FORMAL TOTAL SYNTHESES OF CROCACIN A–D

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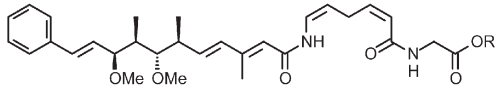
A concise route to the common polyketide fragment **5** of crocacin A–D (**1**–**4**) is presented which has previously been converted into all members of this fungicidal and cytotoxic family of dipeptidic natural products by various means. Our synthesis features a *syn*-selective titanium aldol reaction controlled by a valinol-derived auxiliary, a zinc-mediated, palladium-catalyzed *anti*-selective addition of propargyl mesylate **10** to the chiral aldehyde **9**, as well as a comparison of palladium-catalyzed Stille and Suzuki cross-coupling reactions for the formation of the diene moiety of the target.

Keywords: Aldol reaction; Alkyne; Cross-coupling reactions; Natural product synthesis; Palladium; Polyketides.

Bioassay-guided fractionation of the culture broths of different strains of the myxobacteria *Chondromyces crocatus* and *C. pediculatus* led to the isolation of the structurally rather unusual metabolites crocacin A–D (**1**–**4**) which exhibit promising biological activities (Scheme 1)[1,2]. Most notable is their effective growth inhibition of various fungi and yeasts by interference with the electron flow in complex III of the respiratory chain[2]. Crocacin D (**4**) turned out to be the most active compound in this regard, whereas crocacin C (**3**) devoid of the enamide moiety is virtually inactive. This *in vitro* ranking was confirmed by *in vivo* foliar spray assays against several plant pathogens. As a result, compound **4** constitutes a validated lead in the search for novel agricultural fungicides as evident from the considerable interest shown by industrial laboratories[3,4]. Moreover, the crocacins exhibit significant cytotoxicity, with crocacin D again being significantly more potent than its congeners (**4** > **1** >> **2** >> **3**)[5].

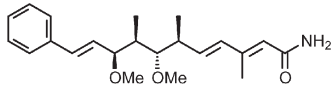
While this structure/activity profile suggests that the conspicuous (*Z*)-enamide present in all crocacins except the inactive **3** is necessary to elicit a biological response, this structural motif poses considerable challenges in preparative terms. In pursuit of previous work in this area[6], we have developed a practical method allowing for the stereoselective forma-

tion of such labile enamides by a Peterson olefination manifold[7]. This highly efficient procedure was successfully applied by Chakraborty et al. to the total syntheses of crocacin A and D [8,9], while other authors pursued different routes for the transformation of **5** (R = H, alkyl) as the common polyketide fragment into the individual members of this interesting family of dipeptidic natural products[10–13]. Outlined below is a concise entry into this key building block **5** which is shorter than the previously published routes. In combination with our Peterson enamide strategy mentioned above or any of the alternative end games reported in the literature, this study represents formal total syntheses of all the crocacins known to date.

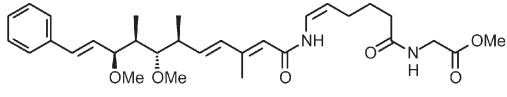


1 *Crocacin A* (R = Me)

2 *Crocacin B* (R = H)



3 *Crocacin C*



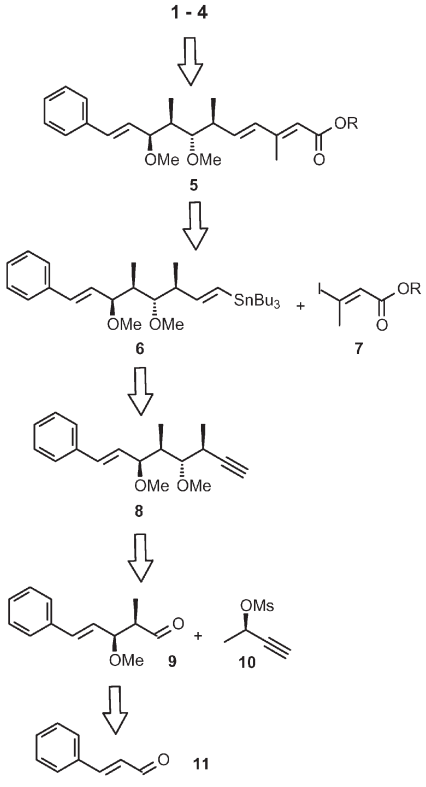
4 *Crocacin D*

SCHEME 1

RESULTS AND DISCUSSION

Since Stille reactions[14] have been extensively used in previous approaches to the crocacins[11,12], we planned to use similar cross-coupling chemistry to install the diene unit of **5** (Scheme 2). To streamline the assembly process, however, it was envisaged to prepare the required stannane **6** from alkyne **8** via palladium-catalyzed hydrostannation[15] rather than by olefination processes as previously described in the literature. The 1,2-*anti* configured centers flanking the alkyne unit in **8** can be installed by addition of an enantiomerically enriched allenylmetal species derived from propargyl mesylate **10** to aldehyde **9**. Pioneered by Marshall et al.[16], such addition reactions can either be performed with the aid of indium iodide[17] or Et_2Zn as promotors and catalytic amounts of Pd(0)[18]. High *anti* selectivity to-

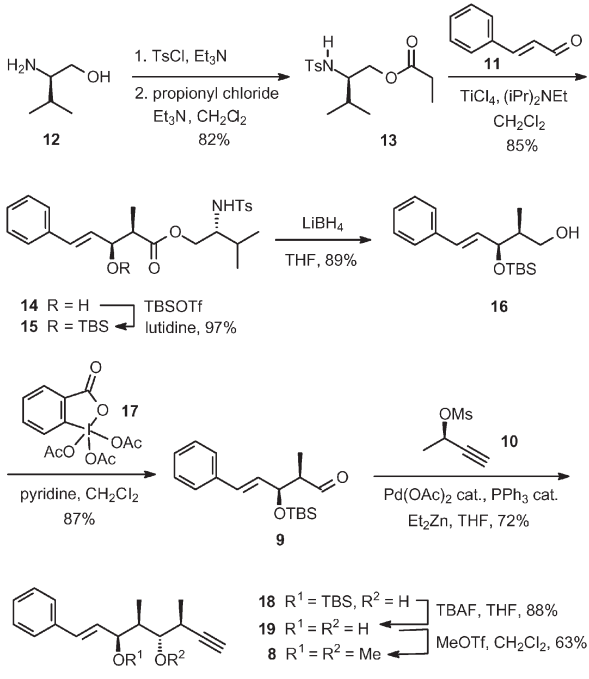
gether with an excellent level of reagent control when applied to chiral aldehydes make this methodology ideally suited in the present context[19]. The precursor aldehyde **9** is readily available by a *syn* selective aldol reaction.



SCHEME 2

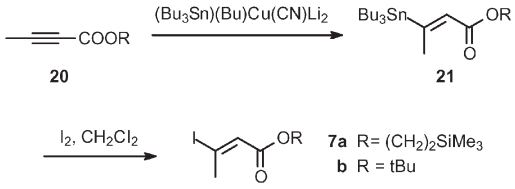
With practicality issues in mind, it was decided to perform this aldol step with ester **13** bearing a valinol-derived auxiliary. Valinol **12** is not only readily available in both enantiomeric forms but is also considerably cheaper than the standard auxiliaries dominating contemporary aldol chemistry. As shown in Scheme 3, the required donor **13** can be conveniently prepared in multigram amounts from **12** in 'one pot' by successive addition of tosyl chloride and propionyl chloride in the presence of excess triethylamine. In accordance with literature precedence[20], addition of the titanium enolate derived from **13** to a cold (–78 °C) solution of cinnamaldehyde pre-complexed with $TiCl_4$ in CH_2Cl_2 furnished the desired *syn* aldol product **14** in 85% isolated yield (d.r. ≈ 10:1, NMR); the reaction could easily be performed on a multigram scale although the yield was

slightly lower (66%, cf. Experimental). Temporary protection of the hydroxyl group in **14** as *tert*-butyldimethylsilyl (TBS) ether followed by reductive cleavage of the auxiliary gave alcohol **16** which was oxidized with Dess–Martin periodinane[21] **17** to provide aldehyde **9**. Slow addition of Et_2Zn to a solution of **9** and the known mesylate[22] **10** in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 at –78 °C followed by warming of the resulting mixture to ambient temperature provided the desired alkyne **18** (d.r. > 12:1) which was immediately deprotected with TBAF in THF. Both hydroxyl groups of the resulting diol **19** were simultaneously O-methylated on exposure to MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine, affording alkyne **8** ready to be processed by hydrometalation/cross-coupling.

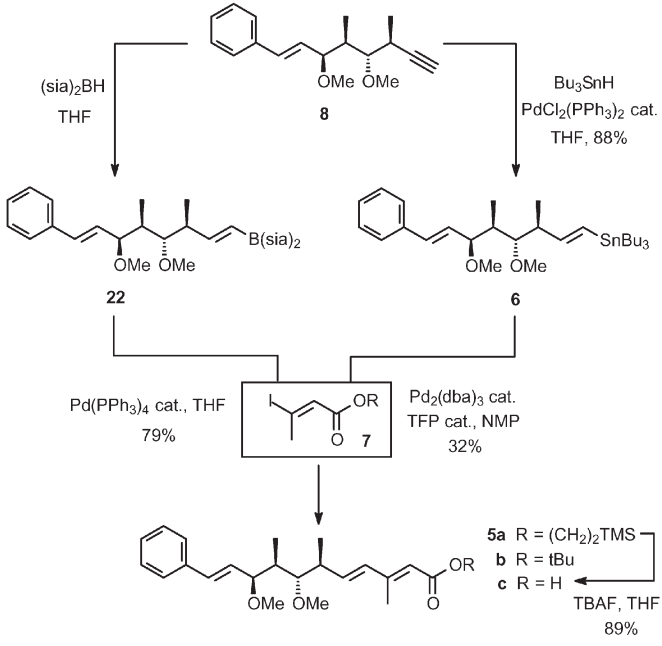


SCHEME 3

Two different iodides **7a**, **7b** were chosen as suitable coupling partners for the formation of the α,β,γ,δ-unsaturated ester in the targeted polyketide fragment **5**. Their synthesis (Scheme 4) is based on the stereoselective addition of stannylcuprate reagents[23] to alkynoate **20** followed by tin–iodide exchange with retention of the stereochemistry at the double bond[24]. A 'higher order' stannylcuprate (derived from Bu_3SnLi, BuLi, CuCN) as well as a 'Gilman-type' stannylcuprate (derived from Bu_3SnLi and $CuBr{\cdot}SMe_2$) performed similarly well[23].



SCHEME 4

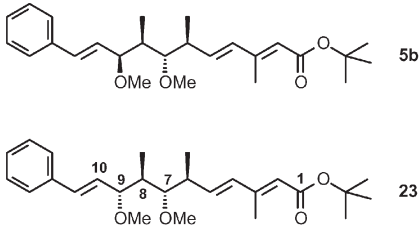


SCHEME 5

With the key components in hand, the crucial cross coupling was attempted to complete the carbon skeleton of compound **5**. Thus, alkyne **8** was hydrostannylated with Bu_3SnH in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ to give the known alkenylstannane[11] **6** in 88% yield (Scheme 5). Although the Stille coupling of this compound with iodides of type **7** has precedence in the literature[11,12], we found this transformation rather capricious and only partly satisfactory. While it proceeds rather slowly when performed with $Pd_2(dba)_3$ as precatalyst and either tris-(2-furyl)phosphine (TFP) or triphenylarsine as ligands at 40 °C in NMP or DMF, serious side reactions come into play when the temperature is raised

to 60 °C. Although occasionally yields of **5a** of up to 70% have been obtained, the reproducibility was poor and the isolated yields were low in most cases (ca. 30–40%, cf. Experimental). As we could not remedy this problem, we explored whether Suzuki coupling[25,26] provides a more robust and practical solution. In fact, hydroboration of **8** with bis(siamyl)borane ($(sia)_2BH$) followed by palladium catalyzed reaction with iodide **7b** gave fully functional polyketide fragment **5b** in a well reproducible and satisfactory yield (79%). At this point, the tentative stereochemical assignments made above for the chiral centers formed in the aldol- and the allenylzinc addition steps could be confirmed by comparison of the spectroscopic properties of compounds **5** and **6** with literature data[10–12]. Moreover, the ^1H NMR pattern signature of product **5b** is distinctly different from that of its 9-epimer **23** which was prepared by an independent route (cf. Table I)[27]. Since various alkyl esters of fragment **5** have previously been converted into the individual members of the crocacin family (notably by application of our Peterson enamide manifold)[7], the novel route outlined above comprising only 9 steps in the longest linear sequence constitutes an effective formal synthesis of each of these interesting bioactive targets.

TABLE I
Characteristic ^1H NMR data (δ, ppm (*J*, Hz)) of crocacin C (**3**)[12b], ester **5b** and its 9-epimer **23**[27]



Position	**3**	**5b**	**23**
7	3.17 (dd, 9.7, 2.0)	3.17 (dd, 9.8, 2.3)	3.04 (dd, 8.3, 3.0)
7-OMe	3.51 (s)	3.52 (s)	3.44 (s)
8	1.55 (m)	1.40–1.50 (m)	1.98–2.07 (m)
9	4.08 (ddd, 7.3, 2.6, 1.1)	4.06 (ddd, 7.2, 2.5, 1.1)	3.88 (ddd, 8.3, 5.3, 0.7)

EXPERIMENTAL

All reactions were carried out under Ar in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N (CaH_2), MeOH (Mg), DMF, NMP (Desmodur®, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received. NMR: Spectra were recorded on a Bruker DPX 300 or AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). Compounds **10** [22], **21** [24] and **7b** [24] were prepared according to the cited literature procedures.

2-(Trimethylsilyl)ethyl (*E*)-3-Iodobut-2-enoate (**7a**)

Bu_3SnH (1.74 g, 5.98 mmol) was added to a solution of freshly prepared LDA (5.98 mmol) in THF (10 ml) at –40 °C and the resulting mixture was stirred at that temperature for 60 min. The mixture was diluted with THF (40 ml) before $CuBr{\cdot}SMe_2$ (1.23 g, 5.98 mmol) was introduced and stirring was continued for 10 min. The resulting dark red solution was cooled to –78 °C before 2-(trimethylsilyl)ethyl but-2-ynoate (848 mg, 4.60 mmol) was injected. The reaction mixture was stirred at –78 °C for 3 h before it was quenched at that temperature with aqueous saturated NH_4Cl. The mixture was warmed to ambient temperature, diluted with *tert*-butyl methyl ether, and the combined organic layers were repeatedly extracted with aqueous saturated NH_4Cl until the aqueous phase was colorless. Evaporation of the solvent followed by flash chromatography of the residue (hexane/EtOAc, 30:1) gave stannane **21a**, which was immediately used in the next step (1.2 g, 55%).

A solution of I_2 (790 mg, 3.11 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of this stannane (987 mg, 2.08 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After stirring for 2 h, the reaction was quenched with aqueous saturated Na_2SO_3, the organic layer was dried over $MgSO_4$, the solvent was evaporated and the residue purified by flash chromatography (hexanes/EtOAc, 50:1) to give iodide **7a** as a colorless syrup (547 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.56 (q, 1 H, *J* = 1.4); 4.14 (d, 2 H, *J* = 3.9); 2.93 (d, 3 H, *J* = 1.4); 0.96 (d, 2 H, *J* = 3.9); –0.02 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.8, 133.2, 121.6, 64.2, 32.5, 18.8, 1.5.

(*R*)-3-Methyl-2-(tosylamino)butyl Propionate (**13**)

p-Toluenesulfonyl chloride (3.81 g, 20 mmol) was added in portions to a solution of (*R*)-valinol (**12**) (2.0 g, 20 mmol) and Et_3N (5.6 ml, 40 mmol) in CH_2Cl_2 (25 ml) at 0 °C. Once TLC control showed complete consumption of the starting material, the reaction was diluted with CH_2Cl_2 (15 ml) and additional Et_3N (2.8 ml, 20 mmol) was introduced. Propionyl chloride (4.44 ml, 51 mmol) was then added and stirring continued overnight. Quenching of the reaction with aqueous saturated $NaHCO_3$ followed by a standard extractive work-up and flash chromatography (EtOAc/hexanes, 1:4 → 1:1) gave analytically pure **13** (5.12 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, 2 H, *J* = 8.1); 7.29 (d, 2 H, *J* = 8.1);

4.93 (d, 1 H, *J* = 8.8); 4.03 (dd, 1 H, *J* = 6.1, 11.1); 3.90 (dd, 1 H, *J* = 4.6, 11.1); 3.35–3.26 (m, 1 H); 2.42 (s, 3 H); 2.22–2.10 (m, 2 H); 1.88–1.76 (m, 1 H); 1.06 (t, 3 H, *J* = 7.3); 0.90–0.80 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.3, 143.3, 138.2, 129.6, 127.0, 63.8, 58.0, 30.0, 27.2, 21.5, 18.9, 18.2, 8.9. IR (neat): 3281, 2964, 2877, 1738, 1598, 1495, 1463, 1390, 1325, 1183, 1160, 1087, 1042, 1020, 974, 813, 707, 665. MS (EI), *m/z* (%): 270 (33), 239 (3), 226 (100), 214 (20), 196 (6), 157 (9), 139 (25), 98 (15), 91 (69), 65 (10), 57 (25). HR-MS (CI): [$C_{15}H_{23}SO_4N$ + Na] calculated 336.12455, found 336.12471.

(*R*)-3-Methyl-2-(tosylamino)butyl (2*R*,3*S*,4*E*)-3-Hydroxy-2-methyl-5-phenylpent-4-enoate (**14**)

$TiCl_4$ (1 mol l^{-1} in CH_2Cl_2, 1.1 ml) was added to a solution of compound **13** (317 mg, 1.01 mmol) in CH_2Cl_2 (10 ml) at 0 °C. After 10 min, $(iPr)_2NEt$ (520 µl, 3 mmol) was added dropwise and stirring was continued at that temperature for 1 h. In a separate flask, a solution of $TiCl_4$ (1 mol l^{-1} in CH_2Cl_2, 3 ml) was added dropwise to a solution of aldehyde **11** (264 mg, 2 mmol) in CH_2Cl_2 (20 ml) at –78 °C. The resulting mixture was stirred for 10 min before the solution of the enolate derived from **13** was slowly added via canula over 30 min. The reaction was allowed to stir at that temperature for 90 min before it was quenched with aqueous saturated NH_4Cl. After warming to ambient temperature, the aqueous layer was repeatedly extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude product purified by flash chromatography with pentane/ether as eluent to afford product **14** as a highly viscous oil (379 mg, 85%). When the same reaction was performed using 3.76 g of ester **13**, aldol **14** was obtained in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (d, 2 H, *J* = 8.3); 7.41–7.20 (m, 7 H); 6.63 (d, 1 H, *J* = 16.0); 6.16 (dd, 1 H, *J* = 6.3, 16.0); 5.28 (d, 1 H, *J* = 9.1); 4.64–4.58 (m, 1 H); 4.08 (dd, 1 H, *J* = 5.6, 11.6); 3.95 (dd, 1 H, *J* = 4.3, 11.6); 3.34–3.26 (m, 1 H); 2.96 (bs, 1 H); 2.61 (dq, 1 H, *J* = 4.0, 7.1); 2.39 (s, 3 H); 1.77 (oct., 1 H, *J* = 7); 1.16 (d, 3 H, *J* = 7); 0.82 (d, 3 H, *J* = 7); 0.79 (d, 3 H, *J* = 7). ^{13}C NMR (100 MHz, $CDCl_3$): 174.8, 143.3, 138.1, 136.4, 131.5, 129.6, 128.7, 128.5, 127.7, 126.9, 126.5, 72.8, 64.0, 57.9, 45.1, 30.0, 21.5, 18.8, 18.4, 10.9. IR (neat): 3498, 3284, 3060, 2966, 1733, 1598, 1578, 1495, 1450, 1326, 1161, 1063, 969, 815, 751, 667. MS (EI), *m/z* (%): 445 (3), 427 (2), 402 (31), 313 (30), 290 (10), 270 (6), 258 (15), 226 (100), 214 (17), 196 (3), 189 (8), 188 (12), 184 (54), 172 (14), 171 (19), 160 (41), 155 (78), 144 (6), 143 (20), 139 (12), 133 (28), 132 (10), 131 (18), 115 (10), 104 (11), 103 (9), 91 (85), 86 (11), 55 (13). HR-MS (CI): [$C_{24}H_{31}SO_5N$ + Na] calculated 468.18207, found 468.18237.

(*R*)-3-Methyl-2-(tosylamino)butyl (2*R*,3*S*,4*E*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-5-phenylpent-4-enoate (**15**)

tert-Butyldimethylsilyl triflate (1.24 ml, 5.39 mmol) was slowly added to a solution of aldol **14** (1.6 g, 3.59 mmol) and 2,6-lutidine (840 µl, 7.18 mmol) in CH_2Cl_2 (40 ml) at 0 °C. After stirring at 0 °C for 45 min and at ambient temperature for 1 h, the mixture was diluted with aqueous saturated $NaHCO_3$, the organic layer was dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (Et_2O/pentane gradient) to give product **15** as a syrup (1.94 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.74 (d, 2 H, *J* = 8.1); 7.36–7.20 (m, 7 H); 6.46 (d, 1 H, *J* = 15.9); 6.09 (dd, 1 H, *J* = 7.1, 16.2); 4.78 (d, 1 H, *J* = 9.1); 4.40 (t, 1 H, *J* = 7.1); 3.92–3.84 (m, 2 H); 3.27–3.19 (m, 1 H); 2.47–2.38 (m, 1 H); 2.40 (s, 3 H); 1.73 (oct., 1 H, *J* = 7.0); 1.14 (d, 3 H, *J* = 7); 0.88 (s, 9 H); 0.78 (d, 3 H, *J* = 7); 0.72 (d, 3 H, *J* = 7); 0.02

(s, 3 H); –0.01 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.1, 143.3, 138.2, 136.5, 130.9, 130.6, 129.6, 128.6, 127.7, 127.0, 126.4, 75.0, 63.9, 57.9, 47.1, 29.7, 25.8, 21.5, 18.9, 18.1, 12.4, –4.0, –5.0. IR (neat): 3282, 3027, 2958, 2930, 2884, 2857, 1737, 1599, 1578, 1495, 1450, 1329, 1252, 1162, 1093, 1063, 970, 836, 814, 777, 747, 694, 667, 551. MS (EI), *m/z* (%): 502 (8), 314 (9), 274 (2), 263 (3), 249 (3), 247 (64), 242 (5), 240 (82), 228 (4), 184 (100), 171 (9), 155 (37), 91 (26), 75 (10), 73 (25). HR-MS (CI): [$C_{30}H_{45}SiSO_5N$ + Na] calculated 582.26854, found 582.26843.

(2*S*,3*S*,4*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-5-phenylpent-4-en-1-ol (**16**)

Finely powdered $LiBH_4$ (958 mg, 44 mmol) and MeOH (1.8 ml, 44 mmol) were added to a solution of compound **15** (4.42 g, 7.90 mmol) in THF (80 ml) and the resulting mixture was stirred overnight at ambient temperature. Standard extractive work-up followed by flash chromatography (acetone/hexanes, 1:4) gave alcohol **16** as a colorless syrup (2.16 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.70–7.36 (m, 2 H); 7.35–7.30 (m, 2 H); 7.27–7.22 (m, 1 H); 6.54 (d, 1 H, *J* = 15.9); 6.25 (dd, 1 H, *J* = 6.8, 15.9); 4.43 (ddd, 1 H, *J* = 1.3, 4.0, 6.8); 3.72 (dd, 1 H, *J* = 8.8, 10.9); 3.53 (dd, 1 H, *J* = 4.3, 10.9); 2.83 (bs, 1 H); 2.13–2.02 (m, 1 H); 0.92 (s, 9 H); 0.86 (d, 3 H, *J* = 7.1); 0.11 (s, 3 H); 0.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 136.8, 131.1, 129.4, 128.6, 127.6, 126.4, 77.2, 65.8, 41.4, 25.8, 18.1, 12.4, –4.3, –5.1. IR (neat): 3412, 3027, 2956, 2929, 2884, 2857, 1600, 1578, 1495, 1472, 1462, 1449, 1254, 1092, 1032, 969, 835, 776, 745, 693, 671. MS (EI), *m/z* (%): 249 (11), 248 (18), 247 (82), 207 (19), 157 (14), 145 (100), 142 (7), 129 (23), 128 (8), 117 (17), 115 (21), 91 (13), 75 (77), 73 (66). HR-MS (CI): [$C_{18}H_{30}SiO_2$ + Na] calculated 329.19128, found 329.19135.

(2*R*,3*S*,4*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-5-phenylpent-4-enal (**9**)

Dess–Martin periodinane **17** (2.53 g, 5.97 mmol) was added in portions to a solution of alcohol **16** (916 mg, 2.99 mmol) in CH_2Cl_2 (80 ml) and pyridine (2.2 ml) and the resulting mixture was stirred at ambient temperature for 7 h. The reaction was quenched with aqueous saturated Na_2SO_3/$NaHCO_3$, the aqueous phase was repeatedly extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to give aldehyde **9** as a colorless oil (792 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.81 (d, 1 H, *J* = 1.3); 7.38–7.30 (m, 4 H); 7.28–7.22 (m, 1 H); 6.58 (d, 1 H, *J* = 15.9); 6.18 (dd, 1 H, *J* = 6.8, 15.9); 4.72 (ddd, 1 H, *J* = 1.3, 4.3, 6.8); 2.56 (ddq, 1 H, *J* = 1.3, 4.3, 7.1); 1.13 (d, 3 H, *J* = 7.1); 0.90 (s, 9 H); 0.08 (s, 3 H); 0.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 204.6, 136.5, 131.2, 129.7, 128.6, 127.8, 126.5, 73.5, 53.0, 25.8, 18.2, 8.5, –4.1, –5.0. IR (neat): 3027, 2956, 2930, 2885, 2857, 2710, 1727, 1600, 1578, 1495, 1472, 1462, 1449, 1361, 1253, 1091, 1071, 1033, 969, 837, 778, 746, 693. MS (EI), *m/z* (%): 249 (6), 248 (21), 247 (100), 189 (20), 171 (4), 155 (4), 131 (11), 129 (80), 128 (9), 117 (15), 116 (12), 115 (98), 91 (12), 85 (12), 75 (42), 73 (64). HR-MS (CI): [$C_{18}H_{28}SiO_2$ + H] calculated 305.19368, found 305.19362.

(3*S*,4*S*,5*R*,6*S*,7*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethyl-8-phenyloct-7-en-1-yn-4-ol (**18**)

A mixture of $Pd(OAc)_2$ (6.9 mg, 0.031 mmol) and PPh_3 (8.9 mg, 0.034 mmol) in THF (3.5 ml) was stirred at –78 °C for 70 min before solutions of aldehyde **9** (234 mg, 0.77 mmol) and mesylate **10** (148 mg, 1.00 mmol) in the minimum amount of THF each

were successively introduced. A solution of $ZnEt_2$ (1 mol l^{-1} in THF, 2.3 ml) was then added over a period of 30 min via syringe pump and stirring was continued at –78 °C for 1 h before the mixture was allowed to reach ambient temperature. At that point, the reaction was rapidly quenched with chilled aqueous saturated NH_4Cl and diluted with *tert*-butyl methyl ether. A standard extractive work-up followed by flash chromatography furnished alkyne **18** as a colorless syrup (200 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.37 (m, 2 H); 7.36–7.30 (m, 2 H); 7.28–7.22 (m, 1 H); 6.55 (d, 1 H, *J* = 16.2); 6.30 (dd, 1 H, *J* = 6.8, 16.2); 4.56 (ddd, 1 H, *J* = 1.0, 3.0, 6.6); 4.14 (d, 1 H, *J* = 3.0); 3.50–3.45 (m, 1 H); 2.63–2.56 (m, 1 H); 2.21–2.11 (m, 1 H); 2.08 (d, 1 H, *J* = 2.5); 1.31 (d, 3 H, *J* = 7.1); 0.93 (s, 9 H); 0.86 (d, 3 H, *J* = 7.1); 0.13 (s, 3 H); 0.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 136.7, 131.4, 128.7, 128.6, 127.6, 126.5, 84.8, 78.1, 75.7, 70.1, 43.0, 30.2, 25.9, 18.2, 17.7, 12.8, –4.4, –5.1. IR (neat): 3474, 3309, 3082, 3060, 3026, 2955, 2931, 2884, 2857, 2112, 1727, 1600, 1578, 1495, 1471, 1462, 1449, 1386, 1362, 1254, 1143, 1112, 1068, 1042, 970, 864, 836, 778, 748, 693, 633. MS (EI), *m/z* (%): 301 (10), 249 (8), 248 (21), 247 (100), 209 (6), 208 (12), 207 (69), 189 (6), 173 (7), 145 (8), 129 (8), 117 (11), 115 (19), 75 (36), 73 (38). HR-MS (CI): [$C_{22}H_{34}SiO_2$ + Na] calculated 381.22258, found 381.22251.

(3*S*,4*S*,5*R*,6*S*,7*E*)-3,5-Dimethyl-8-phenyloct-7-en-1-yn-4,6-diol (**19**)

A solution of compound **18** (453 mg, 1.26 mmol) in THF (10 ml) at 0 °C was treated with TBAF (1 mol l^{-1} in THF, 1.89 ml). After stirring for 1 h, the mixture was diluted with *tert*-butyl methyl ether and quenched with water. A standard extractive work-up followed by flash chromatography (CH_2Cl_2/EtOAc, 3:1) gave product **19** as a colorless syrup (270 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.38 (m, 2 H); 7.35–7.29 (m, 2 H); 7.26–7.10 (m, 1 H); 6.67 (dd, 1 H, *J* = 1.3, 15.9); 6.31 (dd, 1 H, *J* = 5.8, 15.9); 4.67–4.63 (m, 1 H); 3.52 (dd, 1 H, *J* = 3.3, 8.3); 2.89 (bs, 2 H); 2.78–2.70 (m, 1 H); 2.16 (d, 1 H, *J* = 2.5); 2.16–2.07 (m, 1 H); 1.30 (d, 3 H, *J* = 7.1); 0.95 (d, 3 H, *J* = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$): 136.8, 130.9, 129.7, 128.6, 127.6, 126.5, 84.4, 76.8, 74.5, 71.3, 41.7, 30.4, 17.9, 12.1. IR (neat): 3380, 3298, 3082, 3059, 3026, 2975, 2935, 2909, 2878, 2112, 1599, 1578, 1495, 1449, 1383, 1333, 1144, 1112, 1063, 984, 968, 751, 695, 642. MS (EI), *m/z* (%): 226 (3), 211 (5), 173 (11), 145 (12), 133 (100), 132 (17), 131 (29), 129 (10), 128 (6), 122 (6), 117 (11), 115 (26), 105 (19), 104 (23), 103 (11), 94 (10), 91 (20), 79 (24), 77 (15), 55 (24). HR-MS (CI): [$C_{16}H_{20}O_2$ + Na] calculated 267.13609, found 267.13603.

(3*S*,4*S*,5*R*,6*S*,7*E*)-4,6-Dimethoxy-3,5-dimethyl-8-phenyloct-7-en-1-yne (**8**)

MeOTf (330 μl, 2.91 mmol) was added to a solution of compound **19** (142 mg, 0.58 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (477 mg, 2.32 mmol) in CH_2Cl_2 (1.8 ml) and the resulting mixture was stirred at ambient temperature for 72 h. The reaction mixture was extracted with aqueous HCl (1 mol l^{-1}) and water, the organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 15:1) to give alkyne **8** as a colorless syrup (100 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.39 (m, 2 H); 7.35–7.29 (m, 2 H); 7.26–7.21 (m, 1 H); 6.59 (d, 1 H, *J* = 15.9); 6.20 (dd, 1 H, *J* = 7.1, 15.9); 4.14 (dd, 1 H, *J* = 1.0, 7.1); 3.57 (s, 3 H); 3.33 (s, 3 H); 3.15 (dd, 1 H, *J* = 2.5, 9.9); 2.78–2.73 (m, 1 H); 2.06 (d, 1 H, *J* = 2.5); 1.99–1.91 (m, 1 H); 1.35 (d, 3 H, *J* = 7.1); 0.93 (d, 3 H, *J* = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$): 136.8, 132.0, 129.2, 128.6, 127.5, 126.4, 85.1, 84.8, 80.9, 69.9, 61.4, 56.5, 42.8, 29.4, 18.3, 9.9. IR (neat): 3298, 3027, 2976, 2935, 2829, 2117, 1599, 1494, 1494, 1449, 1369, 1189, 1144, 1090, 965, 968, 750, 694, 635, 619.

MS (EI), *m/z* (%): 240 (2), 225 (2), 200 (4), 187 (7), 147 (100), 115 (21), 91 (8), 75 (11). HR-MS (CI): [$C_{18}H_{24}O_2$ + Na] calculated 295.16740, found 295.16747.

2-(Trimethylsilyl)ethyl (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-trienoate (**5a**)

A solution of Bu_3SnH (186 μl, 0.69 mmol) in THF (1 ml) was added over 30 min via syringe pump to a carefully degassed solution of alkyne **8** (94 mg, 0.345 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) in THF (5 ml) and the resulting mixture was stirred for 15 min. After evaporation of all volatile components, the crude product was loaded on top of a silica gel column (deactivated by treatment with Et_3N in hexane) which was first eluted with hexanes to remove all tin impurities before the eluent was changed to hexanes/EtOAc (50:1) to give the known stannane **6** (171 mg, 88%). The spectroscopic data of this sample were in full agreement with those reported in the literature[11b]. ^{1}H NMR (400 MHz, $CDCl_3$): 7.20–7.40 (m, 5 H); 6.57 (d, 1 H, *J* = 16.1); 6.17 (dd, 1 H, *J* = 6.9, 16.1); 5.95 (dd, 1 H, *J* = 7.2, 19.0); 5.86 (d, 1 H, *J* = 19.0); 4.10 (br d, 1 H, *J* = 7.2); 3.53 (s, 3 H); 3.34 (s, 3 H); 3.14 (dd, 1 H, *J* = 2.5, 10.2); 2.43–2.46 (m, 1 H); 1.63 (m, 1 H); 1.40–1.52 (m, 6 H); 1.20–1.34 (m, 12 H); 1.15 (d, 3 H, *J* = 6.6); 0.86 (d, 3 H, *J* = 7.2); 0.85 (t, 9 H, *J* = 7.0). This compound is rather labile, in particular to traces of acid, and was therefore used in the next step without delay.

$Pd_2(dba)_3$ and tris(2-furyl)phosphine (TFP, 2 equivalents to palladium) were dissolved in NMP to give a 0.1 M catalyst solution. An aliquot of this stock solution (150 μl) was added to a carefully degassed solution (5 freeze/pump/thaw cycles) of stannane **6** (171 mg, 0.303 mmol) and iodide **7a** (312 mg, 1.0 mmol) in NMP (3 ml) and the resulting mixture was stirred at 40 °C for 12 h and then at 60 °C for another 48 h. Addition of *tert*-butyl methyl ether followed by a standard extractive work-up and flash chromatography (hexanes/EtOAc, 30:1) gave product **5a** as a colorless syrup (45 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.37 (m, 2 H); 7.34–7.29 (m, 2 H); 7.26–7.20 (m, 1 H); 6.56 (d, 1 H, *J* = 15.9); 6.15 (dd, 1 H, *J* = 7.3, 15.9); 6.14 (dd, 1 H, *J* = 8.1, 15.9); 6.07 (d, 1 H, *J* = 15.9); 5.66 (s, 1 H); 4.21–4.15 (m, 2 H); 4.10–4.05 (d, 1 H, *J* = 8.5); 3.55 (s, 3 H); 3.32 (s, 3 H); 3.19 (dd, 1 H, *J* = 2.3, 9.9); 2.61–2.51 (m, 1 H); 2.26 (d, 3 H, *J* = 1.0); 1.60–1.50 (m, 1 H); 1.19 (d, 3 H, *J* = 6.8); 1.02–0.96 (m, 2 H); 0.84 (d, 3 H, *J* = 7.1); 0.03 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.4, 152.4, 138.0, 136.8, 134.0, 132.0, 129.2, 128.6, 127.6, 126.4, 118.3, 86.4, 81.1, 61.8, 61.5, 56.5, 42.7, 40.1, 18.7, 17.4, 13.9, 9.8, –1.5. IR (neat): 3027, 2955, 2902, 2829, 1709, 1634, 1611, 1495, 1449, 1372, 1354, 1249, 1238, 1152, 1122, 1092, 972, 860, 837, 749, 693. MS (EI), *m/z* (%): 394 (2), 249 (5), 248 (4), 217 (5), 187 (7), 148 (11), 147 (100), 115 (10), 75 (32), 73 (14). HR-MS (CI): [$C_{27}H_{42}SiO_4$ + Na] calculated 481.27501, found 481.27486.

tert-Butyl (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-trienoate (**5b**)

A freshly prepared solution of $(sia)_2BH$ (0.53 mol l^{-1} in THF, 1.51 ml, 0.8 mmol) was added to a solution of alkyne **8** (110 mg, 0.4 mmol) in THF (20 ml) at 0 °C. The resulting mixture was stirred for 1 h before degassed aqueous LiOH (2 mol l^{-1}, 2 ml, 4.0 mmol), iodide **7b** (160 mg, 0.6 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) were successively added. The mixture was vigorously stirred at 40 °C for 18 h before it was quenched with chilled aqueous saturated NH_4Cl and Et_2O. Standard extractive work-up followed by flash chromatography (hexanes/EtOAc, 20:1) gave product **5b** as a colorless oil (130 mg, 79%). ^{1}H NMR (400 MHz,

CD_2Cl_2): 7.42–7.38 (m, 2 H); 7.34–7.28 (m, 2 H); 7.25–7.20 (m, 1 H); 6.57 (d, 1 H, *J* = 16.1); 6.16 (dd, 1 H, *J* = 16.0, 7.2); 6.12 (dd, 1 H, *J* = 15.8, 7.8); 6.06 (d, 1 H, *J* = 15.8); 5.92 (d, 1 H, *J* = 1.1); 4.06 (ddd, 1 H, *J* = 7.2, 2.5, 1.1); 3.52 (s, 3 H); 3.30 (s, 3 H); 3.17 (dd, 1 H, *J* = 9.8, 2.3); 2.60–2.50 (m, 1 H); 2.19 (d, 3 H, *J* = 1.2); 1.44 (s, 9 H); 1.50–1.40 (m, 1 H); 1.17 (d, 3 H, *J* = 6.9); 0.83 (d, 3 H, *J* = 7.0). ^{13}C NMR (100 MHz, CD_2Cl_2): 166.6, 151.1, 137.8, 137.1, 133.9, 131.8, 129.8, 128.6, 127.5, 126.4, 119.9, 86.5, 81.1, 79.5, 61.2, 56.3, 42.7, 40.2, 28.1, 18.6, 13.6, 9.7.

(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-trienoic Acid (**5c**)

A solution of ester **5a** (36 mg, 0.078 mmol) and TBAF (1 mol l^{-1} in THF, 235 μl) in THF (5 ml) was stirred at ambient temperature until TLC showed complete conversion of the substrate. The mixture was diluted with CH_2Cl_2 and extracted with aqueous HCl (1 mol l^{-1}), the organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc/HOAc, 80:20:1) to give acid **5c** as a colorless syrup (24.8 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.42–7.36 (m, 2 H); 7.34–7.27 (m, 2 H); 7.25–7.19 (m, 1 H); 6.56 (d, 1 H, *J* = 16.0); 6.22 (dd, 1 H, *J* = 8.4, 15.8); 6.15 (dd, 1 H, *J* = 7.3, 16.0); 6.10 (d, 1 H, *J* = 15.8); 5.70 (s, 1 H); 4.07 (dd, 1 H, *J* = 8.4, 15.8); 3.54 (s, 3 H); 3.32 (s, 3 H); 3.20 (dd, 1 H, *J* = 2.3, 9.9); 2.64–2.52 (m, 1 H); 2.26 (d, 3 H, *J* = 1.0); 1.60–1.48 (m, 1 H); 1.20 (d, 3 H, *J* = 6.9); 0.85 (d, 3 H, *J* = 7.1). ^{13}C NMR (75 MHz, $CDCl_3$): 170.6, 155.2, 139.3, 136.8, 133.8, 132.1, 129.2, 128.6, 127.6, 126.4, 116.8, 86.4, 81.1, 61.5, 56.4, 42.7, 40.2, 18.7, 14.2, 9.8. IR (neat): 3250, 3026, 2973, 2932, 2830, 1681, 1633, 1607, 1495, 1448, 1371, 1262, 1188, 1156, 1122, 1088, 972, 749, 694. MS (EI), *m/z* (%): 294 (7), 249 (2), 217 (3), 187 (6), 147 (100), 115 (16), 91 (8), 75 (25). HR-MS (CI): [$C_{22}H_{30}O_4$ + Na] calculated 381.20418, found 381.20410.

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4. Note that several important commercial fugicides also inhibit mitochondrial respiration in plant pathogens at complex III, cf. ref.[3] and references therein.
5. The following IC_{50} values were reported in ref.[2] using an assay with L929 mouse fibroblasts: 0.06 mg l^{-1} (**4**), 0.2 mg l^{-1} (**1**), 40 mg l^{-1} (**2**), 140 mg l^{-1} (**3**).

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