Natural Product Synthesis

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Total Synthesis of Cruentaren A**

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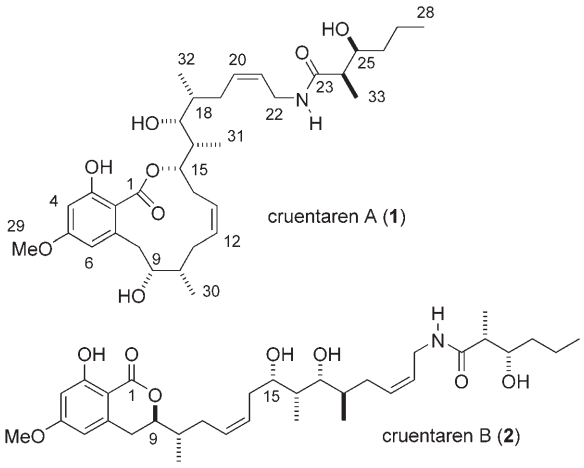
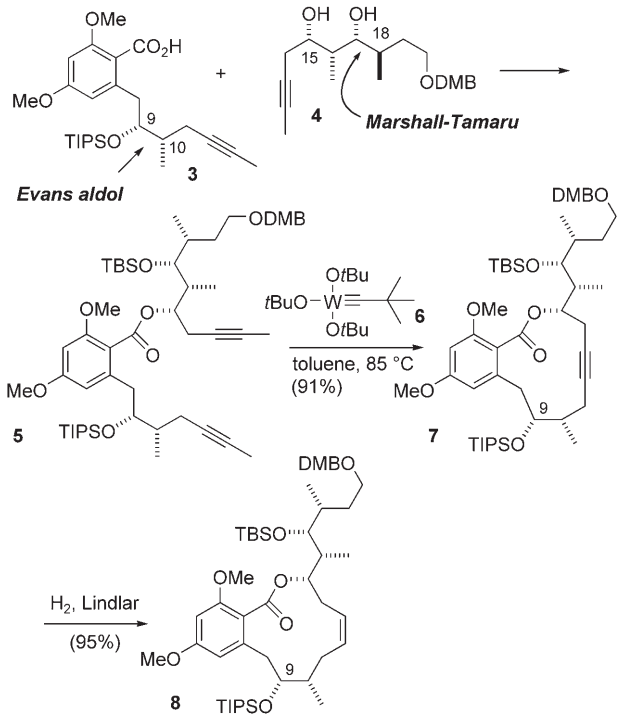
Among the many benzolactones,[1] the recently described cruentaren A[2] (**1**) stands out because of its unique structural features and novel mode of action (Scheme 1). It has



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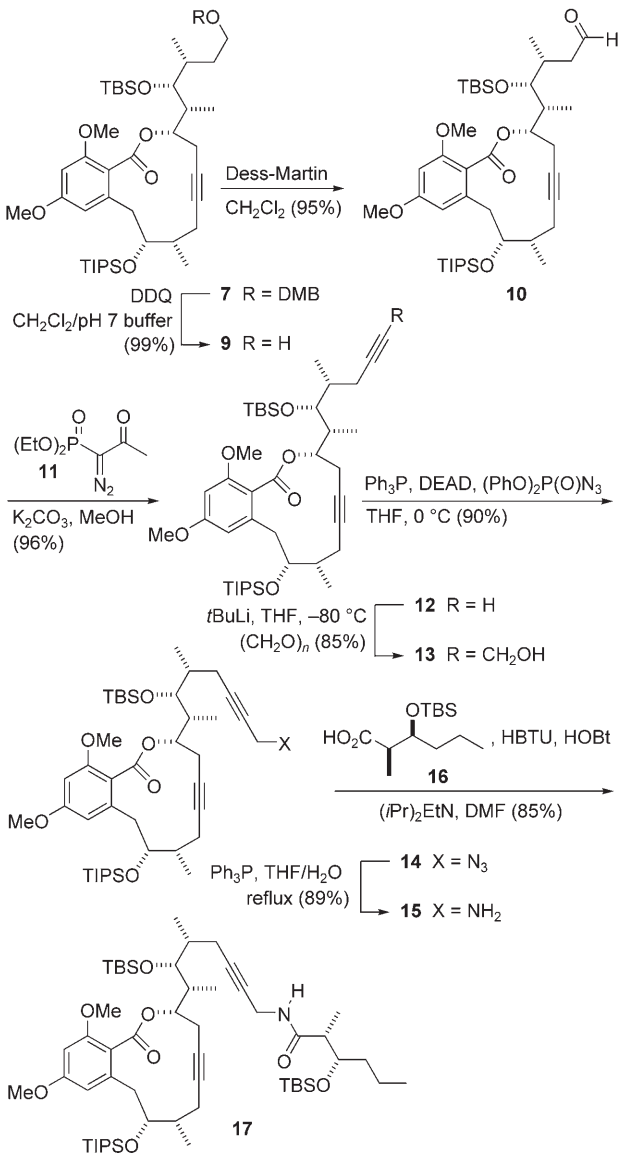
generated in situ from a chiral mesylate. The acetylide function in diol **4** was introduced through an epoxide-opening reaction.

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



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.

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

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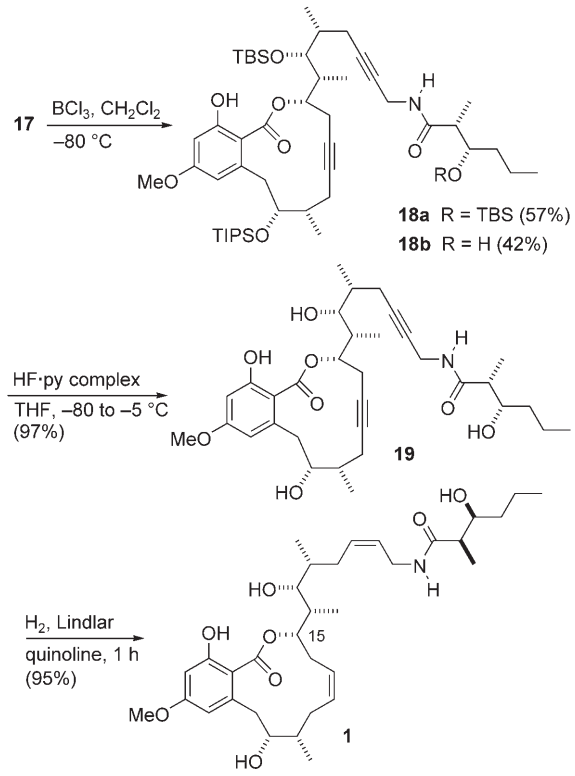

Scheme 4. Completion of the synthesis of cruentaren A (**1**) by selective ether cleavage and final Lindlar hydrogenation. py = pyridine.

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

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