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

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Abstract

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 the 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 regio-selective 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.

Keywords

Total synthesis; antileukemic; natural product; cicutoxin

Introduction

Cicutoxin (Figure 1), a major toxic component of water hemlock (*Cicuta virosa* and *Cicuta maculate*),^[1–3] belongs to the class of C₁₇-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. 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] This legacy natural poison was isolated in 1915^[5] and its structure was first reported in 1953,^[6] and its absolute configuration was identified in 1999 along with its congeners virol A (**2**) and C (**3**).^[1]

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 synthesis 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 co-workers.^[11] Due to its extended conjugation of unsaturation 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 Trippett's group 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] Based on our experience in this area, we planned our first attempt using two known compounds (**4** and **6**) to construct the extended conjugation system as shown in Scheme 1.

The known trienol **4**,^[22] which was first synthesized by Linstrumelle's group 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 the target (**5**).^[23] This procedure usually tolerates reactive carbonyl compounds,^[23] but only gave an average of 20% yield in this case. The trienol compound **4** is not stable for long storage even 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 Oshima's group.^[7] This afforded the racemic 17-carbon frame of cicutoxin with the primary alcohol protected as a tetrahydropyran ether **7**. Attempted kinetic resolution of the racemic secondary alcohol **7** using lipase AK^[24] resulted only in decomposition of the starting material. The three reactions shown in Scheme 1 suffered from either low yielding or complete decomposition. Based on our experience in the synthesis of polyene natural products, we felt that an alternate route to enantioenriched cicutoxin should 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.

The enantiomerically pure (*R*)-1-hexyn-3-ol (**8**, [α]_D +16.9, *c* 0.32) is a known compound and is obtained from a Corey-Bakshi-Shibata reduction of 1-hexyn-3-one.^[25, 26] The known 1,4-diiodo-1,3-butadiene (**9**) is a very useful compound for Suzuki coupling reaction 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] A Sonogashira coupling between **8** and **9** afforded the diynol **10** in 63% yield.^[13] A second palladium-catalyzed coupling under a slightly different condition provided the 17-carbon frame **11** with the stereocenter already in place. The only structural changes needed were a reduction of the triple bond at C5 and removal of the THP protecting group. A regioselective reduction of the C5 triple bond in compound **11** to the corresponding double bond ((*R*)-**7**) was accomplished using Red-Al. The removal of the THP protecting group then gave the enantioenriched (*R*)-(-)-cicutoxin **1**. Non-regioselective reduction was observed when the THP protecting group was removed before the Red-Al reduction. The optical rotation of the synthetic sample is [α]_D -12.5 (*c* 0.02, EtOH), lit. [α]_D -11.8 (*c* 0.55, EtOH),^[3] and [α]_D -14.9 (*c* 1.12, MeOH).^[1] The IR, MS, ¹H, and ¹³C spectra are consistent with the 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 labiality of the target compound. This synthesis took only four linear steps from the known starting materials and was triply convergent. The (*R*)-(-)-cicutoxin was synthesized in an 18% overall yield. Currently we are planning to use this general strategy to the total synthesis of more challenging natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Scheme 1.

Initial attempt of using kinetic resolution to access enantioenriched cicutoxin.

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