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Synthetic Studies and Mechanistic Observations in Nickel-Catalyzed Polycyclizations

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Abstract: A series of polyunsaturated enones were investigated in $Ni(COD)_2$ / organozinc - mediated cyclizations. One substrate class underwent an efficient [2+2+2] cycloaddition reaction to generate a tricyclic ring system from a linear precursor. A discussion of probable mechanisms is provided.

INTRODUCTION

Metal-catalyzed cyclizations of polyunsaturated substrates have proven to be highly efficient in the construction of complex molecules. Recent advances in palladium-catalyzed Heck reactions best demonstrate the utility of metal-catalyzed polycyclizations.[1] Our laboratory has recently devoted considerable attention to the development of nickel-catalyzed cyclizations of enones that possess tethered unsaturation in the preparation of relatively simple mono- and bicyclic molecules.[2] In order to increase the complexity of the structures that may be accessed by enone cyclizations, we have investigated the participation of polyunsaturated enones in nickel-catalyzed couplings. In addition to synthetic implications, the results of this study provide mechanistic insight that should increase the potential for the rational design of more complex variants of nickel-catalyzed enone cyclizations and other related metal-catalyzed processes.

RESULTS AND DISCUSSION

We previously reported that alkynyl enones were efficiently cyclized in the presence of $Ni(COD)_2$ and organozincs (generated *in situ* from organolithiums and $ZnCl_2$).[2] Several mechanistic pathways could potentially be involved. We initially considered the four mechanisms outlined below as most probable (Scheme 1). In a first possible mechanism, oxidative cyclization of a Ni(0) alkynyl enone complex would produce metallacycle **1**. Organozinc transmetallation with **1** would produce species **2**, which could then undergo reductive elimination to form product **3**. A second possible mechanism involves formation of π-allyl complex **4** followed by alkyne insertion and transmetallation to afford the same key intermediate **2**. In a third mechanism, single electron transfer from Ni(0) to the enone would produce allylic ketyl **5** that could undergo free radical cyclization to alkenyl radical **6**. Recombination of the alkenyl radical with the paramagnetic Ni(I) species,

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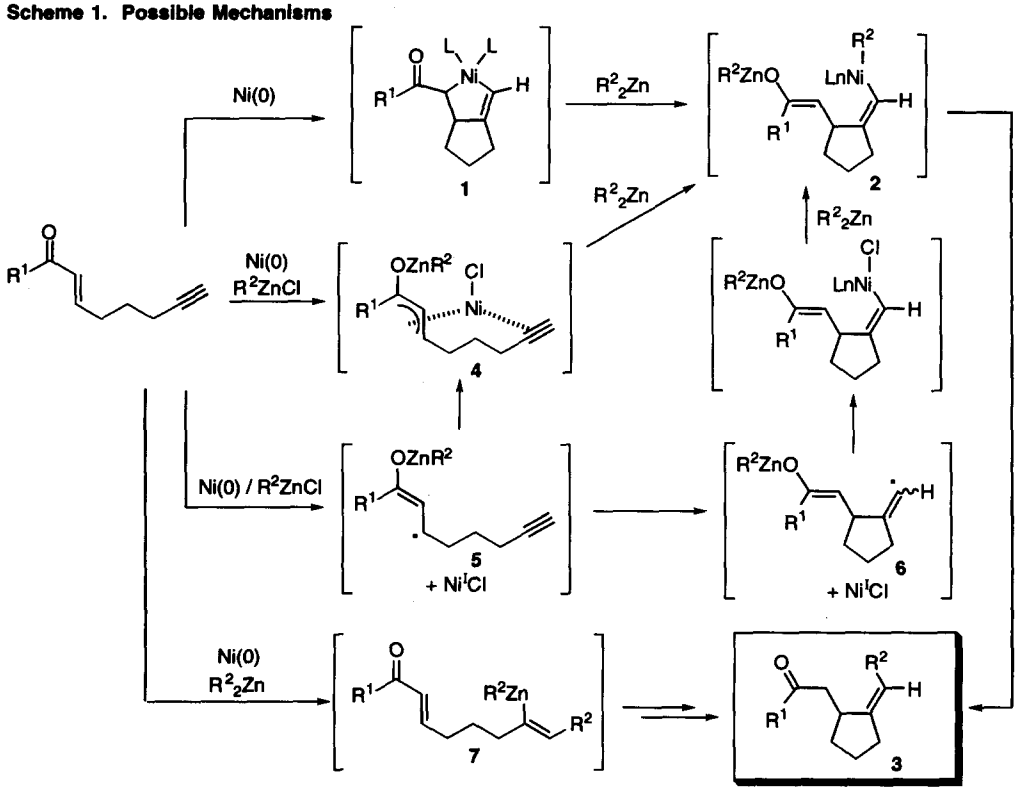
followed by transmetallation would also afford intermediate **2**. A fourth mechanism involves carbozincation of the alkyne to afford alkenylzinc **7** followed by conjugate addition to afford product **3**. As discussed below, the individual steps of each of these mechanisms are reasonably well precedented.

Scheme 1. Possible Mechanisms

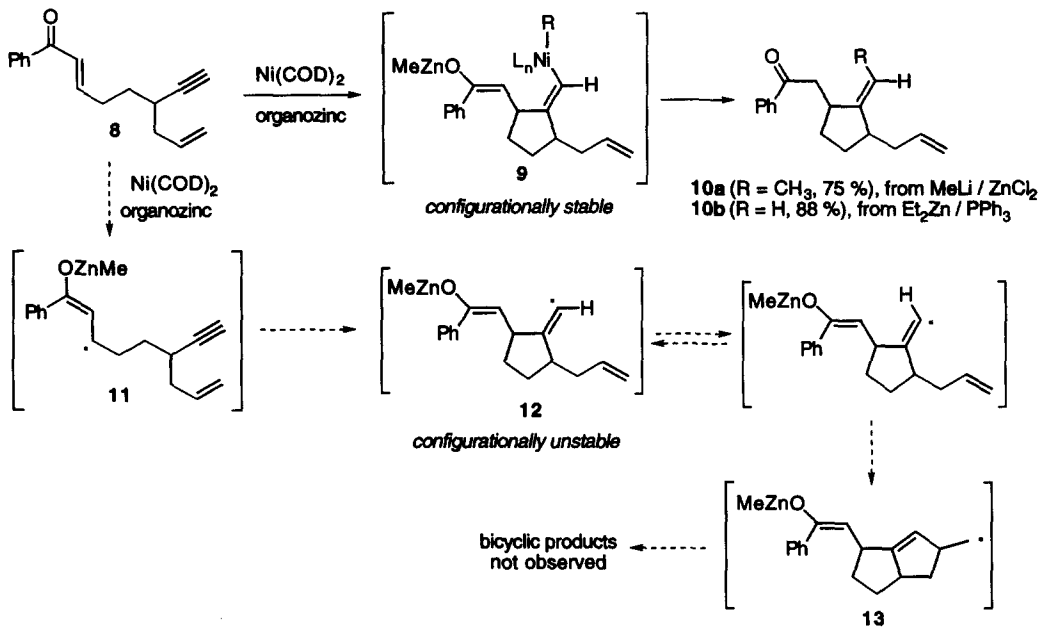


We believed that discriminating between nickel-promoted free radical cyclizations and insertions involving discreet carbon-nickel bonds should first be addressed in order to allow the predictable design of new synthetic applications. Early studies by Schwartz provided evidence that electron transfer was involved in $Ni(acac)_2$ / DIBAL-catalyzed conjugate additions of alkenylzirconocenes to enones.[3] Given that allylic ketyl free radical cyclizations are known to be facile with enone substrates that possess tethered unsaturated groups,[4] free-radical cyclizations could potentially be involved in the Ni(0) / organozinc catalytic system of our studies. Knochel has also provided convincing evidence that free radical cyclizations are involved in the $Ni(acac)_2$ / Et_2Zn-promoted cyclizations of alkyl iodides.[5]

The high configurational stability of vinyl organometallics[6] compared with vinyl radicals[7] appeared to be a reasonable issue to study. Accordingly, substrate **8** was subjected to cyclization conditions (Scheme 2). Given that migratory insertions involving alkynes proceed with high cis selectivities,[6,8] monocycle **10** was

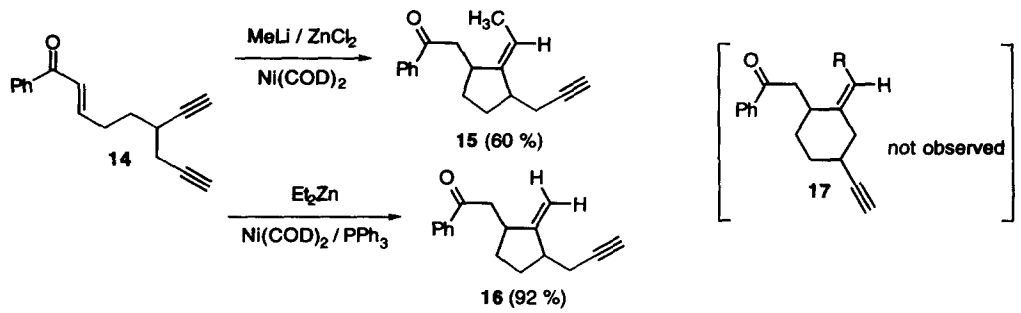
expected by any of the above mechanisms with the exception of a free radical cyclization. Since free radical **11** is allylically stabilized, whereas configurationally unstable alkenyl radical **12** would be much less stable, the rate constant for cyclization of **12** to **13** would be expected to be several orders of magnitude greater than that observed for cyclization of **11** to **12**.[9] On the basis of this expectation, monocyclic products by a free radical mechanism seem unlikely. Clean monocyclization of **8** to produce **10a** (as a 1.1:1 mixture of diastereomers) was observed upon exposure of **8** to $Ni(COD)_2$ and MeLi / $ZnCl_2$, and product **10b** (as a 2:1 mixture of diastereomers) was observed by employing $Ni(COD)_2$ / PPh_3 and Et_2Zn, thus suggesting that free radical cyclizations are likely not involved.

Scheme 2. Radical Probe Studies



The involvement of initial alkyne carbometallation was investigated with closely related diyne substrate **14** (Scheme 3). Knochel very recently documented that alkyne carbozincation readily occurs with $Ni(acac)_2$ under conditions closely related to those of our studies.[10] However, if alkyne carbometallation initiates the reaction sequence, discrimination between the two structurally similar terminal alkynes of **14** should be poor. Both alkylative and reductive cyclizations of **14** led exclusively to five membered ring products, with no six membered ring products such as **17** being observed. The two diastereomers of products **15** and **16** are clearly distinguishable from those of **17** given that the acetylenic protons of each of the cyclized products appear as clean triplets in the ^1H NMR spectra. On the basis of the high regioselectivity observed in reactions of **14**, we believe that interaction of the enone functionality with the nickel catalyst occurs either in concert with or prior to alkyne insertion and that initial alkyne carbo- or hydrometallation is unlikely.[11]

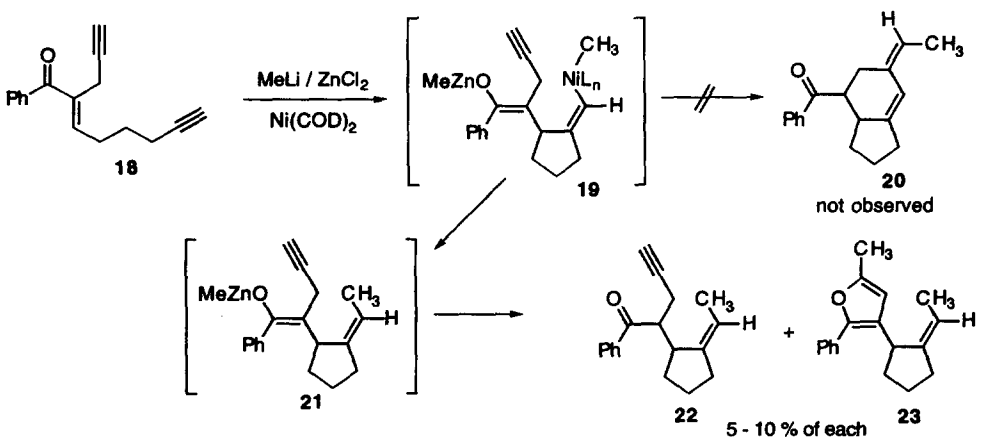
Scheme 3. Five- vs. Six-Membered Ring Competition



We consider a mechanism involving formation of either a π-allyl complex or a metallacycle to be most consistent with the above results. Nickel metallacycles have been rigorously studied by Grubbs,[12] and several examples have been characterized by X-ray crystallography.[13] A catalytic sequence closely related to the metallacycle mechanism described in Scheme 1 was previously proposed by Waymouth in the zirconocene-catalyzed cyclomagnesiation of dienes.[14] Enone-derived π-allyl complexes are also well-precedented entities. In studies most directly related to our experimental conditions, Mackenzie documented that π-allyl complexes were obtained upon treatment of enals with $Ni(COD)_2$ and TBSCl.[15] Alkene insertions into π-allyl complexes are known in several contexts.[16] Ikeda has recently presented data in support of a metallacycle mechanism in a closely-related intermolecular process involving enones, alkynes, and alkynylstannanes.[17]

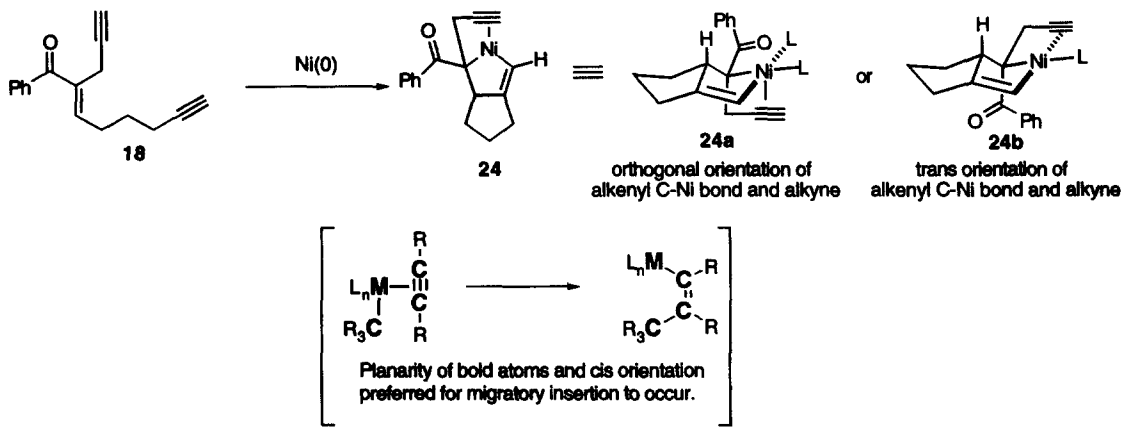
With the goal of developing a polycyclization procedure in mind, we next examined diyne substrates with an orientation of the unsaturated units that might allow polycyclization via either metallacycles or π-allyl complexes (Scheme 4). Substrate **18** was first examined, however insertion of both alkyne units was not observed. Poor mass balances were typically obtained, and the only products identified were monocycle **22** and furan **23**, which were presumably both derived from kinetic enolate **21**.

Scheme 4. An Unsuccessful Attempt at Diyne Bis-Cyclization



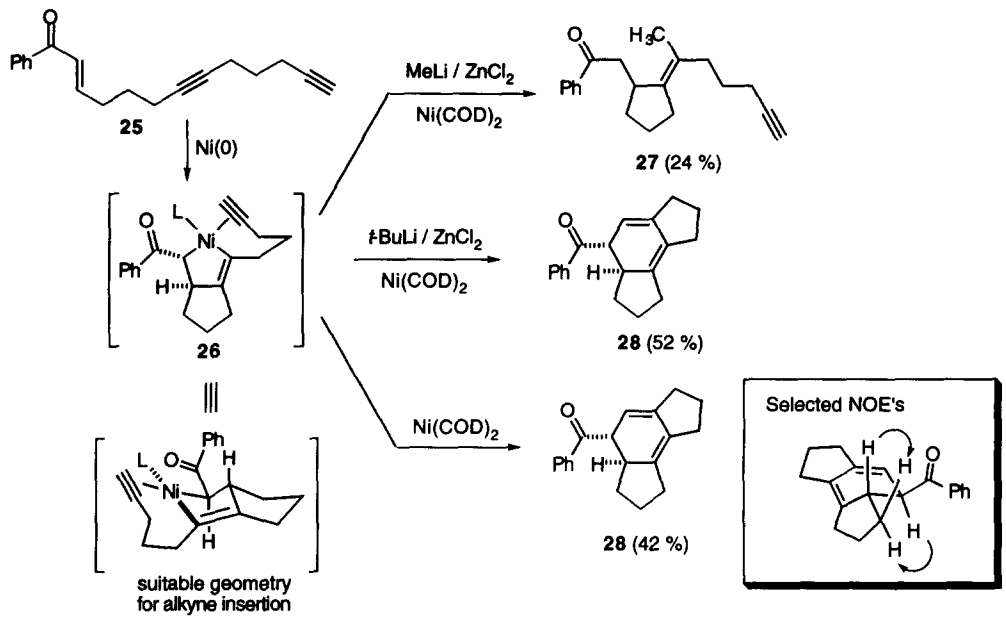
Bicycle **20** was not observed under any conditions in the reactions of substrate **18**, which is perhaps not surprising if intermediate **19** is derived from a metallacycle. An analysis of molecular models suggests that metallacycle **24**, derived from substrate **18**, would likely not undergo further cyclization since the alkenyl carbon-metal bond and tethered alkyne cannot adopt a suitable geometry for migratory insertion to occur (Scheme 5). Theoretical,[18] kinetic,[19] and synthetic[20] studies have provided evidence that migratory insertions of metal carbon bonds and an unsaturated component proceed via an eclipsed (coplanar) conformation with a cis orientation between the two ligands involved in bond formation. In metallacycle **24**, the alkyne is perpendicular to the alkenyl carbon-metal bond in diastereomer **24a**, and trans to the alkenyl carbon-metal bond in diastereomer **24b**, thus disfavoring further cyclization to [3.4.0]-bicyclononane products such as **20**.

Scheme 5. An Analysis of Metallacycle Conformation



Substrate **25**, with the enone functionality at the terminal position rather than an internal position, was next examined (Scheme 6). Upon treatment with dimethylzinc and $Ni(COD)_2$, monocyclic product **27** was obtained in 24% yield along with isomeric mixtures of polycyclic compounds. However, by increasing the bulk of the organozinc, the formal [2+2+2] cycloaddition product **28** was produced in 52% yield as a single isomer. Perhaps most interestingly from a mechanistic perspective, tricycle **28** was also obtained in slightly lower yield in the absence of organozincs.[21] This result clearly demonstrates that carbon-carbon bond formation in alkynyl enone cyclizations does not strictly require a Lewis acidic component. Given that Mackenzie previously demonstrated that Lewis acid catalysis is required in the formation of enone- and enal-derived π-allyl complexes,[15] we suspect that the metallacycle pathway may be operative in nickel-catalyzed organozinc-promoted alkynyl enone cyclizations. Lautens has demonstrated that nickel-catalyzed [2+2+2] cycloadditions in the context of homo-Diels Alder reactions are successful in the absence of Lewis acids,[22] and Ikeda very recently demonstrated that fully intermolecular [2+2+2] cycloadditions involving one enone and two alkynes are successful in the presence of organoaluminum Lewis acids.[23] Further efforts to exploit the novel [2+2+2] cycloaddition pathway and to corroborate the proposed metallacycle intermediacy are in progress.[24]

Scheme 6. A Successful Diyne Cyclization



CONCLUSION

Nickel-catalyzed cyclizations of several classes of polyunsaturated substrates were investigated. A new, fully intramolecular nickel-mediated [2+2+2] cycloaddition was discovered, and the substrate structural features that allow the nickel-catalyzed polycyclizations to occur were delineated. The experimental data appears to be best explained by a mechanism involving metallacycle formation. Analysis of the conformation of the proposed metallacycle intermediates provides a tool for predicting the feasibility of new classes of polycyclizations. The utility of this predictive tool will be the subject of future investigations.

EXPERIMENTAL SECTION

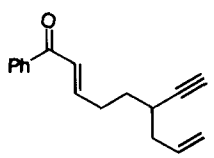
Unless otherwise noted, reagents were commercially available and were used without purification. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone ketyl. Dichloromethane and DMSO were distilled from calcium hydride. Oxalyl chloride was distilled. All organolithium reagents were freshly titrated with 2,5-dimethoxybenzyl alcohol. Zinc chloride was dried at 150 °C at 0.1 mm overnight, then thoroughly ground by mortar and pestle in an inert atmosphere glovebox, and then dried again overnight at 150 °C at 0.1 mm Hg. $Ni(COD)_2$ and anhydrous $ZnCl_2$ were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under a nitrogen or argon atmosphere. Phosphoranes were prepared by literature methods.[25]

General Procedures for Nickel-Catalyzed Reactions

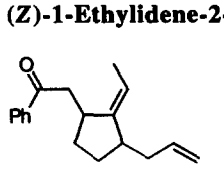
General Procedure A. A 0.2-0.3 M solution of $ZnCl_2$ (3.0 equiv) in THF was stirred at 0 °C, and MeLi (1.4 M ether solution, 4.5 equiv) was added by syringe followed by stirring for 20-30 min at 0 °C. A 0.01 M THF solution of $Ni(COD)_2$ (0.1 equiv) was added, and the resultant mixture was immediately transferred by cannula to a 0.03-0.05 M solution of the unsaturated substrate (1.0 equiv). After consumption of starting material by TLC analysis (typically 0.5-2.0 h at 0 °C), the reaction mixture was subjected to an extractive workup (NH_4Cl / NH_4OH pH = 8 buffer/EtOAc) followed by flash chromatography on SiO_2.

General Procedure B. A 0.03-0.04 M solution of PPh_3 (0.5 equiv) in THF was added to $Ni(COD)_2$ (0.1 equiv) at 25 °C and stirred for 2 min. The nickel solution was transferred to a 0.2-0.3 M solution of Et_2Zn (3.0 equiv) in THF at 0 °C, and the resultant mixture was immediately transferred by cannula to a 0.03-0.04 M 0 °C THF solution of the unsaturated substrate (1.0 equiv). After consumption of starting material by TLC analysis (typically 1.0-3.0 h at 0 °C), the reaction mixture was subjected to an extractive workup (NH_4Cl / NH_4OH pH = 8 buffer/EtOAc) followed by flash chromatography on SiO_2.

(2*E*)-6-Ethynyl-1-(phenyl)nona-2,8-dien-1-one (8). DMSO (0.96 mL, 13.48 mmol) was added dropwise to oxalyl chloride (0.59 mL, 6.75 mmol) in 30 ml CH_2Cl_2 at -78°C. After stirring for 10-15 min. at -78 °C, 4-(ethynyl)hept-6-en-1-ol[26] (0.65 g, 4.73 mmol) was added dropwise, and the mixture was allowed to warm to -40 °C. After the mixture was stirred for 30 min, Et_3N (3.45 mL, 24.75 mmol) was added dropwise and the mixture was stirred for 3 h at 25 °C. The mixture was quenched with 0.1 N HCl, and the CH_2Cl_2 layer was separated, dried with $MgSO_4$ and filtered. The crude aldehyde in CH_3CN (30 mL) was then treated with $Ph_3P{=}CHC(O)Ph$ (2.3 g, 5.9 mmol) and was heated at 75 °C for 12 h. Evaporation and flash chromatography (SiO_2, hexanes / EtOAc 9:1) provided 0.75 g (67% overall yield) of **8** as a pale yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.93 (m, 2H), 7.53-7.56 (m, 1H), 7.44-7.47 (m, 2H), 7.05 (dt, J = 15.5, 7.0 Hz, 1H), 6.92 (d, J = 15.5 Hz, 1H), 5.86 (ddt, J = 10.3, 17.3, 7.3 Hz, 1H), 5.10 (m, 2H), 2.56 (m, 1H), 2.45 (m, 2H), 2.26 (dt, J = 7.0, 1.0 Hz, 2H), 2.14 (d, J = 2.5 Hz, 1H), 1.60-1.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 148.7, 137.9, 135.3, 132.7, 128.5, 126.3, 117.1, 86.3, 70.5, 39.1, 32.6, 30.9, 30.5; IR (film) 1670, 1620 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{18}O$ 238.1358, found 238.1353 (M^+).



(Z)-1-Ethylidene-2-(2-oxo-2-phenylethyl)-5-(prop-2-enyl)cyclopentane (10a). Following general procedure A, enone **8** (40 mg, 0.168 mmol), MeLi (0.5 mL, 0.756 mmol of a 1.4 M diethyl ether solution), $ZnCl_2$ (70 mg, 0.504 mmol), and $Ni(COD)_2$ (5 mg, 0.017 mmol) were employed to produce, after flash chromatography (15:1 hexanes:EtOAc), 32 mg (75%) of **10a** (1.1:1 mixture of diastereomers) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.97 (m, 2H), 7.54-7.58 (m, 1H), 7.45-7.48 (m, 2H), 5.83 (m, 1H), 5.36 (tq, J = 2.0, 7.0 Hz, $1H_{minor}$), 5.29 (tq, J = 2.0, 7.0 Hz, $1H_{major}$), 4.97-5.06 (m, 2H), 3.32 (m, 1H), 3.16 (dd, J = 17.0, 3.5 Hz, $1H_{major}$), 3.02 (dd, J = 16.8, 3.3 Hz, $1H_{minor}$),



2.88-2.97 (m, 1H), 2.44 (m, 1H), 2.32-2.40 (m, 1H), 1.74-2.12 (m, 3H) 1.66 (m, 3H), 1.51-1.55 (m, $1H_{major}$), 1.37-1.46 (m, $1H_{minor}$), 1.21-1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.74, 199.67, 149.6, 149.5, 137.8, 137.5, 137.3, 137.2 133.0, 132.9, 128.59, 128.57, 128.0, 116.3, 115.5, 115.3, 114.9, 44.1, 44.0, 42.91, 42.87, 39.9, 38.2, 36.8, 36.6, 30.7, 30.6, 30.4, 29.9, 14.8, 14.4; IR (film) 1682, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{15}H_{17}O$ 213.1279, found 213.1273 ($(M - CH_2CH{=}CH_2)^+$).

1-Methylidene-2-(2-oxo-2-phenylethyl)-5-(prop-2-enyl)cyclopentane (10b). Following general procedure B, enone **8** (40 mg, 0.168 mmol), Et_2Zn (52 μL, 0.504 mmol), $Ni(COD)_2$ (5 mg, 0.017 mmol), and PPh_3 (22 mg, 0.085 mmol) were employed to produce, after flash chromatography (hexanes), 35.4 mg (88%) of **10b** (2:1 mixture of diastereomers) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 5.82 (ddt, J = 10.5, 17.3, 7.0 Hz, 1H), 4.88-5.06 (m, 4H), 3.27 (dd, J = 16.0, 4.0 Hz, $1H_{minor}$), 3.20 (dd, J = 16.5, 4.5 Hz, $1H_{major}$), 3.10 (m, $1H_{major}$), 3.02 (m, $1H_{minor}$), 2.91-2.99 (m, 1H), 2.55 (m, 1H), 2.33-2.43 (m, 1H), 2.02-2.11 (m, $1H+1H_{minor}$), 1.88-1.96 (m, 1H), 1.76-1.83 (m, $1H_{major}$), 1.16-1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.73, 199.69, 159.0, 158.8, 137.4, 137.2, 133.0, 128.6, 128.1, 115.71, 115.66, 104.9, 104.6, 44.1, 43.9, 43.6, 43.3, 40.3, 40.0, 39.3, 39.2, 31.8, 30.7, 30.5, 29.4; IR (film) 1686, 1597 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{14}H_{15}O$ 199.1123, found 199.1127 ($(M - CH_2CH{=}CH_2)^+$).

(2*E*)-6-Ethynyl-1-(phenyl)non-2-en-8-yn-1-one (14). 4-(Ethynyl)hept-6-yn-1-ol was prepared exactly following the procedure for the synthesis of 4-(ethynyl)hept-6-en-1-ol[26] using propargyl bromide as the alkylating agent. This alcohol was then oxidized by a Swern oxidation as described for compound **8** on a 1.2 mmol scale. The crude aldehyde in 40 mL of C_6H_6 was then treated with $Ph_3P{=}CHC(O)Ph$ and was heated at 70 °C for 12 h. Evaporation and flash chromatography (SiO_2, hexanes / EtOAc 9:1) provided 0.18 g (65% overall yield) of **14** as a pale yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92-7.94 (m, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.06 (dt, J = 15.5, 6.5 Hz, 1H), 6.95 (d, J = 15.5 Hz, 1H), 2.55-2.66 (m, 2H), 2.39-2.52 (m, 3H), 2.20 (d, J = 2.5 Hz, 1H), 2.08 (t, J = 2.5 Hz, 1H), 1.85-1.92 (m, 1H), 1.73-1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 148.3, 137.8, 132.7, 128.5, 126.5, 85.0, 81.0, 70.9, 70.5, 32.0, 30.4, 30.2, 24.7; IR (film) 2118, 1670, 1620 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{15}O$ 235.1123, found 235.1120 ($(M - H)^+$).

(*Z*)-1-Ethylidene-2-(2-oxo-2-phenylethyl)-5-(prop-2-ynyl)cyclopentane (15). Following general procedure A, enone **14** (42 mg, 0.18 mmol), MeLi (0.57 mL, 0.81 mmol of a 1.4 M ethyl ether solution), $ZnCl_2$ (73 mg, 0.53 mmol), and $Ni(COD)_2$ (5 mg, 0.017 mmol) were employed to produce, after flash chromatography (19:1 hexanes:Et_2O), 27 mg (60%) of **15** (1.1:1 mixture of diastereomers) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 5.41 (tq, J = 1.5, 6.5 Hz, 0.5H), 5.35 (tq, J = 2.0, 7.0 Hz, 0.5H), 3.35 (m, 1H), 3.15 (dd, J =

16.5, 3.0 Hz, 0.5H), 2.93-3.02 (m, 1.5H), 2.60 (m, 1H), 2.46 (ddd, J = 16.8, 5.3, 2.5 Hz, 0.5H), 2.39 (ddd, J = 17.0, 5.3, 2.5 Hz, 0.5H), 2.30 (ddd, J = 16.5, 7.8, 2.5 Hz, 0.5H) 2.16 (ddd, J = 17.0, 8.5, 2.5 Hz, 0.5H), 1.76-2.09 (m, 2H), 1.98 (t, J = 2.8 Hz, 0.5H), 1.96 (t, J = 2.5 Hz, 0.5H) 1.66 (m, 3H), 1.55-1.64 (m, 1H), 1.32-1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 199.5, 148.4, 148.3, 137.3, 137.2, 133.0, 128.6, 128.0, 117.2, 115.9, 83.73, 83.70, 68.8, 68.7, 43.8, 43.0, 42.51, 42.49, 36.7, 36.6, 30.9, 30.6, 30.2, 29.8, 24.2, 22.9, 14.8, 14.4; IR (film) 2115, 1682, 1597 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{15}H_{17}O$ 213.1279, found 213.1284 ((M - CH_2CCH)$^+$).

1-Methylidene-2-(2-oxo-2-phenylethyl)-5-(prop-2-ynyl)cyclopentane (16). Following general procedure B, enone **14** (39 mg, 0.165 mmol), Et_2Zn (52 μL, 0.51 mmol), $Ni(COD)_2$ (5 mg, 0.017 mmol), and PPh_3 (22 mg, 0.085 mmol) were employed to produce, after flash chromatography (19:1 hexanes:Et_2O), 36 mg (92%) of **16** (2.2:1 mixture of diastereomers) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.98 (m, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 4.99 (m, 1H), 4.96 (t, J = 2.3 Hz, $1H_{major}$), 4.93 (t, J = 2.5 Hz, $1H_{minor}$), 3.27 (dd, J = 16.3, 4.8 Hz, $1H_{minor}$), 3.21 (dd, J = 16.5, 4.5 Hz, $1H_{major}$), 3.03-3.15 (m, 1H), 2.94-3.01 (m, 1H), 2.65-2.73 (m, 1H), 2.40-2.49 (m, 1H), 2.23-2.30 (m, 1H), 1.88-2.12 (m, 3H), 1.63-1.70 (m, $1H_{major}$), 1.38-1.50 (m,1H), 1.20-1.28 (m, $1H_{minor}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 157.7, 157.5, 137.2, 133.0, 128.6, 128.1, 105.7, 105.4, 83.5, 83.2, 68.8, 68.7, 43.8, 42.9, 42.7, 40.3, 40.0, 31.7, 30.8, 30.5, 29.7, 23.8, 23.7; IR (film) 2116, 1682, 1597 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{18}O$ 238.1358, found 238.1355 (M$^+$).

3-Hydroxy-1-phenyl-2-(3-trimethylsilylprop-2-ynyl)-8-(trimethylsilyl)oct-7-yn-1-one. *n*-BuLi (5.0 mL, 12.5 mmol, 2.5 M hexane solution) was added dropwise to diisopropylamine (1.76 mL, 12.5 mmol) in 40 ml THF at -78°C. After stirring for 30 min at -78 °C, a 5 ml THF solution of 1-phenyl-5-(trimethylsilyl)pent-4-yn-1-one[27] (2.4 g, 10.4 mmol) was added, and the mixture was warmed to 0 °C over 10 min. The enolate solution was cooled to -78 °C, and 6-trimethylsilyl-5-hexynal[28] (1.93 mL, 11.5 mmol) was added dropwise as a 5 mL THF solution. After stirring for 20 min, the mixture was quenched with 50 mL of buffered NH_4Cl solution (pH 8), extracted with EtOAc, dried with $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, 6:1 hexanes:EtOAc) providing 2.75 g (66%) of product (1.6:1 mixture of diastereomers) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.61 (m, 1H), 7.49-7.51 (m, 2H), 3.93-3.99 (m, 1H), 3.71-3.80 (m, 1H), 3.07 (d, J = 9.0 Hz, $1H_{minor}$), 2.93 (m, $1H_{major}$), 2.64-2.77 (m, 2H), 2.20-2.25 (m, 2H), 1.69-1.75 (m, 1H), 1.53-1.65 (m, 3H), 0.114 (s, $9H_{major}$), 0.11, (s, $9H_{minor}$), 0.01 (s, $9H_{minor}$), -0.03 (s, $9H_{major}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 203.8, 137.4, 137.0, 133.7, 133.6, 128.8, 128.72, 128.66, 128.62 106.9, 104.6, 103.7, 87.6, 87.2, 85.0, 72.6, 71.2, 49.7, 49.2, 34.6, 33.8, 25.0, 21.2, 19.6, 19.5, 18.3, 0.1, -0.20, -0.24; IR (film) 3482, 2174, 1678, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{23}H_{34}O_2Si_2$ 398.2097, found 398.2101 (M$^+$).

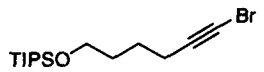
(2*E*)-1-Phenyl-2-(prop-2-ynyl)oct-2-en-7-yn-1-one (18). Methanesulfonylchloride (1.07 mL, 13.82 mmol) was added dropwise to a solution of the product of the previous reaction (2.75 g, 6.91 mmol), Et_3N (1.93 g, 13.82 mmol), and DMAP (20 mg, 0.164 mmol) in 50 mL of CH_2Cl_2 at 25 °C. After stirring for 1 h, the solvent was evaporated, and the residue was dissolved in 40 mL of water, extracted with Et_2O, dried with $MgSO_4$, filtered, and concentrated. The residue was stirred with diazabicycloundecene (DBU) (3.1 mL, 20.73 mmol) in CH_2Cl_2 (60 mL) at 25 °C for 1 h. The reaction was quenched with 1 N HCl, and the organic layer was extracted with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The alkynyl silane was dissolved in THF (60 mL), and tetrabutylammonium fluoride (10.64 mL, 10.64 mmol of a 1 M THF solution) was added at -78 °C. The reaction mixture was allowed to warm to -10 °C, and the mixture was quenched with water, extracted with Et_2O, dried with $MgSO_4$, and concentrated. The residue was chromatographed (SiO_2, 15:1 hexanes:Et_2O), to produce 0.564 g (35% overall) of **18** as a pale yellow oil that was homogenous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.67 (m, 2H), 7.50-7.53 (m, 1H), 7.41-7.44 (m, 2H), 6.34 (t, J = 7.5 Hz, 1H), 3.40 (d, J = 2.5 Hz, 2H), 2.52 (q, J = 7.5 Hz, 2H), 2.24 (td, J = 7.0, 2.5 Hz, 2H), 1.98 (t, J = 2.5 Hz, 1H), 1.97 (t, J = 2.5 Hz, 1H), 1.71 (quintet, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 146.4, 138.1, 136.7, 131.8, 129.4, 128.2, 83.4, 81.3, 69.2, 68.4, 28.1, 27.2, 18.2, 16.3; IR (film) 2117, 1650, 1594 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{15}O$ 235.1123, found 235.1119 ($(M-H)^+$).

(*Z*)-1-Ethylidene-2-[1-(benzoyl)but-3-ynyl]cyclopentane (22). General procedure A was followed except that the reaction was started at -60 °C and then allowed to warm to 0 °C. After stirring for 30 min at 0 °C, the mixture was quenched. Enone **18** (43 mg, 0.18 mmol), MeLi (0.59 mL, 0.82 mmol), $ZnCl_2$ (74 mg, 0.55 mmol), and $Ni(COD)_2$ (5 mg, 0.018 mmol) were employed to produce, after flash chromatography (19:1 hexanes:Et_2O), 2.4 mg (5%) of **22** as a yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.96 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.32-5.36 (m, 1H), 3.79 (dt, J = 6.0, 8.3 Hz, 1H), 3.15 (m, 1H), 2.61 (ddd, J = 16.5, 9.0, 2.5 Hz, 1H), 2.51 (ddd, J = 16.5, 6.0, 3.0 Hz, 1H), 2.07 (m, 2H), 1.88 (t, J = 2.5 Hz, 1H), 1.72 (m, 3H), 1.42-1.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 144.4, 138.6, 133.1, 128.4, 118.1, 82.5, 69.8, 47.4, 42.6, 32.5, 28.8, 22.9, 20.7, 15.4; IR (film) 2119, 1676, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{18}H_{20}O$ 252.1514, found 252.1519 (M^+).

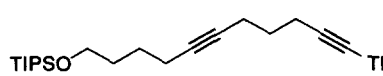
3-[(*Z*)-2-(Ethylidene)cyclopentyl]-5-methyl-2-(phenyl)furan (23). General procedure A was followed except that the reaction was started at -40 °C and then allowed to warm to 0 °C. After stirring for 6 h at 0 °C, the mixture was quenched. Enone **18** (47.5 mg, 0.20 mmol), MeLi (0.68 mL, 0.95 mmol), $ZnCl_2$ (87 mg, 0.64 mmol), and $Ni(COD)_2$ (6 mg, 0.02 mmol) were employed to produce, after flash chromatography (19:1 hexanes:Et_2O), 4.5 mg (9%) of **23** as a colorless oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.64 (m, 2H), 7.38-7.41 (m, 2H), 7.22-7.26 (m, 1H), 5.86 (br s, 1H), 5.42 (qq, J = 6.8, 2.0 Hz, 1H), 3.93 (m, 1H), 2.43-2.50 (m, 1H),

2.40 (m, 1H), 2.30 (d, J = 0.5 Hz, 3H), 2.21-2.27 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.61 (m, 1H), 1.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 145.9, 132.1, 128.4, 126.8, 126.3, 125.4, 117.0, 108.5, 37.4, 36.5, 34.9, 25.4, 14.3, 13.7; IR (film) 1602, 1556 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{18}H_{20}O$ 252.1514, found 252.1513 (M^+).

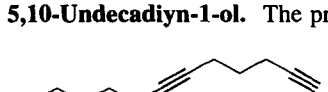
6-Bromo-1-(triisopropylsilyloxy)-5-hexyne. 5-Hexyn-1-ol (1.12 mL, 10.2 mmol) was added to a mixture of imidazole (0.9 g, 13.27 mmol) and DMAP (0.125 g, 1.02 mmol) in 18 mL of CH_2Cl_2 at 0 °C, and then TIPSCl (2.26 mL, 12.24 mmol) was added to the reaction mixture at 0 °C. After stirring for 30 min at 25 °C, the mixture was quenched with NH_4Cl / NH_4OH (pH 8), extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, 49:1 hexane:Et_2O). The intermediate silyl-protected ether was dissolved in acetone (100 mL). To this solution was added *N*-bromosuccinimide (2.18 g, 12.24 mmol) followed by $AgNO_3$ (0.39 g, 2.35 mmol) at 0 °C. The reaction mixture was warmed to 25 °C and was stirred for 1 h. The mixture was quenched with ice-water, extracted with hexane, dried with $MgSO_4$, and concentrated. The residue was chromatographed (SiO_2, 99:1 hexanes:Et_2O), to produce 3.27 g (96% overall) of product as a colorless oil that was homogenous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 3.70 (m, 2H), 2.24 (m, 2H), 1.62 (m, 4H), 1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.3, 62.7, 37.6, 32.0, 24.8, 19.5, 18.0, 12.0; IR (film) 2218 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{12}H_{22}OSiBr$ 289.0624, found 289.0621 ($(M-C_3H_7)^+$).



11-Triisopropylsilyl-1-triisopropylsilyloxy-5,10-undecadiyne. A suspension of zinc dust (0.3 g, 4.59 mmol) in THF (2 mL) containing 1,2-dibromoethane (14 μL, 0.16 mmol) was heated to 65 °C for 2 min and cooled to 25 °C, and TMSCl (17μL, 0.134 mmol) was added.[29] After 15 min at 25 °C, a solution of 1-iodo-5-triisopropylsilyl-4-pentyne[30] (1.46g, 4.17 mmol) in THF (2mL) was slowly added at 30 °C. After the end of the addition, the reaction mixture was stirred 2 h at 40 °C, and then stirred at 35 °C for 12 h. The reaction solution was added at -10 °C to a mixture of CuCN (0.33 g, 3.685 mmol) and LiCl (0.31 g, 7.30 mmol) in THF (4 mL). After 5 min at 0 °C, the solution was cooled to -78 °C and a solution of the product of the previous reaction (0.695 g, 2.085 mmol) in THF (2 mL) was slowly added. The reaction was stirred 3 h at -78 °C. The reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer, hexane), followed by flash chromatography (hexanes), to produce 0.4 g (40%) of product as a colorless oil that was homogenous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (t, J = 6.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.28 (tt, J = 7.0, 2.5 Hz, 2H), 2.17 (tt, J = 7.0, 2.3 Hz, 2H), 1.70 (quintet, J = 7.0 Hz, 2H), 1.61-1.66 (m, 2H), 1.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.2, 80.7, 80.6, 79.3, 63.0, 32.1, 28.4, 25.5, 19.1, 18.62, 18.58, 18.0, 17.9, 12.0, 11.3; IR (film) 2171 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{26}H_{49}OSi_2$ 433.3322, found 433.3330 ($(M-C_3H_7)^+$).



5,10-Undecadiyn-1-ol. The product of the previous reaction (0.771 g, 1.62 mmol) was dissolved in THF (15 mL), and tetrabutylammonium fluoride (6.47 mL, 6.47 mmol of a 1 M THF solution) was added at 0 °C. After stirring for 1 h at 25



°C, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer, Et_2O), followed by flash chromatography (3:1 hexanes:EtOAc), to produce 0.25 g (94%) of product as a colorless oil that was homogenous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (t, J = 6.5 Hz, 2H), 2.24-2.29 (m, 4H), 2.17 (tt, J = 7.0, 2.5 Hz, 2H), 1.94 (t, J = 2.8 Hz, 1H), 1.62-1.70 (m, 5H), 1.51-1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.8, 80.6, 79.3, 68.7, 62.4, 31.8, 27.9, 25.3, 18.5, 17.8, 17.5; IR (film) 3296, 2117 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{11}H_{15}O$ 163.1123, found 163.1118 ($(M-H)^+$).

(2*E*)-1-(Phenyl)trideca-7,12-diyn-2-en-1-one (25). The product of the previous reaction was oxidized by a Swern oxidation as described for compound **8** on a 1.5 mmol scale. The crude aldehyde in C_6H_6 (40 mL) was then treated with $Ph_3P{=}CHC(O)Ph$ and was heated at 70 °C for 12 h. Evaporation and flash chromatography (49:1 hexanes:Et_2O) provided 0.33 g (82% overall) of **25** as a pale yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.99 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.04 (dt, J = 15.5, 6.8 Hz, 1H), 6.91 (d, J = 15.5 Hz, 1H), 2.42 (q, J = 7.0 Hz, 2H), 2.27-2.32 (m, 4H), 2.22 (m, 2H), 1.96 (t, J = 2.5 Hz, 1H), 1.70 (quintet, J = 7.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 148.8, 137.9, 132.7, 128.5, 126.4, 83.7, 79.9, 79.8, 68.7, 31.8, 27.9, 27.4, 18.3, 17.8, 17.5; IR (film) 1670, 1620 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{19}H_{19}O$ 263.1436, found 263.1432 ($(M - H)^+$).

(*E*)-1-(1-Methylhex-5-ynylidene)-2-(2-oxo-2-phenylethyl)cyclopentane (27). Following general procedure A, enone **25** (47 mg, 0.178 mmol), MeLi (0.61 mL, 0.851 mmol of a 1.4 M ethyl ether solution), $ZnCl_2$ (77 mg, 0.567 mmol), and $Ni(COD)_2$ (5 mg, 0.018 mmol) were employed to produce, after flash chromatography (49:1 hexanes:Et_2O), 12 mg (24%) of **27** as a yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.96 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.26 (m, 1H), 2.88-2.97 (m, 2H), 2.33 (m, 1H), 2.21-2.28 (m, 1H), 2.16 (dt, J = 2.5, 7.5 Hz, 2H), 2.04-2.13 (m, 2H), 1.96 (t, J = 2.5 Hz, 1H), 1.74-1.80 (m, 1H), 1.69 (m, 2H), 1.65 (br s, 3H), 1.61 (m, 2H), 1.51-1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 140.5, 137.4, 132.9, 128.6, 128.1, 125.6, 84.7, 68.3, 42.6, 37.9, 34.6, 32.4, 29.6, 26.7, 23.9, 18.7, 18.2; IR (film) 2115, 1684, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{20}H_{24}O$ 280.1827, found 280.1822 (M^+).

5R*,6aR*-5-Benzoyl-1,2,3,5,5a,6,7,8-octahydro-*as*-indacene (28). General procedure B was followed except that *t*-Bu_2Zn was freshly prepared as follows: *t*-BuLi (0.35 mL of a 1.7 M pentane solution, 0.6 mmol) was added dropwise to a -78 °C solution of $ZnCl_2$ (54 mg, 0.4 mmol) in THF (2.2 mL). After stirring for 10 min at -78 °C, the mixture was allowed to warm to 0 °C. Enone **25** (37 mg, 0.14 mmol), $Ni(COD)_2$ (4 mg, 0.014 mmol), and PPh_3 (18 mg, 0.07 mmol) were employed at 25 °C to produce, after flash chromatography (hexanes), 19.3 mg (52%) of **28** as a yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.99 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 5.21 (s, 1H), 4.08 (d, J = 17.0 Hz, 1H), 3.03 (m, 1H), 2.39-2.45 (m, 1H), 2.26-2.34 (m, 5H),

2.02 (m, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.68-1.77 (m, 1H), 1.60 (m, 1H), 1.09-1.18 (dq, J = 7.0, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 143.8, 136.8, 136.4, 132.9, 130.0, 128.8, 128.6, 110.2, 51.3, 43.1, 33.5, 31.3, 28.6, 28.3, 25.3, 24.8; IR (film) 1681, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{19}H_{20}O$ 264.1514, found 264.1511 (M^+).

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