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Total Synthesis of (−)-Minquartynoic Acid: An Anti-Cancer, Anti-HIV Natural Product

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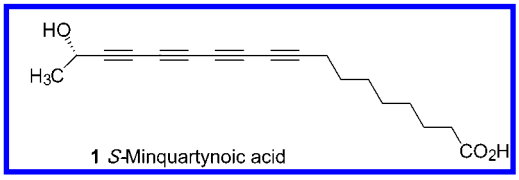
ABSTRACT



The tetraacetylenic compound, (*S*)-minquartynoic acid (1), is synthesized in seven linear steps and 17% overall yield from commercially available azelaic acid monomethyl ester. The key step is a one-pot three-component Cadiot–Chodkiewicz reaction to construct the tetrayne unit without using either a diyne or a triyne intermediate.

Minquartynoic acid (**1**) was initially isolated from the stem bark of *Minquartia guianensis*, which was one of the most potent traditional anthelmintics used by the Quijos Quichua people of Ecuador's Amazonian lowlands.[1] More recently, along with two additional polyacetylenic natural products (**2** and **3**, Figure 1), minquartynoic acid was also isolated from a chloroform extract of the twigs of *Ochanostachys amentacea* from southeast Asia.[2] In recent in vitro tests, **1** showed broad cytotoxicity against 10 different tumor cell lines.[2]

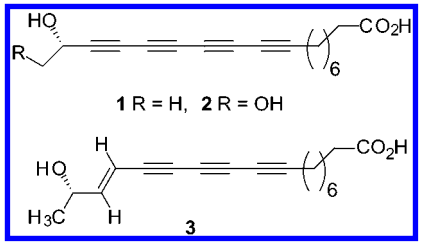


Figure 1. Cytotoxic polyacetylenes from *O. amentacea*: (*S*)-minquartynoic acid **1**, 18-hydroxyminquartynoic acid **2**, and (*E*)-15,16-dihydrominquartynoic acid **3**.

Independent isolation and anti-HIV activity of **1** were also reported by two other groups.[3,4] A strong cytotoxicity of **1** against the P-388 (leukemia) cell line with an ED_{50} of 0.18 μg/mL was reported.[1] Compound **3** exhibited the most potent activity among the three polyacetylenes against the KB, LNCaP (prostate cancer), and SW626 (ovarian cancer) cell lines.[2]

The structure of **1** was determined by a variety of spectroscopic methods and was found to contain the unusual four conjugated triple bonds.[2] The configuration of the chiral center was determined using Mosher's ester method.[2,5] Recently, many other polyacetylenic compounds with biological activities have been reported.[6] Their unusual property combined with their unusual structure has sparked widespread interest in the synthesis of polyacetylenes, both natural[7−11] and unnatural products.[12−14] Recently, we reported

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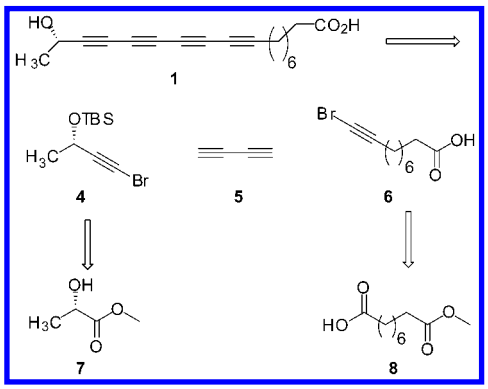
a synthesis of (+)- and (−)-adociacetylene using a two-directional Negishi coupling approach.[15,16] To our knowledge, no tetrayne-containing natural products have been synthesized. The instability of the intermediates involved in these syntheses presents a considerable challenge. Here we report a short synthesis of (−)-minquartynoic acid using a triply convergent approach.

The general strategy for our synthesis of (*S*)-minquartynoic acid is depicted in Scheme 1. The tetrayne unit might be

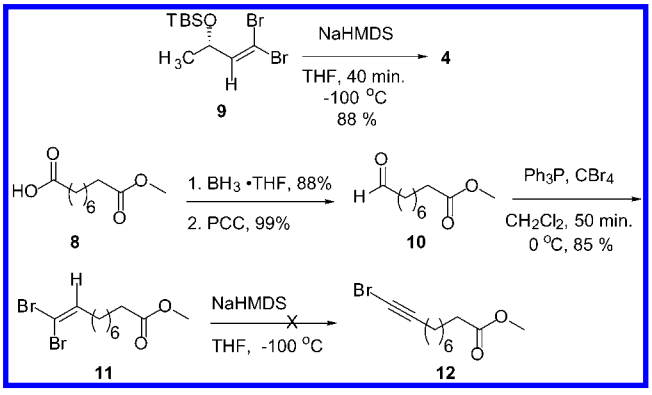
Scheme 1



constructed by the Cadiot−Chodkiewicz reaction through a combination of bromoalkynes **4** and **6** and butadiyne **5**.[17,18] The bromoalkyne **4** should be available from (*S*)-methyl lactate **7**. Butadiyne **5** is known and can be prepared in one step from commercially available 1,4-dichlorobutyne.[17] Bromoalkyne **6** should be obtained from commercially available azelaic acid monomethyl ester **8**.

Dibromoolefin **9** was prepared from lactate **7** following a literature procedure[19] with (1) protection of the −OH group, (2) reduction of the ester function to an aldehyde group, and (3) formation of the dibromoolefin.[20] Significant loss of the TBS protecting group (Scheme 2) was observed when the literature procedure was followed. This procedure was modified by using more hexanes to partition the product in the workup process to avoid the protecting group loss. Elimination of one molar HBr from **9** was achieved with NaHMDS to give bromoalkyne **4** in high yield.[21]

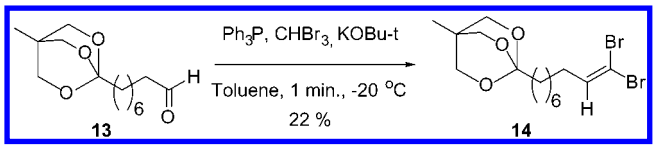
Scheme 2



The preparation of bromoalkyne **12** (Scheme 2) was problematic using the same protocol for the preparation of **4.** The precusor to **12** was obtained uneventfully by the following sequence of reactions. Selective reduction of the carboxylic acid function in **8** was conveniently accomplished by using 1 equiv of BH_3·THF complex in anhydrous THF at 0 °C.[22] Aldehyde **10** was prepared in quantitative yield with PCC in the oxidation of the resulting primary alcohol.[23] Dibromoolefin **11** was obtained uneventfully using a combination of Ph_3P and CBr_4.[20] However, no desired product was isolated during the attempt to prepare bromoalkyne **12** by the elimination of one molar HBr from **11** under various conditions.[21]

Complications from the enolization of ester **11** were considered to be the cause of these unsuccessful trials. To remove the acidity of the α-protons, we decided to protect the carboxylic acid function as an ortho ester (Scheme 3).[24]

Scheme 3



Aldehyde **13** was obtained from azelaic acid monomethyl ester (**8**) in two steps by protecting the carboxylic acid function as an ortho ester and reducing the ester function with DIBAL-H. However, after various reported procedures for introducing the dibromoolefin unit from an aldehyde were attempted,[20,25−27] the desired dibromoolefin **14** could be obtained only in poor yield by following Weinreb's procedure.[26] Significantly, the ortho ester is unstable toward silica gel chromatography. We therefore turned our attention to an alternate two-step procedure (Scheme 4).

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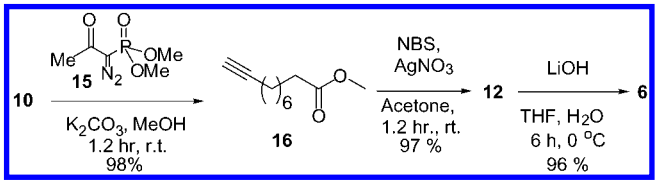
Scheme 4

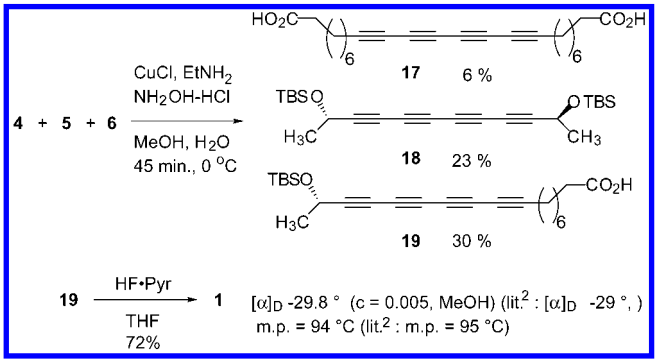


Aldehyde **10** was treated with the Ohira−Bestmann reagent **15** to yield alkyne **16** in nearly quantitative yield.[28,29] The conversion of alkyne **16** to the bromoalkyne **12** was also achieved in excellent yield using $AgNO_3$ and NBS in acetone.[30] Since the Cadiot−Chodkiewicz reaction proceeds best with polar substrates,[17] methyl ester **12** was hydrolyzed to its corresponding carboxylic acid (**6**) using LiOH in a mixture of THF and H_2O.[31]

With bromoalkynes **4** and **6** in hand, the stage was now set for coupling via the Cadiot−Chodkiewicz reaction. Coupling of either **4** and **5** or **5** and **6** produced the corresponding triyne, which decomposed several hours after isolation to a charcoal-like material. This led us to conclude that a stepwise coupling strategy would not be viable.

A one-pot three-component coupling strategy was employed, in which 1 equiv of each of the reactants (**4**−**6**) was loaded into the flask along with other reagents. A typical literature procedure for the coupling reaction is usually conducted at room temperature.[17] However, CuCl caused butadiyne **5** to immediately decompose at room temperature. We modified the general procedure by first charging the flask with all reactants and then adding CuCl to the mixture at 0 °C (Scheme 5). We were pleased to isolate three tetraacetylenic products (**17**−**19**) in a combined yield of 59%, 30% of which was the desired cross-coupling product **19**. The stability of these internal tetraynes is much greater than

Scheme 5



that of the terminal triynes isolated in the initial two-component couplings. All three tetraynes (**17**−**19**) were purified by column chromatography and were stable during ^1H and ^{13}C NMR measurements. The TBS protecting group of **19** was removed using HF·Pyr[31] complex in 72% yield to give a product identical to the reported **1** in all spectroscopic determinations.[2]

In summary, a highly efficient synthesis of (*S*)-minquartynoic acid has been completed in seven linear steps and 17% overall yield from commercially available azelaic acid monomethyl ester. This synthesis is amenable to the preparation of two other constituents (**2** and **3**) isolated from the cytotoxic extract of *O. amentacea*. The total synthesis of **2** and **3** will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of compounds **1** and **4**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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