JOC*Note*

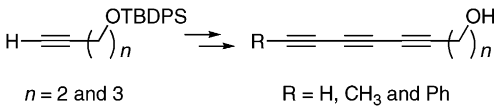
Synthesis and Stability of a Homologous Series of Triynol Natural Products and Their Analogues

Thanh Luu and Rik R. Tykwinski*

Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

rik.tykwinski@ualberta.ca

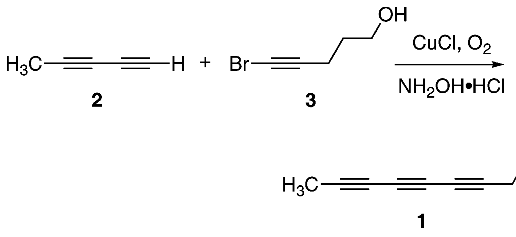
Received July 31, 2006



A series of polyyne natural products **1**, **13**, and **31** and analogues **14**, **21**, and **22** are synthesized in six steps. The key step is a Fritsch−Buttenberg−Wiechell rearrangement in which a triyne framework is formed from the appropriate dibromoolefin precursor. Terminal conjugated triynes **13** and **14** are obtained as highly unstable products that rapidly decompose under ambient conditions. The stability of triynols increases via either the addition of methylene units (i.e., **6** → **31** → **1**) or addition of terminal substituents (i.e., **13** → **21** or **31**).

Naturally occurring polyynes (also called polyacetylenes) have been isolated from a wide variety of plants, fungi, bacteria, and sponges.[1−6] They have proven to be important biologically active compounds that can be used as antibacterial,[7,8] antimicrobial,[9,10] antifungal, and antiviral agents;[11] they also exhibit larvicidal properties[12] and cytotoxicity toward a range of cell lines.[13] Although polyynes are commonly found in nature, obtaining them pure and in significant quantities is often difficult due to their kinetic instability, particularly in the case of terminal polyynes and longer derivatives such as triynes, tetraynes, and pentaynes.[14]

Polyyne natural products featuring an alcohol moiety are frequently encountered, and these molecules also offer the possibility of derivatization through reaction at oxygen. Over the years, a number of metal-catalyzed hetero- and homocoupling reactions have been developed for the formation of polyynols, and the most commonly used method is the Cadiot−Chodkiewicz cross-coupling.[15−17] For example, compound **1** has been synthesized by Prévost et al.,[18] using the cross-coupling of diyne **2** with bromoalkyne **3** (eq 1). However, the requisite starting material **2** and others like it are often difficult to obtain pure and in good yield.[19] Because of these challenges, a carbenoid Fritsch−Buttenberg−Wiechell (FBW) rearrangement has been developed as an alternative method for the formation of biologically interesting polyynes.[20−24]



2 **3** **1**

(1)

Toward the development of new polyynes and their derivatives, we report herein on the formation and chemical stability of conjugated triynols as a function of structure. Using the FBW

---

* To whom correspondence should be addressed. Fax: (780) 492-8231.

(1) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034−1057.

(2) *Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds (NOARC)*; Lam, J., Breteler, H., Arnason, T., Hansen, L., Eds.; Elsevier: New York, 1988.

(3) Bohlmann, F.; Burkhardt, H.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973.

(4) Jones, E. R. H.; Thaller, V. *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: New York, 1978; Part 2, Chapter 14.

(5) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1−48.

(6) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49.

(7) Tsuge, N.; Mori, T.; Hamano, T.; Tanaka, H.; Shin-ya, K.; Seto, H. *J. Antibiot.* **1999**, *52*, 578−581.

(8) Young, K.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K.; Zhang, C.; Kodali, S.; Galgoci, A.; Painter, R.; Brown-Driver, V.; Yamamoto, R.; Silver, L. L.; Zheng, Y.; Ventura, J. I.; Sigmund, J.; Ha, S.; Basilio, A.; Vicente, F.; Tormo, J. R.; Pelaez, F.; Youngman, P.; Cully, D.; Barrett, J. F.; Schmatz, D.; Singh, S. B.; Wang, J. *Antimicrob. Agents* **2006**, *50*, 519−526.

(9) Kobaisy, M.; Abramowski, Z.; Lermer, L.; Saxena, G.; Hancock, R. E. W.; Towers, G. H. N.; Doxsee, D.; Stokes, R. W. *J. Nat. Prod.* **1997**, *60*, 1210−1213.

(10) Fusetani, N.; Toyoda, T.; Asai, N.; Matsunaga, S.; Maruyama, T. *J. Nat. Prod.* **1996**, *59*, 796−797.

(11) Rashid, M. A.; Gustafson, K. R.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **2001**, *15*, 21−26.

(12) Arnason, J. T.; Philogène, B. J. R.; Berg, C.; MacEachern, A.; Kaminski, J.; Leitch, L. C.; Morand, P.; Lam, J. *Phytochemistry* **1986**, *25*, 1609−1611.

(13) Ito, A.; Cui, B.; Chávez, D.; Chai, H.-B.; Shin, Y. G.; Kawanishi, K.; Kardono, L. B. S.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 246−248.

(14) For recent examples of syntheses, see: (a) Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875−5880. (b) López, S.; Fernández-Trillo, F.; Midón, P.; Castedo, L.; Saá, C. *J. Org. Chem.* **2005**, *70*, 6346−6352. (c) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2004**, *69*, 3488−3492. (d) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601−3604.

(15) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633−2657.

(16) Sonogashira, K. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-VCH: New York, 2002; pp 493−529.

(17) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(18) Prévost, S.; Meier, J.; Chodkiewicz, W.; Cadiot, P.; Villemart, A. *Bull. Soc. Chim. Fr.* **1961**, 2171−2175.

(19) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; pp. 46−47.

(20) Shi Shun, A. L. K.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810−6813.

(21) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem. Eur. J.* **2003**, *9*, 2542−2550.

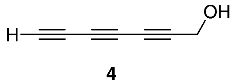
(22) Shi, Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339−1347.

(23) Luu, T.; Shi, W.; Lowary, T. L.; Tykwinski, R. R. *Synthesis* **2005**, 3167−3178.

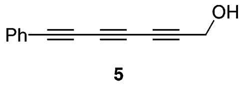
(24) Morisaki, Y.; Luu, T.; Tykwinski, R. R. *Org. Lett.* **2006**, *8*, 689−692.

10.1021/jo061588g CCC: $33.50

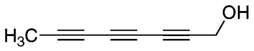
rearrangement as a key step, a homologous series of polyynes terminated with a proton, methyl, or phenyl moiety has been synthesized, including three natural products and three analogues. The stability of these compounds as a function of the terminal group and the length of the methylene tether to the alcohol moiety has been explored in comparison with the three model triynols **4**, **5**, and **6**.[23]



4



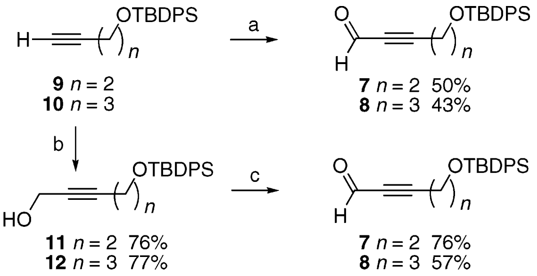
5



6

Aldehydes **7** and **8** were the targeted precursors and could be achieved by two different methods (Scheme 1). Starting with the known precursors **9**[25] or **10**,[26] deprotonation with BuLi in THF generated the lithium acetylide, which was then reacted with DMF to produce either **7** or **8** in moderate yield. Unfortunately, this transformation was often accompanied by a side reaction that resulted from the addition of dimethyl amine to the α,*β*-unsaturated product. To avoid the formation of this byproduct, an alternative route was explored. Acetylene **9** or **10** was deprotonated with BuLi at −78 °C, followed by the addition of excess paraformaldehyde to yield alcohols **11** and **12** in yields of 76% and 77%, respectively, as reported by Baltas and co-workers.[27] The alcohols were purified by column chromatography and oxidized with $BaMnO_4$ to give aldehydes **7** and **8** in good yield. The advantage of the latter route was that the desired products were purified more easily than by the former route, and the overall yield was also slightly higher.

SCHEME 1[a]



[a] Reagents and conditions: (a) BuLi, THF, −78 °C, then DMF; (b) BuLi, THF, −78 °C, then paraformaldehyde; (c) $BaMnO_4$, CH_2Cl_2, rt.

With access to aldehydes **7** and **8**, terminal triynol natural products **13** and **14** were targeted (Scheme 2). The reaction of *i*$Pr_3SiC{\equiv}CLi$ with the appropriate aldehyde at low temperature produced alcohols **15** and **16** in excellent yield (ca. 90%), following workup and column chromatography. Oxidation of the alcohols with $BaMnO_4$ gave the corresponding ketones, which were carried on following workup to dibromoolefination to yield adducts **17** and **18**. The conversion of the dibromoolefins to triynes **19** and **20** was effected via the FBW reaction with BuLi in hexanes at −78 °C.

Exhaustive desilylation of triynes **19** and **20** to give terminal triynes **13** and **14** was more challenging than anticipated. Using typical conditions, for example, triyne **20** was dissolved in wet THF at 0 °C and TBAF was slowly added while the progress of desilylation was monitored by TLC. Addition of Et_2O and aqueous NH_4Cl, however, resulted in an intractable, insoluble black precipitate, suggesting that the deprotected polyynol **14** decomposed during workup. All attempts to spectroscopically determine the structure of the decomposition product(s) have been unsuccessful. Adding a small amount of benzene to the THF solution before the addition of TBAF helped prevent this decomposition. TLC analysis showed that the desilylation was quite efficient, and after quenching and workup, crude **14** was purified on neutral alumina oxide. Upon concentration, however, decomposition once again occurred and identification was limited to IR and crude NMR spectroscopic analysis; no yield could be determined. The IR data for crude **14** were consistent with those reported by Bohlmann,[28] who synthesized **14** via the Cadiot−Chodkiewicz coupling of butadiyne and 5-bromo-4-pentynol (no yield was reported). Chemoselective desilylation (TBDPS versus TIPS) was also attempted but was not successful. For example, the slow addition of TBAF (0.5 equiv) to a solution of **20** in THF at either 0 or −10 °C revealed that indiscriminant desilylation took place at both silyl groups. The use of the desilylation reagent KF was also explored[29] and gave results similar to those obtained with TBAF.

The formation of **13** via desilylation of **19** with either TBAF or KF was also attempted under a number of conditions, and the results were similar to that obtained with **20**. Product **13** was insufficiently stable to be concentrated to dryness, although NMR and IR spectroscopy could be used to confirm its formation. These results were similar to those of Tokimoto et al., who extracted **13** from the neutral culture of *Lentinus edodes* after the attack of *Trichoderma polysporum*[30] and reported that the triynol could be purified via preparative TLC on silica.[31]

The observed instability of **13** and **14** to the conditions of purification and isolation mirrors that of the shorter homologue, natural product **4**, which has been identified and isolated from *Ramaria flava* by Jones and co-workers.[32] Thus, with only a terminal proton, it is concluded that triynols are kinetically unstable species regardless of the number of methylene groups linking the alcohol moiety.

The effect of replacing a terminal proton of the triyne with a phenyl group was then examined through the formation of triynols **21** and **22** (Scheme 3), which are homologues of compound **5**, a natural product isolated from species of *Bidens*.[33,34] Thus, alcohols **23** and **24** were formed in good yield from the reaction of lithium phenylacetylide with the appropriate aldehyde **7** or **8**. The sequence of oxidation with $BaMnO_4$ to ketones **25** and **26** and dibromoolefination to give **27** and **28**

---

[25] Dineen, T. A.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4725−4728.

[26] Baldwin, J. E.; Romeril, S. P.; Lee, V.; Claridge, T. D. W. *Org. Lett.* **2001**, *3*, 1145−1148.

[27] Nacro, K.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013−14030.

[28] Bohlmann, F.; Herbst, P.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 948−957.

[29] Stang, P. J.; Ladika, M. *Synthesis* **1981**, 29−30.

[30] Tokimoto, K.; Fujita, T.; Takeda, Y.; Takaishi, Y. *Proc. Jpn. Acad.* **1987**, *63*, 277−280.

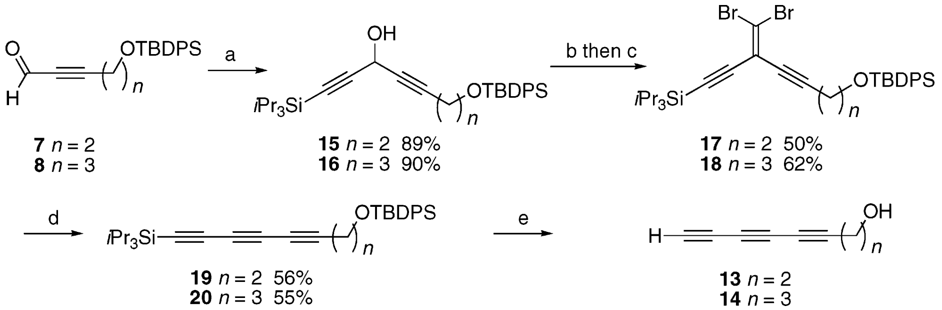
[31] Characterization by ^{1}H NMR spectroscopy and HRMS was described, but confirmation of the terminal C≡C-H by IR spectroscopy was not reported.

[32] Hearn, M. T. W.; Jones, E. R. H.; Pellatt, M. G.; Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2785−2788.

[33] Bohlmann, F.; Arndt, C.; Kleine, K.-M.; Wotschokowsky, M. *Chem. Ber.* **1965**, *98*, 1228−1232.

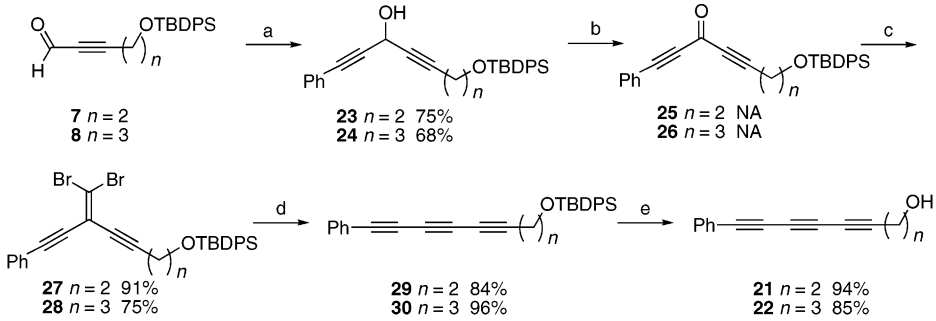
[34] Bohlmann, F.; Bornowski, H.; Kleine, K.-M. *Chem. Ber.* **1964**, *97*, 2135−2138.

SCHEME 2[a]



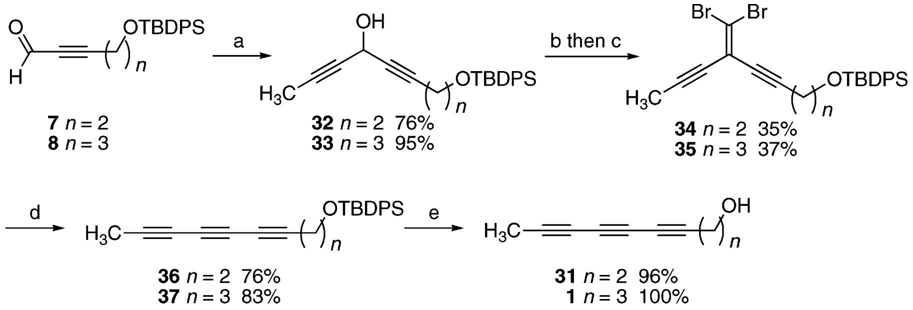
[a] Reagents and conditions: (a) $i\mathrm{Pr_3SiC{\equiv}CLi}$, THF, −78 °C; (b) $\mathrm{BaMnO_4}$, $\mathrm{CH_2Cl_2}$, rt; (c) $\mathrm{CBr_4}$, $\mathrm{PPh_3}$, $\mathrm{CH_2Cl_2}$, 0 °C; (d) BuLi, hexanes, −78 °C; (e) TBAF, THF, 0 °C.

SCHEME 3[a]



[a] Reagents and conditions: (a) $\mathrm{PhC{\equiv}CLi}$, THF, −78 °C; (b) $\mathrm{BaMnO_4}$, $\mathrm{CH_2Cl_2}$, rt; (c) $\mathrm{CBr_4}$, $\mathrm{PPh_3}$, $\mathrm{CH_2Cl_2}$, 0 °C; (d) BuLi, hexanes, −78 °C; (e) TBAF, THF, rt. NA: the crude product was carried to the next step.

SCHEME 4[a]



[a] Reagents and conditions: (a) $\mathrm{MeC{\equiv}CLi}$, THF, −78 °C; (b) $\mathrm{BaMnO_4}$, $\mathrm{CH_2Cl_2}$, rt; (c) $\mathrm{CBr_4}$, $\mathrm{PPh_3}$, $\mathrm{CH_2Cl_2}$, 0 °C; (d) BuLi, hexanes, −78 °C; (e) TBAF, THF, rt.

was accomplished in excellent yield. Although **25** and **26** were reasonably stable intermediates that could be isolated without problem, higher yields were obtained when the crude products were taken on directly to the dibromoolefination step. FBW rearrangement of each dibromoolefin with BuLi provided triynes **29** and **30** in excellent yield, and the desired triynols **21** and **22** were cleanly formed from **29** and **30**, respectively, via desilylation with TBAF. In contrast to terminal triynes **4**, **13**, and **14**, the phenyl derivatives **21** and **22** are kinetically stable to isolation under ambient conditions, as has been reported for **5**.[23] Furthermore, the isolated oils can be stored indefinitely under refrigeration. It is quite clear that the phenyl end-capping groups have a stabilizing effect for the triynols, irrespective of the length of the methylene linker.

Numerous methyl terminated polyynes have been identified as naturally occurring species.[1] This includes compound **31** (Scheme 4), which was isolated from the fungus *Collybia peronata*, first by Higham[35] and later from cultures of *Lentinus edodes* by Tokimoto,[30] as well as triynol **1**, which was extracted from the culture fluids of *Psathyrella scobinacea* by Taha[36] and from *Tridax trilobata* by Bohlmann.[37] The shortest homologue **6** has been obtained from neutral fractions of cultures of the sheathed *Kuehneromyces mutabilis*, *Psilocybe merdaria*, and *Ramaria flava*.[32] Toward the formation of **1** or **31**, the reaction of aldehyde **7** or **8** with $\mathrm{MeC{\equiv}CLi}$ in THF produced alcohols **32** and **33** in good yields. These intermediate products were oxidized with $\mathrm{BaMnO_4}$ to produce the corresponding ketones, and dibromoolefination provided the precursors **34** and **35**. Rather modest yields were obtained in the two−step process,

---

[35] Higham, C. A.; Jones, E. R. H.; Keeping, J. W.; Thaller, V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1991−1994.

[36] Taha, A. A. *Phytochemistry* **2000**, *55*, 921−926.

[37] Bohlmann, F.; Zdero, C.; Weickgenannt, G. *Liebigs Ann. Chem.* **1970**, *739*, 135−143.

amounting to an average of ca. 60% per step. FBW rearrangement yielded the triynol frameworks of **36** and **37**, and liberation of the alcohol moieties with TBAF in THF produced the free alcohols **31** and **1**. Similar to **6**,[23] triynol **31** was obtained as a colorless crystalline solid that turned pink when exposed to light at room temperature. By contrast, compound **1** remained a white, crystalline solid under ambient conditions, with a melting point of 68 °C, showing that the stability of the triynols improves to some extent as a function of the number of methylene units, a useful fact for constructing triynols for further elaboration.[23]

The synthesis of a series of conjugated triynols (**13**, **14**, **21**, **22**, **31**, and **1**) has been accomplished, and their stabilities were compared to those of three known propargylic analogues, triynols **4**, **5**, and **6**. It is determined that the kinetic stability of these compounds can be generalized by three factors: (a) terminal triynols (**4**, **13**, and **14**) are unstable regardless of the number of methylene groups, (b) replacement of the terminal acetylenic proton with a methyl or phenyl group affords increasingly more stable products, and (c) within the series of methyl-endcapped derivatives, more methylene groups is better. Further elaboration of these and related triynols at oxygen through the formation of esters, ethers, and carbohydrates is underway.[23]

Experimental Section

General Procedure for FBW Rearrangement. Synthesis of 1-(*tert*-Butyldiphenylsilanyloxy)-3,5,7-nonatriyne (36). To **34** (488 mg, 0.920 mmol) in dry hexanes (10 mL) at −78 °C was added dropwise BuLi (2.5 M in hexanes; 0.45 mL, 1.13 mmol). The reaction was stirred at −78 °C for 30 min, and then warmed to room temperature for 30 min. Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL) were added. The organic phase was separated, washed with saturated aqueous NaCl (2 × 10 mL), and dried over $MgSO_4$. Solvent removal and purification by column chromatography (hexanes) afforded **36** (260 mg, 76%) as a colorless oil. $R_f = 0.6$ (hexanes/CH_2Cl_2, 3:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.45−7.34 (m, 6H), 3.75 (t, $J = 6.6$ Hz, 2H), 2.51 (t, $J = 6.6$ Hz, 2H), 1.93 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.2, 129.6, 127.6, 75.9, 74.9, 66.7, 64.8, 61.7, 60.5, 59.5, 26.6, 23.4, 19.1, 4.35; IR (microscope) 3071, 2932, 2222, 1112 cm^{-1}; HRMS calcd for $C_{25}H_{26}OSi$ (M^+) 370.1753, found 370.1760.

1-(*tert*-Butyldiphenylsilanyloxy)-4,6,8-decatriyne (37). Reaction of **35** (586 mg, 1.08 mmol) in dry hexanes (10 mL) at −78 °C with BuLi (2.5 M in hexanes; 0.52 mL, 1.30 mmol) as above gave **37** (342 mg, 83%) as a colorless oil. $R_f = 0.5$ (hexanes/CH_2Cl_2, 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.44−7.35 (m, 6H), 3.70 (t, $J = 6.0$ Hz, 2H), 2.43 (t, $J = 6.8$ Hz, 2H), 1.75 (tt, $J = 6.8$ Hz, 6.0 Hz, 2H), 1.94 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.5, 129.5, 127.5, 78.5, 74.7, 65.8, 64.9, 61.9, 60.3, 59.7, 30.8, 26.7, 19.1, 15.8, 4.4; IR (microscope) 3071, 2956, 2221, 1111 cm^{-1}; EIMS *m/z* 384.2 (M^+, 1), 327.1 ([M − *t*-Bu]$^+$, 100); HRMS calcd for $C_{22}H_{19}OSi$ ([M − *t*-Bu]$^+$) 327.1205, found 327.1203.

General Desilylation Procedure. Synthesis of 3,5,7-Nonatriyn-1-ol (31). To **36** (233 mg, 0.629 mmol) in wet THF (10 mL) was added TBAF (0.94 mL, 1.0 M in THF, 0.94 mmol). The reaction was stirred at room temperature until TLC analysis showed that desilylation had taken place. Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL) were added. The organic phase was separated, washed with saturated aqueous NaCl (2 × 10 mL), and dried over $MgSO_4$. Solvent removal and purification by column chromatography (CH_2Cl_2) afforded **31** (80 mg, 96%) as a white crystalline solid that turned purple when exposed to light. Mp: 55−57 °C (lit. 63.5−64 °C).[35] $R_f = 0.3$ (CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, $J = 6.0$ Hz, 2H), 2.54 (t, $J = 6.0$ Hz, 2H), 1.93 (s, 3H), 1.67 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.4, 75.3, 67.5, 64.8, 61.2, 60.6, 59.3, 23.8, 4.5; IR (microscope) 3347, 3264, 2933, 2218, 2036(w), 1055 cm^{-1}; HRMS calcd for C_9H_8O (M^+) 132.0575, found 132.0577. Spectral data were consistent with those reported.[30,35]

4,6,8-Decatriyn-1-ol (1). Reaction of **37** (331 mg, 0.861 mmol) in wet THF (10 mL) with TBAF (1.3 mL, 1.0 M in THF, 1.3 mmol) as decribed above gave **1** (125 mg, 99%) as a white crystalline solid. Mp: 65−68 °C (lit. 68−70.5 °C).[38] $R_f = 0.2$ (CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (t, $J = 6.0$ Hz, 2H), 2.40 (t, $J = 7.0$ Hz, 2H), 1.77 (app. quintet, $J = 6.5$ Hz, 2H), 1.40 (br s, 1H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.1, 75.1, 66.1, 64.9, 61.3, 60.7, 59.6, 30.8, 15.9, 4.5; IR (microscope) 3335, 2901, 2221, 1060 cm^{-1}; HRMS calcd for $C_{10}H_{10}O$ (M^+) 146.0732, found 146.0735. Spectral data were consistent with those reported.[36,38]

Acknowledgment. This work has been generously supported by the University of Alberta and the Natural Sciences and Engineering Research Council of Canada (NSERC) through the Discovery grant program. T.L. thanks the University of Alberta for a Dissertation Fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061588G

---

[38] Bew, R. E.; Chapman, J. R.; Jones, E. R. H.; Lowe, B. E.; Lowe, G. *J. Chem. Soc.* **1966**, 129−135.