Natural Product Synthesis

DOI: 10.1002/ange.200701423

Total Synthesis of Cruentaren A**

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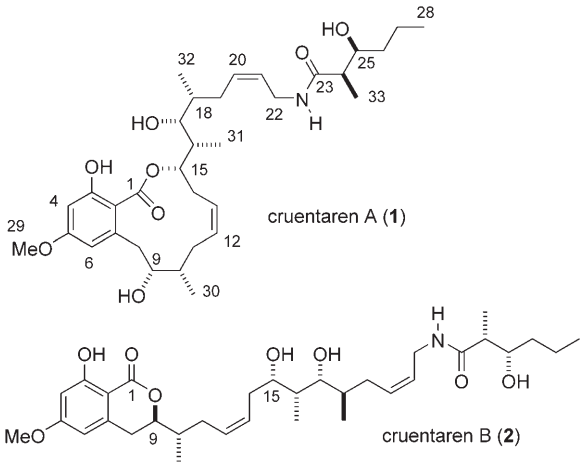
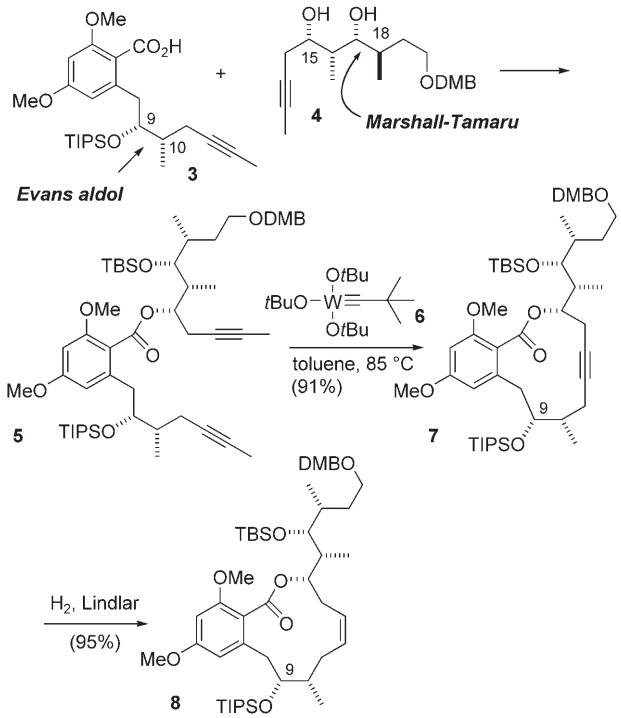
Among the many benzolactones,[1] the recently described cruentaren A[2] (**1**) stands out because of its unique structural features and novel mode of action (Scheme 1). It has



Scheme 1. Structures of cruentaren A (**1**) and cruentaren B (**2**).

transpired that **1** is an inhibitor of mitochondrial F-ATPase from yeast.[3] Cruentaren A shows strong cytotoxicity against the L929 cell line with an IC_{50} value of 1.2 ng mL^{-1}. With its 12-membered macrolactone and a side chain that is terminated with an acylated amino function, cruentaren A has some resemblance to the well-known benzolactone enamides.[4] However, in contrast to cruentaren A, the benzolactone enamides target V-ATPase.[5] Clearly, it would be of interest to identify key structural elements that are essential for the biological activity of cruentaren A. Another unique feature of cruentaren A is the intramolecular hydrogen bond between the 3-OH group and the carboxy function. This might arise from the *Z*-configured double bond in the ring; in other benzolactones, the carbonyl function is commonly more or less orthogonal to the aromatic ring. Besides cruentaren A (270 mg), a small amount (7 mg) of a structural isomer termed cruentaren B (**2**) was isolated from the crude extract (10 g). However, this δ-lactone isomer of cruentaren A turned out to be essentially inactive.

In a previous report we described the synthesis of the core structure **8** of cruentaren A.[6] The macrolactone ring **7** was fashioned by a ring-closing alkyne metathesis reaction[7,8] of the dialkyne substrate **5** using the Schrock catalyst[9] **6** (Scheme 2). A subsequent Lindlar reduction of the triple



Scheme 2. Key steps in the synthesis of the macrolactone core **8** of cruentaren A. DMB = dimethoxybenzyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

bond led to the macrolactone core **8** of cruentaren A. The ester **5** originated from the two building blocks **3** and **4** by reaction of the imidazolidine derivative of acid **3** with the sodium alcoholate of **4**. The two stereocenters in the benzoic acid **3** were created by an Evans aldol reaction.[10,11] A key step in the synthesis of the alkynol **4** was a Marshall–Tamaru reaction[12,13] between an aldehyde and an allenylzinc species,

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[**] Financial support from the Deutsche Forschungsgemeinschaft (grant Ma 1012/20-1) and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Frank Lay (Institute of Organic Chemistry) for important model studies. We also thank the research group of Stefan Berger, University of Leipzig, for measuring the HRMS spectra. We also thank Paul Schuler (Institute of Organic Chemistry) for measuring several NMR spectra (600 MHz) of cruentaren A. Skilful assistance by Marcellino Calá and Vaidotas Navickas (Institute of Organic Chemistry) is also acknowledged. A graduate fellowship for V.V.V. from the state Baden-Württemberg (LGFG) is gratefully acknowledged.

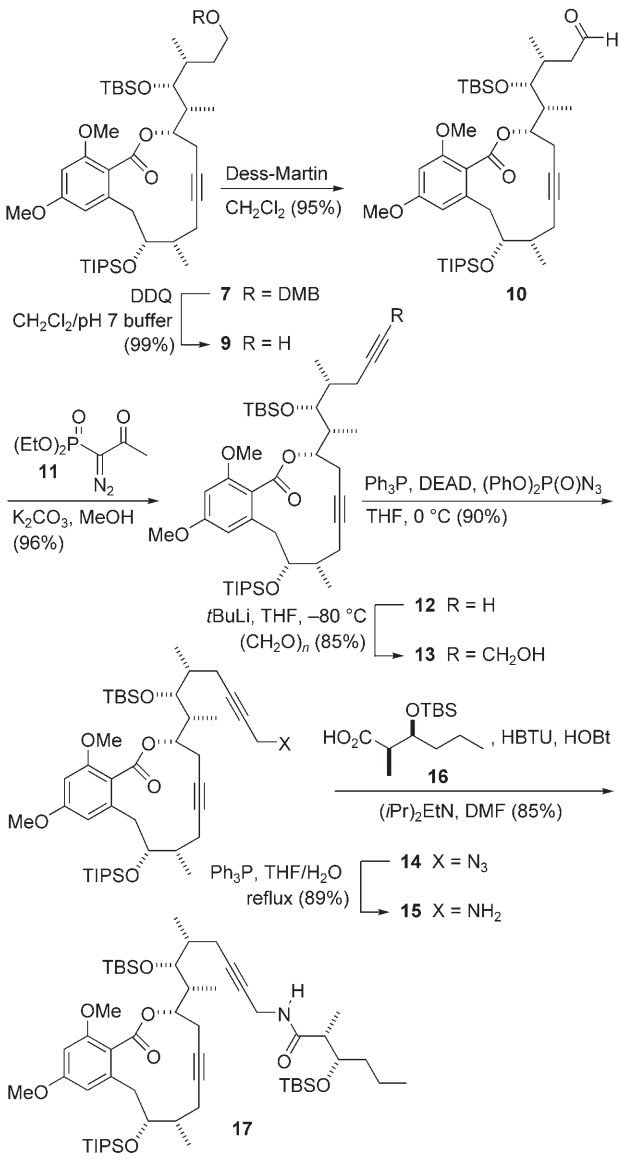
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

generated in situ from a chiral mesylate. The acetylide function in diol **4** was introduced through an epoxide-opening reaction.

Several challenges and potential pitfalls had to be faced before lactones **7** and **8**, respectively, could be used for the synthesis of cruentaren A. First, the problem of the extension of the side chain to a (*Z*)-allylamine or propargylamine had to be addressed. Second, a selective cleavage of the methyl ether adjacent to the carboxyl function would be necessary. A third, and probably the most important, challenge relates to the cleavage of the TIPS ether at C-9. The hydroxy function at C-9 was intentionally protected as a rather robust TIPS ether that would survive the ester hydrolysis during the course of the synthesis of acid **3** and prevent unwanted formation of a δ-lactone from the activated acid. While this was indeed the case, preliminary attempts to cleave the silicon protecting groups on a derivative of lactone **8** with the HF·pyridine complex unfortunately led to the corresponding δ-lactone.[14] As a way out of this dilemma, we relied on the triple bond in the macrolactone to prevent this unwanted intramolecular translactonization through steric effects. Accordingly, a synthetic route was devised with this in mind.

First, the dimethoxybenzyl group of **7** was removed under oxidative conditions[15] using DDQ in a mixture of dichloromethane and pH 7 buffer[16] (Scheme 3). A subsequent oxidation of the resulting primary alcohol **9** with the Dess–Martin periodinane[17] furnished aldehyde **10**. The aldehyde **10** was extended to the alkyne **12** by treating it with diazophosphonate[18] **11** in methanol in the presence of potassium carbonate.[19] With alkyne **12** in hand, a one-carbon homologation was performed by deprotonation of the alkyne followed by addition of dried paraformaldehyde. This approach provided the propargyl alcohol **13**. Mitsunobu conditions were used for the introduction of the azide.[20] Thus, reaction of alcohol **13** with Ph_3P, diethyl azodicarboxylate (DEAD), and diphenylphosphoryl azide provided the azide **14** in excellent yield. Reduction of the azide function to the corresponding amine was accomplished with triphenylphenylphosphine followed by hydrolysis of the intermediate phosphinimine.[21] Condensation of the amine **15** with the hexanoic acid derivative[22] **16** using HBTU in the presence of HOBT in DMF secured the amide **17**.

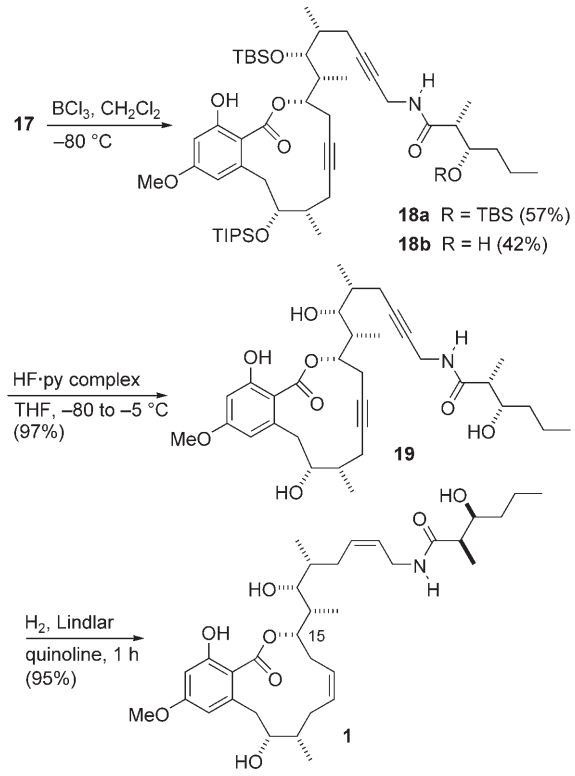
After having established the full skeleton of cruentaren A, we set out to cleave the methyl ether at C-3 in macrolactone **17**. This could be achieved with boron trichloride in dichloromethane at −80 °C (Scheme 4).[23,24] Besides cleavage of the methyl ether, we also observed some cleavage of the silyl ether in the β-hydroxyamide part of the molecule. The mixture of the two compounds **18a** and **18b** was then treated with the HF·pyridine complex[25] in THF, starting at −80 °C.[26] Gratifyingly, we were able to isolate the tetraol **19** in almost quantitative yield. None of the unwanted δ-lactone was formed. The signal for the methine proton of lactone **19** was found at $\delta = 5.34$ ppm in the NMR spectrum, which is typical for the macrolactone. Thus, the triple bond in the lactone nicely served to prevent translactonization. In the final step, a Lindlar reduction on the diyne **19** provided cruentaren A (**1**). The synthetic material was identical in all respects with natural cruentaren A. Since cruentaren A had



Scheme 3. Extension of the side chain of macrolactone **7** to the propargylamine **15** and its acylation with protected 3-hydroxy acid **16**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, HBTU = *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole.

been converted into cruentaren B,[2] this work also represents a formal total synthesis of cruentaren B.

In summary, we have developed an efficient synthesis of the novel macrolide cruentaren A (**1**). Our approach features a ring-closing alkyne metathesis reaction to form the macrolactone. After extension of the side chain to the propargylamine **15**, condensation with the protected β-hydroxy acid **16** provided amide **17**. During the subsequent two steps, that is cleavage of the C-3 methyl ether and the silicon protecting groups, the triple bond in the ring served as a lock that prevented the unwanted translactonization to the δ-lactone. The final step of the synthesis was a Lindlar reduction of the two triple bonds. The sequence is quite concise, and features



Scheme 4. Completion of the synthesis of cruentaren A (**1**) by selective ether cleavage and final Lindlar hydrogenation. py = pyridine.

many high-yielding steps which should allow for the synthesis of various analogues.

Received: April 2, 2007
Published online: May 24, 2007

Keywords: allylamines · benzolactones · natural products · polyketides · protecting groups

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