

Concise Total Synthesis of Cruentaren A**

Alois Fürstner,* Martin Bindl, and Ludovic Jean

Bioassay-guided fractionation of the fermentation broth of the myxobacterium *Byssovorax cruenta* led to the discovery of the benzolactone cruentaren A (**1**) and its ring-contracted

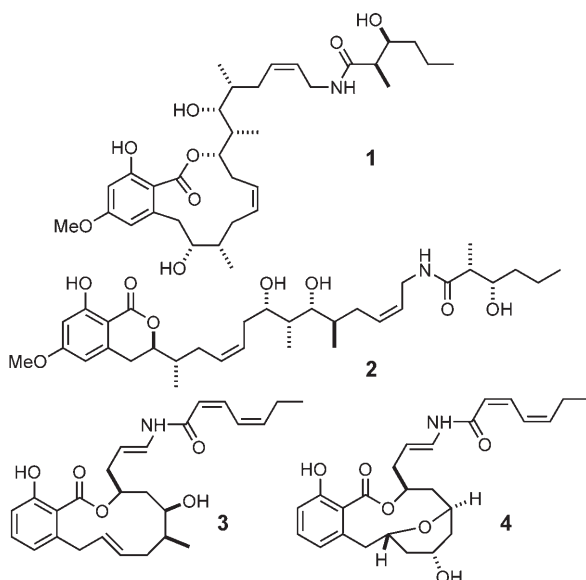
congener cruentaren B (**2**).^[1] While **2** is largely inactive, **1** exhibits pronounced antifungal activity and remarkable cytotoxicity against a panel of human cancer cell lines, with IC₅₀ values in the (sub)nanomolar range,^[1,2] including the multidrug-resistant KB-V1 cell line, for which an IC₅₀ value of 0.6 mg mL⁻¹ has been reported.

Cruentaren A is highly reminiscent of other macrocyclic salicylate lactones such as salicylhalamide (**3**) and apicularen A (**4**),^[3,4] even though it features an allylamine rather than an enamide linkage in its side chain. Yet, preliminary data indicate that this structural resemblance may not translate into functional analogy, since **1** selectively inhibits eukaryotic F-ATPases (IC₅₀ value: 15–30 nM), while being largely ineffective against Na⁺/K⁺- or V-ATPases;^[1,2] **3** and **4**, in contrast, are exceedingly potent inhibitors of these proton pumps.^[3,5] This dissimilar biological profile might be caused by the distinctly different shapes of these compounds, as ascertained

for the solid-state structures.^[1–3] Equally striking is the fact that **1** constitutes one of the most potent inhibitors of F₁-ATPase of mammals and yeast known to date, but does not affect F₁-ATPase in *E. coli* to any noticeable extent.^[2] Given the role of ATPases in the pathophysiology of various human diseases, including cancer, selective inhibitors of such transport proteins constitute promising leads in the quest for novel chemotherapeutic agents.^[3,5,6] It is therefore of considerable interest to evaluate the potential of cruentaren A in more detail. Although **1** can be obtained in up to 3.2 mg L⁻¹ by fermentation,^[1,2] total synthesis provides additional opportunities. Deliberate digression from the ultimately successful path, as accommodated in an adequate synthesis blueprint, will provide analogues with structural changes that are otherwise inaccessible. Therefore, we were prompted to extend our program on the targeted pursuit, structural editing, and biological evaluation of cytotoxic natural products to cruentaren A.^[7] Prompted by the recent disclosure of the first total synthesis of **1** by Vintonyak and Maier,^[8] we now report our conquest of this enticing target.

A combination of ring-closing alkyne metathesis (RCAM) and Lindlar reduction was deemed ideally suited for the construction of the Z alkene embedded in the 12-membered lactone moiety of **1**. RCAM was introduced by our research group in 1998,^[9] and has since then served many total syntheses projects exceedingly well.^[10–12] In parallel to the current application, the total synthesis of **1** by Vintonyak and Maier^[8] also took advantage of this methodology, which allows the target to be dissected into building blocks of similar size and complexity. Our approach to the required salicylic acid segment **14** is notably short and efficient (Scheme 1). Thus, deprotonation of ester **9** derived from the readily available acid **8**^[13] with LDA followed by acylation of the resulting benzyllithium derivative with Weinreb amide **7**^[14] gave ketone **10** on a multigram scale. Subsequent Corey–Bakshi–Shibata (CBS) reduction^[15] afforded alcohol **12** with appreciable diastereomeric purity (*de* ≈ 85%), which was converted into the TBDPS ether **13**. This ether turned out to be sufficiently stable to allow for a selective cleavage of the trimethylsilyl ether with TASF in DMF.

The synthesis of the polyketide sector (Scheme 2) commenced with the alkylation of *ent*-**5**^[16] with propargyl iodide **15**. A sequence comprising a reduction of the resulting product **16** with LiBH₄, Lindlar hydrogenation, and oxidation of the alcohol group afforded aldehyde **18** as a suitable electrophilic partner for the subsequent Evans–aldol reaction,^[16,17] which gave compound **19** (≥ 96% *de*) in high overall yield. Conversion into aldehyde **21** by conventional means allowed us to set the then only missing stereocenter by application of the excellent asymmetric propargylation technology recently disclosed by Soderquist and co-workers.^[18] Specifically, exposure of **21** to the enantiopure allenylborane

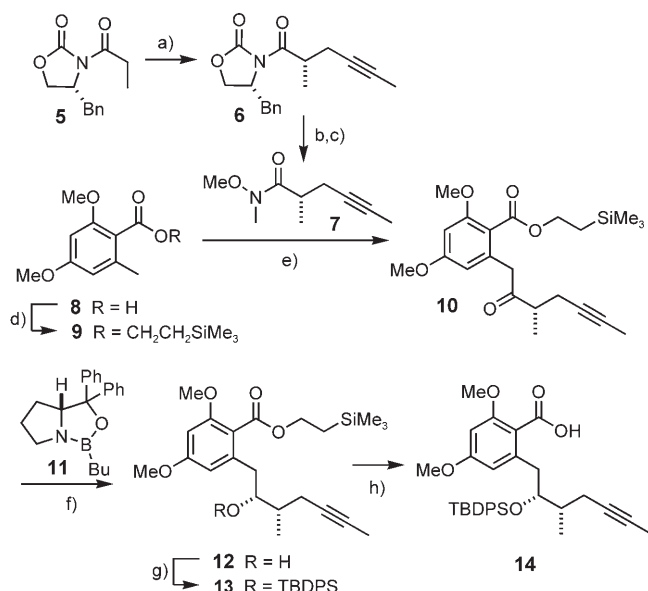


congener cruentaren B (**2**).^[1] While **2** is largely inactive, **1** exhibits pronounced antifungal activity and remarkable cytotoxicity against a panel of human cancer cell lines, with IC₅₀ values in the (sub)nanomolar range,^[1,2] including the multidrug-resistant KB-V1 cell line, for which an IC₅₀ value of 0.6 mg mL⁻¹ has been reported.

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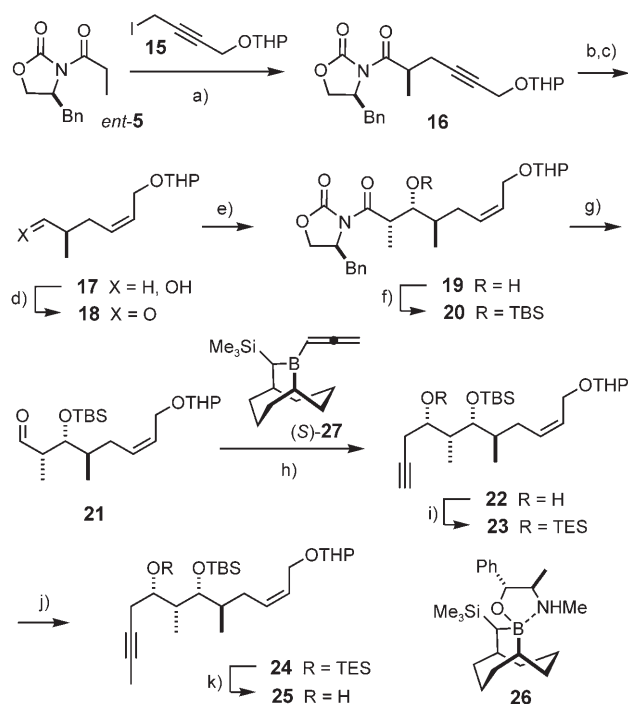


Scheme 1. a) $\text{NaN}(\text{SiMe}_3)_2$, 1-iodo-2-butyne, THF, -78°C , 89%; b) EtOH, $\text{Ti}(\text{OEt})_4$, reflux, 85%; c) $(\text{MeO})(\text{Me})\text{NH}\cdot\text{HCl}$, $i\text{PrMgCl}$, THF, -20°C , 92%; d) 2-trimethylsilylethanol, DIAD, PPh_3 , THF, $0^\circ\text{C} \rightarrow \text{RT}$, 86%; e) 1. LDA, THF, -78°C ; 2. TMEDA, **7**, $-100^\circ\text{C} \rightarrow -78^\circ\text{C}$, 79%; f) **11**, catecholborane, toluene, -78°C , 95% (85% *de*); g) TBDPSOTf , 2,6-lutidine, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{RT}$, 98%; h) TASF , DMF, 0°C , 85%. DIAD = diisopropylazodicarboxylate; LDA = lithium diisopropylamide; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; TBDPS = *tert*-butyldiphenylsilyl; Tf = trifluoromethanesulfonyl, TASF = tris(dimethylamino)-sulfonium difluorotrimethylsilicate.

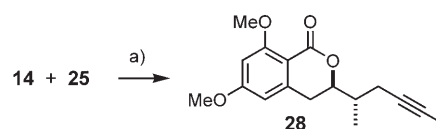
(*S*)-**27**, which can be readily prepared as a storable material from commercial **26** and allenylmagnesium bromide, afforded propargyl alcohol **22** in 75% yield and greater than 95% *de*. The configuration of the newly formed secondary alcohol was ascertained by analysis of the corresponding Mosher esters and is in full accord with the proposed transition-state model.^[18] Temporary protection of the free hydroxy group in **22** paved the way to the nonterminal alkyne **25** as the other required component for the envisaged alkyne metathesis reaction.^[19]

In contrast to the straightforward preparation of the major building blocks, the seemingly trivial esterification of **14** and **25** posed considerable problems. All attempts to join them by using carbodiimide-based reagents, the standard activating agents commonly employed in peptide synthesis, by means of activated esters and thioesters, or by the Yamaguchi method^[20] either led to complete failure or resulted in the decomposition of the valuable materials. Application of 1-methyl-2-chloropyridinium iodide (Mukaiyama's reagent),^[21] which had previously served as the only successful means for a related esterification,^[22] led to only modest yields (<40%). Likewise, the use of carbonyldiimidazole (CDI), employed by Vintonyak and Maier in their approach to **1**,^[8] was unsatisfactory in terms of yield and reaction time, and did not scale well.

Attempts to form the corresponding acid chloride invariably led to the formation of the six-membered lactone **28**, but did not afford any of the desired ester **33** (Scheme 3).^[23] In



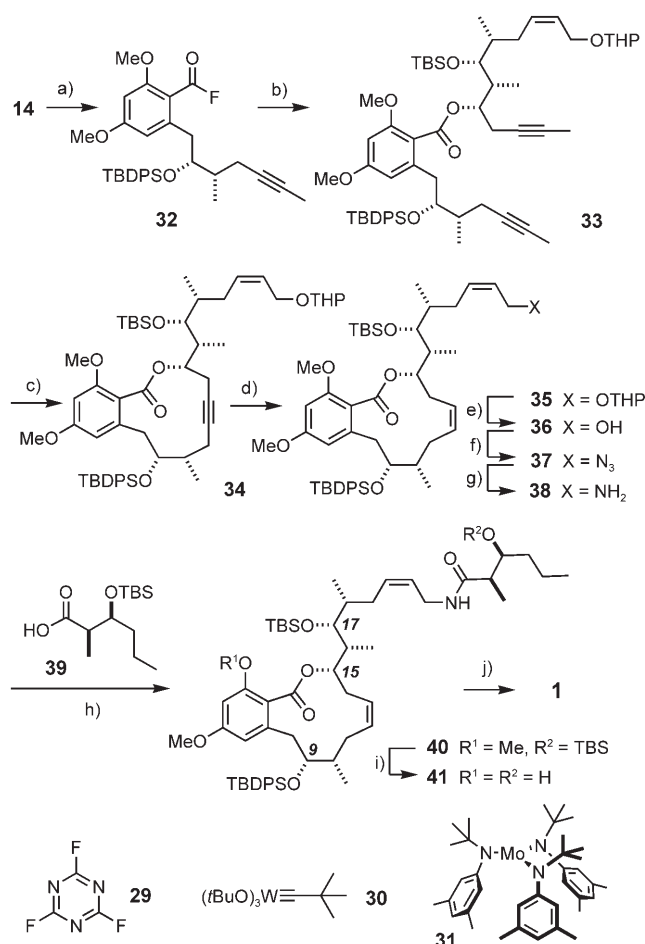
Scheme 2. a) $\text{NaN}(\text{SiMe}_3)_2$, **15**, THF, -78°C , 85%; b) LiBH_4 , THF, MeOH, 0°C , 80%; c) Lindlar catalyst, H_2 (1 atm), EtOAc, pyridine; d) Dess–Martin periodinane, pyridine, CH_2Cl_2 , 0°C , 82% (over two steps); e) *ent*-**5**, Et_2BOTf , $(i\text{Pr})_2\text{NEt}$, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 85%; f) TBSOTf , 2,6-lutidine, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{RT}$, 85%; g) 1. LiBH_4 , THF, MeOH, 0°C , 90%; 2. Dess–Martin periodinane, pyridine, CH_2Cl_2 , 0°C , 87%; h) **27**, Et_2O , -78°C , 75%; i) TESCl , imidazole, DMF, 50°C , 80%; j) $n\text{BuLi}$, THF, MeI, $-78^\circ\text{C} \rightarrow \text{RT}$; k) $\text{HF}\cdot\text{pyridine}$, THF, pyridine, 82% (over both steps). TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.



Scheme 3. a) $\text{Me}_2\text{C}=\text{C}(\text{NMe}_2)(\text{Cl})$, 4-dimethylaminopyridine, Et_3N , $0^\circ\text{C} \rightarrow \text{RT}$, quant.

view of these difficulties, we were pleased to find that the corresponding acid fluoride **32** performed exquisitely well,^[24] thereby resulting in a remarkably clean and highly reproducible formation of **33** (Scheme 4); no trace of δ -lactone **28** or any other by-product was detected in the crude mixture. The acid fluoride **32** was best prepared by treatment of **14** with 2,4,6-trifluoro-1,3,5-triazene (**29**) and pyridine.^[24a] It is also worth mentioning that the ester derived from the minor diastereomer of acid **14**, produced in the CBS reduction step, could be conveniently removed at this stage by flash chromatography.

With a reliable esterification method at hand, the formation of the macrocyclic ring by RCAM was investigated.^[9–12] Although the Schrock alkyldiyne **30**^[25] had proven effective in many advanced cases in the past,^[9,11] only cleavage of the terminal THP acetal was observed when **33** was exposed to this catalyst. Gratifyingly though, the use of



Scheme 4. a) **29**, pyridine, CH_2Cl_2 , -25°C ; b) **25**, $\text{NaN}(\text{SiMe}_3)_2$, THF, $-78^\circ\text{C} \rightarrow \text{RT}$; 91% (over both steps); c) **31** (10 mol%), toluene, CH_2Cl_2 , 80°C , 87%; d) Lindlar catalyst, H_2 (1 atm), EtOAc, quinoline, 96%; e) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, Et_2O , 93%; f) $[\text{Zn}(\text{N}_3)_2 \cdot (\text{pyridine})_2]$, PPh_3 , DIAD, toluene, 0°C , 65%; g) PPh_3 , aq THF, 50°C , 91%; h) **39**, HBTU, HOAt, $(i\text{Pr})_2\text{NEt}$, DMF, 64%; i) BCl_3 , CH_2Cl_2 , -78°C , 83%; j) aq HF (48% w/w), MeCN, $0^\circ\text{C} \rightarrow \text{RT}$, 84%. HBTU = *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOAt = 1-hydroxy-7-azabenzotriazole.

the molybdenum complex **31**, activated in situ by CH_2Cl_2 as previously described by our research group,^[26,27] resulted in the clean cyclization of this polyfunctionalized substrate, thus delivering cycloalkyne **34** in excellent yield (Scheme 4). Lindlar reduction followed by elaboration of the terminal OTHP group into amine **38** proceeded in respectable overall yield, provided that the labile azide **37** was subjected to the Staudinger reduction without undue delay.

Amine **38** was coupled with acid **39**^[16,17] to furnish product **40**, which represents fully protected cruentaren A. In accord with previous findings, treatment of this compound with BCl_3 at -78°C led to the selective cleavage of the methyl ether adjacent to the salicylate carbonyl group, whereas the distal methyl ether remained intact.^[8,28] This convenient elaboration of the correct substitution pattern in the aromatic segment was accompanied by removal of the TBS ether in the amide portion of the molecule. Only the cleavage of the remaining

two silyl groups at O-9 and O-17 in **41** remained to be accomplished to complete the total synthesis.

We were apprehensive that this ultimate synthetic manoeuvre might be far from trivial. The tendency of the 9-OH group to engage in transactonization had already been experienced during our initial attempts to form ester **33** (see Scheme 3), and can be seen even more clearly from the ease with which **1** ring-contracts to **2** under basic as well as acidic conditions.^[1] While our work was in progress, Vintonyak and Maier reported that they could remedy this problem only by carrying the alkyne through to the very end of the synthesis, where it served as a rigidifying structural element to inhibit such ring contraction.^[8] Since we had deliberately chosen to reduce the alkyne early on for synthetic convenience and to protect the endangered 9-OH group as a particularly stable TBDPS ether, it was essential to consider the options for the ultimate deprotection very prudently.

Unsurprisingly, the use of standard fluoride sources met with failure (TBAF with or without HOAc or NH_4Cl ; TASF/DMF, *N,N*-dimethylacetamide (DMA) or MeCN; HF/pyridine); the tempered character of aqueous HF ($\text{p}K_{\text{A}} \approx 3.14$) in MeCN,^[29] however, allowed us to perform this critical step with ease. Under these conditions, the TBS ether at O-17 and the TBDPS ether at O-9 were cleaved within two hours to afford cruentaren A (**1**) in a highly reproducible 84% yield; none of the ring-contracted isomer **2** could be detected in the crude mixture by HPLC/MS analysis ($< 2\%$). Suffice it to say that the analytical and spectroscopic properties of synthetic **1** matched those reported for the natural product in all regards.^[1,8] We have hence completed a convergent total synthesis of this interesting F-ATPase inhibitor, which favorably compares with the previous approach in terms of all usual empirical indices (ca. 3% overall, 21 steps in the longest linear sequence). On this sound basis, we are now attempting to develop an even shorter “second generation” approach, and intend to explore the synthetic modularity inherent in the underlying blueprint.

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