ORGANIC LETTERS

2000
Vol. 2, No. 21
3365−3367

Total Synthesis of (+)-Crocacin C

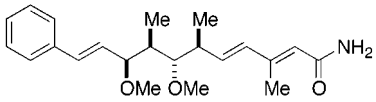
John T. Feutrill, Michael J. Lilly, and Mark A. Rizzacasa*

School of Chemistry, The University of Melbourne, Victoria 3010, Australia

masr@unimelb.edu.au

Received August 16, 2000

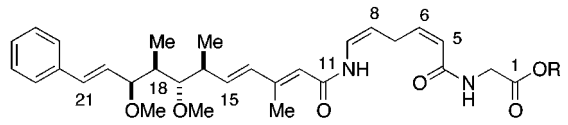
ABSTRACT



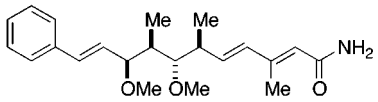
(+)-Crocacin C (**3**)

The first asymmetric synthesis of (+)-crocacin C (3) is described which served to confirm the absolute configuration of this compound. The key step in the sequence was the stereoselective assembly of the (*E*,*E*)-diene amide side chain by a Stille cross-coupling between the stannane 5 and vinyl iodide 6.

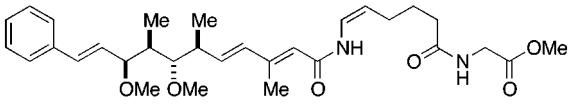
The crocacins A (**1**) and B (**2**) are electron transport inhibitors isolated from a strain of *Chondromyces crocatus* (Cm c2).[1,2]



1 Crocacin A; R = Me
2 Crocacin B; R = H



3 Crocacin C



4 Crocacin D

These compounds were identified as unusual linear dipeptides of glycine and a 6-aminohexadienoic acid which possesses a complex *N*-acylpolyketide residue. The polyketide fragment is a substituted phenylundecatrienoic acid with an *anti-anti-syn* stereotetrad which is also found in *C. crocatus* as its primary amide crocacin C (**3**). However, compound **3** may form in additional amounts during the isolation process due to cleavage of the acid-sensitive enamide bond in **1** and **2**. Crocacin D (**4**) was isolated from *C. pediculatus* and is a dipeptide of glycine and 6-aminohexenoic acid with the same *N*-acylpolyketide residue as compounds **1**−**3**. The relative configurations depicted for **1**−**4** were proposed by Jansen and co-workers using a combination of MM^+ calculations and NOE experiments.[2]

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 (**4**) is the most active of the group against the fungus *Saccharmyces cerevisiae* with an MIC of 1.4 ng mL^{-1} compared to 10 μg mL^{-1} for crocacin A (**1**), 12.5 μg mL^{-1} for crocacin B (**2**), and 100 μg mL^{-1} for crocacin C (**3**).[2] A detailed study revealed that crocacin A (**1**) blocks NADH oxidation in beef heart submitochondrial particles, and the site of inhibition within the electron transport chain was identified as the cytochrome bc_1 segment (complex III).[1] Toxicity was also observed in L929 mouse fibroblast cell culture.[2] We now report the total synthesis of the parent polyketide (+)-

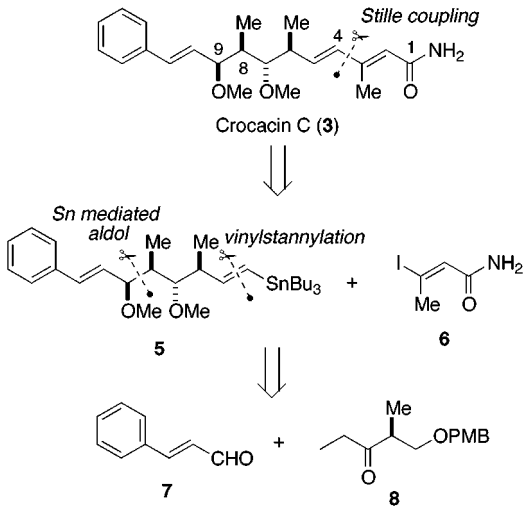
(1) Kunze, B.; Jansen, R.; Höfle, G.; Reichennach, H. *J. Antibiot.* **1994**, *47*, 881.
(2) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085.
(3) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley and Sons: New York, 1997; pp 1−652.
(4) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Rizzacasa, M. A.; Zammit, S. C. *Org. Lett.* **2000**, *2*, 191−194.
(5) (a) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233−4236. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister. M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287−11314.
(6) Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996**, *37*, 8243−8246. Forsyth, C. J.; Lee, C. S. *Tetrahedron Lett.* **1996**, *37*, 6449−6452. Details for the preparation of ketone **8** are given in the Supporting Information.
(7) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

10.1021/ol0064664 CCC: $19.00
Published on Web 09/23/2000

crocacin C (**3**) which confirms the absolute configuration of this compound.

A retrosynthetic analysis of crocacin C (**3**) is shown in Scheme 1. The C1−C5 (*E*,*E*)-dienamide portion of **3** could

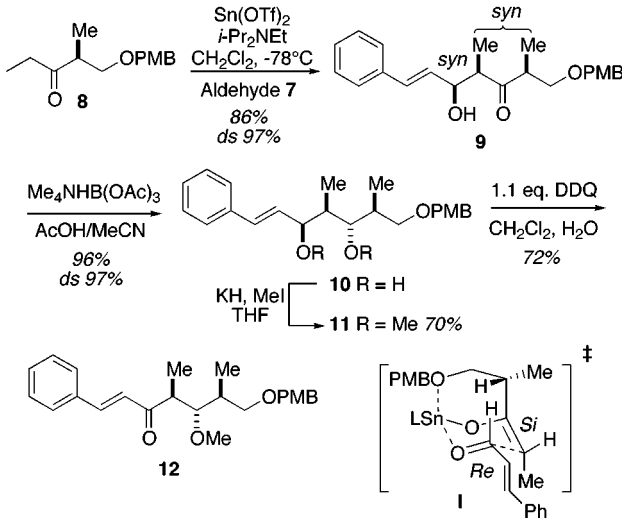
Scheme 1



be constructed by a Stille coupling[3] between the stannane **5** and vinyl iodide **6**. A similar methodology was utilized to secure the related C20−C24 (*E*,*E*)-diene acid portion of reveromycin B in our recent total synthesis.[4] The C8−C9 bond could be constructed using the substrate-controlled asymmetric *syn*-aldol reaction developed by Paterson.[5] This would involve condensation of the tin enolate derived from the known chiral ketone **8**[6] and cinnamaldehyde (**7**) to provide the *syn*-*syn* isomer. Finally, the desired C6−C9 *anti*-*anti*-*syn* stereotetrad could be secured by a directed *anti*-reduction[7] of the aldol adduct.

The sequence began with a tin-mediated aldol reaction between the enolate derived from ketone **8**[6] and aldehyde **7** which gave the *syn*-*syn* adduct **9** in 97% ds (Scheme 2). The minor aldol stereoisomers were easily removed by flash chromatography to afford pure **9** in high yield. Presumably, this aldol reaction proceeds via the chelated transition state **I** (*Si*-face of the enolate reacts with *Re*-face of the aldehyde) as proposed by Paterson.[5b] Stereoselective directed reduction of ketone **9** was achieved using tetramethylammonium triacetoxyborohydride[7] to provide the *anti* diol **10** along with a trace of the *syn* isomer. SmI_2-mediated Evans−Tishchenko reduction of **9** was unsuccessful.[8] The stereochemistry of the diol **10** was confirmed by ^{13}C NMR chemical shift analysis of the derived acetonide.[9] The stereochemistry of the minor *syn*-diol acetonide could be assigned by ^1H coupling constant

Scheme 2



analysis[9] which served to confirm the stereochemistry of the original aldol adduct **9**. Methylation of **10** using KH as base proceeded smoothly to give the dimethyl ether **11**; however, subsequent removal of the PMB ether proved problematic. Treatment of **11** with a slight excess of DDQ[10] in wet CH_2Cl_2 gave a lower R_f compound in high yield which still possessed the PMB ether. The product was identified as the ketone **12** which results from regioselective oxidative demethylation. Thus, DDQ-mediated hydride abstraction occurs exclusively at the conjugated allylic site rather than the desired benzylic site of the PMB group to give a highly stabilized cation which is quenched by water. Subsequent loss of methanol then provides **12**. Attempted PMB group removal with CAN[11] gave a complex mixture of products.

At this point we elected to address the selective removal of the PMB ether rather than change the protecting group on the original ketone **8** used in the aldol reaction. To circumvent the problematic allylic oxidation, the electron density at this center needed to be reduced. This was effected by acetylation of diol **10** to provide diacetate **13** which upon exposure to DDQ gave the debenzylated compound **14** in good yield without any undesired allylic oxidation (Scheme 3). Reprotection of the primary alcohol gave TBDPS ether **15** and reductive removal of the acetates yielded diol **16**. Methylation then afforded the dimethyl ether **17** in excellent yield. Desilylation gave the alcohol **18**, and Dess−Martin oxidation[12] provided the corresponding aldehyde which was subjected to chromium-mediated vinylstannylation using the protocol developed by Hodgson.[13] The resultant (*E*)-stannane **5** was easily purified over NEt_3-deactivated silica gel.

(8) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

(9) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515. Evans, D. A.; Reiger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100. ^{13}C NMR data for *anti*-diol acetonide: δ 100.5 (acetal C), 23.6 (Me), 25.7 (Me). *Syn* diol acetonide: δ 99.2 (acetal C), 19.7 (Me), 30.0 (Me); ^1H NMR δ 3.72 (1H, dd, $J_{7,8} = 1.8$, $J_{7,6} = 9.8$ Hz, H7), 4.53 (1H, ddd $J_{9,11} = 1.8$, $J_{9,8} = 1.8$, $J_{9,10} = 5.6$ Hz, H9).

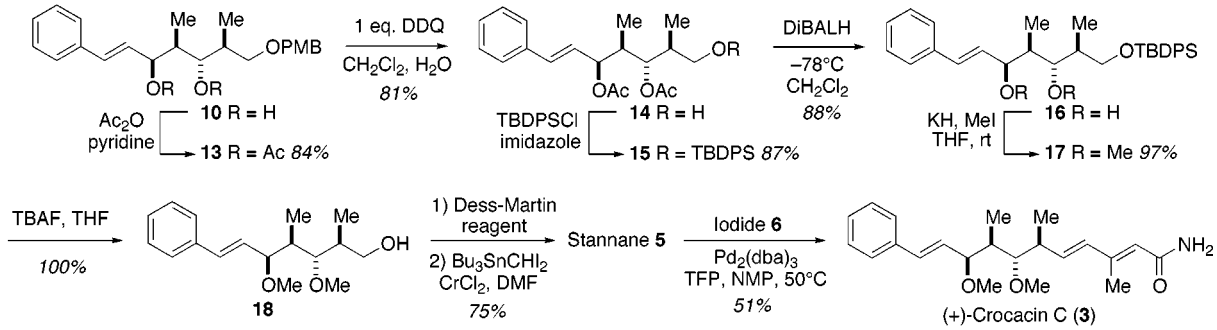
(10) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

(11) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand.* **1984**, *38*, 419−422.

(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

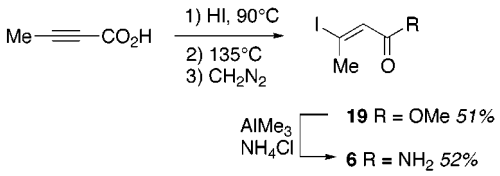
(13) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Tetrahedron Lett.* **1998**, *39*, 6419−6420. Hodgson, D. M.; Foley, A. M.; Boulton, L. T.; Lovell, P. J.; Maw, G. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2911−2922.

Scheme 3



The iodide **6** required for coupling was synthesized from tetrolic acid as shown in Scheme 4. Addition of HI gave the

Scheme 4



(*Z*)-acid which was isomerized to a 70:30 mixture of *E*:*Z* isomers, respectively, by heating at 135 °C for 16 h.[14] Methylation and chromatography gave the pure (*E*)-ester **19**[15] which upon ester−amide exchange[16] provided iodide **6** as a crystalline solid.

Treatment of a solution of the stannane **5** and iodide **6** in NMP with a catalytic amount of $Pd_2(dba)_3$ and TFP[17] at 50 °C afforded (+)-crocacin C (**3**) after purification by silica gel chromatography followed by preparative reverse phase HPLC. The ^{1}H NMR, ^{13}C NMR, UV, and IR spectra of synthetic crocacin C (**3**) were identical to those recorded for the natural product. Furthermore, synthetic **3** had a rotation, $[\alpha]^{18}_D$ +61.3 (*c* 0.3, MeOH), which compared well to that quoted for the natural product, $[\alpha]^{22}_D$ +52.2 (*c* 0.3, MeOH).[2] Therefore, we propose that the absolute configurations of crocacins A−D (**1**−**4**) are as shown.

In conclusion, the first asymmetric synthesis of (+)-crocacin C (**3**) has been achieved which confirmed the proposed relative stereochemistry and determined the absolute stereochemistry of the natural product. Key steps in this route are the concurrent introduction of three of the four asymmetric centers using a substrate-controlled aldol reaction[5] as well as a stereoselective Stille coupling to afford the (*E*,*E*)-dienamide moiety. The synthesis of the other crocacins is underway.

Acknowledgment. We thank Dr. Rolf Jansen and Professor Gerhard Höfle (Gesellschaft für Biotechnologische Forschung) for the NMR spectra and an authentic sample of crocacin C. We also gratefully acknowledge the Australian Research Council for financial support.

Supporting Information Available: Experimental procedures and characterization data for compounds **3**, **5**, **6**, and **8**−**18** as well as ^{1}H and ^{13}C NMR spectra of synthetic and natural crocacin C (**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0064664

(14) LeNoble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897−3899.
(15) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834−5845.
(16) Basha, A.; Lipton, N.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, 989−993.
(17) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.