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Total Synthesis of (+)-Crocacin D†

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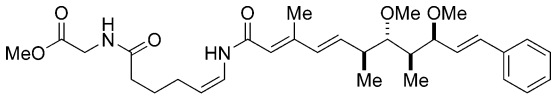

Crocacin D

The total synthesis of (+)-crocacin D is described. The convergent asymmetric synthesis relies on the use of a Stille cross-coupling between an (*E*)-vinyl stannane with an (*E*)-vinyl iodide to establish the (*E*,*E*)-dienamide moiety followed by a mild and efficient copper-catalyzed coupling between (+)-crocacin C and a (*Z*)-vinyl iodide to establish the challenging (*Z*)-enamide function.

Introduction

The crocacins A (**1**), B (**2**), C (**3**), and D (**4**) are a group of compounds that are regularly found in the extracts of the *Chondromyces crocatus* and *Chondromyces pediculatus* strains and represent a second novel group of modified peptides from *C. crocatus* (Figure 1).[1,2] Crocacin C (**3**) is a structure fragment of **1**, **2**, and **4**. The crocacins moderately inhibit the growth of a few gram-positive bacteria and are potent inhibitors of animal cell cultures and several yeasts and fungi. Crocacin D shows higher biological activity against *Saccharomyces cerevisiae* as well as higher toxicity in L929 mouse fibroblast cell cultures, when compared to crocacins A−C. The relative configurations of crocacins A−D were proposed by Jansen and co-workers by means of molecular modeling studies and NOE experiments[2] and were further confirmed by total synthesis.[3−6]

To provide material for more extensive biological evaluation, along with access to novel analogues, we have undertaken the total synthesis of the polyketide (+)-crocacin D (**4**), the most active compound in this series.[5] Crocacin D (**4**), a dipeptide of glycine and 6-aminohexenoic acid, shows four consecutive stereocenters, three (*E*)-double bonds, and a (*Z*)-enamide moiety, which is probably responsible for the pharmacological activity of the crocacins and represents the major synthetic challenge.[7]

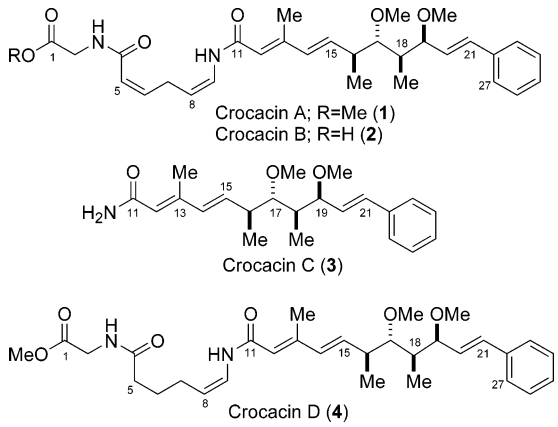

FIGURE 1. Crocacins A−D

† Dedicated to Prof. Timothy John Brocksom for his outstanding contributions to the field of synthetic organic chemistry in Brazil.

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

(2) (a) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085. (b) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

(3) Total synthesis of crocacin A: (a) Feutrill, J. T.; Rizzacasa, M. A. *Aust. J. Chem.* **2003**, *56*, 783. (b) Chakraborty, T. K.; Laxman, P. *Tetrahedron Lett.* **2003**, *44*, 4989.

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(6) For fragment synthesis, see: (a) Raghavan, S.; Reddy, S. R. *Tetrahedron Lett.* **2004**, *45*, 5593. (b) Gurjar, M. K.; Khaladkar, T. P.; Borhade, R. G.; Murugan, A. *Tetrahedron Lett.* **2003**, *44*, 5183.

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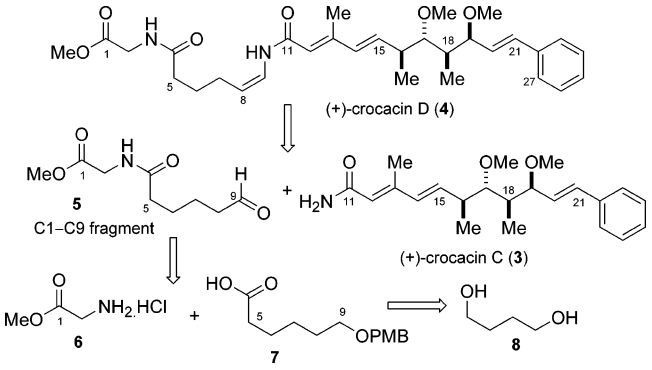
SCHEME 1. First Retrosynthetic Analysis of Crocacin D



Results and Discussion

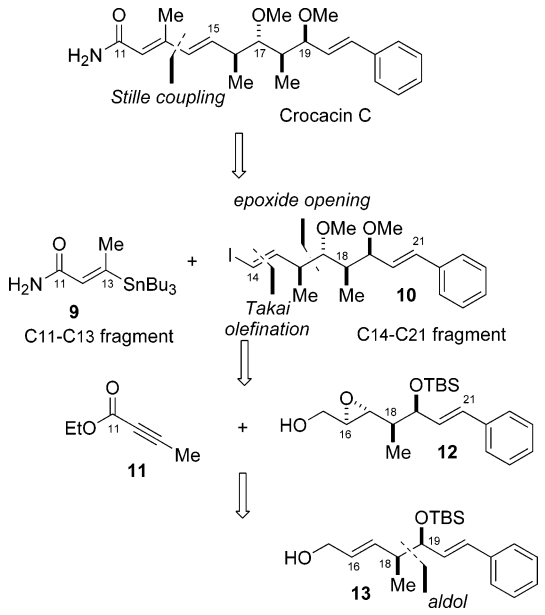
Our first disconnection, summarized in Scheme 1,[8] involved cleavage of the C9−N10 bond to give aldehyde **5** (C1−C9 fragment) and crocacin C (**3**) (C11−C21 fragment). This (*Z*)-enamide bond is viewed as arising from an α-amidoalkyl phenyl sulfone followed by enamide formation, as described by Petrini and co-workers.[7h−j] Fragment C1−C9 (aldehyde **5**) may be further dissected in a straightforward manner to give glycine methyl ester hydrochloride **6** and carboxylic acid **7**, available from 1,4-butanediol **8**.

Our retrosynthetic analysis for crocacin C[4a] is outlined in Scheme 2 and employed a Stille coupling to join fragments C11−C13 ((*E*)-vinyl stannane **9**) and C14−C21 ((*E*)-vinyl iodide **10**).[4a] We anticipated that vinyl stannane **9** would be derived from ethyl 2-butynoate **11** and vinyl iodide **10** from allylic alcohol **13**.

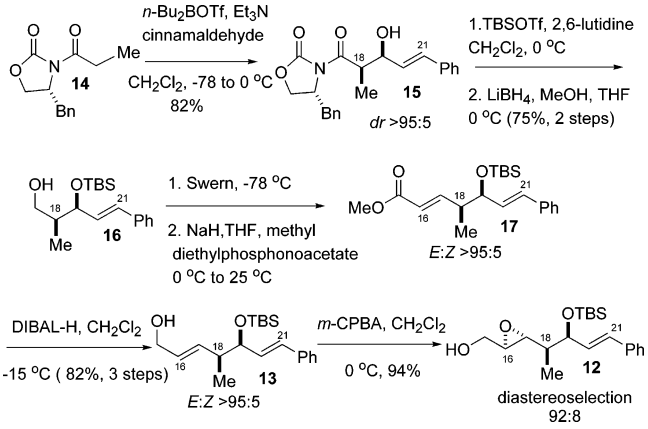
Synthesis of (*E*)-vinyl iodide **10** began with asymmetric aldol addition of the boron enolate derived from *N*-propionyloxazolidinone **14** with cinnamaldehyde to give aldol adduct **15** in 82% yield (ds > 95:5) (Scheme 3).[9]

Silylation of aldol **15** with TBSOTf and 2,6-lutidine was followed by treatment with $LiBH_4$ in MeOH to provide alcohol **16** (75% yield, two steps).[9] Allylic alcohol **13** was obtained in a high overall yield following Swern[10] oxidation of alcohol **16** to the aldehyde, conversion to the α,*β*-unsaturated ester **17**, and treatment of **17** with excess DIBAL-H at 0 °C (82%, three steps). We were pleased to find that epoxidation of allylic alcohol **13** with *m*-CPBA gave the *anti*-epoxy alcohol **12** in 94% yield and 92:8 diastereoselectivity.[4a,12]

SCHEME 2. Retrosynthetic Analysis of Crocacin C



SCHEME 3. Synthesis of Epoxide 12



Treatment of epoxy alcohol **12** with $Me_2CuCNLi_2$ gave diol **18** in 90% yield (Scheme 4).[13,14] Cleavage of the secondary TBS ether in the presence of TBAF followed by selective monoprotection gave diol **19** (89% yield, two steps).[14] Methylation of the OH-functions at C17 and C19 (KH, MeI, THF) followed by removal of the TBDPS group provided alcohol **20** (96% yield, two steps). Dess−Martin[15] oxidation, followed by treatment of the aldehyde with $CrCl_2$ and CHI_3, gave (*E*)-vinyl iodide **10** (*E*:*Z* > 95:05)

(7) Enamide synthesis: (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (c) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (d) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (e) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (f) Wang, Y.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (g) Bayer, A.; Maier, M. E. *Tetrahedron.* **2004**, *60*, 6665. (h) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970. (i) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449. (j) Mecozzi, T.; Petrini, M. *Synlett* **2000**, 73. (k) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955. (l) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217. (m) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735. (n) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (o) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. (p) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397. (q) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185. (r) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993. (s) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1468.

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(9) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675. (d) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

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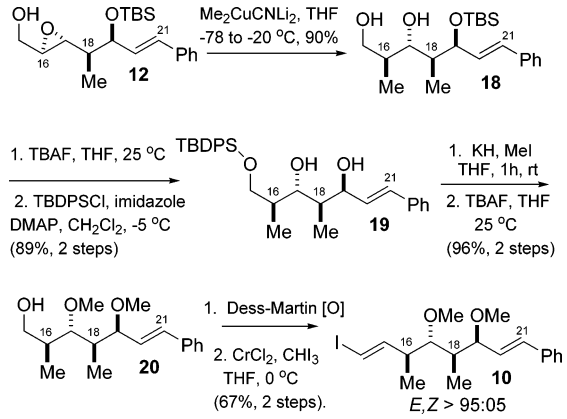
(13) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4347.

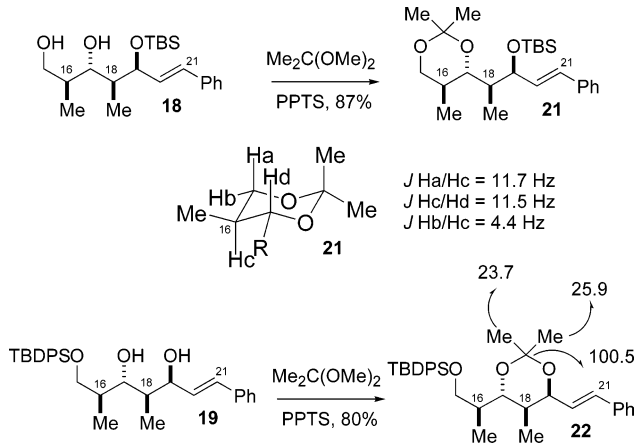
(14) Diols **18** and **19** showed spectral data and physical properties identical in all respects to published data. See ref 3.

(15) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

SCHEME 4. Synthesis of (*E*)-Vinyl Iodide 10



SCHEME 5. Determination of the Relative Stereochemistry for Diols 18 and 19

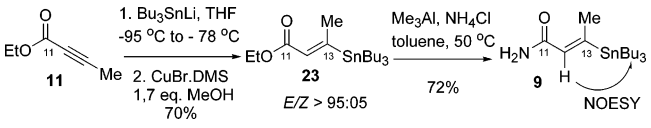


in 67% overall yield for the two-step sequence.[16] Overall this route required 14 steps starting from **14** and resulted in 25% overall yield of **10**.

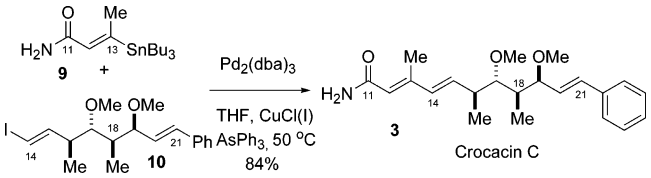
The relative stereochemistry for 1,3-diols **18** and **19** was determined after conversion to their corresponding acetonides **21** and **22** (Scheme 5).[17] Coupling constants between Ha−Hc (11.7 Hz), Hc−Hd (11.5 Hz), and Hb−Hc (4.4 Hz) confirmed the relative stereochemistry for C16−C17 bond in **21**.[14] The stereochemistry at C17 and C19 was determined after analysis of acetonide **22**, which showed ^{13}C NMR resonances at 23.7, 25.9, and 100.5, characteristic of an anti acetonide.[17]

Conjugate organostannyl cuprate addition to ethyl 2-butynoate **11** (−100 °C to −78 °C) gave (*E*)-vinylstannane **23** (*E*:*Z*, > 95:5) (Scheme 6).[18,19] Treatment of vinylstannane **23** with Me_3Al and NH_4Cl in toluene at 50 °C gave (*E*)-vinylstannane **9** in 50% yield for the two-step sequence. The (*E*)-geometry for vinylstannane **9** was confirmed by NOESY interactions between the vinylic hydrogen at C12 and the hydrogens of the tributyltin group.

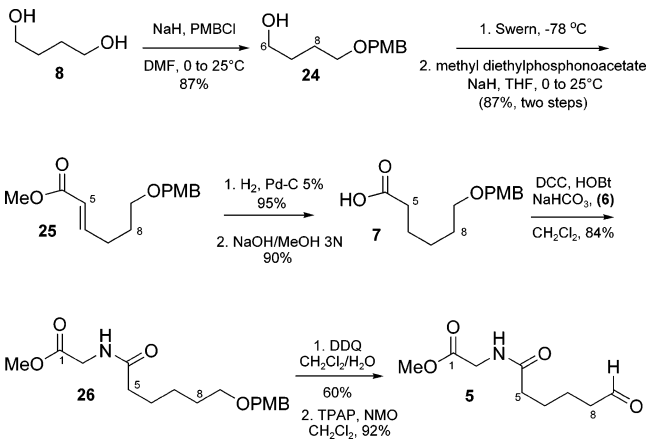
SCHEME 6. Synthesis of (*E*)-Vinylstannane 9



SCHEME 7. Synthesis of Crocacin C: Stille Coupling



SCHEME 8. Preparation of Aldehyde 5



Since our first publication, we were able to further improve the synthesis of crocacin C, especially regarding the Stille[20] coupling reaction between the C11−C13 and C14−C21 fragments (Scheme 7).[4a] Treatment of a solution of (*E*)-vinylstannane **9** and (*E*)-vinyl iodide **10** in THF with a catalytic amount of $Pd_2(dba)_3$ in the presence of $AsPh_3$ and CuCl(I) at 50 °C gave (+)-crocacin C in 84% yield, after purification by silica gel column chromatography (EtOAc/hexane 40%).[4a] The total synthesis of crocacin C was accomplished in 15 steps from *N*-propionyl-oxazolidinone **14** and produced the desired product in 21% overall yield.

Our approach for preparation of fragment C1−C9, corresponding to aldehyde **5**, is described in Scheme 8. Treatment of 1,4-butanediol **8** with NaH and PMBCl in DMF gave primary alcohol **24** (87%), which was submitted to oxidation under the standard Swern[10] conditions. The unpurified aldehyde was directly subjected to a Horner−Emmons[11] homologation with the requisite stabilized reagent, producing α,β-unsaturated ester **25** in 87% overall yield for the two-step sequence. This ester was smoothly hydrogenated (Pd−C 5%, 10% m/m) to give the corresponding saturated ester (95%), which was submitted to basic hydrolysis, providing carboxylic acid **7** (90% yield). Compound **26** is readily prepared from carboxylic acid **7** and glycine methyl ester hydrochloride

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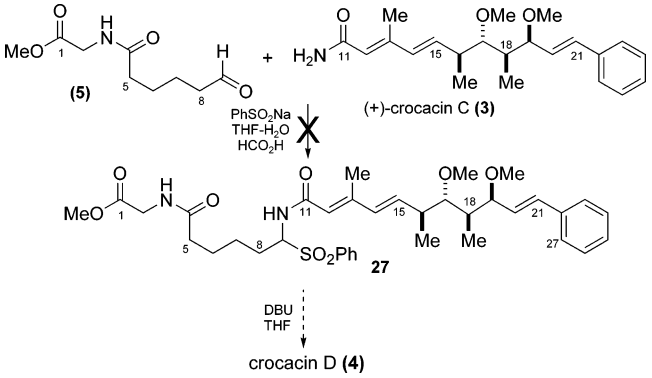
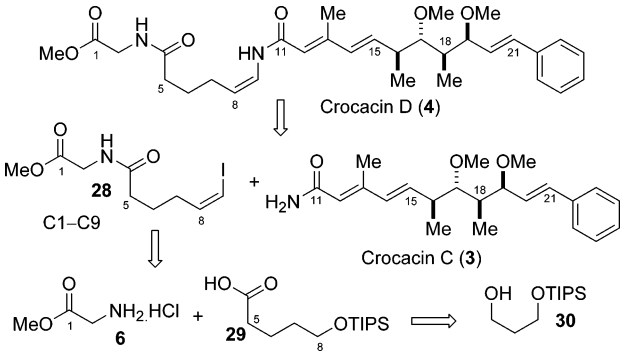
SCHEME 9. Attempted Coupling of Crocacin C (3) with Aldehyde 5



SCHEME 10. Revised retrosynthetic Analysis of Crocacin D



6 by a simple peptide[21] coupling reaction (DCC, HOBt, $NaHCO_3$ in CH_2Cl_2, 84%). Removal of the PMB protecting group (60%) was accomplished by treatment of **26** with DDQ/H_2O. Oxidation of the primary OH-function with TPAP[22] led to aldehyde **5** (92%). The 10-step sequence from **8** to **5** proceeded in an overall yield of 30%.

With fragments **3** (crocacin C) and **5** in hand, we attempted their coupling (Scheme 9). Treatment of (+)-crocacin C (**3**) with sodium benzenesulfinate in THF/H_2O followed by the addition of aldehyde **5** and formic acid at 25 °C did not furnish the desired α-amidoalkyl phenyl sulfone **27**.[7h–j] We expected to isolate the corresponding α-amidoalkyl phenyl sulfone intermediate **27**, which, after treatment with DBU in THF, should lead to the (*Z*)-enamide. After several attempts, we isolated only starting material or a complex mixture of products. In a few cases, we isolated small amounts of what appears to be a mixture of crocacin D with the corresponding (*E*)-enamide isomer, although in very low yields.

Due to the difficulties in forming the α-amidoalkyl phenyl sulfone, we abandoned this strategy and altered our synthetic route. At this point, we were attracted to a study by Buchwald et al.,[7a] who reported the copper-catalysis-promoted substitution of vinyl iodides with amides to give enamides in good yields. On the basis of this precedent and related Cu(I)-catalyzed C−N cross-coupling reactions, we focused our attention on this synthetic strategy.[7]

Scheme 10 illustrates our revised retrosynthetic analysis of crocacin D. Our revised disconnection involved cleavage of the C9−N10 bond to give (*Z*)-vinyl iodide **28** (C1−C9 fragment) and crocacin C (**3**) (C11−C21 fragment).[8] Fragment C1−C9 ((*Z*)-vinyl iodide **28**) may be further dissected in a straightforward manner to give glycine methyl ester hydrochloride **6** and carboxylic acid **29**, available from primary alcohol **30**.

Our approach for the preparation of fragment C1−C9 is described in Scheme 11. Primary alcohol **30**[23] was submitted to oxidation under the standard Swern[10] conditions, and the unpurified aldehyde was directly subjected to a Horner−Emmons[11] homologation, producing α,β-unsaturated ester **31** in 89% overall yield for the two-step sequence. This ester was smoothly hydrogenated to give the corresponding saturated ester (97%), which was submitted to basic hydrolysis, providing carboxylic acid **29** (89% yield).

Compound **32** is readily prepared from carboxylic acid **29** and glycine methyl ester hydrochloride **6** by a simple peptide-coupling reaction[21] (81%), followed by Boc protection under standard conditions (90% yield). At this stage, only four synthetic operations remained to arrive at (*Z*)-vinyl iodide **28**, an intermediate suitable for coupling with crocacin C. Removal of the TIPS protecting group (83%) was accomplished by treatment of **32** with a solution of HF-pyr in a solution of THF/pyridine. Oxidation of the primary OH-function with Dess−Martin periodinane[15] led to aldehyde **33** (90%), which was directly reacted with the phosphorane prepared from treatment of iodomethyl triphenylphosphonium iodide[24] (**34**) with NaHMDS in THF at −78 °C to give the corresponding *N*-Boc-(*Z*)-vinyl iodide in 90% yield and >95:5 selectivity. The last step involved removal of the Boc protecting group, easily accomplished by treatment of the *N*-Boc-(*Z*)-vinyl iodide with CF_3CO_2H to give (*Z*)-vinyl iodide **28** in 85% yield (*Z*:*E* > 95:05). The 10-step sequence from **30** to **28** proceeded in an overall yield of 32% and is easily amenable to a gram scale-up.

With synthesis of crocacin C (**3**) and the requisite (*Z*)-vinyl iodide **28** in hand, their coupling was undertaken (Scheme 12). This was done by using the copper-catalyzed cross-coupling of amides with vinyl halides, recently described independently by Buchwald and co-workers as well as by Ma and co-workers.[7a,b] Treatment of crocacin C (**3**) and (*Z*)-vinyl iodide **28** in THF, using a combination of 5 mol % copper(I) iodide, 20 mol % *N*,*N*′-dimethylethylenediamine, and Cs_2CO_3 as a base, at 70 °C, gave crocacin D in 67% yield after purification by flash column chromatography using Et_3N-deactivated silica gel.[5,7a] The use of 20 mol % *N*,*N*-dimethylglycine in dioxane as a solvent, as described by Ma and co-workers, led to similar results.[7b]

The spectroscopic and physical data [^1H and ^{13}C NMR, IR, $[\alpha]_D$, R_f] were identical in all respects with published data.[2a,25]

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(22) (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (b) Bloch, R.; Brillet, C. *Synlett* **1991**, 829.

(23) Primary alcohol **30** is most conveniently prepared by monoprotection of 1,3-propanediol: McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388. See Experimental Section.

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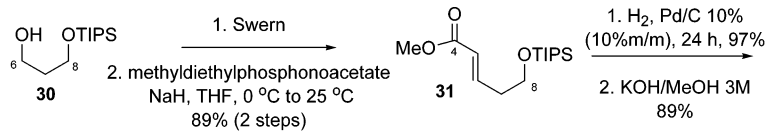
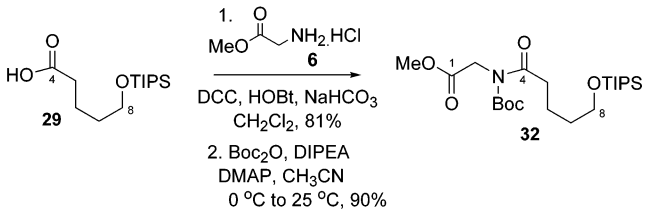
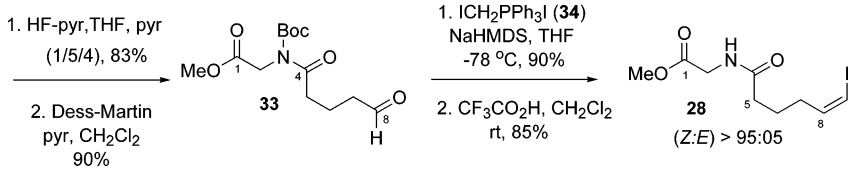
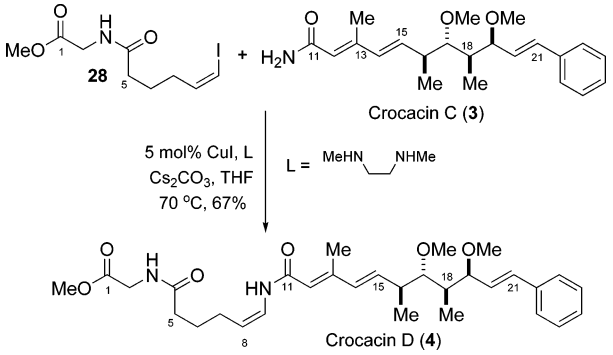
SCHEME 11. Synthesis of (*Z*)-Vinyl Iodide 28







SCHEME 12. Total Synthesis of Crocacin D



The total synthesis of crocacin D has been completed. Notable features of this approach include convergence, a Stille cross-coupling between a vinyl stannane and a vinyl iodide, as well as a mild and efficient copper-catalyzed coupling between crocacin C and a (*Z*)-vinyl iodide to establish the challenging (*Z*)-enamide function. The synthesis required 16-steps from *N*-propionyloxazolidinone **14**[4a] (longest linear sequence) and produced the desired product in 14.0% overall yield. As a result, the route to crocacin D presented here is, in principle, readily applicable for the preparation of other crocacins. Further optimization of the synthesis and application to the preparation of novel structural analogues of crocacin D are underway.[25]

Experimental Section

(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)oxazolidin-2-one (−)-15. Di-*n*-butylboryltrifluoromethanesulfonate (3.78 mL, 15 mmol) was added to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **14** (2.91 g, 12.5 mmol) in 28 mL of CH_2Cl_2 at such a rate as to maintain the internal temperature below +3 °C (type K thermocouple thermometer). Triethylamine (2.26 mL, 16.25 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to −78 °C, and cinnamaldehyde (1.73 mL, 13.75 mmol) was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 18 mL of pH 7.0 aqueous phosphate buffer solution and 60 mL of MeOH (internal temperature below +10 °C, bath temperature = −10 °C). A solution of 40 mL of MeOH and 20 mL of 30% aqueous H_2O_2 was added carefully (internal temperature below +10 °C), and the resulting yellow solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure, and the residue was extracted with three 30 mL portions of Et_2O. The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ and purified by flash column chromatography (EtOAc/hexane 25%) to give 3.74 g of the *syn*-aldol adduct **15** as a white solid (82% yield, >99:1 diastereoselectivity): R_f 0.3 (EtOAc/hexanes, 30:70); mp 116.0 °C; $[\alpha]_D^{20}$ −83.3 (*c* 1.08, CH_2Cl_2); IR ν_{max} (film) 3466, 3084, 3027, 2928, 1769, 1664, 1391, 1346, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* 7.3 Hz, 2H), 7.35−7.23 (m, 6H), 7.21 (d, *J* 7.0 Hz, 2H), 6.68 (d, *J* 15.9 Hz, 1H), 6.22 (dd, *J* 15.9, 6.0 Hz, 1H), 4.70 (m, 1H), 4.68 (ap q, *J* 4.3 Hz, 1H), 4.18 (s, 1H), 4.17 (d, *J* 2.4 Hz, 1H), 3.99 (qd, *J* 7.1, 4.0 Hz, 1H), 3.26 (dd, *J* 13.4, 3.4 Hz, 1H), 2.80 (dd, *J* 13.4, 9.5 Hz, 1H), 1.31 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 153.1, 136.5, 135.0, 131.4, 129.4, 129.0, 128.6, 128.5, 127.7, 127.4, 126.5, 72.7, 66.2, 55.1, 42.9, 37.8, 11.4; HRMS calcd for $C_{22}H_{23}NO_4$ $[M^+]$ 365.1627, found 365.1624. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.31; H, 6.55; N, 4.20.

(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-phenylpent-4-enoyl)oxazolidin-2-one. To a solution of aldol **15** (708 mg, 1.94 mmol) and 2,6-lutidine (0.26 mL, 2.23 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added TBSOTf (0.47 mL, 2.04 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C before it was diluted with CH_2Cl_2 (20 mL) and 15 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). All the organic layers were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes, 25:75) to give the desired product (737 mg, 87%) as a white solid: R_f 0.68 (EtOAc/hexanes, 25:75); mp 82.9−85.7 °C; $[\alpha]_D^{20}$ −59.1 (*c* 1.01, CH_2Cl_2); IR ν_{max} (film) 3084, 3027, 2957, 2928, 1763, 1693, 1467, 1387, 1259, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 10H), 6.52 (d, *J* 16.1 Hz, 1H), 6.25 (dd, *J* 16.1, 7.0 Hz, 1H), 4.55 (m, 1H), 4.49 (td, *J* 6.2, 0.7 Hz, 1H), 4.13 (t,

(25) New compounds and the additional isolated intermediates gave satisfactory ^1H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.

J 6.8 Hz, 1H), 4.09 (dd, *J* 9.0, 2.0 Hz, 1H), 3.92 (dd, *J* 8.2, 7.7 Hz, 1H), 3.27 (dd, *J* 13.3, 2.9 Hz, 1H), 2.78 (dd, *J* 13.3, 9.5 Hz, 1H), 1.30 (d, *J* 7.0 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 153.0, 136.4, 135.2, 130.6, 129.3, 128.8, 128.5, 127.5, 127.2, 126.3, 75.4, 65.9, 55.6, 44.6, 37.8, 25.8, 18.2, 13.0, −4.0, −4.9; HRMS calcd for $C_{28}H_{37}NO_4Si$ [M^+] 479.2492, found 479.2498. Anal. Calcd for $C_{28}H_{37}NO_4Si$: C, 70.11; H, 7.77; N, 2.92. Found: C, 69.77; H, 7.53; N, 2.97.

(2*S*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-phenylpent-4-en-1-ol (+)-16. To a solution of 207 mg (0.433 mmol) of the previously prepared imide and 44 μL (1.08 mmol) of MeOH in 1.8 mL of THF at 0 °C was slowly added 0.54 mL (1.08 mmol) of a 1.0 M solution of $LiBH_4$ in THF (gas evolution). After the reaction mixture was stirred for 2 h at 0 °C, the reaction was quenched by the addition of 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution and the mixture stirred for an additional 10 min. The mixture was then diluted with 5 mL of CH_2Cl_2 and 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution. The layers were separated, and the aqueous layer was extracted with two 5 mL portions of CH_2Cl_2. The combined organic extracts were washed with 5 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes, 25%) to give the desired product **16** (114 mg, 86%) as a viscous oil: R_f 0.24 (EtOAc/hexane, 10:90); $[\alpha]^{20}_D$ +56.5 (*c* 1.15, CH_2Cl_2); IR ν_{max} (film) 3383, 3085, 3059, 3032, 2959, 2853, 1475, 1359, 1253, 1122, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.18 (m, 5H), 6.54 (d, *J* 16.0 Hz, 1H), 6.24 (dd, *J* 16.0, 6.4 Hz, 1H), 4.43 (dd, *J* 6.4, 3.8 Hz, 1H), 3.71 (dd, *J* 10.6, 8.8 Hz, 1H), 3.53 (dd, *J* 10.6, 4.4 Hz, 1H), 2.07 (m, 1H), 0.93 (s, 9H), 0.86 (d, *J* 6.6 Hz, 3H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 131.0, 129.3, 128.5, 127.5, 126.3, 77.2, 65.8, 41.4, 25.9, 18.2, 12.5, −4.1, −4.9; HRMS calcd for $C_{18}H_{30}O_2Si$ [M^+] 306.2015, found 306.2019. Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.13; H, 9.91.

(2*E*,4*S*,5*S*,6*E*)-Methyl 5-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-phenylhepta-2,6-dienoate (+)-17. To a solution of 0.45 mL (6.41 mmol) of DMSO in 15 mL of CH_2Cl_2 at −78 °C was added 0.43 mL (4.97 mmol) of oxalyl chloride (gas evolution). After 10 min, a solution of 633 mg (2.07 mmol) of alcohol (+)-**16** in 10 mL of CH_2Cl_2 was added, forming a cloudy white mixture. This was stirred for 15 min at −78 °C, and then 1.44 mL (10.35 mmol) of triethylamine was added. The reaction mixture was stirred at −78 °C for 40 min, and then the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature then diluted with 30 mL of CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with two 20 mL portions of CH_2Cl_2. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. ^{1}H NMR spectroscopy of the unpurified aldehyde was very clean. To a stirred suspension of NaH (198 mg, 8.28 mmol) in THF (10 mL) at 0 °C under argon was added methyl diethylphosphonoacetate (1.7 mL, 9.31 mmol). The reaction mixture was allowed to warm to ambient temperature, and then a solution of the previously prepared aldehyde (304 mg, 2.07 mmol) in 5 mL of THF was added dropwise. After stirring for 12 h, the reaction was diluted with 15 mL of Et_2O and quenched by the slow addition of 6 mL of H_2O. The layers were separated, and the aqueous phase was extracted with two 15 mL portions of Et_2O. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give unsaturated ester **17** as a viscous oil that was used in the next step without further purification: R_f 0.53 (EtOAc/hexane, 10:90); $[\alpha]_D^{20}$ +28.2 (*c* 1.24, CH_2Cl_2); IR ν_{max} (film) 3022, 2954, 2931, 2863, 1726, 1658, 1437 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 7.03 (dd, *J* 15.7, 7.3 Hz, 1H), 6.49 (d, *J* 15.8 Hz, 1H), 6.10 (dd, *J* 15.8, 6.5 Hz, 1H), 5.82 (dd, *J* 15.7, 1.0 Hz, 1H), 4.22 (apt, *J* 6.5 Hz, 1H), 3.72 (s, 3H), 2.53 (m, 1H), 1.08 (d, *J* 7.0 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 151.3, 136.7, 130.8, 130.4, 128.5, 127.5, 126.4, 120.8, 76.6, 51.4, 43.6, 25.9, 18.3, 14.4, −4.0, −4.7; HRMS calcd for $C_{21}H_{32}O_3Si$ [M^+] 360.2120, found 360.2101. Anal. Calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 69.68; H, 8.51.

(2*E*,4*S*,5*S*,6*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-phenylhepta-2,6-dien-1-ol (+)-(13). To a stirred solution of α,β-unsaturated ester **17** (652 mg, 1.70 mmol) in CH_2Cl_2 (10 mL) at −15 °C was added DIBALH (0.82 mL, 4.55 mmol). After 2 h at −15 °C, aqueous sodium tartrate (0.5 M, 10 mL) was added and the solution was warmed to ambient temperature and stirred for 30 min. Additional sodium tartrate (0.5 M, 10 mL) was added, and the organic layer was diluted with CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography with EtOAc/hexanes (20:80) as the eluant to give allylic alcohol **13** (565 mg, 94%) as a colorless oil (82% over three steps): R_f 0.50 (EtOAc/hexanes, 20:80); $[\alpha]_D^{20}$ +22.4 (*c* 1.18, CH_2Cl_2); IR ν_{max} (film) 3370, 3033, 2954, 2931, 2858, 1690, 1601, 1470, 1360, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 6.47 (dd, *J* 16.2, 0.7 Hz, 1H), 6.14 (dd, *J* 16.2, 6.8 Hz, 1H), 5.74 (dd, *J* 15.0, 6.8 Hz, 1H), 5.64 (dt, *J* 15.0, 5.4 Hz, 1H), 4.12 (m, 3H), 2.38 (sext, *J* 6.5 Hz, 1H), 1.49 (brs, 1H), 1.04 (d, *J* 7.0 Hz, 3H), 0.92 (s, 9H), 0.069 (s, 3H), 0.030 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.3, 131.4, 130.2, 129.0, 128.5, 127.3, 126.3, 77.2, 63.9, 43.3, 25.9, 18.3, 15.1, −4.14, −4.80; HRMS calcd for $C_{20}H_{32}O_2Si$ [M^+] 332.2171, found 332.2166. Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 71.15; H, 9.72.

((2*R*,3*R*)-3-((2*S*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-phenylpent-4-en-2-yl)oxiran-2-yl)methanol (+)-(12). To a stirred solution of allylic alcohol **13** (252 mg, 0.76 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added *m*-CPBA (261 mg, 1.51 mmol, 77% pure), and the resulting white suspension was stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and stirred for 15 min at ambient temperature. After addition of 5% $NaHCO_3$ aqueous solution (15 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O and brine and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography with EtOAc/hexanes (20:80) as the eluant to give epoxide **12** (248 mg, 94%, dr 92:8) as a colorless oil: R_f 0.38 (EtOAc/hexanes, 20:80); $[\alpha]_D^{20}$ +34.3 (*c* 1.20, CH_2Cl_2); IR ν_{max} (film) 3435, 3028, 2922, 2859, 2652, 1704, 1475, 1256, 1073 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 6.55 (d, *J* 15.9 Hz, 1H), 6.18 (dd, *J* 15.9, 6.4 Hz, 1H), 4.50 (m, 1H), 3.92 (dd, *J* 12.4, 2.2 Hz, 1H), 3.63 (dd, *J* 12.4, 4.4 Hz, 1H), 3.02 (dd, *J* 7.7, 2.2 Hz, 1H), 2.98 (m, 1H), 1.76 (brs, 1H), 1.54 (quint d, *J* 7.3, 3.3 Hz, 1H), 0.96 (d, *J* 7.0 Hz, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.064 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 131.2, 130.0, 128.6, 127.4, 126.3, 74.1, 61.8, 58.0, 57.8, 42.7, 25.9, 18.2, 9.9, −4.2, −5.0; HRMS calcd for $C_{20}H_{32}O_3Si$ [M^+] 348.2120, found 348.2118. Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 69.27; H, 9.29.

(2*S*,3*S*,4*S*,5*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-7-phenylhept-6-ene-1,3-diol (+)-(18). To a suspension of copper(I) cyanide (500 mg, 5.58 mmol) in THF (2.3 mL) at −78 °C was added a solution of MeLi in Et_2O (7.7 mL, 10.6 mmol) dropwise. After the solution was stirred at −78 °C for 30 min, a solution of epoxide **12** (216 mg, 0.62 mmol) in THF (3 mL) was added. The reaction mixture was stirred at −20 °C for 20 h, and a 2:1 (3 mL) mixture of saturated aqueous NH_4Cl and 28% aqueous NH_3 was added. The resulting mixture was stirred at room temperature for 1.5 h, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O and brine (5 mL of each), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The

crude product was purified by flash chromatography with EtOAc/hexanes (20:80) as the eluant to give diol **18** (203 mg, 90%) as a colorless oil: R_f 0.38 (EtOAc/hexanes, 20:80); $[\alpha]_D^{20}$ +17.1 (*c* 1.19, CH_2Cl_2); IR ν_{max} (film) 3400, 2962, 2931, 2860, 1640, 1456, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5H), 6.54 (d, *J* 15.9 Hz, 1H), 6.27 (dd, *J* 15.9, 7.0 Hz, 1H), 4.57 (dd, *J* 7.0, 3.3 Hz, 1H), 3.94 (dd, *J* 10.8, 2.7 Hz, 1H), 3.68 (dd, *J* 8.4, 4.0 Hz, 1H), 3.61 (dd, *J* 10.8, 5.0 Hz, 1H), 2.11 (quint d, *J* 8.0, 3.3 Hz, 1H), 1.78 (m, 1H), 1.11 (d, *J* 7.0 Hz, 3H), 0.93 (s, 9H), 0.91 (d, *J* 8.0 Hz, 3H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 131.5, 128.5, 128.1, 127.7, 126.4, 80.2, 78.4, 65.4, 41.5, 36.2, 25.8, 18.1, 15.1, 13.1, −4.0, −4.9; HRMS calcd for $C_{21}H_{36}O_3Si$ [M^+] 364.2433, found 364.2296.

(2*S*,3*S*,4*R*,5*S*,*E*)-2,4-Dimethyl-7-phenylhept-6-ene-1,3,5-triol. To a solution of diol **18** (0.253 g, 0.696 mmol) in 5 mL of THF, at ambient temperature, was added 1.39 mL (1.39 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h and then concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexanes 80%) as the eluant to give the desired triol (172 mg, 99%) as a colorless oil: R_f 0.42 (EtOAc/hexane, 80:20); $[\alpha]_D^{20}$ +9.6 (*c* 0.98, CH_2Cl_2); IR ν_{max} (film) 3294, 3055, 2924, 1755, 1670, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* 7.5 Hz, 2H) 7.31 (t, *J* 7.5 Hz, 2H), 7.24 (apt, *J* 7.5 Hz, 1H), 6.62 (d, *J* 15.9 Hz, 1H), 6.26 (dd, *J* 15.9, 5.8 Hz, 1H), 4.76 (brs, 1H), 4.71 (d, *J* 5.5 Hz, 1H), 4.08 (brs, 1H), 3.88 (dd, *J* 10.7, 3.0 Hz, 1H), 3.66 (m, 3H), 1.99 (m, 2H), 1.04 (d, *J* 7.1 Hz, 3H), 0.93 (d, *J* 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 130.2, 130.0, 128.4, 127.4, 126.3, 82.2, 73.4, 67.8, 39.3, 36.9, 14.1, 11.7; HRMS calcd for $C_{15}H_{22}O_3$ [M^+] 250.1568, found 250.1562. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.27; H, 8.36.

(3*S*,4*R*,5*S*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diol (+)-(19). To a stirred solution of the corresponding triol prepared before (172 mg, 0.69 mmol) in CH_2Cl_2 (4 mL) at −5 °C were added imidazole (59.3 mg, 0.904 mmol) and *tert*-butyldiphenylsilyl chloride (199 mg, 0.765 mmol), and stirring was continued for 1 h. The reaction mixture was partitioned between EtOAc and H_2O, and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude product on silica gel with EtOAc/hexanes (15:85) as the eluant gave the silyl ether **19** (301.5 mg, 90%) as a colorless oil: R_f 0.62 (EtOAc/hexanes, 50:50); $[\alpha]_D^{20}$ +9.6 (*c* 1.10, CH_2Cl_2); lit.[4] $[\alpha]_D^{20}$ +10.1 (*c* 1.35, CH_2Cl_2); IR ν_{max} (film) 3420, 3054, 2962, 2927, 2859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 3H), 7.51−7.38 (m, 8H), 7.32 (tt, *J* 7.3, 1.5 Hz, 2H), 7.22 (tt, *J* 7.3, 1.5 Hz, 2H), 6.67 (dd, *J* 15.8, 1.5 Hz, 1H), 6.27 (dd, *J* 15.9, 5.3 Hz, 1H), 4.77 (d, *J* 2.9 Hz, 1H), 4.72 (m, 1H), 4.29 (d, *J* 2.9 Hz, 1H), 3.88 (dd, *J* 10.2, 3.7 Hz, 1H), 3.72 (m, 1H), 3.69 (dd, *J* 10.2, 7.3 Hz, 1H), 2.10 (quint d, *J* 7.3, 3.7 Hz, 1H), 1.95 (m, 1H), 1.08 (s, 9H), 1.06 (d, *J* 7.3 Hz, 3H), 0.88 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 135.6, 132.3, 132.2, 131.0, 130.1, 130.0, 129.7, 128.5, 127.9, 127.8, 127.2, 126.4, 82.1, 72.8, 69.4, 39.7, 36.7, 26.8, 19.0, 13.7, 11.7; HRMS calcd for $C_{31}H_{40}O_3Si$ [M^+] 488.2747, found 488.2739.

***tert*-Butyl((2*S*,3*S*,4*R*,5*S*,*E*)-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enyloxy)diphenylsilane.** To a stirred suspension of KH (170 mg, 4.24 mmol) in THF (10 mL) at 0 °C under argon was added a solution of diol **19** (346 mg, 0.708 mmol) in THF (12 mL) via cannula; then, MeI (264 μL, 4.24 mmol) was added dropwise, and the reaction mixture was warmed to ambient temperature and stirred for 2 h. The mixture was cooled to 0 °C, and H_2O (5 mL) was cautiously added followed by Et_2O (10 mL); the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified on silica gel using EtOAc/hexanes (5:95) as the eluant to give the dimethyl ether (356 mg, 97%) as a colorless oil: R_f 0.67 (EtOAc/hexanes, 10:90); $[\alpha]_D^{20}$ −17.6 (*c* 1.36, CH_2Cl_2); lit.[4] $[\alpha]_D^{20}$ −17.6 (*c* 1.14, CH_2Cl_2); IR ν_{max} (film) 3050, 2965, 2930, 2890, 2859, 2827, 1469, 1426, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.40−7.29 (m, 10H), 7.23 (t, *J* 7.0 Hz, 1H), 6.53 (d, *J* 16.0 Hz, 1H), 6.12 (dd, *J* 16.0, 7.1 Hz, 1H), 4.01 (dd, *J* 7.1, 2.6 Hz, 1H), 3.76 (dd, *J* 10.0, 5.3 Hz, 1H), 3.56 (dd, *J* 10.2, 8.1 Hz, 1H), 3.46 (s, 3H), 3.31 (s, 3H), 3.19 (dd, *J* 9.1, 2.6 Hz, 1H), 2.02 (m, 1H), 1.75 (m, 1H), 1.12 (d, *J* 7.0 Hz, 3H), 1.03 (s, 9H), 0.81 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 135.5, 133.9, 131.6, 129.6, 129.4, 129.3, 128.4, 127.5, 127.3, 126.2, 85.4, 81.4, 64.8, 61.1, 56.5, 41.7, 38.0, 26.9, 19.3, 16.0, 10.5; HRMS calcd for $C_{33}H_{44}O_3Si$ [M^+] 516.3060, found 516.3090.

(2*S*,3*S*,4*R*,5*S*,*E*)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol (−)-(20). To a solution of the previously prepared dimethyl ether (0.202 g, 0.393 mmol) in 2 mL of THF, at ambient temperature, was added 0.79 mL (0.79 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h and then concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexanes 25%) as the eluant to give primary alcohol **20** (108 mg, 99%) as a colorless oil: R_f 0.35 (EtOAc/hexane, 30:70); $[\alpha]_D^{20}$ −3.6 (*c* 1.80, CH_2Cl_2); lit. $[\alpha]_D^{20}$ −4.1 (*c* 1.87, CH_2Cl_2); IR ν_{max} (film) 3456, 3052, 2971, 2933, 2833, 1613, 1526, 1460, 1378, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* 7.3, 1.5 Hz, 2H), 7.32 (t, *J* 7.3 Hz, 2H), 7.24 (tt, *J* 7.3, 1.5 Hz, 1H), 6.58 (d, *J* 15.9 Hz, 1H), 6.18 (dd, *J* 15.9, 7.3 Hz, 1H), 4.06 (dd, *J* 7.3, 1.8 Hz, 1H), 3.82 (dd, *J* 10.8, 3.7 Hz, 1H), 3.54 (dd, *J* 10.8, 4.8 Hz, 1H), 3.53 (s, 3H), 3.32 (s, 3H), 3.28 (dd, *J* 9.1, 2.6 Hz, 1H), 2.78 (brs, 1H), 1.87 (m, 2H), 1.20 (d, *J* 7.3 Hz, 3H), 0.91 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 131.9, 129.1, 128.4, 127.4, 126.2, 88.2, 81.1, 64.4, 61.5, 56.3, 42.2, 35.9, 16.2, 10.4; HRMS calcd for $C_{17}H_{26}O_3$ [M^+ (278.1882) − H_2CO] 248.1776, found [M^+ − H_2CO] 248.1410. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 72.49; H, 9.41.

***tert*-Butyldimethyl((3*S*,4*S*,*E*)-1-phenyl-4-((4S,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl)pent-1-en-3-yloxy)silane (21).** To a solution of diol **18** (15 mg, 0.041 mmol) in 2,2-dimethoxypropane (3 mL) at ambient temperature were added a few crystals of PPTS. The reaction mixture was stirred at ambient temperature for 2 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel using EtOAc/hexanes (5:95) as the eluant to provide the desired product **21** (14.4 mg, 87%) as a colorless oil: R_f 0.58 (EtOAc/hexanes, 30:70); ^1H NMR (300 MHz, $CDCl_3$) δ 7.17−7.39 (m, 5H), 6.43 (d, *J* 15.7, 1H), 6.30 (dd, *J* 15.9, 7.1 Hz, 1H), 4.40 (dd, *J* 7.0, 5.1 Hz, 1H), 3.69 (dd, *J* 11.5, 4.9 Hz, 1H), 3.46 (dd, *J* 9.9, 4.4 Hz, 1H), 3.39 (dd, *J* 11.7, 9.5 Hz, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.38 (s, 6H), 1.01 (d, *J* 7.0 Hz, 3H), 0.91 (s, 9H), 0.82 (d, *J* 6.6 Hz, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 133.3, 129.4, 128.5, 127.2, 126.3, 98.3, 74.7, 66.2, 43.4, 32.4, 29.7, 29.2, 26.0, 19.7, 18.2, 14.3, 13.2, −3.7, −4.7.

***tert*-Butyldiphenyl((*S*)-2-((4*S*,5*R*,6*S*)-2,2,5-trimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)propoxy)silane (22).** To a solution of diol **19** (14.9 mg, 0.03 mmol) in 2,2-dimethoxypropane (3 mL) at ambient temperature were added a few crystals of PPTS. The reaction mixture was stirred at ambient temperature for 2 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel using EtOAc/hexanes (5:95) as the eluant to provide the desired product **22** (12.9 mg, 80%) as a colorless oil: R_f 0.52 (EtOAc/hexanes, 5:95); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J 7.2 Hz, 4H), 7.39−7.47 (m, 8H), 7.33 (t, *J* 7.3 Hz, 2H), 7.24 (t, *J* 7.1 Hz, 1H), 6.57 (d, *J* 15.9, 1H), 6.18 (dd, *J* 16.2, 6.1 Hz, 1H), 4.54 (ap t, *J* 5.5 Hz, 1H), 3.75 (dd, *J* 10.1, 5.2 Hz, 1H), 3.69 (dd, *J* 10.1, 5.8 Hz, 1H), 3.45 (dd, *J* 7.2, 5.8 Hz, 1H), 2.0 (m, 1H), 1.90 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.08 (s, 9H), 1.04 (d, *J* 6.7 Hz, 3H), 0.93 (d, *J* 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.7, 135.6, 133.9, 130.2, 129.5, 128.4, 127.8, 127.6, 127.3, 126.3, 100.5, 75.8, 70.5, 65.1, 39.9, 38.1, 26.9, 25.9, 23.7, 19.3, 13.8, 13.5.

1-((1*E*,3*S*,4*R*,5*S*,6*S*,7*E*)-8-Iodo-3,5-dimethoxy-4,6-dimethylocta-1,7-dienyl)benzene (−)-(10). To a stirred solu-

tion of the alcohol **20** (41 mg, 0.147 mmol) in CH_2Cl_2 (3 mL) at ambient temperature under argon was added Dess−Martin periodinane (125 mg, 0.294 mmol), and stirring was continued for 15 min. Saturated aqueous $NaHCO_3$ (2 mL), aqueous $Na_2S_2O_3$ (1.5 M, 2 mL), and Et_2O (5 mL) were added, and stirring was continued for 15 min at ambient temperature. The aqueous layer was further extracted with Et_2O, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To a stirred solution of anhydrous chromium(II) chloride (299 mg, 2.44 mmol, gently flame-dried under vacuum: 0.1 mmHg) in dry THF (1 mL) at ambient temperature was added dropwise via cannula a solution of the corresponding aldehyde (40.6 mg, 0.147 mmol) and iodoform (319 mg, 0.814 mmol) in THF (3 mL). The reaction mixture was stirred in the dark at ambient temperature for 1 h, during which time it turned brown. The reaction was quenched by the addition of H_2O (5 mL), and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with $Na_2S_2O_3$ solution (6 mL, 0.5 N aq) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo to give a yellow solid. The crude product was purified by flash column chromatography (EtOAc/hexanes, 5:95) to give the vinyl iodide **10** (39.6 mg, *E*:*Z* > 95:5, 67% for the two steps) as a pale yellow oil: R_f 0.64 (EtOAc/hexanes, 25:75); $[\alpha]_D^{20}$ −6.1 (*c* 1.20, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 7.27−7.07 (m, 5H), 6.80 (dd, *J* 14.4, 9.1 Hz, 1H), 6.48 (d, *J* 16.1 Hz, 1H), 6.08 (dd, *J* 16.1, 7.0 Hz, 1H), 5.78 (d, *J* 14.4 Hz, 1H), 4.12 (ddd, *J* 7.0, 2.2, 1.1 Hz, 1H), 3.35 (s, 3H), 3.20 (s, 3H), 3.06 (dd, *J* 9.7, 2.0 Hz, 1H), 2.23 (m, 1H), 1.70 (m, 1H), 0.98 (d, *J* 7.0 Hz, 3H), 0.87 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 148.0, 137.2, 132.1, 129.6, 128.3, 127.7, 126.8, 86.1, 81.1, 75.4, 61.4, 56.2, 43.7, 43.0, 18.5, 10.1.

(*E*)-Ethyl 3-(Tributylstannyl)but-2-enoate (23). To a solution of LDA (9.36 mmol) was added dropwise tributyltin hydride (2.6 mL, 8.92 mmol) at 0 °C. After cooling to −50 °C, the solution was added to CuBr·Me_2S complex (1.84 g, 8.92 mmol). After 30 min of stirring, a precooled solution of ethyl-2-butynoate **11** (500 mg, 4.46 mmol) and dry MeOH (0.31 mL, 7.58 mmol) in dry THF (30 mL) was added to the cuprate at −95 °C. After stirring for 30 min at −95 °C and 2 h at −78 °C, the mixture was poured into 5% aqueous NH_4OH (3 mL). Extraction with Et_2O (3 × 15 mL), drying, solvent evaporation, and column chromatography (hexanes) gave **23** (1.26 g, 70%) as a colorless oil: R_f 0.69 (hexanes 100%); IR ν_{max} (film) 2930, 1713, 1596, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (q, *J* 1.8 Hz, 1H), 4.16 (q, *J* 7.0 Hz, 2H), 2.40 (d, *J* 1.8 Hz, 3H), 1.50 (m, 6H), 1.31 (m, 9H), 0.96 (m, 6H), 0.90 (t, *J* 7.3 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 164.4, 128.1, 60.3, 28.9, 27.3, 22.3, 14.1, 13.6, 9.4. Anal. Calcd for $C_{18}H_{36}O_2Sn$: C, 53.62; H, 9.00. Found: C, 53.56; H, 9.17.

(*E*)-3-(Tributylstannyl)but-2-enamide (9). To a suspension of NH_4Cl (490 mg, 9.2 mmol) in toluene (5.0 mL) under argon at 0 °C was added dropwise a solution of $AlMe_3$ in toluene (2 M, 4.6 mL, 9.2 mmol). The resulting solution was allowed to warm to ambient temperature and then recooled to 0 °C; a solution of α,β-unsaturated ester **23** (1 g, 2.50 mmol) in toluene (40 mL) was added, and the mixture was heated to 50 °C for 16 h. The reaction mixture was then cooled to 0 °C and treated with EtOAc (75 mL) followed by 10% HCl (25 mL) in saturated NaCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine; the dried solvent was removed. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes, 80:20) as the eluant to give (*E*)-vinylstannane **9** (590 mg, 72%) as a white solid: R_f 0.60 (EtOAc 100%); mp 39.5 °C; IR ν_{max} (film) 3339, 3187, 2960, 2926, 2853, 1656, 1549, 1377 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (q, *J* 1.8 Hz, 1H), 5.46 (brs, 1H), 5.36 (brs, 1H), 2.35 (d, *J* 1.8 Hz, 3H), 1.49 (m, 6H), 1.31 (m, 6H), 0.96 (m, 6H), 0.89 (t, *J* 7.3 Hz, 9H); ^{13}C NMR (75 MHz) δ 167.3, 162.9, 130.2, 29.0, 27.3, 22.1, 13.6, 9.3; HRMS calcd for $C_{16}H_{33}NOSn$ 375.1584, found 375.1453. Anal. Calcd for $C_{16}H_{33}NOSn$: C, 51.36; H, 8.89. Found: C, 51.86; H, 9.01.

(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide (3) [(+)-Crocacin C]. To a stirred suspension of CuI(I) (64 mg, 0.65 mmol) and triphenylarsine (4.5 mg, 0.015 mmol) in THF (5 mL) under argon was added tris(dibenzylideneacetone)dipalladium(0) (6 mg, 0.006 mmol). After 5 min, (*E*)-vinyl iodide **10** (44 mg, 0.11 mmol) in THF (1 mL) was added, and the resulting suspension was stirred for an additional 30 min. A solution of stannane **9** (45 mg, 0.12 mmol) in THF (1 mL) was added, and the resultant brown solution was stirred at 25 °C for 1 h and then warmed to 55 °C and stirred for 15 h. The reaction mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with H_2O and then brine and dried. The crude product was purified on silica gel with EtOAc/hexane (40%) as the eluant to give crocacin C (**3**) (35 mg, 84%) as a white powder: R_f 0.50 (petrol/EtOAc, 1:1); $[\alpha]_D^{20}$ + 53.6 (*c* 0.21, MeOH); lit.[1] $[\alpha]_D^{22}$ +52.2 (*c* 0.3, MeOH); IR ν_{max} (film) 3478, 3349, 3207, 3055, 2976, 2931, 1660, 1448, 1088 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.46 (dd, *J* 8.0, 1.8 Hz, 2H), 7.31 (dd, *J* 8.0, 7.5 Hz, 2H), 7.22 (dd, *J* 7.5, 7.5 Hz, 1H), 6.65 (br s, 1H), 6.59 (d, *J* 16.2 Hz, 1H), 6.25 (dd, *J* 7.1, 16.2 Hz, 1H), 6.10 (br s, 1H), 6.02−6.12 (m, 2H), 5.80 (d, *J* 1.1 Hz, 1H), 4.08 (ddd, J 7.3, 2.6, 1.1 Hz, 1H), 3.29 (s, 3H), 3.52 (s, 3H), 3.19 (dd, *J* 2.2, 9.5 Hz, 1H), 2.62 (m, 1H), 2.21 (d, *J* 1.1 Hz, 3H), 1.58 (m, 1H), 1.20 (d, *J* 6.8 Hz, 3H), 0.88 (d, *J* 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.1, 148.1, 137.9, 137.1, 135.0, 132.5, 130.5, 129.4, 128.3, 127.2, 121.9, 87.1, 81.8, 61.4, 56.5, 43.6, 40.8, 19.3, 13.5, 10.2; HRMS (ESI) calcd for $C_{22}H_{31}NO_3$ [M^+] 357.2304, found 357.2304.

3-(Triisopropylsilyloxy)propan-1-ol (30). To a stirred suspension of NaH (444 mg, 11.1 mmol) in THF (20 mL) at 0 °C under argon was added dropwise a solution of 1,3-propanediol (0.80 mL, 11.1 mmol). After the mixture was stirred for 30 min at room temperature, triisopropylsilyl chloride (1.19 mL, 11.1 mmol) was added in one portion. The reaction mixture was stirred for 18 h at room temperature and diluted with Et_2O (20 mL) followed by addition of H_2O (20 mL). The organic phase was separated; the aqueous layer was further extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified on silica gel using EtOAc/hexanes (10:90) as the eluant to give the desired alcohol **30** (2.20 g, 86%): R_f 0.37 (EtOAc/hexane 20%); IR ν_{max} (film) 3400, 2942, 2863, 1465, 1386, 1267 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (t, *J* 5.5 Hz, 2H), 3.84 (t, *J* 5.5 Hz, 2H), 1.80 (quint, *J* 5.5 Hz, 2H); 1.09 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.5, 62.6, 34.3, 18.0, 11.9; HRMS calcd for $C_{12}H_{28}O_2Si$ [M^+ (232.1859) − $(CH_3)_2CH^+$] 189.1317, found 189.1375.

(*E*)-Methyl 5-(Triisopropylsilyloxy)pent-2-enoate (31). To a solution of 0.60 mL (6.66 mmol) of oxalyl chloride in 50 mL of CH_2Cl_2 at −78 °C was added 1.0 mL (5.55 mmol) of DMSO (gas evolution). After 10 min, a solution of 1.29 g (5.55 mmol) of the alcohol **30** in 20 mL of CH_2Cl_2 was added. The cloudy white mixture was stirred for 15 min at −78 °C, after which 3.8 mL (27.7 mmol) of triethylamine was added. The reaction mixture was stirred at −78 °C for 40 min, and then the reaction was quenched by the addition of 30 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and then diluted with 30 mL of CH_2Cl_2 and 30 mL of saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted with two 30 mL portions of CH_2Cl_2. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. A ^{1}H NMR spectrum of the unpurified aldehyde proved to be very clean. To a stirred suspension of NaH (160 mg, 6.66 mmol) in THF (12 mL) at 0 °C under argon was added methyldiethylphosphonoacetate (1.3 mL, 7.21 mmol). After stirring for 30 min at room temperature, the previously prepared aldehyde in THF (5 mL) was added. The reaction mixture was stirred for 1 h at room temperature

and diluted with Et_2O (20 mL) followed by addition of H_2O (6 mL). The organic phase was separated; the aqueous layer was further extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified on silica gel using EtOAc/hexanes (10:90) as the eluant to give ester **31** (1.42 g, 89% for the two-step sequence): R_f 0.65 (EtOAc/hexane 20%); IR ν_{max} (film) 3051, 2946, 2867, 1730, 1651, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (dt, *J* 15.7, 7.0 Hz, 1H); 5.88 (d, *J* 15.7 Hz, 1H); 3.80 (t, *J* 6.6 Hz, 2H), 3.72 (s, 3H), 2.44 (dt, *J* 7.0, 6.6 Hz, 2H); 1.06 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 146.2, 122.3, 61.8, 51.4, 36.0, 18.0, 12.0; HRMS calcd for $C_{15}H_{30}O_3Si$ [M^+ (286.1964) − $(CH_3)_2CH^+$] 243.1422, found 243.1243.

Methyl 5-(Triisopropylsilyloxy)pentanoate. After two vacuum/H_2 cycles to remove air from the reaction flask, a stirred solution of 1.85 g (6.46 mmol) of the α,β-unsaturated ester **31** and 10% Pd/C (185 mg, 10% m/m) in 10 mL of MeOH was hydrogenated at 1 atm and room temperature for 24 h. The reaction mixture was filtered (Celite) and the filtrate concentrated. Purification by flash chromatography (10% EtOAc in hexane) gave 1.80 g (97%) of the desired saturated ester: R_f 0.65 (EtOAc/hexane 20%); IR ν_{max} (film) 2945, 2860, 1743, 1460, 1383, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (t, *J* 6.6 Hz, 2H), 3.67 (s, 3H), 2.35 (t, *J* 7.0 Hz, 2H), 1.72 (m, 2H), 1.58 (m, 2H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 62.8, 51.4, 33.9, 32.4, 21.5, 18.0, 12.0; HRMS calcd for $C_{15}H_{32}O_3Si$ [M^+ (288.2121) − $(CH_3)_2CH^+$] 245.1579, found 245.1436.

5-(Triisopropylsilyloxy)pentanoic Acid (29). To a stirred solution of the previously prepared saturated ester (1.80 g, 6.25 mmol) in MeOH (3 mL) was added a 3.0 M solution of KOH in MeOH (10 mL). The reaction was stirred for 24 h at room temperature, and citric acid was added in order to neutralize the solution. The solvent was removed, and to the residue was added 10 mL of a saturated aqueous solution of NaCl. The aqueous phase was further extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Purification by flash chromatography (10% EtOAc in hexane) gave 1.52 g (89%) of carboxylic acid **29**: R_f 0.28 (EtOAc/hexane 20%); IR ν_{max} (film) 3539, 2940, 2869, 2718, 1711, 1460, 1379, 1263, 1166, 1112, 1010, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.71 (t, *J* 6.0 Hz, 2H), 2.40 (t, *J* 7.3 Hz, 2H); 1.73 (m, 2H), 1.60 (m, 2H), 1.07 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 62.9, 33.5, 32.1, 21.3, 18.0, 11.9; HRMS calcd for $C_{14}H_{30}O_3Si$ [M^+] 274.1964, found 274.2668.

Methyl 2-(5-(Triisopropylsilyloxy)pentanamido)acetate. To a solution of carboxylic acid **29** (1.67 g, 6.09 mmol) in CH_2Cl_2 (30 mL) at room temperature were added glycine methyl ester **6** (1.15 g, 9.13 mmol), $NaHCO_3$ (0.75 g, 8.89 mmol), HOBt (1.64 g, 12.2 mmol), and DCC (2.51 mg, 12.2 mmol). The resulting mixture was stirred for 18 h at room temperature and concentrated in vacuo to give a residue that was diluted with benzene (10 mL), filtered, and evaporated. Purification by flash chromatography (50% EtOAc in hexane) gave 1.70 g (81%) of the desired peptide: R_f 0.28 (EtOAc/hexane 50%); IR ν_{max} (film) 3302, 2939, 2869, 1751, 1653, 1545, 1460, 1207, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (brs, 1H), 4.05 (d, *J* 5.1 Hz, 2H), 3.76 (s, 3H), 3.70 (t, *J* 6.2 Hz, 2H), 2.29 (t, *J* 7.3 Hz, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 170.3, 62.9, 52.2, 41.1, 36.0, 32.3, 22.1, 18.0, 12.0; HRMS calcd for $C_{17}H_{35}NO_4Si$ [M^+ (345.2335) − $(CH_3)_2CH^+$] 302.1793, found 302.1768.

Methyl 2-(*N*-(*tert*-Butoxycarbonyl)-5-(triisopropylsilyloxy)pentanamido)acetate (32). To a solution of the previously prepared peptide (600 mg, 1.73 mmol) in THF (7.5 mL) at 0 °C were added DIPEA (0.7 mL, 3.48 mmol), DMAP (21 mg, 0.0173 mmol), and Boc_2O (756 mg, 3.48 mmol). The resulting mixture was stirred for 1 h at room temperature (gas evolution) and quenched by addition of brine (10 mL). The aqueous phase was further extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Purification by flash chromatography (10% EtOAc in hexane) gave 0.70 g (90%) of dipeptide **32**: R_f 0.34 (EtOAc/hexane 10%); IR ν_{max} (film) 3055, 2940, 2870, 1747, 1688, 1459, 1365, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 2H), 3.73 (s, 3H), 3.70 (t, *J* 6.2 Hz, 2H), 2.96 (t, *J* 7.0 Hz, 2H), 1.72 (m, 2H), 1.60 (m, 2H), 1.50 (s, 9H), 1.06 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 169.4, 152.0, 83.7, 63.2, 52.1, 45.2, 37.9, 32.5, 28.0, 21.6, 18.1, 12.1; HRMS calcd for $C_{22}H_{43}NO_6Si$ [M^+ (445.2860) − $(CH_3)_2CH^+$] 402.2318, found 402.1926.

Methyl 2-(*N*-(*tert*-Butoxycarbonyl)-5-hydroxypentanamido)acetate. To a solution of carbamate **32** (200 mg, 0.45 mmol) in 6.2 mL of THF at 0 °C was added 6.2 mL of a solution of HF-pyridine/pyridine/THF (1:4:5). The reaction mixture was stirred at ambient temperature for 18 h, diluted with 5 mL of EtOAc, and quenched by the slow addition of powder $NaHCO_3$ (100 mg). The resulting mixture was stirred for 15 min at room temperature, filtered, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexane) gave 0.107 g (83%) of the desired primary alcohol: R_f 0.34 (EtOAc/hexane 10%); IR ν_{max} (film) 3423, 2958, 2876, 1747, 1691, 1347, 1341, 1220, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.44 (s, 2H), 3.72 (s, 3H), 3.64 (t, *J* 6.2 Hz, 2H), 2.96 (t, *J* 7.3 Hz, 2H), 1.79 (brs, 1H), 1.74 (quint, *J* 7.3 Hz, 2H), 1.61 (ap quint, *J* 6.2 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 169.3, 152.0, 83.9, 62.2, 52.2, 45.2, 37.5, 32.0, 28.0, 21.1.

Methyl 2-(*N*-(*tert*-Butoxycarbonyl)-5-oxopentanamido)-acetate (33). To a stirred solution of the previously prepared primary alcohol (150 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added pyridine (0.42 mL, 5.2 mmol), followed by Dess−Martin periodinane (440 mg, 1.04 mmol), and stirring was continued for 1 h at room temperature. Saturated aqueous $NaHCO_3$ (2 mL), aqueous $Na_2S_2O_3$ (1.5 M, 2 mL), and Et_2O (5 mL) were added, and stirring was continued for 15 min at rt. The aqueous layer was further extracted with Et_2O, and the combined organic layers were dried, filtered, and concentrated to give aldehyde **33**: R_f 0.33 (EtOAc/hexane 20%); IR ν_{max} (film) 3419, 2985, 1739, 1150 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 9.75 (apt, *J* 1.1 Hz, 1H), 4.43 (s, 2H), 3.72 (s, 3H), 2.99 (t, *J* 7.1 Hz, 2H), 2.51 (td, *J* 7.3 e 1.1 Hz, 2H), 1.97 (quint, *J* 7.3 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 201.7, 174.6, 169.2, 151.9, 83.9, 52.1, 45.1, 43.0, 37.0, 27.9, 17.5.

(*Z*)-Methyl 2-(*N*-(*tert*-Butoxycarbonyl)-6-iodohex-5-enamido)acetate. To a suspension of iodomethyl triphenylphosphonium iodide **34** (834 mg, 1.57 mmol) in THF (5.0 mL) at room temperature was added a solution of NaHMDS (2.08 mL, 1.24 mmol, 0.6 M in toluene) dropwise. After stirring for 6 min, the reaction mixture was cooled to −78 °C by the time aldehyde **33** (0.52 mmol) in 3 mL of THF was added slowly. After the reaction mixture was stirred for 1 h at −78 °C, the reaction was quenched by the addition of saturaded aqueous NH_4Cl (5 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexanes, 10:90) to give the *N*-Boc-protected (*Z*)-vinyl iodide (>95:5 *Z*:*E*) in 81% yield for the two-step sequence: R_f 0.34 (EtOAc/hexane 10%); IR ν_{max} (film) 2981, 1742, 1685, 1646, 1213, 1150 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.88 (d, *J* 7.1 Hz, 1H), 5.71 (q, *J* 7.1 Hz, 1H), 4.48 (s, 2H), 3.29 (s, 3H), 2.08 (t, *J* 7.3 Hz, 2H), 2.08 (q, *J* 7.2 Hz, 2H), 1.74 (quint, *J* 7.3 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 174.6, 169.3, 152.4, 140.8, 83.0, 82.9, 51.7, 45.4, 37.6, 34.4, 27.9, 23.7.

(*Z*)-Methyl 2-(6-iodohex-5-enamido)acetate (28). To a solution of the previously prepared *N*-Boc-protected (*Z*)-vinyl iodide (15 mg, 0.036 mmol) in 0.2 mL of CH_2Cl_2 was added 1 mL of trifluoroacetic acid. The resulting solution was stirred at room temperature for 18 h before it was concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexanes, 50%) to give (*Z*)-vinyl iodide

28 (9.5 mg, >95:5 *Z*:*E*) in 85% yield: R_f 0.25 (EtOAc/hexane 50%); IR ν_{max} (film) 3300, 3067, 2932, 2850, 1753, 1653, 1541, 1435, 1367 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.90 (d, *J* 7.1 Hz, 1H), 5.68 (q, *J* 7.1 Hz, 1H), 5.26 (brs, 1H), 3.75 (d, *J* 5.1 Hz, 2H), 3.26 (s, 3H), 2.01 (q, *J* 7.0 Hz, 2H), 1.76 (t, *J* 7.3 Hz, 2H), 1.61 (q, *J* 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 170.3, 140.7, 83.1, 51.7, 41.3, 35.2, 34.5, 24.1; HRMS calcd for $C_9H_{14}INO_3$ [M^+] 311.0018, found 311.0015.

Methyl 2-((*Z*)-6-((2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamido)hex-5-enamido)acetate [(+)-Crocacin D] (4). A resealable Schlenk tube was charged with CuI (1.0 mg, 0.0052 mmol), crocacin C (**3**) (44.7 mg, 0.125 mmol), and Cs_2CO_3 (52.0 mg, 0.16 mmol). The tube was evacuated and backfilled with argon, and *N*,*N*′-dimethylethylenediamine (1.15 μL, 0.01 mmol, 10 mol %), (*Z*)-vinyl iodide **28** (31 mg, 0.10 mmol), and THF (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve, and the reaction was stirred at 70 °C for 15 h. After the resulting pale blue suspension was allowed to reach room temperature, ethyl acetate (2 mL) was added. The reaction mixture was filtered through a silica plug eluting with ethyl acetate (15 mL). The filtrate was concentrated, and the residue was purified by column chromatography using Et_3N-deactivated silica gel to provide crocacin D (**4**) (44.9 mg, 67%) as a colorless gum; $[\alpha]_D^{20}$ +104.9 (*c* 0.35, MeOH); lit.[2a] $[\alpha]_D^{20}$ +109.6 (*c* 0.56, MeOH); IR ν_{max} (film) 3301, 2929, 1749, 1654, 1608, 1510, 1263, 1090, 972 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.14 (br d, *J* 10.4 Hz, 1H), 7.60 (br m, 1H), 7.48 (d, *J* 7.2 Hz, 2H), 7.32 (ap t, *J* 7.2 Hz, 2H), 7.21 (ap t, *J* 7.2 Hz, 1H), 6.79 (dd, *J* 10.5, 9.0 Hz, 1H), 6.60 (d, *J* 16.0 Hz, 1H), 6.25 (dd, *J* 16.0, 7.3 Hz, 1H), 6.12 (m, 2H), 5.92 (d, *J* 1.3 Hz, 1H), 4.65 (dt, *J* 9.0, 7.1 Hz, 1H), 4.09 (dd, *J* 7.1, 1.7 Hz, 1H), 3.96 (d, *J* 6.1 Hz, 2H), 3.65 (s, 3H), 3.50 (s, 3H), 3.30 (s, 3H), 3.16 (dd, *J* 9.6, 2.3 Hz, 1H), 2.58 (m, 1H), 2.26 (br s, 3H), 2.26 (t, *J* 7.1 Hz, 2H), 2.11 (dt, *J* 7.1, 6.9 Hz, 2H), 1.68 (tt, *J* 7.1, 6.9 Hz, 2H), 1.55 (ddq, *J* 9.5, 7.0, 2.3 Hz, 1H), 1.18 (d, *J* 6.7 Hz, 3H), 0.83 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.4, 171.3, 164.5, 149.5, 137.7, 135.1, 132.5, 130.3, 129.3, 128.3, 127.1, 123.9, 121.7, 109.7, 87.1, 81.6, 61.5, 56.3, 52.2, 43.5, 41.5, 40.7, 34.4, 26.2, 25.3, 19.2, 13.8, 10.1; HRMS calcd for $C_{31}H_{44}N_2O_6Na$ [M + Na^+] 563.3097, found 563.3110.

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Supporting Information Available: Experimental procedures and product characterization for compounds **5**, **7**, and **24** and selected IR, HRMS, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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