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Application of Photochemical Decarbonylation of Cyclopropenones for the in Situ Generation of Reactive Enediynes. Construction of a Cyclopropenone-Containing Enediyne Precursor by Using a Cyclopropenone Acetal Building Block

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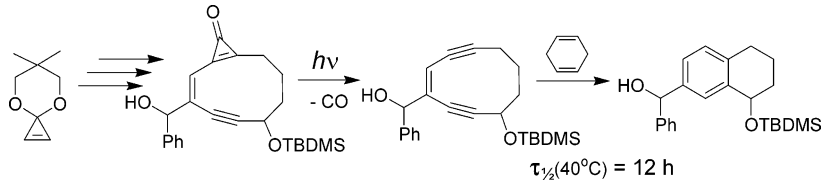

A cyclopropenone-containing enediyne photoprecursor, 6-*tert*-butyldimethylsilyloxy-3-(α-hydroxybenzyl)bicyclo[8.1.0]undeca-1(10),2-diene-4-yn-11-one (**1**), was prepared in 10 steps by sequential modification of the cyclopropenone 2,2-dimethyl-1,3-propanediyl acetal (**5**). The crucial cyclization step was achieved under Nozaki conditions, while the endocylic double bond has been introduced by the allylic rearrangement. UV irradiation of the cyclopropenone **1** results in efficient decarbonylation and the formation of the reactive enediyne **2**. The latter undergoes Bergman cycloaromatization with a half-life of 12 h at 40 °C and in the presence of 1,4-dihydrobenzene quantitatively produces corresponding tetralin **29**.

Introduction

Natural enediyne antibiotics are arguably the most potent antineoplastic agents ever discovered.[1,2] Cytotoxicity of this class of natural products is attributed to the ability of the (*Z*)-3-ene-1,5-diyne fragment to undergo Bergman[3] cyclization. The *p*-benzyne diradical produced in this reaction is believed to abstract hydrogen atoms from both strands of DNA, ultimately causing double-strand DNA scission.[2] A major stumbling block to clinical applications of enediyne antibiotics is their inadequate selectivity, and harnessing the powerful DNA-cleaving activity of this class of molecules is an area of high priority in antitumor drug design. The cycloaromatization of enediynes is also employed in the development of selective nucleases[4] and high-performance linear aromatic polymers for microelectronic fabrication.[5]

Photochemical triggering of Bergman cyclization allows for controlling enediyne reactivity in space and in time. Several examples of light-induced cycloaromatization of acyclic[6,7] and cyclic[8] enediynes, as well as of natural antibiotic Dynemicin A,[9] have been reported in the literature. Our group explores the alternative strategy

(1) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Golic, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-I.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. 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.

(2) For recent reviews see: *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Marcel Dekker: New York, 1995. Jones, G. B.; Fouad, F. S. *Curr. Pharm. Des.* **2002**, *8*, 2415;. Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497. Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16.

(3) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

(4) Dai, W.-M.; Lai, K. W.; Wu, A.; Hamaguchi, W.; Le, M. Y. H.; Zhou, L.; Ishii, A.; Nishimoto, S. *J. Med. Chem.* **2002**, *45*, 758. Tuntiwechapikul, W.; David, W. M.; Kumar, D.; Salazar, M.; Kerwin, S. M. *Biochemistry* **2002**, *41*, 5283. Rawat, D. S.; Zaleski, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 9675. Jones, G. B.; Hynd, G.; Wright, J. M.; Purohit, A.; Plourde, G., II; Huber, R. S.; Mathews, J. E.; Li, A.; Kilgore, M. W.; Bubley, G. J.; Yancisin, M.; Brown, M. A. *J. Org. Chem.* **2001**, *65*, 3688. Takahashi, T.; Tanaka, H.; Yamada, H.; Matsumoto, T.; Sugiura, Y. *Angew. Chem., Int. Ed. Engl.* **1977**, *36*, 1524.

(5) Smith, D. W., Jr.; Babb, D. A.; Snelgrove, R. V.; Townsend, P. H., III; Martin, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 9078. John, J. A.; Tour, J. M. *Tetrahedron* **1997**, *53*, 15515. Chen, X.; Tolbert, L. M.; Hess, D. W.; Henderson, C. *Macromolecules* **2001**, *34*, 4104. Shah, H. V.; Babb, D. A.; Smith, D. W., Jr. *Polymer* **2000**, *41*, 4415.

(6) Kagan, J.; Wang, X.; Chen, X.; Lau, K. Y.; Batac, I. V.; Tuveson, R. W.; Hudson, J. B. *J. Photochem. Photobiol., B* **1993**, *21*, 135. Turro, N. J.; Evenzahav, A.; Nicolaou, K. C. *Tetrahedron Lett.* **1994**, *35*, 8089. Kaneko, T.; Takahashi, M.; Hirama, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1267. Plourde, G., II; El-Shafey, A.; Fouad, F.; Purohit, A.; Jones, G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2985.

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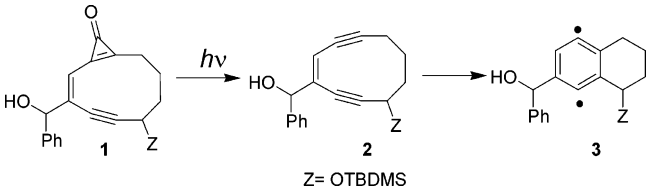
SCHEME 1



of photoactivation: the in situ generation of the reactive enediyne system, which then undergoes thermal Bergman reaction. Among other methods, we employ photochemical decarbonylation of cyclopropenones[10] to produce one of the enediyne triple bonds. Thus, 3,4-benzocyclodeca-1,5-diyne can be quantitatively and efficiently ($\Phi_{300} = 0.45$) generated by the UV irradiation of the precursor, in which one of the triple bonds is replaced by the cyclopropenone group.[11] The cyclization rate of the former ($\tau_{1/2} = 6-24$ h at 84 °C)[12] is substantially lower than that of the parent 3-cyclodecene-1,5-diyne ($\tau_{1/2} = 18$ h at 37 °C),[13] which makes it hardly relevant to biological applications. The low reactivity of benzannulated enediynes is attributed to the increased stability of the initial state due to the incorporation of the double bond into an aromatic system.[12,14] On the other hand, introduction of hydroxy or similar groups in the propargylic position allows for a 3−6-fold increase in the rate of cyclization.[12,15] Here we report the synthesis and reactivity of the cyclopropenone-containing enediyne precursor, 6-hydroxy-3-(α-hydroxybenzyl)bicyclo[8.1.0]undeca-1(10),2-diene-4-yn-11-one (**1**). Photolysis of cyclopropenone **1** results in decarbonylation and the formation of the reactive enediyne **2**, which, in turn, undergoes Bergman cyclization to produce a *p*-benzyne diradical **3** (Scheme 1).

Results and Discussion

Synthesis of Cyclopropenone 1. A number of synthetic methods are available for the preparation of the cyclopropenone group, which is the key component of the photoactivatable enediyne precursor **1**;[16] however, few of them are compatible with such a highly functionalized macrocycle as **1**. In addition, the introduction of cyclopropenone functionality on early stages of the synthesis is difficult due to the high reactivity of this group. Cyclopropenones are very susceptible to a nucleophilic attack, which usually results in ring opening and the formation of acrylic acid derivatives.[17] Alternatively, they react with Lewis acids to give rise to a relatively stable 2π-aromatic oxycyclopropenium cation. The construction of a cyclopropenone-containing enediyne precursor using cyclopropenone 2,2-dimethyl-1,3-propanediyl acetal[18] (**7**) as a building block allows us to circumvent these difficulties and broaden the range of reagents and reaction conditions that can be employed (Scheme 2). It has to be noted, however, that cyclopropenone acetal is extremely susceptible to hydrolysis. Its lifetime is only a few milliseconds in an aqueous solution.[19]

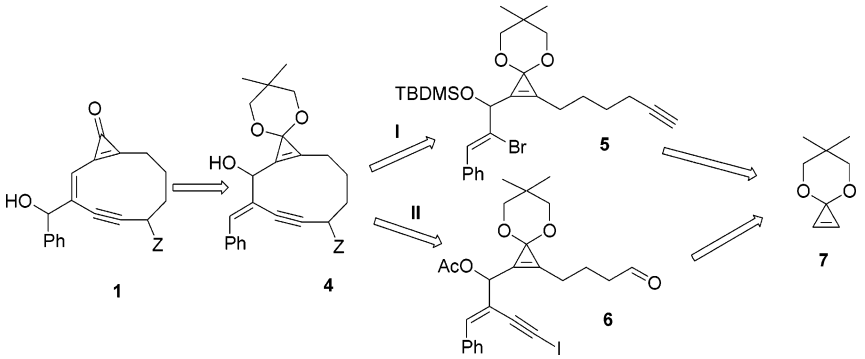
To reduce ring strain, which is generated at the crucial cyclization step, and make the reaction more favorable, we decided to introduce an endocyclic double bond into structure **1** at the later stages of the synthesis using the allylic rearrangement.[20] The ring closure of the 10-membered-ring macrocycle **4** can be achieved either by using a palladium-mediated cross coupling between the terminal acetylene and vinyl bromide (route I, Scheme 2) or by employing the Nozaki cyclization[21] (route II, Scheme 2).

The preparation of the cyclization substrate **5** began with a reaction of the lithium salt of cyclopropenone acetal[18] (**7**) with (6-iodo-1-hexynyl)trimethylsilane[22] (**8**), which produced 67% of (6-trimethylsilyl-5-hexynyl)cyclopropenone acetal (**9**, Scheme 3). The addition of the lithium salt of the latter to α-bromocinnamaldehyde resulted in the formation of alcohol **10** in 84% yield. The TBDMS protection of the secondary hydroxyl group followed by the removal of the trimethylsilyl group from the terminal acetylene gave the target compound **5** in an 87% overall yield. Several attempts to achieve cyclization of **5** under Sonogashira conditions primarily led to the isolation of the starting material. The Pd(0)-mediated reaction of the zinc acetylide of **5** with the vinyl bromide fragment[23] also failed in producing the target macrocycle **4**.

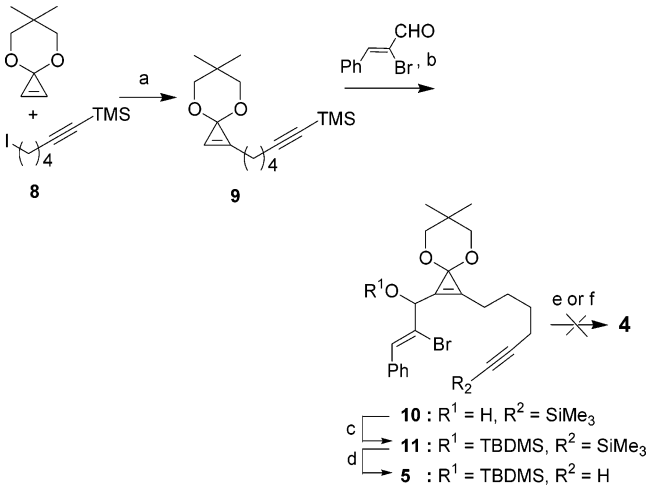
The alternative route to macrocyclic cyclopropenone **1** was based on the well-established methodology for the

(7) Benites, P. J.; Holmberg, R. C.; Rawat, D. S.; Kraft, B. J.; Klein, L. J.; Peters, D. G.; Thorp, H. H.; Zaleski, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 6434. Kraft, B. J.; Coalter, N. L.; Nath, M.; Clark, A. E.; Siedle, A. R.; Huffman, J. C.; Zaleski, J. M. *Inorg. Chem*. **2003**, *42*, 1663.
(8) Choy, N.; Blanco, B.; Wen, J.; Krishan, A.; Russell, K. C. *Org. Lett.* **2000**, *2*, 3761. Funk, R. L.; Young, E. R. R.; Williams, R. M.; Flanagan, M. F.; Cecil, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 3291.
(9) Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795.
(10) Poloukhtine, A.; Popik, V. V. *J. Org. Chem*. **2003**, *68*, 7833.
(11) Poloukhtine, A.; Popik, V. V. *Chem. Commun*. **2004**, in press (B414951C).
(12) Semmelhack, M. F.; Neu, T.; Foubelo, F. *J. Org. Chem.* **1994**, *59*, 5038.
(13) Nicolaou, K. C.; Ogawa, K.; Zuccarello, G.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.
(14) Stahl, F.; Moran, D.; Schleyer, P. v. R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2002**, *67*, 1453.
(15) Semmelhack, M. F.; Gallander, J. *Terahedron Lett.* **1993**, *34*, 4121.
(16) Breslow, R.; Posner, J.; Krebs, A. *J. Am. Chem. Soc.* **1963**, *85*, 234. Chikos, J. C.; Patton, E.; West, R. *J. Org. Chem.* **1974**, *39*, 1647. Weinder, C. H.; Wadsworth, D. H.; Knop, C. S.; Oyefesso, A. I.; Hafer, B. H.; Hartman, R. J.; Mehlenbacher, R. C.; Hogan, S. C. *J. Org. Chem.* **1994**, *59*, 4319. Wadsworth, D. H.; Donatelli, B. A. *Synthesis* **1981**, 285. Chiang, Y.; Grant, A. S.; Kresge, A. J.; Paine, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 4366. Musigmann, K.; Mayr, H. *Tetrahedron Lett.* **1987**, *28*, 4517. Gleiter, R.; Merger, M.; Altereuther, A.; Irngartinger, R. *J. Org. Chem.* **1996**, *61*, 1946. Netland, K. A.; Gundersen, L.-L.; Rise, F. *Synth. Commun.* **2000**, *30*, 1767. Köbrich, G.; Flory, K.; Fischer, R. H. *Chem. Ber.* **1966**, *99*, 1793.
(17) Potts, K. T.; Baum, J. S. *Chem. Rev.* **1974**, *74*, 189. Halton, B.; Banwell, M. G. In *The Chemistry of Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; p 1300. Ciabattoni, J.; Nathan, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 4766. Dehmlow, E. V.; Neuhaus, R.; Schell, H. G. *Chem. Ber.* **1988**, *121*, 569. Dehmlow, S. S.; Dehmlow, E. V. *Naturforsch. B* **1975**, *30b*, 404. Dehmlow, E. V. *Liebigs Ann.* **1969**, *729*, 64.
(18) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727. Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, *48*, 2045.
(19) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027.
(20) Dai, W.-M.; Fong, K. C.; Lau, C. W.; Zhou, L.; Hamaguchi, W.; Nishimoto, S. *J. Org. Chem.* **1999**, *64*, 682.
(21) Takai, K.; Tagashira, M.; Kudora, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. Crevisy, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 3171.
(22) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Exposito Castro, M. A. *J. Org. Chem.* **2003**, *68*, 6153.
(23) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

SCHEME 2



SCHEME 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF−HMPA, then **8**; −78 °C, 67%; (b) *n*-BuLi, THF, then α-bromocinnamaldehyde; −78 °C, 84%; (c) TBDMSCl, imidazole, DMF, 72%; (d) K_2CO_3, MeOH, rt, 87%; (e) $Pd(PPh_3)_2Cl_2$, CuI, PPh_3, Et_3N, THF, 40 °C; (f) *n*-BuLi, $ZnCl_2$, THF; then $Pd(PPh_3)_4$, rt.

preparation of strained macrocycles, i.e., the Nozaki coupling (Scheme 4).[21,24]

The TBDMS-protected 2-(4-hydroxybutyl)cyclopropenone 2,2-dimethyl-1,3-propanediyl acetal (**12**) was prepared by the reaction of the lithium salt of cyclopropenone acetal **7** with (4-iodobutoxy)-*tert*-butyldimethylsilane. The reaction of the lithium salt of **12** with 2-(trimethylsilylethynyl)cinnamaldehyde (**13**) produced **14** in an excellent yield. The next stage of our synthetic plan called for the protection of a secondary hydroxyl group and cleavage of the primary silyl ether. Toward this end, we have prepared *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl ethers of alcohol **14**. We were unable, however, to achieve selective cleavage of the primary silyl ether. Under acidic conditions the deprotection of the primary hydroxy group was accompanied by a much faster hydrolysis of the cyclopropenone acetal group. Application of TBAF resulted in the cleavage of both silyl ethers. We, therefore, decided to convert the 3-hydroxy group of **14** into acetate **15** by treatment with acetic anhydride in the presence of a catalytic amount of DMAP. Both silyl protecting groups in **15** were removed simultaneously with TBAF, and the terminal acetylene group in **16** was iodinated with an iodine/morpholine system to produce iodoalkyne **17** in an 83% yield. The primary hydroxy group was oxidized into aldehyde **6** with use of Dess−Martin periodinane.[25] The crucial ring closure of **6** was achieved by using the Cr(II)/Ni(II) catalytic system,[21] leading to the target macrocycle **18** as a mixture of two diastereomers in a 72% yield. The protection of the secondary hydroxy group in **18** with *tert*-butyldimethylsilyl chloride in the presence of imidazole produced silyl ether **19**. The acetate group of the latter was saponified in a methanolic solution of sodium hydroxide at 0 °C producing unstable alcohol **20**, which has to be processed immediately. The allylic rearrangement, which was supposed to produce the target enediyne precursor **1** from **20**, was the last challenge in the synthetic sequence. Treatment of **20** with 10-camphorsulfonic acid (CSA) in the presence of water or methanol[20,26] led to a complete decomposition of the substrate. Recognizing that the cyclopropenone acetal group and unsaturated macrocycle are extremely sensitive to the acidic media, we turned our attention to the methanesulfonyl chloride-induced migration of a double bond.[27] The reaction of **20** with methanesulfonyl chloride in the presence of diisopropylethylamine at −78 °C finally produced the target cyclopropenone **1** in 35% yield.

It is interesting to note that cyclopropenone acetal building blocks are not suitable for the construction of 3,4-benzannelated enediynes. The Pd(0)-catalyzed coupling of iodoaromatics with zinc salts of various cyclopropenone acetals,[18] which works well in the case of meta- and para-substituted substrates, fails in the case of ortho-substituted benzenes.[28]

Photochemistry of 6-*tert*-Butyldimethylsilyloxy-3-(α-hydroxybenzyl)bicyclo[8.1.0]undeca-1(10),2-diene-4-yn-11-one (1). The UV spectrum of cyclopropenone **1** has a strong absorbance at 289 nm ($\log \epsilon = 3.9$) and a weaker band at 304 nm on the shoulder of the main band (Figure 1). The 254- or 300-nm photolysis of **1** results in the efficient bleaching of the starting absorbance and the formation of a new one with $\lambda_{max} = 276$ nm and similar intensity, which corresponds to 1-*tert*-butyldimethylsilyloxy-4-(α-hydroxybenzyl)-4-cyclodecene-2,6-diyne (**2**) (Fig-

(24) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

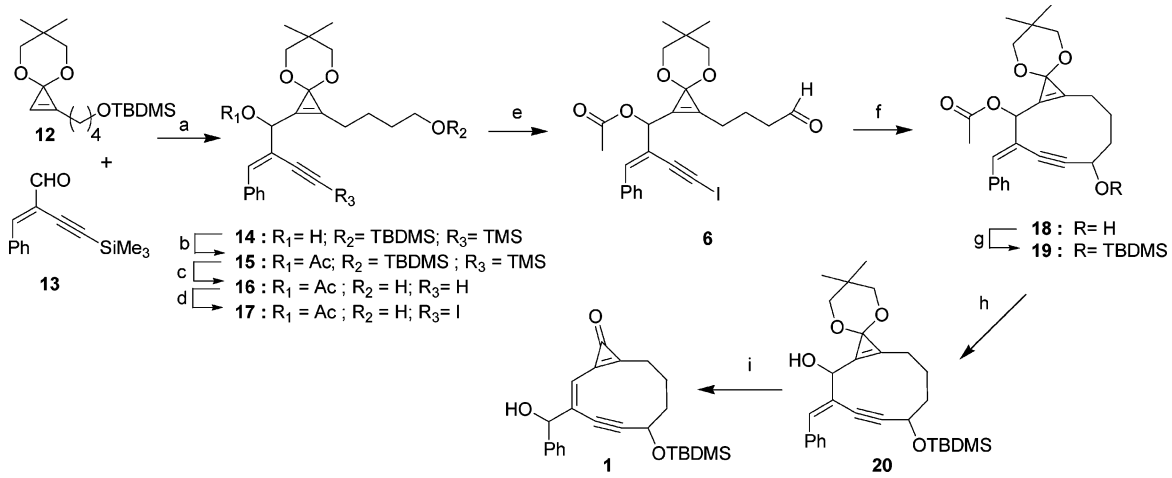
(25) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(26) Dai, W.-M.; Wu, J.; Fong, K. C.; Lee, M. Y. H.; Lau, C. W. *J. Org. Chem.* **1999**, *64*, 5062.

(27) Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishmoto, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 779.

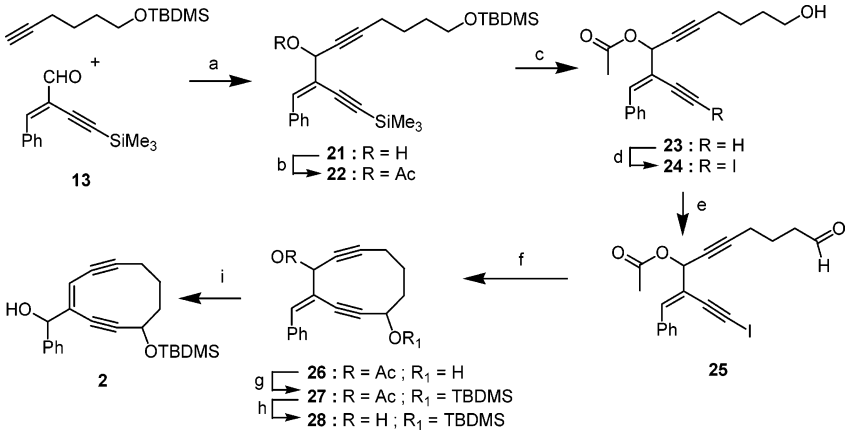
(28) Detailed discussion of this reaction can be found in the Supporting Information.

SCHEME 4[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF−TMEDA, then **13**; −78 °C , 86%; (b) $(CH_3CO)_2O$, CH_2Cl_2, Et_3N, 98%; (c) TBAF/AcOH, 98%; (d) I_2, morpholine, benzene, 83%; (e) Dess−Martin periodinane; CH_2Cl_2, 88%; (f) $CrCl_2$, $NiCl_2$, THF, rt, 72%; (g) TBDMSCl, imidazole, 0 °C, 82%; (h) NaOH, MeOH, 90%; (i) $MeSO_2Cl$, *i*-Pr_2EtN, 35%.

SCHEME 5[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to rt, 98%; (b) $(CH_3CO)_2O$, CH_2Cl_2, Et_3N, 99%; (c) TBAF, AcOH, 99%; (d) I_2, morpholine, benzene, 91%; (e) Dess−Martin periodinane; CH_2Cl_2, 84%; (f) $CrCl_2$, $NiCl_2$, THF, rt, 90%; (g) TBDMSCl, imidazole, 0 °C, 84%; (h) NaOH, MeOH, 90%; (i) CSA, H_2O, CH_2Cl_2, rt, 16%.

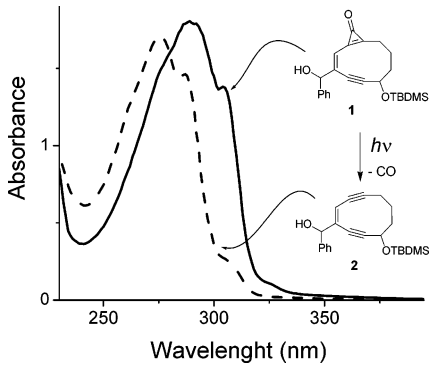


FIGURE 1. UV spectra of 300-nm photolysis of ca. 2×10^{-4} M methanol solutions of cyclopropenone **1**.

ure 1). The preparative 254-nm photolysis of the methanol solution of cyclopropenone **1** produced enediyne **2** as a single product, which was isolated from the reaction mixture in a 55% yield.

To prove the structure of enediyne **2**, we have synthesized it independently (Scheme 5). The reaction of aldehyde **13** with 6-(*tert*-butyldimethylsilyloxy)-1-hexynyl[29] lithium produced propargylic alcohol **21**, which was esterified with acetic anhydride to give enediyne **22**. Both silyl protecting groups were quantitatively removed by the treatment with TBAF. The terminal acetylene group in resulting **23** was treated with I_2 in the presence of morpholine to afford iodoalkyne **24** in a 91% yield. Oxidation of the primary hydroxy group in **24** with Dess−Martin periodinane produced aldehyde **25** in an 84% yield. The Nozaki cyclization of a highly diluted solution of **25** in THF produced a very good yield of enediyne **26**. The secondary hydroxyl group of **26** was smoothly protected by *tert*-butyldimethylsilyl chloride in the presence of imidazole to afford silyl ether **27**. The acetate group was saponified in methanolic sodium hydroxide and the resulting alcohol **28** was treated with 10-camphorsulfonic acid in wet dichloromethane to yield the target enediyne **2**. This compound was found to be identical with the sample isolated from reaction mixtures of photolysis of **1**.

(29) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

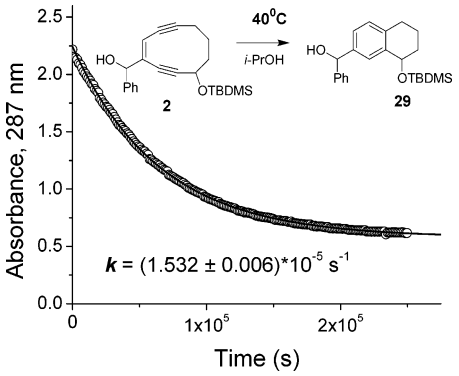


FIGURE 2. Kinetic trace observed at 287 nm following decay of enediyne **2** in 2-propanol at 40 °C. The curve represents the calculated fit to a single-exponential equation.

The Bergman Cyclization of 1-*tert*-Butyldimethylsilyloxy-4-(α-hydroxybenzyl)-4-cyclodecene-2,6-diyne (2). The heating of the degassed benzene solution of enediyne **2** in the presence of 1,4-dihydrobenzene for 4 h at 75 °C results in a complete conversion of **2** into tetralin **29** (Figure 2). The rate of Bergman cyclization of **2** was measured in a 2-propanol solution at 40 °C. The progress of the reaction was followed by the decrease in absorbance of **2** at 287 nm (Figure 2). The observed rate of the Bergman cyclization of **2**, $k_{40\ °C} = (1.532 \pm 0.006) \times 10^{-5}\ s^{-1}$, is close to that of the parent 3-cyclodecene-1,5-diene ($k_{37\ °C} = 1.07 \times 10^{-5}$).[13] Direct comparison of these rates, however, should be done with caution as the rate of enediyne cyclization is known to depend on the solvent, as well as the concentration and nature of hydrogen donor.[12]

The enediyne photoprecursor **1** undergoes a very slow decomposition at 40 °C in the benzene−1,4-dihydrobenzene mixture; however, no enediyne **2** or either product of the Bergman cyclization **29** were detected in the reaction mixture.

Conclusions. The photoprecursor **1** of TBDMS-protected (α-hydroxybenzyl)-4-cyclodecene-2,6-diynol (**2**), in which one of the triple bonds is replaced with a cyclopropenone functionality, was designed and synthesized. The bicyclic cyclopropenone **1** shows no tendency for the Bergman cycloaromatization or for the formation of **2** in the dark. The UV irradiation of **1**, on the other hand, results in the efficient generation of the reactive ten-membered-ring enediyne **2**. The latter undergoes Bergman cyclization at 40 °C with a half-life of 12 h in 2-propanol to produce a benzannulated analogue of *p*-benzyne diradical **3**, which abstracts hydrogen atoms from the available hydrogen donors to form tetralin **29**. The rate of cycloaromatization of **2** is slightly higher than that of the parent 3-cyclodecene-1,5-diyne, apparently due to the electronic influence of the silyloxy substituent in the propargylic position.

Experimental Section

2-(6-Trimethylsilyl-5-hexynyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (9). A solution of 6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene (cyclopropenone acetal **7**)[18] (6.88 g, 49.13 mmol) in THF (45 mL) and HMPA (18 mL) was treated with *n*-BuLi (2.5 M solution in hexanes, 55 mmol, 22 mL) at −78 °C. After the mixture was stirred for 45 min at this temperature, a solution of (6-iodo-1-hexynyl)trimethylsilane[22] (12.32 g, 44 mmol) in THF (5 mL) was added, and the resulting solution was stirred for 4 h at ca. −30 °C (dry ice−EtOH−water 1:1 bath). The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), and diluted with ca. 100 mL of a hexanes−ethyl acetate mixture (4:1). The organic layer was separated, passed through a short silica gel column (ca. 5 cm), and dried over anhydrous sodium sulfate, and solvent was removed in a vacuum. Purification of the residue by chromatography (hexanes−ethyl acetate 14:1 mixture containing 1.5% of Et_3N) gave 8.58 g (29.4 mmol, 67%) of **13** as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.34 (s, 1H), 3.65−3.55 (m, 4H), 2.54, (t, J = 7.2 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H), 1.76−1.68 (m, 2H), 1.65−1.55 (m, 2H), 1.05 (s, 3H), 0.98 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 137.6, 115.8, 107.1, 84.8, 83.6, 77.2, 30.5, 28.1, 26.4, 24.6, 22.5, 22.2, 19.7, 0.27; MS calcd for $C_{17}H_{28}O_2Si$ (M^+) 292, found 292.

2-(2-Bromo-1-hydroxy-3-phenyl)-3-(6-trimethylsilyl-5-hexynyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (10). A solution of **9** (2 g, 6.85 mmol) and TMEDA (ca. 4 equiv, 3.2 mL) in THF (15 mL) was treated with *n*-BuLi (2.5 M solution in hexanes, 7.19 mmol, 2.9 mL) at −78 °C, and the resulting mixture was stirred for 30 min at this temperature. A solution of α-bromocinnamaldehyde (1.45 g, 6.85 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred for another 5 min at −78 °C. The reaction was quenched by addition of the biphosphate buffer and promptly warmed to room temperature. The mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed in a vacuum, and the residue was separated by chromatography on silica gel (hexanes−ethyl acetate 4:1) to yield 2.9 g (5.78 mmol, 84%) of **10** as slightly yellowish thick oil. R_f 0.42 (ethyl acetate:hexanes, 1:2); ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 6 Hz, 2H), 7.45−7.3 (m, 3H), 7.24 (s, 1H), 5.4 (s, 1H) 3.73−3.61 (m, 4H), 2.58 (t, J = 7.2 Hz, 2H), 2.23 (t, J = 7.2 Hz), 1.8−1.69 (m, 2H), 1.68−1.59 (m, 2H), 1.12 (s, 3H), 0.91 (s, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 134.8, 130.9, 129.11, 129.07, 128.9, 128.4, 128.2, 125.8, 107.1, 84.9, 84.7, 77.9, 72.8, 30.3, 28.2, 26.6, 23.7, 22.5, 20.1, 19.5, 0.21; MS calcd for $C_{26}H_{35}BrO_3Si$ (M^+) 502/504, found 502/504.

2-(2-Bromo-1-*tert*-butyldimethylsilyloxy-3-phenyl)-3-(6-trimethylsilyl-5-hexynyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl acetal (11). *tert*-Butyldimethylsilyl chloride (1.74 g, 11.52 mmol) was added to a solution of alcohol **10** (2.9 g, 5.76 mmol) and imidazole (1.57 g, 23.09 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 2 h at room temperature, quenched by biphosphate buffer, and diluted with EtOAc (50 mL). The organic layer was separated, washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed in a vacuum, and the residue was purified by chromatography on silica gel (hexanes−ethyl acetate 8:1) to give 2.55 g (4.14 mmol, 72%) of **11** as a colorless oil. R_f 0.67 (ethyl acetate:hexanes, 1:2); ^1H NMR ($CDCl_3$) δ 7.53 (d, J = 6 Hz, 2H), 7.45−7.3 (m, 3H), 7.29 (s, 1H), 5.41 (s, 1H), 3.75−3.5 (m, 4H), 2.55 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.2 Hz), 1.8−1.7 (m, 2H), 1.69−1.59 (m, 2H), 1.17 (s, 3H), 0.99 (s, 9H), 0.85 (s, 3H), 0.18, 0.17 (s, 6H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.1, 130.4, 131.0, 129.5, 129.0, 128.2, 127.9, 126.1, 107.2, 85.0, 84.5, 78.1, 78.0, 73.3, 31.6, 30.2, 28.3, 26.6, 25.8, 23.4, 22.6, 22.0, 19.5, 18.3, 0.19, −4.8; MS calcd for $C_{32}H_{49}BrO_3Si_2$ (M^+) 616/618, found 616/618.

2-(2-Bromo-1-*tert*-butyldimethylsilyloxy-3-phenyl)-3-(5-hexynyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (5). A solution of **11** (1 g, 1.62 mmol) and K_2CO_3 (0.30 g, 2.11 mmol) in methanol (25 mL) was stirred for 5 h at room temperature. When the reaction was complete, a saturated solution of NH_4Cl (5 mL) was added, and the mixture was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate, and the solvent was removed in a vacuum. The residue was immediately separated on a

silica gel column (ethyl acetate:hexanes 1:6 containing 1.5% of Et_3N) to give 0.77 g (1.41 mmol, 87%) of **5** as a thick slightly yellow oil. R_f 0.67 (ethyl acetate:hexanes, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 6 Hz, 2H), 7.45−7.3 (m, 3H), 7.29 (s, 1H), 5.43 (s, 1H), 3.70−3.53 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.24 (td, J = 7.2, 2.7 Hz 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.8−1.7 (m, 2H), 1.69−1.59 (m, 2H), 1.18 (s, 3H), 0.99 (s, 9H), 0.85 (s, 3H), 0.21, 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 135.1, 134.3, 130.5, 129.4, 129.1, 128.3, 126.1, 85.0, 84.2, 78.1, 77.9, 73.4, 78.5, 31.5, 30.2, 28.0, 26.5, 25.8, 23.3 22.6, 22.0 18.3, 18.0, −4.58; MS calcd for $C_{29}H_{41}BrO_3Si_1$ (M^+) 544/546, found 544/546.

2-(4-*tert*-Butyldimethylsiloxybutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (12). A solution of 6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene (cyclopropenone acetal **7**)[18] (5.57 g, 39.8 mmol) in THF (45 mL) and HMPA (16 mL) was treated with *n*-BuLi (2.5 M solution in hexanes, 41.8 mmol, 16.7 mL) at −78 °C. After the mixture was stirred for 45 min at this temperature a solution of 1-iodo-4-*tert*-butyldimethylsilyloxybutane (10.4 g, 33.2 mmol) in THF (10 mL) was added, and the resulting mixture was stirred for 5 h at −35 °C. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL) and diluted with ca. 100 mL of a hexanes−ethyl acetate mixture, and the organic layer was separated and passed through a short silica gel column (ca. 3 cm). The organic layer was dried over anhydrous sodium sulfate, concentrated in a vacuum, and purified by silica gel chromatography to give 9.23 g of **12** (28.3, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 3.55−3.65 (m, 6H), 2.55 (t, J = 7.2 Hz, 2H), 1.55−1.7 (m, 4H), 1.04 (s, 3H), 0.97 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H),; ^{13}C NMR ($CDCl_3$) δ 137.8, 115.3, 83.4, 77.0, 62.6, 32.1, 30.3, 25.9, 24.7, 23.6, 22.3, 22.1, 18.2,−5.4; MS calcd for $C_{18}H_{34}O_3Si$ (M^+) 326, found 326.

2-Benzylidene-4-trimethylsilyl-3-butynal (13). A solution of α-bromocinnamaldehyde (4.0 g, 18.96 mmol), Et_3N (6 mL), and trimethylsilylacetylene (1.39 g, 14.2 mmol) in degassed THF (90 mL) was added to a stirred suspension of $Pd(PPh_3)_4$ (0.5 g) and CuI (0.43 g) in degassed THF (50 mL) at 0 °C. The reaction mixture was protected from light, stirred for 5 h at 0 °C and then at room temperature for another 5 h, diluted with hexanes (150 mL), and passed through a short silica gel column (ca. 5 cm). The solvent was evaporated in a vacuum and the residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:12) to yield 3.19 g (14.00 mmol, 98%) of **13** as a white powder. Mp 52−53 °C; R_f 0.39 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 9.3 (s, 1H), 7.87 (dd, J = 7.6, 2 Hz, 2H), 7.25 (s, 1H), 7.21−7.18 (m, 3H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 190.8, 152.0, 133.9, 131.7, 130.8, 128.6, 122.4, 107.8, 98.5,−0.36; MS calcd for $C_{14}H_{16}OSi$ (M^+) 228, found 228.

2-(2-Bezylidene-1-hydroxy-4-trimethylsilyloxy-3-butynyl)-3-(4-*tert*-butyldimethylsilyloxybutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (14). *n*-BuLi (2.5 M solution in hexanes, 18.32 mmol, 7.3 mL) was added to a solution of acetal **12** (5.69 g, 17.45 mmol) and 8.4 mL of TMEDA in THF (50 mL) at −78 °C. After 30 min a solution of aldehyde **13** (3.98 g, 17.45 mmol) in THF (10 mL) was added dropwise at −78 °C. In 10 min the reaction was quenched by phosphate buffer and promptly warmed to room temperature. The reaction mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic layer was washed with water (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed in a vacuum, and the residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:4 containing 1.5% of Et_3N) to yield 8.3 g (14.8 mmol, 86%) of **14** as a slightly yellowish thick oil. R_f 0.4 (ethyl acetate:hexanes, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.2 Hz 2 H), 7.35−7.25 (m, 3 H), 6.88 (s, 1 H), 5.25 (s, 1 H), 3.67 (dd, J = 8.8, 2 Hz, 2 H), 3.56 (m, 4 H), 2.51 (t, J = 6.8 Hz, 2 H), 1.70−1.52 (m, 4 H), 1.11 (s, 3 H), 1.01 (t, J = 7.0 Hz, 3 H), 0.85 (s, 9H), 0.23 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 135.7, 135.5, 130.0, 129.6, 129.0, 128.7, 128.1, 121.8, 104.3, 102.2, 85.1, 77.8, 70.6, 62.8, 46.1, 32.4, 30.2, 26.0, 23.9, 23.8, 22.5, 22.0, 18.32, 10.9, −0.3, −5.3; MS calcd for $C_{32}H_{50}O_4Si_2$ (M^+) 554.9, found 555.

2-(1-Acetoxy-2-bezylidene-4-trimethylsilyloxy-3-butynyl)-3-(4-*tert*-butyldimethylsilyloxybutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (15). Acetic anhydride (16 mL, 124 mmol) was added to a stirred solution of alcohol **14** (16.2 g, 29.2 mmol), Et_3N (120 mL), and DMAP (0.3 g) in CH_2Cl_2 (300 mL). The resulting solution was stirred for 2 h at 0 °C, concentrated, and subjected to silica gel chromatography (ethyl acetate:hexanes 1:7 containing 1% of Et_3N) to give 17.06 g (28.6 mmol, 98%) of **15** as slightly yellow oil. R_f 0.66 (ethyl acetate:hexanes 1:2); ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.4 Hz 2 H), 7.35−7.25 (m, 3 H), 6.86 (s, 1 H), 6.41 (s, 1 H), 3.68−3.59 (m, 6 H), 2.51 (t, J = 6.4 Hz, 2 H), 2.17 (s, 3 H), 1.65−1.57 (m, 4 H), 1.16 (s, 3 H), 0.87 (s, 9 H), 0.82 (s, 3 H), 0.24 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.7, 138.0, 135.3, 131.3, 129.3, 128.3, 127.5, 118.2, 104.1, 102.1, 85.0, 77.9, 72.0, 62.9, 32.6, 30.7, 26.1, 24.0, 22.8, 22.2, 21.3, 18.5, −0.2, −5.1; MS calcd for $C_{34}H_{52}O_5Si_2$ (M^+) 596.95, found 596; HRMS calcd for $C_{34}H_{52}O_5Si_2$ (M^+) 596.3353, found 596.3353.

2-(1-Acetoxy-2-bezylidene-3-butynyl)-3-(4-hydroxybutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (16). A solution of TBAF (1 M, 114 mmol, 114 mL) and acetic acid (6.84 g, 114.0 mmol) wereas added to a stirred solution of **15** (17.06 g, 28.6 mmol) in THF (150 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 24 h, quenched by a saturated aqueous solution of $NaHCO_3$ (10 mL), and concentrated in a vacuum. The residue was diluted with ethyl acetate (200 mL), and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:1 with 1.5% of triethylamine) to give 11.50 g (28.03 mmol, 98%) of **16** as a slightly yellow oil. R_f 0.55 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.6 Hz 2 H), 7.39−7.31 (m, 3 H), 6.98 (s, 1 H), 6.42 (s, 1 H), 3.68−3.55 (m, 6 H), 3.41 (s, 1 H), 2.51 (t, J = 6.4 Hz, 2 H), 2.18 (s, 3 H), 1.73−1.63 (m, 4 H), 1.17 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 139.0, 134.7, 130.9, 129.3, 129.1, 128.4, 127.6, 117.0, 85.8, 85.7, 84.8, 80.4, 77.7, 72.1, 62.1, 32.2, 30.2, 23.6, 23.3, 22.6, 21.9, 21.2; MS calcd for $C_{25}H_{30}O_5$ (M^+) 410.50, found 410.

2-(1-Acetoxy-2-bezylidene-4-iodo-3-butynyl)-3-(4-hydroxybutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (17). A solution of iodine (14.2 g, 56.06 mmol) and mophline (14.6 mL, 168.18 mmol) in dry benzene (150 mL) was stirred at 45 °C for 45 min. A solution of **16** (11.50 g, 28.03 mmol) in dry benzene was added to the resulting mixture, which was then stirred for 30 min at 45 °C. The reaction mixture was cooled to room temperature, diluted with benzene (150 mL), washed with saturated solution of $Na_2S_2O_3$ (20 mL), water (25 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was immediately subjected to silica gel chromatography (ethyl acetate:hexanes 1:1 containing 1.5% of Et_3N) to give 12.47 g (23.26 mmol, 83%) of **17** as slightly yellow oil. R_f 0.41 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 7.6 Hz 2 H), 7.41−7.31 (m, 3 H), 6.88 (s, 1 H), 6.38 (s, 1 H), 3.68−3.59 (m, 6 H), 2.55 (t, J = 6.8 Hz, 2 H), 2.18 (s, 3 H), 1.70−1.65 (m, 4 H), 1.18 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 139.2, 134.6, 130.8, 129.4, 128.9, 128.4, 127.5, 118.0, 91.1, 84.7, 77.7, 72.11, 72.05, 62.1, 32.2, 30.2, 23.7, 23.4, 22.6, 22.0, 21.6, 15.8; MS calcd for $C_{25}H_{29}IO_5$ (M^+) 536.40, found 536.

2-(1-Acetoxy-2-bezylidene-4-iodo-3-butynyl)-3-(4-oxobutyl)cyclopropenone 2,2-Dimethyl-1,3-propanediyl Acetal (6). A solution of **17** (1.15 g, 2.14 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of Dess−Martin peridinane (1.18 g, 2.78 mmol) in CH_2Cl_2 (20 mL). The resulting suspension was stirred over 4 h, diluted with ether (50 mL), filtered, concentrated, and subjected to silica gel chromatography (ethyl acetate:hexanes 1:1.5 containing 1.5% of Et_3N) to give 1.01 g (1.89 mmol, 88%) of the aldehyde **6** as a slightly orange oil. R_f

0.75 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1 H), 7.79 (d, J = 7.6 Hz 2 H), 7.41−7.31 (m, 3 H), 6.90 (s, 1 H), 6.38 (s, 1 H), 3.64−3.57 (m, 4 H), 2.58 (t, J = 6.4 Hz, 4 H), 2.18 (s, 3 H), 1.94 (p, J = 7.2 Hz, 2 H), 1.17 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.8, 169.6, 139.34, 139.31, 134.5, 129.9, 129.4, 128.9, 128.4, 117.9, 91.1, 84.5, 77.6, 72.27, 72.17, 53.4, 43.0, 30.1, 23.1, 22.6, 21.9, 21.1, 19.7, 15.9; MS calcd for $C_{25}H_{27}IO_5$ (M^+ − H) 533, found 533; HRMS calcd for $C_{25}H_{27}IO_5$ (M^+ − H) 533.0825, found 533.0829.

2-Acetoxy-3-benzylidene-7-hydroxybicyclo[8.1.0]undec-1(10)-en-4-yn-11-one 2,2-Dimethyl-1,3-propanediyl Acetal (18). A solution of aldehyde **6** (3.26 g, 6.11 mmol) in THF (50 mL) was added via a syringe pump over a period of 15 min to a degassed suspension of $CrCl_2$ (2.6 g, 21.3 mmol) and $NiCl_2$ (0.40 g, 3.1 mmol) in ca. 1.2 L of THF under argon. A 100-mL sample of a saturated solution of NaCl was added to the reaction mixture after 2 h,[30] and the organic layer was separated, washed with brine, (4 × 125 mL), and concentrated. The residue was dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$, concentrated, and subjected to silica gel chromatography (CH_2Cl_2:ethyl acetate 7:1 with 1.5% of triethylamine) to give 1.80 g of **18** (4.42 mmol, 72%) as slightly yellow amorphous crystalline solid. R_f 0.48 (ethyl acetate:CH_2Cl_2 1:2),); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.1 Hz 2 H), 7.40−7.28 (m, 3 H), 6.87 (d, J = 12.6 Hz, 1 H), 6.51 (s, 1 H), 4.66, 4.55 (q, J = 4.8 Hz, t, J = 6.6 Hz, 1 H), 3.61 (m, 4 H), 3.05−2.6 (m, 3 H), 2.18 (d, J = 2.7 Hz, 3 H), 2.15−1.7 (m, 4 H), 1.15 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 3.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 137.3, 136.4, 135.1, 132.3, 131.9, 129.2, 129.1, 129.01, 128.95, 128.69, 128.42, 117.35, 117.22, 102.5, 85.14, 85.02, 83.91, 83.88, 77.87, 77.82, 71.76, 71.68, 36.75, 35.81, 30.26, 23.2, 22.63, 22.61, 22.02, 21.93, 21.36, 21.31, 21.23; MS calcd for $C_{25}H_{28}O_5$ (M^+ − H) 407, found 407; HRMS calcd for $C_{25}H_{28}O_5$ (M^+ − H) 407.1858, found 407.1865.

2-Acetoxy-3-benzylidene-7-*tert*-butyldimethylsilyloxybicyclo[8.1.0]undec-1(10)-en-4-yn-11-one 2,2-Dimethyl-1,3-propanediyl Acetal (19). *tert*-Butyldimethylsilyl chloride (0.40 g, 2.64 mmol) was added to a solution of **18** (0.72 g, 1.76 mmol) and imidazole (0.36 g, 5.28 mmol) in DMF (4 mL) at 0 °C. The resulting solution was stirred for 2 h at room temperature and diluted with ethyl acetate (100 mL) and water (80 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate: hexanes 1:7 with 1.5% of triethylamine) to give 0.75 g (1.43 mmol, 82%) of **19** as a white powder. R_f 0.47 (ethyl acetate: hexanes 1:2); ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2 H), 7.40−7.28 (m, 3 H), 6.87 (d, J = 12.6 Hz, 1 H), 6.51 (s, 1 H), 4.66, 4.55 (d, J = 4.8 Hz, t, J = 6.6 Hz, 1 H), 3.61 (m, 4 H), 3.05−2.4 (m, 2 H), 2.19, 2.17 (s, 3 H), 2.15−1.7 (m, 4 H), 1.15 (s, 3 H), 0.85, 082 (s, 9 H), 0.78 (s, 3 H), 0.14, 0,13, 0.10, 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 136.8, 135.7, 135.2, 132.4, 131.9, 129.0, 128.6, 128.3, 117.7, 117.6, 103.4, 103.0, 85.0, 83.3, 83.25,, 77.89, 77.84, 77.70, 77.62, 71.34, 71.11, 63.05, 61.8, 45.9 36.9, 35.7, 30.3, 25.8, 22.9, 22.7, 22.4, 21.3, 21.2, 18.25, 18.20, −3.5, −4.60, −4.75, −4.91, −5.01; MS calcd for $C_{31}H_{42}O_5Si$ (M^+ − H) 521, found 521; HRMS calcd for $C_{31}H_{42}O_5Si$ (M^+ − H) 521.2723, found 521.2723.

6-*tert*-Butyldimethylsilyloxy-3-(α-hydroxybenzyl)bicyclo[8.1.0]undeca-1(10),2-dien-4-yn-11-one (1). A 1.55-mL sample of a 1 M aqueous solution of NaOH was added to a solution of **19** (0.75 g, 1.43 mol) in methanol (20 mL). After 10 min methanol was removed in a vacuum, and the reaction mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was dissolved in an ethyl acetate−hexanes mixture (1:5) and passed through silica gel. The solvent was removed in a vacuum to give 0.62 g (1.26 mmol, 90%) of crude **20**.

$MeSO_2Cl$ (0.083 mL, 1.05 mmol) was added to a solution of crude **20** (0.505 g, 1.05 mmol) and ethyldiisopropylamine (0.2 mL, 1.58 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The resulting mixture was stirred over 60 min at this temperature, quenched by phosphate buffer, and warmed to room temperature. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate:CH_2Cl_2 5:1) to give 0.158 g (0.40 mmol, 35%) of **1** as slightly yellow oil. R_f 0.4 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.45−7.25 (m, 5H), 5.94 (s, 1H), 5.3 (m, 1H), 4.5 (m, 1H), 3.20−3.05 (m, 1H), 2.90−2.72 (m 1H), 2.05−1.70 (m, 3H), 0.94 (s, 9H), 0.17, 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.6, 161.1, 159.1, 157.4, 157.2, 140.7, 136.8, 128.8, 126.1, 117.9, 117.4, 102.2, 102.5, 83.2, 82.9, 76.8, 62.0, 61.8, 36.7, 25.7, 25.4, 25.2, 20.9, 21.5, 18.2, −4.8, −5.1; MS calcd for $C_{31}H_{42}O_5Si$ (M^+) 394, found 394.

3-Benzylidene-10-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-1,5-decadiyne-4-ol (21). A 5.9-mL sample of a 2.5 M solution of *n*-BuLi in hexanes (14.75 mmol) was added to a solution of 6-(*tert*-butyldimethylsilyloxy)-1-hexyne[29] (3.0 g, 14.15 mmol) in THF (60 mL) at −78 °C. After half an hour a solution of aldehyde **13** (3.23 g, 14.15 mmol) in THF (10 mL) was added dropwise, the reaction mixture was stirred for 30 min at −78 °C, warmed to room temperature, and stirred for another 30 min, and a saturated solution of NH_4Cl (15 mL) was added. The reaction mixture was diluted with 150 mL of ethyl acetate, the organic layer was separated, washed with water (10 mL) and brine (10 mL), and dried with anhydrous $MgSO_4$, and solvent was removed in a vacuum. The residue was subjected to silica gel chromatography (ethyl acetate: hexanes, 1:5) to yield 6.13 g (13.93 mmol, 98%) of **21** as a slightly yellow oil. R_f 0.37 (ethyl acetate:hexanes, 1:5); ^{1}H NMR ($CDCl_3$) δ 7.91 (d, d, J = 8.1, 1.5 Hz, 2 H), 7.40−7.30 (m, 3 H), 6.99 (s, 1 H), 4.99 (s, 1 H), 3.66 (t, J = 5.6, 2 H), 2.33 (m, 2 H), 1.62 (m, 4 H), 0.90 (s, 9 H), 0.29 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 135.7, 135.5, 129.1, 128.8, 128.1, 122.1, 104.2, 102.0, 87.8, 78.7, 66.5, 62.6, 31.9, 26.0, 25.1, 18.7, 18.3, −0.24, −5.2; MS calcd for $C_{26}H_{40}O_2Si_2$ (M^+ − *tert*-butyl) 383, found 383.

4-Acetoxy-3-benzylidene-10-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-1,5-decadiyne (22). A solution of acetic anhydride (11.8 g, 115.9 mmol) in CH_2Cl_2 (20 mL) was added to a solution of alcohol **21** (12.75 g, 28.98 mmol), triethylamine (100 mL), and DMAP (0.5 g) in CH_2Cl_2 (200 mL) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C, concentrated, and subjected to silica gel chromatography (ethyl acetate: hexanes 1:15) to give 13.79 g (28.59 mmol, 99%) of **22** as a slightly yellow oil. R_f 0.72 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.99 (d,d, J = 8.1, 1.5 Hz, 2 H), 7.40−7.30 (m, 3 H), 7.09 (s, 1 H), 6.12 (s, 1 H), 3.66 (t, J = 5.6, 2 H), 2.33 (m, 2 H), 2.15 (s, 3 H), 1.62 (m, 4 H), 0.91 (s, 9 H), 0.28 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169,6, 138.0, 135.1, 129.2, 129.0, 128.1, 118.4, 103.7, 101.9, 88.9, 75.4, 67.3, 62.6, 31.9, 26.0, 25.0, 21.0 18.7, 18.3, −0.31, −5.3; MS calcd for $C_{28}H_{42}O_3Si_2$ (M^+ − *tert*-butyl) 425, found 425; HRMS calcd for $C_{28}H_{42}O_3Si_2$ (M^+) 482.2672, found 482.2683.

7-Acetoxy-8-benzylidene-5,9-decadiyne-ol (23). A 67-mL sample of a 1 M TBAF solution and acetic acid (4 g, 67.0 mmol) was added to a stirred solution of **22** (8.93 g, 18.52 mmol) in THF (90 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 24 h, then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The reaction mixture was concentrated in a vacuum and diluted with 200 mL of ethyl acetate, and the organic layer was separated, washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate: hexanes 1:1) to give 5.43 g (18.52 mmol, 99%) of **23** as slightly yellow oil. R_f 0.53 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.87 (d,d, J = 8.1, 1.2 Hz, 2 H), 7.40−7.30 (m, 3 H), 7.09 (s, 1 H), 6.07

(30) Prolongation of the reaction time results in substantial deprotection of cyclopropenone acetal. We found that the cyclopropenone acetal group in **18** is more susceptible to hydrolysis than acetal **6**.

(s, 1 H), 3.65 (q, $J = 6.0$, 2 H), 3.43 (s, 1 H), 2.33 (m, 2 H), 2.13 (s, 3 H), 1.83 (m, 1 H), 1.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 139.2, 134.8, 129.3, 129.1, 128.3, 117.3, 88.8, 85.4, 80.4, 75.5, 67.7, 62.2, 31.8, 24.6, 21.0 18.7; MS calcd for $C_{19}H_{20}O_3$ (M^+) 296, found 296; HRMS calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1404.

7-Acetoxy-8-benzylidene-10-iodo-5,9-decadiyne-1-ol (24). A solution of iodine (8.68 g, 34.18 mmol) and morpholine (8.92 mL, 102.54 mmol) in dry benzene (110 mL) was heated for 45 min at 45 °C and a solution of **23** (5.06 g, 17.09 mmol) was added dropwise. The resulting mixture was stirred for 30 min at 45 °C, cooled to room temperature, diluted with benzene (50 mL), washed with a saturated solution of $Na_2S_2O_3$ (20 mL), water (25 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was immediately subjected to silica gel chromatography (ethyl acetate:hexanes 1:1) to give 6.56 g (15.55 mmol, 91%) of **24** as slightly yellow oil. R_f 0.53 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.88 (d,d, $J =$ 7.8, 1.5 Hz, 2 H), 7.40−7.30 (m, 3 H), 6.99 (s, 1 H), 6.03 (s, 1 H), 3.67 (t, $J = 12$ Hz, 2 H), 2.34 (t,d, $J = 6.9$, 2.1 Hz, 2 H), 2.14 (s, 3 H), 1.94 (s, 1 H), 1.71−1.63 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.7, 139.4, 134.7, 129.4, 129.0, 128.4, 118.5, 91.2, 88.9, 75.6, 67.8, 62.2, 31.8, 24.7, 21.1 18.7, 15.4; MS calcd for $C_{19}H_{19}O_3I$ (M^+) 422, found 422.

7-Acetoxy-8-benzylidene-10-iodo-5,9-decadiynal (25). A solution of **24** (6.56 g, 15.55 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of Dess−Martin peridinane (7.27 g, 17.11 mmol) and $NaHCO_3$ (4.28 g, 3 equiv) in CH_2Cl_2 (200 mL). The resulting suspension was stirred for an hour, diluted with a solution of $NaHCO_3/Na_2S_2O_3$ 1:1, and stirred for 20 min. The organic layer was separated, diluted with ether, washed with water, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:2) to give 5.51 g (13.12 mmol, 84%) of **28** as a slightly orange oil. R_f 0.50 (ethyl acetate:hexanes 1:1); ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 7.79 (d,d, $J = 8.1$, 1.5 Hz, 2 H), 7.40−7.30 (m, 3 H), 6.96 (s, 1 H), 6.03 (s, 1 H), 2.62 (t,d, $J = 7.5$, 1.2 Hz, 2 H), 2.37 (t,d, $J = 6.9$, 1.8 Hz, 2 H), 2.14 (s, 3 H), 1.87 (p, $J = 7.2$ Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.6, 169.6, 139.5, 134.6, 129.4, 129.0, 128.4, 118.4, 91.2, 87.7, 76.5, 67.7, 42.6, 21.0, 20.8, 18.2, 15.4; MS calcd for $C_{19}H_{17}O_3I$ (M^+) 420, found 420; HRMS calcd for $C_{19}H_{17}O_3I$ (M^+) 420.0222, found 420.0228.

5-Acetoxy-4-benzylidene-2,6-cyclodecadiynol (26). A solution of aldehyde **25** (3 g, 7.14 mmol) in THF (30 mL) was added dropwise to a degassed suspension of $CrCl_2$ (3.66 g, 29.76 mmol) and $NiCl_2$ (0.5 g, 3.85 mmol) in 1500 mL of THF under argon. After 2 h 100 mL of saturated NaCl solution was added, and the organic layer was separated, washed with brine, (5 × 125 mL), and concentrated. The residue was dissolved in CH_2Cl_2, washed with water, dried over anhydrous $MgSO_4$, concentrated, and subjected to silica gel chromatography (CH_2Cl_2:ethyl acetate 15:1) to give 1.88 g (6.40 mmol, 90%) of **26** as slightly yellow oil. R_f 0.73 (ethyl acetate:CH_2Cl_2 1:2); ^{1}H NMR ($CDCl_3$) δ 7.92−7.88 (m, 2 H), 7.43−7.32 (m, 3 H), 6.86, 6.81 (s, 1 H), 6.08, 6.05 (m, 1 H), 4.80, 4.60 (d, $J = 9$ Hz, 1 H), 2.40−2.25 (m, 2 H), 2.14 (s, 3 H), 2.13−2.00 (m, 3 H), 1.70−1.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 138.6, 137.6, 135.0, 129.35, 129.2, 128.9, 119.3, 102.2, 101.9, 93.1, 92.9, 83.4, 83.0, 78.5, 69.0, 68.7, 64.0, 63.4, 37.2, 36.6, 24.1, 22.5, 21.6, 20.4; MS calcd for $C_{19}H_{18}O_3$ (M^+) 294, found 294; HRMS calcd for $C_{19}H_{18}O_3$ (M^+) 294.1256, found 294.1259.

5-Acetoxy-4-benzylidene-1-*tert*-butyldimethylsilyloxy-2,6-cyclodecadiyne (27). *tert*-Butyldimethylsilyl chloride (1.45 g, 9.60 mmol) was added to a solution of alcohol **26** (1.88 g, 6.40 mmol) and imidazole (1.31 g, 19.20 mmol) in DMF (10 mL) at 0 °C. The resulting solution was stirred for 2 h at 0 °C and diluted with 100 mL of ethyl acetate, then biphosphate buffer was added. The organic layer was separated, and the aqueous layer was extracted with 100 mL of ethyl acetate. Combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:10) to give 2.20 g (5.39 mmol, 84%) of **30** as a slightly yellow crystalline solid. R_f 0.50 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.94−7.86 (m, 2 H), 7.41−7.30 (m, 3 H), 6.80, 6.77 (s, 1 H), 6.03 (m, 1 H), 4.76, 4.56 (d, d, $J = 9$, 3.6 Hz, 1 H), 2.31−2.25 (m, 2 H), 2.12 (s, 3 H), 2.12−1.95 (m, 3 H), 1.65−1.55 (m, 1 H), 0.96, 0.93 (s, 9 H), 0.22, 0.19, 0.17, 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.26, 170.14, 137.6, 137.2, 135.2, 129.08, 129.02, 128.3, 119.8, 103.5, 102.9, 93.4, 93.0, 82.4, 82.3, 78.51, 78.46, 69.0, 68.7, 64.5, 63.8, 38.0, 37.5, 25.84, 25.75, 22.5, 22.0, 21.2, 20.4, 18.4, 18.2, −4.6, −4.7, −4.9, −5.0; MS calcd for $C_{25}H_{32}O_3Si$ (M^+) 408, found 408; HRMS calcd for $C_{25}H_{32}O_3Si$ (M^+) 4082121, found 408.2118.

4-(α-Hydroxybenzyl)-1-*tert*-butyldimethylsilyloxy-4-cyclodecene-2,6-diyne (2). A 1.97-mL sample of a 1 M aqueous NaOH solution was added to a solution of **27** (0.48 g, 1.18 mol) in methanol (20 mL) at 0 °C. After half an hour methanol was removed in a vacuum, the mixture was diluted with ethyl acetate, and phosphate buffer was added. The organic layer was separated, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was dissolved in an ethyl acetate−hexanes mixture (1:5) and passed through a short layer of silica gel. The solvent was removed in a vacuum to give 0.41 g (1.12 mmol, 95%) of 2-benzylidene-5-*tert*-butyldimethylsilyloxy-3,9-cyclodecadiynol (**28**) as mixture of two diastereomers. R_f 0.4 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.93−7.90 (m, 2 H), 7.41−7.30 (m, 3 H), 6.85, 6.83 (s, 1 H), 5.01, 4.95 (d, $J = 8.1$ Hz, 1 H), 4.70, 4.60 (d,d $J = 8.7$, 3.0 Hz, 1 H), 2.32−2.23 (m, 3 H), 2.10−1.90 (m, 3 H), 1.63 (s, 1 H), 0.97, 0.94 (s, 9 H), 0.25, 0.22, 0.19, 0.16 (s, 6 H); MS calcd for $C_{23}H_{30}O_2Si$ (M^+) 366, found 366.

A 300-mg sample of CSA and 40 μL of water were added to a solution of crude **28** in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for ca. 2.5 h at 0 °C, diluted with 100 mL of ethyl acetate, washed with saturated solution of $NaHCO_3$ (2 × 20 mL), water, and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:10) to give 71 mg (0.187 mmol, 16% over two steps) of **2** as a colorless crystalline solid. R_f 0.41 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 5 H), 6.00 (s, 1 H), 5.26 (s, 1 H), 4.51 (d, br, $J = 8.1$ Hz, 1 H), 2.41−2.34 (m, 2 H), 2.20−1.90 (m, 4 H), 1.70−1.68 (m, 1 H), 0.93, 0.88, 0.86 (s, 9 H), 0.14, 0.064, 0.023, 0.012 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.18, 140.91, 128.5, 128.13, 128.04, 126.74, 126.51, 119.17, 118.93, 104.98, 104.72, 103.6, 82.64, 82.6, 74.7, 63.7, 38.8, 25.77, 25.65, 24.1, 21.5, 18.0, −3.59, −4.58, −4.98; MS calcd for $C_{23}H_{30}O_2Si$ (M^+) 366, found 366; HRMS calcd for $C_{23}H_{30}O_2Si$ (M^+) 366.2015, found 366.2014.

7-(α-Hydroxybenzyl)-1-*tert*-butyldimethylsilyloxytetralin (29). A degassed solution of enediyne **2** (50 mg, 0.137 mmol) in 10 mL of a benzene:1,4-cyclohaxadiene (4:1) mixture was heated in a sealed vessel for ca. 4 h at 75 °C. Solvent was removed in a vacuum and the residue was subjected to silica gel chromatography (ethyl acetate:hexanes 1:15) to give 42 mg (0.114 mmol, 83%) of **32** as a colorless oil. R_f 0.58 (ethyl acetate:hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.41−7.19 (m, 7 H), 7.04 (d, $J = 8.1$ Hz, 1 H), 5.80 (d, $J = 3$ Hz, 1 H), 4.73 (m, 1 H), 2.85−2.62 (m, 2 H), 2.18−2.15 (m, 1 H), 2.00−1.90 (m, 2 H), 1.80−1.65 (m, 2 H), 0.89, 0.88 (s, 9 H), 0.095, 0.071, 0.061, (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 143.87, 143.84, 141.52, 141.46, 140.13, 140.10, 136.3, 128.9, 128.45, 128.43, 127.41, 127.37, 126.43, 126.39, 126.18, 126.1, 125.3, 125.2, 76.31, 76.25, 69.37, 69.33, 33.0, 28.9, 25.9, 19.77, 19.72, 18.15, −4.2, −4.7; MS calcd for $C_{23}H_{32}O_2Si$ ($M^+ -$ *tert*-butyl) 311, found 311; HRMS calcd for $C_{23}H_{32}O_2Si$ ($M^+ - H$) 367.2093, found 367.2094.

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Supporting Information Available: General experimental methods and details of the Pd(0)-catalyzed reaction of the zinc salt of **12** with ortho-substituted iodobenzenes, as well as ^{1}H and ^{13}C spectra of compounds **1**, **2**, **5**, **6**, **12**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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