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Synthesis of Cross-Conjugated Polyenes via Palladium-Catalyzed Oxidative C-C Bond Forming Cascade Reactions of Allenes

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Supporting Information

ABSTRACT: An efficient palladium-catalyzed oxidative C-C bond forming cascade reaction of allenes involving a coupling between an enallene and an allenyne followed by a carbocyclization of the generated Pd-intermediate was developed. This cascade reaction afforded functionalized cross-conjugated polyenes. The enallene is initially activated by palladium and reacts with the allenyne to give the cross-conjugated polyenes.

INTRODUCTION

Stereo- or regiocontrolled selective construction of unsaturated molecular scaffolds through sequential multiple carbon-carbon (C–C) bond formation remains one of the major challenges in organic chemistry. In particular, in cascade reactions, transition metal-catalyzed cyclizations of allenes provide efficient and atom-economical routes to polyunsaturated molecules.¹ Polyenes and oligoenes occur as structural elements in pharmaceutically active compounds and important natural products such as Vitamin A, Lycopene, β -carotene, Lutein, lissoclinolide, and naturally occurring [3]dendralenes etc. (Scheme 1).² The synthesis of such non-aromatic cross-conjugated [3]dendralenes have recently attracted considerable interest.^{3,4}

Scheme 1. Examples of Polyene Compounds



Scheme 2. Examples of Cross-Conjugated Polyenes applications



In recent years, acyclic cross-conjugated polyenes (dendralenes) have been used in diene transmissive Diels-Alder (DTDA) sequences for rapid generation of complex scaffolds bearing multiple stereogenic centers (Scheme 2).⁵ Due to regioselective functionalization of the multiple olefinic sites, other applications of dendralenes are found in the synthesis of ivyane family compounds,⁶ vinylogous Nazarov reactions,⁷ organocatalytic domino cyclizations,8 oxidative reactions9a and metathesis of [3]dendralene-Fe(CO)₃ complexes.^{9b} However, synthetic methods for the preparation of higher cross-conjugated polyenes are quite limited as one step reactions. In this respect, Hopf, Sherburn, Shimizu and their coworkers reported on acyclic cross conjugated polyenes.^{3b,10,11,12} Recently, the Lipshutz group reported a tandem borylation/Suzuki-Miyaura reaction for the synthesis of cross-conjugated polyenes such as [4]- and [5]dendralene, (Scheme 3A).13

Scheme 3. Example of Polyene Synthesis and Proposal for this Work

A) Example of polyene synthesis (ref. 13).



In the past decade, our research group has focused on Pd(II)-catalyzed oxidative carbocyclization reactions of allenes^{1h} and we reported the synthesis of various types of [3]dendralenes via C–C bond formation.^{3d} Compared to intramolecular reactions of allenes, intermolecular couplings of allenes are more challenging and would provide an array of novel conjugated structures. To the best of our knowledge intermolecular cascade reactions between allenes with C-C bond formation for the synthesis of cross-conjugated polyenes have not yet been reported in a one-pot reaction. We therefore decided to study palladium-(II)catalyzed oxidative coupling and carbocyclization reactions of enallenes with allenynes for the synthesis of polyenes (Scheme 3 B). These cross-conjugated polyenes will have the (*Z*)-configuration at the

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middle double bond. The synthesis of the unsubstituted (*E*)-isomer of the corresponding polyene has been reported by Paddon-Row and Sherburn (lower box, Scheme 3B).^{9b}

In this report, palladium-catalyzed intermolecular carbocyclization cascade reactions provide a wide variety of interesting polyene products in high yield and with excellent regio- and stereoselectivity (Scheme 3, B).

RESULTS AND DISCUSSION

In our initial investigation, allenyne 1a and enallene 2a were chosen as the substrates for this challenging transformation (Scheme 4).

Scheme 4. Cascade Reaction



Method A: 2a (2 equiv), Pd(OAc)₂ (5 mol%), BQ (2 equiv), Na₂CO₃ (20 mol%), CH₃CN, 80 °C, 24 h. **Method B:** Pd(OAc)₂ (5 mol%), BQ (20 mol%), Co(salophen) (5 mol%), Na₂CO₃ (20 mol%), CH₃CN, 80 °C, O₂ balloon, 24 h.

Preparation of Starting Materials. All allenynes 1 were prepared from propargyl malonate and the corresponding bromoallenes (Scheme 5). The eneallenes 2 were synthesized from propargyl alcohol derivatives and subsequent 1,3-rearrangement or iron-catalyzed S_N2^2 Grignard reaction (see Supporting Information).

Scheme 5. Preparation of Allenynes



In preliminary experiments, we observed that treatment of **1a** and 1.1 equiv of **2a** with 5 mol% of Pd(OAc)₂ and 1.1 equiv. of benzoquinone (BQ) in DCE at 80 °C gave a 64 % NMR yield of the regio- and stereodefined dendralene derivative **3a** together with 6% of cycloisomerization product **5**.¹⁴ With these inspiring results in hand, we set out to determine the role of the solvent and the Pd(II) catalyst. In screening of various solvents in the presence of Pd(OAc)₂ catalyst (Table 1, entries 1–8), CH₃CN was found to be the best solvent, which delivered the product **3a** in 75% yield without formation of side product **5** (entry 8). Furthermore, palladium catalyst screening showed that Pd(TFA)₂, Pd(PPh₃)₂Cl₂

Table 1. Optimizatiion of the Reaction^a



^aThe reaction was conducted in the indicated solvent (1 mL) at 80 °C using **1a** (0.1 mmol), allene-ene **2a** (0.11 mmol), and BQ (1.1 equiv) in the presence of palladium catalyst (5 mol%). ^bYield determined by ¹H NMR analysis using anisole as the internal standard. ^cThe reaction was run at 60 °C. ^{*a*}**2a** (2.0 equiv) and 2.0 equiv of BQ was used. ^e0.2 equiv of Na₂CO₃ was used. ^{f1} mol% Pd(OAc)₂ was used. ^g**2a** (1.5 equiv) and 1.5 equiv of BQ was used. ^hReaction time 24 h. ⁱEt₃N (20 mol%). ^jACOH (20 mol%).

and Pd(PhCN)₂Cl₂ were not suitable for the reaction and in these cases the allenyne **1a** and enallene **2a** were recovered (Table 1, entries 9-11). However, Pd(acac)₂ catalyzed the reaction efficiently to give the product **3a** in 60 % yield. (Table 1, entry 12). In further optimizations, treatment of **1a** and 1.5 equiv. of **2a** with 5 mol % of Pd(OAc)₂, and 1.5 equiv. of BQ afforded **3a** in 80 % yield (Table 1, entry 13). Increasing **1a** and BQ to 2.0 equiv. each with 1 mol % of Pd(OAc)₂ improved the yield of **3a** to 83% (Table 1, entry 14). The yield of **3a** further increased with the addition 0.2 equiv. of Na₂CO₃ (Table 1, entry 15). With an increased reaction time, we found that treatment of **1a** and 2.0 equiv. of **2a** with 5 mol % of Pd(OAc)₂, and 2.0 equiv. of BQ in CH₃CN at 80 °C for 24 h afforded **3a** in 94 % yield (Method-A) (Table 1, entry 16). Additives such as Et₃N or AcOH did not improve the yield of **3a** (Table 1, entries 17-18).

To demonstrate the necessity of the olefin group in the enallene $2a^{15}$ comparative experiments with allenes lacking the pending olefin were carried out. Without the pending olefin, these reactions, failed to give any cross-conjugated polyene product **3** with method A in CH₃CN (Scheme 6). Thus, when **4a** and **4b** were allowed to react with **1a**, no detectable amounts of **3** were formed.

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4b R = H or **4a** R = \checkmark Complex mixture

These results are in accordance with previous results that the olefin group of 2a is an indispensable assisting/directing group for activation of the allene.¹⁵

In further studies, we investigated Pd(II)-catalyzed aerobic oxidative coupling-carbocyclization reactions between allenyne 1a and enallene 2a for the synthesis of 3a (Scheme 4, Method B). We have previously developed various biomimetic methods for palladium-catalyzed aerobic oxidation of unsaturated substrates.¹⁶ The employment of an aerobic biomimetic oxidation system is an environmentally benign process associated with high atom economy.¹⁷ A key feature of Scheme 4, Method B is the multistep electron transfer occurring, which enables a mild aerobic oxidation. This multistep electron transfer system involves three redox pairs: Pd^{II}/Pd⁰, (BO)/HO, and Co(salophen)^{ox}/Co(salophen. The BQ and Co(salophen) are used as electron transfer mediators (ETMs) and molecular oxygen is applied as the oxidant. We found that reaction of 1a with 2a in the presence of catalytic amounts of Pd(OAc)₂ (5 mol %), BQ (20 mol %) and Co(salophen) (5 mol %) in CH₃CN at 80 °C under molecular oxygen (1 atm) for 24 h afforded 3a in 85 % yield (Method B). Under optimized reaction conditions method A and B, we investigated the scope of the reaction by using different allenyne substrates (Table 2, 1a-1i).

Under standard non-aerobic conditions (Method A), with methyl groups at the terminal position of the allene moiety of the allenenyne or when these methyl groups were changed to cyclohexylidene or t-Bu, Me, the reaction with 2a gave the corresponding cross-conjugated polyene (Table 2, 3a-3d) in good vields (82-90%). The use of either stoichiometric amounts of BO (Method A) or catalytic amounts of BQ under aerobic conditions (Method B) afforded similar results, as shown in Table 2 from the examples 3a and 3d. It is worth noting that the reaction of allenyne substrates 1e-1j (Table 2) having two methyl ethers, a 1,3 dioxane, or two benzyl ethers in place of the two carboalkoxy groups, along with cyclopentylidene or tertiary butyl on the allene moiety afforded the corresponding polyene derivatives (Table 2, 3e-3j) selectively in good yields (70-81%), except for 1i, which afforded 3i in 34 % yield. These results show that the malonate group of the tether is not necessary for a successful transformation.



^aIsolated yield after column chromatography **Method A**: **2a** (2 equiv), $Pd(OAc)_2$ (5 mol%), BQ (2 equiv), Na_2CO_3 (20 mol%), CH₃CN, 80 °C, 24 h. **Method B**: $Pd(OAc)_2$ (5 mol%), BQ (20 mol%), Co(salophen) (5 mol%), Na_2CO_3 (20 mol%), CH₃CN, 80 °C, O₂ balloon, 24 h.

To expand the scope of the method, we tested differently substituted enallenes 2 for the coupling-carbocyclization cascade reaction using allenyne 1a as the co-substrate. Under standard conditions (Method A), a number of functionalized enallenes 2 served as excellent candidates for formation of cross-conjugated polyenes in good yields. When allyl-substituted 2,3-dienoate (2k)was employed, the reaction gave the desired product 3k in 84% yield. Variation of the methyl groups on the allene moiety of 2, e.g. deuterated methyls (21), cyclohexylidene group (2m), cyclopentylidene group (2n) or one methyl presence (20), in the reaction with 1a provided the corresponding cross-conjugated polyenes in good yields (Table 3, 31-30). Moreover, substrates 2p-2s with methyl, ethyl or phenyl substitution on the olefin moiety afforded 3p-3s (Table 3) in moderate to good yields (52-80%). Reaction of substituted enallenes 2t-2v with 1a afforded the desired products 3t-3v in 60-80% yield (Table 3). As shown in Table 3, the reaction also works under aerobic conditions with catalytic amounts of BQ together with Co(salophen) in catalytic amounts (Method B). Thus, reaction of enallenes 2k, 2m-2n with 1a using molecular oxygen as the oxidant afforded products 3k, 3m-3n in 75-85% yields (Table 3).



^{*a*}Isolated yield after column chromatography. **Method A**: **2a** (2 equiv), $Pd(OAc)_2$ (5 mol%), BQ (2 equiv), Na_2CO_3 (20 mol%), CH₃CN, 80 °C, 24 h. **Method B**: $Pd(OAc)_2$ (5 mol%), BQ (20 mol%), Co(salophen) (5 mol%), Na_2CO_3 (20 mol%), CH₃CN, 80 °C, O₂ balloon, 24 h.

To gain further insight into the reaction mechanism, the deuterium kinetic isotope effects (KIE) were studied (eqs. 1-3). An intermolecular competition experiment was conducted at 75 °C using a 1:1 mixture of **2a** and 2**a**-*d*₆ (eq. 1). The products ratio **3a** and 3**a**-*d*₅ was measured as 1.8:1, from which the competitive KIE was determined to $k_{\rm H}/k_{\rm D} = 3.5$ (see Supporting Information). Furthermore, parallel kinetic experiments afforded a KIE ($k_{\rm H}/k_{\rm D}$ from initial rate) value of 3.4 (eqs. 2 and 3) which indicates the initial allenylic C(sp³)-H bond cleavage is involved in the rate-determining step in the reaction. The large competitive KIE ($k_{\rm H}/k_{\rm D} = 3.5$) in C-H bond cleavage requires that this step is the first irreversible step.

Based on the mechanistic studies including the KIE measurements (eqs. 1-3) and our previous work,¹⁸ we propose the mechanism as shown in Scheme 7. The large deuterium isotope effect found for the C-H bond cleavage of the enallene **2a** indicates that the enallene is the compound first activated and not the allenyne.¹⁹ Initial reaction of Pd(OAc)₂ with enallene **2** would give dienyl–Pd^{II} complex *Int*-**2** via allenic C–H bond cleavage of chelated π -complex *Int*-**1** (Scheme 7). This activation of the allene is

triggered by the coordination of the assisting olefin.¹⁵ Vinylpalladium intermediate *Int-2* would then undergo an insertion of the vinylpaladium bond into the alkyne of allenyne **1**, which leads to *Int-3*. Subsequent intramolecular insertion of the vinylpalladium bond of *Int-3* into the allene would lead to (π -allyl)-



palladium intermediate *Int*-4. Subsequent β -hydride elimination via C(*sp*³)–H bond cleavage would provide the cross-conjugated polyene **3** and release Pd⁰ for the next cycle.

Scheme 7. Proposed Mechanism for the Formation of 3



CONCLUSION

We have developed an efficient one-pot Pd^{II}-catalyzed oxidative coupling–carbocyclization cascade reaction for the synthesis of cross-conjugated polyene via intermolecular C–C bond formation and subsequent carbocyclization. This transformation allows highly regio- and stereoselective formation of cross-conjugated

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polyenes using enallene and allenvne under aerobic conditions with environmentally friendly O₂ as terminal oxidant. These important cross-conjugated polyenes, which are readily obtained in a one-pot cascade reaction in the present work are difficult to prepare by other methods. Further studies on the scope of natural product synthesis and other synthetic application of this new cascade reaction are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. For the synthesis of complex molecules, unless otherwise noted, all reagents were used as received from the commercial suppliers. Pd(OAc)₂ was obtained from Pressure Chemicals and used without further purification. Alkynes were commercially available from Sigma Aldrich or Acros. The palladium-catalyzed cascade reactions could be performed without any efforts to exclude moisture. DCE was distilled using CaH₂, Dry THF and toluene, were obtained from VAC Solvent Purifier. The other dry solvents were purchased from Sigma Reactions were monitored using Aldrich thin-layer chromatography (TLC) (SiO₂). TLC plates were visualized with UV light (254 nm) or KMnO₄ stain. Flash chromatography was carried out with 60Å (particle size 35 - 70 µm) normal flash silica gel. NMR spectra were recorded at 400 MHz (1H) or 500 MHz (1H) and at 100 MHz (13C) or 125 MHz (13C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in CDCl₃ (H = 7.26 and C = 77.0 ppm) as internal standard, and coupling constants (J) are given in Hz. HRMS were recorded using ESI-TOF techniques.

25 Allenvnes $1a^{20}$ and $1c^{21}$ were prepared as described in literature. Allenynes 1b and 1d were prepared from propargylmalonate and 26 the corresponding bromoallene in a similar manner.²⁰ All allene 27 derivatives 2a, 2k-2v and 4a-4b were prepared according to a 28 previously described procedures.3d,15,18c,22 29

Representative Procedure for the Synthesis of 1b, and 1d: 30 Synthesis of 1b. To a suspension of NaH (60% in mineral oil, 0.456 g, 11.4 mmol) in anhydrous THF (60 ml) was added a solution of diethyl propargylmalonate (2.0 g, 8.83 mmol) in anhydrous THF (5 ml) at 0 °C. After the addition, the mixture was stirred for another 20 min at room temperature Then a solution of bromoallene (2.6 g, 17.6 mmol) in anhydrous THF (5 ml) was added at room temperature and the resulting mixture was refluxed for 20 h. After the reaction was complete as monitored by TLC, it was cooled to room temperature. Most of the solvent was 38 removed under vacuum, and then the reaction mixture was diluted with 50 mL of Et₂O and quenched with 10 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over Na₂SO₄. Evaporation and column chromatography on silica gel (pentane/ethyl acetate = 30/1) afforded **1b** (0.71 g, 31%)

Characterization of Allenynes 1b and 1d.

 $Diethyl-2-(3-methyl-2\lambda^5-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)ma$ *lonate (1b).* ¹H NMR (400 MHz, CDCl₃) $\delta = 4.94$ (sept, J = 2.9Hz, 1H), 4.25-4.15 (m, 4H), 2.86 (d, J = 2.7 Hz, 2H), 1.95 (t, J =2.7 Hz, 1H), 1.71 (d, J = 2.9 Hz, 6H), 1.25 (t, J = 7.1 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 201.7, 169.2, 100.5, 87.7, 79.6, 70.4, 61.7, 57.5, 24.3, 19.9, 13.9; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₁₅H₂₀O₄Na: 287.1254; Found 287.1263. Isolated yield: 31% (0.71 g), as a liquid. Column chromatography on silica gel (pentane/ethyl acetate = 30/1).

same 1d In the manner was obtained from 1-bromo-3,4,4-trimethyl-1,2-pentadiene.

Dimethyl-2-(prop-2-yn-1-yl)-2-(3,4,4-trimethyl- $2\lambda^5$ -penta-1,2-dien -1-yl)malonate (1d). ¹H NMR (400 MHz, CDCl₃) $\delta = 5.64$ (q, J =2.9 Hz, 1H), 3.74 (d, J = 9.5 Hz, 6H), 2.87 (d, J = 2.7 Hz, 2H), 1.97 (t, J = 2.7 Hz, 1H), 1.71 (d, J = 2.8 Hz, 3H), 1.02 (s, 9H); ${}^{13}C{}^{1}H$ NMR (100 MHz, CDCl₃) $\delta = 200.0, 169.6, 114.2, 89.2,$ 79.5, 70.7, 57.7, 52.8, 52.7, 33.7, 28.8, 24.6, 14.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{22}O_4Na$: 301.1410; Found: 301.1421. Isolated yield: 32% (0.79 g), as a liquid. Column chromatography on silica gel (pentane/ethyl acetate = 30/1).

Representative Procedure for the Synthesis of 1ax, 1cx, and 1dx: Synthesis of 1ax. To a suspension of LiAlH₄ (171 mg, 4.5 mmol) in anhydrous Et₂O (15 mL) was added a solution of 1a (0.34 g, 1.5 mmol) in anhydrous Et₂O (10 mL) at 0 °C. After the addition, the mixture was stirred for another 2 h at rt. and carefully quenched with H₂O (5 mL). The resulting mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with H₂O (20 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ethyl acetate = 1:3) to yield 1ax (203 mg, 79% yield) as a white solid.

Compounds 1cx and 1dx were prepared from 1c and 1d, respectively, in the same manner.

Characterization of Products 1ax, 1cx and 1dx.

 $2-(3-Methyl-2\lambda^5-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)propane-1,$ 3-diol (1ax). ¹H NMR (400 MHz, CDCl₃) δ = 4.94 (sept, J = 2.9 Hz, 1H), 3.69 (s, 4H), 2.40 (d, J = 2.7 Hz, 2H), 2.04 (bs, 2H), 2.02 $(d, J = 2.7 \text{ Hz}, 1\text{H}), 1.71 (d, J = 3.0 \text{ Hz}, 6\text{H}); {}^{13}\text{C}{}^{1}\text{H} \text{NMR} (100 \text{ L})$ MHz, CDCl₃) δ = 201.7, 98.3, 90.0, 81.1, 70.6, 67.4, 44.5, 22.9, 20.6; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{16}O_2Na$: 203.1043; Found: 203.1049. Isolated yield: 79% (203 mg), as a semi solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:3).

 $2-(2-Cyclohexylidene-2\lambda^5-vinyl)-2-(prop-2-yn-1-yl)propane-1,3-di$ ol (1cx). ¹H NMR (400 MHz, CDCl₃) δ = 4.94 (quint, J = 2.9 Hz, 1H), 3.67 (d, J = 1.0 Hz, 4H), 2.39 (d, J = 2.7 Hz, 2H), 2.39 (bs, 2H), 2.16-2.06 (m, 4H), 2.00 (t, J = 2.7 Hz, 1H), 1.42-1.68 (m, 6H); ${}^{13}C{}^{1}H$ NMR (100 MHz, CDCl₃) δ = 198.3, 105.5, 89.8, 81.1, 70.6, 67.2, 44.4, 31.6, 27.3, 25.9, 22.9; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for C₁₄H₂₀O₂Na: 243.1356; Found: 243.1362. Isolated yield: 81% (268 mg), as a semi solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:2.5).

2-(Prop-2-vn-1-vl)-2-(3,4,4-trimethvl- $2\lambda^5$ -penta-1,2-dien-1-vl)pro *pane-1.3-diol* (1*dx*). ¹H NMR (400 MHz, CDCl₃) δ = 5.01 (q, J = 2.9 Hz, 1H), 3.70 (s, 4H), 2.41 (d, J = 2.7 Hz, 2H), 2.17 (bs, 2H), 2.02 (t, J = 2.7 Hz, 1H), 1.71 (d, J = 2.9 Hz, 3H), 1.05 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 200.0, 111.6, 91.7, 81.2, 70.7, 67.5, 67.4, 44.3, 33.1, 29.0, 29.6, 22.8, 15.4; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{22}O_2Na$: 245.1512; Found: 245.1521. Isolated yield: 97% (323 mg), as a semi solid. Column chromatography (silica gel, pentane/ethyl acetate = 1:3).

Representative Procedure for the Synthesis of 1e, 1f, and 1g: Synthesis of 1e. To a suspension of 1ax (160 mg, 0.89 mmol) in THF (10 mL) was added NaH (60% in mineral oil (142 mg, 3.6 mmol) at 0 °C. The reaction mixture was subsequently stirred for 30 minutes at the same temperature and then MeI (0.45 mL, 7.1 mmol) was added. The reaction mixture was warmed to room temperature, and stirred for 1h. The reaction mixture was quenched by addition of water, and extracted with Et₂O (2 x 20 In the same manner 1f and 1g were obtained from 1cx and 1dx, respectively.

Characterization of Products 1e, 1f and 1g.

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4,4-Bis(methoxymethyl)-7-methyl- $6\lambda^5$ -octa-5,6-dien-1-yne (1e). ¹H NMR (400 MHz, CDCl₃) $\delta = 5.00$ (sept, J = 2.9 Hz, 1H), 3.36-3.31 (m, 10H), 2.32 (d, J = 2.5 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 1.68 (d, J = 2.7 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) $\delta = 201.5, 97.4, 90.7, 81.6, 75.4, 69.7, 59.3, 43.4, 23.4, 20.5;$ HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{20}O_2Na$: 231.1356; Found: 231.1367. Isolated yield: 81% (150 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

 $(3,3-Bis(methoxymethyl)-1\lambda^5-hex-1-en-5-yn-1-ylidene)cyclohex$ ane (1f). ¹H NMR (400 MHz, CDCl₃) $\delta = 5.00$ (quint, J = 2.1 Hz, 1H), 3.34 (d, J = 2.9 Hz, 4H), 3.33 (s, 6H), 2.34 (d, J = 2.7 Hz, 2H), 2.19-2.05 (m, 4H), 1.94 (t, J = 2.7 Hz, 1H), 1.42-1.67 (m, 6H); ${}^{13}C{}^{1}H$ NMR (100 MHz, CDCl₃) δ = 198.0, 104.7, 90.5, 81.5, 75.5, 69.8, 59.4, 43.2, 31.5, 27.3, 26.1, 23.4; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{24}O_2Na$: 271.1669; Found: 271.1670. Isolated yield: 95% (209 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

4,4-Bis(methoxymethyl)-7,8,8-trimethyl- $6\lambda^5$ -nona-5,6-dien-1-yne (1g). ¹H NMR (400 MHz, CDCl₃) δ = 5.08 (q, J = 2.9 Hz, 1H), 3.36-3.29 (m, 10H), 2.32 (d, J = 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.68 (d, J = 2.7 Hz, 3H) 1.04 (s, 9H); ¹¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 199.7, 110.7, 92.5, 81.7, 75.5, 69.9, 59.3, 43.3, 33.1, 29.0, 23.3, 15.2; HRMS (ESI) m/z: [M + Na]+ Calcd for C₁₆H₂₆O₂Na: 273.1825; Found: 273.1829. Isolated yield: 85% (189 mg), as a colerless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 98:2).

Representative Procedure for the Synthesis of 1h and 1i: Synthesis of 1h. To a suspension of 1ax (108 mg, 0.60 mmol) in acetone (5 mL) was added 2,2-dimethoxypropane (72 mg, 0.69 mmol) and p-TsOH H₂O (5.7 mg, 0.03 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched with sat. NaHCO₃ (aq.). Acetone was evaporated and the residue was extracted with Et₂O (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane/ethyl acetate = 97:3) to yield **1h** (111 mg, 84% yield) as a colorless oil.

In the same manner 1i was obtained from 1dx.

Characterization of Products 1h and 1i.

2,2-Dimethyl-5-(3-methyl- $2\lambda^5$ -buta-1,2-dien-1-yl)-5-(prop-2-yn-1-52 *yl*)-1,3-dioxane (1h). ¹H NMR (400 MHz, CDCl₃) δ = 4.88 (sept, J = 2.9 Hz, 1H), 3.70 (qt, J = 14.5 Hz, J = 11.6 Hz, 4H), 2.53 (d, J 54 = 2.6 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.40 (d, J = 3.0 Hz, 6H), 1.39 (d, J = 8.1 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) $\delta =$ 56 201.7, 98.2, 97.9, 89.9, 81.4, 70.4, 66.9, 36.9, 27.6, 23.8, 20.5, 19.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{20}NaO_2$: 243.1356; Found: 243.1364. Isolated yield: 84% (111 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 97:3).

2,2-Dimethyl-5-(prop-2-yn-1-yl)-5-(3,4,4-trimethyl- $2\lambda^5$ -penta-1,2*dien-1-yl)-1,3-dioxane (1i).* ¹H NMR (400 MHz, CDCl₃) δ = 4.98 (q, J = 2.9 Hz, 1H), 3.77-3.61 (m, 4H), 2.54 (qd, J = 13.0 Hz, 2.6 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.70 (d, J = 3.0 Hz, 3H), 1.40 (d, J = 6.5 Hz, 6H), 1.04 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 199.9, 111.6, 97.9, 91.5, 81.5, 70.6, 66.9, 66.8, 36.8, 33.0, 29.0, 27.9, 24.0, 19.5, 15.3; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₁₇H₂₆O₂Na: 285.1825; Found: 285.1822. Isolated yield: 81% (128 mg), as a colorless oil. Flash column chromatography (silica gel, pentane/ethyl acetate = 97:3).

Synthesis and Characterization of 1j.

 $(((2-(3-Methyl-2\lambda^5-buta-1,2-dien-1-yl)-2-(prop-2-yn-1-yl)propa$ ne-1,3-diyl)bis(oxy))bis(methylene))dibenzene (1j). To a suspension of NaH (60% in mineral oil, 124 mg, 3.1 mmol) in anhydrous DMF (3 ml) was added a solution of 1ax (140 mg, 0.78 mmol) in anhydrous DMF (2 ml) at 0 °C. After the addition, the mixture was stirred for another 1 h at 0 °C. Then BnBr (170 µL, 1.4 mmol) was added at 0 °C and the resulting mixture was stirred at rt overnight. Then the reaction mixture was diluted with 20 mL of Et₂O and quenched with 5 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 x 20mL). The combined organic layers were washed with H₂O (10 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/diethyl ether = 100:1) to yield 1j (221 mg, 79% yield) as a liquid; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.34-7.26$ (m, 10H), 5.12 (sept, J = 2.9 Hz, 1H), 4.54 (s, 4H), 3.53 (s, 4H), 2.45 (d, J = 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.70 (d, J = 2.9 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃): $\delta =$ 201.5, 138.7, 128.2, 127.3, 97.4, 90.9, 81.7, 73.3, 73.1, 69.8, 43.8, 23.5, 20.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for C₂₅H₂₈O₂Na: 383.1982; Found: 383.1987.

Method A: Non-aerobic Oxidative Coupling-Carbocyclization for Preparation of 3

Representative Procedure: Synthesis of 3a. In a sealable microwave tube were placed 1a (47.2 mg, 0.2 mmol), Pd(OAc)₂ (2.2 mg, 0.01 mmol), 1,4-benzoquinone (BQ) (43.2 mg, 0.4 mmol), anhydrous Na₂CO₃ (4.2 mg, 0.04 mmol) and 2a (77 mg, 0.4 mmol). To this mixture, 2.0 mL of anhydrous CH₃CN solvent was added and the tube was sealed with the cap. The reaction was stirred at 80 °C in an oil bath for 24 h. After full consumption of starting material 1a as monitored by TLC, the reaction mixture was concentrated in vacuo and purified via short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95) affording 77 mg (90%) of **3a** as a liquid. The reaction was also run on a 1.3 mmol scale using 1a (0,307 g, 1,3 mmol), which afforded 0.45g (81%) of **3a** after short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Method B: Aerobic Oxidative Coupling-Carbocyclization for Preparation of 3.

Representative Procedure: Synthesis of 3a. In a sealable microwave tube were placed 1a (47.2 mg, 0.2 mmol), Pd(OAc)₂ (2.2 mg, 0.01 mmol), Cobalt(salophen) (3.7 mg, 0.01 mmol), 20 mol% of 1,4-benzoquinone (BQ) (4.4 mg, 0.04 mmol), anhydrous Na₂CO₃ (4.2 mg, 0.04 mmol) and **2a** (77 mg, 0.4 mmol). The tube was sealed with the cap. To this mixture was added 2.0 mL of anhydrous CH₃CN via syringe. Then the reaction was stirred at 80 °C in an oil bath under an oxygen atmosphere using molecular

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oxygen balloon connected via a needle for 24 h. After full consumption of starting material **1a** as monitored by TLC, the reaction mixture was concentrated in vacuo and purified via short column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95) afforded 73 mg (85%) of 3a as a liquid.

Characterization of Products 3.

Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)he xa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dic arboxylate (3a). ¹H NMR (400 MHz, CDCl₃) $\delta = 6.24$ (s, 1H), 5.94 (s, 1H), 5.76-5.66 (m, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 5.02 (d, J = 4.9 Hz, 1H), 4.98 (s, 1H), 4.85 (d, J = 1.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.71 (s, 6H), 3.19 (d, J = 4.0 Hz, 4H), 2.93 (d, J = 6.4 Hz, 2H), 1.92 (s, 3H), 1.81 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ${}^{13}C{}^{1}H$ NMR (100 MHz, CDCl₃) δ = 171.9, 170.9, 151.1, 144.2, 142.3, 139.9, 138.0, 135.0, 128.8, 119.5, 116.3, 116.0, 115.9, 63.8, 60.4, 52.7, 38.1, 36.9, 36.7, 23.2, 23.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{32}O_6Na$: 451.2091; Found: 451.2069. Isolated yield: method A-90% (77 mg), method B-85% (73 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Diethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl)hex a-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dica *rboxylate (3b).* ¹H NMR (400 MHz, CDCl₃) δ = 6.24 (s, 1H), 5.95 (s, 1H), 5.76-5.66 (m, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 5.02 (d, J = 6.6 Hz, 1H), 4.98 (s, 1H), 4.86 (s, 1H), 4.22-4.04 (m, 100)6H), 3.19 (s, 4H), 2.94 (d, J = 6.1 Hz, 2H), 1.93 (s, 3H), 1.82 (s, 3H), 1.23 (t, J = 7.1 Hz, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 171.9, 170.5, 151.1, 144.3, 142.6, 140.0, 138.1, 135.0, 129.2, 128.7, 119.4, 116.1, 115.9, 115.8, 64.0, 61.5, 60.4, 38.2, 36.8, 36.7, 23.2, 23.1, 14.1, 13.9; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₇H₃₆O₆Na: 479.2404; Found: 479.2382. Isolated yield: method A-89% (82 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-3-(cyclohex-1-en-1-yl)-4-((Z)-3-(2-ethoxy-2-oxoethy l)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)cyclopent-2-ene-1,1*dicarboxylate (3c).* ¹H NMR (400 MHz, CDCl₃) $\delta = 6.21$ (s, 1H), 5.86 (s, 1H), 5.82-5.80 (m, 1H), 5.78-5.68 (m, 1H), 5.11-5.09 (m, 1H), 5.04-5.02 (m, 1H), 4.99 (s, 1H), 4.85 (d, J = 1.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.71 (s, 6H), 3.20 (s, 2H), 3.18 (d, J =2.2 Hz, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.14-2.10 (m, 4H), 1.82 (s, 3H), 1.72-1.56 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR $(100 \text{ MHz}, \text{CDCl}_3) \delta = 172.0, 171.2, 152.0, 144.2, 142.8, 140.2,$ 135.0, 131.4, 128.5, 128.1, 127.5, 119.2, 115.9, 115.8, 63.8, 60.4, 52.7, 38.2, 36.9, 36.8, 28.6, 25.3, 23.3, 22.7, 22.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for C₂₈H₃₆O₆Na: 491.2404; Found: 491.2392. Isolated yield: method A-83% (77 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-3-(3,3-dimethylbut-1-en-2-yl)-4-((Z)-3-(2-ethoxy-2oxoethyl)-2-(prop-1-en-2-yl)hexa-2,5-dien-1-ylidene)cyclopent-2ene-1,1-dicarboxylate (3d). ¹H NMR (400 MHz, CDCl₃) $\delta = 6.07$ 50 (s, 1H), 5.80 (s, 1H), 5.76-5.63 (m, 1H), 5.25 (d, *J* = 1.4 Hz, 1H), 5.11 (s, 1H), 5.02-4.97 (m, 2H), 4.87-4.86 (m, 1H), 4.74 (d, J = 1.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.19 (s, 2H), 3.17 (d, J = 2.2 Hz, 2H), 2.91 (d, J = 6.4 Hz, 2H), 1.79 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); ¹³C{¹H} NMR (100 MHz, 54 $CDCl_3$) $\delta = 172.0, 171.2, 152.0, 144.3, 142.8, 140.1, 135.0, 131.4, 140.1, 135.0, 131.4, 140.1, 135.0, 131.4, 140.1, 135.0, 131.4, 140.1,$ 128.5, 128.1, 127.5, 119.2, 115.9, 115.8, 63.8, 60.4, 52.7, 38.2, 36.9, 36.8, 28.7, 25.3, 23.3, 22.7, 22.0, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{38}O_6Na$: 493.2561; Found: 493.2573. 58

Isolated yield: method A-82% (78 mg), method B-78% (74 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Ethyl-(Z)-3-allyl-4-((Z)-(4,4-bis(methoxymethyl)-2-(prop-1-en-2-y l)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (3e). ¹H NMR (400 MHz, CDCl₃) δ = 6.18 (s, 1H), 5.85 (s, 1H), 5.78-5.66 (m, 1H), 5.09 (s, 1H), 5.05-4.98 (m, 4H), 4.82 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.31 (s, 6H), 3.26 (s, 4H), 3.19 (s, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.43 (d, J = 2.1 Hz, 2H), 1.91 (s, 3H), 1.79 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, $CDCl_3$) $\delta = 172.2, 148.8, 145.0, 144.6, 140.6, 138.9, 136.1, 135.3, 144.6, 140.6, 138.9, 136.1, 135.3, 144.6, 140.6,$ 127.2, 118.1, 115.8, 115.3, 115.0, 60.3, 59.3, 52.2, 38.0, 36.9,

36.4, 23.3, 23.2, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₅H₃₆O₄Na: 423.2506; Found: 423.2494. Isolated yield: method A-80% (64 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 4:96).

Ethyl-(Z)-3-allyl-4-((Z)-(2-(cyclohex-1-en-1-yl)-4,4-bis(methoxym $ethyl) cyclopent \hbox{-} 2-en \hbox{-} 1-ylidene) methyl) \hbox{-} 5-methyl hexa \hbox{-} 3, 5-dienoat$ e (*3f*). ¹H NMR (400 MHz, CDCl₃) δ = 6.14 (s, 1H), 5.83-5.68 (m, 3H), 5.06-4.98 (m, 3H), 4.81 (dd, J = 2.4 Hz, 0.9 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.31 (s, 6H), 3.26 (s, 4H), 3.19 (s, 2H), 2.94 (d, J = 6.4 Hz, 2H), 2.40 (d, J = 2.1 Hz, 2H), 2.16-2.07 (m, 4H), 1.79 (s, 3H), 1.71-1.57 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR $(100 \text{ MHz}, \text{CDCl}_3) \delta = 172.2, 149.8, 145.5, 144.7, 140.8, 135.3,$ 134.5, 132.1, 126.9, 126.9, 117.7, 115.8, 115.2, 60.3, 59.3, 52.1, 38.1, 36.9, 36.4, 28.7, 25.3, 23.2, 22.9, 22.2, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{40}O_4Na$: 463.2819; Found: 463.2825. Isolated yield: method A-77% (68 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Ethyl-(Z)-3-allyl-4-((Z)-(2-(3,3-dimethylbut-1-en-2-yl)-4,4-bis(me thoxymethyl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-d *ienoate* (3g). ¹H NMR (400 MHz, CDCl₃) $\delta = 5.97$ (s, 1H), 5.76-5.68 (m, 1H), 5.66 (s, 1H), 5.20 (d, J = 1.7 Hz, 1H), 5.07-4.97 (m, 3H), 4.82 (dd, J = 2.4 Hz, 0.9 Hz, 1H), 4.69 (d, J =1.7 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.32 (s, 6H), 3.28 (s, 4H), 3.18 (s, 2H), 2.91 (d, J = 6.4 Hz, 2H), 2.39 (d, J = 2.3 Hz, 2H), 1.76 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); ¹³C{¹H} NMR $(100 \text{ MHz}, \text{CDCl}_3) \delta = 172.3, 152.7, 148.7, 148.5, 144.4, 140.7,$ 136.5, 135.2, 127.1, 117.8, 115.6, 115.5, 112.2, 60.3, 59.3, 52.8, 38.1, 36.8, 35.8, 35.2, 29.5, 23.3, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₈H₄₂O₄Na: 465.2975; Found: 465.2985. Isolated yield: method A-81% (71 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 4:96).

Ethyl-(Z)-3-allyl-4-((Z)-(8,8-dimethyl-3-(prop-1-en-2-yl)-7,9-diox aspiro[4.5]dec-3-en-2-ylidene)methyl)-5-methylhexa-3,5-dienoate (3h). ¹H NMR (400 MHz, CDCl₃) δ = 6.21 (s, 1H), 5.96 (s, 1H), 5.77-5.66 (m, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 5.04-4.99 (m, 3H), 4.84 (d, J = 1.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (d, J =11.3 Hz, 2H), 3.59 (d, J = 11.3 Hz, 2H), 3.20 (s, 2H), 2.93 (d, J = 6.4 Hz, 2H), 2.49 (d, J = 2.2 Hz, 2H), 1.92 (s, 3H), 1.79 (s, 3H), 1.43 (d, J = 5.8 Hz, 6H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR $(100 \text{ MHz}, \text{CDCl}_3) \delta = 172.1, 149.1, 144.5, 144.1, 140.4, 138.8,$ 135.2, 135.1, 127.8, 118.6, 115.9, 115.6, 115.2, 97.5, 68.4, 60.4, 46.5, 38.1, 37.5, 36.8, 24.0, 23.5, 23.3, 23.3, 14.1; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{36}O_4Na$: 435.2506; Found: 435.2497. Isolated yield: method A-75% (62 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Ethyl-(Z)-3-allyl-4-((Z)-(3-(3,3-dimethylbut-1-en-2-yl)-8,8-dimeth yl-7,9-dioxaspiro[4.5]dec-3-en-2-ylidene)methyl)-5-methylhexa-3, 5-dienoate (3i). ¹H NMR (400 MHz, CDCl₃) δ = 6.00 (s, 1H), 5.77 (s, 1H), 5.77-5.66 (m, 1H), 5.21 (s, 1H), 5.09 (s, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.97 (s, 1H), 4.85 (s, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.72 (d, *J* = 11.3 Hz, 2H), 3.60 (d, *J* = 11.3 Hz, 2H), 3.19 (s, 2H), 2.91 (d, *J* = 6.4 Hz, 2H), 2.48 (d, *J* = 2.2 Hz, 2H), 1.77 (s, 3H), 1.43 (d, *J* = 4.3 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 172.3, 152.5, 149.1, 147.4, 144.4, 140.5, 135.5, 135.0, 127.7, 118.7, 115.8, 115.7, 112.5, 97.5, 68.6, 60.4, 47.1, 38.2, 36.8, 36.6, 35.7, 29.6, 24.3, 23.4, 23.3, 14.2;; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₉H₄₂O₄Na: 477.2975; Found: 477.2977. Isolated yield: method A-34% (31 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

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Ethyl(*Z*)-3-allyl-4-((*Z*)-(4,4-bis((benzyloxy)methyl)-2-(prop-1-en-2-yl)cyclopent-2-en-1-ylidene)methyl)-5-methylhexa-3,5-dienoate (*3j*). ¹H NMR (400 MHz, CDCl₃) δ = 7.34-7.23 (m, 10H), 6.19 (s, 1H), 5.93 (s, 1H), 5.80-5.68 (m, 1H), 5.11-4.99 (m, 5H), 4.84 (s, 1H), 4.51 (s, 4H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 4H), 3.21 (s, 2H), 2.95 (d, *J* = 6.4 Hz, 2H), 2.50 (d, *J* = 2.1 Hz, 2H), 1.93 (s, 3H), 1.79 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ = 172.2, 148.9, 145.2, 144.7, 140.7, 139.0, 138.8, 136.4, 135.3, 128.2, 127.3, 127.3, 127.2, 117.9, 115.8, 115.3, 115.0, 73.5, 73.2, 60.4, 52.4, 38.0, 36.9, 36.6, 23.4, 23.3, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₃₇H₄₄O₄Na: 575.3132; Found: 575.3125. Isolated yield: method A-83% (91 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

Dimethyl-(Z)-4-((Z)-3-(ethoxycarbonyl)-2-(prop-1-en-2-yl)hexa-2, 5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1, 1-dicarbox ylate (**3k**). ¹H NMR (400 MHz, CDCl₃) δ = 6.19 (t, *J* = 2.2 Hz, 1H), 6.03 (s, 1H), 5.82-5.72 (m, 1H), 5.19 (s, 1H), 5.07-4.99 (m, 3H), 4.95 (s, 1H), 4.87 (d, *J* = 0.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, *J* = 2.2 Hz, 2H), 3.07 (d, *J* = 6.1 Hz, 2H), 1.93 (d, *J* = 4.0 Hz, 6H), 1.23 (t, *J* = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 172.7, 169.9, 150.9, 145.8, 145.6, 144.7, 137.6, 134.2, 130.5, 129.8, 118.3, 116.6, 116.0, 115.2, 63.9, 60.3, 52.9, 37.0, 34.4, 23.0, 22.7, 13.8; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₄H₃₀O₆Na: 437.1940; Found: 437.1950. Isolated yield: method A-85% (70 mg), method B-87% (72 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-(prop-1-en-2-yl-d5)h exa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-di carboxylate (**31**). ¹H NMR (400 MHz, CDCl₃) δ = 6.26 (s, 1H), 5.95 (s, 1H), 5.73-5.69 (m, 1H), 5.16 (s, 1H), 5.07-4.99 (m, 3H), 4.11 (q, J = 7.0 Hz, 2H), 3.72 (s, 6H), 3.20 (s, 4H), 2.95 (d, J = 5.7 Hz, 2H), 1.94 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ = 172.0, 171.0, 151.2, 144.0, 142.3, 139.9, 138.0, 135.0, 128.9, 128.8, 119.6, 116.3, 116.0, 63.9, 60.4, 52.8, 38.2, 36.9, 36.8, 23.1, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₅H₂₇D₅O₆Na: 456.2410; Found: 456.2393. Isolated yield: method A-72% (62 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((Z)-2-(cyclohex-1-en-1-yl)-3-(2-ethoxy-2-oxoethy l)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1dicarboxylate (**3m**). ¹H NMR (400 MHz, CDCl₃) δ = 6.27 (t, J = 2.2 Hz, 1H), 5.92 (s, 1H), 5.77-5.67 (m, 1H), 5.55 (sept, J = 2.2 Hz, 1H), 5.16-5.15 (m, 1H), 5.06-4.98 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, J = 2.2 Hz, 2H), 3.17 (s, 2H), 2.94 (d, J = 6.1 Hz, 2H), 2.11-2.09 (m, 2H), 1.98-1.93 (m, 5H), 1.60-1.70 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H); $^{13}C{^{1}H}$ NMR (100 MHz, CDCl₃) $\delta = 172.2$, 171.1, 151.4, 141.9, 140.5, 138.1, 137.1, 135.2, 129.1, 128.5, 126.9, 120.1, 116.2, 115.8, 63.9, 60.4, 52.8, 38.3, 37.0, 36.8, 28.9, 25.3, 23.1, 22.7, 21.9, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₈H₃₆O₆Na: 491.2404; Found: 491.2421. Isolated yield: method A-78% (74 mg), method B-80% (76 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((Z)-2-(cyclopent-1-en-1-yl)-3-(2-ethoxy-2-oxoeth yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1, 1-dicarboxylate (**3n**). ¹H NMR (400 MHz, CDCl₃) δ = 6.27 (s, 1H), 5.93 (s, 1H), 5.77-5.67 (m, 1H), 5.58 (s, 1H), 5.15 (s, 1H), 5.07 (s, 1H), 5.03-4.98 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.72 (s, 6H), 3.17 (s, 2H), 3.09 (d, J = 2.2 Hz, 2H), 2.94 (d, J = 6.1 Hz, 2H), 2.36 (dt, J = 40.2 Hz, 7.1 Hz, 4H), 1.94-1.88 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 172.0, 171.0, 150.8, 142.3, 142.1, 137.9, 135.2, 135.0, 130.0, 129.4, 128.7, 120.2, 116.2, 116.0, 63.7, 60.4, 52.8, 38.3, 37.2, 36.7, 36.2, 32.9, 23.4, 23.0, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₇H₃₄O₆Na: 477.2248; Found: 477.2249. Isolated yield: method A-75% (69 mg), method B-77% (71 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((Z)-3-(2-ethoxy-2-oxoethyl)-2-vinylhexa-2,5-dien -1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (**30**). ¹H NMR (400 MHz, CDCl₃) $\delta = 6.64$ (dd, J = 17.1 Hz, 10.5 Hz, 1H), 6.13 (s, 1H), 6.02 (s, 1H), 5.74-5.63 (m, 1H), 5.20-5.13 (m, 4H), 5.03 (d, J = 6.1 Hz, 1H), 5.00 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.71 (s, 6H), 3.25 (s, 2H), 2.98-2.96 (m, 4H), 1.98 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) $\delta =$ 171.2, 170.9, 149.1, 144.0, 137.6, 135.2, 134.9, 132.3, 130.4, 129.6, 119.3, 116.8, 116.6, 116.4, 63.3, 60.7, 52.8, 39.3, 37.1, 36.5, 22.9, 14.1; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₄H₃₀O₆Na: 437.1940; Found: 437.1931. Isolated yield: method A-61% (50 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((2Z,5E)-3-(ethoxycarbonyl)-2-(prop-1-en-2-yl)octa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-di carboxylate (**3p**). ¹H NMR (400 MHz, CDCl₃) δ = 6.21(t, J = 7.1 Hz, 2H), 6.03 (s, 1H), 5.52-5.45 (m, 1H), 5.37-5.30 (m, 1H), 5.19 (pent, J = 1.4 Hz, 1H), 5.07 (s, 1H), 4.95 (pent, J = 1.6 Hz, 1H), 4.87 (dd, J = 1.0 Hz, 1.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (d, J = 2.2 Hz, 2H), 3.01 (d, J = 6.1 Hz, 2H), 1.95-1.93 (m, 8H), 1.23 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 170.7, 170.1, 151.0, 145.7, 145.5, 143.7, 137.7, 134.0, 130.9, 130.3, 124.4, 118.5, 116.6, 115.2, 64.0, 60.3, 52.9, 37.0, 33.4, 25.5, 23.0, 22.7, 13.9, 13.7; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₆H₃₄O₆Na: 465.2248; Found: 465.2239. Isolated yield: method A-76% (67 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 7:93).

Dimethyl-(Z)-4-((ZZ,5E)-3-(ethoxycarbonyl)-6-phenyl-2-(prop-1-e n-2-yl)hexa-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-en e-1,1-dicarboxylate (**3q**). ¹H NMR (400 MHz, CDCl₃) δ = 7.33-7.18 (m, 5H), 6.40 (d, J = 15.8 Hz, 1H), 6.27 (s, 1H), 6.18-6.10 (m, 1H), 6.05 (s, 1H), 5.22-5.20 (m, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.72 (s, 6H), 3.26-3.23 (m, 4H), 1.96 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 170.7, 169.9, 150.9, 146.0, 145.6,

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144.9, 137.7, 137.4, 131.3, 130.6, 129.8, 128.4, 127.0, 126.2, 126.1, 118.4, 116.7, 115.2, 64.0, 60.4, 52.9, 37.1, 33.8, 23.1, 22.7, 13.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{34}O_6Na$: 513.2253; Found: 513.2260. Isolated yield: method A-57% (56 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((Z)-3-(ethoxycarbonyl)-6-methyl-2-(prop-1-en-2yl)hepta-2,5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1, 1-dicarboxylate (**3r**). ¹H NMR (400 MHz, CDCl₃) δ = 6.20 (t, J = 2.2 Hz, 1H), 6.02 (s, 1H), 5.19-5.17 (m, 1H), 5.07-5.04 (m, 2H), 4.93 (s, 1H), 4.86 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.73 (s, 6H), 3.21 (d, J = 2.2 Hz, 2H), 3.01 (d, J = 6.9 Hz, 2H), 1.92 (d, J = 12.5 Hz, 6H), 1.66 (s, 3H), 1.60 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 170.7, 170.2, 150.9, 145.7, 145.3, 142.9, 137.7, 133.1, 131.6, 130.2, 120.2, 118.5, 116.6, 115.2, 63.9, 60.2, 52.9, 37.0, 29.4, 25.6, 23.0, 22.6, 17.8, 13.8; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₆H₃₄O₆Na: 465.2253; Found: 465.2238. Isolated yield: method A-71% (63 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 5:95).

Dimethyl-(Z)-4-((E)-3-allyl-2-(prop-1-en-2-yl)hept-2-en-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1, 1-dicarboxylate (**3t**). ¹H NMR (400 MHz, CDCl₃) δ = 6.26 (s, 1H), 5.89 (s, 1H), 5.77-5.67 (m, 1H), 5.15 (s, 1H), 5.08 (s, 1H), 5.06 (s, 1H), 5.03-4.96 (m, 2H), 4.80 (s, 1H), 3.72 (s, 6H), 3.21 (d, *J* = 2.1 Hz, 2H), 2.86 (d, *J* = 6.1 Hz, 2H), 2.13-2.09 (m, 2H), 1.93 (s, 3H), 1.84 (s, 3H), 1.36-1.27 (m, 5H), 0.88 (t, *J* = 7.1 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ = 171.2, 151.7, 144.7, 140.3, 138.2, 137.5, 136.5, 136.1, 127.7, 120.5, 116.2, 115.1, 63.9, 52.8, 36.9, 36.0, 32.9, 31.5, 23.9, 23.2, 23.0, 13.9; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₅H₃₄O₄Na: 421.2349; Found: 421.2353. Isolated yield: method A-80% (64 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

45 Dimethyl-(Z)-4-((Z)-3-phenyl-2-(prop-1-en-2-yl)hexa-2,5-dien-1-y 46 lidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarboxylate (3u). 47 ¹H NMR (400 MHz, CDCl₃) δ = 7.27-7.15 (m, 10H), 6.42 (t, J = 48 2.2 Hz, 1H), 5.98 (s, 1H), 5.91 (t, J = 2.2 Hz, 1H), 5.83 (s, 1H), 49 5.74-5.65 (m, 2H), 5.21 (s, 2H), 5.15 (s, 2H), 4.90-4.85 (m, 6H), 50 4.73 (s, 1H), 4.70 (s, 1H), 3.73 (d, J = 4.8 Hz, 12H), 3.27-3.20 (m, 8H), 1.98 (d, J = 14.8 Hz, 6H), 1.65 (d, J = 17.4 Hz, 6H); ¹³C{¹H} 51 NMR (100 MHz, CDCl₃) δ = 171.1, 171.0, 152.0, 151.2, 144.4, 52 143.9, 143.1, 142.5, 141.6, 140.3, 139.0, 138.4, 138.0, 137.8, 53 137.5, 136.7, 135.0, 129.4, 128.7, 128.6, 127.8, 127.6, 127.5, 54 126.6, 126.3, 121.9, 121.2, 117.9, 116.3, 116.0, 115.9, 115.5, 55 115.4, 63.9, 63.9, 52.8, 52.8, 39.7, 39.4, 37.1, 36.8, 23.8, 23.5, 56 23.1, 22.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{30}O_4Na$: 57 441.2036; Found: 441.2034. Isolated yield: method A-60% (50 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 3:97).

Dimethy-(*Z*)-4-((*Z*)-3-(2-hydroxyethyl)-2-(prop-1-en-2-yl)hexa-2, 5-dien-1-ylidene)-3-(prop-1-en-2-yl)cyclopent-2-ene-1,1-dicarbox ylate (*3v*). ¹H NMR (400 MHz, CDCl₃) δ = 6.27 (s, 1H), 5.93 (s, 1H), 5.81-5.71 (m, 1H), 5.17 (s, 1H), 5.13 (s, 1H), 5.06-5.01 (m, 3H), 4.84 (s, 1H), 4.45 (s, 1H), 3.73 (s, 6H), 3.67 (q, *J* = 7.1 Hz, 2H), 3.22 (d, *J* = 2.1 Hz, 2H), 2.91 (d, *J* = 6.1 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 1.94 (s, 3H), 1.86 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 171.1, 151.6, 149.4, 144.5, 141.3, 139.4, 138.1, 135.8, 132.6, 128.4, 119.9, 116.3, 116.1, 115.8, 115.6, 63.9, 61.8, 52.9, 36.9, 36.6, 36.2, 24.0, 23.2; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₃H₃₀O₅Na: 409.1985; Found: 409.1986. Isolated yield: method A-63% (49 mg), as a liquid. Column chromatography on silica gel (eluent: ethyl acetate/pentane, 10:90).

ASSOCIATED CONTENT

Supporting Information

General preparation of starting materials, selected optimization results, comparative experiments, mechanistic study, kinetic isotope effect (KIE) experiments and compounds ¹H/¹³C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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