

**Total Synthesis of (+)-Crocacin C
Using a *Hidden Symmetry***

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Supporting informations

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I- General experimental

Anhydrous dichloromethane, diethylether, toluene and tetrahydrofuran were obtained from the BRAUN MB-SPS800 Solvent Purification System. All experiments using anhydrous solvents were performed under an inert atmosphere of argon, using dried apparatus and employing standard techniques for handling air-sensitive materials.

All reagents were obtained from commercial suppliers unless otherwise stated.

Lipozyme RM IM (from *Rhizomucor miehei* lipase, RML) was a gift from Novo Nordisk A/S (Bagsværd, Denmark).

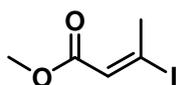
Microwave experiments were performed in a CEM Discover 1 – 300 W oven in sealed tubes (10 mL) equipped with a Teflon coated stirrer bar under argon.

Flash chromatography was performed using Merck 40-63 μm particle-sized silica gel (230- 400 mesh) and eluted with EtOAc in petroleum ether (PE, bp 40-60°C). Analytical thin layer chromatography was performed using 0.20 mm silica gel 60 plates. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with various stains (*p*-anisaldehyde, phosphomolybdic acid...)

Melting points (m.p.) were determined with a melting-point apparatus and were not corrected. High resolution mass spectra (HRMS) were obtained from a spectrometer by electrospray ionisation (the samples for mass spectrum are dissolved in MeOH and then diluted in a 3 mM ammonium acetate methanolic solution or 3mM sodium chloride methanolic solution.)

Proton NMR (^1H) spectra were recorded at 300.13 MHz on a spectrometer using as internal standard the residual CHCl_3 signal for ^1H NMR ($\tau^{\text{M}} = 7.26$). Carbon NMR (^{13}C) spectra were similarly recorded at 75.47 MHz on a spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence and as internal standard the deuteriochloroform (CDCl_3) solvent signal for ^{13}C NMR ($\tau^{\text{M}} = 77.0$). Chemical shifts (δ) are reported in parts per million (ppm). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet or massif, brs: broad signal. Coupling constants (J) are reported in Hertz (Hz).

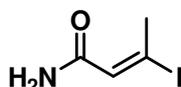
II- Procedures



(E)-methyl 3-iodobut-2-enoate¹: To a solution of (*E*)-3-iodobut-2-enoic acid (530 mg, 2.5 mmol), prepared following the procedure of Parrain *et al.*,² in THF (25 mL), was added cesium carbonate (815 mg, 2.5 mmol) at room temperature and the resulting white suspension was stirred for 15 min. Iodomethane (709 mg, 311 μ L, 5.0 mmol) was then added dropwise and the reaction mixture was stirred for an additional 12 h at room temperature. It was then quenched by adding 20 mL of a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with diethyl ether (3 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 98/2 to 95/5) to afford 526 mg of pure ester (93%), as a light yellow oil. *R*_f = 0.60 (PE/EtOAc : 95/5).

¹H NMR (300 MHz, CDCl₃): δ 6.64 (q, *J* = 1.5 Hz, 1H), 3.69 (s, 3H), 2.98 (d, *J* = 1.5 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 164.6, 131.0, 120.6, 51.4, 31.0.



(E)-3-iodobut-2-enamide (13)³: In a flame dried 25 mL one-necked round bottomed flask, under argon atmosphere, ammonium chloride (235 mg, 4.40 mmol) was suspended in 4 mL of dry toluene. Trimethyl aluminium (2M in hexanes) (2.2 mL, 4.40 mmol) was added dropwise at 0°C and the colorless solution was brought to room temperature and stirred for 30 min. (*E*)-methyl 3-iodobut-2-enoate (100 mg, 0.44 mmol) was then added at 0°C and the reaction mixture was stirred at 50°C for 16 h. It was then cooled to 0°C, ethyl acetate (1 mL) was added followed by a 1N HCl solution until solubilization of aluminium salts (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL), the combined organic layers were washed with saturated aqueous NaHCO₃ (2 X 10 mL), brine (1 x 10 mL), dried (anhydrous MgSO₄), and concentrated in *vacuo*. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 50/50 to 30/70) to afford 85 mg of pure primary amide **13** (91%), as a white solid. m.p. 81-82°C; *R*_f = 0.26 (PE/EtOAc : 1/1).

¹ Chen, S.-H. ; Horvath, R.F. ; Joglar, J. ; Fisher, M. J. ; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834-5845.

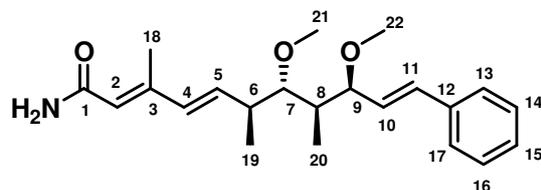
² Abarbri, M.; Parrain, J.-L.; Duchêne, A.; Thibonnet, J. *Synthesis* **2006**, 2951-2970

³ Feutrill, J. T. ; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365-3367

¹H NMR (300 MHz, CDCl₃): δ 6.58 (q, *J* = 1.5 Hz, 1H), 5.36 (brs, 2H_{NH}), 2.98 (d, *J* = 1.5 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 166.0, 132.6, 117.3, 30.7.

Comparison of the ^1H NMR and ^{13}C NMR between natural and synthesized Crocacin C in $[\text{D}_6]$ acetone.



Position	^1H NMR (400.1 MHz)		^{13}C NMR (100.6 MHz)	
	Natural ⁴	Synthesized	Natural ⁷	Synthesized
1	-	-	169.0	169.0
2	5.80, d, J = 1.1 Hz	5.80, d, J = 1.0 Hz	122.0	122.0
3	-	-	148.0	148.1
4	6.09, m	6.10, m	135.0	135.0
5	6.07, m	6.07, m	137.0	137.0
6	2.62, ddq, J = 2.2, 8.1, 6.8 Hz	2.58, m	40.8	40.8
7	3.19, dd, J = 2.2, 9.5 Hz	3.17, dd, J = 2.0, 9.5 Hz	87.1	87.2
8	1.58, ddq, J = 2.5, 9.5, 7.0 Hz	1.55, ddq, J = 2.5, 9.5, 7.0 Hz	43.4	43.5
9	4.08, m	4.08, ddd, J = 7.3, 2.4, 0.9 Hz	81.8	81.8
10	6.25, dd, J = 7.1, 16.2 Hz	6.25, dd, J = 7.0, 16.1 Hz	130.4	130.5
11	6.59, d, J = 16.2 Hz	6.59, d, J = 16.1 Hz	132.5	132.6
12	-	-	137.8	137.9
13	7.46, d, J = 8.0 Hz	7.47, d, J = 7.4 Hz	127.2	127.3
14	7.31, dd, J = 7.5, 8.0 Hz	7.32, dd, J = 7.4, 7.4 Hz	129.3	129.4
15	7.22, dd, J = 7.5, 7.5 Hz	7.22, dd, J = 7.4, 7.4 Hz	128.2	128.3
16	7.31, dd, J = 7.5, 8.0 Hz	7.32, dd, J = 7.4, 7.4 Hz	129.3	129.4
17	7.46, d, J = 8.0 Hz	7.47, d, J = 7.4 Hz	127.2	127.3
18	2.21, d, J = 1.1 Hz	2.21, d, J = 1.0 Hz	13.5	13.5
19	1.20, d, J = 6.8 Hz	1.17, d, J = 7.0 Hz	19.2	19.3
20	0.88, d, J = 7.0 Hz	0.85, d, J = 7.0 Hz	10.1	10.1
21	3.52, s	3.52, s	61.4	61.5
22	3.30, s	3.29, s	56.4	56.5
NH ₂	6.65 (2H)	6.69 (1H) and 6.12 (1H)	-	-

⁴ Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085–1089.

III- Copies of ^1H NMR and ^{13}C NMR

