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Synthesis of the Core Structure of Cruentaren A

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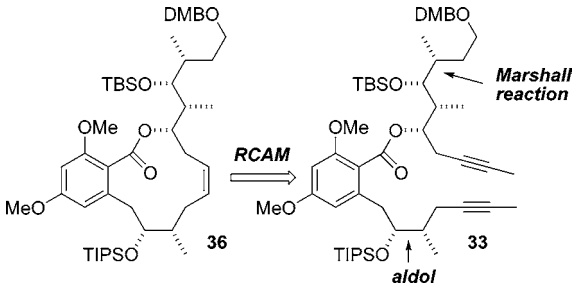
ABSTRACT



The core structure of the macrolactone cruentaren A (1) was prepared via a ring-closing alkyne metathesis reaction. The corresponding ester 33 was constructed from the benzoic acid derivative 14 and the diol 30. As a key step in the synthesis of acid 14, an aldol reaction resulted in the required *anti*-OH/Me pattern. The *anti*-configuration in the stereotetrad of diol 30 was established by a Marshall reaction.

The macrolide cruentaren A (**1**) is a highly cytotoxic and antifungal natural product which was isolated by the Höfle group from the myxobacterium *Byssovorax cruenta* (Figure 1).[1] With an IC_{50} value of 1.2 ng mL^{-1} against the L929

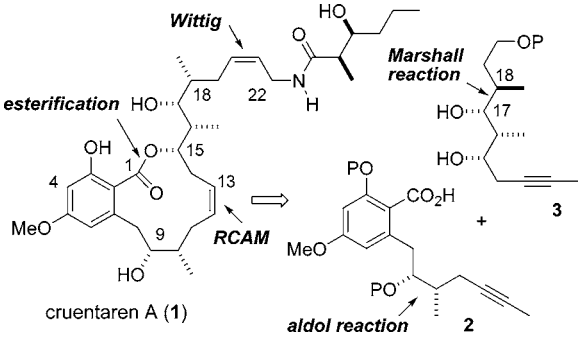


Figure 1. Structure of cruentaren A (**1**) and key disconnections.

cell line, it is among the most cytotoxic compounds found in myxobacteria. Structurally, it resembles the benzolactone enamides, such as apicularen A[2] and salicylihalamide A.[3,4] Initially, cruentaren A was patented as a pesticide,[5] but in the meantime it turned out that it is an inhibitor of mitochondrial F-ATPase from yeast.[6] Interestingly, it does not inhibit V-ATPase, which is the molecular target of the benzolactone enamides.[7] One might speculate that the allylamine rearranges to an enamide, thus generating a precursor for an electrophilic acyliminium ion. One should mention that the allyl amide function is found in other natural products such as leucascandrolide A[8] or ajudazol A.[9]

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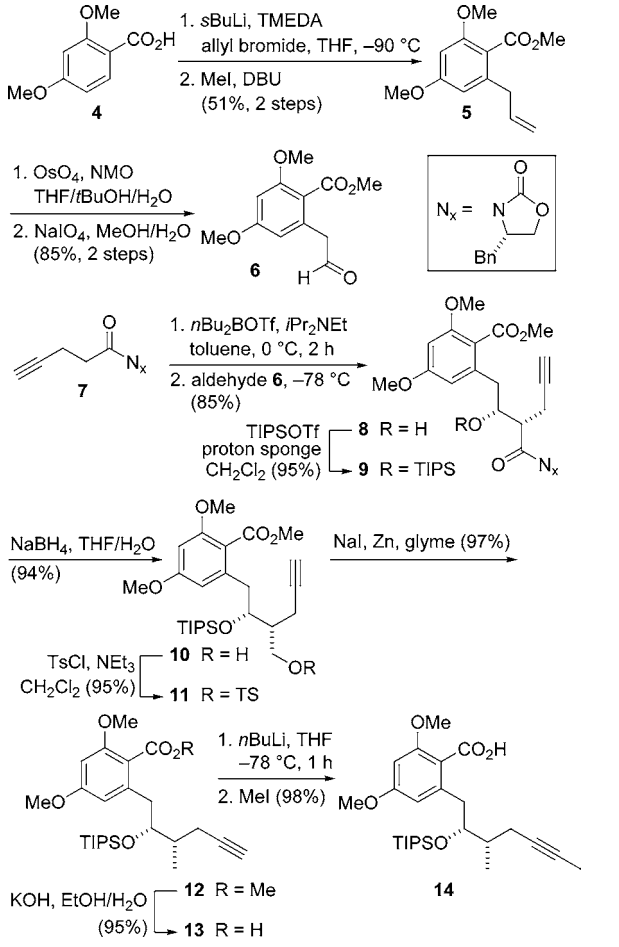
Because of its novel structure and interesting mode of action, we initiated a program aimed at the synthesis of cruentaren A and analogues thereof. The synthetic scheme must address the formation of the stereotetrad that extends into the side chain.[10] In addition, connection of the aryl part with the aliphatic sector poses a certain challenge. Most importantly, the propensity of cruentaren A to rearrange to a less active six-membered lactone (cruentaren B) under acidic or basic conditions has to be considered. A retrosynthetic analysis is shown in Figure 1. Thus, the *Z*-configured allylamine could be fashioned by a Wittig reaction or reduction of a triple bond. As a key step for macrolactone formation, a ring-closing alkyne metathesis (RCAM) followed by Lindlar reduction was deemed appropriate.[11] Of course, classical macrolactonization strategies (Yamaguchi, Mitsunobu) might also be considered.[12] The stereocenters at C9 and C10 could be derived from the product of an aldol reaction. As a key step in the synthesis of a fragment of type **3** containing the stereotetrad, a Marshall reaction was envisioned to fashion the *anti*-configuration at C17/C18. In this paper, we illustrate the synthesis of the core structure of cruentaren A based on these key bond-forming reactions.

The synthesis of a benzoic acid building block corresponding to structure **2** was started with 2,4-dimethoxybenzoic acid (**4**), which was allylated[13] via the dianion followed by esterification (Scheme 1). Degradation of the terminal double bond to an aldehyde function was achieved by a dihydroxylation/periodate cleavage sequence in good overall yield.[14] Aldehyde **6** was combined with pentynyloxazolidinone **7** via an Evans aldol reaction using the standard boron enolate.[15] Protection of the secondary hydroxyl function of aldol product **8** as a triisopropylsilyl ether using TIPS triflate and proton sponge as base[16] followed by reductive cleavage of the chiral auxiliary produced the primary alcohol **10**. Conversion of the primary alcohol to the corresponding methyl group was achieved by tosylation of the alcohol and treatment of the intermediate tosylate **11** with zinc/sodium iodide.[17] After saponification of the methyl ester **12**, the obtained alkynoic acid **13** was converted to the dianion which was alkylated at the acetylide using MeI. This way, the acid **14** containing an internal alkyne required for the alkyne metathesis could be obtained in a concise manner.

As a key step for creation of the stereotetrad of fragment **3**, a Marshall reaction[18,19] of the known aldehyde[20] **16** with

Scheme 1. Synthesis of the Functionalized Benzoic Acid **14**



propargylic mesylate (*S*)-**17** came to use. This transformation to alkyne **18** proceeded with excellent diastereoselectivity (22:1) and good chemical yield (Scheme 2). After silyl protection of the hydroxyl function, the triple bond of **19** was hydroborated with Cy_2BH. The vinylborane intermediate was in situ oxidized to aldehyde **20**.[21] Reduction of the aldehyde gave primary alcohol **21**, which was protected using 3,4-dimethoxybenzyltrichloroacetimidate leading to ether **22** in excellent yield.[22] Cleavage of the acetonide moiety under mild conditions ($CuCl_2 \cdot 2H_2O$, acetonitrile, −5 °C) afforded diol **23**.[23] Other attempts to cleave the acetal of **22** (AcOH in THF at 50 °C, TFA in CH_2Cl_2, $FeCl_3/SiO_2$ in $CHCl_3$) were

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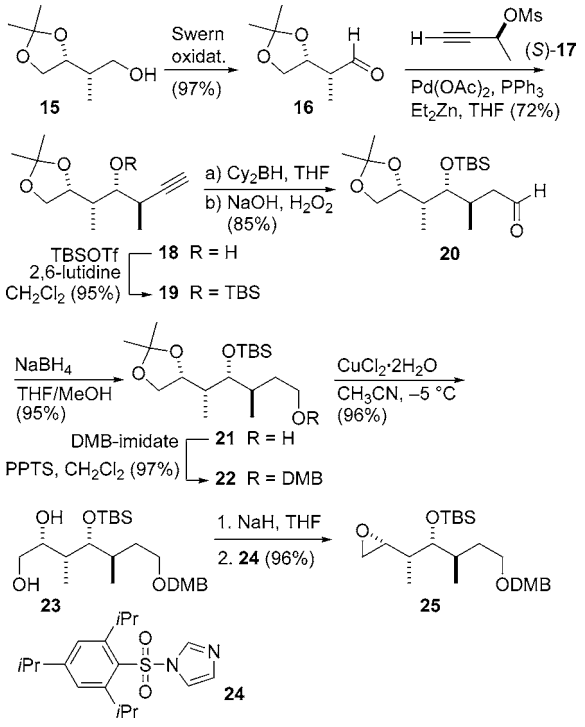
Scheme 2. Synthesis of the Epoxide Building Block **25**[a]

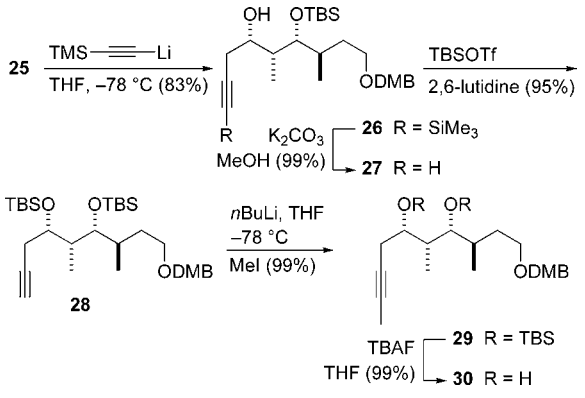


[a] DMB = 3,4-dimethoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl.

unsuccessful. To prepare for the introduction of the alkyne function, diol **23** was converted to the epoxide **25** using a one-pot procedure.[24]

Opening of epoxide **25** with lithium trimethylsilylacetylide resulted in formation of alcohol **26** (Scheme 3). Cleavage

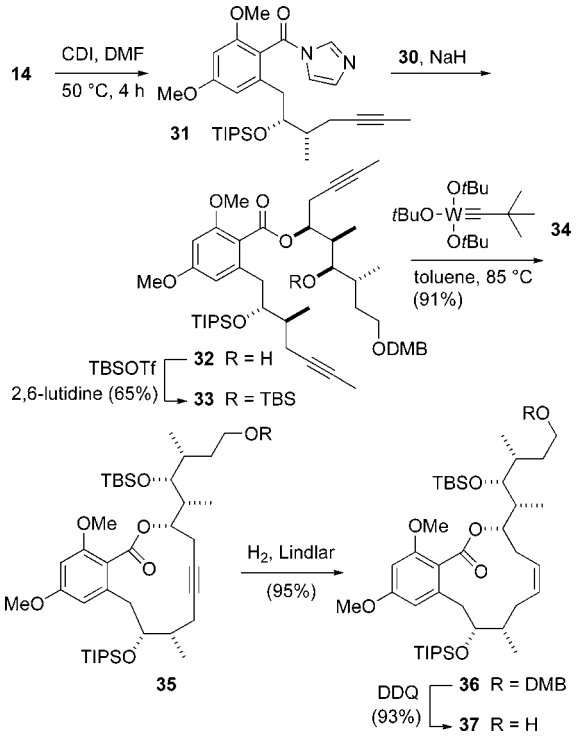
Scheme 3. Synthesis of Diol **30** from Epoxide **25**



of the carbon−silicon bond and protection of the hydroxyl function with TBSOTf afforded alkyne **28**, which then could be methylated to give propyne deriviative **29**. A final treatment of the bis-silyl ether **29** with TBAF furnished diol **30** in excellent yield.

Formation of an ester bond between acid **14** and diol **30** or a monoprotected derivative thereof turned out to be rather difficult. Using standard Mitsunobu,[25] Yamaguchi,[26] or Trost[27] esterification, no trace of product was observed. Also, attempts to make the desired ester using peptide coupling reagents like DCC/DMAP or BOP were not successful. Another option for esterification of sterically hindered acids and alcohols relies on the reaction of an acid chloride with a sodium alcoholate. However, attempted conversion of acid **14** to the coresponding acid chloride was not possible. Instead, formation of the six-membered lactone was observed. Eventually, we found that the desired ester **32** could be obtained by reaction of the imidazolidine derivative[28,29] of acid **14** with the putative disodium alcoholate of diol **30**, prepared by stirring the diol with 2.5 equiv of NaH in DMF (Scheme 4). This reaction resulted in formation of only one

Scheme 4. Formation of Ester **33** and Its Ring-Closing Alkyne Metathesis Reaction To Give Macrolactone **37**



regioisomer. The obtained hydroxy ester **32** was protected as the TBS ether to give **33** in 65% overall yield. At this stage, the regiochemistry of the ester formation could be inferred from the COSY spectrum of ester **33**. Most revealing

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in this context were cross-peaks of the ester methine hydrogen to the vicinal methylene hydrogen atoms. The crucial RCAM reaction of ester **33** proceeded smoothly and resulted in the formation of macrolactone **35** in 91% yield. Thus, addition of the tungsten carbine complex[30] **34** to a solution of the diyne **33** (0.009 M in toluene) and stirring the mixture for 2 h induced an efficient cyclization.[11,31] Creation of the *Z*-double bond was achieved using Lindlar reduction[32] (H_2, Pd on $CaCO_3$, poisoned with lead, EtOAc/quinoline) on the alkyne **35** leading to lactone **36**. Under these conditions, no overreduction was observed. Finally, deprotection of the DMB group with DDQ led to macrolactone **37**, the core structure of cruentaren A.

In summary, we illustrate an efficient route to the 12-membered macrolactone **37** which corresponds to the core structure of the novel macrolide cruentaren A. Key features of the synthesis of the building blocks include an aldol reaction to fashion the *anti*-OH/Me pattern at C9/C10 and a Marshall reaction of aldehyde **16** with the allenyl zinc reagent derived from mesylate **17**, which established the stereotetrad at C15−C18. As a further key reaction a RCAM reaction of ester **33** was used. The presented strategy should allow for the synthesis of the natural products as well as analogues for SAR studies.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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