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A concise synthesis of (+)- and (−)-adociacetylene B

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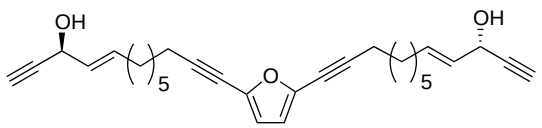
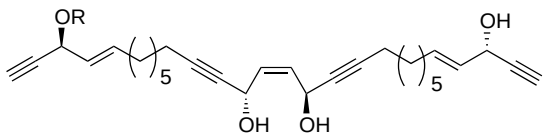
Abstract—The synthesis of (−)-adociacetylene B was completed in six steps in a yield of 9.3%, while the (+)-enantiomer was synthesized in seven steps and 7.5%. An enzymatic resolution of racemic **1** using the lipase from *Pseudomonas* sp. was employed to obtain (+) and (−)-**1**. This synthesis of (*S*,*S*)-**1** represents the first total synthesis of a naturally occurring acetylenic alcohol that has two chiral centers and four acetylene units.

Naturally occurring acetylenic alcohols are an intriguing class of natural products. Acetylene-containing natural products are common components of terrestrial plants.[1–7] However, biologically active polyacetylenes have been reported from marine organisms only during the last 20 years. The uniqueness of these compounds includes their unusual structural features. Many of these polyacetylenes are isolated from the marine sponge, *Petrosia* sp. Adociacetylenes **1** and **2** are cytotoxic constituents of an Okinawan *Adocia* sp. that exhibit activity in an in vitro endothelial cell-neutrophil leukocyte adhesion assay.[8] A closely related compound, petrosynol **3**, was isolated from the Red Sea sponge *Petrocia* sp. and has been found to inhibit the reverse transcriptase of the human immunodeficiency virus (HIV).[4,5] Despite their biological activities, as far as we know, synthetic studies are limited to a few relatively simple members of the acetylenic alcohol family.[9–13] We wish to report the first synthesis of (*S*,*S*) and (*R*,*R*)-adociacetylene B.

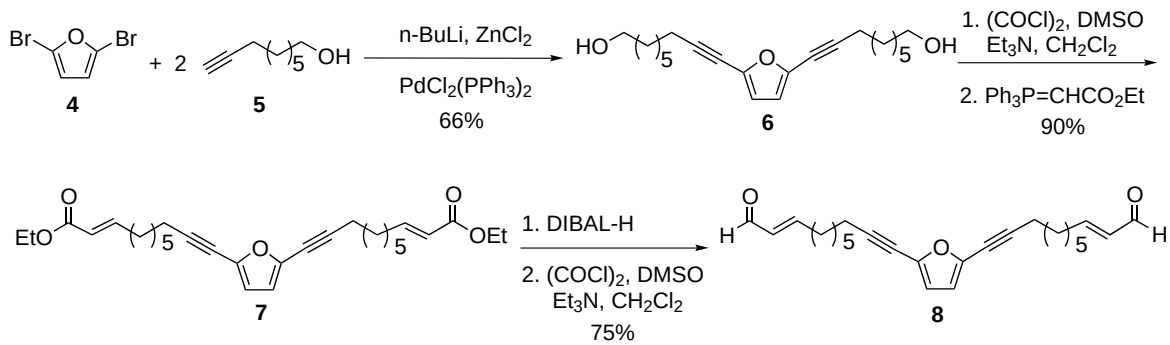


1 Adociacetylene B



2 Adociacetylene C: R = Ac
3 Petrosynol: R = H

Recent approaches to the synthesis of chiral acetylenic alcohols involve numerous functional group transformations. In contrast, our approach avoids using protecting groups limiting the number of steps (Scheme 1). A two-directional strategy is employed to take advan-



4 **5** **6** **7** **8**

Scheme 1.

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tage of the C_2 symmetry.[14,15] The starting materials are 2,5-dibromofuran **4** and 8-nonyn-1-ol **5**.

2,5-Dibromofuran was prepared according to a reported procedure[16] and used immediately following distillation. The terminal alkynol **5** (8-nonyn-1-ol) was prepared from 1-octyne through the addition of the alkynylide to paraformaldehyde followed by a 'zipper'[17,18] reaction of the resulting 2-nonyn-1-ol. The coupling of the terminal acetylene **5** with 2,5-dibromofuran **4** was first carried out using the Sonogashira-type reaction conditions, stirring a mixture of $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, and the two reactants.[19,20] Unfortunately the products from this coupling procedure were contaminated with inseparable impurities.

However, we were pleased to obtain the coupling product **6** in good yield under conditions reported by Negishi,[21] which involve metalation of the terminal acetylene followed by palladium-catalyzed coupling. Other studies also showed that such couplings involving aromatic bromides proceeded with higher yields when prior metalation of the terminal acetylene was performed.[22]

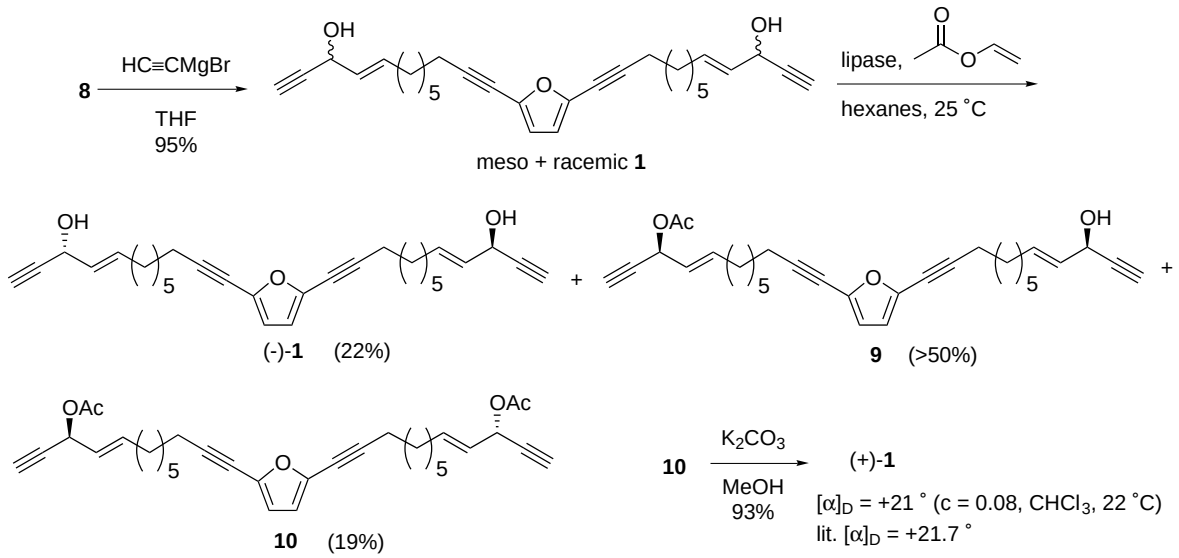
Swern[23] oxidation of the primary alcohol **6** followed by in situ Wittig reaction using an ester-stabilized ylide afforded the (*E*) isomer of the conjugated ester **7** as the major component of a 9:1 mixture. The minor (*Z*) isomer was not separated, but appeared to have isomerized to the (*E*) isomer after the Swern oxidation. The α,β-unsaturated aldehyde **8** was obtained through a diisobutylaluminum hydride (DIBAL-H) reduction of **7** followed by a Swern oxidation of the resulting alcohol.[23]

The next step is the introduction of the terminal acetylene group. Our initial plan involved using an asymmetric synthesis of the propargylic alcohols by an enantioselective addition of terminal alkynes to aldehydes. Carreira recently reported a procedure that involves stirring a mixture of a terminal alkyne and an aldehyde in the presence of $Zn(OTf)_2$, Et_3N and *N*-methylephedrine.[24] No prior metalation of the terminal alkyne is needed. If this method is successfully employed, the stereocenters and the terminal acetylene groups could be introduced in a single step.

As a model study, phenylacetylene was allowed to react with cyclohexanecarbaldehyde under the conditions reported by Carreira.[24] Excellent chemical and optical yields were obtained. With this result, we proceeded using triethylsilylacetylene as the reagent in the addition reaction with aldehyde **8**. Unfortunately, our attempts with $Et_3SiC{\equiv}CH$ were unsuccessful despite numerous trials with up to three-fold of reagents. The fact that phenylacetylene works and $Et_3SiC{\equiv}CH$ does not suggests that the procedure is sensitive to the structure of the terminal acetylene.

Next we turned our attention to enzymatic resolution. The racemic adociacetylene B was obtained along with the *meso* isomer by the addition of acetylenic magnesium bromide to aldehyde **8** (Scheme 2). In a study of enzymatic resolution of secondary alcohols by the lipases from *Pseudomonas* sp. Burgess proposed a simple active site model for predicting enantioselectivity.[25] This model predicts that alcohols resolved most efficiently have one small and one relatively large group attached to the hydroxylmethine functionality. Adociacetylenes appear to be good substrates for these lipases.

For most secondary alcohols, the rate of acylation is faster for the (*R*)-configuration than for the (*S*)-configuration. However, for the acetylenic alcohol **1** the opposite is true because the small acetylenic group has a higher priority in the nomenclature system. Kobayashi has assigned the natural adociacetylene B as possessing (*S*,*S*) configuration by using analogy to petrosynol **3**.[8] Therefore the naturally occurring enan-



Scheme 2.

tiomer of **1** should be acylated faster than the (*R*,*R*)-enantiomer. This was indeed observed in our experiments.

Kinetic resolution of racemic and *meso* **1** mediated by lipase AK from Amano was performed by stirring the propargyl alcohols in hexanes with half the mass of the enzyme and 4 equiv. of vinyl acetate. The reaction was monitored quantitatively by ^{1}H NMR, and qualitatively by TLC. The hydroxymethine proton is characteristic of the change between the starting material **1** and the mono-acylated product **9** and the diacetate **10**. Molecular sieves were added to remove traces of water in the enzyme mediated reaction. Workup of the reaction consisted of simple filtration, rotary evaporation and flash column separation of the diacetate **10** from the mono acetate **9** and the diol **1**.

When the amount of diacetate **10** was about the same as the diol **1**, the reaction was stopped. After separation, the diol was shown to have an $[\alpha]_D = -14$ to $-18°$ in several independent experiments. The absolute configuration for this diol was determined to be 3*R* and 28*R* by the ^{1}H NMR spectrum of its *O*-methyl mandelate ester derivative. The diacetate **10** was treated with K_2CO_3 in methanol to provide the diol, whose optical rotation was found to be $[\alpha]_D = +21°$. The *O*-methyl mandelate ester of diol (*S*,*S*)-**1** was also prepared and its absolute configuration is consistent with the assignment made by Kobayashi.[8] The reported optical rotation for natural adociacetylene B is $[\alpha]_D = +21.7°$. However, the ^{1}H NMR spectrum of the *O*-methyl mandelate ester of the synthetic diol (*S*,*S*)-**1** corresponds to approximately 90% ee.

In summary, the synthesis of adociacetylene B has been completed in seven steps. Although the enantioselective addition of $Et_3SiC{\equiv}CH$ to aldehyde **8** did not give any desirable product, an enzymatic resolution of racemic **1** using the lipase from *Pseudomonas* sp. turns out to be a convenient method of obtaining optically active acetylenic alcohols. This synthesis of (*S*,*S*)-**1** represents the first total synthesis of a naturally occurring acetylenic alcohol that has two chiral centers and four acetylene units.

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