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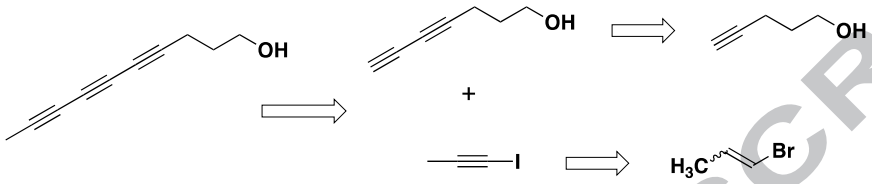

A short and efficient synthesis of the polyacetylene natural product deca-4,6,8-triyn-1-ol

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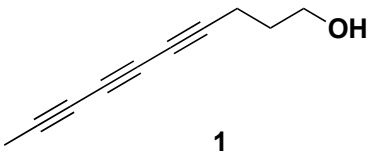
ABSTRACT – A practical and efficient four-step synthesis of the natural product deca-4,6,8-triyn-1-ol has been achieved beginning with (triisopropylsilyl)acetylene. This trialkyne has potential utility as a key intermediate for the total synthesis of the antitumor butenolide natural product vernoniyne.

*Keywords***:** polyacetylenes; Cadiot-Chodkiewicz coupling; halo alkynes

Introduction

Polyacetylenes[1] are a fascinating class of compounds whose chemistry[2] is of longstanding and continuing interest due in part to the diverse biological activity of natural products with structures incorporating this functionality.[3] The polyacetylene natural product deca-4,6,8-triyn-1-ol (**1**) was isolated for the first time in 1969 by Bentley and co-workers from an ethyl ether extract of the roots of *Lactuca plumieri* (Asteraceae), a species native to Southern Europe and belonging to the same genus as lettuce (*Lactuca sativa*).[4] In 1970 Bohlmann reported the presence of **1** in *Tridax trilobata*,[5] and three decades later **1** was isolated from fungi species such as the basidiomycetes *Psathyrella scobinacea*[6] and *Hypsizygus marmoreus.*[7] In many cases triynol **1** has been isolated in mixtures with isomeric

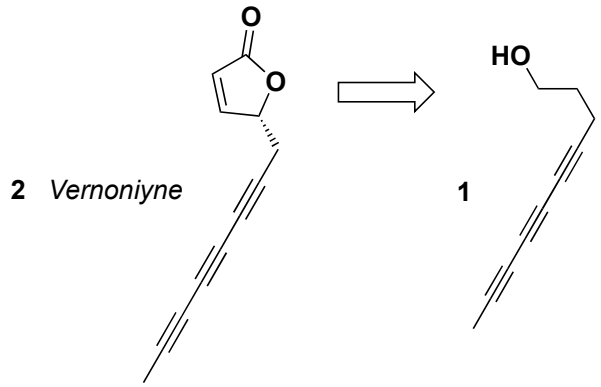
polyacetylenes, polyacetylenic acids, and allenes that are difficult to separate. To our knowledge, the biological activity of triynol **1** has not been explored to date.



1

One of our laboratories has a longstanding interest in polyacetylene natural products and has previously reported the presence of eight new polyacetylenes in *Vernonia scorpioides* (Asteraceae).[8] Among these natural products, vernoniyne (**2**) (*R*-(+)-5-octa-2,4,6-triynyl-furan-2(5H)-one) was found to be the most active anticancer agent, showing cytotoxicity in several cancer cell lines with an IC_{50} ranging from 4.4 to 39.2 μM after 24 and 48 h of incubation, respectively. These promising results *in vitro* have motivated *in vivo* studies in solid and metastatic melanoma in mice which demonstrated that vernoniyne at doses of 5.43 and 54.34 $\mu mol.kg^{-1}$ was able to reduce the tumor mass by 65-80% and also to decrease the number of metastatic nodules induced by intravenous inoculation of B16F10 tumor cells.[9]

As part of our efforts aimed at understanding the mechanism of action of the antitumor activity of vernoniyne, and in view of its low yield from natural sources, we became interested in the total synthesis of this natural product. Deca-4,6,8-triyn-1-ol (**1**) was identified as a potential key intermediate in several possible synthetic approaches to **2**.



2 *Vernoniyne* **1**

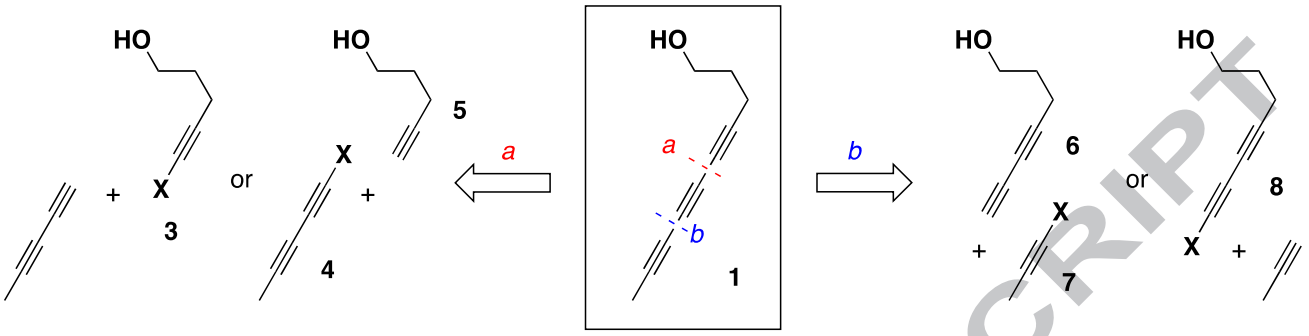
Scheme 1. Vernoniyne (**2**) and deca-4,6,8-triyn-1-ol (**1**) as a key synthetic precursor.

The efficient synthesis of polyacetylenes can present a significant challenge due to the kinetic instability of the target molecules. In addition, the synthesis of these compounds frequently proceeds via polyyne intermediates that are themselves of limited stability.[10] Among the several established strategies for assembling unsymmetrical polyynes, the Cadiot-Chodkiewicz cross-coupling reaction[11] stands apart as the most popular and generally effective method for constructing these systems. The classic Cadiot-Chodkiewicz protocol involves the copper(I)-catalyzed coupling of a terminal alkyne to a bromo alkyne in the presence of an amine such as diethylamine and hydroxylamine hydrochloride.[12]

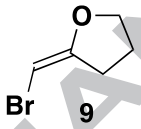
Several alternative strategies for the assembly of triynol **1** based on Cadiot-Chodkiewicz coupling reactions can be envisioned (Scheme 2). While two prior syntheses of **1** were based on the Cadiot-Chodkiewicz coupling (vide infra), the most attractive route to date was reported by Luu and Tykwinski in 2006.[13] Their seven-step synthesis began with 4-pentynol (**5**) and employed a Fritsch-Buttenberg-Wiechell (FBW) rearrangement as a key step. The Fritsch-Buttenberg-Wiechell reaction has been employed by Tykwinski for the synthesis of a variety of polyynes in an outstanding general strategy that circumvents many of the limitations associated with approaches based on the Cadiot-Chodkiewicz coupling.[14]

We based our investigation on the hope that recent work in our laboratory on the synthesis of iodo alkynes might enable the development of a shorter synthetic route to triynol **1** employing the Cadiot-Chodkiewicz coupling. Four disconnections for the construction of the triynol based on the Cadiot-Chodkiewicz coupling are outlined in Scheme 2. The first synthesis of **1** to be reported was disclosed by Cadiot, Chodkiewicz, and co-workers[15] and involved disconnection ***a***, specifically employing the coupling of 1,3-pentadiyne with a bromo alkyne of type **3**. In our view, approaches via disconnection ***a*** are less than ideal due to the need to employ volatile and relatively unstable pentadiyne as an intermediate. In addition, the preparation of halo alkynes of type **3** is not

straightforward. Our attempts to prepare **3** (X = Br) via bromination of pentynol proceeded in unsatisfactory yield and were complicated by formation of the cyclization product **9**.



Scheme 2. Strategies for Assembly of Triynol **1** via Cadiot-Chodkiewicz Coupling.

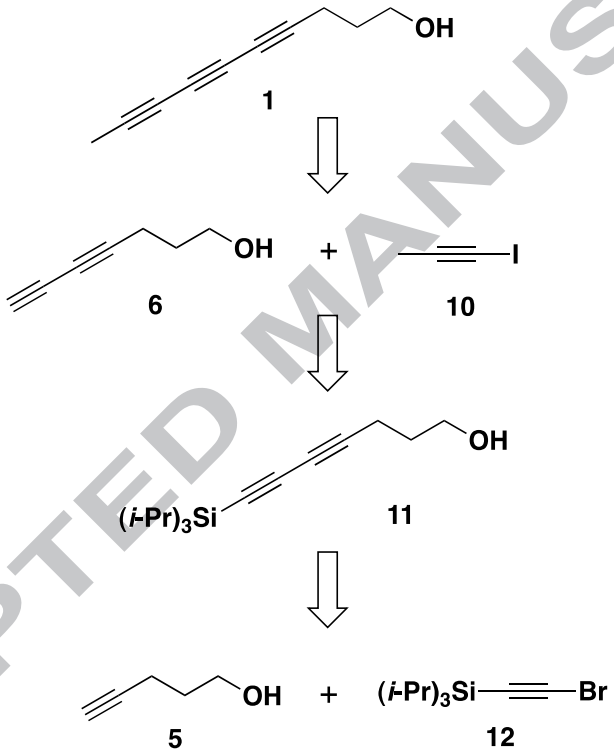


A second synthesis of triynol **1** based on the Cadiot-Chodkiewicz reaction was reported in 1966 by Jones et al. and featured the coupling of heptadiynol **6** with bromopropyne (**7**, X = Br).[16] This key coupling step proceeded in only 22% yield, however, and the author's route to the diyne **6** began with explosive 1,3-butadiyne.

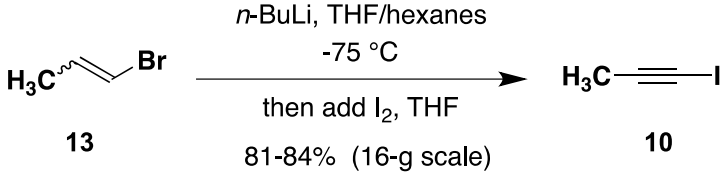
Results and Discussion

We have focused our efforts on developing a practical and scalable synthesis of triynol **1** based on variants of disconnection ***b***. Exploratory experiments involving coupling reactions of diynyl halides of general type **8** with propyne were not promising, and this approach also suffered in our judgment from the requirement to use propyne which is a gas and commercially available at reasonable price only as a mixture with allene and other gaseous impurities. We therefore turned our attention to the alternate "**6** + **7**" strategy in Scheme 2 which is outlined in more detail in Scheme 3.

To avoid the use of 1,3-butadiyne or 1,3-pentadiyne, we envisioned preparing diynol **6** via a Cadiot-Chodkiewicz reaction of commercial pentynol **5** with TIPS-bromoacetylene (**12**). Our plan for the key coupling step called for a Cadiot-Chodkiewicz reaction of 1-iodopropyne with diyne **6**. Recently we reported a practical and convenient one-step synthesis of iodopropyne[17] based on the in situ generation of propynyllithium from commercial 1-bromo-1-propene (**13**) using the general method of Suffert[18] (Scheme 4). In this fashion we expected this route to provide access to triynol **1** in as few as four steps in the longest linear sequence.

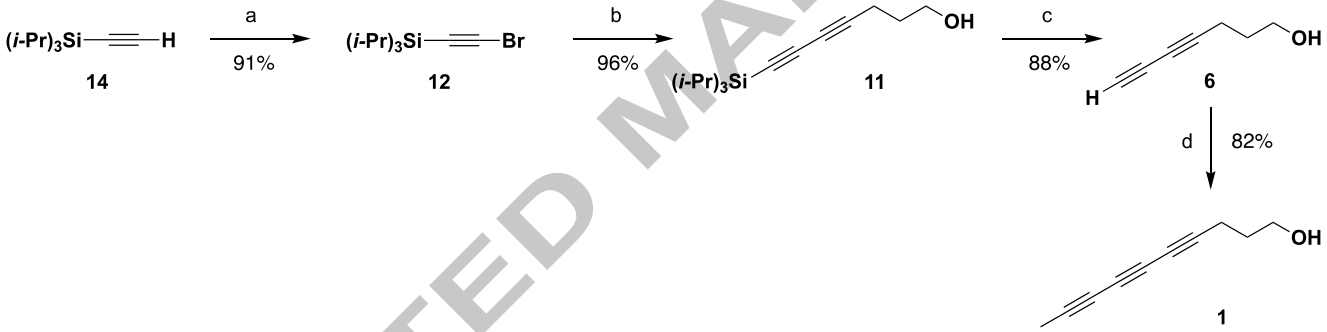


Scheme 3. Retrosynthetic analysis for triynol **1**.



Scheme 4. Synthesis of 1-iodopropyne.

Our synthesis commenced with bromination of commercial (triisopropylsilyl)acetylene with *N*-bromosuccinimide and catalytic silver nitrate according to the general method of Hofmeister[19] to afford the desired bromo alkyne **12**[20] in 91% yield. Note that the use of the TIPS-acetylene is necessary as it is known that (trimethylsilyl)alkynes undergo cleavage under the basic conditions of Cadiot-Chodkiewicz coupling reactions.[21] Reaction of **12** with 4-pentyn-1-ol **5** in the presence of catalytic cuprous chloride (10 mol%), *n*-butylamine, and hydroxylamine hydrochloride then provided the diyne **11** in excellent (96%) yield.[22] Desilylation of **11** proceeded smoothly upon exposure to 1.2 equiv of TBAF in THF and furnished the terminal diyne **6**[23] as a brown oil in 88% yield.[24] The terminal diyne **6** proved to be quite stable, remaining unchanged after storage for 3 months at 4 °C in solution in degassed dichloromethane.



Scheme 5. Synthesis of triynol **1.** *Reagents and conditions*: (a) NBS (1.2 equiv), $AgNO_3$ (5 mol%), acetone, rt, dark, 2 h. (b) 4-Pentyn-1-ol (**5**) (1 equiv), CuCl (10 mol%), NH_2OH-HCl, 30% aq *n*-$BuNH_2$, CH_2Cl_2/MeOH (1:1), 0° C, 1.5 h. (c) TBAF (1 equiv), THF, rt, 2 h. (d) 1-Iodopropyne (**10**) (2 equiv), CuCl (10 mol%), NH_2OH-HCl (1 equiv), 30% aq *n*-$BuNH_2$, CH_2Cl_2/MeOH (1:1), 0 °C, 3 h.

With ample supplies of diyne **6** in hand, conditions were examined for the key Cadiot-Chodkiewicz reaction with 1-iodopropyne. In the event, the desired coupling was achieved in 82% yield by employing the same conditions that were effective for the coupling of **5** and **12**. The desired triyne **1** was obtained as a pale yellow crystalline solid[25] with spectroscopic data[26] in accord with that reported previously.[13]

In summary, we have developed a practical and efficient route to the polyacetylene natural product deca-4,6,8-triyn-1-ol that proceeds in four steps in the longest linear sequence in 63% overall yield. The application of this compound as an intermediate for the synthesis of vernoniyne and other bioactive polyacetylene natural products are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (proton and carbon NMR spectra for diyne **11** and deca-4,6,8-triyn-1-ol **1**) can be found, in the online version, at doi:

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22. 7-(Triisopropylsilyl)hepta-4,6-diyn-1-ol (**11**): yellowish oil; ^{1}H NMR (400 MHz; $CDCl_3$): 3.76 (t, J = 6.2 Hz, 2H), 2.43 (t, J = 7.0 Hz, 2H); 1.80 (m, 2H); 1.60 (brs, 1H); 1.09 (d, J = 1.3 Hz, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.8, 80.4, 77.8, 66.3, 61.3, 30.7, 18.5, 15.7, 11.2. HRMS (ESI) m/z $[M+H]^+$: calculated for $C_{16}H_{28}OSi$ 265.1982; founded 265.1977.
23. For previous syntheses of this alcohol, see refs 5, 15, 16, and (a) Kawanami H, Okada S, Matsuda H, Doi T, Kikuchi N, Hayamizu K, Oikaw H, Nakanishi H. *Mol. Cryst. Liq. Cryst*. 1994; 255: 103. (b) Wang KP, Cho EJ, Yun SY, Rhee JY, Lee D. *Tetrahedron* 2013; 69: 9105
24. Hepta-4,6-diyn-1-ol (**6**): brown oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.75 (t, J = 6.1 Hz, 2H), 2.40 (dt, J = 7.0 Hz, J = 1.2 Hz, 2H), 1.97 (t, J = 1.2 Hz, 1H), 1.79 (m, 2H), 1.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.2, 68.9, 65.8, 65.4, 61.9, 31.3, 16.2.
25. Procedure for Cadiot-Chodkiewicz cross-coupling to generate deca-4,6,8-triyn-1-ol (**1**): A 25-mL, two-necked, round bottomed flask equipped with two rubber septa, a nitrogen inlet needle, and a magnetic stir bar was charged with degassed aqueous 30% *n*-$BuNH_2$ solution(5 mL), CuCl (0.028 g; 0.277 mmol; 10 mol%) and $NH_2OH.HCl$ (0.192 g; 2.77 mmol; 1 equiv). The reaction mixture was cooled to 0 °C (with stirring) and the color changed from blue to colorless within seconds, indicating reduction of Cu(II) to Cu(I). A solution of the terminal diyne **6** (0.300 g; 2.77 mmol; 1 equiv) in 3 mL of 1:1 (v/v) CH_2Cl_2/MeOH was added dropwise via cannula over ca. 4 min followed by a solution of 1-iodopropyne (0.922 g; 5.55 mmol; 2 equiv) in 3 mL of 1:1 (v/v) CH_2Cl_2/MeOH which was added dropwise via cannula over 4 min. The resulting mixture was stirred at 0 °C until TLC analysis

indicated complete consumption of the diyne (3 h) and then 5 mL of saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted with three 40-mL portions of CH_2Cl_2 and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatographic on silica gel (elution with 20% EtOAc-hexanes) afforded 0.332 g (82%) of deca-4,6,8-triyn-1-ol as pale yellow crystals, mp 72-73 °C (lit. 65-68 °C[13], 68-70.5 °C[16]).

26. Deca-4,6,8-triyn-1-ol **(1)**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.73 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.95 (s, 3H), 1.78 (quint, J = 6.2 Hz, 2H), 1.43 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.0; 75.0; 66.1; 64.9; 61.3; 60.7; 59.5; 30.7; 15.9; 4.5; IR (KBr film) 3291, 2925, 2361, 2339, 2220, 1653, 1436, 1062 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{10}H_{10}O$ 147.0804; founded 147.0803.

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Highlights

- Deca-4,6,8-triyn-1-ol is most efficiently prepared by coupling iodopropyne with a heptadiynol
- Iodopropyne can be synthesized in one step from bromopropene
- The heptadiynol is synthesized via a Cadiot-Chodkiewicz coupling