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# A New, Iterative Strategy for the Synthesis of Unsymmetrical Polyynes: Application to the Total Synthesis of 15,16-Dihydrominquartynoic Acid

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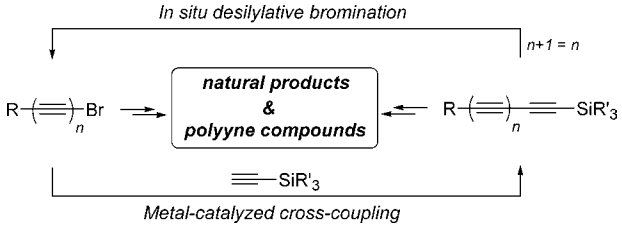
## ABSTRACT




**A new iterative strategy for the synthesis of unsymmetrically substituted polyynes has been developed. The starting bromoalkyne is homologated by one acetylene unit through palladium-catalyzed cross-coupling with a TIPS-protected terminal acetylene and a subsequent in situ one-pot AgF-mediated desilylative bromination. The utility of this new synthetic method is demonstrated by its application to the total synthesis of (*S*)-(*E*)-15,16-dihydrominquartynoic acid.**

Unsymmetrically substituted conjugated diyne and polyyne units continue to attract widespread interest because of their unusual electrical, optical, and structural properties.[1] In addition to their potential applications in materials science, they are also key structural moieties present within a large number of natural products that exhibit a variety of interesting biological activities.[2] Consequently, the development of efficient synthetic approaches toward these rigid units remains an important challenge to synthetic organic chemists.[1−3]

The oxidative homocoupling of two different terminal alkynes under $Cu^{I}/Cu^{II}$ catalysis is not a suitable process for the synthesis of unsymmetrically substituted 1,3-butadiynes and polyynes, because this approach usually leads to the simultaneous and rather predominant formation of the corresponding symmetrical products. One solution to this problem is the $Cu^{I}$-catalyzed cross-coupling of terminal alkynes with 1-haloalkynes in the presence of a suitable amine, i.e., the so-called Cadiot−Chodkiewicz coupling.[4] This method has been used extensively for the preparation of unsymmetrical diynes and polyynes; a number of variations have been developed, including palladium-catalyzed heterocoupling reactions.[3b,5] The major limitation of these reactions, however, is that the vast majority of terminal diynes and higher polyynes required as coupling partners or

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(2) For a recent paper that includes a discussion of this topic, see: (a) Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883−2886. (b) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339−1347.

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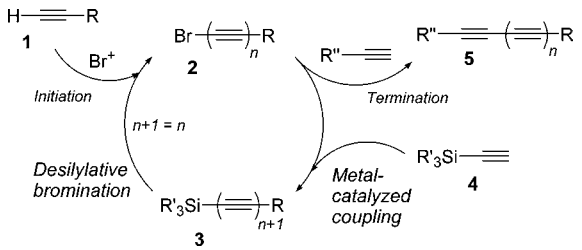
precursors of 1-haloalkynes are highly sensitive molecules that are prone to rapid decomposition.[1,2,6]

The instability of terminal diynes and higher polyynes can be circumvented, for the preparation of symmetrical polyynes, by employing an in situ generation/dimerization protocol.[2a,3,6c] In the case of unsymmetrical polyynes, the rather limited synthetic approaches have been reviewed.[3] For example, Tykwinski and co-worker[7] employed an alkylidene carbenoid rearrangement toward the synthesis of naturally occurring unsymmetrical polyynes. Their protocol eliminates the need for unstable acetylenic precursors required for coupling approaches. Gung and co-workers[8] reported the successful one-pot three-component Cadiot−Chodkiewicz reaction to construct the unsymmetrical tetrayne unit. Very recently, Gung[9] also reported the successful preparation of an unsymmetrical 1,3,5-polyyne ((*S*)-(*E*)-15,16-dihydrominquartynoic acid) via an in situ generated terminal alkyne/cross-coupling protocol. In addition, Mori and co-workers[5b] reported the $Cu^{I}$-catalyzed cross-coupling of chloroalkynes with alkynylsilanes, which are generally more stable than their corresponding terminal alkynes. Although this method seems to be promising for the future preparation of unsymmetrical higher polyynes, an appropriate combination of chloroalkynes and alkynylsilanes is essential for clean formation of the desired cross-coupled products. Herein we report an alternative protocol for the synthesis of unsymmetrical polyynes that uses a two-step homologation sequence.

Scheme 1 depicts a general outline of our iterative protocol. We envisioned that the bromoalkyne **2**, which can be

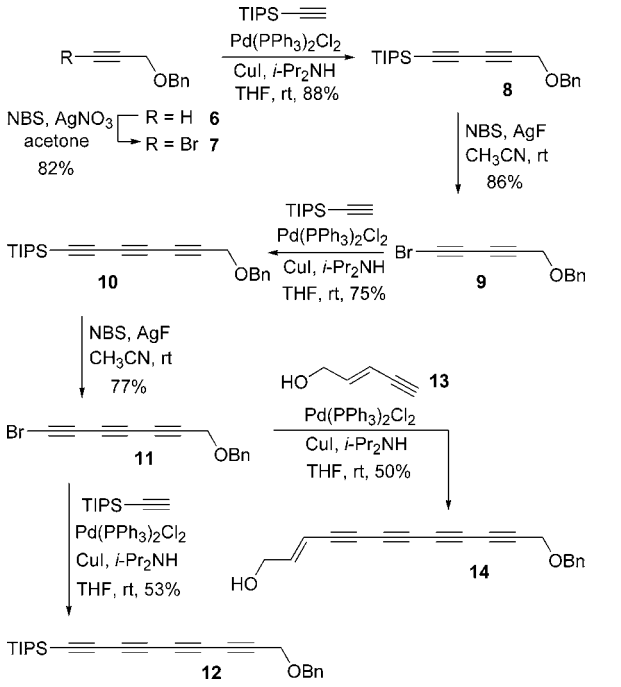
**Scheme 1.** General Iterative Protocol for Synthesis of Unsymmetrical Polyynes




obtained from the simple terminal alkyne **1**, could be homologated by one acetylene unit through cross-coupling with the trialkylsilylacetylene **4** and subsequent desilylative bromination of **3**. Repeating this reaction sequence sequentially would allow the rapid construction of polyyne systems. Finally, cross-coupling with a monosubstituted acetylene or another type of coupling partner should afford the desired unsymmetrical polyyne **5**. The key to the success of this iterative scheme lies in the in situ one-pot desilylative bromination, which avoids the complication encountered with isolating sensitive terminal alkynes. One of the salient features of this protocol is that it allows the preparation of even- and odd-numbered polyynes[10] by controlling the number of iterations of the chain growth cycle.

To test the feasibility of our approach, we conducted our initial studies with the simple terminal alkyne **6** (Scheme 2). Conversion of alkyne **6** to the known bromoalkyne **7**[11]

**Scheme 2.** Synthesis of Unsymmetrical Polyynes




was achieved readily in good yield (82%) with $AgNO_3$ and NBS[12] in acetone. At this point, we decided to employ bulky (trialkylsilyl)acetylenes as the cross-coupling partners for the homologation reactions because it had previously been reported that trimethylsilyl (TMS) acetylene decomposes, possibly by a desilylation pathway, under the basic conditions of the coupling reaction such that no desired cross-coupling product can usually be isolated.[13] When we used the bulkier triisopropylsilyl (TIPS) acetylene, the desired cross-coupling product **8** was obtained under standard Cadiot−Chodkiewicz

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coupling conditions (CuCl, $HONH_2$·HCl, $EtNH_2$, MeOH), but only in modest yield (40%). However, under the modified Sonogashira conditions ($Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, THF),[5f,14] the yield of the product was improved to 88%.

Our first attempts to effect the in situ one-pot desilylative bromination of **8** used the standard NBS/$AgNO_3$ conditions developed by Isobe and co-workers for the conversion of TMS-protected acetylenes to bromoacetylenes.[15] Unfortunately, these conditions led only to the recovery of the starting material, presumably because of the increased stability of the bulky silyl group. Consequently, we needed to develop alternative conditions for the one-pot desilylative bromination of bulkier (trialkylsilyl)acetylenes. We examined the use of different silver sources and solvents for this reaction and found the results of using an AgF/NBS/$CH_3CN$ system to be superior to those from the use of other combinations. When using this system, the reaction occurred at room temperature to give the desired bromodiyne **9** in 86% yield.

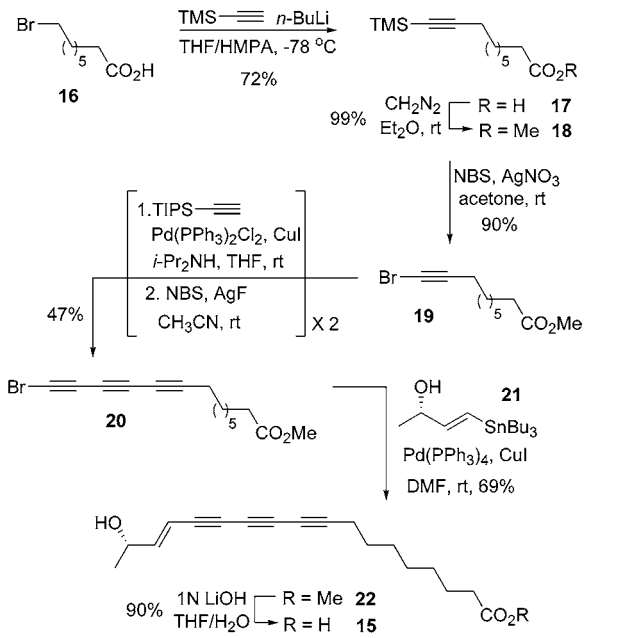
With the optimal reaction conditions in hand, we performed the second iteration in the same manner as just described. We encountered no difficulties when converting bromodiyne **9** into bromotriyne **11** through this two-step sequence. The palladium-catalyzed cross-coupling of **9** with TIPS-acetylene provided TIPS-triyne **10** in 75% yield, and the subsequent AgF-mediated desilylative bromination afforded bromotriyne **11** successfully in 77% yield.

The obtained bromotriyne **11** could be further converted to TIPS-tetrayne **12** under the same cross-coupling reaction conditions in 53% yield, implying that our iterative protocol could be applicable to the synthesis of higher polyynes. The iterative process can be terminated in a number of ways by reactions with various coupling partners. For example, the palladium-catalyzed cross-coupling of bromotriyne **11** with 2-penten-4-yn-1-ol (**13**) led to the formation of the unsymmetrical tetrayne **14** in 50% yield.

We further demonstrated the utility of this iterative protocol by applying it in the total synthesis of a polyacetylenic natural product, (*S*)-(*E*)-15,16-dihydrominquartynoic acid[16] (**15**, Scheme 3), which exhibits potent cytotoxic activity against human hormone-dependent prostate and ovarian cancer cell lines.

The starting material for our synthesis was the commercially available 8-bromooctanoic acid (**16**). Treatment of **16** with an excess of lithium trimethylsilylacetylide at −78 °C furnished the known[17] TMS-protected acetylene **17**

**Scheme 3.** Total Synthesis of (*S*)-(*E*)-15,16-Dihydrominquartynoic Acid




smoothly in 72% yield, and then esterification with diazomethane gave **18** in nearly quantitative yield. In situ desilylative bromination of **18** to the known[8a] bromoacetylene **19** was achieved in 90% yield under standard NBS/$AgNO_3$ conditions. With bromoacetylene **19** in hand, repeating the two-step homologation sequence twice generated the desired bromotriyne **20** readily in 47% overall yield. The cross-coupling of **20** with a slight excess of the vinylstannane (*S*)-**21**[18] (>99% ee, 1.1 equiv), mediated by $Pd(PPh_3)_4$ and CuI,[19] gave enetriyne **22** successfully in 69% yield. Finally, hydrolysis of methyl ester with LiOH afforded the (*S*)-(*E*)-15,16-dihydrominquartynoic acid (**15**) in 90% yield, whose spectroscopic data were in agreement with those reported in the literature.[9,16,20]

In summary, we have developed a new iterative strategy for the synthesis of unsymmetrically substituted polyynes that uses a two-step homologation sequence. In this process, the starting bromoalkyne is homologated by one acetylene unit through palladium-catalyzed cross-coupling with a TIPS-protected terminal acetylene followed by an in situ one-pot AgF-mediated desilylative bromination. We have also accomplished the total synthesis of (*S*)-(*E*)-15,16-dihydrominquartynoic acid from a simple stating material in high overall yield. These results demonstrate that our approach can be applied efficiently to the synthesis of various unsymmetrical polyynes. Further developments and applications of this strategy are now under investigation.

**Acknowledgment.** This research was supported by a grant (PF0321201-01) from Plant Diversity Research Center

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(20) The optical rotation value measured for the synthetic **15** {$[\alpha]_D$ −32.2 (*c* 1.0 MeOH)} is higher than that of the natural product[16] {$[\alpha]_D$ −12.8 (*c* 0.05 MeOH)}.

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**Supporting Information Available:** Full experimental procedures and analytical data of compounds and copies of $^{1}H$ NMR and $^{13}C$ NMR spectra of compounds **12**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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