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Anionic ring expansion reactions of oxabicyclo[4.2.1]heptenones. An efficient entry into the carbon framework of oxygenated cembranoids

Qing Xu, Mahika Weeresakare and Jon D. Rainier*

Department of Chemistry, The University of Arizona, Tucson, AZ 85721, USA

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Abstract—Oxabicyclo[2.2.1]heptenones undergo 2-carbon ring expansion reactions when subjected to anionic condensations and Michael acceptors. They also undergo condensation, fragmentation, and elimination reactions in their anionic couplings with aldehydes. As an outgrowth of this interesting chemistry, we have been able to access the carbon skeleton of oxygenated cembranoids by subjecting bis-activated ene-yne **39** to the enolate from oxabicyclo[2.2.1]heptenone **1**.

1. Introduction

The oxygenated cembranoid family of natural products has received a significant amount of attention from the synthetic chemistry community. Undoubtedly, this is due to their fascinating structural features and their interesting biological properties. To date, this attention has led to the total synthesis of several members of this family (eleutherobin,[1] eleuthosides A and B,[2] sarcodictyin A and B,[3] 7-deacetoxyalcyonin acetate,[4] and sclerophytin A and B[5]) along with a number of approaches to their synthesis.[6]

Our interest in the chemical synthesis of the oxygenated cembranoids directed our attention to the notion that their carbon skeleton could be assembled through the intramolecular cyclization and fragmentation sequence depicted in Scheme 1 (**3**→**5**).[7–9]

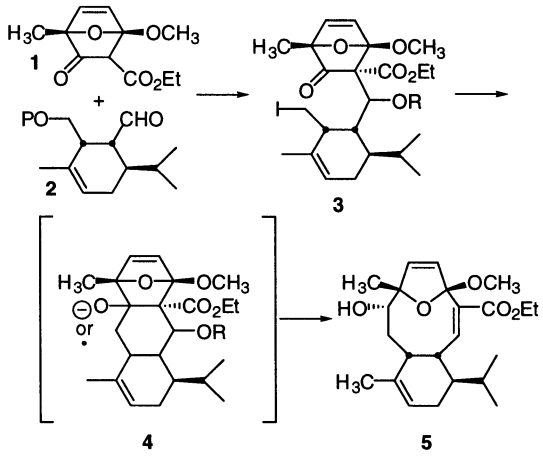
In an attempt to implement this plan, we discovered an interesting anionic coupling and fragmentation reaction of oxabicyclo[2.2.1]heptenones.[7a] This result along with others that came from subsequent experiments,[7b] directed our attention to a modified approach to the eleuthosides. Described herein is a full account of our experiments in these areas including a single flask entry into the carbon skeleton of the oxygenated cembranoids using a tandem anionic cyclization sequence.

2. Results and discussion

2.1. The synthesis of oxabicyclo[2.2.1]heptenone 1

The plan outlined in Scheme 1 required the synthesis of oxabicyclo[2.2.1]heptenone **1**. Dithioketal precursors to **1** and the corresponding 3,6-dihydro derivative **14** (Table 2) came from the condensation of bromopropiolate **8** with 2-methoxy-5-methyl furan or furan followed by dithioketal formation using anionic conditions analogous to conditions used by Leroy for the formation of the cyclic dithioketal derivative of **13** (Table 1).[10]

Leroy had been unsuccessful in his attempts to hydrolyze the cyclic dithiane analog of **13**.[11] Not surprisingly, our attempts to hydrolyze the cyclic dithiane in the more sensitive **11** were equally unsuccessful. Fortunately, we were



Scheme 1.

Keywords: oxygenated cembranoid; eleutherobin; ring expansion; fragmentation; heterocycles.

* Corresponding author. Tel.: +1-520-626-2084; fax: +1-520-621-8407; e-mail: rainier@u.arizona.edu

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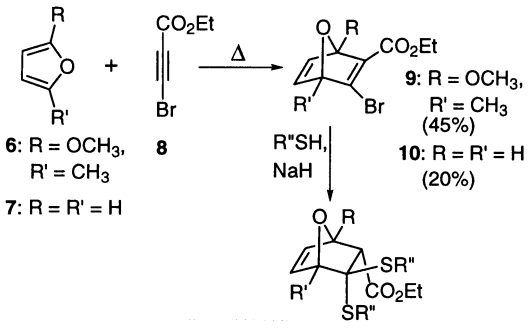
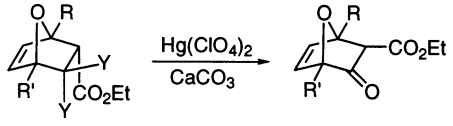
Table 1.



S,S ketal	R	R′	R″	*endo*:*exo*[a]	Yield (%)
11	OCH_3	CH_3	CH_2CH_2	>98:2	95
12	OCH_3	CH_3	Et	>98:2	96
13	H	H	Et	3:1	89

[a] Ratio determined by ^{1}H NMR.

Table 2.



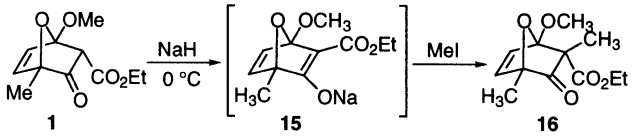
S,S, Ketal	R′	R	Ketone	Yield (%)	*endo*:*exo*[a]
11	CH_3	OCH_3	**1**	–[b]	–
12	CH_3	OCH_3	**1**	44	>98:2
13	H	H	**14**	55	2:1[c]

[a] Ratio determined by ^{1}H NMR.
[b] Attempted hydrolysis under all conditions resulted in the decomposition of the oxabicyclo[2.2.1]heptenone ring.
[c] Partial epimerization took place during thioketal hydrolysis.

able to overcome these problems by turning to the corresponding acyclic dithiane **12**. Hydrolysis using $Hg(ClO_4)_2$ provided a 44% yield of β-ketoester **1**. In a similar fashion, we were able to generate **14** in 55% yield from the hydrolysis of **13**.

2.2. Anionic condensations of 1

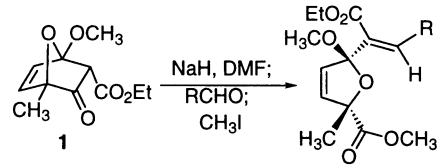
Since the success in the anionic coupling of **1** with **2** (Scheme 1) was dependent upon our ability to overcome a potentially facile β-fragmentation reaction of the enolate from **1** (i.e. **15**, Eq. (1)),[12] we carried out experiments aimed at determining the stability of **15**. We were pleased to find that **15** was stable at 0°C as witnessed by its trapping with MeI. When **15** was allowed to warm to rt, however, products resulting from the decomposition of the bicyclic ring system were isolated.



(1)

Having defined its temperature stability profile, we decided

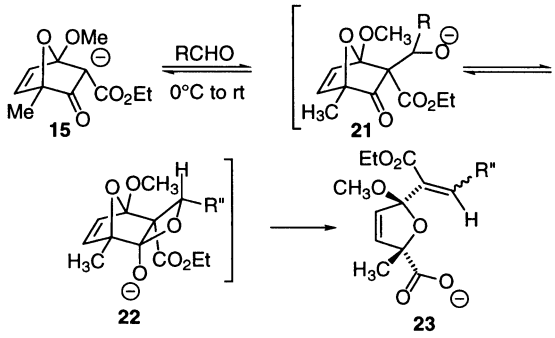
Table 3.



Entry	R	Furan	Yield (%)	*Z*:*E*[a]
1	Ph	**17**	83	>98:2
2	*i*-Pr	**18**	78	>98:2
3	$(CH_2)_3OBn$	**19**	68	>98:2
4	CO_2Et	**20**	91	5.4:1

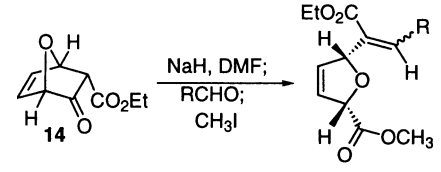
[a] Ratio determined by ^{1}H NMR.

to carry out experiments aimed at gaining an understanding of the reactivity of **15** with aldehydes in an effort to model its coupling with **2**. To our surprise, the addition of benzaldehyde to **15** at 0°C resulted in the formation of dihydrofuran **17** in 83% yield (Table 3).[13] Interestingly, the coupling of **2** with benzaldehyde results in a cascade sequence that mechanistically incorporates several chemical processes including condensation, fragmentation, and elimination. As this represented what could be an interesting entry into the synthesis of substituted furans we decided to explore its scope. We were pleased to find that the reaction was general. In addition to benzaldehyde, isobutyraldehyde, ethyl glyoxylate, and 4-benzyloxybutanal also underwent the condensation and fragmentation sequence to give furans **18**, **19**, and **20** in 78, 68 and 92% yield, respectively. Each of the products existed either predominantly or exclusively as its *Z*-olefin isomer.



Scheme 2.

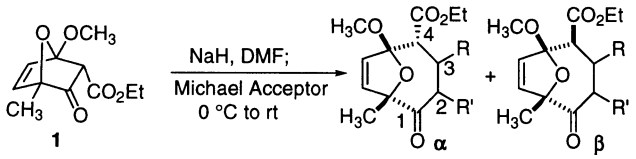
Table 4.



Furan	R	Yield (%)	*Z*:*E*[a]
24	Ph	56	1:3
25	*i*-Pr	45	2:1

[a] Ratio determined by ^{1}H NMR.

Table 5.



Entry	Michael acceptor	Product	R	R′	Yield (%)	α:β
1	Methyl acrylate	**26**	H	CO_2CH_3	70	2.5:1
2	Dimethyl fumarate	**28**	CO_2CH_3	CO_2CH_3	60	–[a]
3	Methylvinyl ketone	**29**	H	$C(O)CH_3$	60	2.5:1
4	4-Pentenylvinyl ketone	**30**	H	$C(O)(CH_2)_3CHCH_2$	70	2.5:1
5	Methacrylate	**31**	H	CH_3	–[b]	–

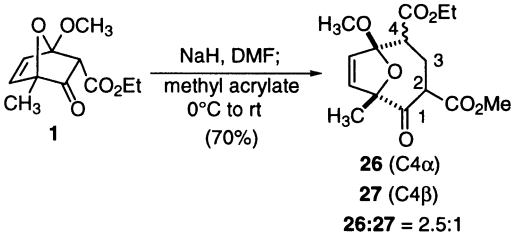
[a] Mix of three diastereomers at C-3 and C-4.
[b] Reaction led to the recovery of starting material.

Our working hypothesis for the condensation, fragmentation sequence is depicted in Scheme 2. Following the initial coupling reaction, oxyanionic cyclization gives oxetane **22**. Fragmentation of the bicyclic ring system with concomitant elimination of the ester leads to the formation of the corresponding olefin and **23**. Workup of the reaction with methyl iodide gives the corresponding methyl ester.

While we do not currently have an explanation for the predominance of the *Z*-olefin from these coupling reactions, we do know that bridgehead substitution is important in the selectivity. That is, in contrast to the condensation chemistry of **1**, the condensation of 2,5-unsubstituted oxabicyclo[2.2.1]heptenone **14** with benzaldehyde and isobutyraldehyde led to mixtures of the *E*- and *Z*-alkenes of **24** and **25**, respectively (Table 4).[14]

2.3. Two- and four-carbon ring expansions of oxabicyclo[2.2.1]heptenones

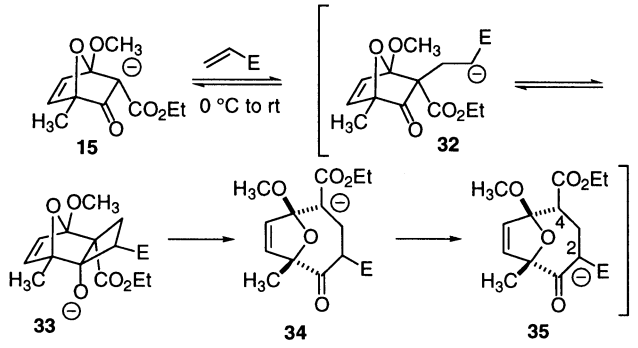
Having discovered the interesting reactions of aldehydes with oxabicyclo[2.2.1]heptenones **1** and **14**, we initiated a program to examine the hypothesis presented in Scheme 2. If **1** could be induced to undergo a Michael addition onto an activated alkene and if the aldehyde mechanism were operative, the Michael adduct would undergo cyclization onto the pendant ketone to generate two-carbon ring expanded products. With this in mind, **1** was subjected to NaH followed by methyl acrylate (Eq. (2)). The products from this reaction proved to be the ring expanded bicycles **26** and **27** as a 2.5:1 mixture of readily separable diastereomers. When combined with our aldehyde condensation studies, this experiment demonstrated that four-membered ring formation is facile in oxabicyclo[2.2.1]heptenone condensations.



(2)

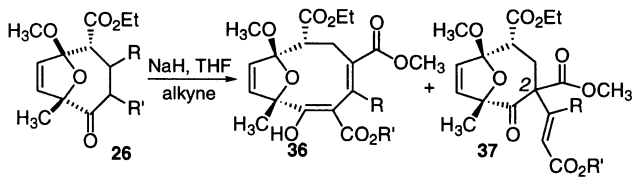
As presented in Table 5, other Michael acceptors also underwent the two-carbon ring expansion cascade with **1**. Thus, dimethyl fumarate, methylvinyl ketone, and 4-pentenylvinyl ketone gave ring expanded products **28**, **29**, and **30**, respectively.

Not surprisingly, proton transfer from the newly formed β-ketoester (1,3-diketone) to the anion from the fragmentation of the [2.2.1] ring systems occurred in the course of the reaction with methyl acrylate (Scheme 3). As proof of this, we were able to incorporate deuterium at C-2 when the reaction was quenched with D_2O.



Scheme 3.

Table 6.

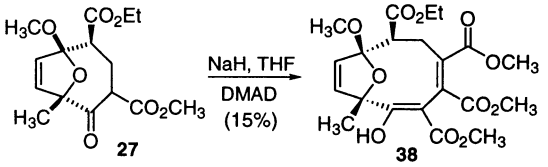


Entry	Alkyne	R	R′	Yield (%)	**36**:**37**
1	$MeO_2C–\equiv–CO_2Me$	CO_2Me	Me	92	1:0
2	$EtO_2C–\equiv–H$	H	Et	44	1:1.3[a]

[a] **37** was isolated as a 1:1 mixture of C-2 diastereomers.

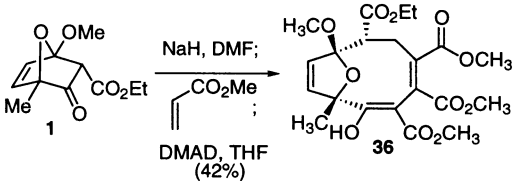
Having demonstrated the two-carbon ring expansions of **1**, we turned our attention back to the synthesis of oxygenated cembranoids. We became intrigued with the possibility of generating their oxygen-bridged 10-membered ring through an anionic two-carbon ring expansion reaction of oxabicyclo[4.2.1]heptenone **26** with activated alkynes using Proctor's protocol.[15] The treatment of **26** with NaH followed by DMAD resulted in the formation of oxygen bridged cyclodecadiene **36** in 92% yield (Table 6). Unfortunately, other activated alkynes were not as reactive as DMAD. For example, when **26** was exposed to NaH followed by ethyl propiolate we isolated a 1:1.3 mixture of ring expanded and Michael adducts **36** and **37**, respectively. As has been discussed by Proctor,[15] the reaction leading to **36** most likely proceeds through the formation of a cyclobutene intermediate followed by a subsequent fragmentation reaction.

Interestingly, the relative stereochemistry at the ethyl ester bearing stereocenter was important in the two-carbon ring expansion reaction of oxabicyclo[4.2.1]nonenes with activated alkynes. When **27** was exposed to NaH, DMAD, and THF we isolated **38** in low yield (Eq. (3)). The majority of the reaction mixture consisted of intractable material.



(3)

By taking advantage of the proton transfer that was observed in the initial two-carbon ring expansion reaction (Scheme 3), we were able to carry out a single flask, four-carbon ring expansion of **1**. That is, by exposing **1** to NaH and DMF followed by methyl acrylate and then DMAD in THF we were able to isolate oxygen bridged cyclodecatriene **36** in 42% overall yield (Eq. (4)).

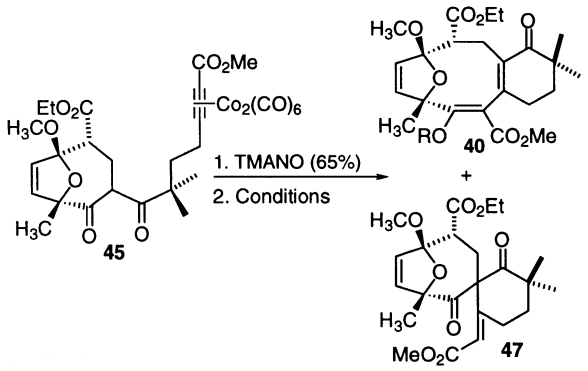


(4)

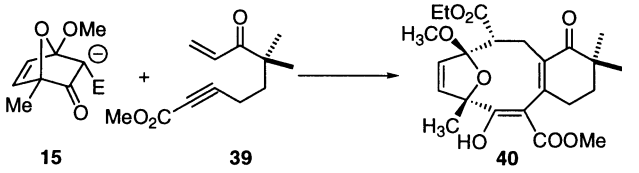
2.4. Tandem anionic ring expansion reactions

Having demonstrated the formation of **36** from **1** and two sequential two-carbon ring expansion reactions, we became curious about the possibility of using a similar protocol to generate the oxygenated cembranoid carbon skeleton. That is, we believed that **40** might come from the anionic coupling of **1** with a molecule containing two Michael acceptors linked to one another through an alkyl chain (e.g. **39**). If this endeavor was successful, we would be in a position to efficiently generate a wide variety of oxygenated cembranoids from relatively simple substrates.

Table 7.

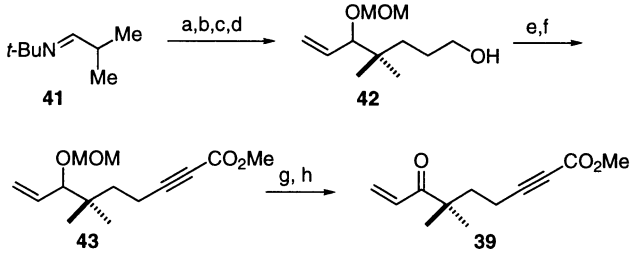


Conditions	R	Yield (%)	**40**:**47**
NaH, DMF, 25°C, 12 h	H	80	1:1
NaH, DMF, 50°C, 12 h	H	40	1:0
KH, DMF, 25°C, 1 h; Ac_2O, DMAP	Ac	50	1:0



(5)

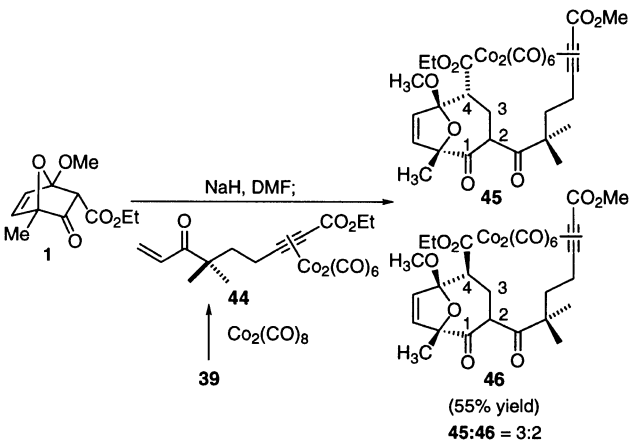
With these goals in mind, we synthesized ene-yne **39** from *t*-butyl imine **41** (Scheme 4). The anionic coupling of **41** with the TBDPS ether of bromopropanol gave **42**[16] after vinyl magnesium bromide addition, MOM ether formation, and hydrolysis of the TBDPS group. Oxidation of the resulting alcohol was followed by alkyne formation using the Corey–Fuchs protocol to give **43** after trapping of the alkynyl anion with methylchloroformate.[17] Methanolysis of the MOM ether and PCC oxidation gave ene-yne coupling precursor **39**.



Scheme 4. (a) LDA; $BrCH_2CH_2CH_2OTBDPS$ (90%); (b) $BrMgCH{=}CH_2$ (65%); (c) MOMCl, $(i\text{-}Pr)_2NEt$ (85%); (d) TBAF (100%); (e) (i) $(COCl)_2$ DMSO, NEt_3; (ii) PPh_3, CBr_4 (2 steps, 65%); (f) BuLi (2 equiv.); $ClCO_2Me$ (87%); (g) HCl, CH_3OH (80%); (h) PCC (79%).

2.4.1. Stepwise generation of oxygenated cembranoid skeleton 40. In an effort to determine the feasibility of the sequential two-carbon ring expansion for the synthesis of **40**,[18] we decided to initially proceed in a stepwise fashion via the formation of oxabicyclo[4.2.1]nonene **45** (Eq. (6)).

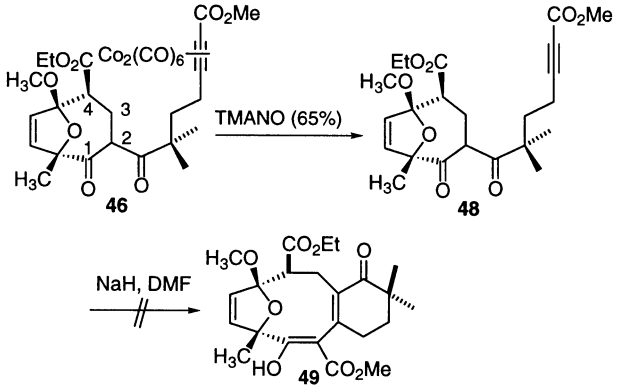
With this in mind, the alkyne in **39** was masked as the corresponding $Co_2(CO)_6$ complex (e.g. **44**).[19] The anionic coupling of **44** with **1** gave a 55% yield of readily separable diastereomeric oxabicyclo[4.2.1]nonenes **45** and **46**.



(6)

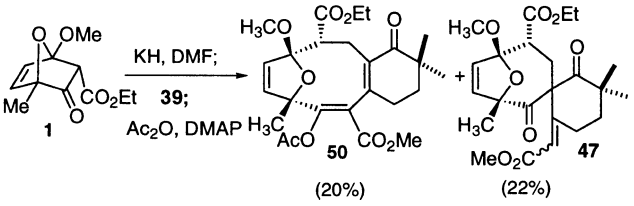
Following oxidative decomplexation of cobalt from the alkyne using trimethylamine-*N*-oxide (TMANO),[20] each of the C-4 diastereomers was subjected individually to the anionic two-carbon ring expansion reaction. When **45** was treated with NaH at rt for 12 h, we isolated a 40% yield of the desired ring expanded product **40** along with a 40% yield of spirofused product **47** as a single diastereomer (Table 7).[21] When the reaction was carried out at 50°C for 12 h, a 40% yield of **40** was isolated. Under these conditions, formation of **47** was not observed.[22] We also examined the effectiveness of KH as the base in the **45**→**40** conversion. When **45** was subjected to KH at 0°C and allowed to warm to rt over 1 h we isolated a 50% yield of the enol acetate of **40** after acylation of the crude reaction mixture.[23] As in the experiment using NaH at elevated temperatures, we did not isolate **47** using these conditions.[22]

Interestingly, in an analogous fashion to what we had observed in the intermolecular ring expansion reaction of 27, C4 β-diastereomer **48** decomposed to unrecognizable products when exposed to the anionic fragmentation conditions (Scheme 5). The reason for the divergent reactivity profiles of uncomplexed **45** and **48** is unclear at the present time but may be due to the facial approach of the activated alkyne onto the intermediate enolate. If this is true and the C-4 ester is directing the attack, approach from the α-face does not appear to be productive.



Scheme 5.

2.4.2. Single flask entry into the oxygenated cembranoid skeleton 40. Having established that **1** could be transformed into the corresponding tricycle in a stepwise fashion, we investigated the single step conversion of **1** into the oxygenated cembranoid skeleton through its reaction with **39** (Eq. (7)).[24] In the event, we isolated **50** in 20% yield by subjecting **1** to **39** and KH at rt followed by in situ acylation of the doubly ring expanded enolate.[25] The main by-product from the reaction (22% yield) was spirofused substrate **47** as a mixture of diastereomers. Although formed in a modest yield, the conversion of **1** into **50** represents an impressive combination of the coupling and fragmentation of six C–C bonds in a single flask and an almost direct entry into the oxygenated cembranoid skeleton.



(7)

In conclusion, we have demonstrated that oxabicyclo-[2.2.1]heptenones undergo anionic coupling and fragmentation sequences with aldehydes and Michael acceptors. These reactions lead to the synthesis of substituted dihydrofurans as well as ring expanded products including the carbon skeleton of oxygenated cembranoids.

3. Experimental

3.1. General

NMR spectra were recorded on either a Bruker EM-600, Bruker EM-500, Bruker AM-250, or a Varian 300 spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (δ=7.24 ppm) as an internal standard. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A and are reported as % relative intensity to the molecular base peak. IR spectra were recorded on a Nicolet Impact 410. Ether, THF, hexanes, benzene, and toluene were distilled from sodium/benzophenone. CH_2Cl_2, $CHCl_3$, TMEDA, $(i\text{-}Pr)_2NEt$, Et_3N, and Et_2NH were distilled from CaH_2. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of argon in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg) with a Büchi Rotavapor. Characterization data for compounds **6**–**14** ,**17**, **18**, **24**, **30**, **36**, and **37** have been reported elsewhere.[7,10]

3.1.1. Preparation of dihydrofuran 19. To a slurry of NaH (2.4 mg, 0.097 mmol) and DMF (0.3 mL) at 0°C was added

a solution of **1** (22 mg, 0.097 mmol) and DMF (0.3 mL). After stirring for 1 h, 4-benzyloxybutanal (87 mg, 0.486 mmol) was added slowly. After stirring for an additional 1 h, MeI (0.3 mL, 0.5 mmol) was added and the reaction mixture was stirred for another 1 h. After quenching with $NaHCO_3$ ((aq, sat) 8 mL), the mixture was extracted with ethyl acetate (3×1 5 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (6:1 hexane/ethyl acetate) provided 27 mg (68%) of furan **19** as a colorless oil.: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 7.26 (m, 1H), 6.61 (t, J=7.7 Hz, 1H), 6.25 (d, J=6.0 Hz, 1H), 6.08 (d, J=6.0 Hz, 1H), 4.49 (s, 2H), 4.24 (m, 2H), 3.71 (s, 3H), 3.48 (t, J=6.5 Hz, 2H), 3.24 (s, 3H), 2.39 (m, 2H), 1.77 (m, 2H), 1.65 (s, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ); ^{13}C NMR (600 MHz, $CDCl_3$) δ 172.3, 167.0, 140.3, 138.7, 133.1, 132.7, 130.9, 128.4, 127.7, 127.5, 123.4, 113.6, 89.6, 73.0, 69.8, 60.6, 52.1, 50.4, 29.3, 26.2, 25.0, 14.3; IR (CCl_4) 2999, 2851, 1785, 1746, 1696 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{30}O_7$ (M+Cs$^+$) 551.1042, found 551.1050.

3.1.2. Preparation of dihydrofuran 20. To a slurry of NaH (2.0 mg, 0.084 mmol) and DMF (0.3 mL) at 0°C was added a solution of **1** (22 mg, 0.097 mmol) and DMF (0.3 mL). After stirring for 1 h, ethyl glyoxylate (43 mg, 0.42 mmol) was then added slowly to the reaction mixture. After an additional 1 h, MeI (0.3 mL, 0.5 mmol) was added and the reaction mixture was stirred for another 1.5 h. After quenching with $NaHCO_3$ (aq, sat. 8 mL), the mixture was extracted with ethyl acetate (3×15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) provided 30 mg (91%) of furan **20** as a 5.4:1 mixture of olefins as a colorless oil. *Z*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.15 (d, J=5.8 Hz, 1H), 6.09 (d, J=5.8 Hz, 1H), 4.30 (dq, J=10.8, 7.1 Hz, 2H),[†] 4.18 (dq, J=10.8, 7.1 Hz, 2H),[†] 3.75 (s, 3H),3.31 (s, 3H), 1.67 (s, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 171.6, 166.3, 164.9, 147.2, 133.9, 129.2, 123.4, 112.6, 90.5, 61.5, 60.9, 52.5, 50.7, 24.8, 14.0, 13.8; IR (CCl_4) 2981, 1752, 1739, 1023 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{22}O_8$ (M+H$^+$) 343.1393, found 343.1396.

Z configuration of the major isomer was confirmed by the vicinal coupling constant ^3J(CO,H) 11.1 Hz.

E-isomer: H NMR (600 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.26 (d, J=5.8 Hz, 1H), 6.21 (d, J=5.8 Hz, 1H), 4.30 (dq, J=10.8, 7.1 Hz, 2H),[†] 4.18 (dq, J=10.8, 7.1 Hz, 2H)[†], 3.73 (s, 3H), 3.27 (s, 3H), 1.59 (s, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.311 (t, J=7.1 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 171.3, 166.0, 165.0, 138.2, 135.1, 129.6, 129.1, 112.4, 90.1, 61.3, 61.0, 52.2, 50.5, 24.5, 14.0, 13.8.

3.1.3. Preparation of 4,4-dimethyl-7-*t*-butyldiphenylsilanyloxy-1-heptene-3-ol. To a solution of vinylmagnesium bromide (1 M solution in THF, 20.3 mmol) at 0°C, was added a solution of 5-*t*-butyldiphenylsilanyloxy-2,2-dimethylpentanal (5.0 g, 13.5 mmol) and THF (15 mL) dropwise over 1 h. After stirring for 0.5 h, the mixture was quenched with NH_4Cl ((sat, aq.) 30 mL). The aqueous phase was extracted with ether (200 mL×3). The organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes/ethyl acetate 5:1) gave 4.0 g (74%) of 4,4-dimethyl-7-*t*-butyldiphenylsilanyloxy-1-heptene-3-ol as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.65 (dd, J=7.8, 1.2 Hz, 4H), 7.42–7.34 (m, 6H), 5.90 (ddd, J=17.3, 10.5, 6.8 Hz, 1H), 5.20 (ddd, J=17.2, 1.2, 1.2 Hz, 1H), 5.15 (ddd, J=10.4, 1.2, 1.2 Hz, 1H), 3.78 (d, J=6.6 Hz, 1H), 3.62 (t, J=6.6 Hz, 2H), 1.58–1.48 (m, 2H), 1.33 (ddd, J=13.2, 6.0, 2.4 Hz, 1H), 1.23 (ddd, J=16.2, 12.0, 6.0 Hz, 1H), 1.04 (s, 9H), 0.86 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 137.9, 135.6, 134.1, 129.5, 127.6, 127.5, 116.4, 79.9, 64.7, 36.9, 34.6, 27.0, 26.9, 22.8, 22.7, 19.2; IR (CCl_4) 2969, 1548 cm^{-1}.

3.1.4. Preparation of 4,4-dimethyl-5-methoxymethoxy-6-heptene-1-ol (42). To a solution of 4,4-dimethyl-7-*t*-butyldiphenylsilanyloxy-1-heptene-3-ol (4.0 g, 10.1 mmol) and CH_2Cl_2 (10 mL) was added MOMCl (1.62 g, 20.2 mmol) followed by a solution of *i*-Pr_2NEt (3.52 mL, 20.2 mmol) and CH_2Cl_2 (10 mL). After stirring for 12 h, the mixture was quenched with $NaHCO_3$ ((sat, aq.) 20 mL). The aqueous phase was extracted with ether (200 mL×3), dried ($MgSO_4$), and concentrated to provide the MOM ether. The MOM ether was taken on to the formation of **42** without further purification.

To a solution of the crude MOM ether from above and THF (30 mL), was added TBAF (17 mL of a 1 M solution in THF, 17.2 mmol). After stirring for 2.5 h, the reaction was quenched through the addition of H_2O (50 mL). The aqueous phase was extracted with ethyl acetate (3× 200 mL). The organic extracts were dried and concentrated. Flash chromatography (hexanes/ethyl acetate 3:2) gave 1.8 g (85%) of **42** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 5.64 (ddd, J=17.4, 10.2, 8.4 Hz, 1H), 5.22 (dd, J=10.2, 1.8 Hz, 1H), 5.13 (dd, J=17.4, 1.2 Hz, 1H), 4.61 (d, J=8.1 Hz, 1H), 4.42 (d, J=8.1 Hz, 1H), 3.63 (d, J=8.4 Hz, 1H), 3.54 (t, J=6.6 Hz, 2H), 3.30 (s, 3H), 2.20 (bs, 1H), 1.56–1.45 (m, 2H), 1.34 (dt, J=13.2, 4.8 Hz, 1H), 1.22 (ddd, J=12.6, 12.6, 4.8 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 134.9, 119.1, 93.8, 84.3, 63.6, 55.6, 36.4, 34.5, 26.9, 23.3, 23.2; IR (CCl_4) 3376, 2944, 2888, 1036 cm^{-1}. HRMS calcd for $C_{11}H_{23}O_3$ (M+H) 203.1647, found 203.1644.

3.1.5. Preparation of 4,4-dimethyl-5-methoxymethoxy-6-heptenal. To a solution of oxalyl chloride (0.87 mL, 9.95 mmol) and CH_2Cl_2 (5 mL) at −60°C was added a solution of DMSO (0.94 mL, 13.3 mmol) and CH_2Cl_2 (5 mL) dropwise. After the resulting solution had stirred for 10 min, a solution of **42** (1.34 g, 6.63 mmol) and CH_2Cl_2 (10 mL) was added. The mixture was stirred for 10 min and a solution of NEt_3 (3.71 mL, 26.5 mmol) and CH_2Cl_2 (10 mL) was added. After warming to rt, the reaction mixture was stirred for 1 h and then quenched with NH_4Cl ((sat, aq.) 30 mL). The aqueous phase was extracted with ether (100×3 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 1.30 g (97%) of 4,4-dimethyl-5-methoxymethoxy-6-heptenal as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 9.75 (t, J=1.8 Hz, 1H), 5.66 (ddd, J=17.0, 10.4, 8.3 Hz, 1H), 5.28 (ddd, J=10.0, 1.9, 0.5 Hz, 1H), 5.17 (ddd, J=17.2, 1.8, 0.6 Hz, 1H),

[†] *Z* multiplet overlapped with *E*.

4.64 (d, J=6.9 Hz, 1H), 4.45 (d, J=6.7 Hz, 1H), 3.64 (d, J=8.3 Hz, 1H), 3.34 (s, 3H), 2.48–2.38 (m, 2H), 1.71 (ddd, J=13.9, 10.1, 6.2 Hz, 1H), 1.54 (ddd, J=13.9, 10.5, 6.1 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 202.9, 134.6, 119.7, 93.8, 84.1, 55.8, 39.0, 36.3, 30.4, 23.3, 23.2; IR (CCl_4) 2956, 2888, 1709, 1042 cm^{-1}.

3.1.6. Preparation of 3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene. To a solution of CBr_4 (4.0 g, 12.0 mmol), PPh_3 (6.3 g, 24.0 mmol), and CH_2Cl_2 (20 mL) at 0°C was added a solution of 4,4-dimethyl-5-methoxymethoxy-6-heptenal (1.2 g, 6.0 mmol) and CH_2Cl_2 (20 mL) over 0.5 h. The reaction mixture was diluted with hexanes (160 mL), filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate 20:1) gave 1.60 g (75%) of 3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.33 (t, J=7.5 Hz, 1H), 5.66 (ddd, J=17.2, 10.3, 8.4 Hz, 1H), 5.26 (dd, J=10.4, 0.5 Hz, 1H), 5.16 (dd, J=17.5, 1.0 Hz, 1H), 4.66 (d, J=6.8 Hz, 1H), 4.47 (d, J=6.8 Hz, 1H), 3.64 (d, J=8.3 Hz, 1H), 3.36 (s, 3H), 2.10–2.00 (m, 2H), 1.43 (ddd, J=13.5, 11.0, 5.5 Hz, 1H), 1.31 (ddd, J=13.5, 11.5, 6.0 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 139.2, 134.8, 119.5, 93.9, 88.3, 84.1, 55.8, 36.7, 36.4, 27.9, 23.2, 23.0; IR (CCl_4) 2963, 2888, 1481, 1153, 1042 cm^{-1}.

3.1.7. Preparation of methyl 6,6-dimethyl-7-methoxymethoxy-8-nonene-2-ynoate (43). To a solution of 3-methoxymethoxy-4,4-dimethyl-8,8-dibromo-1,7-octadiene (1.49 g, 4.18 mmol) and THF (20 mL) at −78°C was added BuLi (5.58 mL of a 1.5 M solution in hexane, 8.37 mmol).

After warming to rt and stirring for 1 h, the reaction mixture was cooled to −78°C and methyl chloroformate (0.97 mL, 12.5 mmol) was added. After stirring for 1 h at rt, the reaction was quenched with NH_4Cl ((sat, aq.) 30 mL). The aqueous phase was extracted with ether (100×3 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate 5:1) gave 0.87 g (82%) of **43** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.58 (ddd, J=17.2, 10.4, 8.2 Hz, 1H), 5.21 (dd, J=10.4, 1.9 Hz, 1H), 5.10 (dd, J=17.1, 2.0 Hz, 1H), 4.58 (d, J=6.9 Hz, 1H), 4.38 (d, J=6.9 Hz, 1H), 3.67 (s, 3H), 3.57 (d, J=8.2 Hz, 1H), 3.30 (s, 3H), 2.30 (ddd, J=17.0, 10.4, 6.1 Hz, 1H), 2.21 (ddd, J=17.0, 10.0, 6.1 Hz, 1H), 1.65 (ddd, J=13.6, 10.0, 6.5 Hz, 1H), 1.47 (ddd, J=13.7, 10.8, 6.1 Hz, 1H), 0.84 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 154.0, 134.4, 127.1, 119.6, 93.6, 90.2, 83.6, 72.4, 55.6, 52.3, 36.5, 36.5, 23.0, 13.4; IR (CCl_4) 2963, 2895, 2240, 1721, 1437, 1266 cm^{-1}; HRMS calcd for $C_{14}H_{23}O_4$ (M+H) 255.1598, found 255.1596.

3.1.8. Preparation of methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate. To a solution of **43** (0.82 g, 3.2 mmol) and MeOH (16 mL) was added six drops of HCl (conc.). The reaction mixture was then heated to reflux for 3 h. After cooling to rt, the reaction was quenched with NH_4Cl ((sat, aq.) 15 mL), and extracted with ether (80 mL×3). The extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 0.55 g (82%) of methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.84 (ddd, J=16.7, 10.4, 6.8 Hz, 1H), 5.21 (d, J=16.8 Hz, 1H), 5.17 (d, J=10.2 Hz, 1H), 3.72 (d, J=6.5 Hz, 1H), 3.68 (s, 3H), 2.33 (ddd, J=16.8, 10.2, 6.0 Hz, 1H), 2.30 (ddd, J=16.8, 10.2, 6.0 Hz, 1H), 1.69 (ddd, J=13.8, 10.2, 6.6 Hz, 1H), 1.56 (d, J=3.6 Hz, 1H), 1.53 (ddd, J=13.8, 10.2, 6.2 Hz, 1H), (m, 1H), 0.82 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 154.2, 137.4, 116.9, 90.5, 79.4, 72.5, 52.4, 37.0, 36.4, 22.6, 22.3, 13.7; IR (CCl_4) 3537, 2963, 2882, 2246, 1721 cm^{-1}; HRMS calcd for $C_{12}H_{19}O_3$ (M+H) 211.1339, found 211.1334.

3.1.9. Preparation of methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate (39). To a solution of methyl 6,6-dimethyl-7-hydroxy-8-nonene-2-ynoate (1.2 g, 5.71 mmol) and CH_2Cl_2 (20 mL) was added PCC (2.46 g, 10.4 mmol). After 3 h, ether (20 mL) was added to the reaction and the mixture was filtered. Concentration and flash chromatography (hexanes/ethylacetate 3:1) gave 1.0 g (80%) of **39** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.72 (dd, J=16.8, 10.2 Hz, 1H), 6.30 (dd, J=16.9, 2.1 Hz, 1H), 5.63 (dd, J=10.3, 2.1 Hz, 1H), 3.68 (s, 3H), 2.19 (m, 2H), 1.84 (m, 2H), 1.12 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 202.5, 154.0, 130.2, 129.2, 89.0, 72.9, 52.4, 45.8, 36.8, 23.6, 14.3; HRMS calcd for $C_{12}H_{17}O_3$ (M+H) 209.1178, found 209.1169.

3.1.10. Preparation of [methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate] dicobalt hexacarbonyl complex (44). A solution of **39** (0.212 g, 1.02 mmol) and ether (1 mL) was added to a solution of dicobalt octacarbonyl (0.348 g, 1.02 mmol) and ether (6 mL) at rt. After 2 h the mixture was concentrated. Flash chromatography (hexanes/ethyl acetate 7:1) gave 0.46 g (92%) of **44** as a dark-red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.80 (bs, 1H), 6.36 (d, J=15.6 Hz, 1H), 5.68 (bs, 1H), 3.82 (s, 3H), 2.68 (s, 2H), 1.90 (s, 2H), 1.20 (s, 6H); IR (CCl_4) 2925, 2104, 2073, 2042, 1709, 1234 cm^{-1}; HRMS calcd for $C_{18}H_{17}O_9Co_2$ (M+H) 494.9537, found 494.9536.

3.1.11. Preparation of [1-methoxy-2-ethyloxycarbonyl-4-(7′-ethyloxycarbonyl-5′-heptyn-2′,2′-dimethyl-1′-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene] dicobalt hexacarbonyl complex (45) and (46). A solution of **1** (0.02 g, 0.088 mmol) and DMF (0.4 mL) was added to a slurry of NaH (0.0026 g, 0.088 mmol) DMF (0.1 mL) at 0°C. After stirring for 0.5 h, a solution of [methyl 6,6-dimethyl-7-oxo-8-nonene-2-ynoate] dicobalt hexacarbonyl complex **44** (0.054 g, 0.11 mmol) and DMF (0.2 mL). The reaction mixture was quenched with $NaHCO_3$ ((sat, aq.) 0.5 mL) after 1 h. The mixture was extracted with ethyl acetate (3×10 mL), the extracts were dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate 3:1) gave 0.02 g (32%) of **45** and 0.012 g (19%) of **46** as red oils. **45**: IR (CCl_4) 2938, 2098, 2067, 2036, 1709, 1227 cm^{-1}; HRMS calcd for $C_{29}H_{31}O_{14}$ Co_2(M+H) 721.0378, found 721.0369.**46**: IR (CCl_4) 2956, 2104, 2067, 2042, 1715, 1234 cm^{-1}. HRMS calcd for $C_{29}H_{31}O_{14}$ Co_2 (M+H) 721.0378, found 721.0369.

3.1.12. Preparation of 1-methoxy-2-ethyloxycarbonyl-4-(7′-ethyloxycarbonyl-5′-heptyn-2′,2′-dimethyl-1′-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene. To a solution of **45** (13 mg, 0.018 mmol) and CH_2Cl_2 was added

TMANO (13 mg, 0.18 mmol). The mixture was concentrated after 1 h. Flash chromatography (hexanes/ethyl acetate 5:1) gave 5 mg (64%) of 1-methoxy-2-ethyloxycarbonyl-4-(7′-ethyloxycarbonyl-5′-heptyn-2′,2′-dimethyl-1′-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.13 (d, J=5.8 Hz, 1H), 6.02 (d, J=5.8 Hz, 1H), 4.58 (dd, J=11.5, 1.5 Hz, 1H), 4.13 (m, 2H), 3.73 (s, 3H), 3.28 (s, 3H), 3.13 (dd, J=13.0, 4.0 Hz, 1H), 2.33 (ddd, J=17.0, 10.0, 5.5 Hz, 1H), 2.27 (ddd, J=17.0, 10.0, 5.5 Hz, 1H), 2.04 (ddd, J=15.5, 12.5, 12.5 Hz, 1H), 1.95 (ddd, J=14.0, 10.0, 6.0 Hz, 1H), 1.82 (ddd, J=13.5, 3.5, 1.5 Hz, 1H), 1.63 (ddd, J=14.0, 10.5, 6.0 Hz, 1H), 1.54 (s, 3H), 1.25 (t, J= 7.1 Hz, 3H), 1.11 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 211.8, 209.2, 171.1, 154.2, 136.3, 129.6, 116.8, 91.9, 89.6, 72.8, 61.0, 56.3, 55.1, 52.5, 51.0, 47.8, 36.6, 28.6, 24.8, 22.5, 21.0, 14.3, 14.1; HRMS calcd for $C_{23}H_{31}O_8$ (M+H) 435.2019, found 435.2018.

3.1.13. Preparation of 1-methoxy-2-ethyloxycarbonyl-4-(7′-ethyloxycarbonyl-5′-heptyn-2′,2′-dimethyl-1′-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene (48). To a solution of **46** (9 mg, 0.0125 mmol) and CH_2Cl_2 was added TMANO (9 mg, 0.125 mmol). After 1 h the reaction mixture was concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 3.5 mg (65%) of **48** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 6.08 (d, J=5.7 Hz, 1H), 5.74 (d, J=5.7 Hz, 1H), 5.72 (dd, J=11.2, 1.9 Hz, 1H), 4.29–4.10 (m, 2H), 3.72 (s, 3H), 3.29 (s, 3H), 2.99 (dd, J=4.7, 2.2 Hz, 1H), 2.26 (ddd, J=9.4, 6.7, 2.7 Hz, 2H), 2.05 (ddd, J=15.9, 11.2, 4.8 Hz, 1H), 1.97 (ddd, J=13.9, 9.3, 6.7 Hz, 1H), 1.76 (dt, J=15.9, 2.2 Hz, 1H), 1.63 (partially obscured ddd, J=13.6, 9.8, 6.2 Hz, 1H), 1.54 (s, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.11 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 213.0, 210.1, 171.8, 155.0, 137.4, 130.1, 116.2, 92.8, 89.8, 73.0, 60.9, 53.0, 52.5, 51.2, 49.0, 48.0, 36.5, 28.0, 24.6, 22.3, 21.0, 14.4, 14.2; IR (CCl_4) 2963, 2240, 1728, 1264 cm^{-1}; HRMS calcd for $C_{23}H_{31}O_8$ (M+H) 435.2019, found 435.2018.

3.1.14. Preparation of acetate (50). A solution of 1-methoxy-2-ethyloxycarbonyl-4-(7′-ethyloxycarbonyl-5′-heptyn-2′,2′-dimethyl-1′-carbonyl)-5-oxo-6-methyl-[4.2.1]-9-oxabicyclic-7-nonene (16 mg, 0.037 mmol) and DMF (1.2 mL) was added to a slurry of KH (4.4 mg, 0.11 mmol) and DMF (0.3 mL) at 0°C. The reaction mixture was immediately warmed to rt. After 1 h, DMAP (4.5 mg, 0.037 mmol) and Ac_2O (11 mg, 0.074 mmol) were added. After another 1 h, the reaction mixture was poured into phosphate buffer (pH 7.5). The aqueous phase was extracted with CH_2Cl_2, the extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 8.5 mg (50%) of enol acetate **50** as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.28 (d, J=6.0 Hz, 1H), 5.96 (d, J=6.0 Hz, 1H), 4.20 (q, J=7.0 Hz, 2H), 3.67 (s, 3H), 3.13 (s, 3H), 2.90 (dd, J=11.3, 1.2 Hz, 1H), 2.71 (dd, J=13.5, 1.5 Hz, 1H), 2.43–2.39 (m, 2H), 2.29 (s, 3H), 2.27 (dd, J=13.5, 11.5 Hz, 1H), 1.91–1.88 (m, 2H), 1.57 (s, 3H), 1.31 (t, J=7.1 Hz, 3H), 1.19 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 202.6, 172.8, 167.9, 164.8, 155.5, 147.3, 135.8, 135.4, 127.9, 118.7, 118.1, 90.5, 60.7, 52.3, 50.4, 50.3, 40.7, 35.8, 28.8, 27.1, 24.2, 24.1, 23.5, 21.3, 14.2; IR (CCl_4) 2938, 1789, 1734, 1672, 1073 cm^{-1}; HRMS calcd for $C_{25}H_{33}O_9$ (M+H) 477.2125, found 477.2132.

3.1.15. Preparation of 50 and 47 from the coupling of 1 with 39. A solution of **1** (22 mg, 0.097 mmol) and DMF (0.4 mL) was added to a slurry of KH (3.9 mg, 0.097 mmol) and DMF (0.4 mL) at 0°C. After 0.5 h, a solution of **39** (22 mg, 0.107 mmol) and DMF (0.5 mL) was added over 1 h. The resulting mixture was warmed to rt and stirred for an additional 0.5 h. To the mixture was added DMAP (11.8 mg, 0.097 mmol) and Ac_2O (0.02 mL, 0.2 mmol). After 0.5 h, the reaction was poured into phosphate buffer (pH 7.5). The aqueous phase was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes/ethyl acetate 2:1) gave 10 mg (22%) of **47** and 9 mg (20%) of enol acetate **50** as colorless oils. **47** (mixture of diastereomers): major isomer: ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm) 6.22 (d, J=5.8 Hz, 1H), 6.16 (d, J=5.8 Hz, 1H), 5.79 (s, 1H), 4.17–4.10 (m, 2H), 3.73–3.70 (m,1H?), 3.69 (s, 3H), 3.29 (s, 3H), 3.20 (dd, J=13.1, 2.8 Hz, 1H), 2.65 (ddt, J=17.8, 6.7, 2.2 Hz, 1H), 2.39 (dd, J=15.3, 13.1 Hz, 1H), 1.75 (?), 1.48 (s, 3H), 1.25 (t, J= 7.2 Hz, 3H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 214.3, 209.0, 171.0, 166.3, 157.9, 135.4, 130.7, 120.2, 117.5, 92.4, 74.4, 61.0, 51.9, 51.3, 51.2, 44.4, 34.0, 32.5, 26.1, 24.2, 22.5, 21.1, 14.1; IR (CCl_4) 2987, 2944, 1734, 1709, 1178 cm^{-1}; HRMS calcd for $C_{23}H_{30}O_8$ (M+H) 435.2019, found 435.2027.

Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.14 (d, J=5.8 Hz, 1H), 6.04 (d, J=5.8 Hz, 1H), 5.52 (s, 1H), 4.13 (m, 2H), 3.68 (s, 3H), 3.35 (m, 1H), 3.27 (s, 3H), 2.88 (m, 1H), 2.33–2.30 (m, 2H), 2.25 (dd, J=15.0, 4.2 Hz, 1H), 1.92 (dd, J=15.0, 12.6 Hz, 1H), 1.67 (dd, J=6.6, 4.8 Hz, 1H), 1.45 (s, 3H), 1.27 (t, J=7.2 Hz, 3H), 1.16 (s, 3H), 1.12 (s, 3H).

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22. We do not have a good explanation for the lack of **47** under these reaction conditions.
23. Ring expanded product **40** was unstable to chromatography. Enol acetate **50** was much more stable.
24. Attempts to carry out the ring expansion using the corresponding bis-activated diene resulted in the formation of the spiro compound analogous to **47**.
25. When NaH was used as the base, we isolated **40** in 10% yield.