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Total Synthesis of (+)-Crocacin C†

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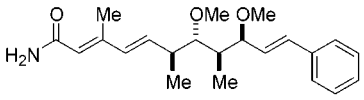
ABSTRACT

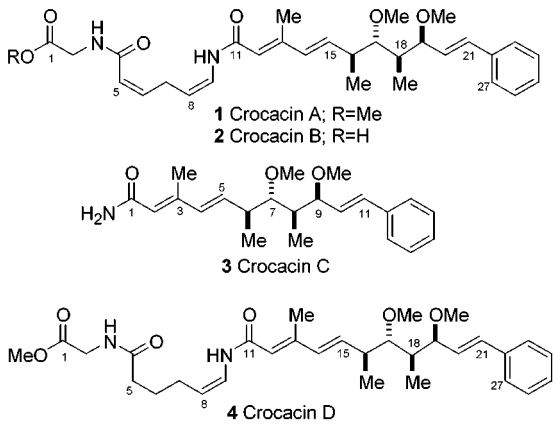


Crocacin C

The total synthesis of (+)-crocacin C is described. The convergent asymmetric synthesis relies on the use of a regio- and diastereoselective epoxidation of an allylic alcohol with *m*-CPBA followed by epoxide opening with $Me_2CuCNLi_2$ and a Stille cross-coupling between *E*-vinyl stannane 5 and *E*-vinyl iodide 6 to establish the (*E*,*E*)-dienamide moiety.

The crocacins A−D (**1**−**4**) are a group of compounds that are regularly found in the extracts of *Chondromyces crocatus* and *Chondromyces pediulatus* and represent a second novel group of modified peptides from *C. crocatus* (Scheme 1).[1,2]

Scheme 1



Crocacin C (**3**) is a structure fragment of **1**, **2**, and **4**. The crocacins moderately inhibit the growth of a few Gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. Crocacin D shows higher biological activity against *Saccharomyces cerevisiae* as well as higher toxicity in L929 mouse fibroblast cell culture when compared to crocacins A−C. The relative configurations of crocacins A−D were proposed by Jansen and co-workers by means of molecular modeling studies and NOE experiments.[2] The relative and absolute configurations for crocacin C have been recently confirmed by its first total synthesis as being 6*S*,7*S*,8*R*,9*S*.[3]

To provide material for more extensive biological evaluation, along with access to novel analogues, we have undertaken the total synthesis of the polyketide crocacin C.[3]

Not surprisingly, our first disconnection, summarized in Scheme 2, involved cleavage of the dienamide portion (C3−C4 bond) to give *E*-vinyl stannane **5** (C1−C3 fragment) and *E*-vinyl iodide **6** (C4−C11 fragment) bearing four stereogenic centers.[4] Of the available options, we speculate that the C6 and C7 stereocenters could be constructed by epoxide opening with $Me_2CuCNLi_2$. Epoxy alcohol **8** may be further dissected in a straightforward manner to give allylic alcohol **9**. The desired C8 and C9 stereocenters in **9** might be established through a boron enolate mediated aldol reaction.

The C1−C3 fragment **5** is viewed as arising from an α,β-acetylenic ester **7** by a stereoselective conjugate organostan-

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(1) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881.

(2) (a) Jansen, R.; Washausen, P.; Kunze, B.; Reichennach, H.; Hofle, G. *Eur. J. Org. Chem.* **1999**, 1085. (b) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

(3) As this work was in progress, the first two asymmetric total syntheses of crocacin C were described: (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365. (b) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, *42*, 497.

(4) The numbering of **3** follows that suggested in ref 2a.

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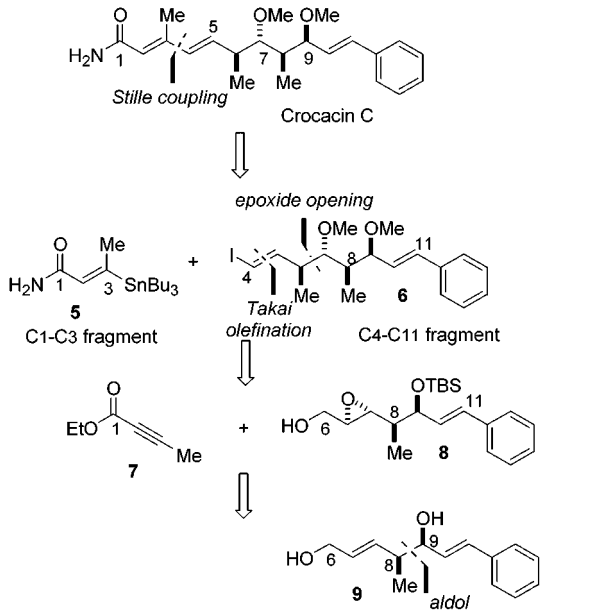
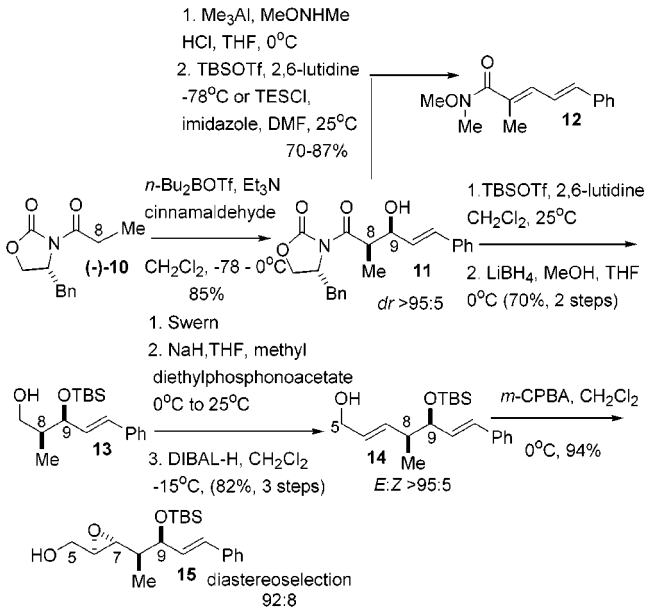
Scheme 2



nyl cuprate addition method, providing control for the *E* geometry of the double bond.

Synthesis of fragment C4−C11 began with the known (−)-acyloxazolidinone, (*R*)-**10**, which was most conveniently prepared by acylation of the corresponding (+)-(*R*)-oxazolidinone, as described by Evans et al. (Scheme 3).[5]

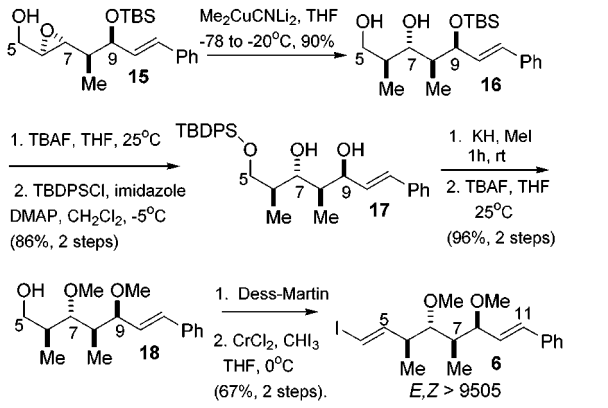
Scheme 3



Asymmetric aldol addition of the boron enolate derived from oxazolidinone (−)-**10** with cinnamaldehyde gave aldol adduct **11** in 85% isolated yield and greater than 95% diastereomeric purity (Scheme 3).[6] Transamidation of aldol **11** followed by treatment of the intermediate Weinreb amide with TBSOTf and 2,6-lutidine or with TESCl and imidazole in DMF yielded only α,*β*,*γ*,*δ*-unsaturated Weinreb amide **12** in good yields.[7] On the basis of this result aldol adduct **11** was converted to primary alcohol **13** after protection of the OH-function as its TBS ether followed by removal of the oxazolidinone auxiliary with $LiBH_4$ in MeOH (70% yield, two steps).[6]

Primary alcohol **13** was submitted to oxidation under the standard Swern conditions,[8] and the unpurified aldehyde was directly subjected to a Horner−Emmons homologation[9] with the requisite stabilized reagent to give an intermediate α,*β*-unsaturated ester that was treated with 2 equiv of diisobutylaluminum hydride at 0 °C, producing allylic alcohol **14** in 82% isolated yield for the three-step sequence. It was with some gratification that epoxidation of allylic alcohol **14** with *m*-CPBA proceeded with high regio- and diastereoselectivity from the opposite side of the C9 *tert*-butyldimethylsilyl group to give the *anti*-epoxy alcohol **15** in high purity (dr 92:8, 94% yield).[4,10] It is noteworthy that the diastereoselectivity associated with this epoxidation was exceptional and compared in both yield and selectivity to related transformations described earlier by Isobe and later on by Miyashita.[10] Epoxide opening proceeded smoothly with high regioselectivity after treatment of epoxy alcohol **15** with $Me_2CuCNLi_2$ to give diol **16** in good yield and selectivity, which possesses the *anti-anti-syn* stereochemistry concerning the four contiguous stereocenters (Scheme 4).[11,13]

Scheme 4



A sequence of TBS removal and selective protection of the primary alcohol functionality (TBDPSCl, imidazole, DMAP, −5 °C) gave **17** in 86% yield (two steps).[13]

(5) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83.

(6) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675. (c) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

(7) Levin, J. I.; Turos, E.; Weinreb, S. *Synth. Commun.* **1982**, *12*, 989.

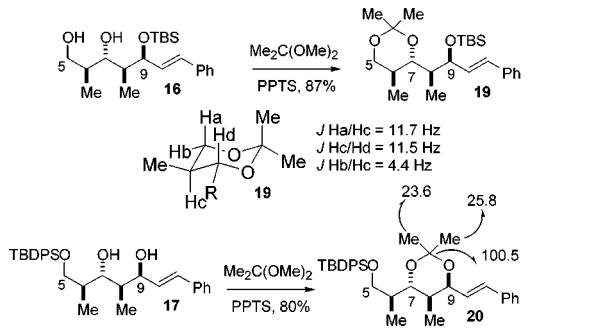
(8) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(9) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(10) (a) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221. (b) Maruyama, K.; Ueda, M.; Sasaki, S.; Iwata, Y.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 4517.

To confirm the relative stereochemistry of the aldol bond construction and epoxidation steps the 1,3-diols **16** and **17** were transformed to their corresponding isopropylidene acetals **19** and **20** in good yields (Scheme 5).[12,13] The large

Scheme 5

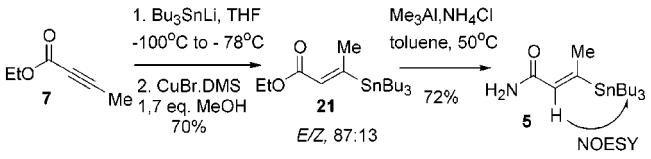


coupling constants between Ha−Hc (11.7 Hz) and Hc−Hd (11.5 Hz), together with the small observed value between Hb−Hc (4.4 Hz), unambiguously established the proposed relative stereochemistry for C6−C7 bond in **19**.[13] The stereochemistry of the secondary alcohols at C7 and C9 was determined on the basis of the ^{13}C NMR analysis of the corresponding 1,3-diol acetonide **20**. ^{13}C NMR resonances at 23.6, 25.8, and 100.5 are characteristic of an *anti* acetonide.[12]

With compound **17** in hand, only four synthetic operations remained to arrive at an intermediate suitable for coupling with *E*-vinyl stannane **5** (Scheme 4). Methylation with KH and MeI followed by removal of the TBDPS protecting group at C5 gave primary alcohol **18** (96% yield, two steps). Dess−Martin oxidation gave the intermediate aldehyde.[14] All that remained was to carry out the necessary Takai olefination reaction. Treatment of the unpurified aldehyde with $CrCl_2$ and CHI_3 produced *E*-vinyl iodide **6** (*E*:*Z* > 95:05), corresponding to the C4−C11 segment of crocacins in 67% overall yield for the two-step sequence.[15] The 14-step sequence starting from (−)-**10** proceeded in 23% overall yield and is amenable to a multigram scale-up.

Our approach for preparation of fragment C1−C3 was initiated with α,β-acetylenic ester **7** following the strategy developed by Piers et al. (Scheme 6).[16,17] Conjugate orga-

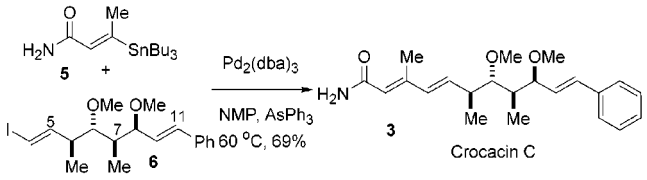
Scheme 6



nostannyl cuprate addition to ethyl 2-butynoate **7** (−100 to −78 °C) led to the *E*-tributylstannyl α,β-unsaturated ester **21** as the major isomer (*E*:*Z* 87:13, 70% yield) after purification by column chromatography. Ester−amide exchange was accomplished by treatment of vinylstannane **21** with Me_3Al and NH_4Cl in toluene at 50 °C, giving *E*-vinylstannane **5** as a crystalline solid after purification by column chromatography (72% yield, mp 39.5 °C). The illustrated NOESY interactions between vinylic hydrogen and the hydrogens of the tributyltin group confirmed the *E*-geometry for vinylstannane **5**.

The two-step sequence from **7** to **5** proceeded in an overall yield of 50.4% and was amenable to a multigram scale-up. With synthesis of the requisite C1−C3 and C4−C11 fragments in hand, their coupling was undertaken. This was done by using Stille coupling conditions (Scheme 7).[18]

Scheme 7



Treatment of a solution of *E*-vinylstannane **5** and *E*-vinyl iodide **6** in NMP with a catalytic amount of $Pd_2(dba)_3$ in the presence of $AsPh_3$ at 60 °C afforded (+)-crocacin C in 69% yield after purification by silica gel column chromatography (petroleum ether/EtOAc, 2:1 then 1:3) followed by preparative RP-HPLC.[19,20]

The spectroscopic and physical data [^1H and ^{13}C NMR, IR, $[\alpha]_D$, R_f] were identical in all respects with the published data.[2a,20]

The total synthesis of crocacin C has been completed. Notable features of this approach include convergence, a regio- and diastereoselective epoxidation of an allylic alcohol, and a Stille cross-coupling between a vinyl stannane and a vinyl iodide. The synthesis required 15 steps (longest linear sequence) and produced the desired product in 16% overall yield. As a result, the route to crocacin C presented here is,

(11) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4347.

(12) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

(13) Diols **16** and **17** showed spectral data and physical properties identical in all respects with published data. See ref 3.

(14) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(15) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Paterson, I.; Lombart, H.; Allerton, C. M. N. *Org. Lett.* **1999**, *1*, 19.

(16) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.

(17) Brabander, J. D.; Vandewalle, M. *Synthesis* **1994**, 855.

(18) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Duncton, A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. (c) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(19) (a) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(20) New compounds and the additional isolatable intermediates gave satisfactory ^1H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.

in principle, readily applicable for the preparation of crocacins A, B, and D. Further optimization of the synthesis, as well as application to the preparation of novel structural analogues of crocacin C is underway, and the results will be described in a full account of this work.

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Supporting Information Available: Experimental details for key transformations, spectral data for key intermediates, and spectroscopic data for synthetic and natural crocacin C (**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

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