upon heating for several hours at only 70 °C. We hypothesized that adventitious acid might be promoting the rearrangement in these cases, and indeed, in the presence of added acid (camphorsulfonic acid, CSA) complete conversion to **26** was observed to take place at only 50 °C. Rearrangement of the tricyclic ketone **25** (with R=H) was slower, and in this case even at 100 °C no reaction was observed in the absence of acid, although the desired rearrangement did occur smoothly in the presence of 2 equiv of CSA.

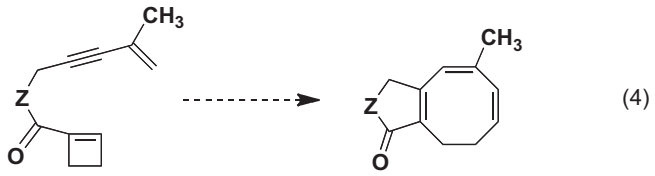
The critical role of acid in promoting the rearrangement of **24** and **25** to **26** and **27** was confirmed by the observation that reaction is inhibited in the presence of an acid scavenger. For example, no electrocyclic ring opening was observed when the bicyclooctadiene intermediate **25** was heated overnight at 100 °C in the presence of calcium carbonate, and the tricyclic ketone was recovered in 83% yield after column chromatography. We attribute the acceleration of the electrocyclic ring opening of intermediates of type **28** relative to the unprotonated ketones to the fact that significant delocalization of positive charge develops in the transition state leading to the eight-membered ring products **29** (Eq. 3). To our knowledge, these transformations represent the first examples of the acceleration of a 6-electrocyclic ring opening reaction by acid. Note, however, that Bergman and Trauner have recently reported the acceleration of 6-electron electrocyclic *ring closure* reactions of hexatrienes by catalytic amounts of Me_2AlCl.[22]



(3)

Efficient [4+4] annulation did not take place in the case of several related acylcyclobutenes, including enyne **30**[23] (with a three-atom rather than four-atom 'tether'[24]) and the ester derivatives **31** and **32**[25] (Eq. 4). In each case, no reaction was observed

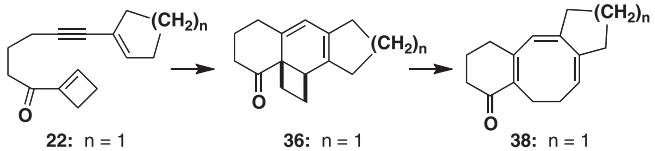
in the presence of acid at rt or below, and complex mixtures of products were formed at elevated temperatures.



(4)

30: Z = CH_2 **33:** Z = CH_2
31: Z = O **34:** Z = O
32: Z = OCH_2 **35:** Z = OCH_2

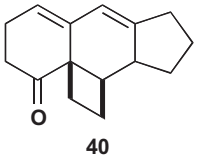
Finally, successful [4+4] annulation was achieved with acylcyclobutenes **22** and **23**, providing access to the tricyclic eight-membered ring containing products **38** and **39** (Scheme 6). In the case of the [4+2] cycloaddition of enyne **22**, reaction with MsOH generated the desired cyclohexadiene intermediate **36** accompanied by a significant amount of an isomeric diene **40**.



22: n = 1 **36:** n = 1 **38:** n = 1
23: n = 2 **37:** n = 2 **39:** n = 2

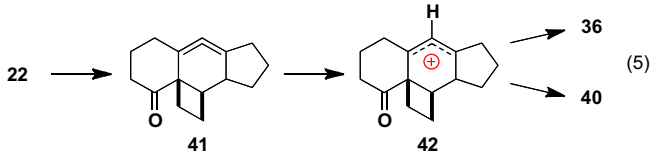
			overall yield
n = 1	2 equiv MsOH CH_2Cl_2, -78 to -60 °C	CH_2Cl_2, 70 °C, 3 h	40%
n = 2	1 equiv MsOH CH_2Cl_2, -78 °C, 3 h	CH_2Cl_2, 70 °C, 14 h	26%

Scheme 6. [4+4] Annulations of acylcyclobutenes **38** and **39**.



40

Formation of the isomeric diene **40** could arise via the pathway outlined in Eq. 5. Under the acid-promoted enyne cycloaddition conditions, isomerization of the intermediate cyclic allene **41** proceeds via protonation to form an allylic carbocation of type **42**. In this case, proton loss apparently produces **40** in addition to the desired endocyclic diene **36**, possibly due to increased ring strain in this tetracyclic system. An analogous isomeric diene byproduct was also observed to form in the cycloaddition of the cyclohexenyl substrate **23**.



(5)

3. Conclusions

A [4+4] annulation strategy for the construction of eight-membered carbocycles has been developed that involves a new variant of the enyne [4+2] cycloaddition in which cyclobutenones and acylcyclobutenes serve as the 2π 'enynophile' reaction partners. The [4+2] cycloaddition products are bicyclo[4.2.0]octadienes that undergo acid-promoted electrocyclic ring opening under mild conditions to afford the desired cyclooctatrienones. These transformations represent the first examples of the application of acid to promote a 6-electron electrocyclic ring opening reaction.

4. Experimental

4.1. General procedures

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on EMD precoated glass-backed silica gel 60 F_{254} 0.25 mm plates.

4.2. Materials

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. CuI was purified by Soxhlet extraction with THF for 48 h followed by drying under vacuum (0.1 mmHg) over P_2O_5 for 24 h. Diisopropylamine, triethylamine, pentane, and boron trifluoride etherate were distilled under argon from calcium hydride. TFAA was distilled under argon. 2-Bromopropene was filtered through activated basic alumina before use. *n*-Butyllithium was titrated according to the method of Watson–Eastham using BHT in THF with 1,10-phenanthroline as an indicator.[26] *tert*-Butyllithium was titrated in pentane with menthol at 0 °C using 1,10-phenanthroline as the indicator. 3-Ethoxycyclobutanone,[12] cyclobutenecarboxylic acid,[20] cyclopentenyl trifluoromethanesulfonate,[27] and 2,4,6-tri(*iso*-propyl)benzenesulfonic acid ($TIPPSO_3H$)[21] were prepared according to the previously reported procedures. Cyclohexenyl trifluoromethanesulfonate was prepared via a minor modification of the published procedure[28] in which LiHMDS was substituted for LDA. Column chromatography was performed on Sorbent Technologies Standard Grade silica gel 60 (230–400 mesh) or on EMD Chromatographic Grade basic alumina (80–325 mesh). Chromatography with acetone-deactivated silica gel was carried out by mixing silica gel with acetone (ca. 10 mL/g) for 5 min, using this slurry to build a column, and then flushing the column with two column volumes of hexanes before applying the sample to be purified.

4.3. Instrumentation

Infrared spectra were obtained using a Perkin–Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were recorded on a Bruker Avance-400 (100 MHz) spectrometer. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High-resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 T Fourier transform mass spectrometer.

4.4. Synthesis of cycloaddition substrates

*4.4.1. General procedure for conversion of alcohols to iodides: 7-iodo-2-methylhept-1-en-3-yne (**6**).* A 50-mL, three-necked, round-

bottomed flask equipped with a stir bar, rubber septum, glass stopper, and argon inlet adapter was charged with the alcohol **5** (0.759 g, 6.12 mmol, 1.0 equiv) and 10 mL of THF. The solution was cooled to 0 °C, and triphenylphosphine (1.60 g, 6.12 mmol, 1.0 equiv), imidazole (0.624 g, 9.16 mmol, 1.5 equiv), and iodine (2.31 g, 9.10 mmol, 1.5 equiv) were each added in one portion. The reaction mixture became dark brown in color. The solution was stirred at 0 °C in the dark for 2.5 h, and then diluted with 100 mL of satd aq $Na_2S_2O_3$ solution and extracted with five 50-mL portions of pentane. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C (20 mmHg). The colorless oil containing some white solid was filtered through a short plug of activated basic alumina using 80 mL of pentane and the filtrate was concentrated at 0 °C (20 mmHg) to give 1.369 g (96%) of iodide **6** as a colorless oil: IR (neat) 3094, 2950, 2919, 2229, 1796, 1614, 1427, 1221, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21–5.24 (m, 1H), 5.17 (app quint, J=1.6 Hz, 1H), 3.32 (t, J=6.8 Hz, 2H), 2.46 (t, J=6.7 Hz, 2H), 2.03 (quint, J=6.8 Hz, 2H), 1.88 (dd, J=1.5, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.2, 121.1, 87.0, 83.1, 32.4, 24.0, 20.5, 5.6; HRMS-ESI (m/z) $[M]^+$ calcd for $C_8H_{11}I$: 233.9900, found: 233.9904.

*4.4.2. 3-(6-Methylhept-6-en-4-ynyl)cyclobut-2-enone (**7**).* A 100-mL, three-necked, round-bottomed flask equipped with a stir bar, rubber septum, thermocouple probe, argon inlet adapter, and 25-mL addition funnel fitted with a rubber septum was charged with the iodide **6** (1.20 g, 5.14 mmol, 1.3 equiv), 4.5 mL of pentane, and 11.4 mL of Et_2O. The solution was cooled at −78 °C while *t*-BuLi solution (1.63 M solution in pentane, 6.34 mL, 10.3 mmol, 2.7 equiv) was added dropwise via the addition funnel over 15 min. The resulting mixture was stirred at −78 °C for 5 min, and then a solution of 3-ethoxycyclobutenone[12] (0.428 g, 3.81 mmol, 1.0 equiv) in 3 mL of Et_2O was added dropwise via cannula over 3 min (2-mL Et_2O rinse). The reaction mixture became dark orange. After 1 h, TFAA (0.92 mL, 1.4 g, 6.6 mmol, 1.7 equiv) was added dropwise via syringe over 30 s. The reaction mixture was stirred at −78 °C for 6 h, and then 11 mL of satd aq $NaHCO_3$ solution was added dropwise via syringe over 5 min. The resulting mixture was allowed to warm to rt over 20 min and then diluted with 40 mL of Et_2O. The aqueous layer was separated and extracted with three 20-mL portions of Et_2O, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 5 °C (20 mmHg) to give 1.314 g of a red brown oil. Column chromatography on 255 g of silica gel (elution with 15–30% Et_2O–pentane) afforded 0.259 g (39%) of cyclobutenone **7** as a yellow-orange oil: IR (neat) 2223, 1767, 1614, 1585, 1452, 1434, 1415, 1051, 1021, 897, 860, and 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 1H), 5.21–5.24 (m, 1H), 5.18 (t, J=1.7 Hz, 1H), 3.20 (s, 2H), 2.71 (td, J=7.6, 1.2 Hz, 2H), 2.43 (t, J=6.9 Hz, 2H), 1.83–1.92 (m 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 180.3, 134.7, 127.1, 121.1, 87.6, 83.1, 51.0, 31.3, 25.3, 23.9, 19.1; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{12}H_{14}O$: 197.0937, found: 197.0938.

*4.4.3. Hept-6-en-4-yn-1-ol (**17a**).* A 100-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, two rubber septa, and thermocouple probe was charged with $PdCl_2(PPh_3)_2$ (0.281 g, 0.401 mmol, 0.02 equiv), CuI (0.152 g, 0.797 mmol, 0.04 equiv), and Et_3N (4.2 mL, 3.0 g, 30 mmol, 1.5 equiv). The orange reaction mixture was cooled to 0 °C and vinyl bromide (40 mL of a 1.0 M solution in THF, 40 mmol, 2.0 equiv) was added in one portion. A solution of 4-pentyn-1-ol (1.86 mL, 1.68 g, 20.0 mmol, 1.0 equiv) in 2.8 mL of THF was added dropwise via cannula over 20 min (1.4-mL THF rinse), and the dark brown reaction mixture was allowed to warm to rt over 30 min. After 1.5 h, the reaction mixture was filtered through a plug of 2 g of silica gel with the aid of 300 mL of Et_2O. The filtrate was washed with two 100-mL portions of satd aq $NaHCO_3$ solution and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C (20 mmHg) to provide 2.38 g of a brown oil. Column chromatography on 54 g of silica gel (elution with 15–40% Et_2O–pentane) gave 1.77 g (81%) of alcohol **17a** as a golden yellow oil: IR (neat) 3334, 2949, 2227, 1841, 1609, 1433, 1061, 975, and 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J=17.5, 11.0, 2.1 Hz, 1H), 5.57 (ddd, J=17.5, 2.2, 0.5 Hz, 1H), 5.41 (ddd, J=11.0, 2.2, 0.4 Hz, 1H), 3.78 (q, J=5.9 Hz, 2H), 2.45 (td, J=6.9, 2.1 Hz, 2H), 1.80 (quint, J=6.5 Hz, 2H), 1.43–1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.0, 117.5, 90.3, 79.9, 61.6, 31.4, 15.9; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_7H_{10}O$: 111.0810, found: 111.0805.

*4.4.4. 5-(Cyclopent-1-en-1-yl)pent-4-yn-1-ol (**17b**).* A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.069 g, 0.10 mmol, 0.02 equiv), CuI (0.038 g, 0.20 mmol, 0.04 equiv), and 10.5 mL of diisopropylamine. The orange reaction mixture was stirred at rt while a solution of cyclopentenyl trifluoromethanesulfonate (1.4 g, 6.5 mmol, 1.3 equiv) in 10 mL of THF was added dropwise via cannula over 2 min (1.8-mL THF rinse). The reaction mixture was stirred for 5 min, and then a solution of 4-pentyn-1-ol (0.46 mL, 0.42 g, 5.0 mmol, 1.0 equiv) in 20 mL of THF was added dropwise via cannula over 27 min. The reaction mixture was stirred at rt for 1 h, 10 mL of H_2O was added, and the resulting mixture was extracted with two 75-mL portions of Et_2O. The combined organic phases were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.5 g of orange oil. Purification by column chromatography on 91 g of silica gel (elution with 5–35% EtOAc–hexanes) afforded 0.654 g (88%) of alcohol **17b** as a red oil: IR (neat) 3332, 2950, 2223, 1611, 1440, 1326, 1057, 950, and 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93–5.98 (m, 1H), 3.78 (q, J=5.9 Hz, 2H), 2.47 (t, J=7.0 Hz, 2H), 2.36–2.45 (m, 4H), 1.89 (quint, J=7.6 Hz, 2H), 1.80 (quint, J=6.2 Hz, 2H), 1.52 (t, J=5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 124.8, 90.6, 78.6, 62.0, 36.7, 33.2, 31.6, 23.4, 16.2; HRMS-ESI (m/z) calcd for $C_{10}H_{14}O$ $[M+H]^+$: 151.1117, found: 151.1113.

*4.4.5. 5-(Cyclohex-1-en-1-yl)pent-4-yn-1-ol (**17c**).* A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.077 g, 0.11 mmol, 0.020 equiv), CuI (0.04 g, 0.22 mmol, 0.04 equiv), and *i*-Pr_2NH (11.5 mL, 8.30 g, 82 mmol, 15 equiv). A solution of cyclohexenyl trifluoromethanesulfonate (1.64 g, 7.12 mmol, 1.3 equiv) in 11 mL of THF was added dropwise over 2 min (2-mL THF rinse), and then a solution of 4-pentyn-1-ol (0.51 mL, 0.46 g, 5.5 mmol, 1.0 equiv) in 20 mL of THF was added dropwise over 22 min. The reaction mixture was stirred at rt for 1 h, and then 75 mL of Et_2O and 10 mL of H_2O were added. The organic phase was separated and washed with 10 mL of H_2O and 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.54 g of red oil. Purification by column chromatography on 152 g of silica gel (elution with 5–30% EtOAc–hexanes) afforded 0.830 g (92%) of alcohol **17c** as a dark red oil: IR (neat) 3334, 2930, 2220, 1631, 1435, 1347, 1136, 1052, 918, 842, 801, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99–6.05 (m, 1H), 3.78 (q, J=5.8 Hz, 2H), 2.43 (t, J=6.9 Hz, 2H), 2.02–2.16 (m, 4H), 1.79 (quint, J=6.3 Hz, 2H), 1,52–1.66 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 121.0, 86.5, 83.2, 62.2, 31.7, 29.7, 25.7, 22.5, 21.7, 16.1; HRMS-DART (m/z) calcd for $C_{11}H_{16}O$ $[M+H]^+$: 165.1274, found: 165.1279.

*4.4.6. 7-Iodohept-1-en-3-yne (**18a**).* Reaction of alcohol **17a** (0.865 g, 7.85 mmol, 1.0 equiv) with imidazole (0.801 g, 11.8 mmol, 1.5 equiv), triphenylphosphine (2.06 g, 7.85 mmol, 1.0 equiv), and iodine (3.010 g, 11.86 mmol, 1.5 equiv) in 13 mL of THF for 1 h according to the general procedure afforded a colorless oil containing some white solid. This material was filtered through a short plug of basic alumina using 50 mL of pentane and the filtrate was concentrated at 0 °C (20 mmHg) to afford 1.625 g (94%) of iodide

18a as a colorless oil containing some white solid: IR (neat) 3097, 3007, 2938, 2905, 2837, 2227, 1841, 1608, 1427, 1220, 1169, 973, and 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J=17.5, 11.0, 2.1 Hz, 1H), 5.58 (ddt, J=17.5, 2.2, 0.6 Hz, 1H), 5.42 (dd, J=11.0, 1.1 Hz, 1H), 3.32 (t, J=6.8 Hz, 2H), 2.47 (td, J=6.7, 2.1 Hz, 2H), 2.03 (quint, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.4, 117.5, 88.8, 80.6, 32.3, 20.6, 5.6; HRMS-ESI (m/z) calcd for C_7H_9I $[M+H]^+$: 220.9827, found: 220.9825.

*4.4.7. 1-(5-Iodopent-1-ynyl)cyclopent-1-ene (**18b**).* Reaction of alcohol **17c** (0.654 g, 4.35 mmol, 1.0 equiv) with triphenylphosphine (1.142 g, 4.35 mmol, 1.0 equiv), imidazole (0.452 g, 6.64 mmol, 1.5 equiv), and iodine (1.401 g, 5.52 mmol, 1.3 equiv) in 8.6 mL of THF for 1.5 h according to the general procedure afforded a yellow oil containing some white solid. Purification by column chromatography on 16 g of silica gel (elution with pentane) furnished 0.927 g (82%) of iodide **18b** as a very pale yellow oil: IR (neat) 2954, 2844, 2221, 1611, 1441, 1427, 1347, 1220, 1167, 949, and 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95–5.99 (m, 1H), 3.32 (t, J=6.8 Hz, 2H), 2.48 (t, J=6.7 Hz, 2H), 2.37–2.45 (m, 4H), 2.13 (quint, J=6.8 Hz, 2H), 1.89 (quint, J=7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 124.8, 89.0, 79.1, 36.7, 33.2, 32.4, 23.4, 20.7, 5.6; HRMS-ESI (m/z) calcd for $C_{10}H_{13}I$ $[M+H]^+$: 261.0135, found: 261.0144.

*4.4.8. 1-(5-Iodopent-1-ynyl)cyclohex-1-ene (**18c**).* Reaction of alcohol **17d** (0.825 g, 5.02 mmol, 1.0 equiv) with imidazole (0.513 g, 7.53 mmol, 1.5 equiv), triphenylphosphine (1.318 g, 5.02 mmol, 1.0 equiv), and iodine (1.912 g, 7.53 mmol, 1.5 equiv) in 8.4 mL for 1 h according to the general procedure afforded a pale yellow oil. This material was filtered through a plug of 7 g of basic alumina with the aid of 75 mL of pentane. The filtrate was concentrated to afford 1.221 g (89%) of iodide **18c** as a pale yellow oil: IR (neat) 3024, 2857, 2221, 1631, 1434, 1346, 1267, 1220, 1166, 1150, 1076, 1048, 916, 842, 800, and 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00–6.06 (s, 1H), 3.31 (t, J=6.8 Hz, 2H), 2.44 (t, J=6.7 Hz, 2H), 2.04–2.13 (m, 4H), 2.01 (quint, J=6.8 Hz, 2H), 1.53–1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 121.0, 85.0, 83.7, 32.6, 29.7, 25.7, 22.5, 21.7, 20.5, 5.7; HRMS-DART (m/z) calcd for $C_{11}H_{15}I$ $[M+H]^+$: 275.0291, found: 275.0295.

*4.4.9. N-Methoxy-N-methylcyclobut-1-enecarboxamide (**19**).* A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with cyclobutenecarboxylic acid[20] (1.13 g, 11.5 mmol, 1.0 equiv) and 70 mL of CH_2Cl_2. Oxalyl chloride (1.02 mL, 1.53 g, 12.0 mmol, 1.0 equiv) and DMF (4 drops) were added, and the resulting mixture was stirred at rt for 1 h (gas evolution) and then cooled to 0 °C. A solution of *N,O*-dimethylhydroxylamine hydrochloride (1.23 g, 12.6 mmol, 1.1 equiv) and triethylamine (3.52 mL, 2.56 g, 25.3 mmol, 2.2 equiv) in 40 mL of CH_2Cl_2 was added dropwise via cannula over 5 min (5-mL CH_2Cl_2 rinse). The pale yellow reaction mixture was allowed to warm to rt and stirred for 1 h in the dark. Water (50 mL) was added and the aqueous layer was separated, neutralized with satd aq $NaHCO_3$ solution, and then extracted with two 125-mL portions of Et_2O. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.748 g of yellow oil. Purification by column chromatography on 52 g of silica gel (elution with 25–35% EtOAc–hexanes) afforded 1.282 g (79%) of Weinreb amide **19** as a very pale yellow oil: IR (neat) 2968, 2936, 1643, 1589, 1416, 1382, and 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (t, J=1.2 Hz, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.79–2.83 (m, 2H), 2.48 (td, J=3.3, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 144.9, 139.6, 61.6, 32.7, 30.7, 27.8; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_7H_{11}NO_2$: 142.0863, found: 142.0869.

*4.4.10. General procedure for the synthesis of cyclobutenyl ketones: 1-cyclobutenylyloct-7-en-5-yn-1-one (**20**).* A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **18a** (1.163 g, 3.58 mmol, 1.1 equiv) and 10.4 mL of Et_2O. The reaction mixture was cooled to −78 °C and *t*-BuLi solution (1.70 M in pentane, 4.25 mL, 7.22 mmol, 2.3 equiv) was added dropwise over 9 min. The bright yellow reaction mixture was stirred at −78 °C for 20 min, and then a solution of Weinreb amide **19** (0.440 g, 3.12 mmol, 1.0 equiv) in 5.2 mL of THF[29] was added dropwise over 8 min. The reaction mixture was stirred at −78 °C for 1 h, and then 20 mL of satd aq NH_4Cl solution was added dropwise over 5 min. The reaction mixture was allowed to warm to 0 °C over 10 min and then diluted with 100 mL of Et_2O and 25 mL of satd aq NH_4Cl solution. The aqueous phase was separated and extracted with two 50-mL portions of Et_2O. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated (5–10 °C, 20 mmHg) to give 1.04 g of yellow oil. Purification by column chromatography on 115 g of acetone-deactivated silica gel (elution with 0–5% EtOAc–hexanes) provided 0.300 g (55%) of enone **20** as a pale yellow oil: IR (neat) 2226, 1671, 1589, 1435, 1372, 1334, 1231, 1190, 1073, 1000, 975, 917, 855, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.76 (dt, J=17.5, 11.0, 2.1 Hz, 1H), 5.54 (dd, J=17.5, 2.1 Hz, 1H), 5.38 (dd, J=11.0, 2.1 Hz, 1H), 2.64–2.73 (m, 4H), 2.46–2.51 (m, 2H), 2.36 (td, J=6.8, 1.7 Hz, 2H), 1.84 (quint, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 147.2, 145.1, 125.9, 117.6, 90.2, 80.2, 36.2, 28.1, 26.7, 23.1, 19.0; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{12}H_{14}O$: 175.1117, found: 175.1126.

*4.4.11. 1-Cyclobutenyl-7-methyloct-7-en-5-yn-1-one (**21**).* Reaction of iodide **6** (0.443 g, 1.89 mmol, 1.2 equiv) with *t*-BuLi solution (1.47 M in pentane, 2.57 mL, 3.78 mmol, 2.4 equiv) and then with Weinreb amide **19** (0.224 g, 1.59 mmol, 1.0 equiv) according to the general procedure gave 0.456 g of pale yellow oil. Purification by column chromatography on 46 g of acetone-deactivated silica gel (elution with 0–7% EtOAc–hexanes) afforded 0.150 g (50%) of enone **21** as a yellow oil: IR (neat) 2224, 1709, 1672, 1614, 1598, 1434, 1372, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (t, J=1.3 Hz, 1H), 5.19–5.22 (m, 2H), 5.14–5.17 (m, 1H), 2.69–2.71 (m, 2H), 2.70 (t, J=7.3 Hz, 2H), 2.48–2.51 (m, 2H), 2.37 (t, J=6.9 Hz, 2H), 1.87 (dd, J=1.5, 1.0 Hz, 3H), 1.85 (quint, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 147.3, 145.2, 127.3, 120.8, 88.5, 82.8, 36.3, 28.2, 26.8, 24.0, 23.3, 19.0; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{16}O$: 211.1093, found: 211.1088.

*4.4.12. 1-Cyclobutenyl-6-(cyclopent-1-en-1-yl)-hex-5-yn-1-one (**22**).* Reaction of iodide **18b** (0.898 g, 3.45 mmol, 1.15 equiv) with *t*-BuLi solution (1.39 M in pentane, 5.00 mL, 6.95 mmol, 2.3 equiv) and then with Weinreb amide **19** (0.423 g, 3.00 mmol, 1.0 equiv) according to the general procedure gave 0.766 g of yellow oil. Purification by column chromatography on 115 g of acetone-deactivated silica gel (elution with 0–5% EtOAc–hexanes) afforded 0.410 g (64%) of enone **22** as a white solid, mp 30–32 °C: IR (thin film) 2932, 1671, 1589, 1441, 1373, 1231, 1071, and 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74–6.79 (m, 1H), 5.91–5.98 (m, 1H), 2.67–2.74 (m, 4H), 2.48–2.52 (m, 2H), 2.36–2.46 (m, 6H), 1.82–1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 147.2, 145.1, 136.4, 124.9, 90.5, 78.8, 36.7, 36.3, 33.2, 28.1, 26.7, 23.4, 23.3, 19.2; HRMS-ESI (m/z) calcd for $C_{15}H_{18}O$ $[M+H]^+$: 215.1430, found: 215.1427.

*4.4.13. 1-Cyclobutenyl-6-(cyclohex-1-en-1-yl)-hex-5-yn-1-one (**23**).* Reaction of iodide **18c** (1.161 g, 4.23 mmol, 1.1 equiv) with *t*-BuLi solution (1.32 M in pentane, 6.45 mL, 8.51 mmol, 2.3 equiv) and then with Weinreb amide **19** (0.522 g, 3.70 mmol, 1.0 equiv) according to the general procedure gave 1.281 g of yellow oil. Purification by column chromatography on 152 g of acetone-deactivated silica gel (elution with 0–4% EtOAc–hexanes) afforded 0.469 g (56%) of enone **23** as a colorless oil: IR (neat) 2222,

1672, 1589, 1436, 1371, 1346, 1231, 1190, 1075, 996, 918, 843, 800, and 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.89–6.03 (m, 1H), 2.66–2.72 (m, 4H), 2.47–2.51 (m, 2H), 2.35 (t, J=6.9 Hz, 2H), 2.12–2.22 (m, 4H), 1.83 (quint, J=7.0 Hz, 2H), 1.53–1.66 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 196.4, 147.3, 145.0, 133.6, 121.1, 86.5, 83.4, 36.4, 29.8, 28.1, 26.7, 25.7, 23.5, 22.6, 21.8, 19.0; HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{16}H_{20}O$: 229.1587, found: 229.1577.

4.5. [4+4] Annulation with cyclobutenones

*4.5.1. (6Z,8Z)-8-Methyl-2,3-dihydro-1H-cyclopenta[8]annulen-5(4H)-one (**8**).* A threaded Pyrex tube (35 mm O.D., 30 mm I.D., 15-cm long) equipped with a stir bar, rubber septum, and argon inlet needle was charged with cyclobutenone **7** (0.206 g, 1.18 mmol, 1.0 equiv), BHT (0.261 g, 1.18 mmol, 1.0 equiv), and 24 mL of CH_2Cl_2. The pale yellow solution was cooled to 0 °C and BF_3-etherate (0.20 mL, 0.23 g, 1.6 mmol, 1.4 equiv) was added dropwise via syringe over 30 s. The reaction mixture was stirred at 0 °C for 20 min while the color changed to orange and then tan. The rubber septum was replaced with a Teflon cap, and the reaction mixture was heated at 50 °C. After 4 h, the solution was cooled to rt and the Teflon cap was replaced with a rubber septum and argon inlet needle. The reaction mixture was cooled to 0 °C and 3 mL of satd aq $NaHCO_3$ solution was added dropwise via syringe over 1 min. The resulting mixture was extracted with two 20-mL portions of CH_2Cl_2 and the combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 10 °C (20 mmHg) to give 0.478 g of a brown oil. Column chromatography on 48 g of silica gel (elution with 5–20% Et_2O–pentane) afforded 0.061 g (30%) of cyclooctatrienone **8** as a yellow oil and 0.075 g (36%) of indan **13** as a yellow oil. For cyclooctatrienone **8**: IR (neat) 3301, 2955, 2916, 2844, 1661, 1615, 1564, 1434, 1286, 1234, 1200, 1029, and 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J=13.3 Hz, 1H), 6.36–6.41 (m, 2H), 2.91 (br s, 2H), 2.49 (app q, J=7.5 Hz, 4H), 2.11 (s, 3H), 1.93 (quint, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 141.4, 139.7, 139.4, 135.4, 132.9, 130.0, 44.4, 36.7, 35.8, 26.7, 23.1; HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{12}H_{14}O$: 197.0937, found: 197.0935. For indan **13**:[2a] ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.24 (s, 1H), 3.21 (t, J=7.4 Hz, 2H), 2.88 (t, J=7.6 Hz, 2H), 2.58 (s, 3H), 2.37 (s, 3H), 2.07 (quint, J=7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 146.6, 142.6, 136.0, 133.9, 129.6, 128.3, 33.9, 32.4, 28.6, 25.5, 21.3.

4.6. [4+4] Annulations with acylcyclobutenes

*4.6.1. (5Z,7Z)-6-Methyl-3,4,9,10-tetrahydrobenzo[8]annulen-1(2H)-one (**26**). Method A*: A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **21** (0.107 g, 0.569 mmol, 1.0 equiv) and 57 mL of CH_2Cl_2. The reaction mixture was cooled to −78 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 2.35 mL, 0.57 mmol, 1.0 equiv) was added dropwise over 5 min. The yellow reaction mixture was stirred at −78 °C for 4 h, and then 10 mL of satd aq $NaHCO_3$ solution was added dropwise over 5 min. The resulting mixture was warmed to 0 °C and then diluted with 10 mL of brine. The organic phase[30] was dried over Na_2SO_4 and filtered into a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 20-cm long). The pale blue reaction mixture was deoxygenated with a stream of argon for 5 min, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 5 h, and then cooled to rt and concentrated to give 0.125 g of brown oil. Purification by column chromatography on 16 g of silica gel (elution with 8% EtOAc–hexanes) afforded 0.074 g (69%) of cyclooctatriene **26** as a yellow oil: IR (neat) 3307, 2932, 1663, 1609, 1433, 1374, 1299, 1176, 1128, 819, 756, and 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (d, J=13.3 Hz, 1H), 5.69 (s, 1H), 5.60 (dt, J=13.3, 2.2 Hz, 1H), 2.54 (t, J=6.0 Hz, 2H), 2.43 (t, J=6.6 Hz, 2H), 2.32–2.38 (m, 2H), 2.30 (t, J=5.9 Hz, 2H), 1.97 (quint, J=5.5 Hz, 2H), 1.95 (d, J=1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 155.8, 138.0, 136.9, 132.7, 127.6, 125.4, 38.1, 36.8, 30.6, 26.2, 23.8, 23.0; HRMS-ESI (m/z) calcd for $C_{13}H_{16}O$ $[M+H]^+$: 189.1279, found: 189.1277.

Method B: A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **21** (0.136 g, 0.722 mmol, 1.0 equiv) and 72 mL of CH_2Cl_2. The reaction mixture was cooled to 0 °C and 2,4,6-triisopropylbenzenesulfonic acid (0.103 g, 0.362 mmol, 0.5 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h during which time the color changed from colorless to purple. Satd aq $NaHCO_3$ solution (70 mL) was added in one portion and the organic phase was separated and washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated at 5–10 °C (20 mmHg). The resulting yellow oil was diluted with 75 mL of CH_2Cl_2 and transferred to a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 20-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. The solution was deoxygenated with a stream of argon for 5 min and then sealed with a threaded Teflon cap. The reaction mixture was heated at 90–95 °C for 20 h and then cooled to rt and concentrated at 5–10 °C (20 mmHg) to give a brown oil. Purification by column chromatography on 12 g of silica gel (elution with 5% Et_2O–pentane) afforded 0.106 g (78%) of cyclooctatriene **26** as a yellow oil.

Method C: A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **21** (0.160 g, 0.850 mmol, 1.0 equiv) and 72 mL of CH_2Cl_2. The reaction mixture was cooled to 0 °C and 2,4,6-triisopropylbenzenesulfonic acid (0.120 g, 0.422 mmol, 0.5 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h during which time the color changed from colorless to purple. Satd aq $NaHCO_3$ solution (100 mL) was added in one portion and the organic phase was separated, washed with 100 mL of satd aq $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated at 5–10 °C (20 mmHg). The resulting yellow oil was diluted with 70 mL of CH_2Cl_2 and transferred to a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 15-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. Camphorsulfonic acid (0.400 g, 1.72 mmol, 2.0 equiv) was added and the solution was deoxygenated with a stream of argon for 5 min. The tube was sealed with a threaded Teflon cap, heated at 50 °C for 17 h, and then cooled to rt and concentrated at 5–10 °C (20 mmHg) to give a brown oil. Purification by column chromatography on 12 g of silica gel (elution with 5% Et_2O–pentane) afforded 0.098 g (61%) of cyclooctatriene **26** as a yellow oil.

*4.6.2. (5Z,7Z)-3,4,9,10-Tetrahydrobenzo[8]annulen-1(2H)-one (**27**).* A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **20** (0.150 g, 0.861 mmol, 1.0 equiv) and 80 mL of CH_2Cl_2. The reaction mixture was cooled to −30 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 3.6 mL, 0.86 mmol, 1.0 equiv) was added over 4 min. The reaction mixture was stirred at −30 to −15 °C for 2.5 h and then 50 mL of satd aq $NaHCO_3$ solution was added in one portion. The organic layer was separated and washed with 50 mL of satd aq $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to give a yellow oil.[31] This material was dissolved in 80 mL of CH_2Cl_2 and transferred to a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 20-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. Camphorsulfonic acid (0.400 g, 1.72 mmol, 2.0 equiv) was added and the solution was deoxygenated with a stream of argon for 5 min. The tube was sealed with a threaded Teflon cap. The reaction

mixture was heated at 100 °C for 15 h and then cooled to rt and concentrated to give a brown oil. Purification by column chromatography on 15 g of silica gel (elution with 3% Et_2O–pentane) afforded 0.083 g (55%) of cyclooctatriene **27** as a yellow oil: IR (neat) 3001, 2932, 2875, 2832, 1661, 1432, 1176, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, J=12.2, 5.9 Hz, 1H), 5.79–5.89 (m, 2H), 5.68–5.76 (m, 1H), 2.58 (t, J=5.8 Hz, 2H), 2.45 (t, J=6.7 Hz, 2H), 2.35–2.46 (m, 2H), 2.34 (t, J=6.0 Hz, 2H), 2.00 (quint, J=6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 154.2, 137.6, 135.2, 128.9, 128.3, 123.3, 37.9, 30.3, 30.0, 23.5, 22.8; HRMS-DART (m/z) calcd for $[M+H]^+$: 175.1117, found: 175.1121.

*4.6.3. (3aZ,11Z)-2,3,5,6,9,10-Hexahydro-1H-benzo[a]cyclopenta[d][8]annulen-7(8H)-one (**38**).* A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **22** (0.095 g, 0.44 mmol, 1.0 equiv) and 44 mL of CH_2Cl_2. The reaction mixture was cooled to −78 °C and 1.82 mL of methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.44 mmol, 1.0 equiv) was added dropwise over 1 min. The pale yellow reaction mixture was stirred at −78 °C for 1 h, and then additional methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.90 mL, 0.22 mmol, 0.50 equiv) was added. After 30 min at −78 °C, the reaction mixture was warmed to −60 °C, stirred for 1 h, and then additional methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.90 mL, 0.22 mmol, 0.5 equiv) was added. The green reaction mixture was stirred at −60 °C for 3 h, and then 10 mL of satd aq $NaHCO_3$ solution was added and the resulting mixture was warmed to 0 °C over 10 min. The blue organic phase[32] was separated, dried over Na_2SO_4, and then filtered into a threaded Pyrex tube (35 mm O.D.; 28 mm I.D.; 15-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. The solution was deoxygenated with a stream of argon for 5 min and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 3 h, and then cooled to rt and concentrated to give 0.124 g of green oil. Purification by column chromatography on 16 g of silica gel (elution with 3–8% EtOAc–hexanes) afforded 0.038 g (40%) of cyclooctatriene **38** as an orange oil: IR (neat) 2929, 1659, 1601, 1433, 1370, 1327, 1299, 1175, 1127, 920, 815, and 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81–5.89 (m, 1H), 5.76–5.80 (m, 1H), 2.61 (td, J=7.5, 1.6 Hz, 2H), 2.51–2.57 (m, 2H), 2.39–2.46 (m, 6H), 2.34 (t, J=6.0 Hz, 2H), 1.90 (quint, J=6.3 Hz, 2H), 1.65 (quint, J=7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 154.9, 145.2, 137.2, 136.5, 129.4, 122.8, 38.05, 38.04, 37.9, 32.0, 31.4, 23.6, 23.1, 21.9; HRMS-DART (m/z) calcd for $C_{15}H_{18}O$ $[M+H]^+$: 215.1430, found: 215.1423.

*4.6.4. (7Z,11aZ)-2,3,5,6,8,9,10,11-Octahydrodibenzo[a,d][8]annulen-4(1H)-one (**39**).* A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **23** (0.017 g, 0.47 mmol, 1.0 equiv) and 47 mL of CH_2Cl_2. The reaction mixture was cooled to −78 °C and 2.02 mL of methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.489 mmol, 1.0 equiv) was added dropwise over 2 min. The reaction mixture was stirred at −78 °C for 3 h, and then 10 mL of satd aq $NaHCO_3$ solution was added dropwise over 5 min. The reaction mixture was warmed to 0 °C over 10 min, and then diluted with 10 mL of brine. The organic phase[33] was separated and dried over Na_2SO_4 and then filtered into a threaded Pyrex tube (35 mm O.D.; 28 mm I.D.; 15-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. The solution was deoxygenated with a stream of argon for 5 min and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 14 h, and then cooled to rt and concentrated to give 0.112 g of brown oil. Purification by column chromatography on 17 g of silica gel (elution with 5% EtOAc–hexanes) provided 0.028 g (26%) of cyclooctatriene **39** as an orange oil: IR (neat) 2248, 1663, 1436, 1372, 1300, 1240, 1177, 1127, 1100, 1025, 956, 917, 854, 821, and 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 5.42 (t, J=4.3 Hz, 1H), 2.41 (t, J=6.7 Hz, 2H), 2.52 (t, J=6.4 Hz, 2H), 2.34 (t, J=5.9 Hz, 2H), 2.29 (t, J=6.0 Hz, 2H), 2.03–2.11 (m, 2H), 1.95 (quint, J=6.4 Hz, 2H), 1.60–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 155.6, 145.0, 137.0, 136.2, 124.0, 122.5, 41.6, 38.7, 38.2, 30.4, 28.9, 28.5, 28.2, 23.8, 23.0; HRMS-DART (m/z) calcd for $C_{16}H_{20}O$ $[M+H]^+$: 229.1592, found: 229.1590.

Acknowledgements

We thank the National Institutes of Health (GM 28273) and Pfizer Inc. for generous financial support. J.M.R and J.F. were supported in part by National Science Foundation Graduate Fellowships. J.M.R. was supported in part by an AstraZeneca Graduate Fellowship and a David A. Johnson Summer Graduate Fellowship.

References and notes

1. For a review, see Wessig, P.; Muller, G. *Chem. Rev.* **2008**, *108*, 2051–2063.
2. For earlier work in this area from our laboratory, see (a) Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514–5515; (b) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378–9379; (c) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777; (d) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917–3920.
3. For reviews on cyclic cumulenes, see: (a) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111–1124; (b) Christl, M. Cyclic Allenes Up to Seven-Membered Rings In *Modern Allene Chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 243–357; (c) Kawase, T. Cyclic Allenes In. *Science of Synthesis*; Krause, N., Ed.; Thieme: Stuttgart, 2007; Vol. 44, pp 395–449; (d) Johnson, R. P.; Konrad, K. M. Strained Cyclic Allenes and Cumulenes In *Strained Hydrocarbons*; Dodziuk, H., Ed.; Wiley-VCH: Weinheim, 2009; pp 122–146.
4. The intermediacy of strained cyclic allenes in these reactions is supported by experimental observations and computational studies. See Refs.1,2a, and Ananikov, V. P. *J. Phys. Org. Chem.* **2001**, *14*, 109–121.
5. Reviews: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821; (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930; (c) Yu, Z.; Wang, Y.; Wang, Y. *Chem.—Asian J.* **2010**, *5*, 1072–1088.
6. For a review of [4+4] cycloaddition strategies, see Sieburth, S. M.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251–6282.
7. For an earlier [4+4] annulation strategy developed in our laboratory, see: Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670–7672.
8. For the construction of eight-membered carbocyclic systems via the [4+4] photocycloaddition of enynes with 2-pyridones, see Kulyk, S.; Dougherty, W. G.; Kassel, W. S.; Fleming, S. A.; Sieburth, S. M. *Org. Lett.* **2010**, *12*, 3296–3299.
9. Reviewed in Marvell, E. B. *Thermal Electrocyclic Reactions*; Academic: New York, NY, 1980.
10. Reviews: (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163; (c) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159; (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
11. For examples of Diels–Alder [4+2] cycloadditions involving cyclobutenones, see (a) Kelly, T. R.; McNutt, R. W. *Tetrahedron Lett.* **1975**, *16*, 285–288; (b) Bienfait, B.; Coppe-Motte, G.; Merenyi, R.; Viehe, H. G. *Tetrahedron* **1991**, *47*, 8167–8176; (c) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 11004–11005.
12. Wasserman, H. H.; Piper, J. U.; Dehmlow, E. V. *J. Org. Chem.* **1973**, *38*, 1451–1455.
13. Prepared by Sonogashira coupling of 4-pentyn-1-ol with 2-bromopropene as described by Hashmi, A. K. S.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432–438.
14. Hydrolysis of the intermediate vinylogous hemiacetal generated in the organolithium addition to 3-ethoxycyclobutenone was best accomplished using the general protocol of Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350–5358.
15. Reviewed in Danheiser, R. L.; Dudley, G. B.; Austin, W. F. Alkenylketenes In. *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23, pp 493–568.
16. The structure of **8** was confirmed by spectroscopic analysis, including comparison of its IR and proton and carbon NMR data with that reported for 2,4,6-cyclooctatrienone. See (a) Adam, W.; Cueto, O.; De Lucchi, O. *Chem. Ber.* **1982**, *115*, 1170–1177; (b) Meier, H.; Lorch, M.; Petersen, H.; Gugel, H. *Chem. Ber.* **1982**, *115*, 1418–1424.
17. For several key and especially relevant examples, see (a) Cope, A. C.; Haven, A. C.; Ramp, F. L.; Trumbull, E. R. *J. Am. Chem. Soc.* **1952**, *74*, 4867–4871; (b) Huisgen, R.; Boche, G.; Dahmen, A.; Hetchl, W. *Tetrahedron Lett.* **1968**, *9*, 5215–5219; (c) Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, *109*, 6528–6530; (d) Fujiwara, T.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283–6286; (e) Computational study: Fry, A. *Tetrahedron* **2008**, *64*, 2101–2103.
18. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
19. Reviewed in (a) Sibi, M. P. *Org. Prep. Proceed. Int.* **1993**, *25*, 15–40; (b) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738.

20. Song, A.; Parker, K. A.; Sampson, N. S. *J. Am. Chem. Soc.* **2009**, *131*, 3444–3445.
21. Prepared by hydrolysis of commercially available $TIPPSO_2Cl$ as described by Jautze, S.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284–9288 The acid was dried over P_2O_5 under vacuum (0.1 mmHg) for 48 h prior to use.
22. Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100–8103.
23. Acylcyclobutene **30** was prepared beginning from 4-butyn-1-ol by a route analogous to that employed for the synthesis of the homologous substrates described in Scheme 4.
24. A similar difference is observed in the rate of intramolecular Diels–Alder reactions. Cycloaddition of 1,7,9-decatrien-3-one (four-atom tether) produces the expected octalone below rt, while reaction of 1,6,8-nonatrien-3-one (with a three-atom tether) requires 180 °C. The diminished rate of cycloaddition in the three-atom tether series has been attributed to increased steric interactions in the connecting chain and to diminished overlap of the carbonyl group with the dienophilic π-bond. See (a) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929–3932; (b) Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877–4880.
25. Esters **31** and **32** were prepared by reaction of cyclobutenecarboxylic acid with oxalyl chloride followed by addition of the appropriate enynyl alcohol.
26. (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–167; (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209–213.
27. Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143–2146.
28. Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767–770.
29. Weinreb amide **19** is sparingly soluble in Et_2O–pentane mixtures at −78 °C so THF was added to form a homogeneous reaction mixture.
30. In a separate run, the organic phase was concentrated to give 0.055 g of brown oil that was determined to be diene **24**: IR (neat) 2936, 1707, 1442, 1365, 1333, 1195, 1020, 885, and 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.68 (dd, *J*=6.9, 3.8 Hz, 1H), 3.43 (q, *J*=8.2 Hz, 1H), 2.50–2.60 (m, 2H), 2.30–2.38 (m, 2H), 2.14–2.28 (m, 4H), 1.82–1.88 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.9, 138.7, 134.4, 122.7, 120.9, 50.6, 35.1, 34.1, 33.1, 29.4, 24.5, 22.4, 21.4.
31. The product of a separate run was purified by silica gel using 3% Et_2O–hexane elution to afford the diene **25**: IR (neat) 2226, 1707, 1432, 1330, 1193, 1072, 899, 821, and 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, *J*=10.0, 2.6 Hz, 1H), 5.79 (dd, *J*=6.6, 3.7 Hz), 5.65–5.75 (m, 1H), 3.44 (q, *J*=8.2 Hz, 1H), 2.50–2.62 (m, 2H), 2.33–2.50 (m, 2H), 2.09–2.33 (m, 2H), 1.97–2.09 (m, 2H) 1.77–1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 138.0, 127.6, 125.9, 123.4, 51.5, 34.9, 34.3, 28.8, 28.0, 22.5, 21.3. HRMS-DART (*m*/*z*) calcd for $[M+Na]^+$: 197.0937, found: 197.0940.
32. This organic phase is presumed to contain diene **36**. In a separate run, the organic phase was concentrated to afford 0.009 g of yellow oil that was shown to be a mixture of enyne **22** and diene **36**. The diene is characterized by the ^1H NMR resonances at 5.62 ppm (s, 1H) corresponding to the alkenyl proton and 3.75–3.83 (m, 1H) corresponding to the allylic methine proton. Diene **40** was observed in the mixture of products of another run and identified by characteristic ^1H NMR alkene resonances at 5.90–5.98 (m, 1H) and 5.70 ppm (s, 1H).
33. The organic phase is presumed to contain diene **37**. In a separate run, the organic phase was concentrated to afford 0.012 g of brown oil that was shown to be a mixture of diene **37** and other compounds. This diene is characterized by the ^1H NMR resonances at 5.58 ppm corresponding to the alkenyl proton and 3.55 ppm corresponding to the allylic methine proton.