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Concise Total Synthesis of (+)-Crocacin C

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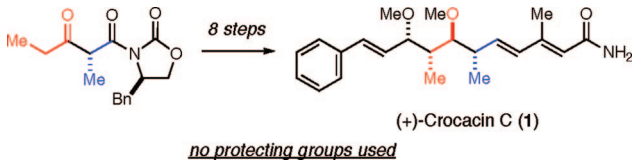


The cytotoxic natural product (+)-crocacin C (**1**) has been synthesized in 10 linear steps from commercially available Evans' chiral propionimide in 5% overall yield (8 steps from Evans' chiral dipropionate synthon). No protecting groups were utilized.

In 1999, Jansen and co-workers reported the structures of crocacin C (**1**) and its congeners crocacins A (**2**), B (**3**), and D (**4**), which were isolated from various strains of the myxobacterium *Chondromyces crocatus* (Figure 1).[1]

These natural products moderately inhibit Gram-positive bacterial growth and possess antifungal and cytotoxic activity.[2] Recently, the crocacins have been identified as novel agricultural pesticide leads.[3] By inspection, crocacin C (**1**) is composed of a polyketide fragment possessing the challenging *anti-anti-syn* stereotetrad (C16−C19) in addition to a conjugated (*E*,*E*)-dienamide system (C11−C15). Crocacins A (**2**), B (**3**), and D (**4**) are further characterized by an acid-sensitive (*Z*)-*N*-acylenamine motif (C7−C11) tethered to a glycine residue. These structural features coupled with an interesting bioactivity profile have made these natural products attractive targets for synthesis. To date, there have been three reported asymmetric total syntheses[4–7] and four asymmetric formal syntheses[8–12] of

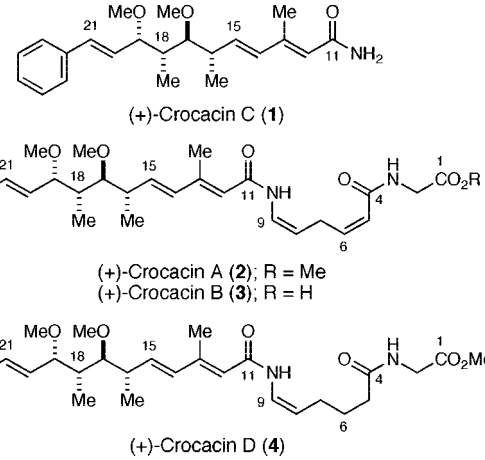
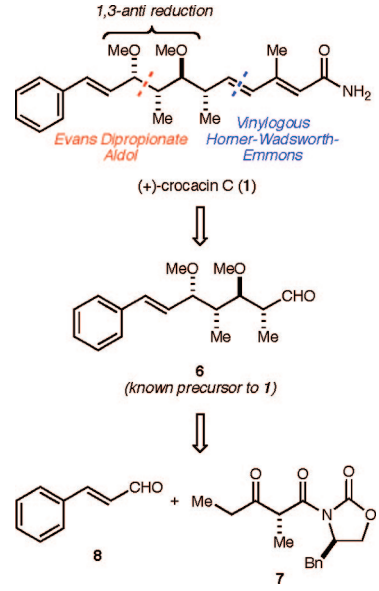


FIGURE 1. Structures of crocacins A−D (**1**−**4**).

SCHEME 1. Retrosynthesis of Crocacin C (1)



crocacin C (**1**). As **1** represents the common structural feature among all congeners, we sought to prepare this natural product in the most efficient manner possible. Toward this end, we began with a retrosynthetic analysis that maximized convergence and avoided protecting groups altogether (Scheme 1).[13]

A disconnection at the C14−C15 olefinic bond yields aldehyde **6** and vinylogous phosphonate **5**,[14] which will be assembled in a forward sense by a vinylogous HWE reaction. Aldehyde **6** is fashioned in turn from an Evans dipropionate aldol reaction between ketoimide **7** and *trans*-cinnamaldehyde

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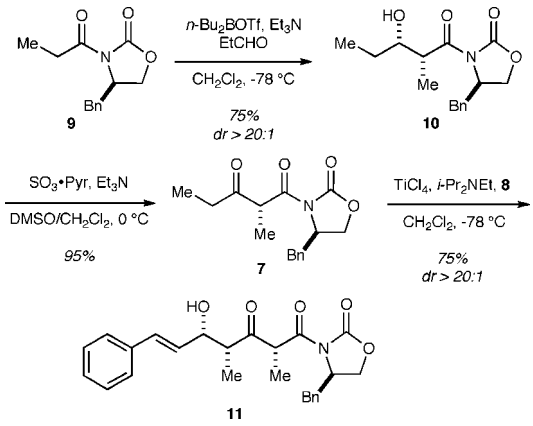
SCHEME 2. Evans Dipropionate Aldol Reaction



(**8**).[15] An obvious strength of this method lies in the ability to (1) exert stereocontrol in the aldol reaction to access either *syn* aldol diastereomer and (2) utilize the newly formed hydroxyl to direct the stereochemical course of the reduction by proper reagent selection, leading to either a 1,3-*syn* or 1,3-*anti* diol.[16]

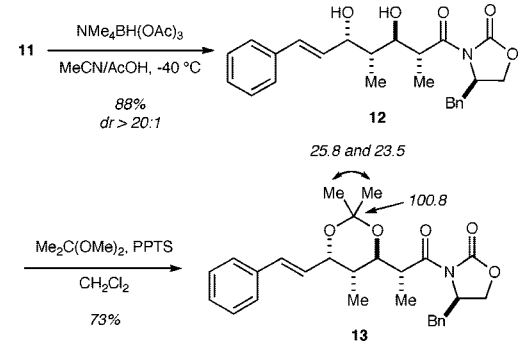
The synthesis commenced with the preparation of ketoimide **7** by an Evans aldol reaction[17] of oxazolidinone **9** and propionaldehyde (dr >20:1) followed by Parikh−Doering oxidation,[18] which proceeded in 71% overall yield. Enolization of **7** with $TiCl_4$ and *i*-Pr_2NEt and subsequent addition of *trans*-cinnamaldehyde (**8**) furnished the desired *syn-syn* aldol **11** (dr >20:1) in 75% yield (Scheme 2).

With aldol **11** in hand, attention was placed on the stereoselective, directed reduction of the C17 ketone with $NMe_4BH(OAc)_3$ to furnish the desired 1,3-*anti* diol.[16] In the event, reduction of **11** in MeCN/AcOH at −40 °C smoothly afforded diol **12** as a single diastereomer. To confirm the relative 1,3-*anti* stereochemistry, diol **12** was converted into an acetonide following standard conditions and subjected to ^{13}C NMR analysis. Resonances from the acetonide NMR (23.5 and 25.8 ppm for the methyls; 100.8 ppm for the ketal carbon) were consistent with those found in a twist-boat conformation, which is indicative of a 1,3-*anti* diol disposition (Scheme 3).[19,20] This analysis is consistent with previous synthetic studies on crocacin C (**1**).[7,21]

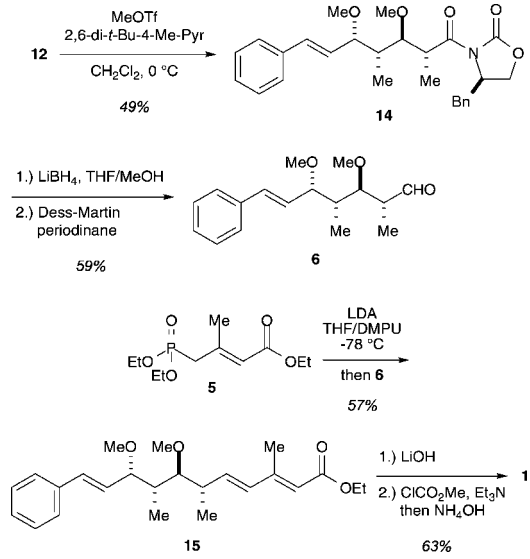
At this point, various methylation protocols were screened to install both requisite methyl ethers.[22] Ultimately, the combination of MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine at 0 °C provided **14** in 49% yield with unproductive elimination accounting for the remaining mass balance (Scheme 4).

Reductive removal of the chiral auxiliary with $LiBH_4$ afforded a known intermediary alcohol, which has been previously converted into crocacin C (**1**) by a number of routes.[4–7] The

SCHEME 3. Reduction of 11 and ^{13}C NMR Acetonide Analysis



SCHEME 4. Completion of the Synthesis



remainder of the synthesis followed known literature protocols. Oxidation of the alcohol with the Dess−Martin periodinane[23] provided aldehyde **6** in 59% yield from **14**. Endgame began with a stereoselective, vinylogous Horner−Wadsworth−Emmons reaction to prepare conjugated *E*,*E*-dienoate **15** in 57% yield as one diastereomer. Saponification of the ester, activation of the intermediary acid with methyl chloroformate, and treatment with aqueous ammonia delivered crocacin C (**1**) in 63% yield from **6**.[6]

In summary, the asymmetric total synthesis of **1** has been accomplished in 10 steps from commercially available Evans' propionimide **9** in 5% overall yield without recourse to protecting groups.

Experimental Section

Aldol 11. To a solution of dipropionimide **7** (1.38 g, 4.77 mmol) in CH_2Cl_2 (19 mL) at −10 °C was added $TiCl_4$ (1.00 g, 5.25 mmol) then freshly distilled *i*-Pr_2NEt (0.68 g, 5.25 mmol). After being stirred for 1 h, the reaction mixture was cooled to −78 °C and freshly distilled aldehyde **8** (0.69 g, 5.25 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min then warmed to −40 °C over a period of 1 h. The reaction mixture was warmed to 0 °C and quenched by the addition of phosphate buffer (7.6 mL, pH 7) and stirred an additional 5 min. The reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined

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organic layers were washed with aqueous $NaHCO_3$ (15 mL) and brine solution (15 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:5) to afford 1.50 g (75%) of aldol **11** as a yellow oil.

$[\alpha]^{20}_D$ −165.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3524, 2252, 1774, 1713, 1391, 1358, 1215, 909, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.13 (m, 10H), 6.63 (dd, J = 16.0, 1.2 Hz, 1H), 6.13 (dd, J = 16.0, 5.6 Hz, 1H), 4.84 (q, J = 7.2 Hz, 1H), 4.78 (br s, 1H), 4.73−4.68 (m, 1H), 4.22−4.12 (m, 2H), 3.24 (dd, J = 13.6, 3.2 Hz, 1H), 3.02−3.00 (m, 2H), 2.74 (dd, J = 13.6, 9.6 Hz, 1H), 1.45 (d, J = 7.6 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 170.0, 153.9, 136.7, 134.9, 130.9, 129.3, 128.9, 128.5, 127.5, 127.4, 126.5, 71.9, 66.6, 55.3, 52.3, 49.7, 37.8, 13.0, 10.5. HRMS (FAB) calcd for $C_{25}H_{27}NO_5 + Na^+$ 444.1786, found 444.1778.

Diol 12. To a stirred solution of $Me_4NBH(OAc)_3$ (5.63 g, 21.40 mmol) in MeCN (10 mL) was added glacial AcOH (10 mL). After being stirred for 30 min, the reaction mixture was cooled to −40 °C and a solution of **11** (1.50 g, 3.57 mmol) in MeCN (10 mL) was added via cannula. After being stirred for 6 h at this same temperature, the reaction mixture was transferred to a refrigerator and allowed to age for 16 h at −20 °C. Aqueous sodium tartrate (0.5 M, 25 mL) was added. The reaction mixture was warmed to rt over 1 h then diluted with additional sodium tartrate (0.5 M, 25 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was back-extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (30 mL) and brine solution (30 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (2:3) to afford 1.32 g (88%) of diol **12** as a yellow oil.

$[\alpha]^{20}_D$ −80.8 (*c* 1.0, CH_2Cl_2); IR (neat) 3460, 3028, 2976, 2360, 2341, 2252, 1779, 1698, 1455, 1385, 1209, 908, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 10H), 6.64 (dd, J = 16.0, 1.2 Hz, 1H), 6.26 (dd, J = 16.0, 5.6 Hz, 1H), 4.77−4.75 (m, 2H), 4.26−4.16 (m, 3H), 3.98 (d, J = 8.4 Hz, 1H), 3.73 (q, J = 6.9 Hz, 1H), 3.31 (br s, 1H), 3.25 (dd, J = 13.2, 3.4 Hz, 1H), 2.81 (dd, J = 13.2, 9.6 Hz, 1H), 1.97−1.90 (m, 1H), 1.31 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 153.3, 136.8, 135.0, 130.5, 130.3, 129.4, 129.0, 128.5, 127.5, 127.4, 126.4, 78.4, 72.8, 66.2, 55.5, 40.3, 39.8, 37.9,15.0, 11.6. HRMS (FAB) calcd for $C_{25}H_{29}NO_5 + Na^+$ 446.1943, found 446.1945.

Acetonide 13. To a stirred solution of diol **12** (80.0 mg, 0.19 mmol) in dimethoxypropane (19 mL) was added a catalytic amount of PPTS. The reaction mixture was stirred for 3 h. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 65.0 mg (73%) of acetonide **13** as a yellow oil.

$[\alpha]^{20}_D$ −50.2 (*c* 1.0, CH_2Cl_2); IR (neat) 3154, 3029, 2986, 2253, 1780, 1698, 1455, 1383, 1263, 1222, 1107, 1022, 969, 909, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.14 (m, 10H), 6.54 (dd, J = 15.8, 0.8 Hz, 1H), 6.09 (dd, J = 15.8, 6.0 Hz, 1H), 4.66−4.54 (m, 1H), 4.57−4.54 (m, 1H), 4.12−4.11 (m, 2H), 4.04−3.96 (m, 1H), 3.67 (dd, J = 9.2, 6.8 Hz, 1H), 3.20 (dd, J = 13.2, 3.2 Hz, 1H), 2.74 (dd, J = 13.2, 9.6 Hz, 1H), 1.93−1.85 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.2, 137.0, 135.3, 130.5, 129.5, 129.0,128.5, 127.4, 127.3, 127.2, 126.4, 100.8, 76.2, 70.0, 66.0, 55.4, 42.9, 38.9, 38.0, 25.8, 23.5, 14.0, 12.8. HRMS (FAB) calcd for $C_{28}H_{33}NO_5 + Na^+$ 486.2256, found 486.2254.

Imide 14. To a stirred solution of the diol **12** (70.0 mg, 0.17 mmol) in $CHCl_3$ (1.5 mL) at 0 °C was added 2,6-di-*tert*-butyl-4-methylpyridine (1.19 g, 5.81 mmol) followed by the addition of MeOTf (0.82 g, 4.98 mmol). The reaction mixture was stirred for 28 h at 0 °C, quenched with MeOH (2 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with brine solution (5 mL), dried (Na_2SO_4) and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to afford 37.0 mg (49%) of imide **14** as a yellow oil.

$[\alpha]^{20}_D$ −74.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3154, 2983, 2253, 1780, 1698, 1470, 1383, 1264, 1094, 907, 733, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.14 (m, 10H), 6.50 (d, J = 21.2, Hz, 1H), 6.08 (dd, J = 21.2, 9.6 Hz, 1H), 4.57−4.56 (m, 1H), 4.13−4.08 (m, 3H), 3.94 (dd, J = 9.6, 4.8 Hz, 1H), 3.41−3.36 (m, 4H), 3.25−3.20 (m, 4H), 2.69 (dd, J = 17.6, 13.0 Hz, 1H), 1.90−1.88 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 9.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 153.1, 136.8, 135.4, 132.3, 129.5, 129.2, 128.9, 128.6, 127.6, 127.3, 126.5, 84.9, 81.8, 66.0, 60.1, 56.5, 55.7, 41.6, 40.7, 37.9, 14.1, 11.0. HRMS (FAB) calcd for $C_{27}H_{33}NO_5 + Na^+$ 474.2256, found 474.2228.

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Supporting Information Available: Experimental procedures for **1**, **6**, and **15**, NMR spectra (^1H and ^{13}C NMR spectra) for **1** and **11**−**14**, and LCMS trace of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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