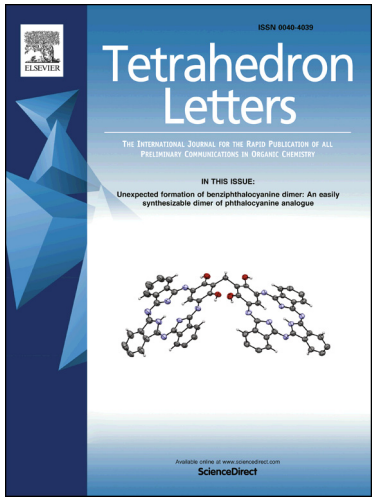

Studies towards the total synthesis of cruentaren A and B: Stereoselective synthesis of fragments C1-C11, C12-C22 and C23-C28

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Studies towards the total synthesis of cruentaren A and B: Stereoselective synthesis of fragments C1-C11, C12-C22 and C23-C28

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ABSTRACT

A convergent and stereoselective approach for the synthesis of C1-C11, C12-C22, and C23-C28 fragments of cytotoxic natural products cruentaren A and B are accomplished. Highlights of the strategy include a Sharpless epoxidation followed by a regioselective opening of epoxide to generate *anti* and *syn*-stereochemistry at C9-C10 and C15-C16, an Alder-Rickert reaction between a 1,5-dimethoxy-1,4-cyclohexadiene and dienophile to construct the aromatic ring, and a lithium-mediated aldol reaction to install the C17-C18 *anti*-stereochemistry. The synthesis of C1-C11 and C12-C22 fragments proceed with a longest linear sequence of 10 and 17 steps from commercially available 2-butyne-1,4-diol and *cis*-2-butene-1,4-diol respectively.

Resorcylic acid lactones (RAL) are common structural motifs found in a numerous natural products,[1] many of them exhibits broad biological profile such as antifungal,[2] antimalarial, antiviral, antiparasitic,[3] cytotoxic,[4] oestrogenic,[5] nematicidal,[6] protein tyrosine kinase and ATPase inhibition activities.[7] In 2006, Höfle and co-workers isolated naturally occurring macrolactones cruentaren A (**1**) and B (**2**) (Figure 1) from myxobacterium *ByssoVorax cruenta*. Cruentaren A (**1**) strongly inhibits the growth of yeast and filamentous fungi, shows high cytotoxicity towards L929 mouse fibroblast cells with an IC_{50} value of 1.2 ng mL^{-1},[8,9] and selectively inhibits mitochondrial F-ATPase, and its ring contracted congener cruentaren B (**2**) showed only minimal cytotoxicity and no antifungal activity.[9] These distinctive biological activities, as well as its fascinating chemical architecture, have attracted the attention of synthetic chemists. Maier[10] and Fürstner[11] independently reported the total synthesis of cruentaren A (**1**) in 2007. After this, two more total synthesis[12] and their synthetic analogues have been published.[10c,11b] There is only one total synthesis of cruentaren B (**2**) was reported by Chakraborty *et al.*[13] As part of our continued effort toward the total synthesis of resorcylic acid lactones containing natural products,[14] we became interested in targeting these natural products for their total synthesis. In this connection, we herein report the synthesis of C1-C11, C12-C22 and C23-C28 key fragments of cruentaren A (**1**) and B (**2**) by employing Sharpless epoxidation, Alder–Rickert reaction and *anti*-aldol reaction following Pirrung-Heathcock's protocol as the key steps.

Retrosynthetically, the cruentaren A (**1**) and B (**2**) can be divided into three subunits are shown in scheme 1. Initially, we planned to utilize an acetylide-triflate cross-coupling reaction similar to that reported by Chakraborty and co-workers[13] to assemble the C1-C11 and C12-C22 fragments of cruentaren A (**1**) and B (**2**). Accordingly, the C1-C11 fragment **3** was planned

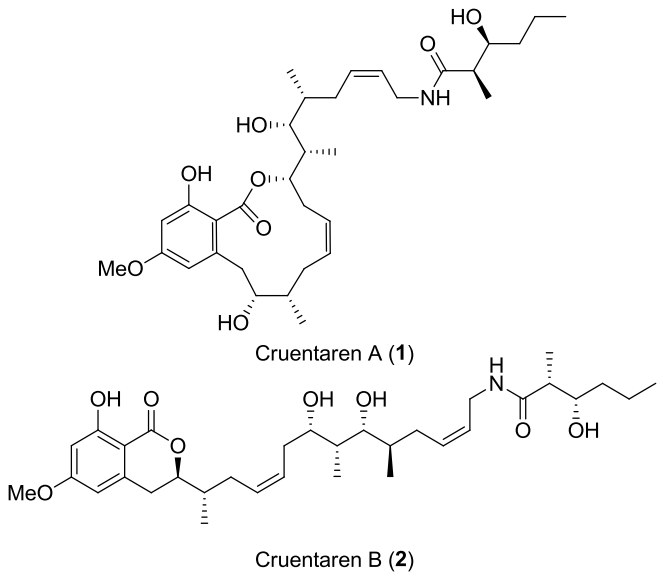
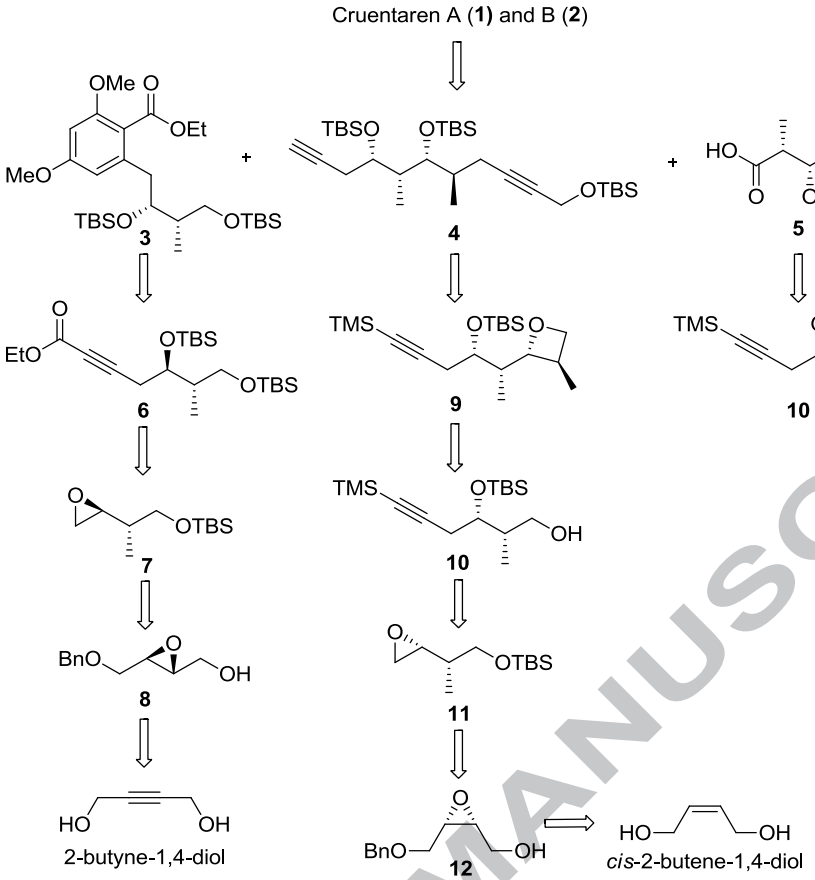


Figure 1. Structures of cruentaren A (**1**) and B (**2**).

to be synthesized from dienophile **6** through the Alder–Rickert reaction. Acetylenic ester **6** can be derived from epoxide **7** by regioselective epoxide opening with ethyl propiolate followed by TBS protection. Compound **7**, in turn, could be obtained from epoxide **8** involving epoxide opening, TBS protection, debenzylation followed by epoxide formation. Epoxide **8** could be prepared from 2-butyne-1,4-diol using a Sharpless epoxidation as one of the key steps. The C12-C22 fragment **4** was intended to be accessed from oxetane **9** *via* oxetane opening, TBS protection followed by TMS deprotection. Compound **9,** in turn, could be generated from propargyl alcohol **10** involving an aldol reaction as the key step followed by reduction, tosylation and oxetane formation. Alcohol **10** would be revealed from epoxide **11** by involving epoxide opening with ethynyltrimethylsilane, TBS

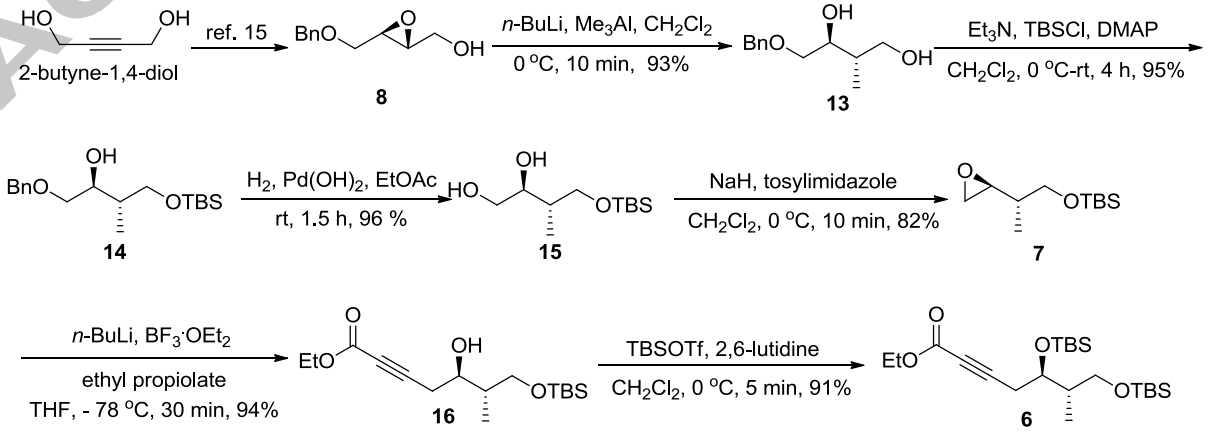


Scheme 1. Retrosynthesis of cruentaren A (**1**) and B (**2**).

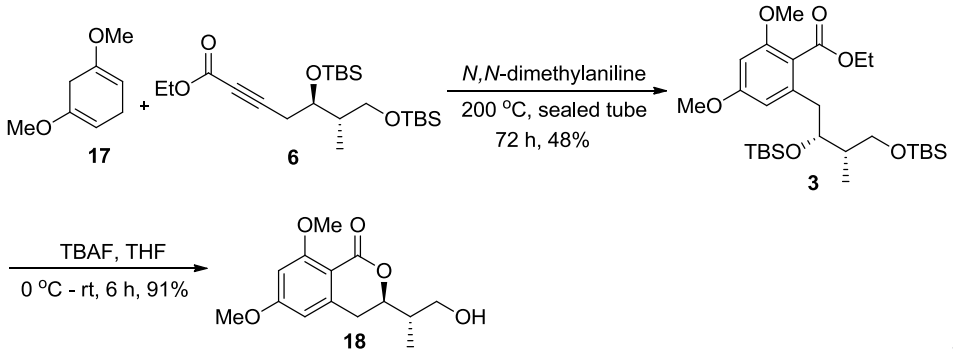
protection followed by primary TBS deprotection. Compound **11**, in turn, could be arisen from epoxide **12** *via* regioselective epoxide opening, TBS protection, debenzylation followed by terminal epoxide formation. Epoxide **12** could be synthesized from *cis*-2-butene-1,4-diol using a Sharpless asymmetric epoxidation. The C23-C28 acid fragment **5** would be derived from propargyl alcohol **10** through simple functional group manipulations.

Our synthesis for functionalized C1-C11 aromatic subunit **3** is depicted in scheme 2 and 3. Consequently, the synthesis commenced from the known chiral epoxy alcohol **8**, which was readily accessed from commercially available 2-butyne-1,4-diol in three steps using a literature procedure.[15] Regio and stereoselective opening of epoxide **8** was achieved in the presence of Me_3Al and *n*-BuLi give 1,3-diol **13** in 93% yield.[16] The *anti*-diol **13** was selectively protected as its primary silyl ether **14**, and the benzyl ether was removed with Pearlman's catalyst in ethyl acetate provided 1,2-diol **15** in excellent yield. The resulting diol **15** was readily converted to terminal epoxide **7** in one step by treating with 1-(*p*-toluenesulfonyl)imidazole and NaH, which underwent opening with ethyl propiolate under Yamaguchi conditions[17] to deliver the propargylic ester **16** in 94% yield. Secondary alcohol **16** was protected to TBS ether by treating with TBSOTf to afford acetylenic dienophile **6** in 91% yield.

Having accessed dienophile **6** in hand, to construct highly substituted aromatic precursor, we adopted to pursue the Alder-Rickert reaction[18] with diene **17** and dienophile **6** (Scheme 3). The reaction was carried out in a sealed tube at 200 ^oC with a catalytic amount of *N*,*N*-dimethylaniline to generate the desired product **3** in 48% yield. Deprotection of silyl ether **3** followed by lactonization was achieved with TBAF in THF gave the benzolactone fragment **18** of cruentaren B (**2**) in 91% yield.



Scheme 2. Synthesis of dienophile (**6**)

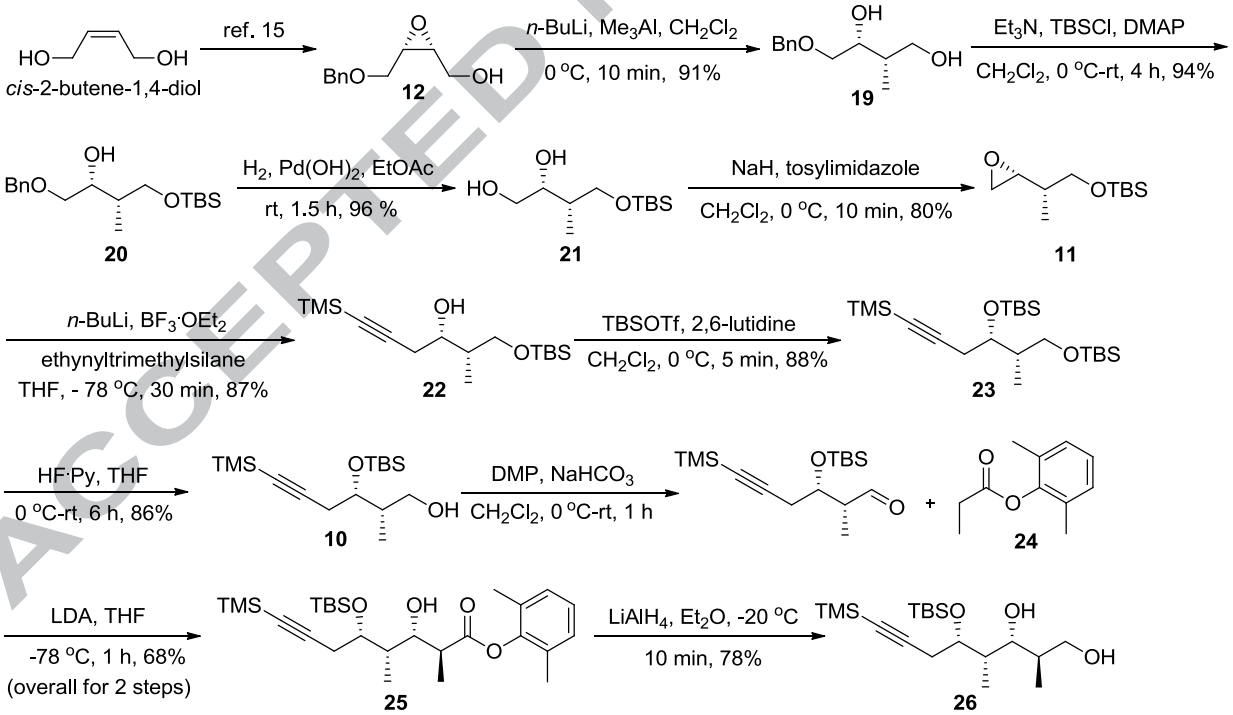


Scheme 3. Synthesis of C1-C11 fragment (**3**).

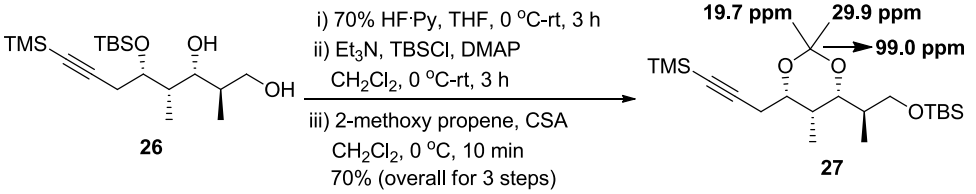
With the C1-C11 subunit in hand, we turned our focus to the synthesis of C12-C22 polyketide fragment **4**, beginning with chiral epoxide **12** (scheme 4), which was obtained by the protection of known *cis*-2-butene-1,4-diol followed by Sharpless epoxidation in two steps.[15] From here, the synthetic route employed a similar sequence as applied in our earlier C1-C11 fragment to produce acetylenic compound **23**. The primary TBS group was selectively deprotected with 70% HF·pyridine in THF provided alcohol **10** in 86% yield. DMP oxidation[19] of the alcohol produced the corresponding aldehyde, which was immediately treated with lithium enolate of dimethylphenyl propionate **24** in THF at -78 °C under Pirrung-Heathcock's aldol protocol[20] to obtain the desired *anti*-aldol product **25** in 68% yield with good diastereoselectivity (93:7).[21] Whereupon the ester functionality was reduced with lithium aluminum hydride in diethyl ether at -20 °C resulted in diol **26** in 78% yield.

The stereochemistry of the aldol product was confirmed by conversion to acetonide derivative **27** (Scheme 5). ^{13}C NMR spectrum of **27** shows signals at δ 99.0 ppm for a quaternary carbon and at δ 19.7 and 29.9 ppm for the methyl carbons confirms the presence of 1,3-*syn* stereochemistry.[22]

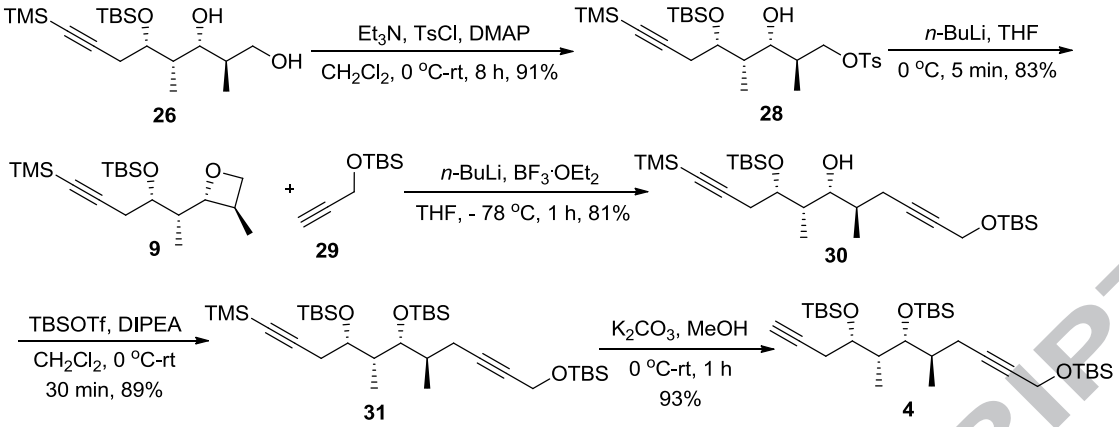
After acquiring the preferred structural configuration, we proceeded further with the alcohol **26** for selective tosylation with Et_3N and tosyl chloride to obtain mono-tosylate **28** (scheme 6), which on exposure to *n*-BuLi in THF at 0 °C afforded the oxetane **9** in 83% yield. The TBS protected propargylic alcohol[23] **29** was metallated with *n*-BuLi and then treated with oxetane **9** in the presence of $BF_3{\cdot}OEt_2$ as described by Yamaguchi[24] delivered the chiral homo-propargyl alcohol **30** in 81% yield. The alkynol **30** was protected as its corresponding silyl ether **31** with TBSOTf in the presence of Hunig's Base in 89% yield. Selective deprotection of trimethylsilyl group was achieved with K_2CO_3 in methanol resulted alkyne **4** in 93% yield.



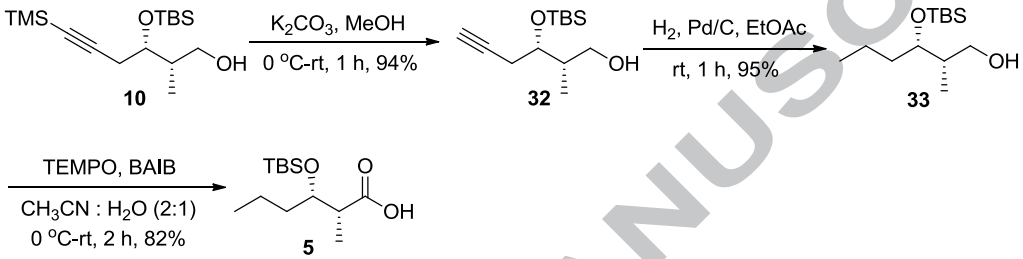
Scheme 4. Synthesis of diol (**26**).



Scheme 5. Synthesis of acetonide derivative (**27**).



Scheme 6. Completion of C12-C22 fragment (**4**).



Scheme 7. Synthesis of C23-C28 acid fragment (**5**).

With the two key fragments in hand, we shifted our attention to synthesize the C23-C28 acid fragment **5** (Scheme 7), starting from the readily available alkynol **10** in three steps. Removal of the TMS group followed by hydrogenation with Pd/C gave the alcohol **33** in 95% yield. Oxidation of primary alcohol with TEMPO and BAIB[25] afforded an acid **5** in 82% yield.

In conclusion, we have successfully accomplished the synthesis of C1-C11, C12-C22 and C23-C28 fragments of cruentaren A (**1**) and B (**2**). The C1-C11 aromatic precursor **3** was accessed in 7 steps from known chiral epoxide **8** using Sharpless epoxidation and Alder-Rickert reaction as the key steps with 28.5% overall yield and the C12-C22 polyketide fragment **4** was achieved in 15 steps from known epoxide **12** employing Sharpless epoxidation, *anti*-aldol reaction following Pirrung-Heathcock's protocol and oxetane opening under Yamaguchi conditions as the key steps with 11.6% overall yield. Total synthesis of cruentaren A (**1**) and B (**2**) are our future interest and efforts in this direction are currently underway.

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Supplementary data

Experimental procedures, Spectral data and Copies of ^{1}H NMR, ^{13}C NMR spectra of all compounds are available.

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21. The diastereomeric ratio was determined to be 93:7 by LCMS [column: Atlantis C18, 4.6X150 mm, 5 µm; mobile phase: 90% acetonitrile + 10% water; flow rate: 1.0 $mLmin^{-1}$; detection: 210 nm] See supporting information.
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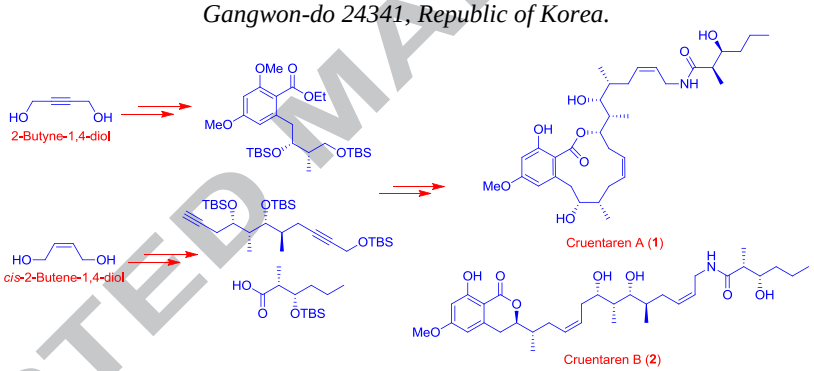

Highlights

- Three key fragments C1-C11, C12-C22 and C23-C28 of cruentaren were synthesized
- Achieved Pirrung-Heathcock's anti aldol reaction with good diastereoselectivity
- Regioselective Alder-Rickert reaction was successfully utilized for aromatic fragment
- C1-C11 fragment was accomplished very effectively with 25.8% overall yield
- C12-C22 fragment was accomplished very efficiently which have four stereo centers in 15 linear steps with 11.6% overall yield