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Ring Size and Substituent Effects in Oxyanion-Promoted Cyclizations of Enyne-allenes: Observation of a Myers−Saito Cycloaromatization at Cryogenic Temperature

Michelle K. Waddell, Tefsit Bekele, and Mark A. Lipton*

Department of Chemistry and Cancer Center, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

lipton@purdue.edu

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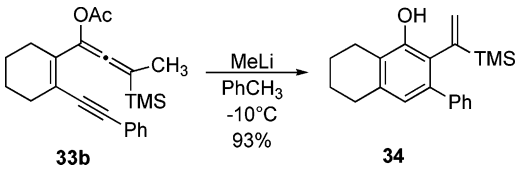


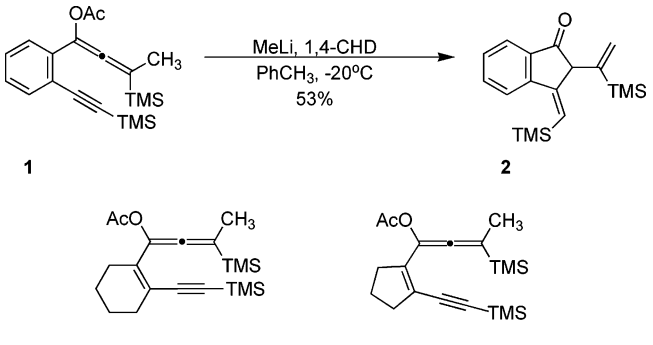
33b **34**

A series of acetoxy-substituted enyne-allenes, fused to cyclopentene and cyclohexene ring systems, were synthesized and treated with methyllithium to generate the corresponding enolates. It was found that whereas the cyclohexannulated examples underwent either C^2-C^7 (Myers−Saito) cycloaromatization or C^2-C^6 (Schmittel) cyclization depending on their terminal subsituents, the cyclopentannulated examples either failed to cyclize altogether or underwent C^2-C^7 cyclization. Both of these results lie in contrast to the behavior of their benzannulated analogues, which underwent exclusive C^2-C^6 cyclization independent of substituents. These findings are rationalized on the basis of both ring strain effects and the steric encumbrance of the terminal alkynyl and allenyl subsituents.

Introduction and Background

In previous studies from this laboratory, the benzannulated, acetoxy-substituted enyne-allene **1** was shown to undergo a rapid C^2-C^6 (Schmittel) cyclization to the corresponding indenone **2** (Scheme 1).[1] In an effort to understand the outcome of this and related reactions,[2] theoretical studies conducted by ourselves[3] and Musch and Engels[4] suggested that the benzannulation of the substrate plays a significant role in biasing the reaction toward the C^2-C^6 rather than the C^2-C^7 (Myers−Saito) cyclization product. In light of these findings, it was decided to replace the benzene ring of **1** with a saturated ring, so the cyclohexenyl (**3**) and cyclopentenyl (**4**) analogues of **1** were chosen to study the effect of the ring size and saturation on the outcome of the cyclization reaction.

SCHEME 1. C^2-C^7 Cyclization of Oxyanion-Substituted Enyne-allenes



1 **2** **3** **4**

Similar studies on the thermal C^2-C^6 cyclization have been reported by Schmittel et al. in 1997.[2f] In their studies, it was found that the cyclopentenyl-based substrate **5a** cycloaromatized via the C^2-C^7 pathway to form **6a**, whereas the cyclohexenyl-based substrate **5b** appeared to cyclize by a C^2-C^6 pathway, though the instability of the reaction product **6b** precluded complete characterization (Scheme 2). Schmittel rationalized

(1) Brunette, S. R.; Lipton, M. A. *J. Org. Chem*. **2000**, *65*, 5114−5119.
(2) (a) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999−1002. (b) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843−1845. (c) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165−166. Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975−4978. (d) Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem.*−Eur. J. **1997**, *3*, 807−816. (f) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38*, 6177−6180. (g) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M. Strittmatter, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1960−1963.
(3) Wenthold, P. G.; Lipton, M. A. *J. Am. Chem. Soc*. **2000**, *122*, 9265−9270.
(4) Musch, P. W.; Engels, B. *J. Am. Chem. Soc*. **2001**, *123*, 5557−5562.

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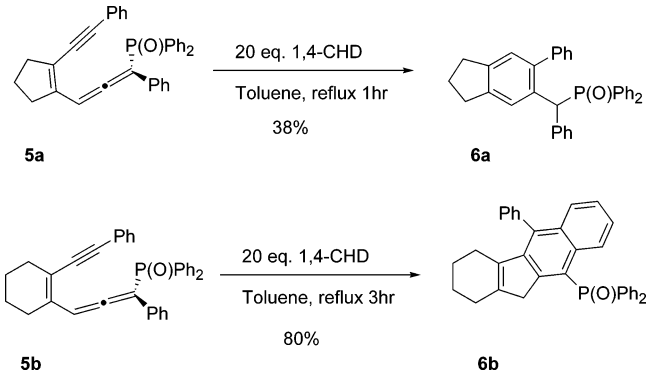
SCHEME 2. Divergent Thermal Cyclizations of Annulated Enyne-allenes[4]



these results on the basis of ring strain, arguing that the strain of a bicyclo[3.3.0]octa-1,7-diene ring system was too great to permit facile C^2-C^6 cyclization, whereas a 1,2-dihydroindene skeleton—the product of C^2-C^7 cyclization—was stable enough to form under the reaction conditions.

Applying this same logic, we sought to investigate whether the cyclopentenyl enyne-allene **4** could be coerced to cycloaromatize via a C^2-C^7 pathway, using a combination of ring strain and elimination of benzylic stabilization of the C^2-C^6 pathway. The cyclohexenyl analogue **3** was included to dissect the effects of ring strain and aromaticity on the reaction outcome.

Results and Discussion

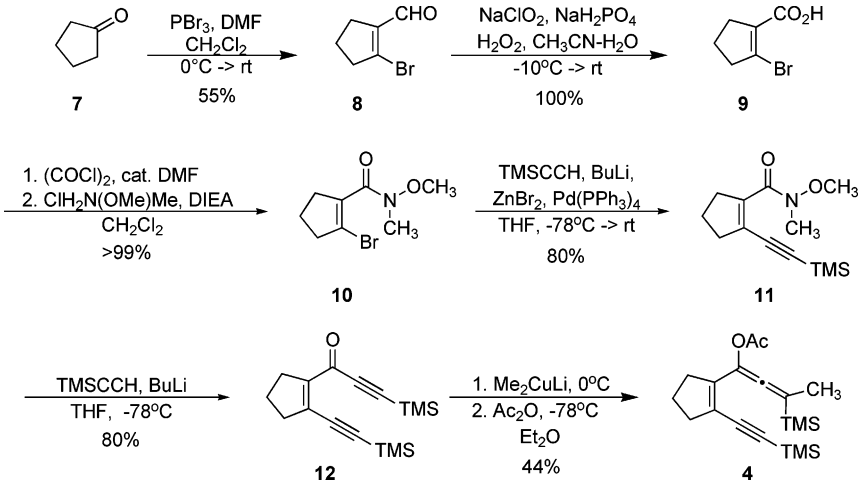
The synthesis of **4** began with the Vilsmier−Haack reaction of cyclopentanone to form vinyl bromide **8**,[5] followed by oxidation to **9** and conversion to Weinreb amide **10** (Scheme 3). Negishi coupling of **10** with trimethylsilylacetylene led to the formation of acetylenic ketone **11** in 80% yield. Nucleophilic addition of trimethylsilylacetylide to **11** afforded **12** in 80% yield. Reaction of **12** with lithium dimethylcuprate and subsequent trapping of the resultant enolate with acetic anhydride resulted in the formation of enol acetate **4**.

The lithium enolate was liberated from **4** by use of methyllithium and was allowed to react at various temperatures. In contrast to what was observed in the benzannulated system **1**, we were unable to observe any cyclization of **4** and were only able to isolate the enones **13** and **14** (Scheme 4). It was hypothesized that the bulk of the allene and alkyne substitutents sterically prevents cyclization from occurring.

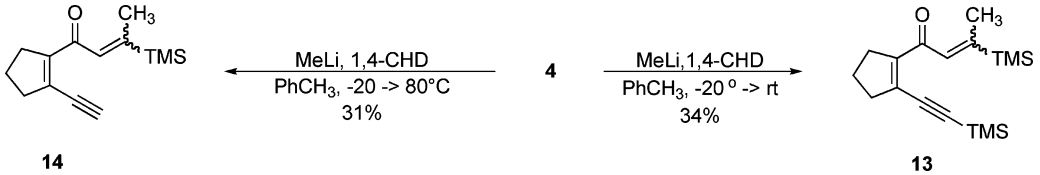
Engels and Schmittel and co-workers[2g] have reported that the C^2-C^7 transition state is sensitive to steric bulk around C^7: substitution at the terminal alkyne with a *t*-Bu or phenyl substituent increases the activation energy of the C^2-C^7 transition state by 6−7 kcal/ mol. It was also observed that a phenyl substituent electronically stabilizes the C^2-C^7 transition state, allowing for the formation of the Myers cyclization products. As a result, we decided to further investigate our model system using phenyl substituents to both electronically stabilize the desired C^2-C^7 transition state and reduce the steric encumbrance of the terminal substituents.

Enyne-allene **17** was synthesized under reaction conditions similar to those outlined in Scheme 3. Weinreb amide **10** underwent nucleophilic addition with phenylacetylide to produce ketone **15** in 94% yield. Sonagashira coupling of **15** with phenylacetylene followed by cuprate addition results in the formation of enyne-allene **17** (Scheme 5). However, after removal of the acetate group no cyclization products were again observed. Subsequent heating of **17** to 50 °C accomplished the formation of the Myers product **18** in 40% yield. Upon examining the structure of **17**, it appears that the phenyl group on the allene is forced to twist out of conjugation, thereby making it sterically quite demanding and keeping the steric barrier to cyclization high. In our pursuit of developing a model system that would cyclize under cryogenic conditions, it was decided to make an analogue with a phenyl substituent on the alkyne and a trimethylsilyl substituent on the allene.

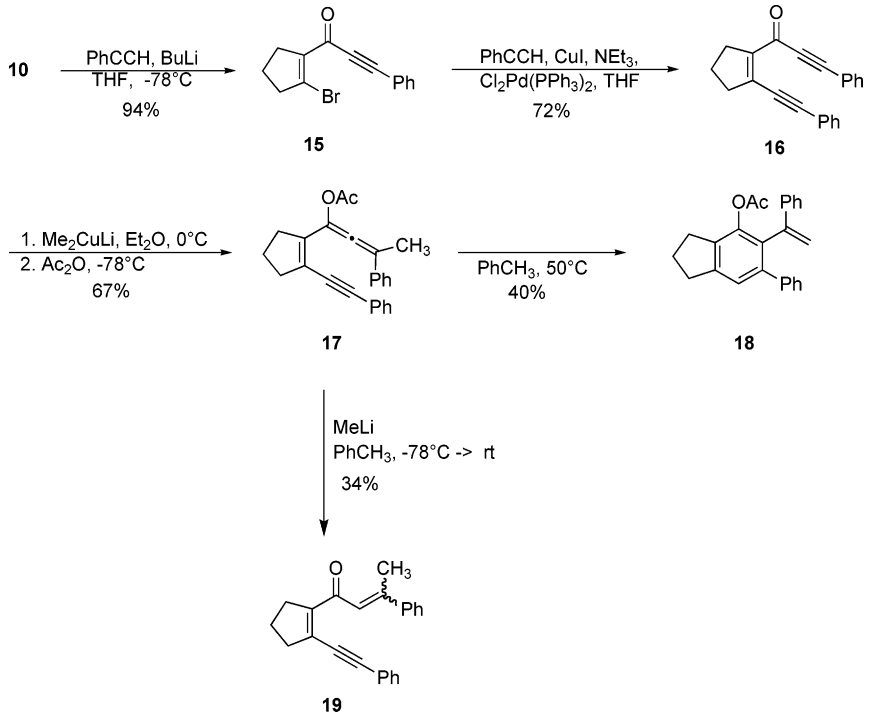
SCHEME 3. Preparation of Cyclopentannulated Enyne-allene 4



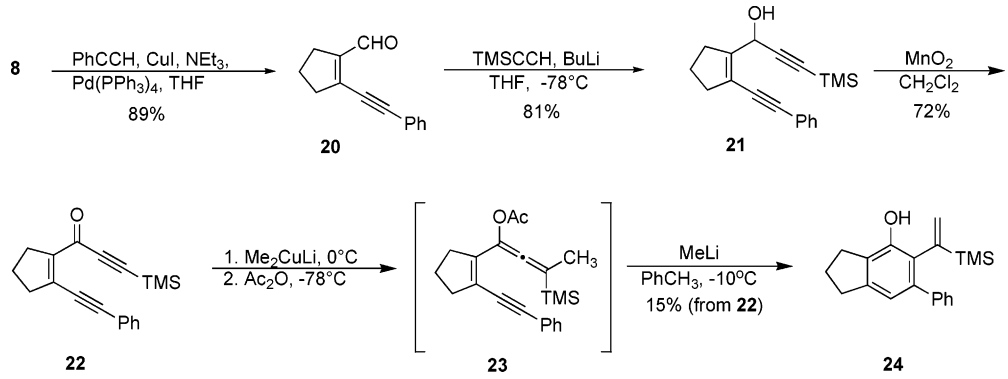
SCHEME 4. Attempted Cycloaromatization of 4



SCHEME 5. Thermal C^2-C^7 Cyclization and Attempted Anionic Cyclization of 17



SCHEME 6. C^2-C^7 Cyclization of Cyclopentannulated Enyne-allene 23



Application of our previous strategy to the synthesis of such a derivative proved problematic, so a modified strategy was employed (Scheme 6). Cross-coupling of aldehyde **8** with phenylacetylene resulted in **20** in 89% yield. Addition of trimethylsilylacetylide to the aldehyde gave the propargyl alcohol **21**, which was oxidized to ketone **22** in good yield. Ketone **22** was subjected to cuprate addition to form allene **23**. However, **23** quickly decomposes on silica gel and as a result was carried on to the next reaction without purification. Reacting **23** with methyllithium resulted in the formation of the C^2-C^7 cyclization product **24** in 15% yield. When 1,4-cyclohexadiene was added to the reaction, the didehydro product **24** was still the only cyclization product isolated. It thus appears that the combination of cyclopentannulation and the placement of a phenyl group on the alkyne promotes C^2-C^7 cyclization at cryogenic temperature through the combination of ring strain (disfavoring C^2-C^6 cyclization) and relief of steric congestion at the termini (permitting C^2-C^7).

We next turned our focus toward investigating the behavior of the cyclohexannulated enyne-allene model system. We began our synthesis with the literature aldehyde **25**, obtained from reaction of cyclohexanone with tribromophosphine and DMF,[6] which was cross-coupled with trimethylsilylacetylide to obtain **26** in good yield. Aldehyde **26** was reacted with trimethylsilylacetylide to form propargyl alcohol **27** in 87% yield (Scheme 7). Oxidation to the ketone **28** was followed by cuprate addition to afford allene **3** in 80% yield.

Several attempts were made to cyclize **3** by removing the acetate group with methyllithium. Unfortunately, no cyclization products were isolated, only various uncharacterized degradation products. However, when **3** was heated to 50 °C in toluene, it cyclized to the C^2-C^6 product **29** (Scheme 8). This result is in line with the observations made by Wang and co-workers[7] during the thermolysis of similar enyne-allene systems; they

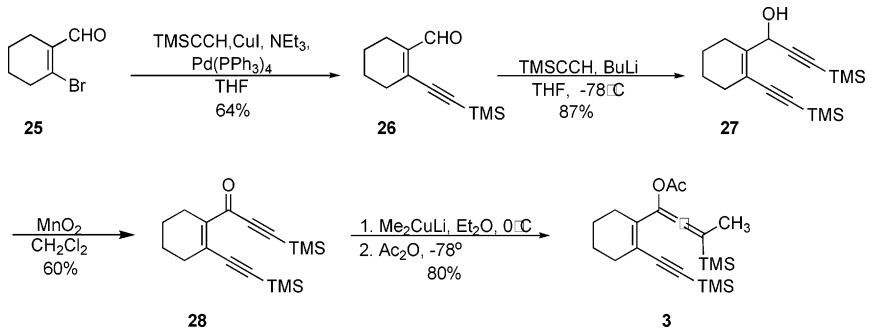
(5) Bekele, T.; Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 8471−8479.

(6) Arnold, Z.; Holý, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059.

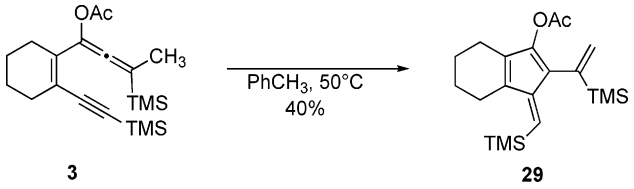
(7) Dai, W.; Peterson, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647−6652.

(8) Allene **33b** had limited stability when isolated, precluding its analysis by either combustion or HRMS and requiring that it be further reacted within a few hours of its isolation.

SCHEME 7. Preparation of a Cyclohexannulated Enyne-allene



SCHEME 8. Thermal C^2-C^6 Cyclization of Cyclohexannulated Enyne-allene 3



noted that bulky substituents disfavor the formation of C^2-C^7 cyclization products by distorting the alignment of the allene with respect to the alkyne.

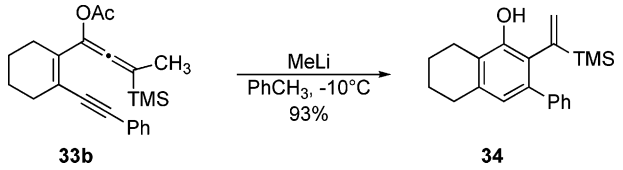
To do a direct comparison between the cyclopent- and cyclohexannulated systems, the trimethylsilyl substituents on the alkynes were changed to phenyls to produce six-membered analogues of the allenes **17** and **23**. Synthesis of these analogues began with Sonogashira cross-coupling of aldehyde **25** with phenyl acetylene to form **30** in 74% yield (Scheme 9). Nucleophilic addition of either phenyl acetylene or trimethylsilyl acetylene to the aldehyde **30** yielded alcohols **31a,b** in 69% and 85% yields, respectively. Both alcohols were readily oxidized to the corresponding ketones **32a,b** before being subjected to cuprate addition. Although **32b** reacted to form allene **33b** in 53% yield,[8] we were unable to form the allene **33a**. We hypothesize that this lack of reactivity may be a result of steric repulsion between the two phenyl rings that disfavors rehybridization of the acetylenic ketone to an allene.

Allene **33b** was then subjected to acetate deprotection conditions (Scheme 10). In less than 30 min, cycloaromatization of the resultant oxyanion-substituted allene at −10 °C was complete, giving rise to the C^2-C^7 cyclization product **34** in 93% yield. It is intriguing to note that, contrary to the findings of Schmittel, even the cyclohexannulated derivative **33b** gives exclusively C^2-C^7 cyclization under these conditions. Reacting **33b** with methyllithium and a 1:1 mixture of toluene and 1,4-cyclohexadiene resulted in the exclusive formation of cyclization product **34**.

Conclusion

Oxyanion-promoted cyclization of enyne-allenes, like its thermal counterpart, appears to be subject to two distinct factors. First, the size and nature of the ring in which the enyne-allene is embedded plays a critical role in determining whether C^2-C^6 cyclization can take place. In the benzannulated and cyclohexannulated systems, formation of a new fulvene system does not result in a highly strained ring system, as it would in the cyclopentannulated system. However, a further distinction is apparent when the benzannulated and cyclohexannulated systems are compared: in the former case, C^2-C^6 cyclization is facile and occurs at cryogenic temperatures, whereas in the latter case, C^2-C^6 cyclization occurs only under thermal conditions akin to those used by Schmittel in his studies. This distinction can be at least partly attributed to the effects of the

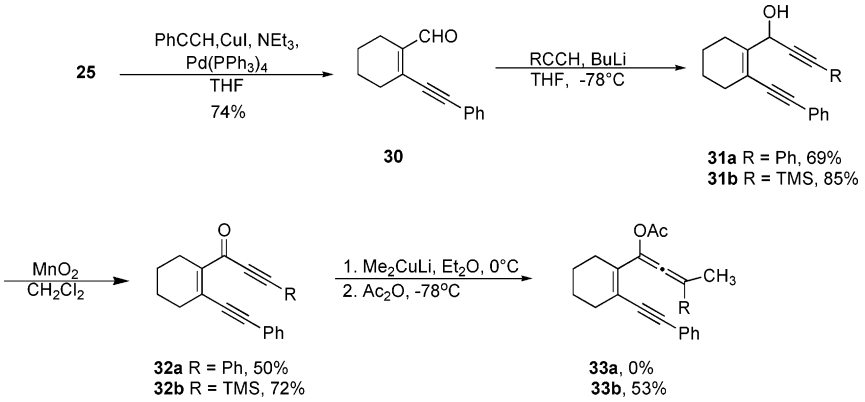
SCHEME 10. Oxyanion-Promoted C^2-C^7 Cycloaromatization of 33b



preexisting aromatic system of the benzannulated examples.[3]

A second factor affecting the mode of cyclization is the steric bulk of the substituents on the allene and alkyne. In both the cyclopentannulated and cyclohexannulated systems, bis-TMS

SCHEME 9. Variation of Substituents on the Cyclohexannulated Enyne-allene



substitution results in a complete lack of C^2-C^7 cyclization, which has been previously noted to be more sensitive to steric influences than the competing C^2-C^6 cyclization. When the alkynyl substituent is changed from TMS to phenyl, the resulting relief of steric strain in the C^2-C^7 transition state permits C^2-C^7 cyclization to occur at cryogenic temperature. The higher yield and faster reaction in the cyclohexannulated system can possibly be attributed to a lower degree of ring strain encountered in the C^2-C^7 transition state.

Although our results are mostly in agreement with those of Schmittel et al.,[2f] we note that whereas Schmittel found exclusive C^2-C^6 cyclization for his cyclohexannulated systems, we observe the thermal C^2-C^6 cyclization of the bis-TMS system **3** and the cryogenic C^2-C^7 cyclization of the mixed TMS/phenyl-substituted enyne-allene **33b**. The anomalous C^2-C^7 cyclization of **33b** can be explained by the greater steric demand of the TMS substituents used in our study, resulting in the destabilization of the C^2-C^7 pathway. It is also noteworthy that the cyclizations of oxyanion-substituted enyne-allenes in our study occur at far lower temperatures than the analogous cyclizations of neutral enyne-allenes. The presence of the oxyanion presumably lowers the activation energy of both cyclization pathways by resonance stabilization by the oxyanion of the incipient diradicals in the transition states of these cyclizations. The C^2-C^7 cyclization of **33a** represents one of the fastest examples of a Myers−Saito cycloaromatization ever reported.[9]

Experimental Section

2-Bromocyclopent-1-ene-*N*-methoxy-*N*-methylcarboxamide (10). To a solution of carboxylic acid **9** (1.55 g, 8.10 mmol) in CH_2Cl_2 (27 mL) was added $(COCl)_2$ (1.42 mL, 16.2 mmol), followed by catalytic DMF (50 μL). The reaction was stirred at room temperature for 1 h, at which time the solution was concentrated in vacuo with minimal exposure to air. The crude acid chloride was redissolved in CH_2Cl_2 (27 mL) and cooled to 0 °C. To this solution was added $ClH_2N(OMe)Me$ (0.87 g, 8.9 mmol), followed by Hunig's base (3.1 mL, 18 mmol). The mixture was allowed to warm to room temperature over 4 h. The reaction mixture was diluted with EtOAc and poured into 0.1 M HCl. The aqueous layer was extracted with EtOAc (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 30% EtOAc−petroleum ether, affording **10** as a colorless foamy solid (1.6 g, 100% yield): mp = 60−62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.70 (m, 4H), 2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 121.0, 61.7, 40.7, 34.3, 22.7; IR (NaCl, cm^{-1}) 2960, 2928, 2254, 1631, 1387, 1260, 1097, 920, 760; HRMS *m*/*z* (EI/CI) expected 233.0051, found 233.0056.

2-Trimethylsilylacetylenylcyclopent-1-ene-*N*-methoxy-*N*-methylcarboxamide (11). To a solution of BuLi (0.90 mL, 2 M in hexanes, 1.8 mmol) in THF (0.9 mL) at −78 °C was added trimethylsilylacetylene (0.30 mL, 2.0 mmol), and the mixture was stirred for 20 min. This mixture was added to a separate round-bottom flask containing dry $ZnBr_2$ (flame-dried under vacuum, 0.40 g, 1.8 mmol) in THF (0.9 mL) at −10 °C and stirred for 5 min. To this solution was added Weinreb amide **10** (0.19 g, 0.80 mmol) in THF (0.9 mL), followed by $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol), and the resulting reaction slowly warmed to room temperature over 3 h. The reaction was diluted with EtOAc and poured into saturated, aqueous NH_4Cl. The aqueous phase was separated and extracted with EtOAc (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 25% EtOAc−petroleum ether, affording **11** as a pale yellow liquid (0.16 g, 80% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 2.70 (t, 2H, J = 5.3 Hz), 2.60 (t, 2H, J = 5.3 Hz), 2.00 (m, 2H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 125.1, 101.5, 100.0, 61.4, 37.7, 35.0, 22.8, 0.0; IR (NaCl, cm^{-1}) 2984, 2086, 1741, 1240, 1047, 847, 634; HRMS *m*/*z* (EI/CI) expected 251.1342, found 251.1344.

1-(2-Trimethylsilylacetylenylcyclopent-1-enyl)-3-trimethylsilylpropyn-1-one (12). To a solution of BuLi as a 1.6 M solution in hexanes (5.8 mL) in THF (8 mL) at −78 °C was added trimethylsilylacetylene (1.60 mL, 11.1 mmol), and the mixture was stirred for 20 min. To this solution was added acetylated amide **11** (0.93 g, 3.7 mmol) in THF (4.3 mL), and the mixture was stirred for 30 min. The reaction was diluted with Et_2O and poured into saturated, aqueous NH_4Cl. The aqueous phase was separated and extracted with Et_2O (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 5% Et_2O−petroleum ether to give a colorless liquid **12** (0.85 g, 80%(: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (m, 4H), 1.9 (m, 2H) 0.27 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 145.9, 136.1, 109.1, 102.7, 100.9, 99.8, 40.9, 33.6, 22.3, 0.06, 0.05; IR (NaCl, cm^{-1}) 2985, 2086, 1740, 1373, 1240, 1046, 737; HRMS *m*/*z* (EI/CI) expected 288.1366, found 288.1370.

1-(2-Phenylacetylenylcyclopent-1-enyl)-3-phenylbuta-1,2-dienyl Acetate (17). CuI (0.26 g, 1.35 mmol) was suspended in Et_2O (1.0 mL) and cooled to 0 °C. To this suspension was added MeLi (1.7 mL, 1.4 M in Et_2O, 2.4 mmol). The solution was stirred for 5 min and cooled to −78 °C. A solution of ketone **16** (0.20 g, 0.68 mmol) dissolved in Et_2O (1.0 mL) was added dropwise via syringe to the reaction, which immediately turned dark red-orange. Acetic anhydride (0.13 mL) in Et_2O (0.2 mL) was then added dropwise to the reaction, which was allowed to slowly warm to room temperature over 1 h. The reaction was diluted with Et_2O and poured into saturated, aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 10% Et_2O−petroleum ether to give 17 as a pale yellow liquid (0.16 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.7 (m, 10H), 2.8 (m, 2H), 2.6 (m, 2H), 2.3 (s, 3H), 2.2 (s, 3H), 2.0 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 169.3, 138.5, 137.9, 135.4, 131.4, 129.1, 128.6, 128.4, 128.3, 128.2, 126.8, 125.4, 123.7, 122.2, 119.7, 112.2, 39.7, 34.2, 21.1, 17.9; IR (NaCl, cm^{-1}) 2956, 2200, 1759, 1491, 1206; HRMS *m*/*z* (EI/CI) expected 354.1620, found 354.1623.

1-(2-Phenylacetylenylcyclopent-1-enyl)-3-trimethylsilylpropyn-1-one (22). To a solution of **21** (0.13 g, 0.46 mmol) in CH_2Cl_2 (4.5 mL) was added activated MnO_2 (0.91 g, 10 mmol) and the mixture was stirred for 12 h. The reaction mixture was filtered over Celite, concentrated under reduced pressure, and purified by flash chromatography with 10% Et_2O−pentane to give **22** as a pale yellow liquid (0.102 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 2H), 7.2 (m, 3H), 2.75 (m, 4H), 1.8 (q, 2H, J = 7.6 Hz), 0.0 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 146.0, 137.2, 131.8, 129.1, 128.4, 122.8, 102.5, 102.3, 99.9, 85.6, 40.6, 33.0, 21.9, −0.7; IR (NaCl, cm^{-1}) 3123, 2948, 2916, 2852, 2191, 2151, 1599, 1492, 1448, 1401, 1357, 1250; HRMS *m*/*z* (EI/CI) expected 292.1283, found 292.1290.

2,3-Dihydro-6-phenyl-5-(1-trimethylsilylvinyl)inden-4-ol (24). To a solution of enyne-allenoate **23** (0.102 g, 0.29 mmol) dissolved in $PhCH_3$ (1.82 mL) at −10 °C was added MeLi as a 1.6 M solution in Et_2O (0.27 mL) dropwise, and the solution turned deep red-orange. The reaction was allowed to stir at −10 °C for 3 h. The reaction was diluted with Et_2O and poured into saturated, aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 5% Et_2O−petroleum ether to give **24** as a pale yellow liquid (0.013 g, 15%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 5H), 7.0 (s, 1H), 6.0 (s, 1H), 5.3 (s, 1H), 4.7 (s, 1H), 2.8 (m, 2H), 2.5 (m, 2H), 2.1 (m, 2H), 0.2 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 149.2,

(9) The cycloaromatization of didehydro[10]annulene is the fastest reported example, occurring spontaneously at −45 °C: Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1992**, *114*, 10986−10987.

146.4, 140.8, 139.4, 137.6, 130.6, 128.8, 128.1, 127.2, 119.9, 115.6, 33.2, 29.7, 25.3, 1.6; HRMS *m*/*z* (EI/CI) expected 308.1596, found 308.1597.

4,5,6,7-Tetrahydro-2-(1-Trimethylsilylvinyl)-1-(trimethylsilylmethylidene)indenyl Acetate (29). A solution of **3** (0.045 g, 0.13 mmol) dissolved in $PhCH_3$ (0.42 mL) was heated to 50 °C for 3 h. The solvent was removed in vacuo. The crude product was purified by flash chromatography with 10% Et_2O−pentane to give **29** as a red-orange liquid (0.018 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.1 (s, 1H), 5.7 (m, 2H), 5.6 (m, 2H), 2.5 (m, 2H), 2.3 (s, 3H), 1.7 (m, 4H), 1.4 (m, 2H), 0.3 (s, 9H), 0.1 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 169.6, 156.2, 147.0, 145.5, 138.7, 138.5, 127.8, 124.8, 24.8, 23.4, 22.4, 21.0, 1.7, 1.0; IR (NaCl, cm^{-1}) 2944, 2243, 2132, 1745, 1247, 1211; UV (MeOH, nm) 289; HRMS *m*/*z* (EI/CI) expected 360.1941, found 360.1944.

1-(2-Phenylacetylenyl)cyclohex-1-enecarbaldehyde (30). To a reaction flask containing $Pd(PPh_3)_4$ (0.306 g, 0.264 mmol) and CuI (0.10 g, 0.53 mmol) was added **25** (0.500 g, 2.64 mmol) dissolved in THF (8.8 mL), and the mixture was stirred for 10 min. To this solution, was added phenylacetylene (0.58 mL, 5.3 mmol), followed by NEt_3 (0.92 mL, 6.6 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature over 3 h. The reaction was diluted with Et_2O, poured into saturated, aqueous NH_4Cl, and extracted with Et_2O (3×). The combined organic layer was dried over Na_2SO_4 and purified by flash chromatography with 10% EtOAc−petroleum ether to give **30** as a pale yellow liquid (0.407 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.3 (s, 1H), 7.4 (m, 2H), 7.3 (m, 3H), 2.5 (m, 2H), 2.3 (m, 2H), 1.7 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 142.6, 140.1, 131.7, 129.1, 128.5, 122.4, 98.7, 86.3, 32.4, 22.1, 21.9, 21.1; IR (NaCl, cm^{-1}) 2944, 2865, 2248, 2200, 1769, 1669, 1603, 1490; HRMS *m*/*z* (EI/CI) expected 210.1045, found 210.1047.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for **3**, **4**, **9**, **13**, **14**−**21**, **26**−**28**, **31a,b**, **32a,b**, **33b**, and **34**; ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **9**−**22**, **24**, **26**−**30**, **31a**,**b**, **32a**,**b**, **33b**, and **34**; and NOESY spectrum of compound **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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