Polyyne Library

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Solid-Phase Library Synthesis of Polyynes Similar to Natural Products[**]

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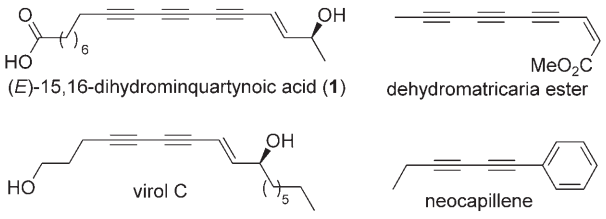
Naturally occurring polyynes are a structurally diverse class of compounds that contain two or more conjugated triple bonds (Scheme 1).[1] To date, more than a thousand polyyne compounds have been isolated from various natural sources.[2] This structurally unique class of compounds exhibit a variety of biological effects, including antimicrobial, antitumor, and antiangiogenic activities.



Scheme 1. Structures of representative polyyne natural products.

As a consequence of their biological significance and interesting physicochemical properties,[1,3] natural polyynes have been the subject of numerous synthetic studies, most of which have been well-summarized in recent reviews.[2,4] Most natural polyynes pose a substantial synthetic challenge because of their highly unsaturated nature. The method most commonly used for the preparation of unsymmetrical diyne and polyyne natural products is the Cadiot–Chodkiewicz coupling reaction,[4,5] that is, the metal-catalyzed cross-coupling of a 1-haloalkyne with a terminal alkyne. The major limitation of this coupling reaction is that the vast majority of terminal diynes and higher polyynes required as coupling partners or precursors of 1-haloalkynes are often unstable.[3,6] Many elegant alternative methods have been explored to overcome this challenge.[3,7] Within this context, we previously developed an iterative strategy for the synthesis of unsymmetrically substituted polyynes.[8] Our iterative strategy entails a two-step acetylene homologation sequence, namely, in situ desilylative bromination of alkynylsilanes followed by a cross-coupling reaction with a trialkylsilylacetylene.

The importance of natural products for medicinal applications has meant that the demand for the generation of libraries of molecules based on natural products has grown significantly.[9] Given the attractive and versatile biological activities of polyyne natural products, it would be interesting to obtain a library of compounds containing the common structural motif of natural polyynes. Such libraries might be useful for discovering ligands or probes for either unknown or discovered biological targets. To the best of our knowledge, however, there has been no literature precedent related to the systematic synthesis of a polyyne library. Therefore, we focused our attention on the construction of a library of natural-product-like polyynes by employing solid-phase combinatorial synthesis techniques and our iterative acetylene homologation strategy.

One of the salient features of our iterative protocol in the synthesis of a library of compounds is that it allows at least three points of diversity, including the number of incorporated acetylene units. Furthermore, the reaction conditions of our iterative process are mild enough to tolerate a variety of functional groups and are suitable for application to solid-phase synthesis. Herein, we report the first solid-phase synthesis of a combinatorial library of natural-product-like polyynes.

To test the feasibility of the process on a solid support[10] we focused our initial studies on the preparation of the triyne natural product (*S*)-(*E*)-15,16-dihydrominquartynoic acid (**1**, Scheme 1),[11] which we had previously synthesized by using the solution-phase iterative acetylene homologation strategy.[8] We chose a 2-Cl-trityl resin because **1** could be cleaved from this solid support under mild conditions with high efficiency. Furthermore, the resin was compatible with the reactions employed during the synthesis.

Our successful solid-phase synthesis of **1** is depicted in Scheme 2. Thus, 9-decynoic acid was loaded onto the commercially available 2-Cl-trityl resin **2** (1.3 $\text{mmol}\,\text{g}^{-1}$) with high efficiency to give the resin-bound terminal alkyne **3** (loading level = 1.10 $\text{mmol}\,\text{g}^{-1}$, 85 %). Conversion of the terminal alkyne **3** into bromoalkyne **4** was achieved readily in excellent yield (96 %)[12] with NBS/$AgNO_3$ in DMF. The resulting resin-bound bromoalkyne **4** was anticipated to react with triisopropylsilyl-protected acetylene similarly to the solution-phase reaction under the modified Sonogashira conditions ([$PdCl_2(PPh_3)_2$] CuI, *i*Pr_2NH, THF).[13] However, the use of the solution-phase reaction conditions did not afford the desired cross-coupling product **5** with sufficient purity and yield. Unexpectedly, substantial amounts of the homocoupled product[14]—the dimer of a 9-decynoic acid—

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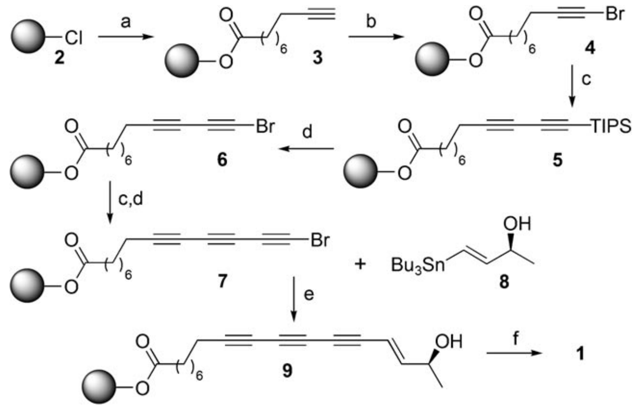
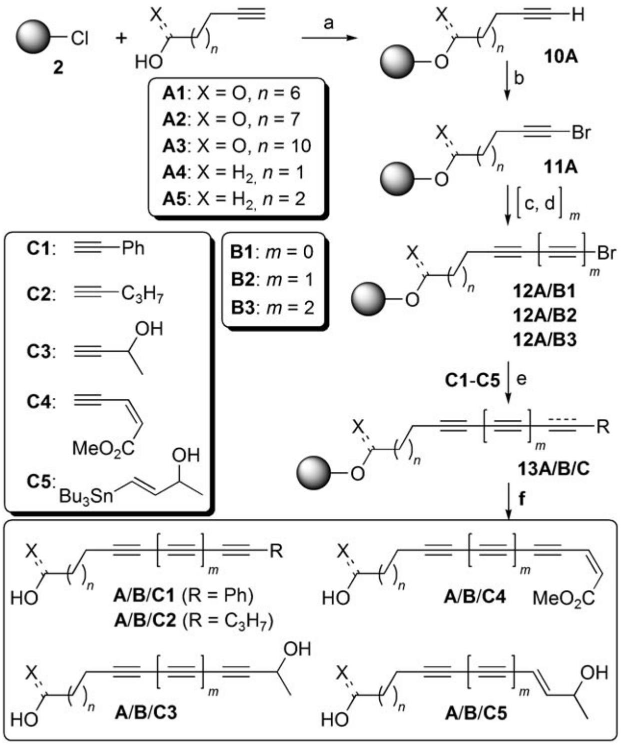


Scheme 2. Solid-phase synthesis of (*S*)-(*E*)-15,16-dihydrominquartynoic acid (**1**). a) 9-Decynoic acid (1.2 equiv), DIPEA (4.0 equiv), CH_2Cl_2, RT, 6 h; b) NBS (8.0 equiv), $AgNO_3$ (0.2 equiv), DMF, RT, 0.5 h; c) TIPSA (4.0 equiv), $[PdCl_2(PPh_3)_2]$ (0.4 equiv), CuI (0.4 equiv), THF/*i*Pr_2NH (1:1), RT, 3 h; d) NBS (8.0 equiv), AgF (4.0 equiv), DMF, RT, 2 h; e) **8** (4.0 equiv), $[Pd(PPh_3)_4]$ (0.4 equiv), CuI (0.4 equiv), DMF, RT, 3 h; f) 1% TFA/CH_2Cl_2, RT, 10 min, 23% (overall, from **3**). DIPEA = *N*,*N*-diisopropylethylamine, NBS = *N*-bromosuccimide, TIPSA = (triisopropylsilyl)acetylene.

was also observed after cleavage with TFA. The pseudodilution effect of the polymer matrix was considered not to work properly in this operation. We surmised that this outcome could be the result of poor swelling of the resin. Therefore, the resin loaded with bromoalkyne **4** was swelled with THF/*i*Pr_2NH (1:1) before the addition of TIPS-protected acetylene and coupling catalysts. This mixed solvent system resulted in a better swelling of the resin and led to a high yield (87%) and purity of the desired cross-coupling product **5**. In this case, no homocoupled by-product was detected.

Under our recently developed in situ AgF-mediated desilylative bromination conditions (NBS/AgF in DMF),[15] the resultant TIPS-diyne **5** was successfully converted into the corresponding bromodiyne **6** in high yield (93%). At this stage, a washing step with pyridine was needed to completely release any impurities and metal salts out of the polymer matrix. 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 the resin-bound bromodiyne **6** into bromotriyne **7** through this two-step sequence (63% over 2 steps). The cross-coupling reaction of bromotriyne **7** with vinylstannane **8**,[16] mediated by $[Pd(PPh_3)_4]$ and CuI, successfully gave enetriyne **9**. Finally, the final product was cleaved from the solid support using 1% TFA in CH_2Cl_2 and then purified by column chromatography on silica gel to give the desired **1** in 23% overall yield (based on the resin-loading level of **3**).

With the successful development of a solid-phase synthesis of natural product **1**, we sought to evaluate the versatility of the sequence toward a combinatorial library synthesis by introducing three points of diversity: the starting terminal alkynes, the number of incorporated acetylene units, and the final cross-coupling partners. Thus, five terminal alkynes **A** (**A1**–**A5**) of two different types, which bear a carboxylic acid or hydroxy group at the tail, were anchored to resin **2** through an ester or ether linkage to give **10A** (Scheme 3). The resin-bound terminal alkyne **10A** was treated with NBS/$AgNO_3$ to give bromoalkyne **11A**. The resulting bromoalkyne **11A** was homologated by one acetylene unit through the above-mentioned two-step sequence to afford bromodiyne **12A/B2**. Repeating the two-step homologation sequence generated the homologated bromotriyne **12A/B3**.



Scheme 3. Solid-phase combinatorial synthesis of a library of natural-product-like polyynes. a) DIPEA (4.0 equiv), CH_2Cl_2, RT; b) NBS (8.0 equiv), $AgNO_3$ (0.2 equiv), DMF, RT; c) TIPSA (4.0 equiv), $[PdCl_2(PPh_3)_2]$ (0.4 equiv), CuI (0.4 equiv), THF/*i*Pr_2NH (1:1), RT; d) NBS (8.0 equiv), AgF (4.0 equiv), DMF, RT; e) **C1**–**C4** (4.0 equiv), $[PdCl_2(PPh_3)_2]$, (0.4 equiv), CuI (0.4 equiv), THF/*i*Pr_2NH (1:1), RT or **C5** (4.0 equiv), $[Pd(PPh_3)_4]$ (0.4 equiv), CuI (0.4 equiv), DMF, 60°C; f) 1% TFA/CH_2Cl_2, RT, 10 min.

The obtained bromoalkyne **11A** (identical to **12A/B1** in Scheme 3), bromodiyne **12A/B2**, and bromotriyne **12A/B3** were cross-coupled with five different coupling partners **C** (**C1**–**C5**) in a combinatorial manner to give **13A/B/C**. In this coupling process, a uniform set of Sonogashira conditions was employed throughout except for the case of vinylstannane **C5**, for which the Stille coupling conditions was used. The resulting resin-bound product **13A/B/C** was cleaved from the solid support using 1% TFA in CH_2Cl_2 to provide the polyyne products **A/B/C**. In most cases, one major product was detected by TLC and isolated by chromatography. However, in the cases of tetraynes derived from the coupling of bromotriyne **12A/B3** with **C3** and **C4**, TLC showed the presence of a complex mixture with no major product. This result could be attributed to the markedly lower stability of those tetraynes, which discouraged us from isolating the compounds. Therefore, we were able to obtain 65 compounds out of the planned 75 (87% success rate) with an average purity higher than 95%. Most of the obtained polyynes were stable under refrigerator conditions for at least two weeks, while **A5/B1/C4** and **A5/B2/C4** decomposed rapidly at room temperature under air.

Table 1 shows the compounds obtained and their yields and purities. ^{1}H NMR spectroscopy and MS were used to confirm the identity of each isolated compound.[17] The overall yields ranged from 12% to 97%, based on the resin-loading level of **10 A**. As expected, the overall yield decreased as the number of incorporated acetylene units increased. Other variables did not significantly affect the yield.

Among the various biological properties, cytotoxic activity is one of the most intriguing properties of natural polyynes. Therefore, as a demonstration of its usefulness and a preliminary evaluation of the polyyne library, members of this obtained library were individually evaluated[18] for cytotoxic activity against various cancer cells by using the sulforhodamine B method.[19] It was found that the cytotoxic potency was highly dependent on the type of cells and the chemical composition of the polyynes. As a representative example, the cytotoxic activities of the library members against HCT116 human colon cancer cells are shown in Figure 1, where the cells were treated with 10 μM of each compound. The observed data revealed important structural requirements of the polyynes for cytotoxicity.[20] In general, a higher number of acetylene units elicited a higher cytotoxicity. Building blocks **A4**, **A5**, and **C1** caused enhanced cytotoxic potency. The most active members of the library had IC_{50} values in the micromolar range, with the most potent compound being **A5/B3/C1** (IC_{50} 1.2 μM).[21] This biological study implies that our polyyne libraries can be used as biochemical tools or as the source of new lead compounds for future development.

In conclusion, we have developed a facile solid-phase synthetic pathway to generate a library of natural-product-like polyynes that might be difficult to obtain by other means. Sixty-five polyynes out of the planned seventy-five could be

Table 1: A combinatorial library of natural-product-like polyynes.

Product	Yield [%][a]	Purity [%][d]	Product	Yield [%][a]	Purity [%][d]
A1/B1/C1	77	96	**A3/B2/C4**	50	98
A1/B1/C2	70	98	**A3/B2/C5**	40	98
A1/B1/C3	65	94	**A3/B3/C1**	14	96
A1/B1/C4	63	94	**A3/B3/C2**	12	98
A1/B1/C5	67	94	**A3/B3/C3**	–[b]	–
A1/B2/C1	55	98	**A3/B3/C4**	–[b]	–
A1/B2/C2	43	94	**A3/B3/C5**	17	95
A1/B2/C3	54	90	**A4/B1/C1**	96	98
A1/B2/C4	53	98	**A4/B1/C2**	86	98
A1/B2/C5	38	97	**A4/B1/C3**	97	97
A1/B3/C1	22	97	**A4/B1/C4**	58	96
A1/B3/C2	27	99	**A4/B1/C5**	37	94
A1/B3/C3	–[b]	–	**A4/B2/C1**	89	97
A1/B3/C4	–[b]	–	**A4/B2/C2**	64	94
A1/B3/C5	23	94	**A4/B2/C3**	74	96
A2/B1/C1	76	98	**A4/B2/C4**	37	94
A2/B1/C2	68	99	**A4/B2/C5**	58	94
A2/B1/C3	53	97	**A4/B3/C1**	48	90
A2/B1/C4	65	98	**A4/B3/C2**	32	96
A2/B1/C5	54	90	**A4/B3/C3**	–[b]	–
A2/B2/C1	56	97	**A4/B3/C4**	–[b]	–
A2/B2/C2	47	98	**A4/B3/C5**	13	85
A2/B2/C3	50	96	**A5/B1/C1**	92	97
A2/B2/C4	53	98	**A5/B1/C2**	79	98
A2/B2/C5	43	98	**A5/B1/C3**	79	98
A2/B3/C1	21	95	**A5/B1/C4**	58[c]	96
A2/B3/C2	27	99	**A5/B1/C5**	71	90
A2/B3/C3	–[b]	–	**A5/B2/C1**	82	98
A2/B3/C4	–[b]	–	**A5/B2/C2**	68	96
A2/B3/C5	25	95	**A5/B2/C3**	68	80
A3/B1/C1	77	99	**A5/B2/C4**	37[c]	87
A3/B1/C2	69	97	**A5/B2/C5**	57	93
A3/B1/C3	67	98	**A5/B3/C1**	19	96
A3/B1/C4	67	94	**A5/B3/C2**	27	96
A3/B1/C5	60	98	**A5/B3/C3**	–[b]	–
A3/B2/C1	55	96	**A5/B3/C4**	–[b]	–
A3/B2/C2	47	99	**A5/B3/C5**	27	87
A3/B2/C3	58	96			

[a] Yield of isolated product after column chromatography (calculated from the loading of **10 A**). [b] Product was not obtained. [c] The isolated compound was unstable to air at room temperature. [d] After isolation, the purity was determined immediately by reverse-phase HPLC by measuring the peak area, with monitoring by UV at 220 nm (gradient, 20–100% $MeOH/H_2O$ with 0.1% TFA, 30 or 60 min).

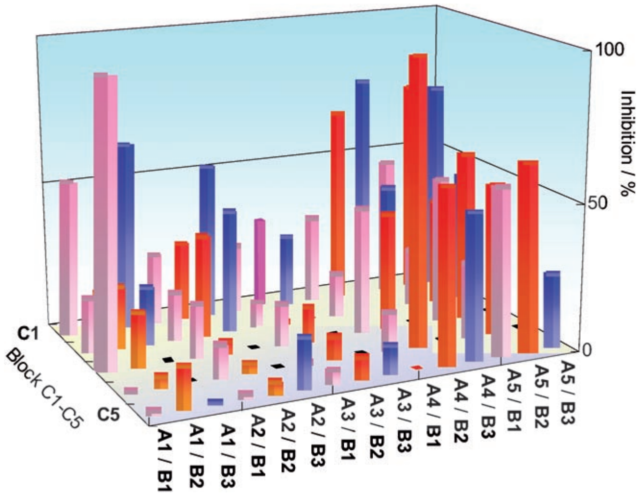


Figure 1. Cytotoxic activities of library members against HCT116 human colon cancer cells. The assay was carried out in triplicate at 10 μм.

obtained using the iterative acetylene homologation strategy. The library was evaluated against cancer cells to demonstrate its possible utility as a chemical tool to unravel cellular processes or as a platform for drug discovery and design. The development of this solid-phase method considerably reduced the time required for the construction of the polyyne library, and thus will allow for the preparation of a more diversified and expanded library.

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