Effects of Propargylic Substitution and Annelation on the Cycloaromatization of a Bicyclo[7.3.1] Enediyne

David K. Moss, John D. Spence, and Michael H. Nantz*

Department of Chemistry, University of California, Davis, California 95616

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The cycloaromatization kinetics of two bicyclo[7.3.1] enediynes are presented. Silyl protection of a propargylic alcohol positioned on the enediyne core was found to moderate enediyne cycloaromatization. However, the presence of multiple fused ring systems exerts geometrical constraints that prevent cycloaromatization of the otherwise facile cyclization previously observed for the core system.

Introduction

The naturally occurring bicyclo[7.3.1] enediynes calicheamicin and esperamicin have generated many synthetic and mechanistic studies due to their DNA-cleaving abilities.[1,2] The biological activity of these compounds has been linked to the cycloaromatization of the enediyne core, referred to as Bergman cyclization.[3] In addition to syntheses of natural calicheamicin γ_1^I,[4] many simplified 10-membered ring enediynes have been prepared and their cycloaromatization behavior investigated.[5] Magnus and co-workers were the first to determine the reactivity of bicyclo[7.3.1] enediyne analogues[6] and showed that the enediyne ring of **1** (Figure 1) was resistant to cycloaromatization at ambient temperature, but reacted slowly[7] at 71 °C to form the corresponding benzenoid product. A change in hybridization of the one-carbon bridge (C13) from Csp^2 to Csp^3 (**1** → **2**) was shown to effect a dramatic increase in the rate of cycloaromatization.[8] In contrast, we have shown that the analogous enediyne **3** undergoes cycloaromatization 1 order of magnitude faster than **1**.[9] Furthermore, rehybridization of the one-carbon bridge (C1) in **3** resulted in the remarkably stable bicyclo[7.3.1] enediyne **5**, contrasting again with the previously observed behavior for the core system. To understand these anomalous cycloaromatization results, we have examined the influence of the propargylic substituent on the cycloaromatization of **3**. Our findings and an account of our synthetic attempts to position the enediyne core onto a spirocyclic construct are presented herein.

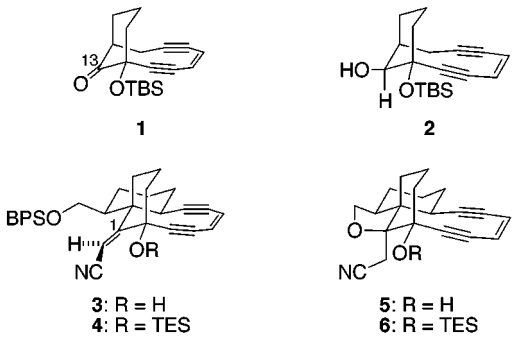

Figure 1.

Results and Discussion

Having achieved a rapid synthesis of terminal alkyne **7** (Scheme 1),[10] we explored a route to complete the enediyne core. Our initial attempts concentrated on a simplified system lacking the Michael acceptor of **3** and **4**. Our strategy for ring closure relied on the well-established coupling of terminal alkynes with vinyl halides to introduce the remaining enediyne carbons.[11] Diol **7** was reacted with (*Z*)-chloroenyne **8**[12] in the presence of $Pd(PPh_3)_4$ and copper iodide to provide the corresponding enediyne. Results using commercially available $Pd(PPh_3)_4$ were irreproducible. As such, Pd-

* To whom correspondence should be addressed. Phone: 530-752-6357. Fax: 530-752-8995. E-mail:mhnantz@ucdavis.edu.

(1) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *Ibid.* **1987**, *109*, 3466. (c) Golik, J.; Clardy, J.; Dubay, G.; Groenwold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.: Ohkum, H.; Saitoh, K.; Doyle, T. W. *Ibid.* **1987**, *109*, 3461. (d) Golik, J.; Clardy, J.; Dubay, G.; Groenwold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkum, H.; Saitoh, K.; Doyle, T. W. *Ibid.* **1987**, *109*, 3462.

(2) For reviews of enediyne chemistry and biology, see: (a) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (b) Maier, M. E. *Synlett* **1995**, 13. (c) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (d) Doyle, T. W., Borders, D. B., Eds. *Enediyne Antibiotics as Antitumor Agents*; Marcel-Dekker: New York, 1994.

(3) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (c) Lockhart, T. P.; Commita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (d) Darby, N.; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516.

(4) (a) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, C. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082. (b) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, C. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *Ibid.* **1993**, *115*, 7625. (c) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H.; Danishefsky, S. J. *Ibid.* **1995**, *117*, 5750.

(5) For syntheses of calicheamicinone and calicheamicin analogues, see ref 2; for recent reports, see: (a) Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y.-J.; Meignan, G. *J. Am. Chem. Soc.* **1996**, *118*, 4904. (b) Churcher, I.; Hallett, D.; Magnus, P. *Ibid.* **1998**, *120*, 3518.

(6) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921.

(7) The rate of cycloaromatization for enediyne **1** at 71 °C was measured at $k = 1.07 \times 10^{-4}$ s^{-1}, $t_{1/2}(\tau) = 2.10$ h; the extrapolated rate at 37 °C is reported as $k = 1.85 \times 10^{-6}$ s^{-1}; see: (a) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986. (b) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *Ibid.* **1992**, *114*, 2544.

(8) Enediyne **2** undergoes complete cycloaromatization at 20 °C within 30 min; see ref 6.

(9) Nantz, M. H.; Moss, D. K.; Spence, J. D.; Olmstead, M. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 470.

(10) Spence, J. D.; Wyatt, J. K.; Bender, D. M.; Moss, D. K.; Nantz, M. H. *J. Org. Chem.* **1996**, *61*, 4014.

(11) For a review, see: Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 127.

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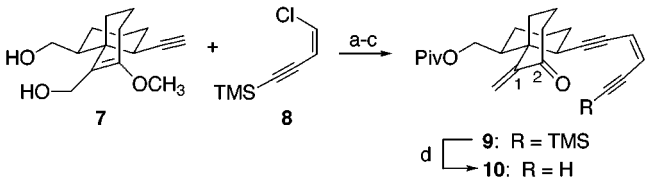
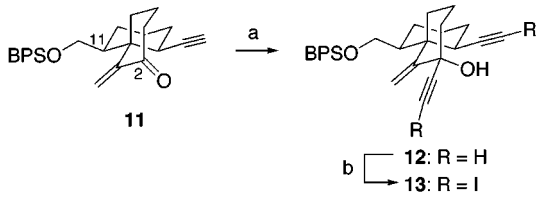
Scheme 1[a]



[a] $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, C_6H_6; (b) CF_3CO_2H, $CHCl_3$, H_2O; (c) $(CH_3)_3CC(O)Cl$, DMAP, CH_2Cl_2, 39% (three step); (d) CsF, Ac_2O, CH_3CN, 60%.

Scheme 2[a]

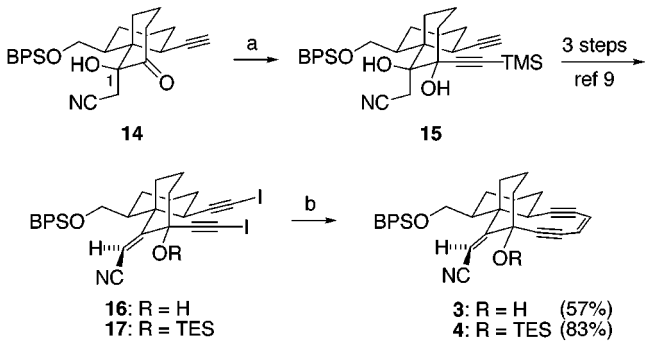


[a] HCCLi, $CeCl_3$, THF, −78 °C, 89%; (b) $AgNO_3$, *N*-iodosuccinimide, acetone, 0 °C, 74%.

$(PPh_3)_4$ was freshly prepared as a yellow crystalline product according to the procedure of Coulson.[13] The crude enediyne was then subjected to aqueous acid to effect enol ether hydrolysis with β-elimination of water to yield the enone. Subsequent alcohol protection using pivaloyl chloride gave **9** in 39% yield from **7**. At this stage we envisioned that closure of the enediyne core would occur via acetylenic anion 1,2-addition to the resident enone at C(2). Wender has shown[14] that acetylenic anion addition to an aldehyde in the presence of acetic anhydride is an effective means for achieving enediyne ring closure. In this reaction, the intermediate oxyanion is trapped as the corresponding acetate. Thus, silyl acetylene **9** was treated with cesium fluoride in the presence of acetic anhydride to effect ring closure. Unfortunately, only desilylated terminal alkyne **10** was isolated in this case. Presumably the C(3)-protons of **9** are accessible to the acetylenic anion, and the competitive deprotonation prevents the addition from occurring.

The inability to achieve enediyne ring closure via an *intra*molecular 1,2-addition prompted us to examine *inter*molecular possibilities.[15] The problems associated with α-deprotonation of the enone may be circumvented by the use of cerium acetylides.[16] The strategy of adding excess acetylide required a different alcohol protecting group for the C(11) hydroxymethyl, and thus the alcohol was protected as a *tert*-butyldiphenylsilyl (BPS) ether (Scheme 2). The addition of cerium acetylide[17] to enone **11** resulted in the formation of a single 1,2-addition product identified as diyne **12**. The stereochemistry of **12** was determined by conversion of the terminal alkyne

Scheme 3[a]



[a] TMSCCLi, $CeCl_3$, THF, −78 °C, 88%; (b) (*Z*)-$Me_3SnCHCHSnMe_3$, $Pd(PPh_3)_4$, LiCl, DMF, 50 °C.

moieties into acetylenic iodides.[18] X-ray analysis of crystalline diiodide **13** reveals that the 1,2-addition proceeds to give the undesired equatorial alkyne at C(2).[19]

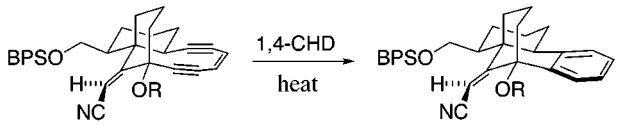
Although the stereochemical outcome of the acetylide addition was opposite from that which we required, we were encouraged that the attachment of an alkyne group to C(2) via intermolecular reaction proceeded in good yield. Examination of molecular models suggested another possibility to achieve the desired stereoselectivity. The trajectory for axial addition is promoted when C(1) is made tetrahedral, a consequence of a conformational ring flip on rehybridization of C(1). Cerium (trimethylsilyl)acetylide addition to ketone **14**, available from **7** in four steps,[9] proceeds to give diyne **15** in good yield (Scheme 3). Diiodide **16** is available from diyne **15** in 54% three-step yield. Ring closure was accomplished by palladium-catalyzed cross-coupling of **16** with (*Z*)-1,2-bis(trimethylstannyl)ethene[20] to afford enediyne **3**.[9,21]

We have shown that the cycloaromatization of **3** proceeds 1 order of magnitude faster than the analogous enediyne core of **1** at 37 °C.[9] Notable differences between **1** and **3** are the additional fused cyclohexyl ring in **3** and differing propargylic substituents. In an elaborate study by Wittman, propargylic substitution with alcohol groups was shown to effect the rate of cycloaromatization for 10-membered ring enediynes.[22] To examine the possibility that the decreased rate of cycloaromatization for **1** is attributable to the presence of the silyl protecting group, propargylic ether **4** was prepared from alcohol **16** by silylation using TESOTf. Subsequent palladium-mediated coupling with the appropriate stannane gave silyl-protected enediyne **4** in high yield.

Enediynes **3** and **4** were heated in d_6-benzene containing excess 1,4-cyclohexadiene (1,4-CHD) and monitored using ^{1}H NMR. As listed in Table 1, enediyne **3** has a rate of cycloaromatization roughly seven times faster

(12) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.
(13) Coulson, D. R. *Inorg. Synth.* **1974**, *13*, 121.
(14) Wender, P. A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209.
(15) For a survey on methods for the closure of enediyne rings, see: Konig, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 165.
(16) For papers illustrating the use of cerium-derived nucleophiles, see: (a) Imamoto, T. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 1.8 and references therein. (b) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747. For comparison of the lithium and cerium ion-pair acidities of some terminal alkynes, see Gareyev, R.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 1742.
(17) Prepared by the condensation of dry acetylene gas into THF at −78 °C followed by treatment with n-BuLi (see, Midland, M. M.; McLoughlin, J. I.; Werley, R. T. *Org. Synth.* **1989**, *68*, 14) and transmetalation with cerium chloride.
(18) (a) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727. (b) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.
(19) Crystal data for **13** may be obtained from Cambridge Crystallographic Data Centre; deposition CCDC 107106.
(20) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257.
(21) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.
(22) Wittman, M. D.; Kadow, J. F.; Pham, K.; Leung, K.; Mastalerz, H. A.; Vyas, D. M.; Rose, W. C.; Solomon, W.; Zein, N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2925.

Table 1. Kinetic Parameters for the Thermal Cyclization of 3 and 4

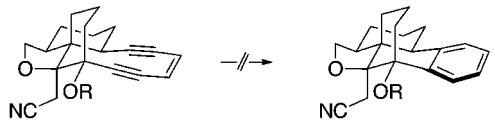


3: R = H
4: R = TES

18: R = H (76%)
19: R = TES (71%)

enediyne	product	T (°C)	k (s^{-1})	$t_{1/2}$ (min)
3	**18**	62	4.13×10^{-4}	28
3	**18**	71	7.22×10^{-4}	16
3	**18**	85	1.56×10^{-3}	7.4
4	**19**	71	1.11×10^{-4}	104
4	**19**	100	3.44×10^{-4}	34
4	**19**	115	6.14×10^{-4}	19

than its silyl ether counterpart **4** at 71 °C. The cycloaromatization rate of **4** and that reported for **1** are essentially identical at 71 °C.[7] Thus, the silylation of a propargylic alcohol positioned within the 10-membered enediyne carbocycle appears to significantly slow the rate of cycloaromatization. Also, from this experiment we infer that the influence of the fused six-membered ring in **3** on the cycloaromatization kinetics is minimal. The reasons for deceleration of the Bergman cyclization on alcohol silylation are unclear at present and may be due either to electronic or steric factors, despite that enediynes **1** and **4** have different silyl groups yet undergo cyclization at the same rate.



5: R = H
6: R = TES

20: R = H
21: R = TES

As stated previously, a change in hybridization at the one-carbon bridge ($Csp^2 \rightarrow Csp^3$) of bicyclo[7.3.1] enediynes is a transformation that has been shown to actuate cycloaromatization.[7] However, enediynes **5** and **6** are resistant to cycloaromatization. Heating a solution of **5** in 1,4-CHD to 60 °C for one week, or a solution of **6** to 71 °C for 24 h resulted in complete recovery of the starting materials.[23] Since the influence of the annelated cyclohexyl ring has been determined to be negligible, the unusual stability of **6** likely is a consequence of the geometrically constricting influence of the tetrahydrofuranyl ring.

In summary, our results suggest that in the absence of overriding geometrical constraints, the cycloaromatization kinetics of a bicyclo[7.3.1] enediyne may be moderated by propargylic alcohol silylation.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen. CH_2Cl_2 was distilled from calcium hydride immediately prior to use. THF and Et_2O were distilled from sodium benzophenone ketyl immediately prior to use, and benzene was distilled from sodium. All amine reagents were distilled from CaH_2. Column chromatography was carried out using 230−400 mesh silica gel, slurry-packed in glass columns, and eluted with the solvents indicated. TLC was performed on kieselgel 60 F_{254} plates, staining with an ethanolic solution of *p*-anisaldehyde containing 5% concentrated H_2SO_4. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ unless otherwise noted. High-resolution mass spectrometry was performed by Mass Spectrometry Service Labs of the University of California, Davis, the University of Minnesota (Minneapolis), and the University of Colorado (Boulder). Infrared (IR) data were obtained on neat samples.

7-{[(*tert*-Butylcarbonyl)oxy]methyl}-1-methylidenyl-11-(6-(trimethylsilyl)hex-3-ene-1,5-diyne)spiro[5.5]undecan-2-one (9). To a solution of chloroeneyne **8** (0.485 g, 3.0 mmol) in benzene (3.0 mL) at room temperature was added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). After stirring 15 min, *n*-$BuNH_2$ (0.20 mL, 2.0 mmol) was added followed by the addition of CuI (0.06 g, 0.3 mmol) and a solution of diol **7** (0.27 g, 1.0 mmol) in benzene (7.0 mL). After stirring overnight, the mixture was diluted with Et_2O and water, the layers were separated, and the organic extract was washed with saturated aqueous NH_4Cl, $NaHCO_3$, brine, and dried ($MgSO_4$). The solvents were removed in vacuo, and the residual oil was immediately subjected to hydrolysis by dissolving in $CHCl_3$ (2.0 mL) and transferring via cannula to a 50% solution of TFA in H_2O (2.0 mL). After vigorous stirring for 2 h at room temperature, the solution was diluted with $CHCl_3$ and water, the layers were separated, and the organic extract was washed with water, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). The solvents were removed in vacuo, and the crude enone was isolated as a light yellow oil. The crude material was dissolved in CH_2Cl_2 (5.0 mL) and followed by addition of Et_3N (0.08 mL. 0.6 mmol), DMAP (0.03 g, 0.25 mmol), and pivaloyl chloride (0.067 mL, 0.54 mmol). After stirring 3 h, the solution was diluted with $CHCl_3$ and water, the layers were separated, and the organic extract was washed with saturated aqueous Na_2CO_3 and brine and dried (Na_2SO_4). The solvents were removed in vacuo, and the residual oil was purified by flash column chromatography (2:2:1 hexane/ethyl acetate/chloroform) to afford **9** (0.18 g, 39% from **7**) as a light orange oil: IR 3023, 2211, 2142, 1726, 1695, 1250 cm^{-1}; ^1H NMR δ 6.39 (s, 1H), 5.77 (d, J = 11.0 Hz, 1H), 5.70 (d, J = 11.0 Hz, 1H), 5.63 (s, 1H), 4.10 (dd, J = 10.8, 3.9 Hz, 1H), 3.84 (dd, J = 10.8, 9.1 Hz, 1H), 2.50−2.42 (m, 3H), 2.05−1.79 (m, 7H), 1.59−1.37 (m, 4H), 1.17 (s, 9H), 0.20 (s, 9H); ^{13}C NMR δ 201.1, 178.4, 150.9, 123.0, 120.5, 119.1, 102.2, 102.0, 100.0, 81.2, 65.2, 47.0, 45.5, 44.3, 38.7, 38.6, 28.9, 27.1, 24.9, 24.8, 24.4, 20.3, −0.13. Exact mass calculated for $C_{27}H_{38}O_3Si$ 438.2590, found 438.2586.

7-{[(*tert*-Butylcarbonyl)oxy]methyl}-11-(hex-3-ene-1,5-diyne)-1-methylidenylspiro[5.5]undecan-2-one (10). To a flask containing dried 3 Å mol sieves and CH_3CN (1.6 mL) were added $NaHCO_3$ (7.7 mg, 0.09 mmol) and Ac_2O (5 μL, 0.06 mmol). A solution of enediyne **9** (10 mg, 0.023 mmol) in CH_3CN (0.5 mL) was added to the reaction mixture via cannula. After stirring 5 min, anhydrous CsF (35 mg, 0.23 mmol) was added, and the solution was stirred overnight. The mixture was passed through a short column of SiO_2, and the solvents were removed in vacuo. Flash column chromatography (7:3 hexane/ethyl acetate) on the residual oil provided terminal alkyne **10** (5 mg, 60%) as a yellow oil: ^1H NMR δ 6.42 (s, 1H), 5.81 (dd, J = 10.6, 1.2 Hz, 1H), 5.72 (dd, J = 10.6, 1.4 Hz, 1H), 5.63 (s, 1H), 4.08 (dd, J = 10.8, 3.6 Hz, 1H), 3.82 (dd, J = 10.8, 8.9 Hz, 1H), 3.25 (d, J = 1.5 Hz, 1H), 2.61−2.37 (m, 3H), 2.11−1.77 (m, 7H), 1.63−1.39 (m, 4H), 1.18 (s, 9H).

11-{[*tert*-Butyldiphenylsilyl)oxy]methyl}-2,7-diethynyl-1-methylidenespiro[5.5]undecan-2-ol (12). Acetylene (3.0 mL of a 2.7 M solution in THF at −78 °C, 8.1 mmol) was added via cannula to a solution of THF (1.0 mL) cooled to −78 °C. *n*-BuLi (0.7 mL of a 2.5 M solution in hexanes, 1.75 mmol) was added dropwise with a continuous purge of dry nitrogen. After stirring 30 min, the resulting solution was transferred via cannula to a vigorously stirred slurry of dry $CeCl_3$ (0.59 g, 2.4 mmol) in THF (1.0 mL) at −78 °C. After stirring 1.5 h, a solution of enone **11** (60 mg, 0.13 mmol) in THF (1.0 mL) at −78 °C was added via cannula. After stirring 1 h, the mixture was transferred to a separatory funnel containing Et_2O and 5% HCl. The organic layer was separated and the aqueous

(23) In each case, the ^1H NMR spectra for the recovered materials were identical to those of the purified starting compounds **5** and **6**.

layer extracted with Et_2O. The combined organic layer was washed with 5% HCl, saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4). The solvents were removed in vacuo, and the residual oil was purified by flash column chromatography (4:1 hexane/ethyl acetate) to provide diyne **12** (57 mg, 89%) as a clear oil: IR 3540, 3295, 3071, 2248, 2109, 1620 cm^{-1}; ^1H NMR δ 7.60 (m, 4H), 7.38 (m, 6H), 5.95 (s, 1H), 5.29 (s, 1H), 3.83 (dd, J = 9.6, 3.0 Hz, 1H), 3.40 (t, J = 9.6 Hz, 1H), 2.63 (s, 1H), 2.43 (dt, J = 12.1, 2.7 Hz, 1H), 2.12 (m, 1H), 2.05 (m, 2H), 1.96−1.49 (m, 9H), 1.43−1.18 (m, 3H), 1.03 (s, 9H); ^{13}C NMR δ 155.4, 135.6, 134.0, 129.4, 127.6, 116.3, 88.4, 87.7, 71.4, 70.2, 69.8, 65.2, 52.7, 45.7, 44.2, 37.0, 28.7, 26.9, 25.2, 24.3, 22.9, 19.2, 18.3. Exact mass calculated for $C_{33}H_{40}O_2Si$ 496.2797, found 496.2786.

11-{[*tert*-Butyldiphenylsilyl)oxy]methyl}-2,7-bis(1-iodoethynyl)-1-methylidenespiro[5.5]undecan-2-ol (13). To a stirred solution of diyne **12** (19 mg, 0.038 mmol) in acetone (0.6 mL) at 0 °C and protected from light were added *N*-iodosuccinimide (19 mg, 0.084 mmol) and silver nitrate (1.9 mg, 0.011 mmol). After stirring 4 h, the reaction was quenched by the addition of cold water and diluted with Et_2O. The aqueous layer was extracted three times with Et_2O, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were removed in vacuo, and the residual oil was purified by flash column chromatography (8.5:3.5 hexane/ethyl acetate) to provide **13**[19] (21 mg, 74%) as a white solid: ^1H NMR δ 7.64−7.58 (m, 4H), 7.42−7.33 (m, 6H), 5.86 (s, 1H), 5.22 (s, 1H), 3.73 (dd, J = 9.5, 3.0 Hz, 1H), 3.39 (t, J = 9.5 Hz, 1H), 2.57 (dd, J = 12.0, 3.3 Hz, 1H), 2.43 (s, 1H), 2.06 (m, 1H), 1.90 (m, 1H), 1.81−1.58 (m, 8H), 1.36−1.20 (m, 3H), 1.04 (s, 9H).

1-(Cyanomethyl)-7-[[[(1,1-dimethylethyl)diphenylsilyl]-oxy]methyl]-11-ethynyl-2-((trimethylsilyl)ethynyl)spiro-[5.5]undecan-1-ol (15). To a solution of (trimethylsilyl)-acetylene (55 mL, 0.39 mmol) in THF (0.5 mL) at 0 °C was added ^{n}BuLi (0.16 mL of a 2.5 M solution in hexane, 0.39 mmol). After stirring for 30 min at 0 °C, the reaction was cooled to −78 °C and added to a flask containing a suspension of $CeCl_3$ (140 mg, 0.568 mmol) in THF (1 mL) at −78 °C. The transmetalation reaction was stirred at −78 °C for 1 h, followed by addition of a solution of ketone **14** (18 mg, 0.036 mmol) in THF (0.3 mL). The reaction was stirred at −78 °C for 1.5 h. The reaction was poured into Et_2O and washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine. The combined aqueous layers were extracted with Et_2O. The organic fractions were combined and dried over Na_2SO_4. The solvents were removed by rotary evaporation. Purification of the residue by silica gel chromatography (4:1 hexane:EtOAc) provided **9** (19 mg, 88%); IR 3519, 3299, 3072, 3052, 2239, 2169, 2106 cm^{-1}; ^1H NMR δ 7.63 (m, 4H), 7.45 (m, 6H), 7.35 (br s, 1H), 4.16 (br s, 1H), 3.47 (1/2 ABq, J = 17.1 Hz, 1H), 3.40 (m, 2H), 3.33 (s, 1H), 2.89 (m, 1H), 2.84 (1/2 ABq, J = 17.4 Hz, 1H), 2.06 (d, J = 2.7 Hz, 1H), 2.02−1.47 (overlapping m, 12H), 1.08 (s, 9H), 0.20 (s, 9H); ^{13}C NMR δ 135.6, 131.8, 131.4, 130.2, 130.1, 128.0, 127.9, 120.1, 106.9, 93.0, 86.0, 77.2, 73.3, 70.4, 66.5, 48.1, 38.4, 37.8, 30.8, 27.2, 26.6, 23.7, 23.1, 21.0, 19.6, 19.0, 17.6, −0.5; exact mass calcd for $C_{37}H_{48}NO_2Si_2$ $(M\text{-}OH)^+$ 594.3223, found 594.3257.

7-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-1-(*Z*)-(Cyanomethylidenyl)-2,11-bis(1-iodoethynyl)-2-(triethylsilyloxy)-spiro[5.5]undecane (17). To a solution of TESOTf (20 μL, 0.09 mmol) and pyridine (7 μL, 0.09 mmol) in Et_2O (0.25 mL) and CH_3CN (0.25 mL) at room temperature was added a solution of diiodide **16** (23 mg, 0.03 mmol) in Et_2O (0.25 mL), CH_3CN (0.25 mL), and DMF (0.25 mL) via cannula. The reaction was stirred at room temperature for 4 h. The reaction was quenched by the addition of H_2O and was diluted in Et_2O. The organic layer was separated and washed with brine. The aqueous was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, and solvent was removed by rotary evaporation. Purification of the crude by flash chromatography (9:1 hexane/EtOAc) provided **17** (18 mg, 69%) as a clear oil; IR 3072, 2875, 2212, 2175, 1589, 1471 cm^{-1}; ^1H NMR δ 7.72 (m, 4H), 7.22 (m, 6H), 6.12 (s, 1H), 3.66 (dd, J = 9.8, 3.4 Hz, 1H), 3.61 (dd, J = 11.4, 3.4 Hz, 1H), 3.34 (t, J = 9.9 Hz, 1H), 2.71 (m, 1H), 2.19 (m, 1H), 1.91 (m, 4H), 1.76 (m, 2H), 1.58 (m, 2H), 1.23 (m, 3H), 0.97 (s, 9H), 0.67 (t, J = 7.9 Hz, 9H), 0.33 (q, J = 7.9 Hz, 6H); ^{13}C NMR δ 170.9, 144.2, 135.5, 133.9, 133.4, 129.5, 129.4, 127.6, 127.5, 117.3, 98.9, 96.5, 73.4, 64.7, 48.7, 46.1, 42.3, 36.9, 32.4, 28.9, 26.7, 24.7, 23.8, 22.0, 18.9, 16.8, 11.4, 6.7, 5.7; exact mass calcd for $C_{36}H_{42}I_2NO_2Si_2$ $(M - C_4H_9)^+$ 830.0844, found 830.0820.

13-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-17-(*Z*)-(Cyanomethylidenyl)-8,12-methano-8-(triethylsilyloxy)bicyclo[10.4.0]hexadec-4-ene-2,6-diyne (4). To a solution of **17** (17 mg, 0.019 mmol) in deoxygenated DMF (0.3 mL) at room temperature was added $Pd(PPh_3)_4$ (2 mg, 0.002 mmol). The resultant yellow reaction mixture was stirred for 10 min, followed by addition of LiCl (2 mg, 0.04 mmol). The resultant clear solution was heated to 50 °C, followed by dropwise addition of a solution of (*Z*)-bis(trimethylstannyl)ethylene (14 mg, 0.038 mmol) in deoxygenated DMF (0.3 mL) via cannula. The reaction was stirred at 50 °C for 45 min in the dark and then was diluted with Et_2O and washed with H_2O and brine. The aqueous layer was extracted with Et_2O. The combined organic fraction was dried over Na_2SO_4, and the solvent was removed by rotary evaporation. Purification of the crude by silica gel chromatography (9.5:0.5 hexane/EtOAc) provided **4** (11 mg, 83%) as a yellow oil; IR 3072, 3055, 2956, 2252, 2210, 1605 cm^{-1}; ^1H NMR δ 7.68 (m, 4H), 7.19 (m, 6H), 6.10 (s, 1H), 5.85 (d, J = 9.4 Hz, 1H), 5.74 (d, J = 9.5 Hz, 1H), 3.75 (m, 1H), 3.61 (dd, J = 9.2, 3.5 Hz, 1H), 3.41 (t, J = 9.3 Hz, 1H), 2.81 (m, 1H), 2.46 (m, 1H), 2.18 (m, 1H), 1.82 (m, 4H), 1.56 (m, 2H), 1.29 (m, 4H), 1.05 (s, 9H), 0.88 (t, J = 7.7 Hz, 9H), 0.64 (m, 6H); ^{13}C NMR δ 172.9, 135.6, 133.9, 133.4, 129.7, 129.6, 127.7, 125.3, 120.6, 117.9, 105.2, 100.8, 94.7, 89.6, 81.7, 71.2, 65.4, 49.2, 48.9, 41.9, 34.4, 28.6, 26.9, 24.9, 24.2, 19.3, 18.5, 17.6, 6.9, 6.1; exact mass calcd for $C_{42}H_{53}NO_2Si_2$ 659.3615, found 659.3622.

Aromatic Vinyl Nitrile (19). A solution of enediyne **4** (7 mg, 0.01 mmol) in 1,4-cyclohexadiene (1 mL) was heated to 71 °C in a sealed tube for 16 h. The reaction was diluted with Et_2O and was added to a small recovery flask. The solvents were removed by rotary evaporation. Purification of the crude by flash chromatography (9.5:0.5 hexane/EtOAc) provided **19** (5 mg, 71%) as a clear oil; IR 3072, 3049, 2954, 2213, 1620 cm^{-1}; ^1H NMR δ 7.71 (m, 4H), 7.41 (m, 8H), 7.20 (m, 2H), 5.92 (s, 1H), 3.96 (dd, J = 10.3, 3.6 Hz, 1H), 3.69 (dd, J = 10.3, 5.0 Hz, 1H), 2.98 (m, 1H), 2.89 (m, 1H), 2.41 (m, 1H), 2.24 (m, 1H), 2.08 (m, 2H), 1.81 (m, 2H), 1.61 (m, 4H), 1.28 (m, 2H), 1.07 (s, 9H), 1.01 (t, J = 7.9 Hz, 9H), 0.74 (m, 6H); ^{13}C NMR δ 170.9, 144.0, 138.6, 135.9, 135.7, 129.5, 129.4, 127.5, 127.1, 124.0, 123.9, 117.7, 110.5, 88.2, 80.0, 64.8, 53.0, 49.5, 43.7, 42.5, 27.2, 26.9, 25.8, 24.8, 24.4, 20.1, 19.3, 7.4, 7.2; exact mass calcd for $C_{42}H_{55}NO_2Si_2$ 661.3771, found 661.3775.

General Experimental for Rate Determination of 4 → 19. To an NMR tube charged with a solution of enediyne **4** (2.0 mg, 3 μmol) in C_6D_6 (ca. 1.0 mL) at room temperature was added 1,4-cyclohexadiene (50 μL, 0.53 mmol). The sample was then incubated at the given temperature and subsequently examined by ^1H NMR spectroscopy at 15 min intervals.[24] Integration of the isolated and well-separated *tert*-butyl protons of **4** and **19** at δ 1.17 and 1.29, respectively, enabled determination of $t_{1/2}$ (τ) and rate constant values. The experiment was repeated a minimum of three times for each temperature that was examined, and the mean value is reported.

Cyclic Ether (6). To a solution of alcohol **5** (1.5 mg, 4.9 μmol) in a mixture of Et_2O (0.25 mL) and CH_3CN (0.25 mL) at room temperature was added via cannula a solution of TESOTf (10 μL, 0.05 mmol) in pyridine (4 μL, 0.05 mmol), Et_2O (0.25 mL), and CH_3CN (0.25 mL). The reaction was stirred at room temperature for 30 min. The reaction was then diluted with Et_2O and washed with brine. The aqueous fraction was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, and solvent was removed by rotary evaporation.

(24) Grissom, J. W.; Calkins, T. L. *J. Org. Chem.* **1993**, *58*, 5422.

Purification of the crude by flash chromatography (4:1 hexane/EtOAc) provided **6** (1.0 mg, 49%) as a clear oil; ^{1}H NMR δ 5.89 (d, J = 9.7 Hz, 1H), 5.84 (d, J = 9.5 Hz, 1H), 4.09 (t, J = 7.7 Hz, 1H), 3.57 (dd, J = 11.6, 8.1 Hz, 1H), 3.45 (1/2ABq, J = 17.2 Hz, 1H), 3.09 (1/2ABq, J = 17.3 Hz, 1H), 3.01 (m, 1H), 2.59 (m, 1H), 1.93 (m, 2H), 1.75 (m, 2H), 1.29 (m, 4H), 0.98 (m, 4H). 0.70 (t, J = 7.8 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H); exact mass calcd for $C_{26}H_{35}NO_2Si$ 421.2437, found 421.2444.

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Supporting Information Available: ^{13}C NMR spectra of compounds **4**, **9**, **12**, **15**, **17**, and **19**, and ^{1}H NMR spectra of **6** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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