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

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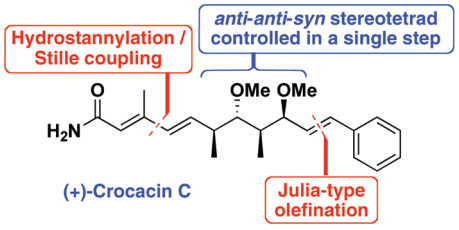

A highly convergent and protecting-group-free synthesis of (+)-crocacin C, featuring an enzymatic enantioselective desymmetrization of a *meso*-diol, a base-induced ring opening of a THP ring, and a one-pot hydrostannylation/Stille coupling as the key steps, is reported. The natural product was obtained in 11 steps and 22.3% overall yield starting from readily available oxabicycle **1**. Finally, a unique enantioselective step, an enzymatic desymmetrization, revealed four stereogenic centers and created one in C4 of the THP furnishing the dense building block **4** with high enantioselectivity (ee >98%).

Introduction

In natural product synthesis, the detection of potential hidden symmetry can dramatically simplify retrosynthetic analysis.[1] In this context, the design of new readily available *meso* compounds and their enantioselective desymmetrizations[2] have become important challenges for synthetic chemists.

We recently disclosed the synthesis of a new family of *meso*-tetrahydropyranyl diols, which were asymmetrically desymmetrized with a high level of enantioselectivity using *Rhizomucor miehei* lipase.[3] Moreover, we showed that it was possible to convert the resulting desymmetrized monoacetate into both enantiomers of a polypropionate fragment with complete diastereo- and enantioselectivity.

In the present paper, we report on the application of this methodology to the synthesis of a biologically active natural product, (+)-crocacin C, which belongs to a family of four natural products (crocacins A−D), isolated from *Chondromyces crocatus* and *Chondromyces pediulatus*[4] in 1994 (Figure 1). The structure of these natural products, elucidated by Jansen et al. in 1999[5] (relative configuration), was confirmed through synthesis.[7a] Crocacins present, as a common framework, a polyenic polypropionate structure bearing an *anti-anti-syn* stereotetrad. Hence, each crocacin is recognizable by the nature of its

(1) For a review on prochiral and *meso* compounds bearing a mirror plan, see: (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765–1784. (b) Rovis T. Recent Advances in Catalytic Asymmetric Desymmetrization Reactions. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: New York, **2007**; pp 275−312, Chapter 10. For a review on centrosymmetric molecules, see: (c) Anstiss, M.; Holland, J. M.; Nelson, A.; Titchmarsh, J. R. *Synlett* **2003**, 1213–1220. Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354.

(2) Some significant examples. Vannusal B: Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8605–8610. Tamiflu: Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895–4902. Ionomycin: Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879–1882. *cis*-Solamin: Göksel, H.; Stark, B. W. *Org. Lett.* **2006**, *8*, 3433–3436. Quadrigemine C and Psycholeine: Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009.

(3) Candy, M.; Audran, G.; Bienaymé, H.; Bressy, C.; Pons, J.-M. *Org. Lett.* **2009**, *11*, 4950–4953.

(4) Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881–886.

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

(6) Crowley, P. J.; Aspinall, I. H.; Gillen, K.; Godfrey, C. R. A.; Devillers, I. M.; Munns, G. R.; Sageot, O. A.; Swanborough, J.; Worthington, P. A.; Williams, J. *Chimia* **2003**, *57*, 685–691.

(7) (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365–3367. (b) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, *42*, 497–499. (c) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9461–9467. (d) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2001**, *3*, 3951–3954. (e) Sirasani, G.; Paul, T.; Andrade, R. B. *J. Org. Chem.* **2008**, *73*, 6386–6388. (f) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085. For a general review on crocacins syntheses see: (g) Andrade, R. B. *Org. Prep. Proced. Int.* **2009**, *41*, 359–383.

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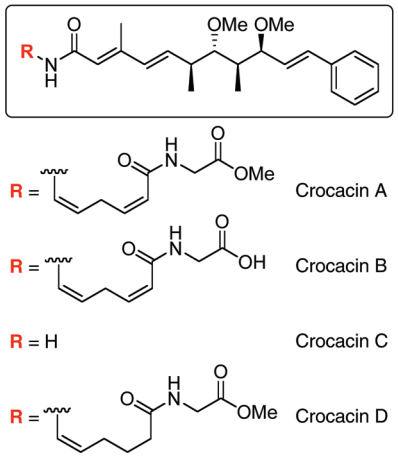
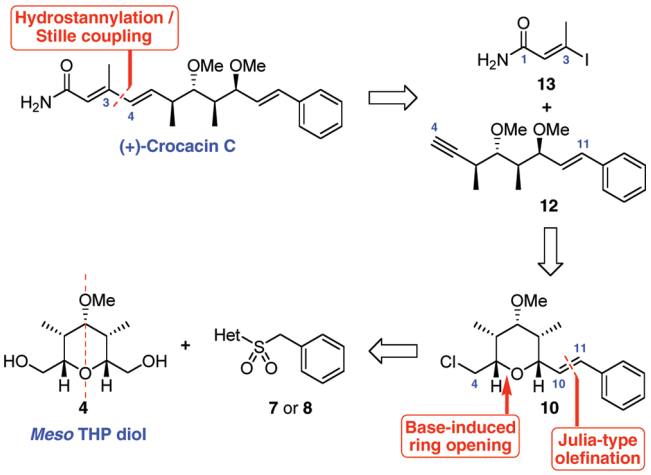


FIGURE 1. Structure of crocacins A−D.

SCHEME 1. Retrosynthetic Plan

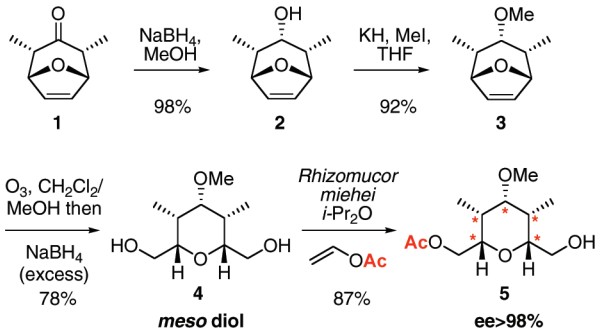


enamide side chain. Crocacins were found to exhibit moderate antibacterial, antifungal, and cytotoxic activities; however, crocacin D presents an important cytotoxicity against the L929 mouse fibroblast cell culture (IC_{50} of 0.06 mg L^{-1}). Finally, a pesticide activity was recently identified for crocacins.[6]

Since the discovery of these natural products, five total syntheses[7] and four formal syntheses[8] of (+)-crocacin C were accomplished, mainly based on aldol chemistry and using chiral auxiliaries. Among all of these approaches, one took advantage of the hidden symmetry of the molecule using a desymmetrization of oxabicycle **1** (structure represented in Scheme 2) by asymmetric hydroboration;[8c] however, an 18-step sequence was still required, starting from **1**, to achieve a formal synthesis of the natural product. Concerning the construction of the dienamide system, two approaches were employed: olefination with Horner−Wadsworth−Emmons reaction[7a,e] or Julia-type reaction[8c] to form the C4−C5 bond, or palladium-catalyzed cross-coupling using Stille reaction[7a,d,f] or Suzuki reaction[8b] to form the C3−C4 bond.

(8) (a) Raghavan, S.; Reddy, S. R. *Tetrahedron Lett.* **2004**, *45*, 5593–5595. (b) Beşev, M.; Brehm, C.; Fürstner, A. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1696–1708. (c) Yadav, J. S.; Reddy, P. V.; Chandraiah, L. *Tetrahedron Lett.* **2007**, *48*, 145–148. (d) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Synlett* **2007**, 2049–2052.

SCHEME 2. Synthesis of the Desymmetrized Monoacetate 5



Moreover (+)-crocacin C could present an interest as a pivotal scaffold for the synthesis of other members of its family as shown by Dias et al.[9]

Results and Discussion

Retrosynthetic Analysis. Our strategy for the synthesis of (+)-crocacin C (Scheme 1) relied on a one-pot hydrostannylation/Stille coupling between Fürstner's intermediate alkyne **12**[8b] and Rizzacasa's iodide **13**,[7a] a base-induced ring opening of the THP ring present in compound **10**, a Julia-type olefination involving sulfones **7** or **8**, and an asymmetric enzymatic desymmetrization of *meso*-THP diol **4**.

Synthesis and Desymmetrization of Diol 4. *meso*-THP diol **4** was built in three steps on a multigram scale starting from the easily available oxabicycle **1** (Scheme 2). This precursor was obtained through a highly diastereoselective [4 + 3] cycloaddition between an oxoallyl cation and furan following conditions described by Lubineau and Bouchain.[10] Hence, oxabicycle **1** was reduced in a complete diastereoselective fashion using sodium borohydride in methanol, and the resulting alcohol was etherified in the presence of potassium hydride and methyl iodide in THF. The resulting methylether was then subjected to ozonolysis [O_3, MeOH/CH_2Cl_2 (1.5/2), −60 °C] ended by a reductive treatment ($NaBH_4$ in excess, −60 °C to rt) to afford the desired *meso*-diol in 70% yield over three steps. The achiral diol **4** was then desymmetrized using *Rhizomucor miehei* [15% weight of the substrate,[11] rt, in *i*-Pr_2O/vinyl acetate (1/1), 18 h]. This crucial transformation could be run on two gram scale without any noticeable loss of yield or enantioselectivity (87%, > 98% ee).[3] It is worth noting that this desymmetrization step allowed the control of five contiguous stereogenic centers, in one single transformation, in addition to the generation of a dense building block.

Olefination by Julia-Type Reaction. Monoacetate **5** was then oxidized under standard Swern conditions,[12] and the resulting crude aldehyde was directly submitted to a Julia-type olefination[13] (Table 1). Two different sulfones, **7**[14]

(9) Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70*, 2225–2234.

(10) (a) Lubineau, A.; Bouchain, G. *Tetrahedron Lett.* **1997**, *38*, 8031–8032. (b) Lautens, M.; Bouchain, G. *Org. Synth.* **2002**, *79*, 251–253.

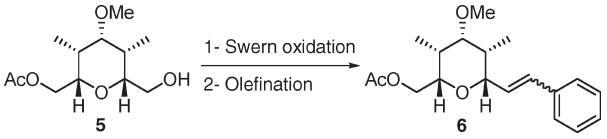
(11) We reported previously the use of 50−60% weight of enzyme compared to the substrate. On a larger scale, this amount could be notably reduced without loss of reactivity or selectivity.

(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

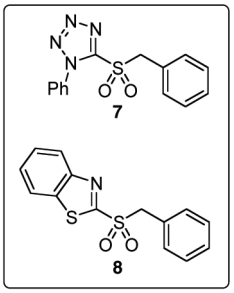
(13) For a review on the Julia-type olefination see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

(14) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

TABLE 1. Swern Oxidation/Julia-Type Olefination Sequence

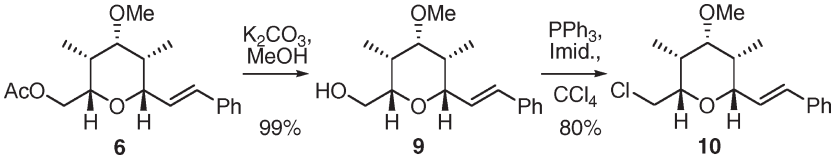


entry	sulfone	base	solvent	*E*/*Z* ratio[a]	yield[b] (%)
1	**7**	KHMDS	THF[c]	63/37	72
2	**7**	NaHMDS	THF[c]	81/19	76
3	**7**	KHMDS	DME[d]	89/11	72
4	**7**	NaHMDS	DME[d]	79/21	87
5	**8**	KHMDS	THF[c]	86/14	85
6	**8**	NaHMDS	THF[c]	85/15	85
7	**8**	NaHMDS	DME[d]	81/19	75
8	**8**	KHMDS	DME[d]	87/13	87 (75)[e]

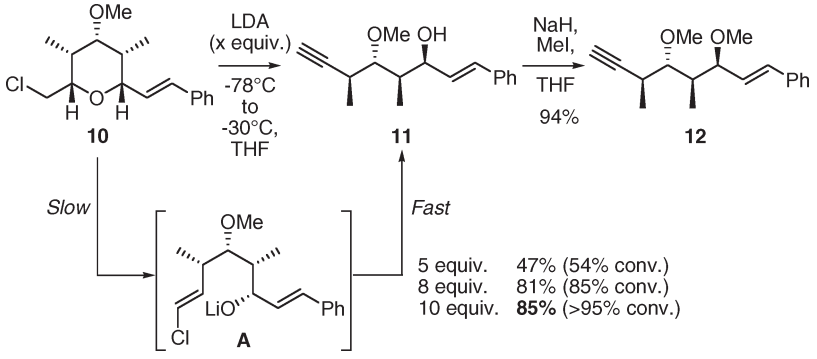


[a]Determined by ^{1}H NMR of the crude experiment. [b]Isolated yields of the *E*/*Z* mixture. [c]Performed at −78 °C for 30 min then warmed up to 0 °C. [d]Performed at −60 °C for 30 min then warmed up to 0 °C. [e]Isolated yield of *E*-isomer.

SCHEME 3. Synthesis of the α-Chloromethyltetrahydropyran 10



SCHEME 4. Base-Induced Ring Opening of the Chloride 10



and **8**,[15] were tested changing two parameters (solvent, base) under Barbier's conditions (Table 1). Best results were observed when performing the reaction with sulfone **8**, KHMDS as the base, and DME as the solvent (Table 1, entries 3 and 8). The corresponding olefin **6** was thus obtained in 87% (*E*/*Z* ratio = 87/13) yields. The two isomers were easily separable by conventional column chromatography on silica gel (Table 1, entry 8).

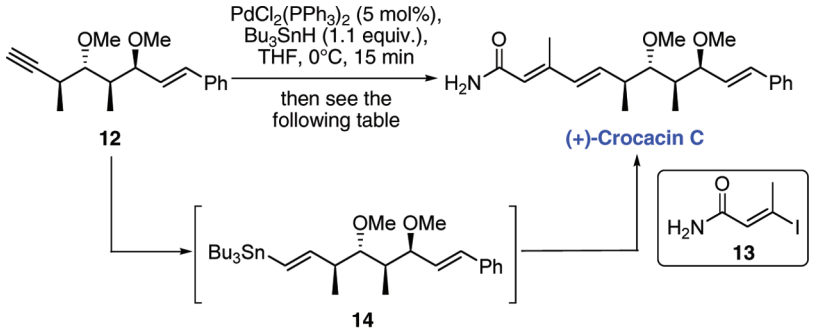
Base-Induced Ring Opening of Chloride 10. Next, treatment of acetate (*E*)-**6** with potassium carbonate in methanol afforded alcohol **9**, which was then chlorinated using standard conditions (PPh_3, imidazole, CCl_4, reflux) (Scheme 3).

The resulting halogenated intermediate **10** was isolated in 80% yield over two steps. A base-induced THP ring opening of intermediate **10** allowed the formation of alkyne **11** (Scheme 4). This methodology, which has been applied to several α-chloromethylcycloethers of various ring size,[16] required some optimization in order to obtain decent yields. Hence, when using

(15) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.

(16) For examples of α-chloromethylepoxides opening, see: (a) Takano, S.; Samizu, K.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem Commun.* **1989**, 1344–1345. (b) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046. For examples of α-chloromethyltetrahydrofurans opening, see: (c) Eglinton, G.; Jones, E. R. H.; Whiting, M. C. *J. Chem Soc.* **1952**, 2873–2882. (d) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455–5458. For examples of α-chloromethyltetrahydropyrans opening, see: (e) Herault, V. *Bull. Soc. Chim. Fr.* **1963**, 2105–2113. (f) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397–4401.

SCHEME 5. End of the synthesis



Condition	Specific end of the procedure	Yield[a] (%)
A	then addition of **13** (1.1 equiv.), $Pd_2(dba)_3$ (5 mol%), TFP (30 mol%), 60°C, 6h.	20[b]
B	then addition of **13** (1.1 equiv.), 60°C, 12h.	42[b]
C	then addition of **13** (1.1 equiv.), 100°C, MW irradiation, 10 min then addition $Pd(PPh_3)_4$ (3 mol%), 100°C, MW irradiation, 10 min.	76
D	then addition of **13** (1.1 equiv.), 100°C, MW irradiation, 15 min.	73

5 equiv of LDA at temperatures ranging from −78 to −30 °C, the corresponding alkoxyalkyne **11** was obtained as the only product in 47% yield, and 46% of the starting material was recovered without a trace of the protonated form of intermediate vinyl chloride **A**. This result suggested that the elimination step from vinyl chloride intermediate **A** occurred faster than its formation through the ring-opening step. In order to optimize this transformation, an adjustment of the amount of LDA was operated to convert all chloride **10** during the reaction. After close examination, it was found that 10 equiv was necessary to observe the complete consumption of the starting material and to obtain alkyne **11** in up to 85% yields.

Final Coupling. The synthesis of (+)-crocacin C was then achieved in two steps (Scheme 5). First, the etherification of the free hydroxyl group of alkyne **11** was conducted under classical conditions (NaH, MeI, THF, 0 °C to rt), affording the desired diether **12** in 94% yield. Finally, we envisioned to directly convert alkyne **12** into (+)-crocacin C via a coupling with (*E*)-iodoacrylamide **13**.[17] The synthesis of the dienamide moiety of the natural product involved a one-pot palladium-catalyzed sequence involving a hydrostannylation[18] and a Stille coupling.[19] While a similar process had been reported in the literature by Maleczka et al.,[20] we were surprised by the lack of application in total synthesis. This procedure circumvented the purification of vinylstannane intermediate **14** and, as a consequence, should prevent its partial protodestannylation.

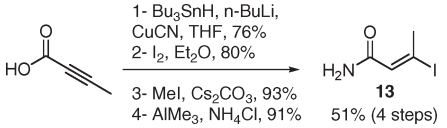
A set of four reaction conditions was (Scheme 5) tested to obtain (+)-crocacin C directly from alkyne **12**. The hydrostannylation step involved standard conditions [$PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 0 °C], which were common to all four protocols.

First, we performed the hydrostannylation using $PdCl_2(PPh_3)_2$ followed by the Stille coupling in the presence of $Pd_2(dba)_3$ and tri-2-furylphosphine[21] (TFP) (condition A). Under these conditions, the natural product was obtained in a poor yield along with degradation products.

The use of $PdCl_2(PPh_3)_2$ to promote both the hydrostannylation and the coupling (condition B) notably improved the yield, up to 42%, but degradation products were observed.

In order to suppress the decomposition during the coupling step, a microwave activation[20b,22] (MW) was tested to reduce heating time (conditions C and D). Hence, when $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were used, respectively, for the hydrostannylation and the coupling, the natural product

(17) Vinyl iodide **13** was obtained stereoselectively using the following sequence which involves the stannylcupration of but-2-ynoic acid (Abarbri, M.; Parrain, J.-L.; Duchêne, A.; Thibonnet, J. *Synthesis* **2006**, 2951−2970), followed by an iododestannylation, an esterification, and a transamidation:



(18) For review on hydrostannylation, see: (a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3282. (b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853–887. For seminal work on Pd-catalyzed hydrostannylation see: (c) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.

(19) For a review on Pd-catalyzed reaction in total synthesis, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.

(20) (a) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622–9623. (b) Maleczka, R. E., Jr.; Lavis, J. M.; Clark, D. H.; Gallagher, W. P. *Org. Lett.* **2000**, *2*, 3655–3658. (c) Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384–385. (d) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204.

(21) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(22) First example of a microwave-assisted Stille coupling: Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584.

was obtained in 76% (condition C) after two irradiation periods of 10 min each at 100 °C.

A simplified procedure (condition D), with a unique catalyst source ($PdCl_2(PPh_3)_2$), gave the natural product in similar yield after 15 min heating in a microwave oven. We were pleased to observe that this last step proceeded with complete regioselectivity and stereospecificity in favor of the target molecule.

Spectroscopic data of the synthesized product were identical in all respects with those reported for the natural product {$[\alpha]^{25}_D = +56.2$ ($c = 0.5$, MeOH); lit.[5] $[\alpha]^{22}_D = +52.2$ ($c = 0.3$, MeOH)}.

Conclusion

(+)-Crocacin C has been synthesized from oxabicycle **1** in 22.3% overall yield, following a convergent protecting-group-free[23] sequence of 11 steps. In addition, the establishment of the hidden symmetry of a significant portion of the natural product has allowed a synthetic plan based on the use of a *meso* compound. This non-aldol strategy offered to control through a single enantioselective step the four contiguous stereogenic centers of (+)-crocacin C. Moreover, the synthesis was achieved by the rapid building of the dienamide system using a Pd-catalyzed one-pot sequence involving a hydrostannylation and microwave-assisted Stille coupling reactions. We are currently working on the extension of this methodology to other natural molecules bearing a polypropionate segment.

Experimental Section

(+)-((2*S*,3*R*,4*R*,5*S*,6*R*)-6-(Hydroxymethyl)-4-methoxy-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)methyl acetate (5). *Rhizomucor miehei* lipase (300 mg) was added to a solution of diol **4** (2.0 g, 9.79 mmol) in iPr_2O (50 mL) and vinyl acetate (50 mL), and the mixture was stirred magnetically in a hermetically stoppered one-necked flask at room temperature (the course of the reaction being monitored by TLC). After 18 h, the reaction mixture was filtered through a pad of Celite, and the cake was washed with dry Et_2O. The filtrate was concentrated in vacuo and purified by silica gel column flash chromatography (PE/EtOAc, gradient elution: 80/20 to 60/40) to afford 2.1 g of pure monoacetate **5** as white crystals (87% yield): mp 80−81 °C; $R_f = 0.28$ (PE/EtOAc 1/1); ee >98% determined on chiral HPLC column, Sepapak-2-HR; mobile phase, hexane/isopropanol 80/20, 1 mL/min, temperature = 25 °C, retention time (+)-isomer = 9.78 min, retention time (−)-isomer = 7.52 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (m, 2H), 3.76 (dd, $J = 12.1$, 9.5 Hz, 1H), 3.62 (m, 1H), 3.51 (m, 2H), 3.36 (t, $J = 5.3$ Hz, 1H), 3.32 (s, 3H), 2.09 (m, 2H), 2.06 (s, 3H), 0.90 (d, $J = 7.2$ Hz, 3H), 0.86 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 80.8, 80.7, 77.4, 65.2, 63.7, 55.3, 33.6, 33.2, 20.9, 8.5, 8.2; HRMS (ESI TOF) calcd for $C_{12}H_{23}O_5$ $(M + H)^+$ 247.1540, found 247.1543.

((2*S*,3*R*,4*R*,5*S*,6*S*)-4-Methoxy-3,5-dimethyl-6-((*E*)-styryl)-tetrahydro-2*H*-pyran-2-yl)methyl acetate (6).

Swern Oxidation: In a flame-dried 100 mL one-necked round-bottomed flask, under an atmosphere of argon, dimethylsulfoxide (253 mg, 233 μL, 3.24 mmol) was added dropwise at −78 °C to a solution of oxalyl chloride (386 mg, 268 μL, 3.04 mmol) in 15 mL of dry dichloromethane. The resulting colorless solution was stirred for 5 min, and a solution of alcohol **5** (500 mg, 2.03 mmol) in 5 mL of dry dichloromethane was added dropwise via cannula at −78 °C. After stirring for an additional 15 min, at this temperature, triethylamine (1.03 g, 1.4 mL, 10.15 mmol) was added dropwise and the reaction mixture was slowly warmed to room temperature (30 min). It was then quenched by adding 20 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic layers were washed with water (2 × 20 mL) and brine (1 × 20 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. To the crude product was added diethyl ether (10 mL); the rest of the ammonium salts were filtered off, and the solvent was evaporated to afford the crude aldehyde (492 mg, 99%) as a pale yellow solid, which was used in the Julia reaction without further purification.

General Procedure for the Julia-Type Olefination: In a flame-dried 10 mL one-necked round-bottomed flask, under an atmosphere of argon, sulfone **7** or **8** (0.27 mmol, 1.3 equiv) and the crude aldehyde (50 mg, 0.20 mmol, 1.0 equiv) were weighed out and dried in high vacuum for 15 min. The appropriate solvent (1.5 mL) was added, and the reaction mixture was cooled to −78 °C (−60 °C for DME). The base (0.27 mmol, 1.3 equiv) dissolved in 1 mL of the same solvent was added dropwise at this temperature, and the resulting orange-red mixture was stirred for 30 min and warmed to 0 °C over a period of 30 min. It was quenched by adding 3 mL of saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3 × 3 mL), and the combined organic layers were washed with water (2 × 5 mL) and brine (1 × 5 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The *E*/*Z* ratio was determinated by ^{1}H NMR of the crude product, which was then purified by silica gel column flash chromatography (PE/AcOEt mixture, gradient elution: 90/10 to 85/15) to afford pure *E*- and *Z*-isomers as colorless oils. Yields and conditions are reported in Table 1. *E*-isomer (**6**): $R_f = 0.51$ (PE/EtOAc 8/2); $[\alpha]^{30}_D = +24.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 6.65 (dd, $J = 16.1$, 1.1 Hz, 1H), 6.23 (dd, $J = 16.1$, 5.7 Hz, 1H), 4.23 (dd, $J = 11.5$, 7.7 Hz, 1H), 4.16 (dd, $J = 11.5$, 4.5 Hz, 1H), 4.11 (ddd, $J = 5.7$, 4.3, 1.1 Hz, 1H), 3.71 (ddd, $J = 7.7$, 4.5, 2.6 Hz, 1H), 3.47 (t, $J = 5.3$ Hz, 1H), 3.37 (s, 3H), 2.15 (m, 2H), 2.08 (s, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 0.95 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 136.9, 130.3, 128.5 (2C), 128.2, 127.4, 126.4 (2C), 81.2, 80.4, 77.2, 65.2, 55.3, 36.8, 33.3, 21.0, 9.0, 8.3; HRMS (ESI TOF) calcd for $C_{19}H_{30}NO_4$ $(M + NH_4)^+$ 336.2169, found 336.2167. *Z*-isomer (**6**): $R_f = 0.66$ (PE/EtOAc: 8/2); $[\alpha]^{30}_D = -82.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 to 7.28 (m, 5H), 6.70 (d, $J = 11.7$ Hz, 1H), 5.90 (dd, $J = 11.7$, 8.7 Hz, 1H), 4.23 (dd, $J = 8.7$, 2.6 Hz, 1H), 4.17 to 4.15 (m, 2H), 3.70 (ddd, $J = 7.7$, 5.3, 2.6 Hz, 1H), 3.37 (t, $J = 5.3$ Hz, 1H), 3.32 (s, 3H), 2.13 (m, 2H), 2.09 (s, 3H), 1.08 (d, $J = 7.2$ Hz, 3H), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 136.7, 132.9, 128.9, 128.7 (2C), 128.3 (2C), 127.4, 80.9, 76.8, 76.1, 65.7, 55.3, 35.8, 33.2, 21.0, 8.9, 8.4; HRMS (ESI TOF) calcd for $C_{19}H_{26}O_4$ $(M + H)^+$ 319.1904, found 319.1902.

((2*S*,3*R*,4*R*,5*S*,6*S*)-4-Methoxy-3,5-dimethyl-6-((*E*)-styryl)-tetrahydro-2*H*-pyran-2-yl)methanol (9). To a solution of acetate **6** (530 mg, 1.66 mmol) in methanol (16 mL) was added potassium carbonate (460 mg, 3.32 mmol) at room temperature, and the resulting white suspension was stirred for 30 min. It was then quenched by adding 20 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 80/20 to 60/40) to afford 452 mg of pure alcohol **9** (99%), as colorless oil: $R_f = 0.17$ (PE/EtOAc 8/2); $[\alpha]^{30}_D = +25.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 to 7.23 (m, 5H), 6.64 (dd, $J = 16.1$, 1.3 Hz, 1H), 6.23 (dd, $J = 16.1$, 5.7 Hz,

(23) In our case, the acetate group should be considered as a desymmetrizing group. For a review on protecting-group-free syntheses, see: (a) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193–205. (b) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404–408. (c) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541.

1H), 4.13 (ddd, J = 5.7, 4.3, 1.3 Hz, 1H), 3.85 (dd, J = 10.4, 7.3 Hz, 1H), 3.63 to 3.54 (m, 2H), 3.47 (t, J = 5.3 Hz, 1H), 3.36 (s, 3H), 2.38 (br s, $1H_{OH}$), 2.17 (m, 1H), 2.10 (m, 1H), 0.95 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 130.2, 128.5 (2C), 128.3, 127.5, 126.4 (2C), 81.3, 80.7, 80.3, 64.0, 55.3, 36.9, 33.9, 9.0, 8.7; HRMS (ESI TOF) calcd for $C_{17}H_{28}NO_3$ $(M + NH_4)^+$ 294.2064, found 294.2059.

(2*S*,3*R*,4*R*,5*S*,6*S*,7*E*)-2-(Chloromethyl)-4-methoxy-3,5-dimethyl-6-styryltetrahydro-2*H*-pyran (10). In a 25 mL one-necked round-bottomed flask, equipped with a reflux condenser, alcohol **9** (200 mg, 0.72 mmol) was dissolved in 4 mL of carbon tetrachloride. Triphenylphosphine (569 mg, 2.17 mmol) was added followed by imidazole (147 mg, 2.17 mmol), and the resulting light yellow solution was stirred at 70 °C for 2 h. After being cooled to room temperature, the reaction mixture was quenched by adding 10 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column flash chromatography using solid deposit (3 g of silica) (PE/EtOAc mixture, gradient elution: 98/2 to 95/5) to afford 168 mg of pure chloride **10** (80%), as a colorless oil: R_f = 0.66 (PE/EtOAc 9/1); $[\alpha]^{30}_D$ = +40.5 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 to 7.23 (m, 5H), 6.66 (dd, J = 16.1, 1.1 Hz, 1H), 6.21 (dd, J = 16.1, 5.6 Hz, 1H), 4.13 (ddd, J = 5.6, 4.3, 1.1 Hz, 1H), 3.67 (m, 2H), 3.53 (m, 1H), 3.47 (t, J = 5.3 Hz, 1H), 3.38 (s, 3H), 2.30 (m, 1H), 2.17 (m, 1H), 0.96 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 130.4, 128.5 (2C), 127.9, 127.5, 126.4 (2C), 81.2, 80.6, 79.4, 55.4, 43.6, 36.7, 32.9, 9.0, 8.7; HRMS (ESI TOF) calcd for $C_{17}H_{24}O_2Cl$ $(M + H)^+$ 295.1459, found 295.1456.

(3*S*,4*R*,5*S*,6*S*,1*E*)-5-Methoxy-4,6-dimethyl-1-phenyloct-1-en-7-yn-3-ol (11). In a flame-dried 25 mL one-necked round-bottomed flask, under an atmosphere of argon, a solution of chloride **10** (140 mg, 0.47 mmol) in dry THF (2 mL) was added dropwise at −78 °C to a solution of LDA (freshly prepared by adding 1.9 mL (4.7 mmol) of *n*-BuLi (2.5 M in hexanes) to diisopropylamine (665 μL, 480 mg, 4.7 mmol)) in 3 mL of dry THF. The resulting yellow solution was warmed to −30 °C and stirred for 2 h at this temperature. After completion of the reaction (TLC check), it was quenched by adding 10 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 90/10 to 70/30) to afford 105 mg of pure alkyne **11** (85%), as a white solid: mp 81−82 °C; R_f = 0.25 (PE/EtOAc 9/1); $[\alpha]^{30}_D$ = +0.5 (c = 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.32 (m, 2H), 7.23 (m, 1H), 6.69 (dd, J = 16.1, 1.7 Hz, 1H), 6.29 (dd, J = 16.1, 5.1 Hz, 1H), 4.64 (m, 1H), 3.58 (s, 3H), 3.23 (dd, J = 7.7, 4.2 Hz, 1H), 2.86 (br s, $1H_{OH}$), 2.84 (m, 1H), 2.12 (d, J = 2.6 Hz, 1H), 2.10 (m, 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 131.1, 129.8, 128.5 (2C), 127.4, 126.3 (2C), 87.1, 85.5, 72.6, 70.1, 61.2, 41.1, 29.3, 17.6, 11.6; HRMS (ESI TOF) calcd for $C_{17}H_{22}O_2Na$ $(M + Na)^+$ 281.1512, found 281.1513.

((3*S*,4*R*,5*S*,6*S*,7*E*)-3,5-Dimethoxy-4,6-dimethyloct-1-en-7-ynyl)benzene (12). In a flame-dried 25 mL one-necked round-bottomed flask, under an atmosphere of argon, alkyne **11** (157 mg, 0.61 mmol) was dissolved in 5 mL of dry THF. To this solution was added portionwise sodium hydride (60% dispersion in mineral oil) (43 mg, 1.82 mmol) at 0 °C. The resulting light yellow alcoholate was stirred at room temperature for 30 min; iodomethane (77 μL, 173 mg, 1.22 mmol) was added dropwise, and the reaction mixture was stirred for 12 h at room temperature. The reaction was then quenched by adding 10 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column flash chromatography (PE/EtOAc mixture, gradient elution: 95/5 to 90/10) to afford 156 mg of pure alkyne **12** (94%), as a white solid: mp 55−56 °C; R_f = 0.62 (PE/EtOAc 9/1); $[\alpha]^{30}_D$ = +24.8 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.33 (m, 2H), 7.24 (m, 1H), 6.62 (d, J = 16.1 Hz, 1H), 6.21 (dd, J = 16.1, 7.2 Hz, 1H), 4.16 (ddd, J = 7.2, 2.3, 1.0 Hz, 1H), 3.57 (s, 3H), 3.33 (s, 3H), 3.17 (dd, J = 9.8, 2.5 Hz, 1H), 2.78 (qt, J = 7.0, 2.5 Hz, 1H), 2.07 (d, J = 2.5 Hz, 1H), 1.96 (m, 1H), 1.36 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 132.0, 129.2, 128.6 (2C), 127.5, 126.4 (2C), 85.1, 84.8, 80.9, 69.9, 61.4, 56.4, 42.8, 29.4, 18.2, 9.9; HRMS (ESI TOF) calcd for $C_{18}H_{24}O_2Na$ $(M + Na)^+$ 295.1669, found 295.1667.

(+)-Crocacin C. In a flame-dried 10 mL MW vial, under an atmosphere of argon, alkyne **12** (40 mg, 0.147 mmol) was dissolved in 2 mL of dry THF. The solvent was degassed (three freeze−pump−thaw degassing cycles), and $PdCl_2(PPh_3)_2$ (5 mg, 7.3 μmol) was added followed by tributyltin hydride (44 μL, 47 mg, 0.161 mmol) at 0 °C over a period of 15 min. The reaction mixture was stirred at this temperature, and the formation of the stannane was monitored by TLC (15 min). Vinyl iodide **13** (34 mg, 0.161 mmol) was added in one portion, and the tube was submitted to MW irradiation (15 min at 100 °C). The reaction mixture was filtered through a short pad of silica, washed with ethyl acetate, and the resulting filtrate was concentrated in vacuo. The residue was purified by two consecutive silica gel columns flash chromatography (PE/EtOAc mixture, gradient elution: 50/50 to 30/70) to afford 39 mg of (+)-crocacin C (73%), as a white solid: mp 87−88 °C; R_f = 0.25 (PE/EtOAc 1/1); $[\alpha]^{25}_D$ = +56.2 (c = 0.5, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 6.59 (d, J = 16.1 Hz, 1H), 6.17 (dd, J = 16.1, 7.2 Hz, 1H), 6.09 to 5.99 (m, 2H), 5.63 (s, 1H), 5.37 (br s, $2H_{NH}$), 4.09 (dd, J = 7.2, 1.3 Hz, 1H), 3.54 (s, 3H), 3.32 (s, 3H), 3.20 (dd, J = 10.0, 2.2 Hz, 1H), 2.55 (m, 1H), 2.25 (d, J = 1.0 Hz, 3H), 1.54 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 149.7, 137.2, 136.7, 133.9, 132.0, 129.2, 128.6 (2C), 127.6, 126.4 (2C), 119.40, 86.4, 81.0, 61.9, 56.4, 42.6, 40.0, 18.7, 13.8, 9.7; HRMS (ESI TOF) calcd for $C_{22}H_{31}NO_3Na$ $(M + Na)^+$ 380.2196, found 380.2188.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.