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Total Synthesis of Aquatolide

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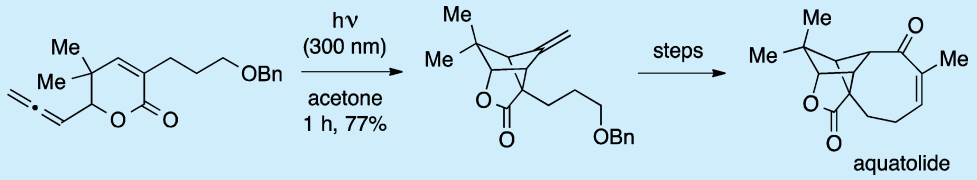
Supporting Information



ABSTRACT: A total synthesis of the sesquiterpene lactone aquatolide has been accomplished. The central step is an intramolecular [2 + 2]-photocycloaddition of an allene onto an α,β-unsaturated δ-lactone. Other key steps are an intramolecular Horner−Wadsworth−Emmons reaction to close the lactone and an intramolecular Mukaiyama-type aldol reaction to cyclize the eight-membered ring. Racemic aquatolide has been resolved using preparative HPLC.

Aquatolide is a natural product isolated from *Asteriscus aquaticus*, a plant of the Compositae family with yellow flowers that is native to the Mediterranean countries. San Feliciano et al. published its isolation and structure determination as **1** on the basis of spectroscopy in 1989 (see Figure 1).[1] This sesquiterpene lactone featured a very rare

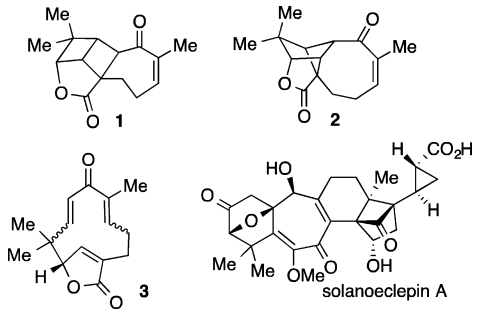


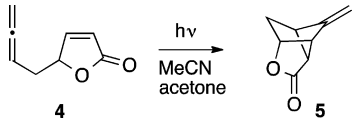
Figure 1. Structures of reported natural products **1**-**3** from *Asteriscus aquaticus*, and solanoeclepin A.

ladderane substructure. Recently, Tantillo and co-workers reinvestigated the compound because of serious doubts about structure **1** on the basis of quantum-chemical NMR calculations.[2] After reisolation of the natural product and an X-ray crystallographic study, the structure was revised to **2**, an isomer of **1**.[2]

There is an interesting relationship between structures **1** and **2** as they are in principle the straight and crossed [2 + 2]-photocycloaddition products from the asteriscunolides (**3**), of which all four geometric isomers also occur in the same plant.[3] These interesting butenolides bridged with a large ring have been found to have anticancer activity,[4] and two of the isomers, asteriscunolide C and D, have been prepared by total synthesis.[5] However, we do not know whether photochemical [2 + 2]-cycloadditions of these compounds were ever studied.

The real structure of aquatolide (**2**) caught our attention because we recently developed a synthesis of bicyclic lactones of type **5** through irradiation of allenic butenolides of type **4** (Scheme 1).[6] This latter research is related to our work on a

Scheme 1. Synthetic Approach to the Aquatolide Core



synthetic approach toward the potato cyst hatching agent solanoeclepin A (Figure 1),[7] which also contains the rare bicyclo[2.1.1]hexane skeleton as present in **2**.

We were curious whether this methodology could provide a useful synthetic route to **2** using **6** as a crucial intermediate (Scheme 2). In principle, tricyclic lactone **6** can be accessed through a photochemical [2 + 2]-cycloaddition from two different allenic lactones, namely butenolide **7** and pentenolide **8**. In this paper, we present a total synthesis of aquatolide **2**, which proceeds via pentenolide **8**.

Our first synthetic target was thus pentenolide **8** in which the R group should allow facile closure of the eight-membered ring in the final stages of the total synthesis. The allene was expected to be readily accessible from the alkyne through a Crabbé reaction. Therefore, for the construction of **8** the aldol product **9** and some derivative of acid **10** were deemed suitable starting materials.

The synthesis started with the crossed-aldol reaction between propynal and isobutyraldehyde (see Scheme 3). After much experimentation, it appeared that the conditions developed by Oshima[8] gave the best results. A mixture of KOtBu and

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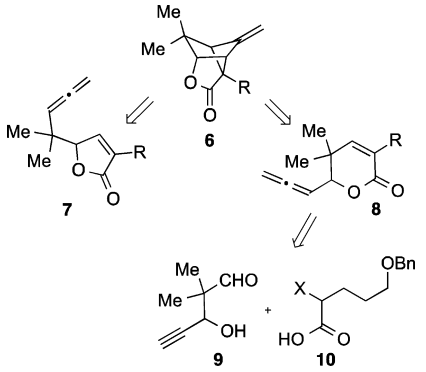
Scheme 2. Retrosynthetic Modes of the Aquatolide Core

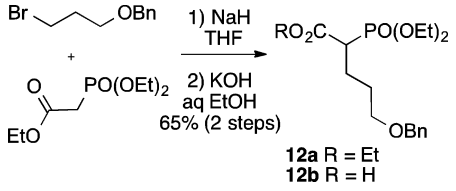


$Ti(OiPr)_4$ effected the desired aldol coupling, but the product aldehyde isolated after acidic workup appeared rather unstable. It was therefore immediately converted, by using trimethyl orthoformate and catalytic *p*-TsOH, into its methyl acetal **11**, which was stable enough for chromatographic purification.[9]

Alcohol **11** was then esterified with acid **10** (X = H),[10] but all attempts to cyclize the resulting ester under basic conditions failed. We then decided to examine a Horner–Wadsworth–Emmons-type cyclization to arrive at the pentenolide **8**. Thus, alcohol **11** was esterified with the phosphonate containing acid **12b**, which was readily synthesized as shown in Scheme 4. The resulting ester **13** was then subjected to excess sodium hydride under dilute conditions which caused the desired cyclization to pentenolide **14** in satisfactory yield. Finally, the acetylene was readily converted into the allene **15** using the Crabbé homologation.[11] This product showed characteristic double bond protons in the ^{1}H NMR spectrum at 6.29 ppm (ring C4 proton), at 5.22 ppm for the internal allene proton, and at 4.83–4.96 ppm for the two terminal allene protons. In the IR spectrum the allene appeared at 1958 cm^{-1} and the unsaturated lactone carbonyl at 1719 cm^{-1}.

With the substrate **15** in hand, the key photochemical [2 + 2]-cycloaddition was investigated. Irradiation of **15** in a degassed mixture of acetonitrile/acetone 9:1 with 300 nm light led to full conversion into a new product within 3 h (see Scheme 5). In neat acetone, the reaction was complete in 1 h, and a pure product was obtained in 77% yield after chromatographic purification. The lactone carbonyl now resonated at 1771 cm^{-1}, indicative of a saturated γ-lactone.[12] The two remaining double-bond protons now appeared in the NMR spectrum as singlets at 4.71 and 4.70 ppm. These spectral data were sufficient evidence that the photochemical reaction provided the desired product **16**.

Scheme 4. Synthesis of the Phosphonate

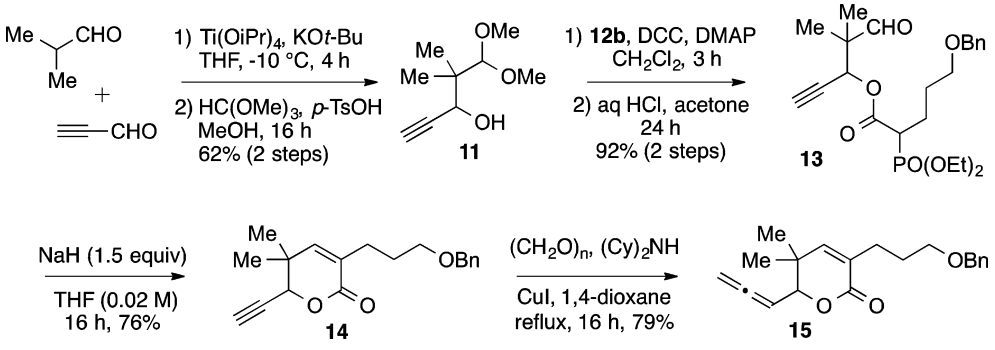


To construct the requisite eight-membered ring, alkene **16** was first subjected to hydroboration. This addition reaction proved to be very slow, indicating considerable steric hindrance. It appeared that 6 equiv of the BH_3·THF complex was required to obtain a reasonable yield (36%) of a pure product after oxidation of the borane adduct. Much to our satisfaction, NOE measurements proved the desired relative configuration of **17**, as strong NOE effects were observed between one of the methyl groups at 1.21 ppm and the newly introduced proton in the hydroboration at 2.49 ppm (the other methyl group at 1.05 ppm did not show this NOE effect). One reason for the disappointing yield of **17** was probably competitive reduction of the lactone carbonyl group.[13]

The final part of the total synthesis was determined by the choice for the intramolecular Mukaiyama-type aldol reaction to cyclize the eight-membered ring as pioneered by Kocienski.[14] Alcohol **17** was oxidized to the aldehyde by using Dess–Martin periodinane (DMP). The aldehyde was then treated with ethylmagnesium bromide to give a 58:42 mixture of secondary alcohols, which was not purified but directly subjected to hydrogenolysis. The crude product was oxidized with excess DMP to finally produce ketoaldehyde **18** as a single product in 49% yield over four steps.

The aldehyde **18** was then chemoselectively converted into methyl acetal **19** in 81% yield under the influence of cerium(III) chloride as developed by Luche and Gemal.[15] Regioselective enolate silylation proceeded cleanly, and the crude silyl enol ether was directly subjected to cationic cyclization caused by BF_3·OEt_2 to provide a mixture of stereoisomers. This crude mixture was refluxed in toluene in the presence of *p*-toluenesulfonic acid, which furnished a single crystalline product (mp 148–149 °C) in 59% yield over the last three steps. Both the ^{1}H and the ^{13}C NMR spectra of our racemic material were identical to those published by Tantillo[2] for natural aquatolide (see the full comparison of chemical shifts in the Supporting Information). The racemate was resolved on preparative HPLC to provide the pure enantiomers, which showed $[\alpha]_D$ values of +27.7 and −29.0 (c = 1, $CHCl_3$) and mp 180–182 °C, identical for both

Scheme 3. Synthesis of the Substrate for the Photochemical [2 + 2]-Cycloaddition



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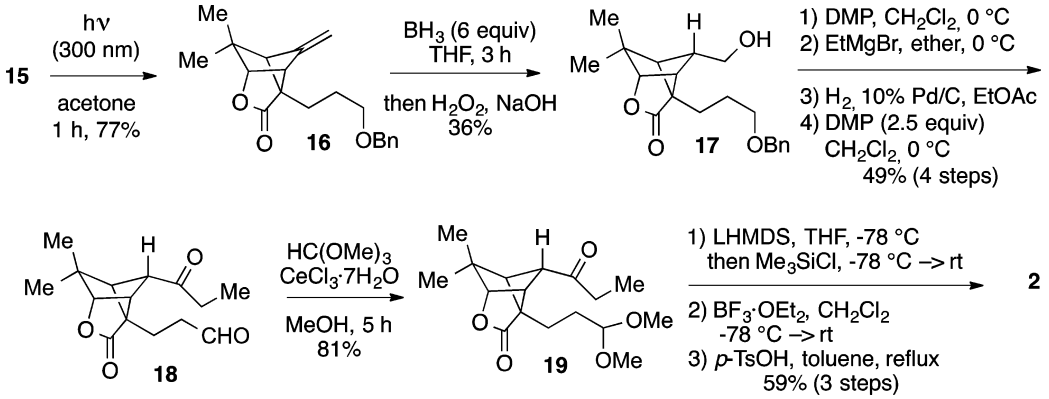
Scheme 5. Photochemical [2 + 2]-Cycloaddition and Completion of the Total Synthesis of Aquatolide



enantiomers (literature data for the natural product: $[\alpha]_D$ +29.2 (c = 0.05, $CHCl_3$), mp 175−176 °C).[2]

In conclusion, we report here the total synthesis of racemic aquatolide in a total of 16 steps (longest linear chain) in 2.2% overall yield. The synthesis shows the power of photochemistry to construct strained cyclic structures,[16] although the approach chosen here is different from the probable biosynthetic route from **3**. Other noteworthy steps in the present synthesis are two cyclization processes, namely the Horner−Wadsworth−Emmons reaction of **13** to access the δ-lactone and the Mukaiyama aldol condensation of **19** to close the eight-membered ring. Our present work is directed at an enantioselective synthesis of aquatolide.

■ ASSOCIATED CONTENT

Supporting Information

General experimental remarks and procedures; comparison of the NMR data of our synthetic aquatolide and the literature data on the natural product; copies of the NMR spectra of the products; copies of the chromatograms of the HPLC resolution of racemic aquatolide. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01888.

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Notes

The authors declare no competing financial interest.

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