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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

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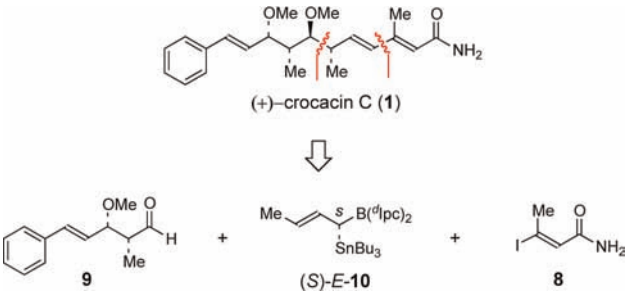
ABSTRACT



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 crotylborane reagent (*S*)-*E*-10. The total synthesis of (+)-crocacin C was accomplished in seven steps (longest linear sequence) starting from commercially available precursors.

The crocacins A−D are a family of natural products isolated from *Chondromyces crocatus* and *Chondromyces pediulatus* (Figure 1).[1] Crocacins 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 crocacins display antifungal and cytotoxic activities. Compared to crocacins 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 crocacins is crucial for their biological properties.[1] Recent crystallographic data suggest that the crocacins 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 crotylmetal 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 crotylboronate **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 crotylborane reagent **6** gave a 1:3 mixture of diastereomers, again favoring the undesired diastereomer **4**.

(1) (a) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881. (b) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **1999**, 1085.

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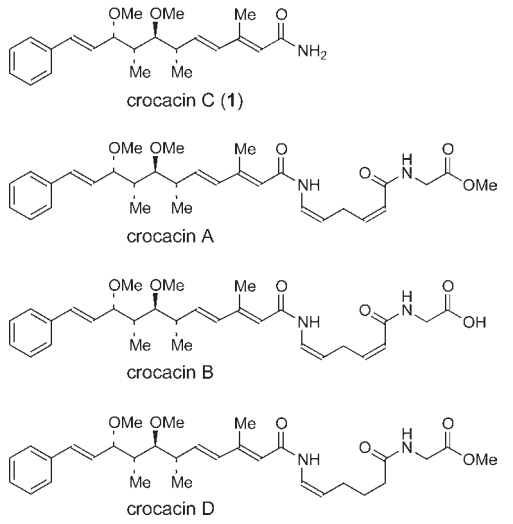

Figure 1. Structures of crocacins A−D.

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 methods[7] 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 described[8] 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

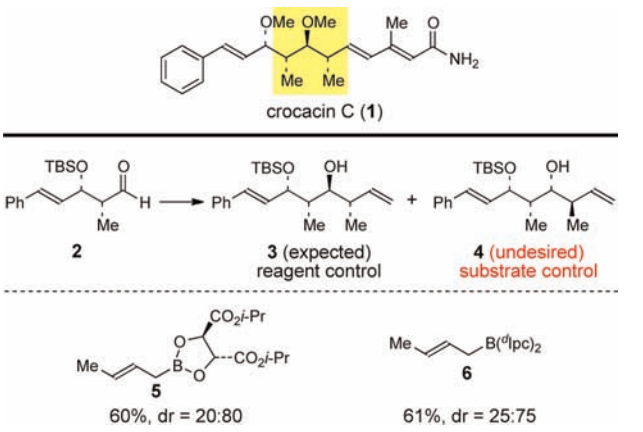

Figure 2. Attempted mismatched double asymmetric crotylboration reactions of aldehyde **2** with reagents **5** and **6** for synthesis of the *anti,anti*-stereotriad of crocacin C.[5f]

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, Stille[10] 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]

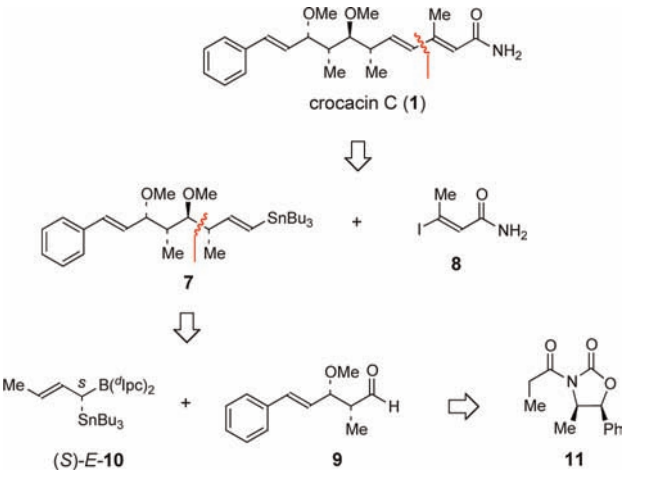

Figure 3. Crocacin C, retrosynthetic analysis.

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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(9) (a) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744. For synthetic applications of reagent (*S*)-*E*-**10**, see: (b) Sun, H.; Abbott, J. R.; Roush, W. R. *Org. Lett.* **2011**, *13*, 2734. (c) Yin, M.; Roush, W. R. *Tetrahedron* **2011**, *67*, 10274. (d) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 426.

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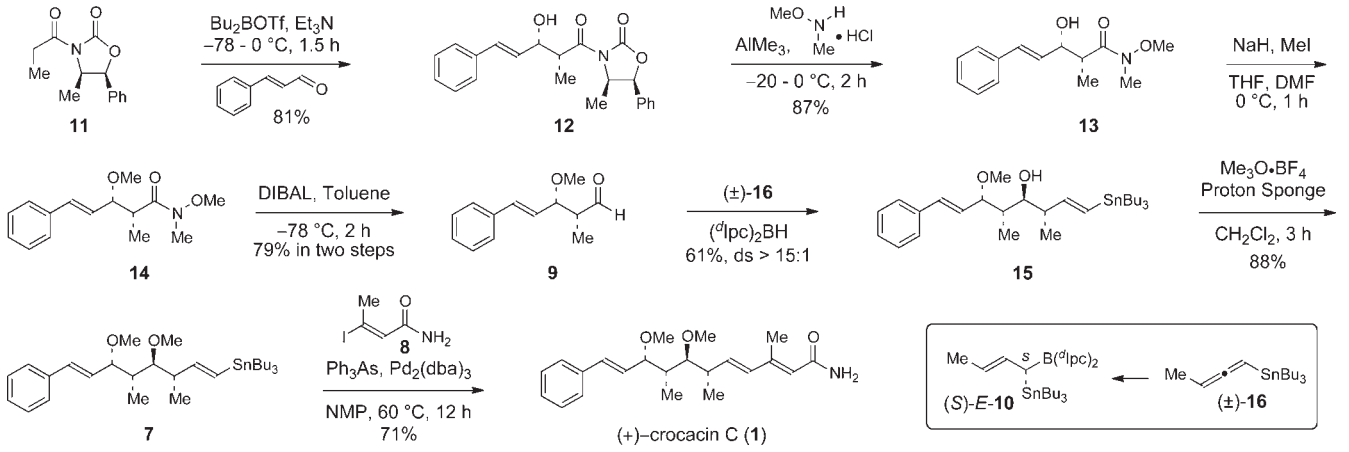
(11) Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70*, 2225.

Scheme 1. Total Synthesis of (+)−Crocacin C (**1**)



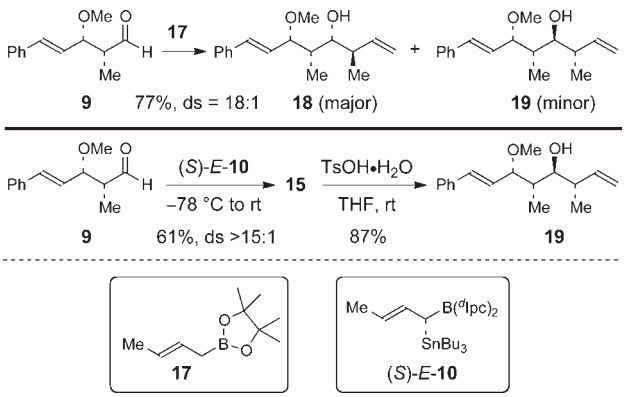
enantioconvergent hydroboration of racemic allenylstannane (±)-**16**[13] with (^{d}Ipc)$_2$BH, at −78 °C followed by warming the reaction mixture to ambient temperature for a 24 h reaction period provided the targeted *anti,anti*-stereotriad **15** in 61% yield and with >15:1 diastereoselectivity.

Methylation of the secondary alcohol of **15** with $Me_3O•BF_4$ 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 (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) 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•H_2O) 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 case[8] 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 °C). The exceptional enantioselectivity of (*S*)-*E*-**10** defines a new standard of excellence that all future methodological studies on enantioselective crotylboration or crotylmetal−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 signficant 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.

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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.