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Step-Economic Synthesis of (+)-Crocacin C: A Concise Crotylboronation/[3,3]-Sigmatropic Rearrangement Approach†

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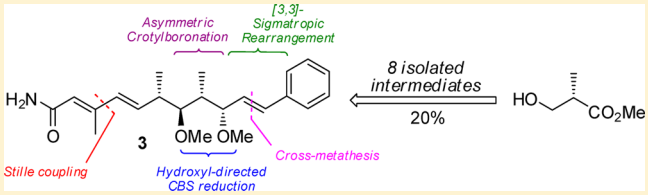
Supporting Information

ABSTRACT: The step-economic total synthesis of (+)-crocacin C has been achieved in 20% yield from commercially available starting materials. This approach requires the isolation of only 8 intermediates and can provide a reliable supply of (+)-crocacin C for the development of new antifungal and crop protection agents.



The crocacins are a family of four antifungal and cytotoxic antibiotics, isolated in 1994 from two different strains of *Chondromyces* bacteria by Höfle and co-workers (Figure 1).[1]

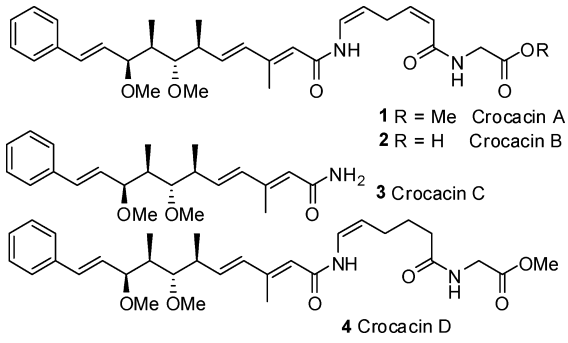


Figure 1. Crocacins A–D.

Biologically, the crocacins exhibit a range of activities. Crocacin A **1** has shown remarkable activity as a growth inhibitor of fungi and yeasts through inhibition of the electron flow within the cytochrome bc_1 segment (complex III) of the respiratory chain, while crocacin D **4** has shown a MIC of 1.4 ng/mL against *S. cerevisiae*.[2]

Crucial for this bioactivity is the highly reactive enamide moiety. It has been postulated that the enamide unit is protonated, and the resultant *N*-acyliminium ion can then be trapped by a nucleophile to generate the enzyme complex responsible for activity.[2]

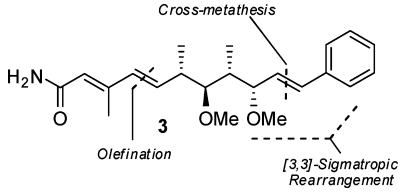
Despite their relative instability, the crocacins have been the subject of industrial antifungal research as they inhibit strains of yeast that have been genetically modified for antifungal resistance,[3] as well as vine downy mildew (*Phytophthora infestans*) and wheat brown rust (*Puccinia recondite*). Crocacins A **1**, B **2**, and D **4** are unusual dipeptides incorporating glycine and a 6-aminohexenoic or 6-aminohexadienoic acid in which the nitrogen is protected by a complex polyketide derived acyl residue. Crocacin C **3** is the free carboxamide unit. The promising biological activity, together with their low natural abundance and interesting structural features, has made them attractive synthetic targets. This interest has resulted in a number of formal and total syntheses.[4−11]

As part of our efforts toward the development of stable crocacin analogues starting from (+)-crocacin C as a synthetic platform, we have recently reported our initial modular synthetic approach to the formal synthesis of (+)-crocacin C **3**.[11] However, despite the fact that our approach was successful in completing the formal synthesis of (+)-crocacin C **3**, it was deemed unsuitable for scale-up due to the number of steps required and its low overall efficiency. Challenged by this outcome, we sought to develop an alternative route, and in this contribution we report our efficient, step-economic, and cost-effective second generation synthesis of (+)-crocacin C **3** from commercially available starting materials.

RESULTS AND DISCUSSION

In planning our current approach, we envisioned that crocacin C **3** could be derived following a route featuring a concise crotylboronation, cross-metathesis, and [3,3]-sigmatropic rearrangement (Scheme 1).

Scheme 1. Second Generation Retrosynthetic Analysis of (+)-Crocacin C 3



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Scheme 2. Synthesis of Enone 13

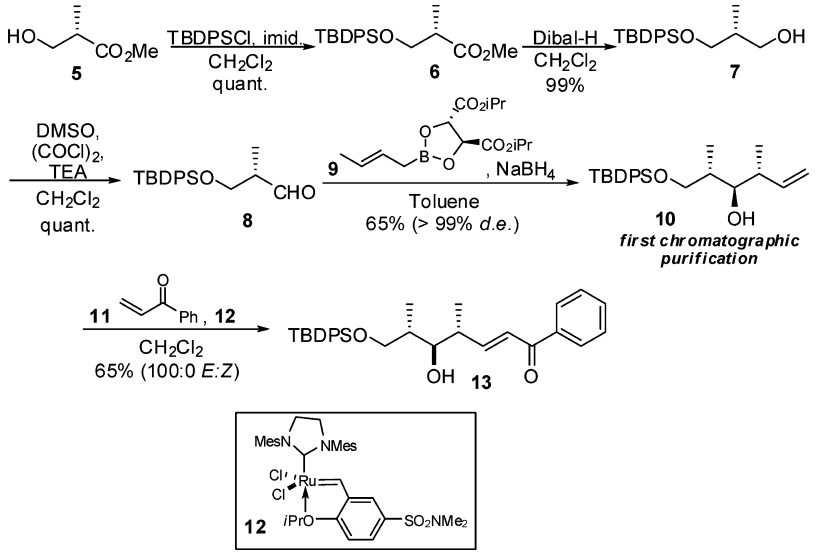
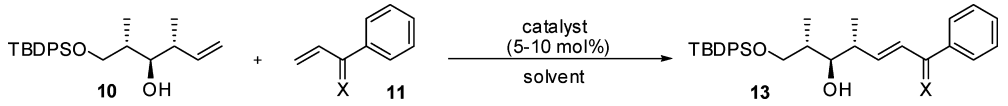


Table 1. Cross-Metathesis Studies for the Synthesis of Enone 13[a]



entry	equiv **10**	equiv **11**	X	conditions	**13** (%)
1	1.0	1.5	H, OAc	HGII, 0.1 MDCM, 40 °C, 12 h	only poor homodimerization
2	1.0	1.5	H, OAc	GII, 0.1 MDCM, 40 °C, 12 h	only poor homodimerization
3	1.0	3.0	H, OAc	GII, 0.1 MDCM, 45 °C, 24 h	only poor homodimerization
4	1.0	3.0	H, OAc	HGII, 0.05 M DCM, 80 °C, MW, 12 h	no rxn, SM epimerized
5	1.0	1.0	H, OH	GII, 0.05 M DCM, 80 °C, MW, 12 h	decomposition
6	1.0	3.0	H, OH	HGII, 0.1 MDCM, 80 °C, 2 h	decomposition
7	5.0	1.0	H, OAc	GII, 0.1 MDCM, 45 °C, 72 h	decomposition/epimerization
8	10.0	1.0	H, OAc	GII, 0.1 M toluene, 45 °C, 72 h	decomposition/epimerization
9	1.0	4.0	O	HGII, 0.2 M DCM, 50 °C, 120 h	21
10	1.0	5.0	O	HGII, 0.25 M DCM, 40 °C,, MW, 48 h	43
11	1.0	5.0	O	HGII, 0.3 MDCM, 40 °C, 48 h	40
12	1.0	5.0	O	Zhan 1B, 0.3 M DCM, 40 °C, 48 h	65

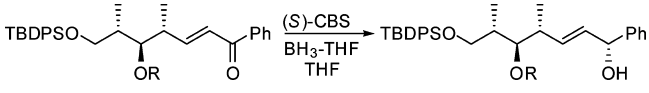
[a]GII = Grubbs second generation; HGII = second generation Hoveyda–Grubbs.

Our synthesis of (+)-crocacin C **3** began with the commercially available Roche ester **5** (Scheme 2). Silyl protection and reduction–oxidation of the resultant methyl ester **6** gave aldehyde **8** (Scheme 2). Diastereoselective crotylboronation of aldehyde **8** under Roush's conditions yielded the desired *anti,anti*-adduct **10**.[12] It is worth noting that alcohol **10** is the first intermediate in the synthesis that required purification. The pivotal crotylboronation allowed the insertion of two stereocenters to generate the required *anti,anti* stereotriad in a single transformation and provided us with an olefinic handle from which a cross-metathesis could be explored.

Despite extensive experimentation, the cross-metathesis of olefin **10** with either vinyl acetophenone **11** or its reduced form proved extremely difficult, most likely due to the low reactivity of both coupling partners (Table 1). However, application of the cross-metathesis methodology recently reported by Donohoe[13] using the Zhan 1B catalyst **12** successfully coupled the two olefins in good yield and with excellent stereocontrol to give the desired *E*-enone **13**.

Subsequent Corey–Bakshi–Shibata reduction of enone **13** afforded the desired allylic alcohol **14** in excellent yield and in >99% *d.e.*[14] Interestingly, we observed a long-range influence exerted by the homoallylic alcohol on the outcome of this reduction (Table 2). For example, when the alcohol was acetylated, the epimeric alcohol **14a** was observed as the major diastereomer in poor yield. However, when the allylic alcohol was methylated, the yield was improved significantly, but no stereocontrol was observed during the reduction. In the case of

Table 2. Long-Range Neighboring Group Effects Observed during CBS Reductions



entry	R	*T* (°C)	isolated yield (%)		(*R*)/(*S*)
1	Ac **13a**	−40	40	**14a**	1.0/2.0
2	Me **13b**	−10	99	**14b**	1.1/1.0
3	H **13**	−40	93	**14**	>99.0/1.0

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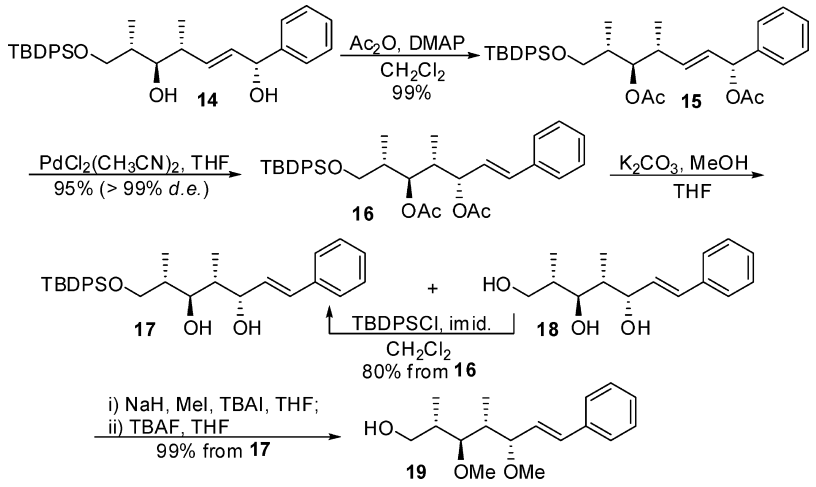
Scheme 3. Synthesis of Alcohol 19

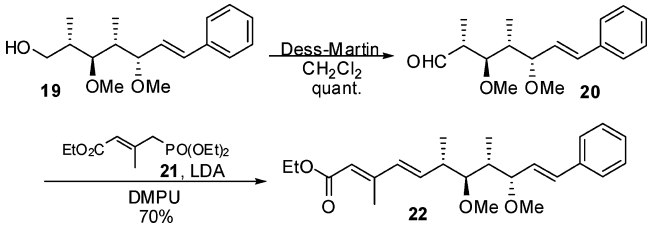


the unprotected alcohol **13**, the reduction proceeded with complete stereocontrol to generate the desired diol **14**. Although the reasons for this remarkable change in behavior are not completely clear, it is possible that coordination between the free alcohol and the oxazaborolidine is responsible for the enhancement in stereoselectivity observed.

The newly generated diol **14** was acetylated to generate the bis-acetate **15**, allowing us to implement the key [3,3]-sigmatropic rearrangement. Gratifyingly, when treated with $PdCl_2(CH_3CN)_2$, bis-acetate **15** gave the desired *anti,anti,syn*-product **16** as a single diastereomer in excellent yield (Scheme 3).[15] Hydrolysis of the bis-acetate **16** afforded the free diol **17** together with triol **18**, which could be recycled to afford diol **17** in very good overall yield. Methylation of diol **17** followed by silyl-group removal provided the desired alcohol **19** in near quantitative yield over the two steps.

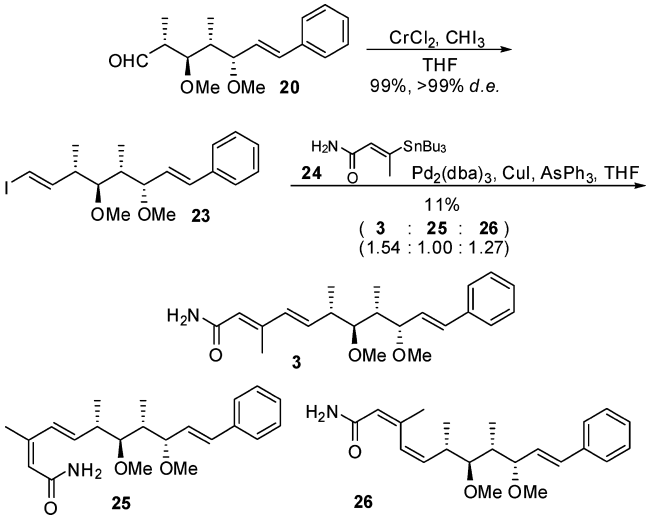
With alcohol **19** in hand, the final steps of the synthesis were explored. Careful oxidation of alcohol **19** produced aldehyde **20**, which upon Horner–Wadsworth–Emmons olefination gave the expected dienoate ester **22** as a single diastereomer (Scheme 4).[5a] Unfortunately, all attempts to hydrolyze ester **22** resulted in degradation.

Scheme 4. Horner–Wadsworth–Emmons Approach



As a consequence of this initial setback, an alternative end game was required for the synthesis of (+)-crocacin C **3**. In order to introduce the amide functionality without necessitating a final functional group interconversion, a strategy involving a metal-mediated coupling with the amide unit already in place was pursued.[6a] Treatment of aldehyde **20** under Takai conditions afforded the desired *E*-iodo-alkene **23** in excellent yield and with complete stereocontrol (Scheme 5).[16] With the *E*-iodo-alkene **23** in hand, a Stille coupling with the known stannyl enamide **24**[6a] was then performed. Although the

Scheme 5. Preliminary Stille Coupling



coupling afforded (+)-crocacin C **3** in poor yield, an exciting mixture of products containing two novel isomeric crocacin analogues **25** and **26** was also obtained.

The promising Stille coupling results prompted us to consider a reverse coupling strategy for the completion of the synthesis whereby the enamide unit is introduced as the vinyl halide and the C4–C11 framework of (+)-crocacin C **3** is brought forward as the vinyl stannane.[4a] Hodgson olefination of aldehyde **20** provided us with the key *E*-vinyl stannane unit **27** in moderate yield (Scheme 6).[17,4a] Microwave-assisted Stille coupling of vinyl stannane **27** with the vinyl iodide bearing amide **28** yielded (+)-crocacin C **3** as a single double bond isomer in much improved yield.

Although the Stille coupling of vinyl stannane **27** with vinyl iodide **28** yielded (+)-crocacin C **3** as a single alkene isomer, the process was not amenable to scale-up, often resulting in protodestannylation during purification of vinyl stannane **27**.

In a variant of the highly promising Stille coupling, which would allow us to circumvent the protodestannylation issues, aldehyde **20** was subjected to Ohira–Bestmann homologation conditions to generate alkyne **30** in quantitative yield (Scheme 7).[18] To our delight, *in situ* conversion of alkyne **30** into the *E*-vinyl stannane with concomitant Stille coupling (with vinyl

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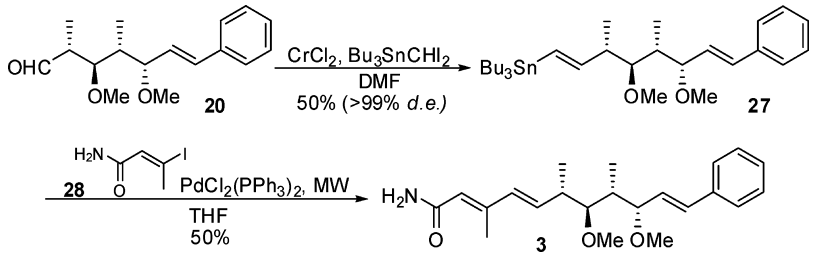
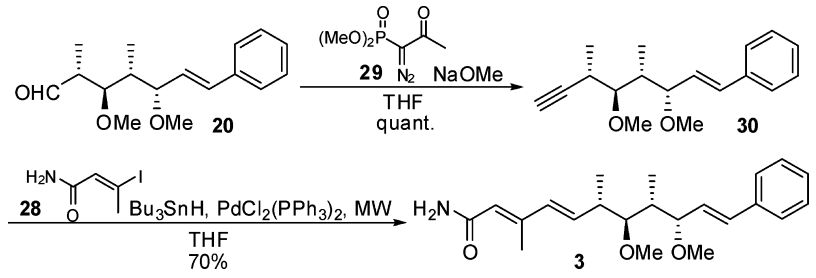
Scheme 6. Reverse Stille Coupling Strategy



Scheme 7. End-Game Strategy to (+)-Crocacin C 3



iodide **28**) using Bressy and Pons' conditions[9] afforded (+)-crocacin C **3** in high yield and as a single isomer.

CONCLUSIONS

In conclusion, we have developed a reliable, flexible, and highly efficient synthesis of (+)-crocacin C **3** from commercially available starting materials that compares favorably with previous syntheses. Our approach is amenable to scale-up and is able to generate (+)-crocacin C **3** in 14 steps (8 isolated intermediates) and 20% overall yield from commercially available Roche ester **5**. Efforts are currently underway to develop new antifungal agents based on the frameworks of (+)-crocacin C and the structurally isomeric analogues **25** and **26**.

EXPERIMENTAL SECTION

General. All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF) and toluene were purified through a solvent purification system. Anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), dimethylformamide (DMF), and methanol (MeOH) were obtained commercially. Dichloromethane (CH_2Cl_2) was freshly distilled over CaH_2. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C unless otherwise stated. IR spectra were recorded as neat films using a Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded at, respectively, 400/500 MHz and 100/125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (3) and coupling constant (J) quoted in Hertz to the nearest 0.1 Hz. High resolution mass spectra were recorded by electrospray (ESI), fast atom bombardment (FAB), electron impact (EI), or chemical ionization (CI) using a mass spectrometer operating at a resolution of 15,000 full widths at half height. Flash chromatography was performed using silica gel (40−63 μm) as the stationary phase. TLC was performed on aluminum sheets precoated with silica (silica gel 60 F254) unless otherwise stated where aluminum oxide plates were used. The plates were visualized by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with potassium permanganate or *p*-anisaldehyde followed by heating.

(*S*)-Methyl 3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanoate, 6. To a 0 °C solution of (*S*)-methyl 3-hydroxy-2-methylpropanoate **5** (7.0 g, 59.3 mmol) and imidazole (4.8 g, 71.1 mmol) in CH_2Cl_2 (300 mL) was added TBDPSCl (17.0 mL, 65.2 mmol) in small portions, and the reaction mixture was allowed to warm to room temperature and stir until completion as indicated by TLC analysis (12 h). The reaction was then quenched with satd aq $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were collected, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford 21.15 g of the desired ester **6** as colorless oil (quant) which required no further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.65 (m, 4H), 7.45−7.37 (m, 6H), 3.86 (1H, dd, J = 9.8, 6.9 Hz), 3.76 (1H, dd, J = 9.8, 5.9 Hz), 3.71 (3H, s), 2.79−2.68 (1H, m), 1.18 (3H, d, J = 7.0 Hz), 1.06 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 135.7, 133.6, 129.8, 127.8, 66.0, 51.7, 42.5, 26.8, 19.4, 13.6. R_f 0.44 (hexane/EtOAc, 9:1); $[\alpha]^{22}_D$ +6.8 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3073−2859, 1740, 1472, 1427, 1389, 1362, 1258, 1198, 1177, 1106, 824, 739, 702 cm^{-1}. HRMS (CI+/ISO) calcd for $C_{21}H_{29}O_3Si$ $[M + H]^+$: 357.1886, found 357.1888.

(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol, 7. A 0 °C solution of ester **6** (22.0 g, 61.7 mmol) in dry CH_2Cl_2 (300 mL) was treated with the dropwise addition of DIBAL-H (1 M in CH_2Cl_2, 135.7 mL, 135.7 mmol), and the resulting reaction mixture was allowed to stir at 0 °C until completion by TLC analysis (3 h). The reaction mixture was quenched at 0 °C by the careful addition of satd aq Rochelle's salt (250 mL), and the biphasic system was allowed to stir at room temperature for 12 h. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford 20.1 g of alcohol **7** as colorless oil (99% yield) The crude product was clean enough and could be used without the need of any further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71−7.66 (m, 4H), 7.47−7.37 (m, 6H), 3.74 (1H, dd, J = 9.9, 4.5 Hz), 3.68 (2H, m), 3.61 (1H, dd, J = 10.1, 7.7 Hz), 2.56 (1H, bs), 2.06−1.95 (1H, m), 1.07 (9H, s), 0.84 (3H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.9, 133.3, 129.9, 127.9, 68.9, 67.8, 37.4, 26.9, 19.3, 13.3. R_f 0.29 (hexane/EtOAc, 9:1), $[\alpha]^{25}_D$ +4.0 (c 1.0, $CHCl_3$); IR ν_{max} (film) 3387, 3073−2859, 1472, 1427, 1391, 1362, 1111, 1086, 1028, 939, 822, 802, 739, 698 cm^{-1}. HRMS (CI+/ISO) calcd for $C_{20}H_{29}O_2Si$ $[M + H]^+$: 329.1937, found 329.1933.

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(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropanal, 8. A solution of oxalyl chloride (2.15 mL, 24.5 mmol) in freshly distilled CH_2Cl_2 (195 mL) was cooled to −78 °C and treated dropwise with a solution of dimethylsulfoxide (3.5 mL, 49.0 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was stirred under argon at −78 °C for 30 min. A solution of (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol **7** (4.02 g, 12.25 mmol) in CH_2Cl_2 (8 mL) was added dropwise, and the reaction was allowed to stir at −78 °C for 1 h. The reaction mixture was quenched at −78 °C by the addition dropwise of triethylamine (13.7 mL, 98.0 mmol), and the obtained solution was stirred at −78 °C for 10 min and then at room temperature for a further 30 min. The reaction mixture was washed with satd aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford 4.02 g of aldehyde **8** as a yellow oil in quantitative yield (4.02 g, 12.3 mmol). The crude product was taken straight onto the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1H, d, J = 1.7 Hz), 7.68−7.62 (4H, m), 7.45−7.38 (6H, m), 3.95−3.82 (2H, m), 2.65−2.50 (1H, m), 1.10 (3H, d, J = 6.8 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 135.7, 129.9, 127.9, 64.2, 48.9, 26.9, 19.3, 10.4. R_f 0.38 (hexane/Et_2O, 9:1); $[\alpha]^{26}_D$ +5.0 (c 2.0, $CHCl_3$); IR ν_{max} (film) 3073−2720, 2114, 1738−1713, 1472, 1428, 1111, 1026, 1008, 808, 826, 739, 698, 689, 615 cm^{-1}. HRMS (CI+/ISO) calcd for $C_{20}H_{27}O_2Si$ $[M + H]^+$: 327.1780, found 327.1774.

(2*S*,3*R*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhex-5-en-3-ol, 10. A slurry of 300 mg of 4 Å powdered molecular sieves (previously dried under vacuum using a heatgun) in dry toluene (15 mL) was treated with (4*S*,5*S*)-diisopropyl 2-((*E*)-but-2-enyl)-1,3,2-dioxaborolane-4,5-dicarboxylate, **9**[12b] (13.8 mL, 13.8 mmol, 1.0 M solution in dry toluene). The heterogeneous solution was stirred at room temperature for 10 min and was then cooled to −78 °C. A solution of (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal **8** (3.0 g, 9.2 mmol) in dry toluene (15 mL) was then added dropwise to the mixture via a cannula over a 20 min period. Once the addition was complete, the solution was maintained at −78 °C for 16 h. Excess ethanolic $NaBH_4$ (200 mg in 3 mL of absolute EtOH) was then introduced dropwise via a pipet, and the resulting solution was allowed to warm to 0 °C. The reaction mixture was then diluted with 1 N NaOH (25 mL) and stirred vigorously for 2 h. The phases were separated, and the aqueous phase was extracted with diethyl ether (5 × 150 mL). The combined organic layers were dried over K_2CO_3 and concentrated under vacuum to afford yellow oil as crude product. Purification of the crude residue (90:10 hexane/Et_2O) yielded 2.3 g (65%) of alkene **10** as colorless oil.[1] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59−7.56 (4H, m), 7.36−7.24 (6H, m), 5.86 (1H, ddd, J = 10.5, 8.4, 2.1 Hz), 5.00−4.94 (2H, m), 3.66−3.58 (2H, m), 3.39 (1H, dd, J = 3.3, 0.6 Hz), 3.36−3.32 (1H, m), 2.33−2.22 (1H, m), 1.77−1.70 (1H, m), 1.02 (3H, d, J = 7.0 Hz), 0.97 (9H, s), 0.72 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 135.7, 132.9, 129.9, 127.8, 79.7, 68.9, 41.2, 37.9, 26.9, 19.1, 17.8, 13.6. R_f 0.32 (hexane/Et_2O, 9:1); $[\alpha]^{28}_D$ +14.6 (c 4.0, $CHCl_3$); IR ν_{max} (film) 3050, 2062, 1430, 1210, 1010, 915, 864, 702, 610, 420, 350 cm^{-1}. HRMS (CI+/ISO) calcd for $C_{24}H_{35}O_2Si$ $[M + H]^+$: 383.2406, found 383.2410.

1-Phenylprop-2-en-1-ol. Vinylmagnesium bromide (1.0 M in THF, 47.1 mL, 47.1 mmol) was added dropwise to a solution of benzaldehyde (5.0 g, 47.1 mmol) in dry THF (250 mL) at 0 °C. After stirring for 10 min the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction was then quenched by addition of satd aq NH_4Cl (200 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated under vacuum to afford 6.23 g (quant) of 1-phenylprop-2-en-1-ol as crude yellow oil, which was taken directly onto the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.36 (5H, m), 6.05 (1H, ddd, J = 17.1, 10.3, 6.1 Hz, 1H), 5.38−5.33 (1H, m), 5.22−5.17 (1H, m), 4.66 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 140.3, 128.7, 128.6, 127.8, 126.4, 115.2, 75.4. R_f 0.21 (hexane/Et_2O, 8:2); IR ν_{max} (film) 3371, 1667, 1451, 1119, 950, 865, 780, 706, 630, 410, 360 cm^{-1}. HRMS (EI+) calcd for $C_9H_{10}O$ $[M]^+$: 134.0732, found 134.0733.

1-Phenylprop-2-en-1-one, 12. A solution of 1-phenylprop-2-en-1-ol (6.23 g, 47.1 mmol) in anhydrous CH_2Cl_2 (500 mL) was treated with TEMPO (147 mg, 0.94 mmol) and iodobenzene diacetate (38.0 g, 118 mmol) at room temperature. The resulting mixture was stirred at room temperature until completion as indicated by TLC analysis (12 h). The reaction mixture was quenched by the addition of satd aq $Na_2S_2O_3$ (200 mL) and left to stir for 1 h. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford an orange-yellow residue. Purification of the crude product by flash column chromatography (silica gel, 80:20 hexane/Et_2O) gave 5.3 g (85%) of enone **12** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97−7.93 (2H, m), 7.60−7.56 (1H, m), 7.49−7.47 (2H, m), 7.16 (1H, dd, J = 17.1, 10.6 Hz), 6.45 (1H, dd, J = 17.1, 1.7 Hz), 5.94 (1H, dd, J = 10.6, 1.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 137.5, 133.1, 132.6, 130.3, 128.8, 128.7. R_f 0.37 (hexane/Et_2O, 8:2); IR ν_{max} (film) 2967, 2932, 2874, 1768, 1668, 1618, 1449, 1364, 1252, 1215, 1090, 1015, 916, 775, 735 cm^{-1}. HRMS (CI+/ISO) calcd for C_9H_9O $[M + H]^+$: 133.0653, found 133.0650.

(4*R*,5*R*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4,6-dimethyl-1-phenylhept-2-en-1-one, 13. A 0.5 − 2 mL microwave vial, fitted with a magnetic follower, was charged with Zhan 1B catalyst (15 mg, 5 mol %). The vial was sealed with a rubber septum and purged with argon. A solution of alcohol **10** (145 mg, 0.38 mmol) and 1-phenylprop-2-en-1-one **12** (250 mg, 1.89 mmol) in freeze−thaw degassed CH_2Cl_2 (1.5 mL) was added, and the resulting green solution was heated at 40 °C for 12 h. After this period, a further portion of Zhan 1B catalyst (15 mg, 5 mol %) in 1.5 mL of freeze−thaw degassed CH_2Cl_2 was added, and the resulting brown solution was subjected to an additional heating cycle at 40 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and concentrated under vacuum to afford a dark brown crude oil. Purification of the crude residue by flash column chromatography (silica gel, 80:20 hexane/EtOAc) afforded 120 mg (65%) of enone **13** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95−7.91 (2H, m), 7.69−7.65 (4H, m), 7.49−7.36 (9H, m), 7.20 (1H, dd, J = 15.8, 8.6 Hz), 6.86 (1H, d, J = 15.7 Hz), 3.96 (1H, d, J = 2.7 Hz), 3.74 (1H, dd, J = 10.4. 4.0 Hz), 3.68−3.64 (1H, m), 3.61−3.58 (1H, m), 2.69−2.61 (1H, m), 1.88−1.80 (1H, m), 1.23 (3H, d, J = 6.9 Hz), 1.05 (9H, s), 0.80 (3H, d, J = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.5, 151.2, 138.2, 135.8, 135.7, 132.7, 130.1, 130.0, 128.8, 128.6, 128.0, 127.9, 126.9, 80.2, 69.6, 40.7, 38.0, 26.9, 19.2, 17.4, 13.6. R_f 0.29 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ +188.6 (c 0.1, $CHCl_3$); IR ν_{max} (film) 3450, 2974, 2931, 2857, 1670, 1618, 1473, 1428, 1112, 998, 823, 741, 700 cm^{-1}. HRMS (EI+) calcd for $C_{31}H_{37}O_2Si$ $[M - OH]^+$: 469.2563, found 469.2557.

(1*R*,4*R*,5*R*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diol, 14. A room temperature solution of (*S*)-CBS (348 mg, 1.25 mmol) dry THF (15 mL) was treated with the dropwise addition of BH_3·THF (1 M solution in THF, 1.25 mL, 1.25 mmol). The resulting mixture was stirred vigorously at room temperature for 30 min and then cooled to −40 °C before being treated dropwise with a solution of (4*R*,5*R*,6*S*,*E*)-7-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-4,6-dimethyl-1-phenylhept-2-en-1-one **13** (500 mg, 1.03 mmol) in dry THF (15 mL). The reaction mixture was stirred at −40 °C until complete disappearance of the starting material by TLC (5 h). The reaction was quenched with MeOH (10 mL) and concentrated under vacuum to afford a yellow crude oil. Purification of the crude residue by flash column chromatography (silica gel, 60:40 hexane/EtOAc) yielded 467 mg (93%) of diol **14** as clear yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69−7.65 (4H, m), 7.46−7.43 (2H, m), 7.42−7.37 (6H, m), 7.36−7.32 (2H, m), 7.29−7.25 (1H, m), 5.93 (1H, ddd, J = 15.6, 8.5, 0.9 Hz), 5.69 (1H, ddd, J = 15.6, 7.1, 0.7 Hz), 5.22 (1H, dd, J = 6.9, 3.4 Hz), 3.72−3.64 (3H, m), 3.46−3.43 (1H, m), 2.40−2.36 (1H, m), 2.03 (1H, d, J = 3.6 Hz), 1.81−1.75 (1H, m), 1.13 (3H, d, J = 7.0 Hz), 1.06 (9H, s), 0.74 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 135.7, 133.6, 133.3, 132.9, 130.1, 130.0, 128.6, 128.0, 127.9, 127.6, 126.2, 80.2, 75.3, 69.2, 39.8, 37.9,

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26.9, 19.2, 18.1, 13.6. R_f 0.19 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ −4.8 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 2974, 2931, 2859, 1473, 1428, 1383, 1112, 986, 823, 741, 699 cm^{-1}. HRMS (ESI+) calcd for $C_{31}H_{41}O_2Si$ $[M - OH]^+$: 473.2870, found 473.2868.

(1*R*,4*R*,5*R*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-2-ene-1,5-diyl diacetate, 15. A solution of diol **14** (500 mg, 0.87 mmol) in dry CH_2Cl_2 (50 mL) was treated with acetic anhydride (1.0 mL, 10.47 mmol) followed by DMAP (11 mg, 0.09 mmol), and the resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 h). The solvent was then removed under vacuum to afford a yellow-brown crude product. Purification of the crude residue by flash column chromatography (silica gel, 80:20 hexane/EtOAc) yielded 495 mg (99%) of diacetate **15** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66−7.61 (4H, m), 7.45−7.27 (11H, m), 6.18 (1H, bd, *J* = 4.6 Hz), 5.59 (2H, bd, *J* = 6.8 Hz), 4.76 (1H, t, *J* = 6.2 Hz), 3.61 (1H, dd, *J* = 10.0, 4.5 Hz), 3.46−3.39 (1H, m), 2.59−2.46 (1H, m), 2.08 (3H, s), 1.99−1.89 (1H, m), 1.73 (3H, s), 1.04 (9H, s), 0.95 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 139.8, 135.8, 135.4, 133.8, 133.7, 129.7, 129.4, 128.7, 128.1, 127.8, 127.7, 127.6, 126.9, 77.9, 76.2, 64.9, 39.0, 37.2, 26.9, 21.5, 20.7, 19.3, 17.5, 14.5. R_f 0.46 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ −8.4 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 2974, 2963, 2928, 2857, 2360, 2343, 1739, 1472, 1428, 1370, 1233, 1112, 10018, 964, 824, 756, 699 cm^{-1}. HRMS (ESI+) calcd for $C_{31}H_{37}OSi$ $[M - 2OAc]^+$: 453.2608, found 453.2606.

(3*S*,4*R*,5*S*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diyl diacetate, 16. A solution of diacetate **15** (420 mg, 0.73 mmol) in anhydrous THF (30 mL) was treated with $PdCl_2(CH_3CN)_2$ (10 mg, 0.03 mmol, 5 mol %), and the resulting mixture was allowed to stir at room temperature until reaction completion as indicated by TLC analysis (12 h). The solution was filtered through Celite, and the Celite was washed using EtOAc (50 mL) as the eluent. The EtOAc washings were then concentrated under vacuum to afford a yellow-brown crude oil, which upon purification by flash column chromatography (silica gel, 80:20 hexane/EtOAc) afforded 399 mg (95%) of the desired 1,3-diacetate **16** a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70−7.65 (4H, m), 7.42−7.37 (6H, m), 7.35−7.21 (5H, m), 6.46 (1H, dd, *J* = 16.1, 1.0 Hz), 6.06 (1H, dd, *J* = 15.9, 5.8 Hz), 5.53−5.49 (1H, m), 4.94 (1H, dd, *J* = 9.7, 3.2 Hz), 3.76 (1H, dd, *J* = 10.2, 6.1 Hz), 3.47 (1H, dd, *J* = 10.3, 6.8 Hz), 2.32−2.25 (1H, m), 2.21−2.13 (1H, m), 2.08 (3H, s), 1.99 (3H, s), 1.04 (9H, s), 0.96 (3H, d, *J* = 6.9 Hz), 0.94 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.6, 136.6, 135.6, 133.8, 133.7, 131.8, 129.8, 129.7, 128.7, 127.9, 127.8, 126.9, 126.6, 76.3, 73.0, 64.7, 38.9, 36.8, 26.9, 21.3, 20.9, 19.3, 15.3, 11.1. R_f 0.54 (hexane/EtOAc, 8:2); $[\alpha]^{25}_D$ −7.6 (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3071, 2961, 2932, 2857, 1739, 1237, 1112 cm^{-1}. HRMS (ESI+) calcd for $C_{35}H_{44}O_5NaSi$ $[M + Na]^+$: 595.2850, found 595.2852.

(3*S*,4*R*,5*S*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diol, 17 and (2*S*,3*S*,4*R*,5*S*,*E*)-2,4-Dimethyl-7-phenylhept-6-ene-1,3,5-triol, 18. A solution of diacetate **16** (195 mg, 0.34 mmol) in MeOH (10 mL) was treated dropwise with a 1.0 M K_2CO_3 solution in H_2O (1.7 mL), and the resulting mixture was allowed to stir at room temperature until completion of reaction as indicated by TLC analysis (12 h). The reaction was quenched with satd aq NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford crude pale yellow oil. The crude product was purified by flash column chromatography (silica gel, elution gradient 80:20 hexane/EtOAc, then 60/40 hexane/EtOAc) to yield 33 mg (20%) of the desired diol **17** as a colorless oil as well as 51 mg of the known triol **18** as a pale yellow oil.

Triol **18** (51 mg, 0.21 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and treated with imidazole (18 mg, 0.27 mmol), and the resulting mixture was cooled to −5 °C. A solution of TBDPSCl (62 mg, 0.23 mmol) in dry CH_2Cl_2 (1 mL) was then added dropwise to the reaction mixture, and the resulting solution was allowed to stir at −5 °C until complete disappearance of the starting material by TLC analysis (30 min). The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and concentrated under vacuum to afford 100 mg (60%) of the desired silyl ether **17** as colorless oil. The total yield for the silyl ether over the two steps was 133 mg (80%).

(3*S*,4*R*,5*S*,6*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyl-1-phenylhept-1-ene-3,5-diol, 17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.67 (4H, m), 7.49−7.40 (8H, m), 7.34−7.19 (3H, m), 6.66 (1H, dd, *J* = 15.9, 1.2 Hz), 6.26 (1H, dd, *J* = 15.9, 5.4 Hz), 4.78 (1H, d, *J* = 2.8 Hz), 4.73−4.68 (1H, m), 4.28 (1H, d, *J* = 2.8 Hz), 3.87 (1H, dd, *J* = 10.3, 3.7 Hz), 3.75−3.70 (1H, m), 3.67 (1H, dd, *J* = 10.3, 7.6 Hz), 2.14−2.04 (1H, m), 1.99−1.89 (1H, m), 1.07 (9H, s), 1.04 (3H, d, *J* = 7.2 Hz), 0.86 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 135.8, 135.7, 132.6, 132.5, 131.2, 130.2, 130.1, 129.9, 128.6, 128.1, 128.0, 127.4, 126.6, 82.2, 73.0, 69.5, 39.9, 36.9, 26.9, 19.2, 13.9, 11.9. R_f 0.60 (hexane/EtOAc, 7:3); $[\alpha]^{27}_D$ +3.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3418, 3072, 2963, 2932, 2855, 1427, 1111 cm^{-1}. HRMS (ESI+) calcd for $C_{31}H_{37}OSi$ $[M - 2OH]^+$: 453.2608, found 453.2609. Triol **18** matched the literature data: *Org. Lett.* **2001**, *3*, 395−3954.

***tert*-Butyl((2*S*,3*S*,4*R*,5*S*,*E*)-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enyloxy)diphenylsilane.** A suspension of NaH (85 mg, 2.13 mmol) in dry THF (2 mL) was treated with a solution of diol **17** (130 mg, 266 μmol) in dry THF (2 mL), and the resulting mixture was stirred at room temperature for 10 min. The solution was then treated sequentially with MeI (0.3 mL, 4.26 mmol) and TBAI (8 mg, 21.3 μmol), and the resulting reaction mixture was stirred at 60 °C until TLC analysis indicated reaction completion (12 h). The reaction was quenched with satd aq solution of NH_4Cl (5 mL), and the layers were separated. The organic layer was washed with brine (5 mL), and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the fully protected triol as pale yellow oil, which could be used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.66 (4H, m), 7.45−7.23 (11H, m), 6.54 (1H, d, *J* = 16.0 Hz), 6.14 (1H, dd, *J* = 16.0, 7.2 Hz), 4.03 (1H, dd, *J* = 7.2, 2.0 Hz), 3.77 (1H, dd, *J* = 10.0, 5.3 Hz), 3.58 (1H, dd, *J* = 9.9, 7.9 Hz), 3.47 (3H, s), 3.33 (3H, s), 3.23−3.19 (1H, m), 2.09−1.99 (1H, m), 1.81−1.71 (1H, m), 1.15 (3H, d, *J* = 7.0 Hz), 1.05 (9H, s), 0.83 (3H, d, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1, 135.8, 135.7, 134.2, 134.1, 131.9, 131.8, 129.8, 129.7, 129.6, 128.7, 127.7, 127.6, 126.5, 85.6, 81.5, 64.9, 61.5, 56.6, 41.8, 38.1, 27.0, 19.4, 16.0, 10.5.

(2*S*,3*S*,4*R*,5*S*,*E*)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol, 19. A 0 °C solution of *tert*-butyl((2*S*,3*S*,4*R*,5*S*,*E*)-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-enyloxy)diphenylsilane (138 mg, 0.266 mmol) in THF (5 mL) was treated with TBAF (1 M in THF, 0.8 mL, 0.798 mmol), and the resulting reaction mixture was allowed to warm and stir at room temperature until completion as indicated by TLC analysis (12 h). The reaction was quenched with distilled water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a crude pale yellow oil. The crude product was purified by flash column chromatography (silica gel, 60:40 hexane/EtOAc) to afford 73 mg of alcohol **19** (99%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43−7.39 (2H, m), 7.36−7.31 (2H, m), 7.27−7.23 (1H, m), 6.58 (1H, d, *J* = 16.3 Hz), 6.19 (1H, dd, *J* = 15.8, 7.1 Hz), 4.08−4.05 (1H, m), 3.89−3.82 (1H, m), 3.57−3.51 (1H, m), 3.53 (3H, s), 3.32 (3H, s), 3.29 (1H, dd, *J* = 9.4, 2.7 Hz), 2.92−2.87 (1H, m), 1.92−1.82 (2H, m), 1.21 (3H, d, *J* = 7.2 Hz), 0.91 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.9, 132.3, 129.5, 128.8, 127.8, 126.6, 88.6, 81.3, 64.7, 61.8, 56.5, 42.5, 35.9, 16.4, 10.5. R_f 0.14 (hexane/EtOAc, 8:2); $[\alpha]^{22}_D$ −5.2 (*c* 1.0, $CHCl_3$); IR ν_{max} (film) 3440, 2972, 2935, 2831, 1497, 1449, 1100 cm^{-1}. HRMS (ESI+) calcd for $C_{17}H_{26}O_3Na$ $[M + Na]^+$: 301.1774, found 301.1772.

(2*R*,3*R*,4*R*,5*S*,*E*)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-enal, 20. A solution of (2*S*,3*S*,4*R*,5*S*,*E*)-3,5-dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-ol **19** (30 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) was treated with Dess−Martin periodinane (92 mg, 0.22 mmol), and the resulting mixture was stirred at room temperature until completion as indicated by TLC analysis (40 min). The reaction was

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quenched by the sequential addition of satd aq $Na_2S_2O_3$ (2 mL) and satd aq $NaHCO_3$ (2 mL) and diluted with diethyl ether (5 mL). The resulting mixture was stirred for 20 min at room temperature, and the layers were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford 29.8 mg (quant.) of the desired aldehyde **20** as pale yellow oil, which was taken straight onto the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1H, d, J = 1.8 Hz), 7.43−7.23 (5H, m), 6.57 (1H, d, J = 16.0 Hz), 6.15 (1H, dd, J = 16.0, 7.3 Hz), 4.11−4.06 (1H, m), 3.55 (1H, dd, J = 9.3, 2.6 Hz), 3.49 (3H, s), 3.33 (3H, s), 2.73−2.65 (1H, m), 1.93−1.82 (1H, m), 1.20 (3H, d, J = 7.1 Hz), 0.87 (3H, d, J = 7.1 Hz). R_f 0.37 (hexane/EtOAc, 8:2).

((1*E*,3*S*,4*R*,5*S*,6*S*,7*E*)-8-Iodo-3,5-dimethoxy-4,6-dimethylocta-1,7-dienyl)benzene, 23. A stirred suspension of anhydrous $CrCl_2$ (226 mg, 1.84 mmol, previously gently flame-dried under vacuum) in dry THF (2 mL) at room temperature was treated carefully with a solution of aldehyde **20** (29.8 mg, 0.11 mmol) and iodoform (255 mg, 0.65 mmol) in dry THF (1 mL) transferred via cannula. The resulting brown mixture was stirred in the dark at room temperature until completion as indicated by TLC analysis (30 min). The reaction mixture was quenched by addition of H_2O (5 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum to afford a crude yellow solid. Purification of the crude residue by flash column chromatography (silica gel, 95:5 hexane/EtOAc) yielded 43 mg (99%) of iodoolefin **23** as a white solid. ^{1}H NMR (500 MHz, C_6D_6): δ 7.24−7.04 (5H, m), 6.77 (1H, dd, J = 14.5, 9.2 Hz), 6.44 (1H, d, J = 16.0 Hz), 6.04 (1H, dd, J = 16.0, 7.0 Hz), 5.74 (1H, d, J = 14.6 Hz), 4.10−4.07 (1H, m), 3.31 (3H, s), 3.16 (3H, s), 3.02 (1H, dd, J = 9.9, 2.1 Hz), 2.23−2.12 (1H, m), 1.71−1.60 (1H, m), 0.94 (3H, d, J = 7.0 Hz), 0.83 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 147.9, 137.2, 132.1, 129.5, 128.6, 128.4, 128.2, 126.7, 85.9, 80.9, 75.1, 61.1, 55.9, 43.5, 42.7, 18.2, 9.8. R_f 0.64 (hexane/EtOAc, 7.5:2.5); $[\alpha]^{24}_D$ +1.84 (c 1.0, $CHCl_3$); IR ν_{max} (film) 2963, 2924, 2361, 2334, 1728, 1651, 1585, 1597, 1497, 1451, 1335, 1188, 1088, 972, 748, 694 cm^{-1}.

(*E*)-Ethyl 3-(tributylstannyl)but-2-enoate. A 0 °C solution of diisopropylamine (0.3 mL, 1.87 mmol) in dry THF (1 mL) was treated dropwise with *n*-BuLi (1.6 M in hexanes, 1.2 mL, 1.87 mmol), and the resulting mixture was allowed to stir for 10 min. The solution was then treated with tributyltin hydride (0.5 mL, 1.78 mmol), and the reaction was cooled at −50 °C. At this point, the mixture was added to a suspension of CuBr·Me_2S (368 mg, 1.78 mmol) in anhydrous THF (2 mL) at −50 °C, and the newly formed suspension was stirred at −50 °C for 30 min. The solution was then cooled to −95 °C and treated with a precooled solution of ethyl-2-butynoate (100 mg, 0.89 mmol) and dry MeOH (0.01 mL, 1.52 mmol) in anhydrous THF (3 mL). Once the addition was complete, the resulting mixture was stirred for 30 min at −95 °C, followed by warming up to −78 °C, where the reaction was stirred for an additional 2 h. The reaction was quenched with 5% aq NH_4OH (5 mL), and the phases were separated. The aqueous phase was then extracted with Et_2O (3 × 5 mL), and the combined organic layers dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a crude yellow oil. Purification of the crude product by flash column chromatography (silica gel, hexanes) gave 343 mg (96%) of (*E*)-ethyl 3-(tributylstannyl)but-2-enoate as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (1H, q, J = 1.8 Hz), 4.16 (2H, q, J = 7.1 Hz), 2.39 (3H, d, J = 1.9 Hz), 1.54−1.45 (6H, m), 1.34−1.27 (9H, m), 0.97−0.93 (6H, m), 0.91−0.87 (9H, t, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.6, 128.2, 59.7, 29.1, 27.5, 22.5, 14.5, 13.8, 9.5. R_f 0.08 (hexane); IR ν_{max} (film) 2957, 2925, 2852, 1714, 1599, 1464, 1377, 1366, 1338, 1258, 1164, 1099, 1039, 960, 862, 689, 664 cm^{-1}. HRMS (ESI+) calcd for $C_{18}H_{37}O_2Sn$ $[M + H]^+$: 405.1810, found 405.1813.

(*E*)-3-(Tributylstannyl)but-2-enamide, 24. A 0 °C suspension of NH_4Cl (170 mg, 3.18 mmol) in dry toluene (10 mL) was treated dropwise with a solution of $AlMe_3$ (2 M in toluene, 1.6 mL, 3.18 mmol), and the resulting mixture was allowed to warm to room temperature, before being cooled back down to 0 °C. A solution of (*E*)-ethyl 3-(tributylstannyl)but-2-enoate (343 mg, 0.86 mmol) in dry toluene (5 mL) was then added, and the resulting reaction mixture was warmed and heated at 50 °C for 16 h. The reaction was then allowed to cool and was then diluted with EtOAc (10 mL) and quenched at 0 °C by addition of 10% HCl in a saturated NaCl aqueous solution (20 mL total volume). The organic phase was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a thick pale yellow oil. Purification of the crude product by flash column chromatography (silica gel, hexane/EtOAc, 20/80) gave 124 mg (78%) of amide **24** as a pure white solid. Mp: 33 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (1H, q, J = 1.7 Hz), 5.64 (1H, bs), 5.39 (1H, bs), 2.35 (3H, d, J = 1.8 Hz), 1.54−1.44 (6H, m), 1.35−1.27 (6H, m), 0.96−0.92 (6H, m), 0.88 (9H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 162.9, 130.5, 29.1, 27.5, 22.2, 13.8, 9.5. R_f 0.62 (EtOAc); IR ν_{max} (film) 3402, 3202, 2955, 2924, 2847, 2361, 1659, 1597, 1458, 1397, 1312, 1072, 1312, 1072, 1003, 872, 733, 687 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{34}ONSn$ $[M + H]^+$: 376.1657, found 376.1651.

Tributyl(diiodomethyl)stannane. A solution of $Bu_3SnCHBr_2$ (300 mg, 0.65 mmol) in anhydrous acetone (4 mL) was treated with NaI (390 mg, 2.60 mmol), and the reaction mixture was stirred at room temperature in te absence of light for 24 h. The reaction mixture was concentrated and then diluted with hexane (10 mL) and the solids filtered off. The resultant solution was concentrated under vacuum in absence of light, diluted with chloroform (10 mL) and the newly precipitated solids were filtered off. The solution was concentrated once again under vacuum in the absence of light to afford 361 mg (quant) of the desired diiodomethylstannane as light yellow oil, which required no further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (1H, s), 1.64−1.58 (6H, m), 1.33 (6H, sext, J = 7.2 Hz), 1.12−1.09 (6H, m), 0.92 (9H, t, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.6, 27.5, 15.7, 13.8, 13.1. R_f 0.50 (PE).

Tributyl((1*E*,3*S*,4*S*,5*R*,6*S*,7*E*)-4,6-dimethoxy-3,5-dimethyl-8-phenylocta-1,7-dienyl)stannane, 27. A 0 °C bright green suspension of anhydrous $CrCl_2$ (135 mg, 1.1 mmol, previously gently flame-dried under vacuum) in freeze−thaw degassed DMF (1 mL) in the absence of light was treated via cannula with a solution of aldehyde **20** (21.8 mg, 0.08 mmol) and freshly prepared diiodomethyltributyltin (120 mg, 0.22 mmol) in freeze−thaw degassed DMF (1 mL). The resulting reaction mixture was allowed to warm to room temperature in the dark until completion as indicated by TLC analysis (10 h). The reaction mixture was quenched by addition of H_2O (5 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum to afford the crude product as yellow oil. The crude product was purified by fast vacuum filtration on silica gel (90:10 hexane/EtOAc + 1% Et_3N) to afford 22.3 mg (50%) of stannane **27** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.20 (5H, m), 6.57 (1H, d, J = 16.2 Hz), 6.17 (1H, dd, J = 16.2, 6.9 Hz), 5.96 (1H, dd, J = 19.2, 7.2 Hz), 5.86 (1H, d, J = 19.2 Hz), 4.11 (1H, dd, J = 7.2, 1.1 Hz), 3.53 (3H, s), 3.34 (3H, s), 3.14 (1H, dd, J = 10,2, 2.4 Hz), 2.46 (1H, m), 1.63 (1H, m), 1.51−1.41 (6H, m), 1.33−1.21 (12H, m), 1.15 (3H, d, J = 7.0 Hz), 0.85 (3H, d, J = 7.2 Hz), 0.84 (12H, t, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 137.1, 131.8, 129.7, 128.7, 127.5, 127.2, 126.5, 86.4, 81.4, 61.3, 56.7, 44.9, 42.7, 29.3, 27.4, 18.5, 13.8, 9.6, 9.5. R_f 0.47 (PE/EtOAc, 40:1, 1% Et_3N).

(*E*)-Methyl 3-iodobut-2-enoate. A mixture of (*E*)-3-iodobut-2-enoic acid and (*Z*)-3-iodobut-2-enoic acid[4a] (*E*/*Z* ratio 1.7/1.0) (984 mg, 4.64 mmol) in anhydrous THF (50 mL) was treated with Cs_2CO_3 (1.51 g, 4.64 mmol), and the resulting mixture was stirred at room temperature for 5 min. Iodomethane (0.6 mL, 9.28 mmol) was then added, and the resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 h). The reaction was quenched with satd aq NH_4Cl (30 mL), and the resulting layers were separated. The aqueous phase was extracted with diethyl ether (2 × 30 mL), and the combined organic layers were washed with brine (30 mL) and concentrated under vacuum to afford thick brown-yellow oil as crude product. Interestingly, ^{1}H NMR

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analysis of the crude mixture indicated that the product was a mixture of (*E*)-methyl 3-iodobut-2-enoate and (*Z*)-methyl 3-iodobut-2-enoate in a 15:1 *E*/*Z* ratio in favor of the desired *E*-isomer. Purification of the crude product by flash column chromatography (silica gel, 95:5 PE/EtOAc) yielded 210 mg (32%) of the *E*-iodo-butenoate as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (1H, q, J = 1.5 Hz), 3.70 (3H, s), 2.98 (3H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 131.0, 120.7, 51.4, 31.0. R_f 0.6 (PE:EtOAc, 9.5:0.5); IR ν_{max} (film) 2954, 2922, 2853, 1718, 1617, 1456, 1444, 1331, 1263, 1176, 1073, 907 cm^{-1}. HRMS (CI+/ISO) calcd for $C_5H_8O_2I$ $[M + H]^+$: 226.9569, found 226.9566.

(*E*)-3-Iodobut-2-enamide, 28. A 0 °C suspension of NH_4Cl (488 mg, 9.1 mmol) in dry toluene (8.5 mL) was treated by the dropwise addition of $AlMe_3$ (2.0 M solution in toluene, 4.55 mL, 9.1 mmol), and the resulting solution was allowed to warm to room temperature. The reaction was cooled back down to 0 °C, and (*E*)-methyl 3-iodobut-2-enoate (206 mg, 0.91 mmol) was added. The resulting mixture was stirred at 50 °C until completion as indicated by TLC analysis (16 h). The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The solution was then cooled to 0 °C and quenched by addition of 10% HCl in brine (10 mL total volume). The phases were separated, and the organic layer was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum to afford a crude pale yellow oil. The crude product was purified by flash column chromatography (silica gel, 1:1 PE/EtOAc) to afford 97 mg (50%) of iodo-amide **28** as a white solid. Mp: 105−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (1H, q, J = 1.5 Hz), 5.31 (2H, bs), 2.99 (3H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 132.5, 117.6, 30.7. R_f 0.27 (PE:EtOAc, 1:1); IR ν_{max} (film) 3354, 3181, 2359, 2330, 1651, 1597, 1397, 1364, 1302, 1067 cm^{-1}. HRMS (CI+/ISO) calcd for C_4H_7NOI $[M + H]^+$: 211.9572, found 211.9574.

((3*S*,4*R*,5*S*,6*S*,*E*)-3,5-dimethoxy-4,6-dimethyloct-1-ene-7-ynyl)benzene, 30. A −78 °C solution of Ohira−Bestmann's reagent (138 mg, 0.72 mmol) in dry THF (2.5 mL) was treated dropwise with NaOMe (25% solution in MeOH 0.17 mL, 0.72 mmol). After 20 min of stirring, a solution of aldehyde **20** (50 mg, 0.18 mmol) in dry THF (2.5 mL) was incorporated dropwise. The reaction mixture was allowed to slowly warm to room temperature over 30 min and was then quenched with satd aq NH_4Cl (5 mL). The mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum to afford the crude product as yellow oil. Initial purification by flash column chromatography (silica gel, elution gradient 100% hexanes to 9:1 hexane/EtOAc) followed by a second flash column purification (silica gel, 1:1 PE/dichloromethane) afforded 49 mg (99%) of alkyne **30** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42−7.40 (2H, m), 7.34−7.31 (2H, m), 7.26−7.23 (1H, m), 6.59 (1H, d, J = 16.0 Hz), 6.20 (1H, dd, J = 16.0, 7.2 Hz), 4.15 (1H, ddd, J = 7.2, 2.2, 1.1 Hz), 3.57 (3H, s), 3.33 (3H, s), 3.15 (1H, dd, J = 9.9, 2.5 Hz), 2.77 (1H, qt, J = 7.0, 2.5 Hz), 2.06 (1H, d, J = 2.5 Hz), 1.99−1.93 (1H, m), 1.35 (3H, d, J = 7.1 Hz), 0.93 (3H, d, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 136.9, 132.2, 129.4, 128.7, 127.7, 126.5, 85.1, 84.9, 81.1, 70.1, 61.5, 56.6, 42.9, 29.6, 18.4, 10.1. $[\alpha]^{27}_D$ +24.4 (*c* 1.0, $CHCl_3$).

(+)-Crocacin C, 3; (2*Z*,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, 25, and (2*Z*,4*Z*,6*S*,7*S*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide, 26. *Method A.* A room temperature solution of iodoolefin **23** (43 mg, 0.11 mmol) and (*E*)-3-(tributylstannyl)but-2-enamide **24** (45 mg, 0.12 mmol) in anhydrous THF (7 mL) was treated with CuI (3.4 mg, 0.65 mmol), $AsPh_3$ (4.5 mg, 15 μmol), and $Pd_2(dba)_3$ (6 mg, 6 μmol), and the resulting reaction mixture was stirred at 60 °C until completion as indicated by TLC analysis (6 h). The reaction was quenched with H_2O (5 mL), and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a crude yellow residue. The sample was purified on a Varian HPLC from Agilent Technologies (Santa Clara, CA, USA) equipped with SD-1 pumps, a model 325 UV−vis detector, a model 410 autosampler, and a model 701 fraction collector. Mobile phase A was water with 0.1% ammonium hydroxide and mobile phase B was acetonitrile. The flow rate was 60 mL/min. The method started at 40% B for 1 min, then raised to 80% B over the next 9 min, was held at 80% B for another minute, then raised to 95% B in 0.2 min, held at 95% for 1.5 min, then lowered back to 40% B in 0.2 min, and held at 40% B for an additional 1.5 min. The column was a 30 mm × 100 mm, 10 μm Gemini-NX from Phenomenex (Torrance, CA, USA). The UV collection was done using a wavelength of 254 nm. (+)-Crocacin C **3** eluted at 6.2 min. (+)-Crocacin C and the two isomeric (*Z*) analogues **25** and **26** were isolated in a 1.54/1.00/1.27 ratio, in a total yield of 11% (4.2 mg total weight).

Method B. In a flame-dried 2−5 mL MW vial, stannane **27** (22.3 mg, 39.6 μmol) and the vinyl iodide (13 mg, 43.6 μmol) were dissolved in freeze−thaw degassed THF (2 mL), and the resulting homogeneous solution was treated with $PdCl_2(PPh_3)_2$ (1.4 mg, 2 μmol, 5 mol %). The vial was submitted to MW irradiation (15 min, 100 °C), and then the reaction was filtered and concentrated under vacuum to afford a crude brown oily residue. The crude product was purified by flash column chromatography (silica gel 1:1 PE/EtOAc) to afford 7 mg (50%) of (+)-crocacin C **3** as a white solid.

Method C. In a flame-dried 5 mL microwave vial under an inert atmosphere, a solution of alkyne **30** (50 mg, 183.5 μmol) in anhydrous THF (2.5 mL) was degassed by three freeze−pump−thaw cycles. $PdCl_2(Ph_3P)_2$ (7.0 mg, 10.3 μmol) was then incorporated, and the solution was cooled to 0 °C before Bu_3SnH (56 μL, 203 μmol) was added dropwise. The resultant brown solution was stirred at 0 °C until the starting material was consumed as indicated by TLC (25 min). Vinyl iodide **28** (42 mg, 197 μmol) was added, and the solution was heated to 100 °C in a microwave reactor for 15 min. The reaction mixture was filtered through a small pad of silica using EtOAc as the eluent, and the filtrate was concentrated *in vacuo* to give crude yellow oil. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 1:1 PE/EtOAc to 2:3 PE/EtOAc) afforded 46 mg (70%) of (+)-crocacin C **3** as a white solid.

(+)-Crocacin C, 3. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.48−7.47 (2H, m), 7.34−7.31 (2H, m), 7.25−7.22 (1H, m), 6.70 (1H, bs), 6.59 (1H, d, J = 16.0 Hz), 6.26 (1H, dd, J = 16.1, 7.3 Hz), 6.13 (1H, bs), 6.12−6.04 (2H, m), 5.80 (1H, s), 4.09−4.07 (1H, m), 3.52 (3H, s), 3.29 (3H, s), 3.16 (1H, dd, J = 9.6, 2.0 Hz), 2.61−2.56 (1H, m), 2.22 (3H, d, J = 1.1 Hz), 1.58−1.52 (1H, m), 1.17 (3H, d, J = 6.9 Hz), 0.85 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, acetone-d_6): δ 169.0, 148.1, 137.9, 137.0, 135.1, 132.6, 130.5, 129.4, 128.3, 127.3, 122.1, 87.1, 81.8, 61.5, 56.5, 43.5, 40.8, 19.3, 13.5, 10.1. R_f 0.25 (PE:EtOAc, 1:1); $[\alpha]^{26}_D$ +54.0 (*c* 0.1, MeOH); IR ν_{max} (film) 3479, 3395, 3343, 3184, 2963, 2926, 1655, 1601, 1449, 1368, 1261, 1088, 972 cm^{-1}. HRMS (FAB+) calcd for $C_{22}H_{31}O_3NNa$ $[M + Na]^+$: 380.2202, found 380.2207. Mp: 95−100 °C.

(2*Z*,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, 25. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.82 (1H, d, J = 16.3 Hz), 7.51−7.47 (2H, m), 7.38−7.29 (2H, m), 7.25−7.21 (1H, m), 6.71 (1H, bs), 6.59 (1H, d, J = 16.0 Hz), 6.26 (1H, dd, J = 15.9, 7.1 Hz), 6.07 (1H, bs), 6.05 (1H, dd, J = 16.2, 9.0 Hz), 5.69 (1H, bs), 4.09−4.07 (1H, m), 3.54 (3H, s), 3.30 (3H, s), 3.18 (1H, dd, J = 9.6, 2.1 Hz), 2.65−2.55 (1H, m), 1.90 (3H, d, J = 1.0 Hz), 1.58−1.52 (1H, m), 1.18 (3H, d, J = 7.2 Hz), 0.86 (3H, d, J = 7.2 Hz). ^{13}C NMR (125 MHz, acetone-d_6): δ 169.0, 146.9, 137.9, 137.8, 132.7, 130.5, 129.4, 129.3, 128.3, 127.3, 120.1, 87.2, 81.9, 61.5, 56.5, 43.5, 41.2, 21.0, 19.3, 10.1. $[\alpha]^{26}_D$ +32.0 (*c* 0.1, MeOH); IR ν_{max} (film) 3460, 3391, 3339, 3086, 2972, 2928, 1659, 1595, 1456, 1321, 1261, 1085, 1024, 750, 694, 677 cm^{-1}.

(2*Z*,4*Z*,6*S*,7*S*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienamide, 26. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.50−7.47 (2H, m), 7.35−7.31 (2H, m), 7.26−7.23 (1H, m), 6.83 (1H, bs), 6.60 (1H, d, J = 16.0 Hz), 6.26 (1H, dd, J = 16.1, 7.4 Hz), 6.14 (1H, bs), 5.89 (1H, d, J = 12.1 Hz), 5.84 (1H, s), 5.60 (1H, t, J = 11.3 Hz), 4.05−4.02 (1H, m), 3.52 (3H, s), 3.29 (3H, s), 3.10 (1H, dd, J = 9.6, 2.2 Hz), 3.07−2.98 (1H, m), 2.20 (3H, d, J = 1.1 Hz), 1.58−1.50 (1H, m), 1.18 (3H, d, J = 7.3 Hz), 0.79 (3H, d, J = 7.3 Hz). ^{13}C NMR (125 MHz, acetone-d_6): δ 168.7, 148.9, 137.8,

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134.9, 133.0, 132.8, 130.6, 129.4, 128.4, 127.3, 121.3, 86.9, 81.9, 61.6, 56.4, 43.8, 36.0, 19.7, 19.5, 10.0. $[\alpha]^{26}_{D}$ −44.0 (*c* 0.1, MeOH); IR ν_{max} (film) 3460, 3391, 3339, 3086, 2972, 2928, 1659, 1595, 1456, 1368, 1296, 1088, 1017, 747, 669 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data of the described compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†Dedicated to Professor Philip S. Beauchamp.

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