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Synthesis of a 1,3-Bridged Macrobicyclic Enyne via Chemoselective Cycloisomerization Using Palladium-Catalyzed Alkyne−Alkyne Coupling

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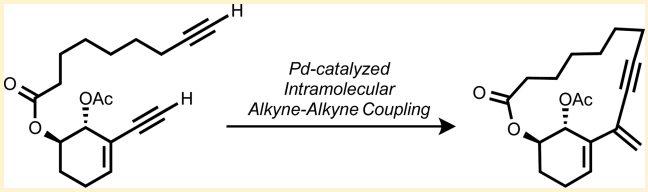
Supporting Information

ABSTRACT: A unique intramolecular Pd-catalyzed alkyne−alkyne coupling is presented. This transformation generates a strained, 1,3-bridged, macrocyclic enyne. The process was readily executed on gram scale, and the structure of the product was elucidated via X-ray crystallographic analysis. A mechanistic rationale for the observed chemoselectivity is provided.



Conjugated enynes constitute an important class of unsaturated compounds. 1,3-Enynes and their derivatives have proven to be useful intermediates in the synthesis of various small molecules,[1,2] including those possessing biological activity.[3] Of particular significance are conjugated enynes that bear an element of π-unsaturation constrained within a cyclic system, as this structural motif occurs in both natural products and natural product precursors.[4] A notable example is tricholomenyn B (Scheme 1), a macrocyclic enyne that possesses potent antimitotic activity.[5]

Transition metal catalysis is a powerful method for the synthesis of functionalized molecules, especially those bearing π-unsaturation. Transition-metal-catalyzed $sp-sp^2$ coupling, in particular, has become an effective means of preparing enynes.[6] Nevertheless, in the specific context of the synthesis of enynes that contain an acetylene unit within a ring system, such couplings are not without limitations. In several reported cases, these reactions proceeded with modest yields and/or required the use of stoichiometric quantities of transition metals.[7−10] The reduced effectiveness of these processes may have been a consequence of the strain associated with the bridging of nonadjacent carbon atoms in macrocyclic structures: this strain would necessarily develop in the transition states leading to the products, and it could potentially hinder the efficacy of the coupling.

Relative to metal-catalyzed $sp-sp^2$ coupling, the transition-metal-catalyzed coupling of alkynes is a distinctly different approach to the synthesis of enynes. These processes have proven highly effective in various synthetic endeavors,[11] and such catalytic addition reactions embody the ideals of atom[12] and step[13] economy. Since the early 1980s, our research group has maintained an interest in the palladium-catalyzed coupling of alkynes as a means to generate enynes, and we have investigated this transformation in both its inter- and intramolecular variants.[14] In an example of the latter application, it was discovered that the combination of palladium acetate and the electron-rich, sterically encumbered ligand tris(2,6-dimethoxyphenyl)phosphine (TDMPP, **1**) catalyzed the intramolecular alkyne−alkyne coupling of symmetrical diyne **2** to 14-membered macrocycle **3** (Scheme 1A).[15]

Analogous reactions of unsymmetrical alkynes present an important question of chemoselectivity, as one alkyne group must act as a donor in the coupling event and the other as the acceptor. To this end, the observation that the unsymmetrical, propargyl alcohol-derived diyne **4** was converted to exclusively macrocycle **5** (Scheme 1B) suggested that electronic factors could engender chemoselectivity. In this case, it was postulated that the presence of the oxygen substituent on the propargyl alcohol unit served to lower the energy of the LUMO of the corresponding alkyne group, thereby facilitating acetylide addition across this C−C triple bond.[16]

Intramolecular couplings between terminal and internal alkynes have also been examined. In these studies, the ability of an electron-withdrawing substituent to activate an alkyne group as the acceptor was identified. Representative of this behavior was the reaction of compound **6**: in the event, the propiolate moiety of this diyne served as the acceptor alkyne, and macrocycle **7** was obtained as the exclusive product (Scheme 1C). The utility of this process in complex molecule synthesis was demonstrated in the synthesis of bryostatin 16.[17]

These examples illustrate the utility of the palladium-catalyzed alkyne−alkyne coupling in the synthesis of enynes that contain an element of π-unsaturation constrained within a ring system. They also demonstrate the ability of certain functional groups, such as propargylic alcohols or propiolates, to direct the chemoselectivity of these intramolecular coupling processes. Nevertheless, the application of this unique method of enyne synthesis to the synthesis of more significantly strained systems—such as those that bind nonadjacent carbons in a macrocyclic framework—has not been explored. Herein, we report an intramolecular alkyne coupling reaction that

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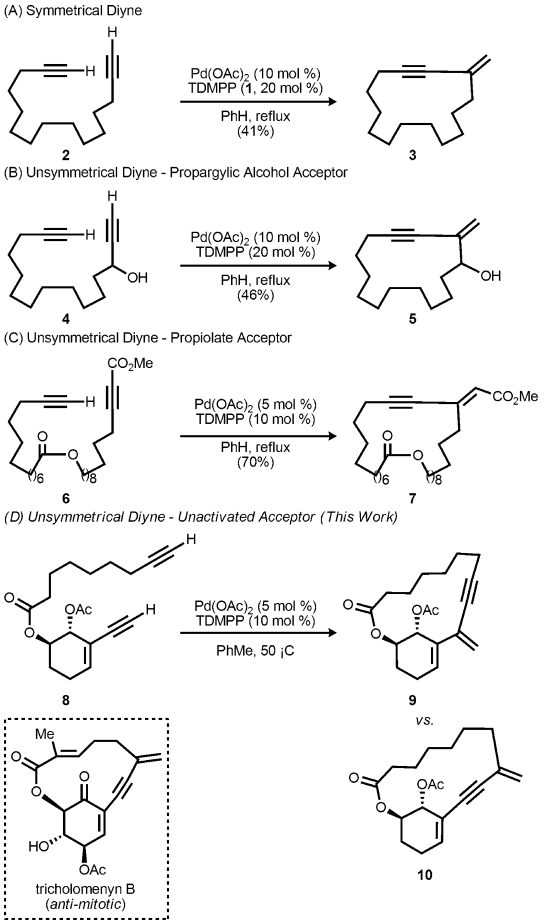
Scheme 1. Palladium/TDMPP-Catalyzed Intramolecular Alkyne−Alkyne Couplings To Generate Macrocyclic Enynes



explores this important chemoselectivity issue in an unusual metacyclophane synthesis, a 1,3-bridged enyne, via a cross-coupling between two different terminal alkynes of a cyclohexene-derived diyne substrate (**8** → **9** or **10**, Scheme 1D). Remarkably, the process occurs with complete chemoselectivity, as none of isomeric compound **10** is detected. The execution of the transformation on gram scale is demonstrated. Additionally, the structure of the product is unequivocally established through X-ray crystallographic analysis.

The synthesis of the cyclohexenyl core of the diyne substrate began with the nucleophilic epoxidation of commercially available 2-cyclohexen-1-one (**11**, Scheme 2). By the action of aqueous hydrogen peroxide and a catalytic amount of aqueous sodium hydroxide, compound **11** was converted to known epoxy ketone **12**[18] in good yield (74%). After deprotonation with LDA, triflation with Comin's reagent (*N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide, **13**) provided vinyl triflate **14** in 75% yield. *N*-Phenylbis(trifluoromethanesulfonimide) was successfully used in place of Comin's reagent to obtain the same product, although the reaction yield was reduced (52%).

A regio- and stereoselective epoxide opening occurred upon dissolution of compound **14** in acetic acid in the presence of a catalytic amount of trifluoroacetic acid (13 mol %). *trans*-Alcohol **15** was thus isolated cleanly and in good yield (68%). In the absence of the trifluoroacetic acid catalyst, this solvolysis occurred at a reduced rate: **15** was obtained in 50% yield after 5 days at room temperature (71% yield based on recovered **14**). The Sonogashira coupling between triflate **15** and trimethylsilyl acetylene (**16**) occurred in high yield (89%) to deliver enyne **17**. Esterification of the latter with 8-nonynoic acid (**18**) under Steglich conditions (*N*,*N*′-dicyclohexylcarbodiimide, catalytic 4-dimethylaminopyridine) furnished ester **19** in 87% yield, and alkyne desilylation using TBAF in THF provided the key diyne substrate **8** in 75% yield.

With diyne **8** in hand, our attention turned to the palladium-catalyzed macrocyclization event. Performing the slow addition of a toluene solution of this compound to a mixture of $Pd(OAc)_2$ (5 mol %) and TDMPP (10 mol %) at room temperature afforded macrocyclic enyne **9** as the sole

Scheme 2. Synthesis of Macrocyclization Precursor 8

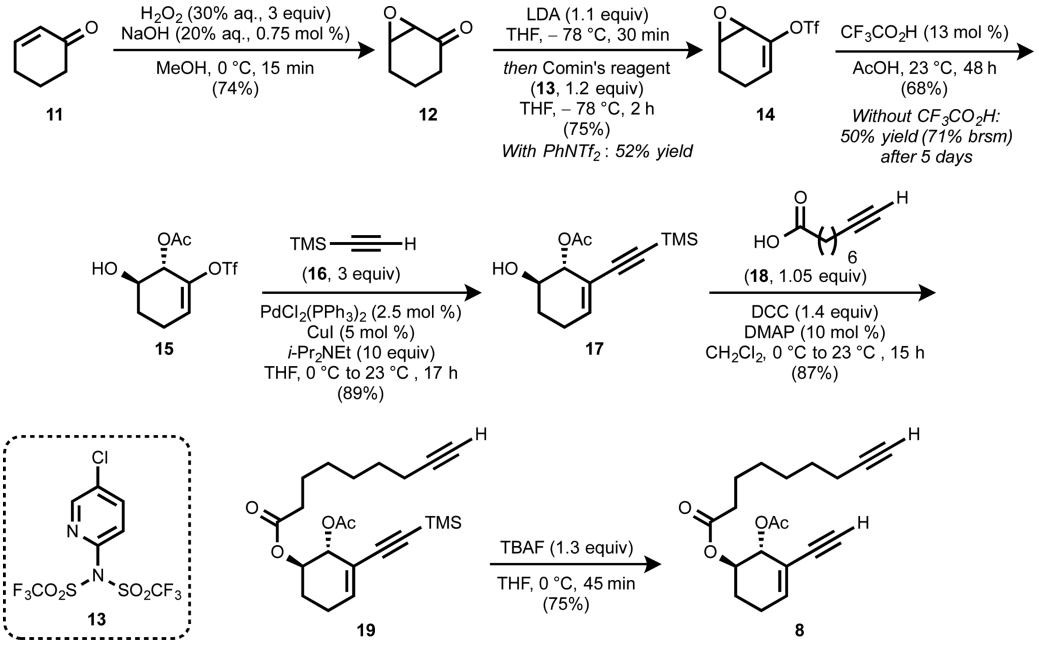


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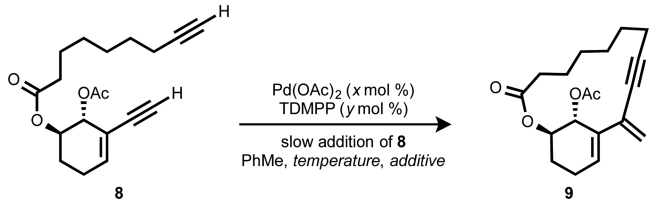
Table 1. Influence of Palladium to Phosphine Ratio and Reaction Temperature on the Intramolecular Alkyne−Alkyne Coupling of 8[a]



entry	temp	x (mol %)	y (mol %)	additive	conversion (%)[b]	yield (%)[c]
1	23 °C	5	10	–	82	47
2	23 °C	10	5	–	63	35
3	23 °C	5	5	–	80	34
4	*50 °C*	*5*	*10*	–	>95	*50*
5	50 °C	5	10	AcOH (1 equiv)	<5	N/A
6	50 °C	5	10	NaOAc (1.6 equiv)	>95	52
7	50 °C	5	10	Et_3N (1 equiv)	>95	53
8[d]	*50 °C*	*5*	*10*	*Et_3N (1 equiv)*	>95	*60*

[a]Reaction conditions: Except where otherwise indicated, a solution of **8** in PhMe (0.10 M) was added via syringe pump to a solution of $Pd(OAc)_2$ and TDMPP in PhMe (0.005 M in $Pd(OAc)_2$) over the course of 4−6 h, and then the mixture was stirred for a total of 13 h. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield after chromatography. [d]Following the slow addition of **8**, the reaction mixture was stirred for an additional 30 min (4 h 30 min total reaction time).

identifiable product after filtration of the reaction mixture through Florisil. Compound **9** was obtained in 47% isolated yield after chromatography on silica gel (Table 1, entry 1). This result served as the starting point for further optimization. The use of a 2:1 ratio of TDMPP relative to $Pd(OAc)_2$ proved ideal: inverting the ratio (1:2 TDMPP/$Pd(OAc)_2$) led to a decrease in both conversion and yield (entry 2), as did the use of an equimolar ratio of these species (entry 3).[19] When the reaction was performed with the 2:1 TDMPP/$Pd(OAc)_2$ system and the temperature was increased from 23 to 50 °C, complete conversion was achieved in 13 h, and **9** was isolated in 50% yield (entry 4).[20]

The effects of reaction additives and of reaction duration were next examined. The addition of 1 equiv of acetic acid completely inhibited the reaction (entry 5), but a slight improvement in yield was observed upon the introduction of base. Both sodium acetate (entry 6) and triethylamine (entry 7) served well in this capacity. Given our goal of a readily scalable process, we selected triethylamine as the basic additive due to its homogeneity in toluene. We were pleased to find that, when the slow addition was performed over the standard 4 h at 50 °C in the presence of triethylamine, complete consumption of **8** was observed after a total reaction time of only 4 h 30 min (entry 8). From this reaction, product **9** was isolated in 60% yield.

Encouraged by this operationally convenient and expedient synthesis of macrocycle **9**, we pursued its preparation on a larger scale. Thus, the reaction conditions of Table 1, entry 8 were applied to a gram-scale (3.16 mmol) cyclization of **8** without further modification. In this event, the intramolecular coupling proceeded smoothly to deliver macrocycle **9** as the only product isomer and in 47% isolated yield.

From this larger-scale reaction, **9** was obtained as an amorphous solid. Its careful crystallization from diethyl ether afforded material suitable for X-ray crystallographic analysis (colorless, block-like crystals). This mode of analysis was employed in order to ascertain both the relative stereochemistry of the product and the sense of chemoselectivity with which the alkyne−alkyne coupling had proceeded. Indeed, X-ray analysis confirmed the following: (a) that the solvolytic epoxide opening with acetic acid (**14** → **15**) had yielded the *trans*-product, (b) that acetate addition occurred at the allylic position, and (c) that a chemoselective alkyne coupling had occurred wherein the pendant terminal alkyne acted as the donor and the cyclohexenyl alkyne acted as the acceptor (Figure 1).

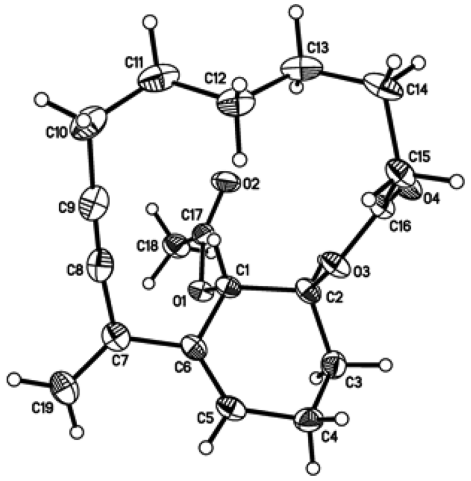


Figure 1. X-ray-derived ORTEP representation (50% probability level) of enyne **9**.

A plausible mechanistic pathway for the synthesis of macrocycle **9** is illustrated in Scheme 3. The process may commence with the formation of a palladium acetylide. To this end, coordination of phosphine-ligated palladium to the donor alkyne and carboxylate-assisted deprotonation would generate complex **20**, with the concomitant formation of acetic acid (step a).[14] It is possible that the poor reactivity observed upon introduction of acetic acid was due to inhibition of this stage, whereas the benefit observed upon introduction of base was due to its acceleration. The palladium atom of complex **20** may then coordinate to the acceptor alkyne (step b), leading to

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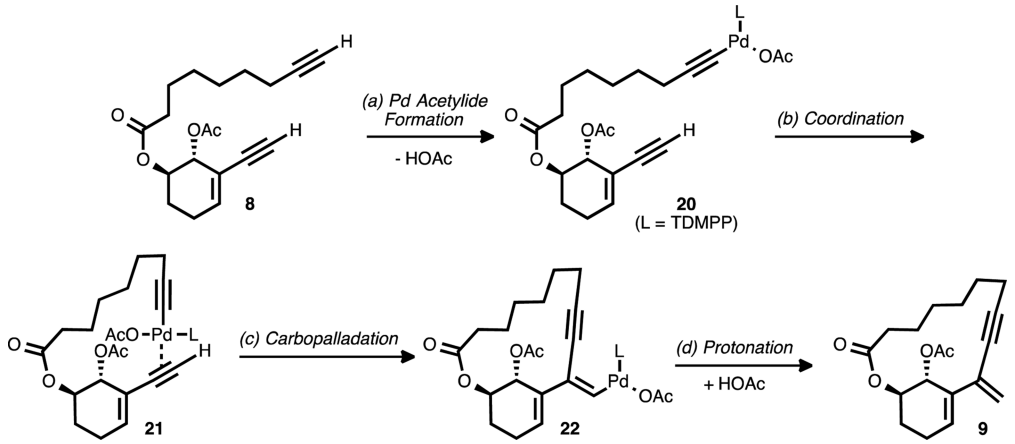
Scheme 3. Proposed Mechanism for the Intramolecular Alkyne−Alkyne Coupling



complex **21**. Upon *syn*-carbopalladation (step c), vinylpalladium compound **22** would result. Protonolysis of the C−Pd bond by acetic acid or triethylammonium acetate (step d) would regenerate the palladium catalyst and would release product **9**.

The sense of chemoselectivity in this macrocyclization is remarkable and deserving of comment. As described in prior reports,[16] terminal enynes typically react preferentially as donor alkynes when they are engaged in cross-coupling reactions with other terminal alkynes. This has been attributed to the greater acidity of enynes relative to simple acetylenes. The fact that the enynyl moiety of compound **8** acted as the acceptor suggests that, in the present case, the chemoselectivity is not purely a function of alkyne acidity. Instead, the selectivity may have been the result of subtle steric interactions. The alkyne bonded to the cyclohexene core is obstructed by the steric bulk of the cyclohexene ring and its two carboxylate substituents, whereas the alkyne situated on the aliphatic chain is, comparatively, more accessible. Thus, coordination of the palladium catalyst to the latter alkyne and subsequent formation of an active palladium acetylide may have occurred preferentially at this position, facilitating the coupling process depicted in Scheme 3.

Alternatively, it may have been the case that the presence of the two carboxylate substituents was sufficient to electronically activate the enynyl alkyne as the acceptor, in the same manner that has been observed with propargylic alcohols (i.e., by lowering the energy of the alkyne LUMO). Indeed, both the described steric bias and this potential electronic preference may have acted in concert to promote the selective coupling observed herein. Additional explanations can also be envisioned, including the possibility of a Curtin−Hammett scenario wherein palladium acetylide formation from either terminal alkyne is fast and reversible but wherein intermediate **20** undergoes carbopalladation at a faster rate. Nevertheless, it appears that, in the subject macrocyclization process, subtle steric and/or electronic factors beyond simple alkyne acidity acted to influence the chemoselectivity of the coupling.

CONCLUSIONS

We report a chemoselective intramolecular alkyne−alkyne coupling that generates a structurally unique, strained, 1,3-bridged macrocyclic enyne. Careful evaluation of the influence of catalyst loading, reaction additives, temperature, and duration led to optimized conditions that were highly effective on both milligram and gram scales. In all cases, only a single product isomer was observed. The structure of this product was determined unambiguously via X-ray crystallographic analysis. In contrast to prior examples of cross-couplings between terminal enynes and other terminal alkynes, the enyne of substrate **8** acted selectively as the *acceptor* in the present case. The excellent atom economy, operational simplicity, and robustness of the procedure compare favorably with other known methods for the synthesis of macrocycles that contain alkyne functional groups within their ring systems.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise indicated, all reactions were performed in oven- or flame-dried glassware with magnetic stirring under a nitrogen or an argon atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via oven-dried, stainless steel syringe or cannula and were introduced into the reaction vessel through rubber septa. Anhydrous CH_2Cl_2 and THF were obtained from a solvent purification system. PhMe was distilled over CaH_2.

Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates. Visualization was performed by ultraviolet light fluorescence quenching and/or by staining with potassium permanganate, ceric ammonium molybdate, or *para*-anisaldehyde solutions followed by heating. Unless otherwise indicated, flash column chromatography was performed using 40−63 μm silica gel using compressed air. The eluent employed for flash chromatography is reported as volume/volume ratios. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired using 300, 400, 500, or 600 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak: proton ($CHCl_3$, 7.26 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet (range of multiplet is given). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using 75, 100, 125, or 150 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak: carbon ($CHCl_3$, 77.16 ppm).

Infrared spectroscopic data were recorded using thin films of the sample on NaCl plates. The absorbance frequencies are recorded in wavenumbers (cm^{-1}). Melting points are uncorrected. HRMS data were obtained using time-of-flight electrospray ionization (ESI-TOF).

*7-Oxabicyclo[4.1.0]heptan-2-one (**12**).* A flame-dried 500 mL round-bottom flask equipped with a stir bar was charged with 2-cyclohexen-1-one (**11**, 9.60 g, 100 mmol, 1 equiv) and methanol (100 mL). The vessel was cooled to 0 °C, and to the homogeneous solution was added hydrogen peroxide (30% aqueous solution, 30 mL, 300 mmol, 3 equiv). To the reaction mixture was added aqueous sodium hydroxide (20% aqueous solution, 0.15 mL, 0.75 mmol, 0.75 mol %). The reaction mixture was stirred for 15 min, at which point it was poured into a separatory funnel containing ice (150 g) and brine (200 mL). The resulting suspension was extracted with CH_2Cl_2 (3 × 150

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mL), and the pooled organic phases were dried over $MgSO_4$, filtered, and concentrated. Distillation of the resulting residue under reduced pressure (11 mmHg) afforded the title compound (8.3 g, 74%, bp range 60−75 °C) as a clear oil (*ca.* 85% purity as judged by ^{1}H NMR, with traces of residual 2-cyclohexen-1-one remaining but suitable for use in the next step). ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.58 (m, 1H), 3.22 (d, J = 3.9 Hz, 1H), 2.56−2.51 (m, 1H), 2.28−2.24 (m, 1H), 2.11−1.88 (m, 3H), 1.70−1.63 (m, 1H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 206.0, 55.9, 55.1, 36.3, 22.8, 17.0. *These ^{1}H and ^{13}C NMR data were in agreement with previously reported data.*[18]

*7-Oxabicyclo[4.1.0]hept-2-en-2-yl Trifluoromethanesulfonate (**14**).* To a solution of freshly distilled diisopropylamine (0.83 mL, 5.82 mmol, 1.1 equiv) in THF (5.82 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 2.32 mL, 5.82 mmol, 1.1 equiv). After 15 min, the cooling bath was replaced with a 0 °C bath, and the solution was stirred for 30 min. The vessel was again cooled to −78 °C, and a solution of 7-oxabicyclo[4.1.0]heptan-2-one (**12**, 0.66 g, 5.3 mmol) in THF (1.5 mL) was added via cannula. After 30 min, a solution of Comin's reagent (**13**, *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide, 2.57 g, 6.35 mmol, 1.2 equiv) was added as a solution in THF (6 mL + 2 mL rinse), yielding a homogeneous and dark red solution. After 2 h, the reaction mixture was poured into a separatory funnel containing water (25 mL) and ice (50 g). The mixture was extracted with Et_2O (3 × 75 mL), and the pooled organic phases were washed with 10% aqueous KOH (20 mL) and then brine (2 × 50 mL), dried over K_2CO_3, filtered, and concentrated. Purification by column chromatography (10:1 hexanes/Et_2O) afforded the title compound (969 mg, 75%) as an oil. R_f = 0.34 (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.91−5.88 (m, 1H), 3.67 (td, J = 2.7, 1.3 Hz, 1H), 3.41 (dd, J = 4.3, 2.8 Hz, 1H), 2.30 (ddq, J = 13.6, 5.1, 2.6 Hz, 1H), 2.19−2.14 (m, 2H), 1.72−1.64 (m, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 145.0, 120.7, 118.8 (q, J = 319 Hz), 56.0, 48.7, 20.3, 19.0. IR (film): 2906, 1693, 1649, 1403, 1194, 1125, 1071, 1030, 946, 880, 811, 778 cm^{-1}. HRMS: Calculated for $C_7H_8F_3O_4S$ $(M + H)^+$: 245.0090; found 245.0093.

*trans-6-Hydroxy-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-2-en-1-yl Acetate (**15**).* To a solution of 7-oxabicyclo[4.1.0]hept-2-en-2-yl trifluoromethanesulfonate (**14**, 1.0 g, 4.1 mmol, 1 equiv) in acetic acid (3.0 mL) was added trifluoroacetic acid (40 μL, 0.30 mmol, 6.5 mol %). The reaction mixture was stirred for 24 h at room temperature, after which time additional trifluoroacetic acid (40 μL, 0.30 mmol, 6.5 mol %) was added. After an additional 24 h, the reaction mixture was diluted with Et_2O (15 mL) and poured into saturated aqueous Na_2CO_3 (60 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 70 mL). The pooled organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (2:1 hexanes/EtOAc) afforded the title compound (842 mg, 68%) as a yellow oil. R_f = 0.20 (2:1 hexanes/EtOAc). ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.10 (t, J = 4.0 Hz, 1H), 5.32−5.30 (m, 1H), 4.06−4.03 (m, 1H), 2.48−2.39 (m, 1H), 2.34−2.26 (m, 1H), 2.15 (s, 3H), 1.93−1.79 (m, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.2, 143.2, 124.4, 118.5 (q, J = 319 Hz), 71.6, 69.1, 25.0, 20.9, 20.3. IR (film): 3400 (br), 2899, 1724, 1399, 1353, 1200, 1126, 879, 815 cm^{-1}. HRMS: Calculated for $C_9H_{11}F_3NaO_6S$ $(M + Na)^+$: 327.0121; found 327.0122.

*trans-6-Hydroxy-2-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl Acetate (**17**).* To a solution of *trans*-6-hydroxy-2-(((trifluoromethyl)-sulfonyl)oxy)cyclohex-2-en-1-yl acetate (**15**, 5.6 g, 18.4 mmol, 1 equiv) in THF (75 mL) was added $PdCl_2(PPh_3)_2$ (322 mg, 0.46 mmol, 2.5 mol %) and CuI (175 mg, 0.92 mmol, 5 mol %). Freshly distilled diisopropylethylamine (32 mL, 184 mmol, 10 equiv) was added, the heterogeneous mixture was cooled to 0 °C, and trimethylsilyl acetylene (7.8 mL, 55.2 mmol, 3 equiv) was added. The resulting heterogeneous, black mixture was allowed to warm to room temperature and stir for 17 h, at which point it was diluted with Et_2O (50 mL) and vacuum filtered through a pad of Celite. The pad was washed with additional Et_2O (200 mL). The filtrate was washed with saturated aqueous NH_4Cl (3 × 200 mL) and then brine (200 mL), and then it was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (4:1 to 2:1 hexanes/EtOAc) afforded the title compound (4.13 g, 89%) as a viscous oil. R_f = 0.34 (1:1 hexanes/EtOAc). ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.31−6.28 (m, 1H), 5.31 (ddt, J = 6.6, 2.7, 1.8 Hz, 1H), 3.83 (ddd, J = 10.3, 6.7, 3.6 Hz, 1H), 2.61 (br s, 1H), 2.33−2.16 (m, 2H), 2.14 (s, 3H), 1.98−1.91 (m, 1H), 1.72 (dddd, J = 13.2, 10.4, 8.9, 6.2 Hz, 1H), 0.15 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.6, 139.2, 119.4, 102.5, 94.0, 74.9, 69.7, 27.6, 24.0, 21.2, −0.03. IR (film): 3394 (br), 2990, 2916, 2859, 2119, 1719, 1411, 1351, 1232, 1161, 1067, 1033, 928, 898, 833, 793, 750, 688, 607 cm^{-1}. HRMS: Calculated for $C_{13}H_{20}NaO_3Si$ $(M + Na)^+$: 275.1074; found 275.1076.

*trans-2-Acetoxy-3-((trimethylsilyl)ethynyl)cyclohex-3-en-1-yl non-8-ynoate (**19**).* A flame-dried 50 mL flask equipped with a stir bar was charged with non-8-ynoic acid (**18**, 1.62 g, 10.5 mmol, 1.05 equiv). A solution of *trans*-6-hydroxy-2-((trimethylsilyl)ethynyl)-cyclohex-2-en-1-yl acetate (**17**, 2.52 g, 10 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was introduced via syringe. The homogeneous solution was cooled to 0 °C, and then DMAP (4-dimethylaminopyridine, 122 mg, 1.0 mmol, 10 mol %) was added followed by DCC (*N*,*N*′-dicyclohexylcarbodiimide, 2.89 g, 14 mmol, 1.4 equiv). After 5 min, the cooling bath was removed, and the light yellow, heterogeneous mixture was stirred at room temperature for 15 h. The mixture was then diluted with 1:1 hexanes/Et_2O (20 mL) and vacuum filtered through a pad of Celite. The pad was washed with additional Et_2O, and the filtrate was concentrated. Purification by column chromatography (8:1 hexanes/EtOAc) delivered the title compound (3.36 g, 87%) as an oil. R_f = 0.34 (2:1 hexanes/EtOAc). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.30 (t, J = 4.0 Hz, 1H), 5.49 (dd, J = 6.3, 1.5 Hz, 1H), 4.97 (ddd, J = 9.5, 6.3, 3.3 Hz, 1H), 2.29−2.24 (m, 4H), 2.18−2.14 (m, 2H), 2.07 (s, 3H), 1.94−1.89 (m, 2H), 1.81−1.75 (m, 1H), 1.59 (quintet, J = 7.5 Hz, 2H), 1.50 (quintet, J = 7.3 Hz, 2H), 1.42−1.36 (m, 2H), 1.32−1.28 (m, 2H), 0.14 (s, 9H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.0, 170.0, 138.7, 119.5, 102.3, 94.3, 84.6, 70.6, 70.1, 68.4, 34.4, 28.6, 28.4, 28.3, 24.9, 24.6, 23.4, 21.0, 18.4, −0.10. IR (film): 3246, 2896, 2120, 1716, 1412, 1351, 1211, 1032, 904, 833, 750 cm^{-1}. HRMS: Calculated for $C_{22}H_{32}NaO_4Si$ $(M + Na)^+$: 411.1962; found 411.1956.

*trans-2-Acetoxy-3-ethynylcyclohex-3-en-1-yl Non-8-ynoate (**8**).* To a light yellow, homogeneous solution of *trans*-2-acetoxy-3-((trimethylsilyl)ethynyl)cyclohex-3-en-1-yl non-8-ynoate (**19**, 3.04 g, 7.82 mmol, 1 equiv) in THF (40 mL) at 0 °C was added TBAF (tetrabutylammonium fluoride, 0.25 M in THF, 40 mL, 10 mmol, 1.3 equiv). The resulting homogeneous, red-yellow mixture was stirred for 45 min at 0 °C, after which time it was diluted with Et_2O and poured into water (150 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 150 mL). The pooled organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) delivered the title compound (1.86 g, 75%) as a light yellow oil. R_f = 0.29 (4:1 hexanes/EtOAc). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.39 (td, J = 4.0, 1.1 Hz, 1H), 5.48 (dq, J = 5.9, 1.8 Hz, 1H), 4.99 (ddd, J = 9.0, 5.9, 3.2 Hz, 1H), 2.80 (s, 1H), 2.30−2.25 (m, 4H), 2.17 (td, J = 7.0, 2.7 Hz, 2H), 2.09 (s, 3H), 1.96−1.91 (m, 2H), 1.86−1.80 (m, 1H), 1.63−1.57 (m, 2H), 1.54−1.48 (m, 2H), 1.44−1.38 (m, 2H), 1.34−1.29 (m, 2H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.0, 170.2, 140.0, 118.4, 84.6, 81.3, 77.0, 70.3, 69.8, 68.4, 34.4, 28.6, 28.4, 28.3, 24.9, 24.2, 23.2, 21.0, 18.4. IR (film): 3243, 2895, 1720, 1351, 1213, 1031 cm^{-1}. HRMS: Calculated for $C_{19}H_{24}NaO_4$ $(M + Na)^+$: 339.1567; found 339.1567.

*Lactone of 10-(6-Acetoxy-5-hydroxycyclohex-1-en-1-yl)undec-10-en-8-ynoic acid (**9**), 0.10 mmol Scale.* Palladium acetate (5.0 mg, 0.022 mmol) and tris-2,6-dimethoxyphenylphosphine (TDMPP, 20.0 mg, 0.044 mmol) were combined in a flame-dried 2-dram vial equipped with a stir bar. The vial was sealed with a septum and flushed with nitrogen, and then freshly distilled PhMe (4.4 mL) was added. The resulting homogeneous, light red solution was stirred for 15 min at room temperature. A portion of this catalyst solution (1.0 mL, corresponds to 0.005 mmol palladium acetate (5 mol %) and 0.010 mmol TDMPP (10 mol %)) was transferred via syringe to a separate flame-dried 2-dram vial equipped with a stir bar that had previously been flushed with nitrogen. This vessel was heated to 50 °C, and then

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triethylamine (14 uL, 0.10 mmol, 1 equiv) was added. A solution of *trans*-2-acetoxy-3-ethynylcyclohex-3-en-1-yl non-8-ynoate (**8**, 31.6 mg, 0.10 mmol, 1 equiv) in freshly distilled PhMe (1.0 mL) was added via syringe pump over 4 h. After 4 h 30 min, TLC analysis (2:1 hexanes/Et_2O) indicated complete consumption of the starting material. The reaction mixture was diluted with Et_2O/CH_2Cl_2 (1:1, 2.5 mL) and filtered through a pipet plug of Florisil, which was washed with additional Et_2O/CH_2Cl_2 (1:1). The filtrate was concentrated, and the crude material was purified via preparative thin-layer chromatography (2:1 hexanes/Et_2O) to afford the title compound (18.9 mg, 60%) as a white solid.

1.0 g Scale: A flame-dried 100 mL flask equipped with a stir bar was charged with palladium acetate (35.5 mg, 0.158 mmol, 5 mol %) and tris-2,6-dimethoxyphenylphosphine (TDMPP, 140 mg, 0.316 mmol, 10 mol %). The vessel was purged with nitrogen, and freshly distilled PhMe (31.6 mL) was added. The resulting homogeneous, light red solution was stirred for 30 min at room temperature, and then the vessel was immersed in an oil bath preheated to 50 °C. To this solution was added freshly distilled triethylamine (0.44 mL, 3.16 mmol, 1 equiv). A solution of *trans*-2-acetoxy-3-ethynylcyclohex-3-en-1-yl non-8-ynoate (**8**, 1.0 g, 3.16 mmol, 1 equiv) in freshly distilled PhMe (31.6 mL) was added via syringe pump over 4 h. After 4 h 30 min, TLC analysis (2:1 hexanes/Et_2O) indicated complete consumption of the starting material. The reaction mixture was diluted with 1:1 Et_2O/CH_2Cl_2 (2.5 mL) and filtered through a column of Florisil, which was rinsed with 1:1 Et_2O/CH_2Cl_2 and then with Et_2O until TLC analysis (2:1 hexanes/Et_2O) confirmed complete elution of the product. The filtrate was concentrated. Purification of the residue by column chromatography (2:1 hexanes/Et_2O) afforded the title compound (470 mg, 47%) as a white solid. R_f = 0.40 (2:1 hexanes/Et_2O). Mp = 64−66 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.11 (dd, J = 4.8, 2.8 Hz, 1H), 5.68−5.65 (m, 1H), 5.32 (d, J = 1.9 Hz, 1H), 5.22 (q, J = 2.7 Hz, 2H), 2.45−2.29 (m, 5H), 2.21−2.15 (m, 1H), 2.03 (s, 3H), 1.94−1.84 (m, 3H), 1.63−1.46 (m, 5H), 1.37−1.27 (m, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 173.0, 169.3, 134.4, 132.7, 130.6, 119.6, 93.4, 79.8, 67.5, 65.7, 33.3, 27.93, 27.90, 27.2, 25.0, 21.17, 21.15, 21.0, 18.9. IR (film): 3413, 2891, 2819, 2191, 1722, 1576, 1421, 1344, 1293, 1261, 1208, 1153, 1114, 1055, 1039, 1007, 974, 949, 898, 835, 783, 721 cm^{-1}. HRMS: Calculated for $C_{19}H_{24}NaO_4$ $(M + Na)^+$: 339.1567; found 339.1563.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01920.

X-ray crystallographic information file associated with compound **9** (CIF)

^{1}H and ^{13}C NMR spectra of all new compounds, a full-size ORTEP representation of compound **9** (PDF)

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Notes

The authors declare no competing financial interest.

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(20) In this case and in related experiments, the mass balance of the reaction consisted of a complex mixture of unidentified byproducts, as judged by ^{1}H NMR analysis of the crude reaction output.

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