ORGANIC LETTERS

2002
Vol. 4, No. 4
525−527

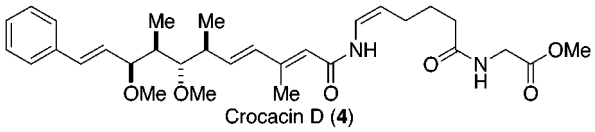
Total Synthesis of (+)-Crocacin D

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 November 21, 2001

ABSTRACT

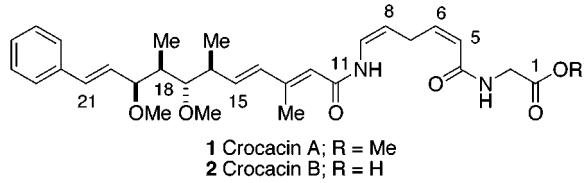


Crocacin D (**4**)

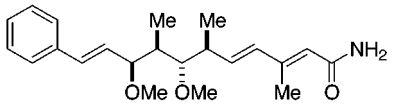
The first asymmetric synthesis of (+)-crocacin D (4) is described. The key steps in the sequence are the stereoselective assembly of the stereotetrad via a substrate-controlled aldol reaction and *anti*-selective reduction, formation of the (*E*,*E*)-diene by a Stille cross-coupling between the stannane 8 and vinyl iodide 9, and the acylation of (*Z*)-enecarbamate 6 with the acid chloride derived from polyketide fragment 16 which introduced the (*Z*)-enamide functionality.

The crocacins A (**1**), B (**2**), C (**3**), and D (**4**) are a group of electron transport inhibitors recently isolated from myxobacteria belonging to the *Chondromyces* genus.[1,2] These unusual linear dipeptides contain a reactive *N*-acyl enamine or enamide functionality which is present in a number of other myxobacteria metabolites[3] as well as natural products isolated from marine sponges.[4] Compounds **1**−**4** moderately inhibit the growth of a few Gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. The most active is crocacin D (**4**) which showed an MIC of 1.4 ng mL^{-1} against the fungus *Saccharomyces cerevisiae* and strong toxicity (IC_{50} of 0.06 mg L^{-1}) toward L929 mouse fibroblast cell culture.[2]

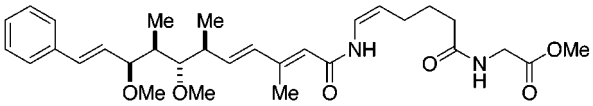
We reported the first total synthesis of the parent polyketide crocacin C (**3**)[5] which served to confirm the absolute configuration of this compound. This first synthesis has been followed by two others which are in agreement with our original assignment.[6] We now report the first stereoselective total synthesis of the most active compound in this series, (+)-crocacin D (**4**).



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



3 Crocacin C



4 Crocacin D

The (*Z*)-enamide present in crocacin D (**4**) represents a synthetic challenge, and we were mindful of the sensitivity of this functional group. In fact, it has been proposed that an amount of crocacin C (**3**) may arise from hydrolysis of the enamide in the other crocacins during isolation.[2] This functionality is also probably responsible for the biological activity of this series of compounds since the primary amide **3** is essentially inactive.[2] Furthermore, it has been shown that compounds which contain an enamide functionality are rendered inactive on chemical modification of this group,

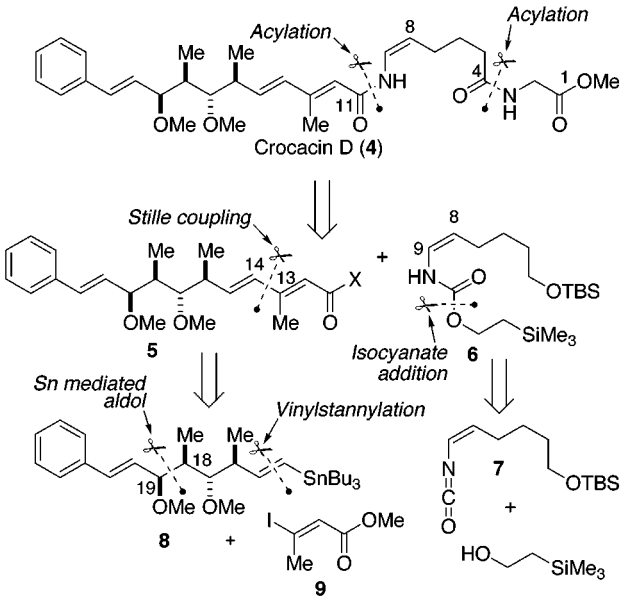
(1) Kunze, B.; Jansen, R.; Höfle, G.; Reichenmach, H. *J. Antibiot.* **1994**, *47*, 881.
(2) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085.
(3) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.
(4) (a) Erickson, K. L.; Beutler, J. A., Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) Murray, L.; Lim, T. K.; Currie, G.; Capon, R. J. *Aust. J. Chem.* **1995**, *48*, 1253. (c) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laasko, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805.
(5) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365.
(6) (a) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, *42*, 497. Chakraborty, T. K.; Jayaprakash, S. Laxman, P. *Tetrahedron* **2001**, *57*, 9461. (b) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, *3*, 3951.

10.1021/ol017092x CCC: $22.00
Published on Web 01/22/2002

e.g., saturation of the enamide double bond.[7] It has therefore been postulated that the mode of action involves protonation of the enamide group followed by nucleophilic attack of the resultant *N*-acyliminium ion to form an enzyme conjugate.[7,8]

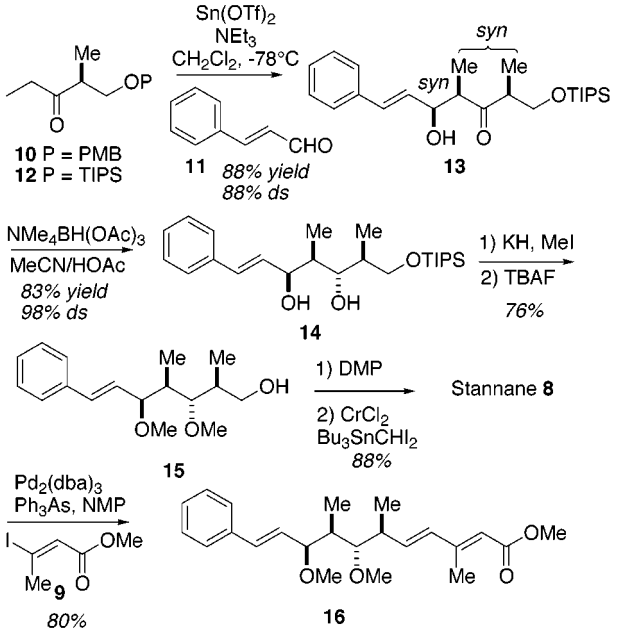
We elected to investigate a synthetic approach to crocacin D (**4**) which involves acylation[9] of the anion derived from (*Z*)-enecarbamate **6** with an appropriate acyl-activated polyketide fragment **5** as shown in Scheme 1. This would

Scheme 1



provide a protected (2-trimethylsilylethyl carbamate or Teoc) enamide[10] which would be more stable to subsequent chemical manipulation and then easily be unveiled in a final deprotection step. The enecarbamate **6** could be prepared from the corresponding (*Z*)-vinylisocyanate **7** by addition of trimethylsilylethanol[9b,10] while the isocyanate **7** is secured via Curtius rearrangement of the corresponding (*Z*)-*N*-acyl azide. The required precursor to polyketide **5** could be constructed by a Stille coupling[11] between the known stannane **8** and vinyl iodide **9** based on our successful approach to crocacin C (**3**).[5] The C18−C19 bond is constructed using the highly selective substrate-controlled asymmetric *syn*-aldol reaction developed by Paterson,[12] and the desired C16−C19 *anti-anti-syn* stereotetrad is finally secured by a directed *anti*-reduction[13] of the aldol adduct. Our earlier report of the synthesis of stannane **8** utilized a Paterson aldol reaction between the tin enolate derived from ketone **10** and cinnamaldehyde (**11**).[5] In this route, we encountered problems with deprotection of the PMB ether in the presence of an allylic methoxy group which necessitated excessive protective group manipulation so we chose to utilize the TIPS-protected chiral ketone **12**[14] instead (Scheme 2).

Scheme 2

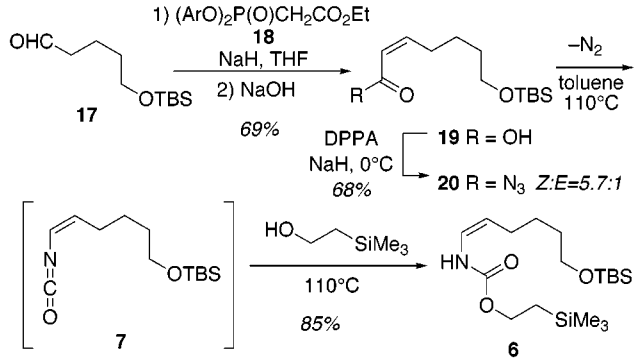


A tin-mediated aldol reaction[12,14] between the enolate derived from ketone **12** and aldehyde **11** gave a high yield of the *syn-syn* adduct **13** (77% + 11% mixture of diastereoisomers), and subsequent stereoselective directed reduction[13] provided pure *anti*-diol **14** after flash chromatography. Methylation then afforded the dimethyl ether and desilylation gave known alcohol **15**.[5,6] This new sequence to the common key intermediate **15** is highly efficient (4 steps from aldehyde **11**, 48% overall yield) and represents a significant improvement when compared to our original route (8 steps from **11**, 39% overall)[5] and those of the other reported syntheses of crocacin C (**3**) (both 12 steps from **11**, 16%[6a] and 31%[6b] overall). Conversion of alcohol **15** into stannane **8** followed our published proceedure[5,15] and Stille coupling[16] between **8** and the known iodide **9**[17] mediated by $Pd_2(dba)_3$ in the presence of Ph_3As[18] gave the diene ester **16** in excellent yield.

The synthesis of the (*Z*)-enecarbamate **6** began with aldehyde **17**[19] (Scheme 3). A modified WHE reaction using

(7) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241.
(8) Gentle, C. A.; Bugg, T. D. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1279.
(9) (a) Shimasaki, H.; Kagechika, H.; Fukasawa, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1995**, *43*, 100. (b) Roush, W. R.; Pfeifer, L. A. *J. Org. Chem.* **1998**, *63*, 2062.
(10) Smith, A. B., III; Zheng, J. *Synlett* **2001**, 1019.
(11) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Farina, V.; Krishnamurthy V. Scott W. J. In *Organic Reactions*; J. Wiley and Sons: Paquette, L. A., Ed.; New York, 1997; p 1.
(12) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.
(13) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(14) (a) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (b) Paterson, I.; Chen, D. Y.-K.; Aceña, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513.
(15) Hodgson, D. M.; Foley, A. M.; Boulton, L. T.; Lovell, P. J.; Maw, G. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2911.
(16) Dominguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071.

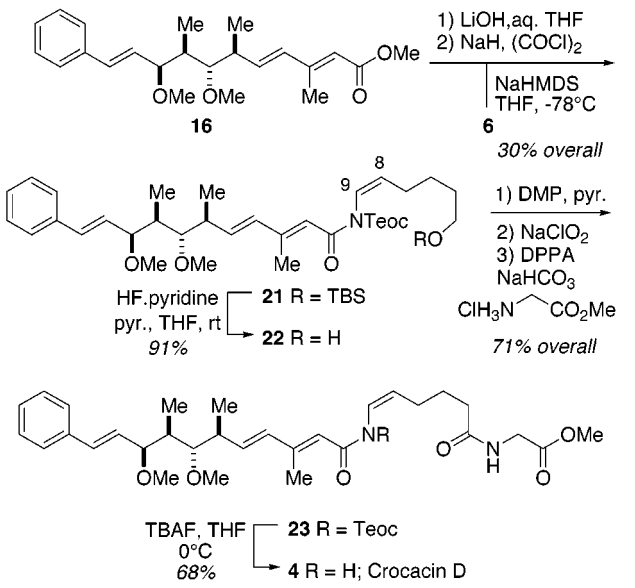
Scheme 3



the phosphonate **18** (Ar = *o*-MeC_6H_4) described by Ando[20] gave the (*Z*)-α,*β*-unsaturated ester which on hydrolysis provided the (*Z*)-acid **19**. In the past, the production of (*Z*)-enamides by nucleophilic addition to a vinyl isocyanate has proved problematic due to isomerization of the double bond.[21] Kitahara recognized that this occurred in the step involved with the synthesis of the *N*-acyl azide and found that the use of diphenylphosphoryl azide (DPPA) in the presence of NaH at 0 °C reduced isomerization and allowed for the production of (*Z*)-vinyl isocyanates.[22] To our delight, treatment of acid **19** with DPPA and NaH gave acyl azide **20** and the corresponding (*E*)-isomer in a favorable ratio of 5.7:1, respectively, which were easily separated by flash chromatography. Heating azide **20** in toluene at 110 °C afforded the (*Z*)-vinyl isocyanate **7** which could be isolated but was in practice simply treated with trimethylsilylethanol in situ[9b,10] to afford the enecarbamate **6** in excellent yield.

The final steps to crocacin D (**4**) are shown in Scheme 4. Hydrolysis of ester **16** gave the derived acid which was converted into its sodium salt and treated with oxalyl chloride. A solution of the anion obtained from deprotonation of **6** with NaHMDS in THF was then added to the resultant crude acid chloride and this sequence afforded, after chromatographic purification, the desired enamide **21**. The coupling constant measured between H8 and H9 was in accord with the *Z* stereochemistry ($J_{8,9}$ = 8.1 Hz) while the chemical shift for H8 (5.49 ppm) indicated the electron density at this center was reduced in comparison to crocacin D itself (H8: δ 4.67 ppm)[2] imparting the desired increased stability to the enamide system. Selective deprotection of the primary alcohol in the presence of the Teoc group was achieved using HF.pyridine buffered with pyridine[23] to provide alcohol **22**. Two-step oxidation (Dess−Martin periodinane[24] and then $NaClO_2/NaH_2PO_4$[25]) cleanly afforded

Scheme 4



the required acid which was coupled[26] with glycine methyl ester to give dipeptide **23** in good yield. Exposure of **23** to TBAF in THF at 0 °C provided (+)-crocacin D (**4**) {$[\alpha]_D$ +102.7 (*c* 0.22, MeOH); lit.[2] $[\alpha]_D$ +109.6 (*c* 0.56, MeOH)} which was easily purified by flash chromatography using NEt_3-deactivated silica gel. The synthetic material was identical to the natural product by all the usual criteria (^1H and ^{13}C NMR, UV, IR, MS and TLC).

In conclusion, the first asymmetric synthesis of (+)-crocacin D (**4**) was achieved in 15 linear steps (4.4% overall yield) from cinnamaldehyde (**11**). Key steps in this route are the concurrent introduction of three of the four asymmetric centers using a substrate-controlled aldol reaction as well as a Stille coupling to afford the (*E*,*E*)-diene system. Acylation of an enecarbamate anion with an acid chloride installed the (*Z*)-enamide moiety. The synthesis of the other crocacins as well as analogues using this methodology is currently underway in our laboratory.

Acknowledgment. We are indebted to Dr. Rolf Jansen (Gesellschaft für Biotechnologische Forschung) for copies of the ^1H and ^{13}C NMR spectra of crocacin D as well as a generous amount of authentic sample. We also gratefully acknowledge funding from the Australian Research Council.

Supporting Information Available: Characterization data for key intermediates as well as NMR spectra of synthetic and natural crocacin D (**4**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL017092X

(17) (a) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834. (b) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Rizzacasa, M. A.; Zammit, S. C. *J. Org. Chem.* **2001**, *66*, 2382.

(18) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(19) Prepared in two steps from 1,5-pentanediol: (1) NaH, TBSCl, 0 °C, THF; (2) Dess−Martin periodinane, CH_2Cl_2, rt.

(20) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.

(21) For an example, see: Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.

(22) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397.

(23) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. For the selective deprotection of a primary TBS ether in the presence of Tmse esters using the same conditions, see ref 17b.

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

(25) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

(26) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 849.