A Divergent Synthesis of Triyne Natural Products and Glycosylated Analogues Using a Carbenoid Rearrangement

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Abstract: Using a carbenoid rearrangement to introduce the conjugated acetylenic framework, a series of triynols has been synthesized in five steps from 1,4-butynediol. Several of the triyne alcohols are known natural products and others are glycosylated analogues. This route avoids the use of terminal diynes as precursors, which can be unstable and/or difficult to prepare. It is therefore procedurally attractive in comparison to more traditional routes such as the Cadiot–Chodkiewicz and Sonogashira coupling reactions.

Key words: polyacetylenes, polyynes, carbohydrates, Fritsch–Buttenberg–Wiechell reaction, carbenoids, natural products

Introduction

Natural products bearing a conjugated polyyne framework have been isolated from plants, fungi, bacteria, sponges, and even an insect. In fact, they are surprisingly common natural products, despite the fact that these compounds can demonstrate significant instability as a result of their often fragile sp-hybridized carbon core. When sufficient quantities of the natural product are available, studies of biological and physiological function have revealed a broad scope of activities such as larvicidal, anti-microbial, anti-viral (HIV), and cytotoxicity toward a range of cell lines. Due to their inherently unstable nature, however, polyynes are often difficult to isolate from natural sources, particularly in the case of longer derivatives such as triynes, tetrynes, and pentaynes. Over the past 50 years, there have been a number of strategies used for the synthesis of polyyne-based natural products. The most common method by far is the copper-catalyzed oxidative coupling procedure developed by Cadiot and Chodkiewicz, as well as the palladium-catalyzed variants that have been subsequently developed. There are, however, a number of challenges associated with the implementation of this strategy, including the significant instability of one or both of the precursors and the formation of troublesome byproducts due to competition from oxidative homocoupling reactions. There is thus a need for the development of alternative synthetic methods, in particular, those that allow for the versatile and expedient synthesis of these molecules using readily available starting materials.

Numerous polyynes found in nature feature a propargylic alcohol group at one terminus of the molecule. In the case of triynes with this motif, e.g. 1, retrosynthetic analysis suggested that the six-carbon triyne segment could be constructed via a Fritsch–Buttenberg–Wiechell (FBW) rearrangement of a suitably functionalized dibromoolefin. This precursor, in turn, would be readily available in three steps from aldehyde 3, via acetylide addition, oxidation, and dibromoolefination. The divergent nature of this approach would result from the ability to vary the pendent group R as a function of the metal acetylide used in the initial reaction with 3. Finally, aldehyde 3 would be available in two steps (monoprotection and oxidation) from a commercially available feedstock, 1,4-butynediol.

Methodology and Model Systems

The initial route to explore triyne formation employed the TBDMS-protected alcohol 4 (Scheme 2), the synthesis of which has been reported by Diederich. Reaction of lithiated trimethylsilylacetylene with 4 in THF gave the alcohol 5, which was readily oxidized to ketone 6 with MnO2. The next step in the synthesis, however, proved problematic, and all attempts to convert 6 to the dibromoolefin 7
met with limited success. Typical Corey–Fuchs dibromooxamolification conditions, when applied to 6, were met primarily with frustration, and modifications of this standard protocol did little to improve the outcome of the reactions. Yields were consistently low with a maximum 17% yield. The formation of numerous byproducts was observed in all cases, including propargyl bromide derivative 8, the result of desilylation and subsequent bromination of the alcohol, as has been previously reported by Mattes and Benezra. Further complicating the formation and use of 7 was its kinetic instability. The pure compound decomposed over a period of days, even when stored at low temperature, necessitating additional purification. Analysis of the decomposed material suggested that removal of the TMS group was slowly occurring.

**Biographical Sketches**

**Thanh Luu** (upper right) was born in Saigon, Vietnam in 1971. He received a BSc in Chemistry from the University of Alberta in 2002. During his final undergraduate year he explored the chemistry of acetylenic macromolecules. In the fall of 2002, he entered the graduate program in Chemistry at the University of Alberta to continue research on the topic of polynes. He is currently working on his PhD thesis under the supervision of Prof. Rik Tykwinski on synthetic methodology and characterization of polynes for use in natural products and materials chemistry.

**Wei Shi** (lower right) was born in Anhui, China, in 1971. He studied chemistry at the Shanghai Jiao Tong University where he obtained a BSc degree in 1993 and at the East China University of Science and Technology where he earned a MSc degree in 2000. He is currently working on his PhD thesis at the University of Alberta on the synthesis and evaluation of new analogues of doxorubicin as potential topoisomerase inhibitors under the supervision of Prof. Todd L. Lowary.

**Todd Lowary** (upper left) was born in 1966 in Canton, IL. He received his BA in Chemistry from the University of Montana in 1988 and obtained his PhD in Organic Chemistry under the supervision of Prof. Ole Hindsøgaard at the University of Alberta in 1993. He carried out postdoctoral research with Prof. David Bundle at the University of Alberta (1993–1995), and then with Dr. Morten Meldal at the Carlsberg Laboratory in Copenhagen, Denmark (1995–1996). In 1996, he took a position in The Department of Chemistry at The Ohio State University as an Assistant Professor and in 2002 was promoted to Associate Professor. In 2003, he returned to the University of Alberta where he is an Associate Professor in the Department of Chemistry and a member of the Alberta Ingenuity Centre for Carbohydrate Science. Research in the Lowary group is focused on the areas of synthetic carbohydrate chemistry, conformational analysis of furanose-containing oligosaccharides, and the identification of novel anti-tuberculosis agents and topoisomerase inhibitors.

**Rik R. Tykwinski** (lower left) was born in 1965 in Marshall, MN. He completed his BSc degree in 1987 at the University of Minnesota, Duluth, where he also developed his interest in organic chemistry working as an undergraduate researcher with Prof. Ron Caple. With Prof. Peter J. Stang at the University of Utah, he explored the chemistry of alkynyl iodonium salts, receiving his PhD in 1994. He was awarded an Office of Naval Research Postdoctoral Fellowship and moved to ETH Zürich (1994–1997) to work with Prof. François Diederich on the chemistry of functionalized tetraethynylethenes and their material properties. He joined the faculty at the University Alberta in 1997, where he is now Professor of Chemistry. He is currently preoccupied with the development of synthetic methods for assembling oligo(enynes) and polynes, characterization of their electronic properties, applications of conjugated systems to nonlinear optics, and mountain biking.
when 7 was stored either as a neat oil or in solutions of, for example, hexanes.

Similar results were arrived at when TIPS was used in place of the TMS group as a protecting group to prevent the premature desilylation (Scheme 3). Addition of \( i\text{-Pr}_3\text{Si}=\text{Cl}\) to aldehyde 4 gave 9 in good yield, following workup and column chromatography.\(^{15}\)

![Scheme 2](image)

**Scheme 2** Reagents and conditions: a) \( \text{Me}_2\text{Si}=\text{Cl}\), THF, \(-78^\circ\text{C}\); b) \( \text{MnO}_2\), \( \text{CH}_2\text{Cl}_2\), r.t.; c) \( \text{CBr}_4\), \( \text{PPh}_3\), \( \text{CH}_2\text{Cl}_2\), \( \text{Et}_3\text{N}\), \(-78^\circ\text{C}\).

Using \( \text{BaMnO}_4\), alcohol 9 was cleanly oxidized to the ketone 10 in 91% yield. Ultimately, it was determined that the dibromoolefination reported by McIntosh et al. using one equivalent of \( \text{Et}_3\text{N}\) gave the best results in the formation of 11.\(^{18}\) Using this protocol, reducing the reaction time to 3 min, and workup with aqueous \( \text{NaHCO}_3\) gave 11 in yields as high as 77%. This reaction was, however, remarkably irreproducible, and lower yields were more common than higher yields due to the loss of the TBDMS protecting group during the reaction. Nonetheless, pure 11 was considerably more stable under ambient conditions than its analogue 7. With 11 in hand, conversion to triyne 12 was effected via reaction with \( \text{BuLi}\) at \(-78^\circ\text{C}\). It is worth noting that while the isolated yield of 12 was reasonable in some cases (up to 61%), its formation was always accompanied by that of 13, a byproduct formed by reaction of the intermediate carbenoid of the FBW reaction with water in the medium.\(^{13a}\) Frustratingly, all procedures that have been previously effective in preventing this side reaction were in this case unsuccessful. As a result of the difficulties encountered in the formation of precursor 11, the persistent presence of byproduct 13, and the similar retention times of 12 and 13 on common chromatographic supports that made separation difficult and time-consuming, a third protection scheme was explored.

The more resilient nature of TBDPS ethers suggested this as a reasonable option for solving the problems encountered with the TBDMS ether as a protecting group. In a sequence of steps analogous to that used in the formation of 4, reaction of 1,4-butyne-1,5-diol with TBDPSCI in the presence of DMAP gave the mono-protected product 14 (Scheme 4), which was then cleanly oxidized to aldehyde 15 with \( \text{BaMnO}_4\) in 58% yield (84% yield based on recovered starting material). Reaction of 15 with \( i\text{-Pr}_3\text{Si}=\text{Cl}\) in THF gave alcohol 16, which was then oxidized to ketone 17 using \( \text{BaMnO}_4\). While conversion of ketone 17 to dibromoolefin 18 proceeded in moderate yield under standard conditions, the reaction was devoid of the troublesome byproducts that accompanied the formation of 7 and 11. Use of \( \text{Et}_3\text{N}\), which had improved the yield of 11, had no effect on the yield of 18. Other attempts to optimize the formation of 18 included the use of zinc as the reductant in place of \( \text{PPh}_3\).\(^{19}\) Monitoring the reaction using \(^1\text{H}\) NMR spectroscopy, however, showed less than 10% conversion in this reaction based on integration of the propargylic methylene protons. The FBW rearrangement of 18 effectively formed 19 in 41% yield as a relatively stable oil. While yields of 19 were slightly lower than that of 12, the reactions were free of the monoprotonated olefin byproduct that had plagued the formation of the latter. Global protodesilylation with TBAF gave the terminal triyne 20. While this product could be identified and characterized in solution via IR spectroscopy, it was insufficiently stable to be isolated. The highly unstable 20 was the first natural C7 polypenate to be identified and was isolated from the fungus *Ramaria flava* by Jones and coworkers.\(^{20}\)
Synthesis of Naturally Occurring Triynols

With ready access to a protecting group scheme that would tolerate the chemical transformations requisite for the FBW approach, the divergent nature of this synthetic scheme was explored. Jones and coworkers isolated the triynol 21 from the neutral fractions of cultures of the sheathed (or two-toned) woodtuft (*Kuehneromyces mutabilis*), a very commonly encountered toadstool, as well as from three other fungal sources (Scheme 4).20 The triyne framework of 21 could be assembled in a manner similar to that used for 20.21 Reaction of 15 with LiC≡CCH₃ gave alcohol 22 as a colorless oil in quantitative yield. This alcohol was oxidized to the ketone 23 with BaMnO₄, and then converted directly to the dibromoolefin 24. A penultimate carbenoid rearrangement afforded the triyne framework of 25, from which the product 21 could be accessed through desilylation with TBAF at room temperature.

The kinetic instability of triynes resulting from the presence of a terminal alkyne moiety is highlighted by comparison of the behavior of 20 and 21. Whereas triynol 20 was far too unstable to be isolated in neat form, the presence of a terminal methyl group in 21 allowed for standard chromatographic purification on silica, affording a crystalline solid with a melting point of 92 °C.

The triynol 26 and triyne acetate 27 (Scheme 6) were first isolated by Bohlmann and coworkers from several species of the genus *Bidens*, including *B. pilosus* and *B. leucanthus*,22,23 and later in trace amounts by Lam and coworkers from the flowering perennial *Dahlia pinnata*.24 The formation of these triynes was initiated with the reaction of the PhC≡CLi with 15 in THF, which efficiently generated alcohol 28 in 85% yield as a light yellow oil. The typical sequence of oxidation with BaMnO₄ to ketone 29 and dibromoolefination to 30 was then accomplished with reasonable yields in both steps. It was found that while the mild oxidant BaMnO₄ alone was effective for a small-scale conversion of 28 to 29 (< 2 g), on a larger scale the reaction would fail to go to completion, regardless of the amount of BaMnO₄ employed. Thus, MnO₂ was utilized to force the reaction to completion in these cases. Carbenoid FBW rearrangement effected on 30 with BuLi gave the triyne 31 in 90% yield as an oil. Liberation of the alcohol moiety with TBAF gave 26, which could then be easily acylated to give 27.25

It is interesting to compare the biological activity of polyynes. Towers and coworkers have studied the activity of numerous polyynes from the aster family (Asteraceae) as larvicidal agents against the mosquito *Aedes aegypti*, including compound 26 and the structurally related natural products phenylheptatriyne (PHT, 32) and diyne 33 (Figure 1).26 Whereas PHT and enediynol 33 show substantial larvicidal activity, the triynol 26 was found to be inactive. Furthermore, this activity was clearly linked to a polyyne chromophore present within the molecules, while ruling out any mechanism based on metabolic action(s) of the polyyne.

**Scheme 5** Synthesis of polyyne natural product 21. Reagents and conditions: a) CH₃C≡CLi, LiBr, THF, –78 °C; b) BaMnO₄, CH₂Cl₂, r.t.; c) CBr₄, PPh₃, CH₂Cl₂, 0 °C; d) BuLi, hexanes, –78 °C; e) TBAF, THF, r.t.

**Scheme 6** Synthesis of polyyne natural products 26 and 27. Reagents and conditions: a) PhC≡CLi, THF, –78 °C; b) BaMnO₄, CH₂Cl₂, r.t.; c) PPh₃, CBr₄, Et₃N, CH₂Cl₂, 0 °C; d) BuLi, hexanes, –78 to 10 °C; e) TBAF, THF, r.t.; f) Ac₂O, DMAP, Et₃N, CH₂Cl₂, r.t.
A number of polyyne glycosides have been isolated from natural sources and have been shown to possess a host of different biological activities including the inhibition of nitric oxide production, antibacterial activity, the modulation of blood glucose levels, as well as the inhibition of histamine release. This latter function has led to the exploration of these compounds as anti-allergic agents. Despite the range of biological processes influenced by these glycoconjugates, their synthesis has not been widely investigated. Indeed, to the best of our knowledge, only a single paper has described the synthesis of such species. In 2004, Gung and Fox described the synthesis of bidensyneosides A2 and C, which are glucosides of enediyne alcohols that have been isolated from Bidens parviflora. There are no reports of the synthesis of triynol glycosides. Given the lack of syntheses of glycosylated triyne alcohols, we were interested in exploring methods for their preparation. As targets, we selected three such species, in which phenyltriynol was conjugated to glucopyranose, galactopyranose, or mannopyranose to give 34–36.

In theory, coupling triynol to different sugar moieties could be achieved through the use of a number of different glycosylation protocols. We chose to investigate three standard methods, each employing a different class of glycosylating agent: glycosyl acetates, glycosyl halides, and glycosyl imidates.

We first explored the use of glycosyl acetates, and. Thus, reaction of each donor with 26 and BF3·OEt2 yielded the corresponding glycosides 40, 41, or 42 in yields ranging from 61–78% (Scheme 7). The use of donors with an acetoxy group at C-2 ensured good selectivity for the 1,2-trans-glycoside via the initial formation of a dioxolenium ion intermediate. In addition to the glycoside product, in all reactions we also isolated significant (ca. 20%) quantities of the acetylated triynol. The formation of the acetylated acceptor species in glycosylation reactions is well precedented when acetylated donors are used.

We next studied the synthesis of these glycosides using glycosyl bromide donors, by reacting 26 with 43 in the presence of silver triflate and collidine in dichloromethane (Figure 2). However, the rate of the reaction was very slow and after several days the reaction gave only low yields (<20%) of the desired product, 40. Although we are unsure as to why this reaction was so sluggish, it is possible the preferential complexation of the silver promoter to the alkyne moieties reduces the rate of glycosylation. In principal this could be circumvented by using a large excess of silver triflate; however, for cost reasons, we do not view this as a viable solution. We then explored the reaction of 26 with trichloroacetimidate in dichloromethane in the presence of BF3·OEt2. In this case, glycosylation led to a number of products (by TLC) from which 40 could be isolated in only low yield. Glycosyl trichloroacetimidates are among the most useful glycosylating agents and the reasons for why they perform poorly here are unknown. Therefore, based on these results, it appears that the glycosyl acetates are the best of the glycosylation methods.
these three donor types for the synthesis of triynol glycosides.

Deprotection of the acetate esters from the products of the glycosylation reactions was more difficult than anticipated. The use of KOMe (generated from K₂CO₃ in MeOH) at room temperature provided chromatographically pure compounds 34, 35, and 36 in somewhat modest yields (ca. 70%) compared to those usually obtained for deacylation reactions. In addition, following purification by chromatography, NMR spectroscopy in CDCl₃ revealed that these supposedly pure compounds were contaminated with inseparable impurities, the structures of which could not be determined. We considered that these deprotected glycosides might form partial aggregates in CDCl₃, which could account for the apparent impurities. To test this hypothesis, a few drops of benzene-d₆ were added to a solution of 34 in CDCl₃ and the NMR spectra were recorded again. No significant differences were seen thus suggesting that aggregation in CDCl₃ does not occur. We then explored acidic conditions (1 M HCl in MeOH) for cleavage of the acetate esters. However, under these conditions significant degradation of the products was observed given their sensitivity to acidic reaction medium. Eventually, we found that deacetylation could be achieved under basic conditions by initiating the reaction at –78 °C, and allowing the reaction mixture to warm to room temperature. Under these conditions the purity of the products was good, although the yields were still modest.

Conclusions

In summary, we have established a protecting group sequence that allows for the divergent formation of dibromoolefins in four steps starting from 1,4-butyne-1,2-diol. These dibromoolefins are suitable precursors for effecting a Fritsch–Buttenberg–Wiechell rearrangement that affords triynol products. While yields under this protocol are at times modest, the use of highly unstable precursors that have been necessary in previous syntheses is conveniently avoided. This general route has been used to assemble four known natural products and several silyl-protected derivatives. An optimized procedure was then developed to provide three glycosylated triynols that are interesting analogues to naturally occurring polyyne glycosides.

Reagents were purchased as reagent grade from commercial suppliers and were used without further purification. Et₂O and THF were distilled from Na/benzophenone ketyl, and hexanes and CH₂Cl₂ were distilled from CaH₂ immediately prior to use. Anhyd MgSO₄ or Na₂SO₄ were used as the drying agent after aqueous workup. Evaporation and concentration in vacuo was done at water-aspirator pressure. All reactions were performed in standard, dry glassware under an inert atmosphere of Ar. Column chromatography: silica gel-60 (230–400 mesh) from General Intermediates of Canada. TLC: aluminum sheets covered with silica gel-60 F₂₅₄ from Macherey-Nagel; visualization by UV light or KMnO₄ stain. Mp: Gallenkamp apparatus; uncorrected. IR spectra: Nicolet Magna-IR 750 (neat) or Ntc-Plan IR Microscope (solids). 1H and 13C NMR: Varian Gemini-300, 400, or 500 instruments, at r.t. in CDCl₃, CD₂CN, or CD₃OD; solvent peaks (7.26, 4.13, 4.78, and 3.30 ppm, respectively, for 1H NMR and 77.0, 1.8, and 49.0 ppm, respectively, for 13C NMR) as reference. MS (EI): Kratos MS50 instrument. MS (ESI): PerSeptive Biosystem Mariner instrument. For mass spectral analyses, low-resolution data are provided in cases when M+ is not the base peak; otherwise, only high-resolution data are provided. Optical rotation (°·mL/g·dm): Perkin-Elmer 241. Elemental analyses were effected by Spectral Services at the University of Alberta. In cases where crude reaction mixtures were passed through a plug of silica gel and celite, the following procedure was employed: to a fritted funnel, a mixture of silica and hexanes was added, which was then covered by celite; a sample solution was introduced and flushed with the solvent (as indicated below); progress of separation was monitored by means of TLC.

6-(tert-Butyldimethylsilanyloxy)-1-trimethylsilylhex-1,4-dyn-3-ol (5)

To Me₃Si=CH (341 mg, 3.47 mmol) in THF (14 mL) at –78 °C was added BuLi (2.4 M, hexanes; 1.4 mL, 3.4 mmol). After stirring for 1 h at –78 °C, aldehyde 4 (0.561 g; 2.81 mmol) was added in one portion and the reaction was warmed to r.t. Et₂O (14 mL) and sat. aq NH₄Cl (14 mL) were added. The organic phase was separated, washed with sat. aq NH₄Cl (2 × 14 mL), sat. aq NaCl (2 × 14 mL), and dried over MgSO₄. Solvent removal and purification by column chromatography (CH₂Cl₂) afforded 5.

Yield: 572 mg (69%); light yellow oil; Rf 0.4 (CH₂Cl₂).

IR (cast, CHCl₃): 2958, 2930, 2858, 2229, 2147, 1634 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.12 (d, J = 7 Hz, 1 H), 4.37 (s, 1 H), 2.16 (d, J = 7 Hz, 1 H), 0.95 (s, 9 H), 0.18 (s, 9 H), 0.13 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 101.7, 89.5, 83.2, 81.9, 52.6, 51.7, 25.8, 18.3, –0.3, –5.0.

MS (EI, 70 eV): m/z (%) = 239.1 (8) [M – t-Bu⁺], 147.1 (100).

HRMS (EI): m/z calcd for C₁₀H₁₆O₂Si₂ [M – t-Bu⁺]: 239.0924; found: 239.0923.

Anal. Calcd for C₁₀H₁₆O₂Si₂: C, 60.75; H, 9.52. Found: C, 60.60; H, 9.46.

6-(tert-Butyldimethylsilanyloxy)-1-trimethylsilylhex-1,4-dyn-3-ol (6)

To 5 (442 mg, 1.49 mmol) in anhyd CH₂Cl₂ (7 mL) at r.t. was added MnO₂ (1.55 g, 17.8 mmol) in one portion. After stirring for 8 h at r.t., the mixture was filtered through a plug of celite and silica gel (CH₂Cl₂) affording 6.

Yield: 257 mg (59%); yellow oil; Rf 0.6 (hexanes–CH₂Cl₂, 1:2).

IR (cast, CHCl₃): 2958, 2930, 2858, 2229, 2147, 1634 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 4.47 (s, 2 H), 0.89 (s, 9 H), 0.23 (s, 9 H), 0.13 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 160.0, 102.2, 99.5, 91.5, 84.8, 51.6, 25.7, 18.2, –0.99, –5.22.

MS (EI, 70 eV): m/z (%) = 294.1 (1) [M⁺], 237.1 (95) [M – t-Bu⁺], 209.1 (100) [M – t-Bu – Me₂].

HRMS (EI): m/z: calcld for C_{15}H_{26}O_{2}Si_{2} [M – t-Bu]+: 237.0767; found: 237.0767.
Anal. Calcld for C_{15}H_{26}O_{2}Si_{2}: C, 61.17; H, 8.90. Found: C, 61.03; H, 8.84.

6-(tert-Butyldimethylsilanyloxy)-3-(dibromomethylidene)-1-trimethylsilylhexa-1,4-diyn-3-one (8)

To CBr_{4} (512 mg, 1.54 mmol) in CH_{2}Cl_{2} (3 mL) at 0 °C was added PPh_{3} (809 mg, 3.08 mmol) and the mixture was stirred for 30 min. The mixture was added to 6 (227 mg, 0.772 mmol) in CH_{2}Cl_{2} (3 mL) at 0 °C and stirred for 3 h. The mixture was filtered through silica and purified by column chromatography (petroleum ether, bp 35–60 °C) affording 7 and 8.

Yield: 57.5 mg (17%); light yellow oil; R_{f} 0.2 (hexanes).
IR (cast, CHCl_{3}): 2957, 2929, 2857, 2159 cm⁻¹.

To CBr_{4} (648 mg, 1.95 mmol) in CH_{2}Cl_{2} (8 mL) at 0 °C was added PPh_{3} (1.02 g, 3.90 mmol). The mixture was stirred for 30 min and Et,N (0.1 mL) was added. The mixture was transferred to a soln of 10 (369 mg, 0.974 mmol) in CH_{2}Cl_{2} (1 mL) at 0 °C and stirred for 3 min. The mixture was poured into sat. aq NaHCO_{3} (13 mL). The organic phase was separated, washed with sat. aq NH_{4}Cl (2 × 30 mL), sat. aq NaCl (2 × 30 mL), and dried over MgSO_{4}. The mixture was reduced to 10 mL and hexanes (10 mL) was added. The crude mixture was filtered through silica and purified by column chromatoography (hexanes–CH_{2}Cl_{2}, 2:1) affording 11.

Yield: 402 mg (77%); colorless oil; R_{f} 0.7 (hexanes–CH_{2}Cl_{2}, 2:1).
IR (cast, CHCl_{3}): 2942, 2891, 2865, 2154 cm⁻¹.

7-(tert-Butyldimethylsilanyloxy)-1-triisopropylsilanyl-1,3,5-heptatriyne (12) and 5-(tert-Butyldimethylsilanyloxy)-1-bromo-3-yn-1-pentene (13)

To 11 (402 mg, 0.751 mmol) in anhyd hexanes (6 mL) at –78 °C was added dropwise BuLi (2.5 M, hexanes; 0.6 mL, 1.5 mmol). The reaction was stirred at –78 °C for 5 min and then warmed to 10 °C for 30 min. Et_{3}O (10 mL) and sat. aq NH_{4}Cl (6 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 6 mL), and dried over MgSO_{4}. Solvent removal and purification by column chromatography (hexanes) afforded 12.

Yield: 172 mg (61%); colorless oil; R_{f} 0.5 (hexanes–CH_{2}Cl_{2}, 6:1).
IR (cast, CHCl_{3}): 2945, 2865, 2194, 2164, 2078, 1463 cm⁻¹.

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Yield: 172 mg (61%); colorless oil; R_{f} 0.5 (hexanes–CH_{2}Cl_{2}, 6:1).
IR (cast, CHCl_{3}): 2945, 2865, 2194, 2164, 2078, 1463 cm⁻¹.

1H NMR (400 MHz, CDCl_{3}): δ = 4.43 (s, 2 H), 0.89 (s, 9 H), 0.20 (s, 9 H), 0.13 (s, 6 H).
13C NMR (100 MHz, CDCl_{3}, APT): δ = 114.3, 111.6, 102.7, 102.3, 99.7, 99.6, 82.5, 14.1, –0.53.
MS (EI, 70 eV): m/z (%): 399.8 (46) [M⁺], 101.0 (100).
HRMS (EI): m/z: calcld for C_{10}H_{22}SiBr_{2}B_{2}= 399.3188; found: 399.3188.
HRMS (EI): m/z: calcld for C_{10}H_{22}SiBr_{2}B_{2}= 399.3186; found: 397.3159.

6-(tert-Butyldimethylsilanyloxy)-1-triisopropylsilanylhexa-1,4-diyne-3-ol (9)

To i-Pr_{2}Si=CH (565 mg, 3.10 mmol) in THF (10 mL) at –78 °C was added BuLi (2.5 M, hexanes; 1.25 mL, 3.1 mmol). After stirring for 2 h at –78 °C, aldehyde 4 (514 mg, 2.58 mmol) was added in one portion and the reaction was warmed to r.t. overnight. EtO (10 mL) and sat. aq NH_{4}Cl (10 mL) were added. The organic phase was separated, washed with sat. aq NH_{4}Cl (2 × 10 mL), sat. aq NaCl (2 × 10 mL), and dried over MgSO_{4}. Solvent removal and purification by column chromatography (CH_{2}Cl_{2}, 2:1) afforded 9. Spectral data were consistent with the literature. 18b

Yield: 805 mg (82%).

7-(tert-Butyldimethylsilanyloxy)-1-triisopropylsilanylhexa-1,4-diyne-3-one (10)

To 9 (576 mg, 1.52 mmol) in anhyd CH_{2}Cl_{2} (30 mL) was added BaMnO_{4} (1.31 g, 5.12 mmol) in one portion. After stirring overnight at r.t., the mixture was filtered through a plug of celite and silica gel, CH_{2}Cl_{2}, affording 10. Spectral data were consistent with the literature. 18b

Yield: 523 mg (91%).

REFERENCES

1. Anal. Calcd for C_{15}H_{26}O_{2}Si_{2}: C, 61.17; H, 8.90. Found: C, 61.03; H, 8.84.
2. HRMS (EI): m/z: calcld for C_{15}H_{26}O_{2}Si_{2} [M – t-Bu]+: 237.0767; found: 237.0767.
3. IR (cast, CHCl_{3}): 2957, 2929, 2857, 2159 cm⁻¹.
4. 1H NMR (400 MHz, CDCl_{3}): δ = 4.43 (s, 2 H), 0.89 (s, 9 H), 0.20 (s, 9 H), 0.13 (s, 6 H).
5. 13C NMR (100 MHz, CDCl_{3}, APT): δ = 114.3, 111.6, 102.7, 102.3, 99.7, 99.6, 82.5, 14.1, –0.53.
6. MS (EI, 70 eV): m/z (%): 399.8 (46) [M⁺], 101.0 (100).
7. HRMS (EI): m/z: calcld for C_{10}H_{22}SiBr_{2}B_{2}= 399.3188; found: 399.3188.
8. HRMS (EI): m/z: calcld for C_{10}H_{22}SiBr_{2}B_{2}= 399.3186; found: 397.3159.
9. 6-(tert-Butyldimethylsilanyloxy)-3-(dibromomethylidene)-1-trimethylsilylhexa-1,4-diyn-3-one (10)

To 9 (576 mg, 1.52 mmol) in anhyd CH_{2}Cl_{2} (30 mL) was added BaMnO_{4} (1.31 g, 5.12 mmol) in one portion. After stirring overnight at r.t., the mixture was filtered through a plug of celite and silica gel, CH_{2}Cl_{2}, affording 10. Spectral data were consistent with the literature. 18b

Yield: 523 mg (91%).
washed with sat. aq NH₄Cl (2 × 100 mL), sat. aq NaCl (2 × 100 mL), and dried over MgSO₄. Solvent removal and purification by column chromatography (CH₂Cl₂) afforded 14 (starting material 1,4-butynediol was also recovered).

Yield: 8.38 g (84%); colorless oil; Rf 0.3 (CH₂Cl₂).

IR (cast, CHCl₃): 3344, 3070, 2957, 2857, 1589 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.71–7.68 (m, 4 H), 7.44–7.36 (m, 6 H), 4.35 (t, J = 2.0 Hz, 2 H), 4.18 (t, J = 2.0 Hz, 2 H), 1.33 (br s, 1 H), 1.04 (s, 9 H).

13C NMR (500 MHz, CDCl₃): δ = 135.7, 133.1, 129.8, 127.7, 84.3, 83.4, 52.6, 51.2, 26.7, 19.1.

MS (El, 70 eV): m/z (%) = 267.1 (41) [M − t-Bu]+, 199.2 (100).

HRMS (EI): m/z calcd for C₁₅H₂₃O₂Si: 267.1385; found: 267.1384.

To 4-(tert-Butyldiphenylsilyl)oxy)-2-butyn-1-ol (16) was added (576 mg, 2.67 mmol) in CH₂Cl₂ (30 mL) at r.t. was added BuLi (2.5 M, hexanes; 0.17 mL, 0.42 mmol). The reaction was stirred for 10 °C. Et₂O (15 mL) and sat. aq NH₄Cl (2 × 10 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 10 mL), and dried over MgSO₄. Solvent removal and purification by column chromatography (hexanes–CH₂Cl₂, 2:1) afforded 15.

Yield: 498 mg (58%, 84% based on recovered starting material); colorless oil; Rf 0.7 (CH₂Cl₂).

IR (cast, CHCl₃): 3071, 2942, 2864, 2224, 2156, 1589, 1471 cm⁻¹.

HRMS (EI): m/z (%) = 267.1 (41) [M − t-Bu]+, 199.2 (100).

HRMS (EI): m/z calcd for C₃₅H₄₄O₂Si₂Na: 527.2772; found: 527.2770.


7-(tert-Butyldiphenylsilyl)-1-trisopropylsilyl-1,3,5-heptatriyne (19) To 18 (228 mg, 0.345 mmol) in anhyd hexanes (15 mL) at –78 °C was added dropwise BuLi (2.5 M, hexanes; 0.17 mL, 0.42 mmol). The reaction was warmed to 10 °C. Et₂O (15 mL) and sat. aq NH₄Cl (15 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 15 mL), and dried over MgSO₄. Solvent removal and purification by column chromatography (hexanes–CH₂Cl₂, 1:4) afforded 19.

Yield: 71.0 mg (41%); colorless oil; Rf 0.6 (hexanes–CH₂Cl₂, 4:1).

IR (cast, CHCl₃): 3071, 2943, 2864, 2179 cm⁻¹.

HRMS (EI): m/z (%) = 498.3 (4) [M⁺], 441.2 (24) [M − t-Bu]+, 199.1 (100).

HRMS (EI): m/z calcd for C₃₅H₃₄O₂Si₂ [M⁺]: 498.2776; found: 498.2774.

2,4,6-Heptatriyn-1-ol (20) To 19 (60.3 mg, 0.121 mmol) in wet THF (2 mL) at –20 °C was added TBAF (1.0 M, THF; 0.2 mL, 0.2 mmol). The reaction was stirred and warmed to r.t. until TLC analysis showed that desilylation had taken place. Et₂O (10 mL) and sat. aq NH₄Cl (5 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 5 mL), and dried over MgSO₄. The product was insusceptible to isolate and attempted purification by column chromatography (hexanes–EtOAc, 4:1) led to decomposition.

Rf 0.5 (hexanes–EtOAc, 4:1).

IR (cast, CHCl₃): 3350, 3286, 2960, 2179 cm⁻¹.

1-(tert-Butyldiphenylsilyl)hepta-2,5-diyne-4-ol (22) To excess propyne, condensed in THF (300 mL) at –78 °C, was added BuLi (1.6 M, hexanes; 5.3 mL, 8.5 mmol) and LiBr (0.5 g, 6 mmol). After stirring for 2 h at –20 °C, aldehyde 15 (1.82 g, 5.65
mmol) was added in one portion and the reaction was warmed to r.t. overnight. EtO (100 mL) and sat. aq NH4Cl (100 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 100 mL), and dried over MgSO4. Solvent removal and purification by column chromatography (hexanes–CH2Cl2, 1:4) afforded 22.

Yield: 2.04 g (100%); light yellow oil; Rf 0.4 (hexanes–CH2Cl2, 1:4).

IR (cast, CHCl3): 3396, 3071, 2958, 2893, 2258, 2226, 1472 cm–1.


1H NMR (400 MHz, CDCl3): δ = 7.72–7.68 (m, 4 H), 7.45–7.35 (6, m, 6 H), 4.99 (br s, 1 H), 4.353 (s, 1 H), 1.91 (br s, 1 H), 1.84 (s, 3 H) 1.04 (s, 9 H).

13C NMR (100 MHz, CDCl3): δ = 153.70, 153.69, 153.68, 153.67, 153.65, 153.64, 85.9, 84.4, 83.3, 82.3, 52.7, 52.6, 26.7, 19.2, 4.8.

To CBr4 (826 mg, 2.45 mmol) in CH2Cl2 (16 mL) at 0 °C was added tert-BuMnO4 (1.05 g, 4.10 mmol) in one portion. After stirring overnight. Et2O (100 mL) and sat. aq NH4Cl (100 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 100 mL) and dried over MgSO4. Solvent removal and purification by column chromatography (CH2Cl2) afforded 21.

Yield: 26.9 mg (75%); magenta crystals; mp 89–92 °C (Lit. 21b 93 °C); Rf 0.3 (CH2Cl2).

IR (cast, CHCl3): 3383, 3070, 3050, 2930, 2231, 1589 cm–1.

HRMS (EI): [M–Bu]+, 199.1 (100).

To phenylacetylene (558 mg, 5.46 mmol) in THF (100 mL) at –78 °C was added BuLi (2.5 M, hexanes; 2.2 mL, 5.4 mmol). After stirring for 1 h at –78 °C, aldehyde 15 (1.46 g, 4.52 mmol) was added in one portion and the reaction was warmed to r.t. Et2O (100 mL) and sat. aq NH4Cl (100 mL) were added. The organic phase was separated, washed with sat. aq NaCl (2 × 100 mL), and dried over MgSO4. Solvent removal and purification by column chromatography (CH2Cl2) afforded 28.

Yield: 1.63 g (85%); light yellow oil; Rf 0.4 (CH2Cl2).

IR (cast, CHCl3): 3383, 3070, 3050, 2930, 2231, 1589 cm–1.

HRMS (EI): [M–Bu]+, 199.1 (100).

To 28 (519 mg, 1.22 mmol) in anhyd CH2Cl2 (27 mL) at r.t. was added BaMnO4 (940 mg, 3.67 mmol) in one portion. After stirring for 8 h at r.t., the mixture was filtered through a plug of celite and silica gel (CH2Cl2) affording 29.

Yield: 459 mg (89%); yellow oil; Rf 0.4 (hexanes–CH2Cl2, 1:1).

IR (cast, CHCl3): 3070, 2958, 2893, 2196, 1596 cm–1.
[1H NMR (500 MHz, CDCl3); δ = 7.71–7.69 (m, 4 H), 7.59–7.57 (m, 2 H), 7.49–7.37 (m, 9 H), 4.47 (s, 2 H), 1.06 (s, 9 H)].

13C NMR (100 MHz, CDCl3); δ = 136.5, 132.9, 131.6, 129.9, 129.2, 128.4, 127.8, 122.1, 113.9, 107.9, 95.7, 94.4, 86.1, 81.5, 53.2, 26.7, 19.2.

MS (EI, 70 eV): m/z (%) = 520.9 (27) [M–H]+, 491.0 (100). HRMS (EI): m/z calcd for C29H26OBr2Si: C, 60.22; H, 4.53. Found: C, 59.63; H, 4.51.

IR (cast, CHCl3): 3070, 2998, 2958, 2216, 2192, 1471 cm–1.

19.2.

HRMS (EI): m/z (%) = 422.2 (2) [M+], 365.1 (100) [M – t-Bu]+.

HRMS (EI): m/z calcd for C29H26OBr2Si [M+]: 418.1753; found: 418.1753.

HRMS (EI): m/z (%) = 418.2 (2) [M+], 361.1 (23) [M – t-Bu]+, 199.1 (100).


To 30 (548 mg, 0.945 mmol) in anhyd hexanes (32 mL) at –78 °C was added dropwise BuLi (2.4 M, hexanes; 0.8 mL, 2 mmol). The mixture was stirred for 30 min. Et3N (0.4 mL) was added to the mixture at 0 °C. The mixture was transferred to 29 (1.26 g, 2.97 mmol) in CH2Cl2 (5 mL) at 0 °C and stirred for 5 min. The reaction was poured over NaHCO3 (50 mL). The organic phase was separated, washed with sat. aq NH4Cl (2 × 50 mL), sat. aq NaCl (2 × 50 mL), and dried over MgSO4. Solvent removal and purification by column chromatography (hexanes–EtOAc, 4:1) afforded 27.

IR (cast, CHCl3): 3070, 2998, 2958, 2216, 2192, 1471 cm–1.

1H NMR (400 MHz, CDCl3); δ = 7.73–7.70 (m, 4 H), 7.51–7.47 (m, 2 H), 7.43–7.30 (m, 9 H), 4.39 (s, 2 H), 1.06 (s, 9 H).

13C NMR (100 MHz, CDCl3); δ = 135.6, 132.9, 131.6, 129.9, 129.2, 128.4, 127.8, 122.1, 113.9, 107.9, 95.7, 94.4, 86.1, 81.5, 53.2, 26.7, 19.2.

MS (EI, 70 eV): m/z (%) = 520.9 (27) [M–H]+, 491.0 (100). HRMS (EI): m/z (%) = 245.0573; found: 245.0571.

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**Synthesis of Triene Natural Products and Glycosylated Analogues**

Yield: 66 mg (78%); yellow oil; \( \text{Rf} 0.3 \) (hexanes–EtOAc, 2:1); \( \delta_{\text{Rf}} -27.1 \) (c 3.0, CHCl\(_3\)).

HRMS (ES, MeOH–toluene, 3:1): \( m/z \) calcd for C\(_{19}\)H\(_{18}\)O\(_6\)Na [M + Na\(^+\)]: 365.0996; found: 365.0996.

1H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.51–7.32 \) (m, 5 H), 5.40 (dd, \( J_1,6 = 3.4 \) Hz, \( J_{2,3} = 1.0 \) Hz, 1 H, H-2), 5.06 (dd, \( J_{3,4} = 10.4 \) Hz, \( J_{3,6} = 3.4 \) Hz, 1 H, H-3), 4.70 (d, \( J_{3,4} = 7.9 \) Hz, 1 H, H-1), 4.52 (d, \( J_{1,6} = 17.1 \) Hz, 1 H, propargyl CH\(_3\)), 4.48 (d, \( J_{1,2} = 17.1 \) Hz, 1 H, propargyl CHF), 4.18 (dd, \( J_{3,6} = 11.4 \) Hz, \( J_{3,5} = 6.6 \) Hz, 1 H, H-4), 4.15 (dd, \( J_{3,6} = 11.4 \) Hz, \( J_{3,5} = 6.6 \) Hz, 1 H, H-4), 3.95 (dd, \( J_{3,6} = 11.4 \) Hz, \( J_{3,5} = 6.6 \) Hz, 1 H, H-4), 3.25–3.29 (m, 2 H, H-5), 2.96 (s, 3 H, C(O)CH\(_3\)), 2.07 (s, 3 H, C(O)CH\(_3\)), 1.99 [s, 3 H, C(O)CH\(_3\)].

IR (microscope, CH\(_2\)Cl\(_2\)): 3368, 2191 cm\(^{-1}\).

Yield: 6.0 mg (69%); white solid; \( \text{Rf} 0.2 \) (CH\(_2\)Cl\(_2\)–MeOH, 10:1); \( \delta_{\text{Rf}} -112.2 \) (c 0.4, MeOH).

IR (cast, CH\(_2\)Cl\(_2\)): 3374, 2190 cm\(^{-1}\).

7-Phenylhepta-2,4,6-triynyl 2,3,4,6-Tetraacetyl-\( \beta \)-D-Galactopyranoside (35)

To a soln of 41 (12.3 mg, 0.0241 mmol) in MeOH (2 mL) at –78 °C was added K\(_2\)CO\(_3\) (1.7 mg, 0.01 mmol). The soln was allowed to warm to r.t. over 18 h and then concentrated. Purification by column chromatography (CH\(_2\)Cl\(_2\)–MeOH, 1:10) afforded 35.

Yield: 5.3 mg (64%); white solid; \( \text{Rf} 0.2 \) (CH\(_2\)Cl\(_2\)–MeOH, 10:1); \( \delta_{\text{Rf}} -71.3 \) (c 0.3, MeOH).

IR (microscope, CH\(_2\)Cl\(_2\)): 3368, 2191 cm\(^{-1}\).

7-Phenylhepta-2,4,6-triynyl \( \beta \)-D-Mannopyranoside (36)

To a soln of 42 (34.0 mg, 0.0666 mmol) in MeOH (3 mL) at –78 °C was added K\(_2\)CO\(_3\) (6.0 mg, 0.04 mmol). The soln was allowed to warm to r.t. over 18 h and then concentrated. Purification by column chromatography (CH\(_2\)Cl\(_2\)–MeOH, 10:1) afforded 36.

Yield: 17.5 mg (77%); white solid; \( \text{Rf} 0.2 \) (CH\(_2\)Cl\(_2\)–MeOH, 10:1); \( \delta_{\text{Rf}} +75.4 \) (c 0.5, MeOH).

IR (cast, MeOH): 3364, 2191 cm\(^{-1}\).

1H NMR (600 MHz, CD\(_3\)OD): \( \delta = 7.53–7.37 \) (m, 5 H, Ar), 4.57 (s, 2 H, propargyl CH\(_3\)), 4.38 (d, \( J_{1,2} = 7.4 \) Hz, 1 H, H-1), 3.82 (dd, \( J_{1,6} = 3.3 \) Hz, \( J_{1,6} = 1.0 \) Hz, 1 H, H-6), 4.15 (dd, \( J_{1,6} = 11.4 \) Hz, \( J_{1,6} = 1.1 \) Hz, 1 H, H-6), 3.77 (dd, \( J_{1,6} = 11.4 \) Hz, \( J_{1,6} = 7.0 \) Hz, 1 H, H-6), 3.51–3.55 (m, 2 H, H-2, H-5), 3.48 (dd, \( J_{1,6} = 9.7 \) Hz, \( J_{1,6} = 3.3 \) Hz, 1 H, H-3).

HRMS (ES, MeOH): \( m/z \) calcd for C\(_{27}\)H\(_{26}\)O\(_{10}\)Na [M + Na\(^+\)]: 365.0996; found: 365.0996.

1H NMR (600 MHz, CD\(_3\)OD): \( \delta = 7.53–7.57 \) (m, 5 H, Ar), 4.57 (s, 2 H, propargyl CH\(_3\)), 4.38 (d, \( J_{1,2} = 7.4 \) Hz, 1 H, H-1), 3.82 (dd, \( J_{1,6} = 3.3 \) Hz, \( J_{1,6} = 1.0 \) Hz, 1 H, H-6), 4.15 (dd, \( J_{1,6} = 11.4 \) Hz, \( J_{1,6} = 1.1 \) Hz, 1 H, H-6), 3.77 (dd, \( J_{1,6} = 11.4 \) Hz, \( J_{1,6} = 7.0 \) Hz, 1 H, H-6), 3.51–3.55 (m, 2 H, H-2, H-5), 3.48 (dd, \( J_{1,6} = 9.7 \) Hz, \( J_{1,6} = 3.3 \) Hz, 1 H, H-3).

HRMS (ES, MeOH): \( m/z \) calcd for C\(_{27}\)H\(_{26}\)O\(_{10}\)Na [M + Na\(^+\)]: 365.0996; found: 365.0996.
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References
(1) The term polyyne is meant to denote compounds with a structural sequence of two or more consecutive (conjugated) acetylene units. The term polyyne has been often used in this context as well, but this term can be ambiguous due to its more common use in reference to polymerized acetylene.

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