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A Concise Synthesis of *R*-(–)-Cicutoxin, a Natural 17-Carbon Polyenyne

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A concise synthesis of the natural polyenyne *R*-(–)-cicutoxin (**1**) is described. After several trials, the successful synthesis commenced with three key fragments, *R*-(–)-1-hexyn-3-ol (**8**), 1,4-diiodo-1,3-butadiene (**9**), and THP-protected 4,6-heptadiyn-1-ol (**6**). Sonogashira coupling of compound **9** with acetylenes **6** and **8** gave the 17-carbon frame, which upon regioselective reduction of a triple bond with Red-Al and removal of the THP protecting group afforded the natural product in four linear steps. The triply convergent synthesis gave *R*-(–)-cicutoxin in 18% overall yield.

Introduction

Cicutoxin (**1**, Figure 1), a major toxic component of water hemlock (*Cicuta virosa* and *Cicuta maculate*),[1–3] belongs to the class of C_{17}-polyacetylenes bearing a long π-bond conjugation system. Cicutoxin is known to have lethal toxicity to the central nervous system, causing respiratory paralysis and death. The most recent report of fatal poisoning was in 2001, when a native North American boy died after ingesting a carrot-like plant containing cicutoxin.[4] The natural poison was isolated in 1915[5] and its structure was first reported in 1953;[6] its absolute configuration was identified in 1999 along with its congeners virol A (**2**) and C (**3**).[1]

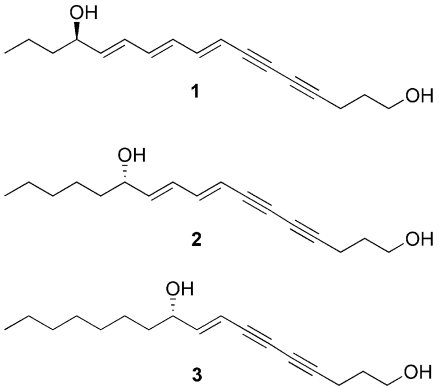

Figure 1. The structure of *R*-(–)-cicutoxin (**1**) and its congeners virol A (**2**) and C (**3**) from *Cicuta virosa* and *Cicuta maculate*.

Cicutoxin (**1**, Figure 1) and its congeners virol A (**2**) and C (**3**) are chemically and biologically interesting polyacetylenic alcohols not only for the acute toxicity displayed by cicutoxin, but also for its potent antileukemic activity.[2,3] These interesting biological properties have prompted several total syntheses of virols A (**2**) and C (**3**).[7–10] However, the only synthetic study on cicutoxin (**1**) itself was reported in 1955 by Trippett and coworkers.[11] As a result of its extended unsaturation conjugation and a smaller end capping group, cicutoxin is considerably more labile than its congeners. Despite the low yield in the final step (≈4%), it was a significant accomplishment that the group of Trippett was able to synthesize the racemic cicutoxin without the benefit of modern coupling reactions.[11] The more recent syntheses of virols took advantage of either Cadiot–Chodkiewicz[12] or Sonogashira coupling reactions.[13] Despite being equipped with these modern techniques, no enantioselective synthesis of cicutoxin has been reported. As previously reported,[14,15] polyacetylenic compounds are sensitive to light and air and in general are very reactive in nature. It is reasonable to assume that the reactive characteristics of cicutoxin have prevented a stereoselective total synthesis of this astonishing natural toxin.

Results and Discussion

Our interest in the total synthesis of biologically active acetylenic alcohols prompted us to tackle this challenging problem. Recently, we completed the total syntheses of several polyacetylenic natural products including adociacetylene, minquartynoic acids, bidensyneosides, duryne, and dideoxypetrosynol.[16–21] On the basis of our experience in this area, we planned our first attempt by using known compounds **4** and **6** to construct the extended conjugation system as shown in Scheme 1.

Known trienol **4**,[22] which was first synthesized by the group of Linstrumelle from the commercially available starting materials propargyl alcohol and 1,2-*trans*-dichloroethene, was subjected to a one-pot Swern oxidation–Grignard addition reaction to produce the left half of target

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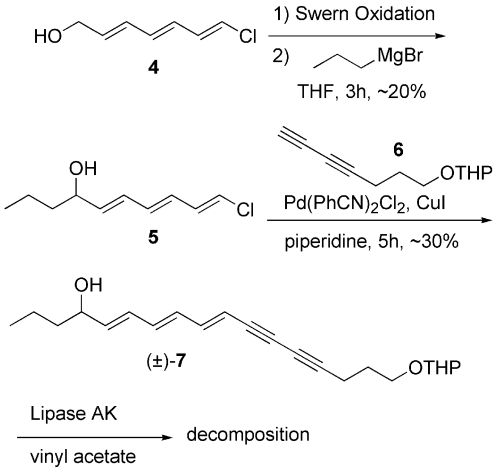
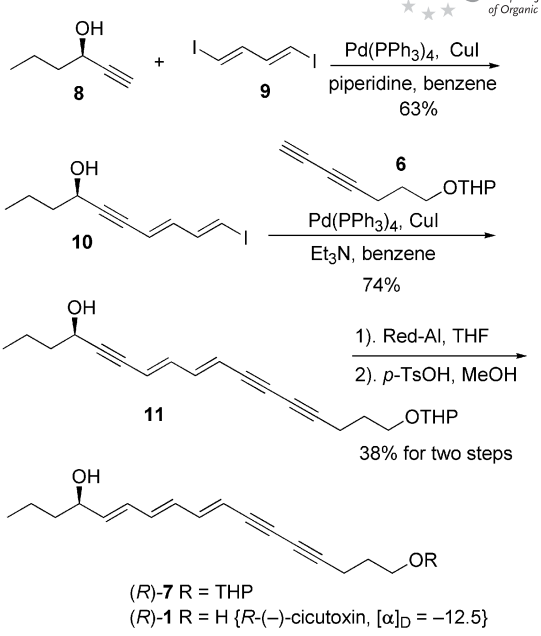


Scheme 1. Initial attempt at kinetic resolution for access to enantioenriched cicutoxin.



Scheme 2. Triply convergent synthesis of *R*-(–)-cicutoxin.

5.[23] This procedure usually tolerates reactive carbonyl compounds,[23] but only gave an average of 20% yield in this case. Trienol compound **4** cannot be stored for long periods of time, as it is not even stable when stored in a freezer. With limited supply of compound **5**, a cross-coupling reaction was performed with the known tetrahydropyranyl (THP) ether protected diynol **6**, first reported by the group of Oshima.[7] This afforded the racemic 17-carbon frame of cicutoxin with the primary alcohol protected as tetrahydropyran ether **7**. Attempted kinetic resolution of racemic secondary alcohol **7** by using lipase AK[24] resulted only in decomposition of the starting material. The three reactions shown in Scheme 1 suffered from either low yields or complete decomposition. On the basis of our experience in the synthesis of polyyne natural products, we felt that an alternate route to enantioenriched cicutoxin would be to assemble the extended conjugation system at a later stage.

Although the first attempt failed to yield the enantiomerically enriched cicutoxin, valuable lessons were learned. This led to the decision that all difficult reactions should be done before the assembly of the conjugation system. Therefore, the stereocenter should be prepared in a fragment before the final assembly. The improved plan is shown in Scheme 2.

Enantiomerically pure (*R*)-1-hexyn-3-ol (**8**, $[\alpha]_D$ = +16.9, *c* = 0.32) is a known compound and was obtained by Corey–Bakshi–Shibata reduction of 1-hexyn-3-one.[25,26] Known 1,4-diiodo-1,3-butadiene (**9**) is a very useful compound for Suzuki coupling to unsaturated systems,[27] yet it has received little attention. Compound **9** is readily available by dimerization of acetylene accompanied by addition of iodine in the presence of a platinum(IV) catalyst and sodium iodide.[28] Sonogashira coupling between **8** and **9** afforded dienynol **10** in 63% yield.[13] A second palladium-catalyzed coupling reaction under slightly different conditions provided 17-carbon frame **11** with the stereocenter already in place. The only structural changes needed were reduction of the triple bond at C5 and removal of the THP protecting group. Regioselective reduction of the C5 triple bond in compound **11** to the corresponding double bond [(*R*)-**7**] was accomplished by using Red-Al. Removal of the THP protecting group then gave enantioenriched (*R*)-(–)-cicutoxin (**1**). Nonregioselective reduction was observed when the THP protecting group was removed before Red-Al reduction. The optical rotation of the synthetic sample is $[\alpha]_D$ = –12.5 (*c* = 0.02, EtOH) {ref.[3] $[\alpha]_D$ = –11.8 (*c* = 0.55, EtOH) and ref.[1] $[\alpha]_D$ = –14.9 (*c* = 1.12, MeOH)}. The IR and ^{1}H and ^{13}C NMR spectra, in addition to the MS data, are consistent with reported data, although samples sent for HRMS analysis suffered decomposition.

Conclusions

In summary, we have completed a concise synthesis of the natural product (*R*)-(–)-cicutoxin by adopting a strategy to manage the lability of the target compound. This synthesis took only four linear steps from the known starting materials and was triply convergent. (*R*)-(–)-Cicutoxin was synthesized in 18% overall yield. Currently we are planning to use this general strategy for the total synthesis of more challenging natural products.

Supporting Information (see footnote on the first page of this article): Experimental details, ^{1}H and ^{13}C NMR and IR spectra for compounds **1**, (*R*)-**7**, **10**, and **11**.

Acknowledgments

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