

Enantioselective Synthesis of (+)-Crocacin C. An Example of a Highly Challenging Mismatched Double Asymmetric δ -Stannylcrotylboration Reaction

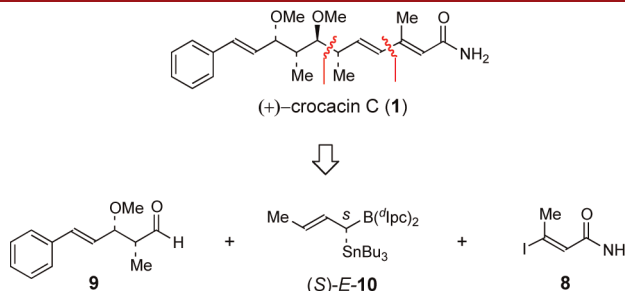
Ming Chen and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States

roush@scripps.edu

Received February 25, 2012

ABSTRACT



A concise, enantioselective synthesis of (+)-crocacin C is described, featuring a highly diastereoselective mismatched double asymmetric δ -stannylcrotylboration of the stereochemically demanding chiral aldehyde **9** with the bifunctional crotylboration reagent (S)-E-10. The total synthesis of (+)-crocacin C was accomplished in seven steps (longest linear sequence) starting from commercially available precursors.

The crocacin A–D are a family of natural products isolated from *Chondromyces crocatus* and *Chondromyces pediulatus* (Figure 1).¹ Crocacin A, B, and D are dipeptides of glycine and a 6-aminohexenoic or a 6-aminohexadienoic acid with a polyketide-derived acyl residue connected to the nitrogen atom, while crocacin C is a primary amide of the acyl polyketide fragment. Initial biological studies revealed that the crocacin A–D display antifungal and cytotoxic activities. Compared to crocacin A–C, only crocacin D exhibited potent activity against *Saccharomyces cerevisiae* with a MIC of 1.4 ng/mL, which indicates that the dipeptide moiety of the crocacin A–D is crucial for their biological properties.¹ Recent crystallographic data suggest that the crocacin A–D are a new class of inhibitors of the cytochrome *bc*₁ complex.²

A characteristic structural feature of crocacin C is the *anti,anti*-dipropionate stereotriad (highlighted in yellow in Figure 2). It is evident that a mismatched double asymmetric crotylation reaction of an aldehyde substrate, such as **2**, with a chiral crotylmethyl reagent would be a direct, logical approach to this structural motif.^{3,4}

However, an attempted^{5f} mismatched double asymmetric crotylboration of aldehyde **2** with crotylborationate **5** provided a 1:4 diastereomeric mixture in 60% yield, favoring the undesired 3,4-*anti*-4,5-*syn*-stereotriad **4** (Figure 2). Attempted crotylboration of aldehyde **2** using Brown's crotylboration reagent **6** gave a 1:3 mixture of diastereomers, again favoring the undesired diastereomer **4**.

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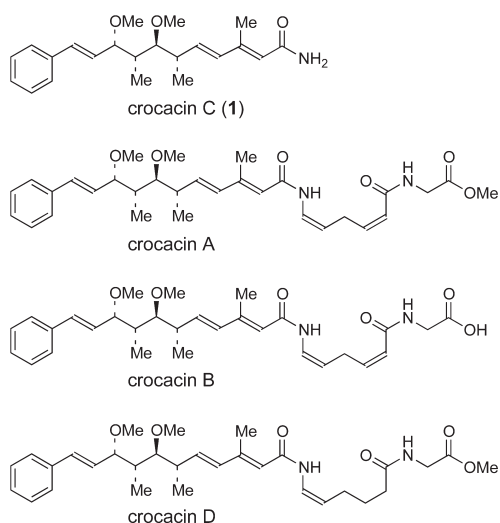


Figure 1. Structures of crocacin A–D.

Owing to the inability to directly access this requisite *anti, anti*-stereotriad (e.g., **3**), the central theme of multiple approaches developed for the synthesis of crocacin C^{5,6} utilize indirect methods⁷ to prepare the *anti,anti*-stereotriad with high diastereoselectivity. Strategies involving aldol reactions,^{5a,e–h} epoxide ring-opening reactions,^{5b–d} or the desymmetrization of *meso* cyclic precursors^{5i,6d} have been adopted to access the *anti,anti*-stereotriad units of crocacin C precursors.

We recently described⁸ highly diastereoselective syntheses of *anti,anti*-stereotriads using mismatched double asymmetric δ -stannylcrotylboration reactions of chiral aldehydes with crotylborane reagent (*S*)-**E-10**⁹ (Figure 3). Because it has been reported that reagents such as **5** and **6** are incapable of overriding the intrinsic diastereofacial preference of aldehyde **2** (Figure 2), we were intrigued

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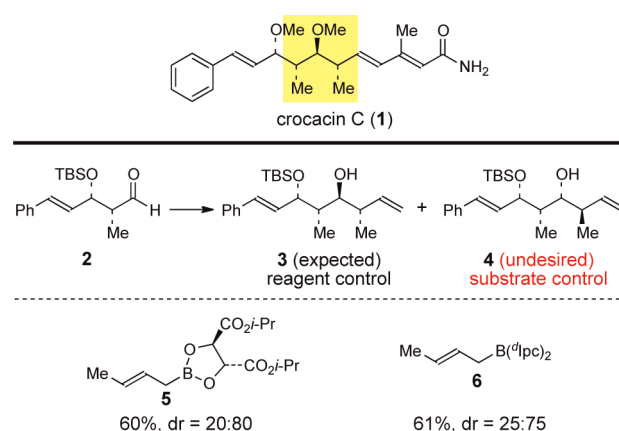


Figure 2. Attempted mismatched double asymmetric crotylboration reactions of aldehyde **2** with reagents **5** and **6** for synthesis of the *anti,anti*-stereotriad of crocacin C.^{5f}

whether our new reagent (*S*)-**E-10** could be adopted for synthesis of the *anti,anti*-stereotriad unit in **7**. Furthermore, the vinylstannane unit in **7** can be used in subsequent C–C bond forming reactions, for example, Stille¹⁰ coupling with vinyl iodide **8**.^{5a} We chose crocacin C as the target molecule for this study because it can be converted into other members of the crocacin family using a Cu-catalyzed coupling reaction as demonstrated by Dias and co-workers.¹¹

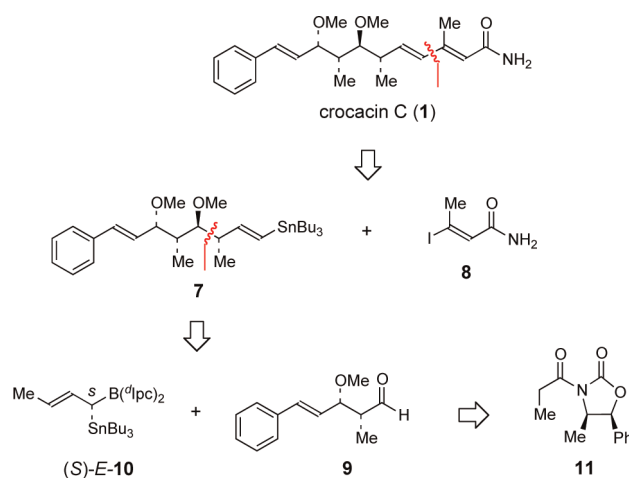


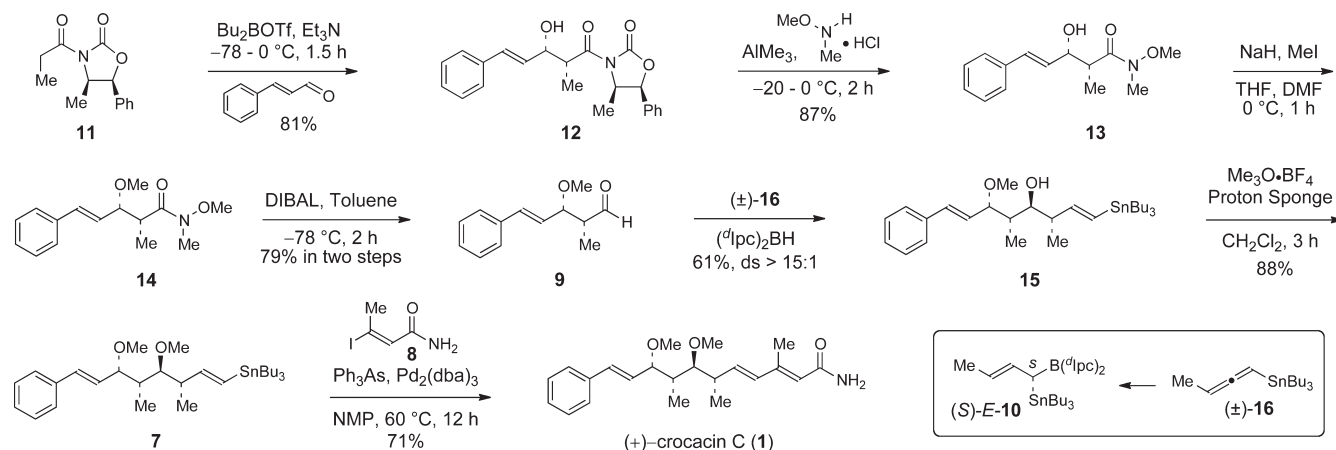
Figure 3. Crocacin C, retrosynthetic analysis.

Starting from acyl oxazolidinone **11**, aldehyde **9** was obtained in four steps according to known procedures (Scheme 1).¹² Addition of aldehyde **9** to the crotylborane reagent (*S*)-**E-10**, generated from the enantioselective and

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Scheme 1. Total Synthesis of (+)-Crocacin C (1)



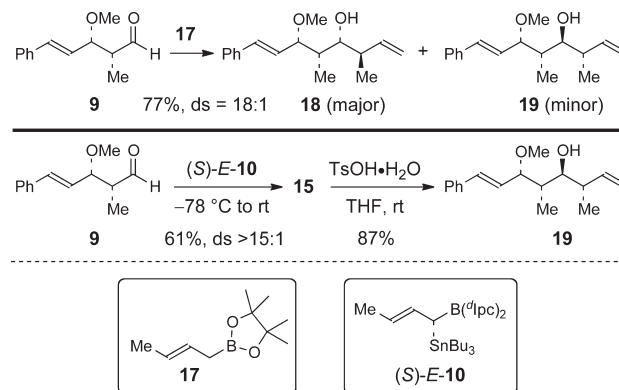
enantioconvergent hydroboration of racemic allenylstannane ($\pm$)-**16**¹³ with (d Ipc)₂BH, at $-78\text{ }^{\circ}\text{C}$ followed by warming the reaction mixture to ambient temperature for a 24 h reaction period provided the targeted *anti,anti*-stereotriad **15** in 61% yield and with $> 15:1$ diastereoselectivity.

Methylation of the secondary alcohol of **15** with Me₃O·BF₄ and Proton Sponge provided methyl ether **7**^{5a} in 88% yield. A Pd(0)-catalyzed Stille coupling^{5a,10} of vinylstannane **7** with vinyl iodide **8**^{5a} gave (+)-crocacin C (**1**) in seven steps (longest linear sequence) and in 21% overall yield from **11** without any protecting group manipulations. The spectroscopic data (¹H NMR, ¹³C NMR, [α]_D) of synthetic (+)-crocacin C were in excellent agreement with the data previously reported for the natural product.^{1,5}

The intrinsic diastereofacial preference of aldehyde **9** was assessed by using an anti-crotylboration reaction with the achiral pinacol (*E*)-crotylboronate **17** (Scheme 2). This reaction provided an 18:1 mixture of 3,4-*anti*-4,5-*syn*-stereotriad **18** and *anti,anti*-stereotriad **19** in 77% yield, with **18** as the major product (as expected^{3,14}). In contrast, the mismatched double asymmetric δ -stannylcrotylboration of aldehyde **9** with (*S*)-*E*-**10** provided the *anti,anti*-stereotriad **15** with $> 15:1$ diastereoselectivity. No other crotylation diastereomers were observed in the reaction mixture. Protodestannylation of **15** under acidic conditions (TsOH·H₂O) provided alcohol **19** in 87% yield, which matched the minor isomer obtained from crotylboration of **9** with achiral crotylboronate **17**.

The mismatched double asymmetric δ -stannylcrotylboration of **9** with (*S*)-*E*-**10** thus represents yet another case⁸ where a significant intrinsic diastereofacial barrier, as

Scheme 2. Crotylboration Studies of Aldehyde 9



presented by chiral aldehyde **9**, is overridden by the chiral reagent (*S*)-*E*-**10**. The free energy contribution of reagent (*S*)-*E*-**10** (i.e., the enantioselectivity of the reagent expressed in energetic terms) necessary to override the 18:1 intrinsic diastereofacial preference of **9** and to generate homoallylic alcohol **15** with $> 15:1$ mismatched diastereoselectivity is ≥ 3.3 kcal/mol (reaction at $23\text{ }^{\circ}\text{C}$). The exceptional enantioselectivity of (*S*)-*E*-**10** defines a new standard of excellence that all future methodological studies on enantioselective crotylboration or crotylmethyl-carbonyl addition reactions should be judged against.

In conclusion, the total synthesis of (+)-crocacin C (**1**) was completed in seven steps (longest linear sequence), which represents the shortest synthesis of **1** reported to date. Most importantly, the mismatched double asymmetric δ -stannylcrotylboration of aldehyde **9**, with a significant 18:1 intrinsic diastereofacial preference, was achieved with exceptional selectivity ($> 15:1$) by using the crotylborane reagent (*S*)-*E*-**10**. The vinylstannane unit in the derived *anti,anti*-stereotriad **15** facilitates the subsequent Stille reaction that was used to complete this short synthesis of crocacin C. Other applications of reagent

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(*S*)-**E-10** in the synthesis of biologically active natural products will be reported in due course.

Acknowledgment. Financial support provided by the National Institutes of Health (GM038436) and Eli Lilly (for a predoctoral fellowship to M.C.) is gratefully acknowledged.

Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.