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High Temperature Radical Cyclization Anomalies in the Tandem Enediyne-*Bis*-Radical Cyclization

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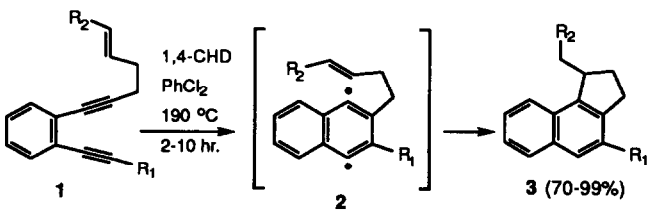
Abstract: Previous reports have shown that the thermolysis of aromatic enediynes containing radical accepting tethers will undergo tandem enediyne-radical cyclizations. Herein will be reported several examples of the tandem enediyne-*bis*-radical cyclization where non-radical accepting tethers will undergo cyclizations to aromatic rings to result in cyclization products. Most of the unusual products result from 1,5-hydrogen abstraction, followed by either β-elimination or radical addition to the aromatic ring. The synthesis of the aromatic enediynes, mechanisms, as well as, the thermolysis products are described.

The chemistry and biological activity of the enediyne antitumor antibiotics continue to attract widespread attention in the scientific community.[1] These naturally occurring enediynes such as Esperamicin,[2] Calicheamicin[3] and Dynemicin[4] undergo a Bergman cyclization[5,6] to yield a biradical which can cleave DNA by aryl radical abstraction of hydrogen from the sugar backbone of DNA. The use of aryl radicals generated from a Bergman process in radical cyclization reactions is an area that has been exploited by our research group. For example, the Bergman cyclization of **1** yields biradical **2** which can undergo a radical cyclization with a wide variety of radical acceptors to yield tricycles such as **3** in excellent yields (Scheme 1).[7] Herein we report several examples of the tandem enediyne-*bis*-radical cyclization which include several examples of acyl and alkyl radicals which undergo an addition to an aromatic ring.

Scheme 1

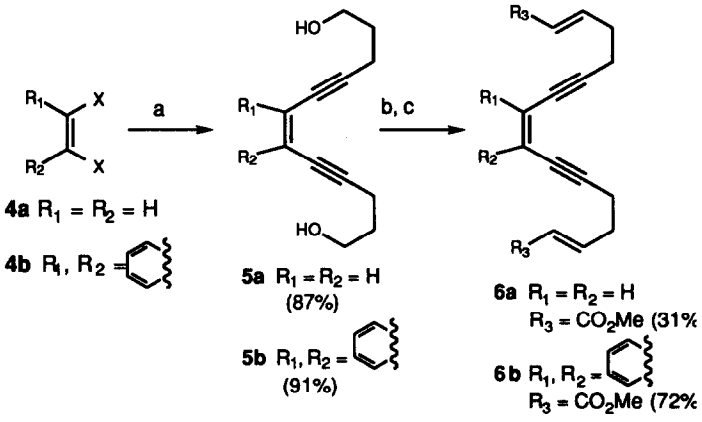


R_1 = H, $CH_2OTBDMS$
CH_2OH
R_2 = CO_2R, CH_2OH
OAc, OMe

Preparation of Enediynes

The synthesis of precursors **6a** and **6b** was straightforward. The present study involved both aromatic and non-aromatic enediynes. Non-aromatic enediyne **6a** was prepared from 1,2-dichloroethylene **4a** which was subjected to a modified Castro-Stevens coupling[8] with 2 equiv 4-pentynol to give diol **5a** in 87% yield (Scheme 2). PCC oxidation followed by a Roush-Masamune variation of the Horner-Emmons reaction[9] provided **6a** in 31% yield over two steps. Aromatic enediyne **6b** was synthesized in an analogous fashion starting from 1,2-diiodobenzene and 2 equiv 4-pentynol which yielded diol **5b** (91%). Swern oxidation followed by a Horner-Emmons reaction gave **6b** in 72% yield over two steps.

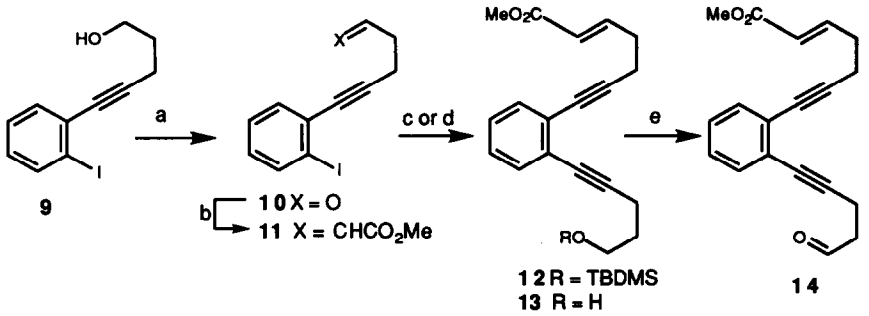
Scheme 2



a) 2 equiv 4-pentynol (for **5a** and **5b**), 0.017 equiv $(PPh_3)_4Pd$, 0.04 equiv CuI, PhH, 40 °C; b) 3.5 equiv PCC, CH_2Cl_2 (for **6a**) or ClCOCOCl, DMSO, NEt_3 (for **6b**); c) 2.5 equiv trimethylphosphonoacetate, 2.5 equiv DBU, 4 equiv LiCl, CH_3CN.

The mixed enediyne **14** was prepared from 1,2-diiodobenzene by a modified Castro-Stevens coupling with 4-pentynol to give the *mono* coupled product **9**. Oxidation of **9** with PCC provided aldehyde **10** (77%) which was immediately subjected to a Horner-Emmons reaction to yield the α,β-unsaturated ester **11** (96%). A second modified Castro-Stevens coupling with the t-butyldimethylsilyl (TBDMS) protected 4-pentynol gave **12** (83%). Enediyne **13** was synthesized by a modified Castro-Stevens coupling of **11** with 1 equiv 4-pentynol (83%) followed by a PCC oxidation to give **14** (55%).

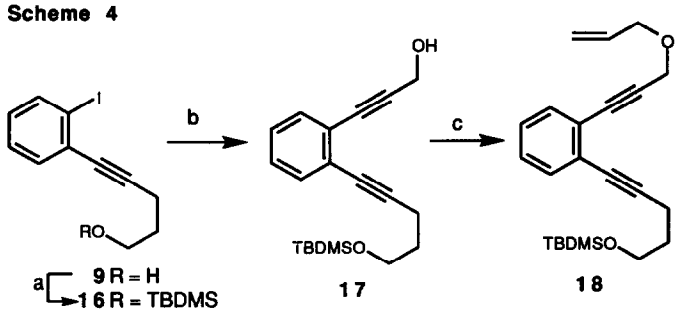
Scheme 3



a) PCC, Celite, CH_2Cl_2 (77%); b) 2.5 equiv trimethylphosphonoacetate, 2.5 equiv DBU, 4 equiv LiCl, CH_3CN (96%); c) 2 equiv TBDMS-4-pentynol, 0.017 equiv $(PPh_3)_4Pd$, 0.04 equiv CuI, PhH, 40 °C (78%); d) 2 equiv 4-pentynol, 0.017 equiv $(PPh_3)_4Pd$, 0.04 equiv CuI, PhH, 40 °C (83%); e) PCC, Celite, CH_2Cl_2 (55%)

The synthesis of enediyne **18**, started with *mono* coupled alcohol **9**,[7d] which was protected as its TBDMS ether to give **16** in 87% yield. A modified Castro-Stevens coupling with propargyl alcohol yielded **17** (92%). Subsequent allylation of the propargylic alcohol gave enediyne **18** (75%).

Scheme 4



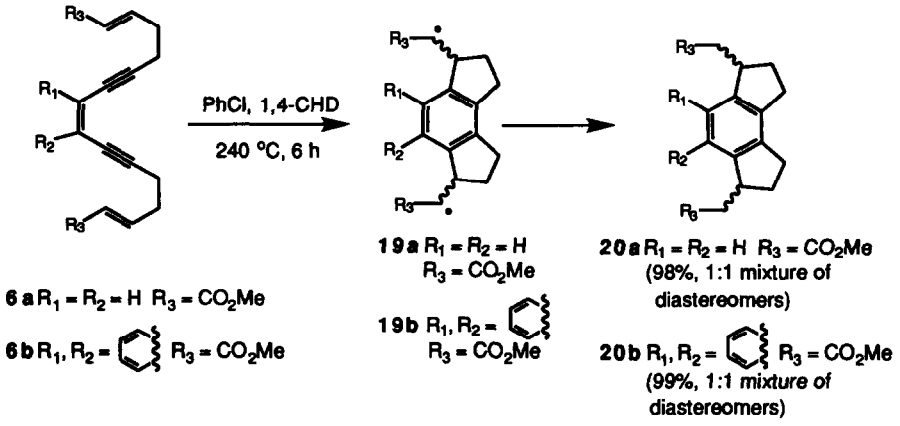
a) TBDMSCl, DMF, imidazole (87%); b) 2 equiv propargyl alcohol, 0.017 equiv $(PPh_3)_4Pd$, 0.04 equiv CuI, PhH, 40 °C (92%); c) NaH, allyl bromide (75%).

Thermal Cyclization of Enediynes

The thermolysis of **6a** at 240 °C in the presence of 1,4-cyclohexadiene yielded the tricycle **20a** in 98% as a 1:1 mixture of diastereomers (Scheme 5). A similar reaction utilizing the aromatic enediyne **6b** also proceeded in excellent yield to give **20b** (99%, 1:1 mixture of diastereomers). Unfortunately, when the olefin substituent was changed from an ester to a methoxy group or to a hydroxymethyl group only polymerization and decomposition were observed. A rationale for the success of **6a** and **6b** vs. the enol acetate and allylic alcohol is that the high temperature required to effect an enediyne cyclization also causes sidechain decomposition in in the latter compounds, while the α,β–unsaturated esters of **6a** and **6b** are stable under these conditions. Upon the formation of the unstable aromatic biradicals from the enediyne cyclization, there

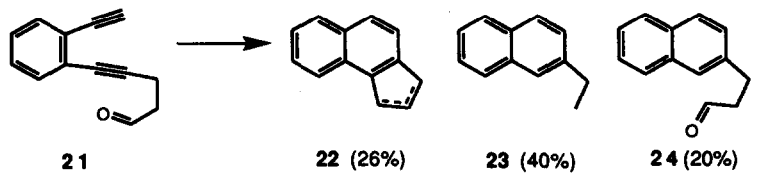
proceeds a rapid radical cyclization to form the *bis* α-carbomethoxy substituted biradicals **19a** and **19b**. These biradicals are stabilized by the electron withdrawing groups and quenched with 1,4-CHD to form the products **20a** and **20b**.

Scheme 5



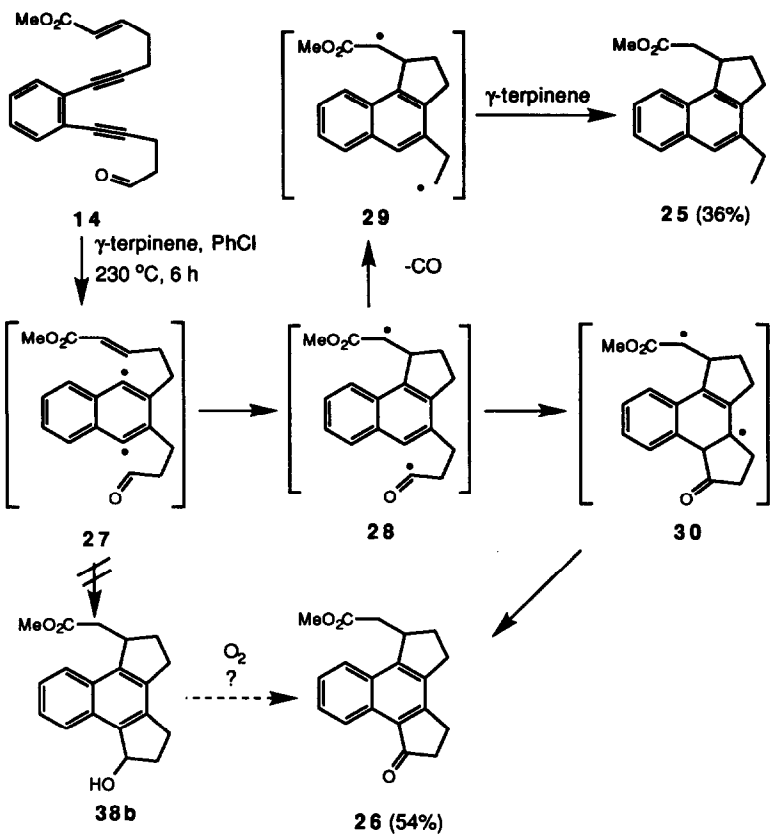
Previous work in our laboratories has demonstrated that the tandem enediyne-radical cyclization onto aldehyde acceptors (such as with enediyne **21**)[10,11] yields a mixture of products arising from a radical cyclization of the aryl radical onto the aldehyde to form **22** (26%), an intramolecular 1,5-hydrogen shift to form an acyl radical which either decarbonylated to form **23** (40%), or was quenched by a hydrogen source to form **24** (20%) (Scheme 6).[12] In a surprising result, the tandem enediyne-radical cyclization of **14**, which also contained an aldehyde acceptor, yielded a product mixture which contained the tricycle **25** (36%) and the tetracycle **26** (54%) (Scheme 7).

Scheme 6



21 **22** (26%) **23** (40%) **24** (20%)

Scheme 7

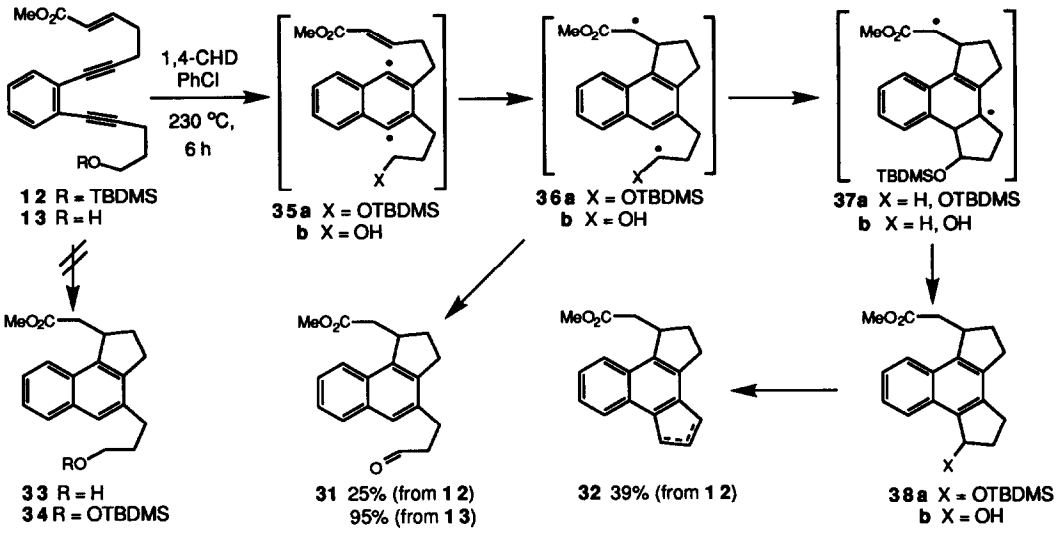


A mechanism explaining the formation of **25** and **26** proceeds through the biradical **27** which results from the enediyne cyclization of **14** (Scheme 7). While one of the aryl radicals undergoes a standard radical cyclization onto the α,β-unsaturated ester, the other aryl radical undergoes a 1,5-hydrogen shift to give the biradical **28**. This intermediate can either lose carbon monoxide to form biradical **29** which abstracts hydrogen from γ-terpinene to yield tricycle **25**, or the acyl radical can intramolecularly add to the aromatic ring to form **30** followed by disproportionation to give **26**. The transformation of **30** to **26** presumably requires a hydrogen source such as γ-terpinene to assist in the disproportionation step, since without it, the thermolysis of **14** leads only to polymerization. An alternative explanation for the formation of **26** involves an air oxidation of the desired product **38c**.[13] This mechanism is less probable because we have never seen air oxidation in compounds such as **38c**; we have only observed elimination (see scheme 6).[12] The observation of tricycle **25** is in accord with our previous results, but the sequence of reactions leading to **26** is unusual. In the tandem enediyne-*mono*-radical cyclization onto aldehydes, the radical corresponding to the acyl radical in **28** undergoes only decarbonylation or hydrogen abstraction rather than addition to the aromatic ring. What is

noticeably absent is any product such as **38b** which would come from a 5-*exo* cyclization of an aryl radical onto an aldehyde acceptor.

In the study of the tandem enediyne-*mono*-radical cyclization, it was surprising to find that the thermolysis of enediyne **12** did not lead to the expected product **33**, but instead gave a mixture of **31** and **32** in 25% and 39% yields respectively (Scheme 8).

Scheme 8



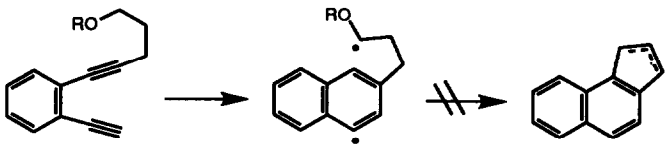
Mechanistically, the enediyne cyclization of **12** leads to the biradical **35a** which does a radical cyclization and 1,5-hydrogen abstraction to give biradical **36a** which suffers one of two fates (Scheme 8). First, the α-siloxy radical in **36a** undergoes a radical cyclization onto the aromatic ring to give **37a** followed by disproportionation to give **38a**. A thermally induced elimination of the siloxy group followed by isomerization of the resulting double bond yields the tetracycle **32** as a mixture of olefin regioisomers. A similar thermal elimination of water was observed in the tandem enediyne-*mono*-radical cyclization using an aldehyde as a radical acceptor. Alternatively, the same α-OTBDMS radical in **36a** extrudes the silyl radical to yield the oxidation product **31**. A β-elimination of the silyl radical is not unexpected given the elevated temperatures of this reaction.

To see whether these tetracyclic products such as **32** could be formed in similar substrates, enediyne **13** was thermolyzed. The only products formed arose from a β-elimination of the hydrogen atom from **36b** to give the aldehyde **31** in 95% yield (Scheme 8). The tandem enediyne-radical cyclization product **34** was not formed and products arising from an addition of the α-hydroxy radical in **36b** to the aromatic ring to give products derived from **38b** were not observed.

In a mechanistic probe of these radical cyclization anomalies, **39** and **40** were subjected to similar thermolysis conditions. A complex reaction mixture resulted which did not show any formation of **22**

(Scheme 9). Apparently, a cyclization and disproportionation pathway similar to that leading to **32** needs to be preceded by a diyl stabilization which results from the 5-*exo* radical cyclization to give the α-carbomethoxy stabilized radical such as that seen in **36**. The aromatic biradicals **41** and **42** must be too unstable, therefore they lead to only to polymerization products.

Scheme 9



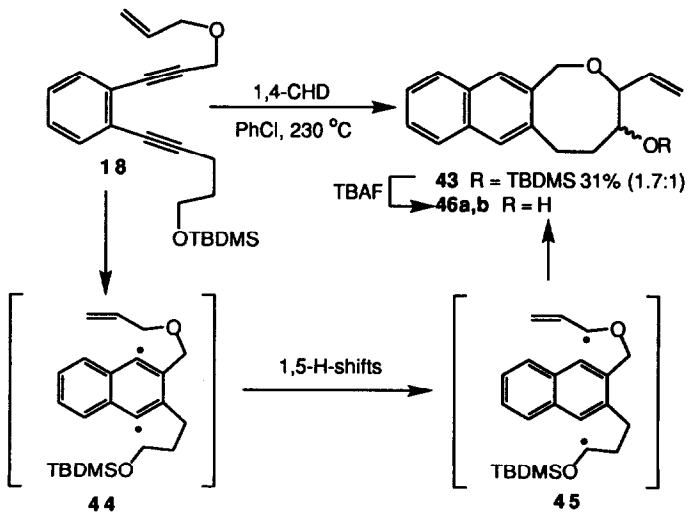
39 R = H
40 R = TBDMS

41 R = H
42 R = TBDMS

22

Enediyne **18** was prepared and thermolyzed in an attempt to find another compound where the non-olefinic sidechain would undergo an addition to the aromatic ring. Thermolysis of **18** unexpectedly yielded the eight-membered ether **43** in 31% as a 1.7:1 mixture of diastereomers (Scheme 10). Due to difficulties in separating both diastereomers, desilylation yielded the two diastereomers **46a** and **46b** which were easily separable. Presumably **18** cyclizes to form the biradical **44** which undergoes two 1,5-hydrogen shifts to give the stabilized biradical **45** followed by recombination to yield the cyclic ether **43**. The allylic portion of the biradical **45** is stable and traps the unstable α-OTBDMS radical before it has a chance to β-eliminate a silyl group, to add to the aromatic ring or to polymerize. An analogous eight-membered ring formation was observed by Bergman in his initial studies on enediyne cyclizations.[5]

Scheme 10



18

44

45

In summary, the tandem enediyne-radical cyclization is an unpredictable reaction. However, in some cases it leads to clean polycyclic products in synthetically useful yields. One of the requirements for the success of this reaction is that the radical acceptor sidechains must be able to withstand the high reaction temperatures and that the radicals that result are stabilized. In several examples, anomalous products were observed where the formation of two five-membered rings occurred when there was only one radical accepting tether. Most of the unusual products resulted from 1,5-hydrogen shifts, addition of radicals to aromatic rings, decarbonylations and intramolecular radical couplings. Although in theory, some of these anomalous reactions could be used for the preparation of five-membered and eight-membered ring polycycles, the unpredictability of these processes severely limits their usefulness. Since these reactions occur at elevated temperatures, methods are being explored to lower the temperatures so the tandem enediyne-radical cyclization can be successfully used in the preparation of natural products.

EXPERIMENTAL SECTION

General. Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula. Thermolysis at temperatures of less than 210 °C were carried out in an #11 Ace screw top joint which had been sealed by a glass blower. Reactions requiring temperatures of >210 °C were carried out in a thick walled glass tube which had been sealed under high vacuum and then placed in a stainless steal reaction vessel which had been machined by our in house machine shop. Reaction mixtures were deoxygenated with slow bubbling of dry N_2 for 20-30 min.

All solvents were distilled before use: dichloromethane from calcium hydride; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl and triethylamine from calcium hydride. Chloro- and dichlorobenzene were purified by passing through basic alumina. Reagents were purchased from Aldrich Chemical Co., Pfaltz and Bauer, Lancaster and Jannsen Chemica and were used without further purification. Flash columns were packed with 230-400 mesh silica gel (EM Science).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Varian XL-300 or Varian Unity-300 (300 MHz) instrument. The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane or upfield from $CHCl_3$. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz on a Varian XL- 300 or Varian Unity-300 instrument and are reported (ppm) relative to the center line of a triplet at 77.0 ppm for $CDCl_3$. Infrared (IR) spectra were measured with a Perkin-Elmer 298 infrared spectrophotometer. Mass spectra were determined on a Finnigan MAT 95 High Resolution Gas Chromatograph/Mass Spectrometer with Finnigan MAT ICIS II operating system.

Preparation of *cis*-dodec-6-ene-4,8-diyne-1,12-diol (5a). To a flame dried 250 mL round-bottomed flask under N_2 was added 110 mL anhydrous benzene, *cis*-dichloroethylene (0.88 g, 9.08 mmol, 0.685 mL), 0.017 equiv tetrakistriphenylphosphine palladium (0) (0.178 g, 0.15 mmol), 0.04 equiv copper (I) iodide (0.069 g, 0.36 mmol), 4.2 equiv n-butyl amine (2.65 g, 36.32 mmol, 3.59 mL), and 2.1 equiv 4-pentynol (1.87 g, 19.5 mmol, 2.07 mL) and the mixture was heated to 40 °C for 24 h. The reaction mixture was filtered through Celite and Florosil with ethyl ether, and concentrated *in vacuo* . The product was purified

via column chromatography with hexanes / ethyl acetate (1 : 1) to yield 1.75 g (87%) as a brown oil. R_f 0.36 hexanes / ethyl acetate (1 : 1); IR (neat) 3346, 2216, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (pentet, 4H, J = 6.5 Hz), 2.46 (t, 4H, J = 6.5 Hz), 3.65 (br s, 2H), 3.70-3.75 (m, 4H), 5.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 31.0, 61.0, 78.8, 96.9, 119.0; HRMS-EI *m/z* calcd for $C_{12}H_{16}O_2$ (M^+) 192.1137, found 192.1144.

Preparation of methyl *trans,cis,trans*-(15-carbomethoxy)pentadec-2,8,14-triene-6,10-diynoate (6a). To a predried 25 mL round-bottomed flask was added **10** (0.247 g, 1.12 mmol), 15 mL CH_2Cl_2, 1 g Celite, and 3.5 equiv PCC (1.01 g, 3.92 mmol), and the reaction was stirred under N_2 for 1.5 hours. The reaction was filtered through Florosil with anhydrous Et_2O and concentrated *in vacuo*. The dialdehyde was purified *via* radial chromatography with hexanes / ethyl acetate (3 : 1) and concentrated *in vacuo*. The purified aldehyde was then carried directly to the next step. To a predried 25 mL round-bottomed flask was added 10 mL CH_3CN, 2.5 equiv trimethylphosphonoacetate (0.509 g, 2.8 mmol, 0.453 mL), 2.5 equiv DBU (0.426 g, 2.8 mmol, 0.384 mL), and 4 equiv LiCl (0.189 g, 4.5 mmol). The aldehyde, in 3 mL CH_3CN, was added in one portion *via* pipet. The reaction was over instantaneously. The reaction was ether / water extracted and the organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified *via* column chromatography with hexanes / ethyl acetate (3 : 1) to yield 0.094 g (31% over two steps) as a yellow oil. R_f 0.45 hexanes / ethyl acetate (3 : 1); IR (neat) 2214, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38-2.47 (m, 4 H), 2.51-2.56 (m, 4H), 3.69 (s, 6H), 5.70 (s, 2H), 5.87 (dt, 2H, J = 15.7, 1.5 Hz), 6.98 (dt, 2H, J = 15.7, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 31.3, 51.4, 79.0, 95.8, 119.0, 121.9, 146.8, 166.6. HRMS-EI *m/z* calcd for $C_{18}H_{20}O_4$ (M^+) 300.1384, found 300.1378.

Preparation of 5-(2-iodophenyl)-4-pentynal (10). To a predried 100 mL round-bottomed flask was added **9**[7d] (1.05 g, 3.5 mmol), 50 mL CH_2Cl_2, 3 g Celite, and 3.5 equiv PCC (2.64 g, 12.3 mmol), and the reaction was stirred under N_2 for 1.5 hours. The reaction was filtered through Florosil with anhydrous Et_2O and concentrated *in vacuo*. The aldehyde was purified *via* silica gel radial chromatography with hexanes / ethyl acetate (3 : 1) and concentrated *in vacuo* and isolated as a yellow oil 0.81 g (77%). R_f 0.73 hexanes / ethyl acetate (3 : 1); IR (neat) 3059, 2233, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.81-2.83 (m, 4H), 6.98 (td, 1H, J = 7.8, 1.8 Hz), 7.30 (td, 1H, J = 7.6, 1.2 Hz), 7.41 (dd, 1H, J = 7.8, 1.6 Hz), 7.83 (dd, 1H, J = 7.6, 1.2 Hz), 9.91 (s, 1H); ^{13}C NMR (75 MHz) δ 12.8, 42.2, 83.6, 92.0, 100.9, 127.6, 127.6, 129.0, 132.3, 138.4, 200.3; HRMS-EI *m/z* calcd for $C_{11}H_9IO$ (M^+) 283.9689, found 283.9693.

Preparation of methyl 7-(2-iodophenyl)hept-2-ene-6-ynoate (11). To a 25 mL round bottom flask charged with 27 mL anhydrous CH_3CN was added 1.5 equiv trimethylphosphonoacetate (0.794 g, 4.05 mmol, 0.71 mL), 1.5 equiv DBU (0.616 g, 4.05 mmol, 0.55 mL) and 2 equiv LiCl (0.228 g, 5.4 mmol). The reaction mixture was stirred for 10 minutes at room temperature, then 1 equiv **10** (0.808 g, 2.7 mmol) in 4 mL CH_3CN was added dropwise to the reaction mixture *via* cannulae / N_2. The reaction was over instantaneously. The reaction mixture was extracted with ether (2 x 25 mL) and washed with saturated

ammonium chloride (1 x 25 mL) and the organics were dried over $MgSO_4$. Purification *via* silica gel radial chromatography on a 2 mm plate with hexanes / ethyl acetate (93 : 3), and concentrated *in vacuo*. yielded 0.90 g of **11** as a yellow oil (96%). R_f 0.43 hexanes / ethyl acetate (3 : 1); IR (neat) 3062, 2234, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.50-2.65 (m, 4H), 3.72 (s, 3H), 5.95 (dt, 1H, *J* =15.6, 1.4 Hz), 6.94 (t, 1H, *J* = 7.3 Hz), 7.08 (dt, 1H, *J* = 15.6, 6.7 Hz), 7.24 (t, 1H, *J* = 7.3 Hz), 7.37 (d, 1H, *J* = 7.6 Hz), 7.79 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz) δ 18.6, 31.1, 51.5, 83.9, 92.4, 100.8, 122.2, 127.6, 128.9, 130.0, 132.4, 138.5, 146.9, 166.8; HRMS-EI *m/z* calcd for $C_{16}H_{14}O_2$ (M^+) 339.9959, found 339.9950.

Preparation of methyl 7-(2-(4-pentyn-1-oxo-5-yl)phenyl)hept-2-ene-6-ynoate (12). To a predried 50 mL round-bottomed flask under N_2 was added 20 mL anhydrous NEt_3, 1 equiv **11** (0.592 g, 1.73 mmol), 0.05 equiv tetrakistriphenylphosphine (0.10 g, 0.086 mmol), 0.1 equiv CuI (0.032 g, 0.176 mmol) and the reaction was allowed to stir for 10 minutes. Then 1 equiv 4-pentynol (0.145 g, 1.73 mmol, 0.171 mL) was added *via* syringe. The reaction mixture was allowed to stir overnight upon which all of the alcohol had been consumed. The reaction mixture was filtered through a 60 mL course fritted funnel and the precipitated ammonium salt was washed with anhydrous Et_2O. The mother liquor was concentrated *in vacuo* and purified by silica gel chromatography with hexanes / ethyl acetate (3 : 1) to yield 0.400 g (78%) as a clear oil. R_f 0.39 hexanes / ethyl acetate (1 : 1); IR (neat) 3447, 3059, 2228, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (pentet, 2H, *J* = 6.7 Hz), 1.98 (s, 1H), 2.47-2.64 (m, 6H), 3.71 (s, 3H), 3.82 (t, 2H, *J* = 6.2 Hz), 5.93 (dt, 1H, *J* = 15.7, 1.5 Hz), 7.07 (dt, 1H, *J* = 15.7, 6.6 Hz), 7.14-7.20 (m, 2H), 7.32-7.37 (m, 2H); ^{13}C NMR (75 MHz) δ 16.2, 18.6, 31.4, 31.4, 51.5, 61.7, 80.0, 80.6, 91.9, 93.2, 122.0, 125.8, 126.0, 127.3, 127.5, 131.8, 132.0, 147.2, 167.0; HRMS-EI *m/z* calcd for $C_{19}H_{20}O_3$ (M^+) 296.1413, found 296.1413.

Preparation of methyl 7-(2-(1-tertbutyldimethylsilyloxy-4-pentyn-5-yl)phenyl)hept-2-ene-6-ynoate (13) Compound **11** (0.129 g, 0.38) was reacted and isolated in a similar manner as in the preparation of **12** with 1.1 equiv tertbutyldimethylsiloxypent-4-yne (0.087 g, 4.2 mmol) to yield 0.114 g **13** (83%) as a brown oil. R_f 0.73 hexanes / ethyl acetate (3 : 1); IR (neat) 3061, 2229, 1728, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.80 (p, 2H, *J* = 6.0 Hz), 2.46-2.62 (m, 6H), 3.70 (s, 3H), 3.75 (t, 2H, *J* = 6.0 Hz), 5.91 (dt , 1H, *J* = 15.7, 1.3 Hz), 7.04 (dt, 1H, *J* = 15.7, 6.4 Hz), 7.14-7.18 (m, 2H), 7.31-7.37 (m, 2H); ^{13}C NMR (75 MHz) δ -5.1,18.3, 18.6, 25.6, 25.8, 31.4, 51.4, 52.3, 80.3, 83.4, 91.4, 92.2, 122.0, 125.2, 125.9, 127.4, 127.9, 132.0, 132.1, 147.0, 166.9; HRMS-EI *m/z* calcd for $C_{21}H_{25}SiO_3$ (M^+ - C_4H_9) 353.1559, found 353.1566.

Preparation of methyl 7-(2-(4-pentyn-1-oxo-5-yl)phenyl)hept-2-ene-6-ynoate (14) Compound **14** (0.081 g) was prepared in a similar manner as **10** and isolated as a yellow oil (55%). R_f 0.38 hexanes / ethyl acetate (3 : 1); IR (neat) 3059, 2231, 1724, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45-2.53 (m, 2H), 2.57-2.61 (m, 2H), 2.62-2.78 (m, 4H), 3.68 (s, 3H), 5.92 (dt, 1H, *J* = 15.7, 1.4 Hz), 7.05 (dt, 1H, *J* = 15.7, 5.5 Hz), 7.13-7.18 (m, 2H), 7.31-7.34 (m, 2H), 9.82 (t, 1H, *J* = 1.3 Hz); ^{13}C NMR (75

MHz) δ 12.8, 18.5, 31.3, 42.4, 51.4, 80.3, 80.3, 91.4, 92.0, 122.0, 125.5, 125.8, 127.4, 127.5, 131.8, 131.9, 146.9, 166.7, 200.5; HRMS-EI *m/z* calcd for $C_{19}H_{18}O_3$ (M^+) 294.1234, found 294.1245.

Preparation of 5-(2-iodophenyl)-1-*tert*-butyldimethylsiloxypent-4-yne (16). To a solution of 5-(2-iodophenyl)pent-4-yn-1-ol (**1**) (250.0 mg, 0.87 mmol) in 1.5 mL DMF was added imidazole (125.0 mg, 1.84 mmol), and *tert*-butyldimethylsilyl chloride (211.0 mg, 1.40 mmol). The reaction mixture was stirred at ambient temperature under N_2 for 3 h, quenched with sat. NH_4Cl, and then extracted with CH_2Cl_2 (20 mL x 3). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* . Purification was achieved *via* silica gel flash chromatography using a 9:1 mixture of hexanes / ethyl acetate to provide **2** (303.0 mg, 87%) as a yellow oil: IR (neat) 3435, 2955, 2361, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (5, 6H), 0.89 (s, 9H), 1.84 (pentet, J = 6.3 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 6.3 Hz, 2H), 6.80 - 7.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 15.9, 18.3, 25.9, 31.6, 61.7, 82.9, 94.3, 101.0, 127.7, 128.7, 130.5, 132.4, 138.6. HRMS-EI *m/z* calcd for $C_{13}H_{16}IOSi$ (M^+ -$C_4H_9^+$) 343.0020, found 342.0017.

Preparation of 5-(2-(1-hydroxypropyn-3-yl)phenyl)-1-*tert*-butyldimethylsiloxypent-4-yne (17). 16. (290.0 mg, 0.724 mmol) was dissolved in 7.0 mL NEt_3, then tetrakis-triphenylphosphinepalladium (0) (17.0 mg, 0.0147 mmol) was added. The mixture was allowed to stir for 5 min after which copper (I) bromide (6.3 mg, 0.022 mmol) was added. The reaction mixture was stirred for an additional 5 min and propargyl alcohol (61.67 mg, 1.10 mmol) was added in one portion *via* syringe. The reaction was stirred over night at r.t. under N_2, then the solvent was removed *in vacuo* and the residue was plugged through silica gel using a 2:1 mixture of hexanes / ethyl acetate. Purification by flash chromatography with a 95:5 mixture of hexanes / ethyl acetate provided **17** (220.0 mg, 92%) as a yellow oil: IR (neat) 3405, 2953, 2249, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.83 (quintet, J = 6.3 Hz, 2H), 2.51 (t, J = 6.3 Hz, 2H), 2.66 (br s, 1H), 3.83 (t, J = 6.3 Hz, 2H), 4.49 (s, 2H), 7.10 - 7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 15.9, 18.3, 25.9, 31.7, 51.4, 61.9, 79.6, 84.2, 91.0, 94.1, 125.1, 126.4, 127.2, 128.0, 131.6, 131.8. HRMS-EI *m/z* calcd for $C_{16}H_{19}O_2Si$ (M^+ -$C_4H_9^+$) 271.1149, found 271.1157.

Preparation of 5-(2-(1-allyloxypropyn-3-yl)phenyl)-1-*tert*-butyldimethylsiloxypent-4-yne (18). To a solution of **17** (180.0 mg, 0.55 mmol) in THF (25.0 mL) was added sodium hydride (132.0 mg, 5.5 mmol) under N_2 and the resulting mixture was allowed to stir at r.t. for 5 min. Allyl bromide (200.0 mg, 143.0 μl, 1.65 mmol) was then added in one portion *via* syringe. The reaction mixture was stirred at r.t. under N_2 for 7.5 h, and then quenched with H_2O. The reaction mixture was extracted twice with diethyl ether (2 x 25 mL), the organic phase was separated and then dried over $MgSO_4$, filtered, and concentration *in vacuo* . Purification was achieved *via* silica gel flash chromatography with a 95:5 mixture of hexanes / ethyl acetate to afford **18** (153.0 mg, 75%) as a yellow oil: IR (neat) 2930, 2230, 1481, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.046 (s, 6H), 0.88 (s, 9H), 1.80 (pentet, J = 7.2, 6.0 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 3.74

(t, J = 6.0 Hz, 2H), 4.16 (ddd, J = 5.7, 1.5, 0.9 Hz, 1H), 4.42 (s, 2H), 5.22 (ddt, J = 10.5, 3.3, 1.5 Hz, 1H), 5.33 (ddt, J = 17.4, 3.3, 1.5 Hz, 1H), 5.93 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 7.15 - 7.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.3, 16.1, 18.3, 25.9, 31.8, 57.9, 61.6, 70.4, 79.4, 85.3, 88.4, 94.2, 117.8, 124.9, 126.6, 127.2. HRMS-EI *m/z* calcd for $C_{23}H_{32}O_2Si$ 311.1467, found 311.1449.

Thermal Cyclization of 6a (20a). (0.008 g, 0.02 mmol) was dissolved in 8 mL dichlorobenzene in a thick walled reaction tube and N_2 was bubbled through the solution for 20 min followed by subsequent addition of 1,4-cyclohexadiene (0.042 g, 0.5 mmol, 0.061 mL) *via* syringe. The reaction tube was sealed under high vacuum and then placed in a steal reaction bomb which was subsequently filled with dichlorobenzene. The bomb was sealed and heated to 245 °C for 3 hours. The crude reaction mixture was plugged through a plug of silica gel with hexanes to remove the dichlorobenzene, then Et_2O to yield 0.0078 g **20** (98%) as an inseparable 1 : 1 mixture of diastereomers. R_f 0.50 hexanes / ethyl acetate (3 : 1); IR (neat) 1736 cm^{-1}. All NMR data is reported as a mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67-1.80 (m, 4H), 2.34-2.45 (m, 8H), 2.67-2.87 (m, 12H), 3.50-3.62 (m, 4H), 3.70 (s, 6H), 3.72 (s, 6H), 6.97 (s, 2H), 6.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6, 29.7, 39.9, 40.0, 41.2, 51.6, 121.3, 121.3, 139.8, 144.3, 144.5, 173.2, 173.2; Diastereomer **1** HRMS-EI-GC *m/z* calcd for $C_{18}H_{22}O_4$ (M^+) 302.9860. found 302.9871; Diastereomer **2** *m/z* calcd for $C_{18}H_{22}O_4$ (M^+) 302.9860, found 302.9889.

Thermal Cyclization of 6b (20b) To a predried reaction vial was added **6b**[7d] (0.067 g, 0.2 mmol), and ≈ 8 mL anhydrous dichlorobenzene. The reaction mixture was degassed with N_2 for 20 minutes, 20 equiv 1,4 cyclohexadiene (0.285 g, 4 mmol, 0.336 mL) were added *via* syringe. The reaction vial was heated to 245 °C for 3 hours, upon which all of the starting material had been consumed by thin layer chromatography. Workup was performed in the usual manner to yield 0.067 g (>99%) as a clear oil. (All analytical data gathered on an inseperable (1 : 1) mixture of diastereomers. Some of the NMR shifts in the ^{13}C are indistinguishable between the two diastereomers R_f 0.6 hexanes / ethyl acetate (3 : 1); IR (neat) 3061, 1718, 1041 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3) δ 2.11 (m, 2H), 2.29-2.45 (m, 4H), 2.75 (dd, 1H, J = 9.6, 3.2 Hz), 2.80 (dd, 1H, J = 9.6, 3.2 Hz), 2.86-2.90 (m, 2H), 2.99-3.17 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 4.10-4.14 (m, 2H), 7.44-7.48 (m, 4H), 7.85-7.89 (m, 4H); ^{13}C NMR (75 MHz) δ 30.0, 31.0, 31.1, 38.7, 38.8, 40.5, 51.7, 124.6, 125.1, 125.2, 129.0, 129.0, 137.7, 137.8, 140.5, 173.4; HRMS-EI *m/z* calcd for $C_{22}H_{24}O_4$ (M^+) 352.1668, found 352.1671.

Thermal cyclization of 14 (25, 26). Compound **14** (0.018 g, 0.06 mmol) was reacted in a similar manner as **6a** using γ-terpinene as the hydrogen source to yield **25** 0.010 g (54%) as a yellow solid and **26** 0.006 g (36%) as a yellow oil. **25** R_f 0.38 hexanes / ethyl acetate (1 : 1); IR (neat) 1734, 1691, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (dddd, 1H, J = 13.7, 7.4, 1.7, 1.2), 2.37-2.54 (m, 2H), 2.75-2.82 (m, 3H), 2.97-3.19 (m, 4H), 3.72 (s, 3H), 4.16-4.24 (m, 1H), 7.52-7.63 (m, 2H), 7.88 (dd, 1H, J = 8.0, 1.7 Hz), 9.21 (dd, 1H, J = 8.0, 1.7 Hz); ^{13}C NMR (75 MHz) δ 24.9, 28.9, 30.9, 36.9, 38.5, 41.1, 51.8, 123.8, 124.9, 126.7, 127.5, 127.7, 128.7, 129.4, 130.7, 137.9, 149.2, 155.5, 172.8, 207.2; HRMS-EI *m/z* calcd

for $C_{19}H_{18}O_3$ (M^+) 294.1252, found 294.1254. **26** R_f 0.74 hexanes / ethyl acetate (1 : 1); IR (neat) 3055, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.7 Hz), 2.12 (dddd, 1H, J = 13.0, 7.4, 1.8, 1.3 Hz), 2.31-2.35 (m, 2H), 2.75 (dq, 2H, J = 7.7, 0.9 Hz), 2.80 (ddd, 1H, J = 15.3, 3.1, 0.9 Hz), 2.94-3.12 (m, 2H), 3.72 (s, 3H), 4.10-4.17 (m, 1H), 7.35-7.45 (m, 2H), 7.50 (s, 1H), 7.77-7.81 (m, 2H); ^{13}C NMR (75 MHz) δ 14.1, 26.7, 29.7, 30.7, 38.7, 40.5, 51.7, 123.4, 124.8, 124.9, 125.3, 128.2, 130.8, 133.6, 138.7, 140.3, 140.7, 173.4; HRMS-EI *m/z* calcd for $C_{18}H_{20}O_2$ (M^+) 268.1473, found 268.1468.

Thermal cyclization of 12 (31, 32)

Compound **12** (0.099 g, 0.24 mmol) was reacted in a similar manner as **6a** using 1,4-CHD as the hydrogen source to yield **32** 0.025 g (39%) as a yellow oil and **31** 0.017 g (25%) as a yellow oil. For characterization purposes, the regioisomers of **31** were hydrogenated to give one compound. To a predried three-necked round-bottomed flask was added an excess of Pd/C 10% and the flask was evacuated under high vacuum for 1 hr. To the reaction flask was added a degassed (*via* bubbling N_2) solution of 15 mL ethanol and 1 equiv **31** (0.025 g, 0.09 mmol). Then an atmosphere of H_2 was added to the reaction flask and then stirred for 0.5 hr. The reaction was filtered through a SiO_2 plug, concentrated *in vacuo* and purified *via* silica gel radial chromatography with hexanes / ethyl acetate (95 / 5) to yield 0.021 g (79%) of **31** as a clear oil. **31** R_f 0.72 hexanes / ethyl acetate (3 : 1); IR (neat) 3063, 1736 cm^{-1}; HRMS-EI *m/z* calcd for $C_{19}H_{18}O_2$ (M^+) 278.1307, found 278.1307. **31b** R_f 0.78 hexanes / ethyl acetate (3 : 1); IR (neat) 3059, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (dddd, 1H, J = 13.1, 7.5, 1.2, 1.1 Hz), 2.45 (pentet, 2H, J = 7.4 Hz), 2.32-2.45 (m, 2H), 2.79 (ddd, 1H, J = 15.4, 3.3, 0.8 Hz), 2.92 (ddd, 1H, J = 16.1, 9.0, 1.1 Hz), 3.00 (t, 2H, J = 7.4 Hz), 3.00-3.14 (m, 1H), 3.24 (t, 2H, J = 7.4 Hz), 3.72 (s, 3H), 4.08 -4.16 (m, 1H), 7.39-7.46 (m, 2H), 7.77-7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 30.1, 31.1, 31.3, 32.4, 38.9, 40.5, 51.6, 124.1, 124.7, 125.0, 125.3, 128.5, 129.8, 137.8, 138.0, 139.1, 139.4, 173.4. **32** R_f 0.24 hexanes / ethyl acetate (3 : 1); IR (neat) 3057, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (dddd, 1H, J = 13.2, 7.3, 1.4, 1.4 Hz), 2.26-2.40 (m, 2H), 2.72 (dd, 2H, J = 15.2, 3.2 Hz), 2.79 (m, 2H), 2.92 (ddd, 1H, J = 16.1, 9.2, 1.4 Hz), 2.97-3.09 (m, 3H), 3.66 (s, 3H), 4.04-4.12 (m, 1H), 7.31-7.42 (m, 2H), 7.41 (s, 1H), 7.71-7.75 (m, 2H), 9.81 (t, 1H, J = 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 29.8, 30.7, 38.6, 40.5, 43.7, 51.7, 123.5, 125.1, 125.8, 128.3, 128.4, 133.5, 134.9, 140.1, 141.4, 173.3, 201.5; HRMS-EI *m/z* calcd for $C_{19}H_{20}O_3$ (M^+) 296.1428, found 296.1420.

Thermal cyclization of 13 to yield 31. Compound **13** (0.021 g, 0.07 mmol) was reacted in a similar manner as **6a** using γ-terpinene as the hydrogen source to yield **29** 0.020 g (95%) as a yellow oil.

Thermal cyclization of 18 to yield 43 a,b (80.0 mg, 0.217 mmol) was dissolved in 7.0 mL chlorobenzene in a high pressure tube with Teflon screw cap, the 1.4 cyclohexadiene (0.75 mL, 7.93 mmol) was added *via* syringe, the solution was degassed with dry N_2 for 20 min and the vial was sealed. The high pressure vial was slowly heated up to 217 °C and kept at this temperature for 30 h. Then the reaction mixture was cooled to ambient temperature, the solvent was removed *in vacuo*. Purification by flash chromatography

using a 98:2 mixture of hexanes / ethyl acetate afforded a mixture of **43a** and **43b** (25.0 mg combined, 31%). **43a** and **43b** (25.0 mg, 0.065 mmol) were dissolved in THF (2.0 mL), then TBAF (1.0 M solution in THF, 129.0 µl, 0.129 mmol) was added. The reaction mixture was stirred at r.t. under N_2 for 3 h. The mixture was then plugged through silica gel using a 1:1 mixture of hexanes / ethyl acetate). The solvent was removed *in vacuo* and the residue was subjected to column chromatography with a 95:5 mixture of hexanes / ethyl acetate provided **46a** (3.5 mg, 6% from **18**) as a white solid and **46b** (6.2 mg, 11% from **18**) as a pale yellow solid: **46a** IR (neat) 3400, 2921, 1502, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 1H), 2.35 (m, 1H), 2.58 (m, 1H), 2.80 (m, 1H), 3.51 (m, 1H), 3.70 (br s, 1H), 4.01 (m, 1H), 4.94 (s, 1/2H), 4.89 (s, 1/2H), 5.19 (ddd, J = 10.5, 15, 0.6 Hz, 1H), 5.26 (s, 1/2H), 5.31 (s, 1/2 H), 5.32 (ddd, J = 17.1, 1.5, 0.6 Hz, 1H), 5.90 (ddd, J = 17.1, 10.5, 5.4 Hz, 1H), 7.40 - 7.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 38.7, 70.3, 71.9, 83.8, 115.9, 125.7, 126.1, 127.1, 127.2, 127.2, 129.7, 132.0, 133.5, 134.8, 136.8, 140.4: HRMS-EI m/z calcd for $C_{17}H_{18}O_2$ (M^+ - $C_4H_9^+$) 254.1302 , found 254.1302. **46b**: IR (neat) 3400, 2923, 1503, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (br s, 1H), 1.64 (m, 1H), 3.00 (m, 1H), 2.46 (m, 1H), 3.40 (m, 1H), 3.61 (m, 1H), 3.86 (m, 1H), 4.85 (s, 1/2H), 4.90 (s, 1/2H), 5.17 (d, J = 0.9 Hz, 1/2H), 5.22 (d, J = 0.9 Hz, 1/2H), 5.27 (m, 1H), 5.32 (m, 1H), 5.92 (m, 1H), 7.40 - 7.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0, 38.1, 71.8, 72.0, 81.5, 118.5, 125.7, 126.0, 126.7, 127.1, 127.2, 129.6, 132.0, 133.5, 135.2, 136.5, 140.4; HRMS-EI m/z calcd for $C_{17}H_{18}O_2$ (M^+ - $C_4H_9^+$) 254.1302 , found 254.1299.

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