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# Total synthesis of (+)-crocacin C

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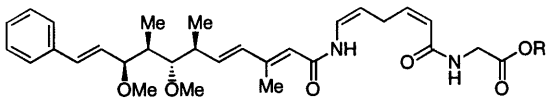
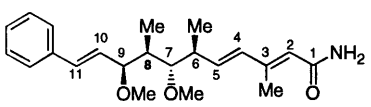
**Abstract**—The first synthesis of (+)-crocacin C (**3**) in optically pure form is achieved following a convergent strategy. The synthesis also establishes the absolute stereochemistries of this novel class of potent antifungal and highly cytotoxic compounds. The naturally occurring crocacin C has (6*S*,7*S*,8*R*,9*S*) configuration, which is also the same for other congeners of the family, crocacins A, B and D. 

Crocacins A–D (**1**–**4**), novel antifungals and highly cytotoxic metabolites were isolated from the myxobacterial strains of *chondromyces crocatus* and *chondromyces pediculatus*.[1,2] The biological activity of the major component, crocacin A, consists of an effective growth inhibition of fungi and yeasts, caused by inhibition of the electron flow within the cytochrome $bc_1$ segment (complex III) of the respiratory chain.[3] Crocacin D shows a distinctly higher biological activity against *Saccharomyces cerevisiae* and higher toxicity in L929 mouse fibroblast cell culture compared to other crocacins.

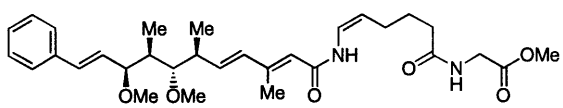
The structures of crocacin molecules with polyketide-derived four consecutive stereocentres, unusual dipeptides of glycine and a 6-aminohexenoic (in crocacin D) or -hexadienoic acid (in crocacins A and B) and large number of double bonds with their respective geometric constraints make their total synthesis a challenging task. Although the relative configurations of these molecules were deduced using 2D-NMR experiments and molecular modelling studies,[1] their absolute stereochemistries are yet to be determined. We envisaged that the total synthesis of these molecules would not only provide an access to larger quantities of them necessary for further biological studies, but also help to establish their absolute stereochemistries. In this paper, we describe the first total synthesis of (+)-crocacin C in optically pure form following an efficient, convergent approach. Our synthesis affirms the relative stereochemistry of the molecule deduced earlier[1] and establishes the absolute configuration of the natural product as (6*S*,7*S*,8*R*,9*S*).



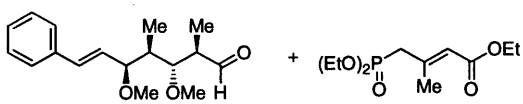
**1**: crocacin A (R = Me)
**2**: crocacin B (R = H)



**3**: crocacin C



**4**: crocacin D



**5** **6**

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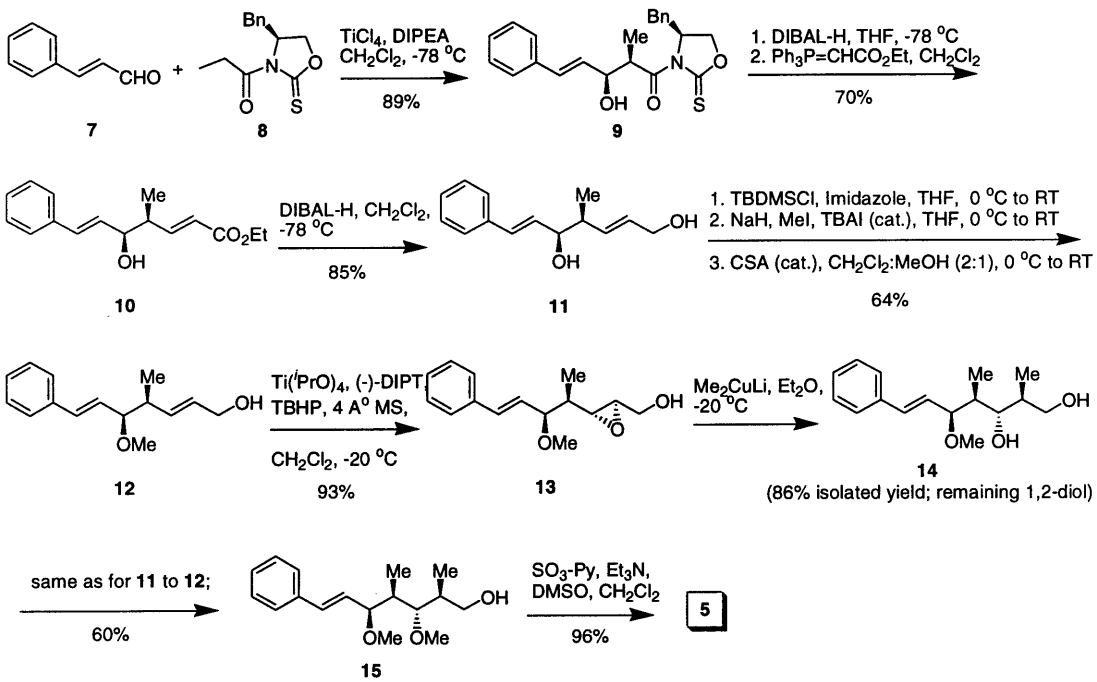
Retrosynthetically, crocacin C can be dissected into two halves, an aldehyde component **5** and the diethylphosphonate **6**,[4] which could be coupled using Horner–Wadsworth–Emmons olefination method. The salient feature of our synthesis is a Ti(IV)-mediated diastereoselective aldol reaction[5] using a 2-oxazolidinethione-based chiral auxiliary,[6] which was expected to fix the $C_8$ and $C_9$ stereocentres. The remaining two centres, $C_6$ and $C_7$, were planned to be constructed employing Sharpless asymmetric epoxidation followed by lithium dimethylcuprate opening of the epoxide ring.

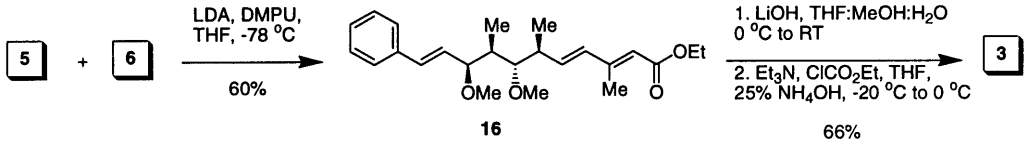
Scheme 1 outlines in detail the stereoselective synthesis of the aldehyde **5**. Asymmetric aldol addition of the titanium enolate derived from the acyloxazolidinethione **8**[6] to cinnamaldehyde **7** gave the 'non-Evans' *syn* aldol product **9**[5] as the only isolable diastereomer in 89% yield.[7] The relative and absolute stereochemistry of the product were assigned on the basis of earlier reported work.[5] Controlled reduction of **9** with 1 equivalent of DIBAL-H gave an intermediate aldehyde,[8,9] which was reacted with the stabilised ylide to obtain α,β-unsaturated ester **10** in 70% yield from **9**. The ester function of **10** was subsequently reduced to furnish the diol **11**.[7] Routine functional group manipulations were carried out next to methylate the secondary hydroxyl in three steps in 64% overall yield: selective protection of primary alcohol as a silyl ether, methylation of secondary hydroxyl group and finally deprotection of the primary alcohol. The resulting allylic alcohol **12** was subjected to Sharpless asymmetric epoxidation using (−)-DIPT to furnish the expected epoxy alcohol **13** as the only diastereomer in 93% isolated yield. Regioselective opening of the epoxy alcohol **13** using $Me_2CuLi$ gave the required 1,3-diol **14** as the major product.[10] The minor 1,2-diol could be removed easily by standard silica gel column chromatography to obtain 86% yield of **14**. The bulky substituent at the '3-position' of the '2,3-epoxy-alcohol' moiety in **13** and also electronic factors helped to open the epoxide ring more favourably at the less crowded '2-position' giving an excellent yield of the 1,3-diol. Next, the same three steps, mentioned above for the conversion of **11** to **12**, were repeated on intermediate **14** to methylate its secondary alcohol furnishing the desired product **15**[11] in 60% overall yield. Oxidation of **15** using $SO_3$–pyridine gave the aldehyde **5** in 96% yield.[7]

The stage was now set to carry out the coupling of aldehyde **5** and the diethylphosphonate **6**, which was prepared following the procedure reported earlier.[4] Treatment of **5** (Scheme 2) with the anion generated from **6** using LDA in presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at −78°C for 8 h gave the desired *E*-olefin **16** in 60% yield (based on 20% recovered starting aldehyde). Although the olefination was slow at −78°C, the reaction temperature could not be raised due to the formation of considerable amounts of eliminated product at higher temperatures. The basic framework of crocacin C in **16** was finally converted to the natural product **3**[11] in two steps in 66% yield: saponification followed by conversion of the acid to the amide by a mixed anhydride method.

Our synthetic crocacin C showed rotation $[\alpha]_D^{20}$ +53.8 (*c* 0.2, MeOH); lit. value: $[\alpha]_D^{22}$ +52.2 (*c* 0.3, MeOH).[1] It was identical in all respects with the naturally occurring crocacin C having all spectroscopic data[11] matching with those reported for the natural product.[1] Thus, the naturally occurring crocacin C has the (6*S*,7*S*,8*R*,9*S*) configuration of the synthetic product reported here. Since crocacin C is the biogenetic precursor of crocacin




**Scheme 1.** Stereoselective synthesis of aldehyde **5**.




**Scheme 2.** Coupling of aldehyde **5** and the diethylphosphonate **6** to furnish crocacin C (**3**).

A, B and D, these compounds should also have the same absolute configuration. Efforts are now on to achieve the total synthesis of other members of the family.

## Acknowledgements

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11. Selected physical data for **15**. $R_f = 0.4$ (silica, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}$ −6.5 (*c* 1, $CHCl_3$); IR (neat): $\nu_{max}$ 3450, 2975, 2940, 2875, 2825, 1450, 1100 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$, atom numberings of **3**): $\delta$ 7.36–7.17 (m, 5H, aromatic), 6.54 (d, $J = 16$ Hz, 1H, C11-*H*), 6.14 (dd, $J = 16$, 7.2 Hz, 1H, C10-*H*), 4.04 (dd, $J = 7.2$, 2 Hz, 1H, C9-*H*), 3.79 (dd, $J = 11.2$, 3.4 Hz, 1H, C5-*H*), 3.53 (s, 3H, $OCH_3$), 3.49 (dd, $J = 11.2$, 4.3 Hz, 1H, C5-*H*′), 3.3 (s, 3H, $OCH_3$), 3.25 (dd, $J = 9.5$, 2.6 Hz, 1H, C7-*H*), 2.6 (br s, 1H, O*H*), 1.85 (m, 2H, C6-*H* and C8-*H*), 1.19 (d, $J = 6.9$ Hz, 3H, $CH_3$), 0.89 (d, $J = 7.2$ Hz, 3H, $CH_3$); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 136.72, 132.09, 129.29, 128.51, 127.51, 126.33, 88.24, 81.16, 64.4, 61.41, 56.28, 42.22, 35.98, 16.1, 10.34; MS (LSIMS): *m*/*z* (%): 301 (20) $[M^+ + Na]$, 246 (10) $[M^+ - CH_3OH]$, 215 (20) $[M^+ + H - 2CH_3OH]$.
Selected physical data for **3**. $R_f = 0.5$ (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20}$ +53.8 (*c* 0.2, MeOH); IR (neat): $\nu_{max}$ 2925, 1655, 1600, 1190 $cm^{-1}$; $^1H$ NMR (500 MHz, acetone-$d_6$, the amide protons are exchanged and were not observed): $\delta$ 7.45 (d, $J = 8.0$ Hz, 2H, aromatic, *ortho*-protons), 7.31 (dd, $J = 8.0$, 7.4 Hz, 2H, aromatic, *meta*-protons), 7.22 (t, $J = 7.4$ Hz, 1H, aromatic, *para*-proton), 6.58 (br d, $J = 16.1$ Hz, 1H, C11-*H*), 6.23 (dd, $J = 16.1$, 7.24 Hz, 1H, C10-*H*), 6.09 and 6.07 (m, 2H, C4-*H* and C5-*H*), 5.79 (d, $J = 1.1$ Hz, 1H, C2-*H*), 4.07 (ddd, $J = 7.24$, 2.4, 1 Hz, 1H, C9-*H*), 3.51 (s, 3H, C7-$OCH_3$), 3.29 (s, 3H, C9-$OCH_3$), 3.16 (dd, $J = 9.5$, 2.3 Hz, 1H, C7-*H*), 2.58 (m, 1H, C6-*H*), 2.21 (d, $J = 1.1$ Hz, 3H, C3-$CH_3$), 1.56 (m, 1H, C8-*H*), 1.16 (d, $J = 6.95$, 3H, C6-$CH_3$), 0.84 (d, $J = 7.1$ Hz, 3H, C8-$CH_3$); $^{13}C$ NMR (125 MHz, acetone-$d_6$): $\delta$ 169.19, 148.20, 137.89, 137.12, 135.00, 132.56, 130.49, 129.38, 128.27, 127.25, 121.88, 87.21, 81.83, 61.44, 56.47, 43.63, 40.77, 19.26, 13.52, 10.16; MS (LSIMS): *m*/*z* (%): 380 (30) $[M^+ + Na]$, 358 (10) $[M^+ + H]$, 326 (44) $[M^+ + H - CH_3OH]$, 294 (16) $[M^+ + H - 2CH_3OH]$.