Total Synthesis of (+)-Crocacin C

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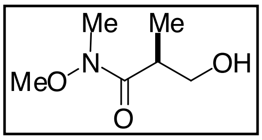
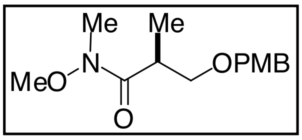
Supporting Information

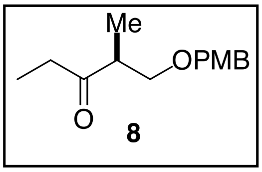
General. Unless otherwise stated, ^{1}H NMR (300 MHz or 400 MHz) and proton decoupled ^{13}C NMR spectra (75.5 MHz or 100 MHz) were recorded for deuterochloroform solutions with residual chloroform as internal standard. Optical rotations were recorded in a 10cm microcell. HRMS mass spectra were run on a Bruker 4.7T BiOAPEX FTMS mass spectrometer at Monash University, Clayton, Victoria. Microanalyses were carried out at the University of Otago, Dunedin, New Zealand. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from sodium metal/benzophenone under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petrol refers to the fraction boiling between 40-60°C.



(*S*)-*N*-Methoxy-*N*-methyl-3-hydroxy-2-methylpropanamide. To a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (585mg, 6.0mmol) in toluene (2.0mL) under argon at 0˚C was added a solution of $AlMe_3$ in toluene (2.0M, 3.0mL, 6.0mmol) and the mixture was warmed to rt for 15min. The solution was cooled to 0˚C and added to methyl (*S*)-3-hydroxy-2-methylpropanoate (222μL, 2.00mmol) *via* cannula and the resultant solution was warmed to 50˚C for 2h. The reaction mixture was transferred *via* cannula into 10% HCl in saturated NaCl (6.0mL) and EtOAc (20mL) at 0˚C and stirred vigorously for 1.5h. The aqueous layer was extracted further with EtOAc and the combined organic layers were washed with saturated aqueous $NaHCO_3$, then dried (Na_2SO_4), filtered and evaporated. The residue was purified on silica gel with EtOAc as eluant to give the amide (189mg, 64%) as a colourless oil: R_f 0.28 (100% EtOAc); $[\alpha]^{21}_D$ +50.8 (*c* 1.28, CH_2Cl_2); IR υ_{max} (film) 3423, 2978, 2941, 2879, 1643, 1466, 1426, 1389, 1181 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.15 (d, *J* 6.9 Hz, 3H), 2.59 (br s, 1H), 3.03 (m, 1H), 3.20 (s, 3H), 3.66-3.77 (m, 2H), 3.71 (s, 3H); ^{13}C NMR (75.5 MHz) δ 13.5, 31.9, 37.5, 61.4, 64.7, 176.8; HRMS (ESI) calc. for $C_6H_{13}NNaO_3$ [M+Na^+]: 170.0793. Found: 170.0786.

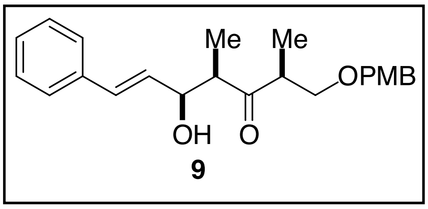


(*S*)-*N*-Methoxy-*N*-methyl-3-(*p*-methoxybenzyl)oxy-2-methylpropanamide. To a rapidly stirred suspension of NaH (10.2mg, 0.427mmol) in Et_2O (5.0mL) at rt under argon was added a solution of *p*-methoxybenzyl alcohol (590mg, 4.27mmol) in Et_2O (4.0mL) and stirring was continued for 30min. The resulting solution was cooled to 0˚C and trichloroacetonitrile (427μL, 4.27mmol) was then added dropwise and the solution was warmed to rt and stirred for 4h. The solvent was evaporated under reduced pressure and dry pentane (6.0mL) and MeOH (17μL) were added. The mixture was filtered through celite and concentration of the filtrate gave the crude *p*-methoxybenzyltrichloroacetimidate (1.133g, 94%) as a pale yellow oil. A solution of (*S*)-*N*-methoxy-*N*-methyl-3-hydroxy-2-methylpropanamide (189mg, 1.28mmol) and the crude *p*-methoxybenzyltrichloroacetimidate (1.133g, 4.01mmol) in CH_2Cl_2 (3.0mL) was treated with 10-camphorsulfonic acid (30.0mg, 0.128mmol) and stirred at rt under argon for 17h. The reaction mixture was filtered through celite, diluted with CH_2Cl_2 (50mL) then washed with saturated aqueous $NaHCO_3$, dried, filtered and concentrated. The crude product was purified on silica gel with petrol:EtOAc (5:1 then 2:1) as eluant to give the PMB ether (278mg, 81%) as a pale yellow oil: R_f 0.39 (petrol:EtOAc, 2:1); $[\alpha]^{20}_D$ +3.76 (*c* 2.13, CH_2Cl_2); IR υ_{max} (film) 2938, 2862, 1659, 1613, 1514, 1465, 1248, 1303, 1099 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (d, *J* 7.2 Hz, 3H), 3.13 (s, 3H), 3.16 (m, 1H), 3.32 (dd, *J* 6.6, 9.0 Hz, 1H), 3.60 (dd, *J* 1.8, 9.0 Hz, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.33 (d, *J* 11.7 Hz, 1H), 4.41 (d, *J* 11.7 Hz, 1H), 6.79 (d, *J* 8.7 Hz, 2H), 7.16 (d, *J* 8.7 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.1, 32.0, 35.8, 55.1, 61.4, 72.2, 72.8, 113.6, 129.0, 130.4, 159.0, 175.8; HRMS (ESI) calc. for $C_{14}H_{21}NNaO_4$ [M+Na^+]: 290.1368. Found: 290.1358.



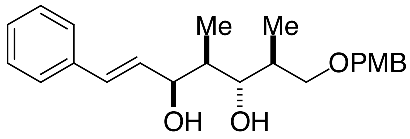
8

(*S*)-1-(*p*-Methoxybenzyl)oxy-2-methyl-3-pentanone 8. To a stirred solution of (*S*)-*N*-methoxy-*N*-methyl-3-(*p*-methoxybenzyl)oxy-2-methyl-propanamide (377mg, 1.41mmol) in THF (10mL) at 0˚C under argon was added a solution of EtMgBr in Et_2O (1.0M, 2.82mL, 2.82mmol) dropwise and the resulting solution was stirred for 1h. The solution was transferred into saturated aqueous NH_4Cl (30mL) and the aqueous layer was back extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude ketone was purified on silica with petrol:EtOAc (20:1, 15:1 then 9:1) as eluant to give the ketone **8** (301mg, 90%) as a colourless oil: R_f 0.46 (petrol:EtOAc, 9:1); $[\alpha]^{22}_D$ –2.31 (*c* 0.80, CH_2Cl_2); IR υ_{max} (film) 2970, 2933, 2835, 1613, 1514, 1248, 1091 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.03 (t, *J* 6.9 Hz, 3H), 1.05 (d, *J* 6.9 Hz, 3H), 2.50 (q, *J* 6.9 Hz, 2H), 2.80-2.92 (m, 1H), 3.42 (dd, *J* 5.4, 9.0 Hz, 1H), 3.59 (dd, *J* 8.1, 9.0 Hz, 1H), 3.80 (s, 3H), 4.41 (d, *J* 2.1 Hz, 2H), 6.84-6.89 (m, 2H), 7.19-7.23 (m, 2H); ^{13}C NMR (75.5 MHz) δ 7.5, 13.6, 35.2, 46.1, 55.2, 72.0, 72.8, 113.7, 129.1, 120.1, 159.1, 213.8; HRMS (EI) calc. for $C_{14}H_{20}O_3$ [M^+]: 236.1412. Found: 236.1414.



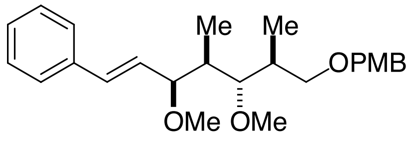
Aldol adduct 9. To a rapidly stirred suspension of $Sn(OTf)_2$ (1.32g, 3.16mmol) in CH_2Cl_2 (5.0mL) at rt under argon was added triethylamine (551μL, 3.96mmol) dropwise and the resulting solution was cooled to –78°C. A solution of pentanone **8** (374mg, 1.58mmol) in CH_2Cl_2 (2mL) was added *via* cannula and the solution was stirred for 2h at –78°C and freshly distilled cinnamaldehyde (399μL 3.16mmol) was added dropwise. The reaction mixture was stirred for a further 1h at –78°C then quenched with pH 7 buffer solution (50mL) and the mixture was and stirred vigorously for 10min at rt then filtered through celite. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified on silica gel using petrol:EtOAc (9:1 then 5:1) as eluant to give the ketone **9** (498mg, 86%) as a pale yellow oil: R_f 0.25 (petrol:EtOAc, 5:1); $[\alpha]^{26}_D$ –11.0 (*c* 4.57, CH_2Cl_2); IR υ_{max} (film) 3466, 2969, 2935, 2874, 1708, 1613, 1513, 1249 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.04 (d, *J* 6.9 Hz, 3H), 1.12 (d, *J* 6.9 Hz, 3H), 2.93 (dq, *J* 3.3, 6.9 Hz, 1H), 3.30 (m, 1H), 3.28 (br s, 1H), 3.46 (dd, *J* 4.8, 8.4 Hz, 1H), 3.62 (t, *J* 8.7 Hz, 1H), 3.77 (s, 1H), 4.40 (d, *J* 3.9 Hz, 2H), 4.70 (m, 1H), 6.11 (dd, *J* 6.3, 15.9 Hz, 1H), 6.58 (d, *J* 15.9 Hz, 1H), 6.87 (m, 2H), 7.19-7.37 (m, 5H); ^{13}C NMR (75.5 MHz) δ 9.9, 13.4, 29.6, 45.2, 51.3, 55.1, 71.8, 72.7, 73.0, 113.7, 126.4, 127.4, 128.4, 129.0, 129.3, 129.5, 130.6, 136.7, 159.2, 217.7; HRMS (ESI) calc. for $C_{23}H_{28}NaO_4$ [M+Na^+]: 391.1885. Found: 391.1877. Further elution gave a mixture of aldol adducts (19mg, 3%).

Diol 10. To a stirred solution of $Me_4NBH(OAc)_3$ (1.05g, 4.00mmol) in MeCN (2.0mL) was added



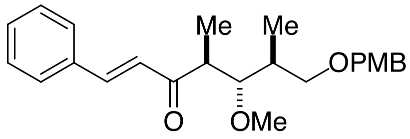
10

glacial AcOH (2.0mL) at rt under argon and the resulting solution was stirred for 30min. The mixture was cooled to –40°C, a solution of ketone **9** (246mg, 0.668mmol) in MeCN (2mL) was added *via* cannula and stirring was continued for 5h and the reaction mixture was then refrigerated (-20°C) for a further 16h. Aqueous sodium tartrate solution (0.5M, 5mL) was added and the mixture was warmed to rt over 1h, diluted with further sodium tartrate (0.5M, 20mL) and CH_2Cl_2 (20mL) and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$ and brine, then dried, filtered and evaporated. Purification of the crude product on silica gel using petrol:EtOAc (5:1, 4:1, 3:1 then 2:1) as eluant gave the *anti*-diol **10** (238mg, 96%) as a yellow oil: R_f 0.50 (petrol:EtOAc, 2:1); $[\alpha]^{17}_D$ +2.22 (*c* 0.98, CH_2Cl_2); IR υ_{max} (film) 3413, 2965, 2933, 2876, 1613, 1514, 1250 cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (d, *J* 7.2 Hz, 3H), 1.02 (d, *J* 7.5 Hz, 3H), 1.90 (m, 1H), 2.14 (dq, *J* 3.6, 7.2 Hz, 1H) 3.46 (dd, *J* 7.5, 9.0 Hz, 1H), 3.60-3.65 (m, 1H) 3.70 (dd, *J* 3.6, 9.0 Hz, 1H), 3.81 (s, 3H), 4.21 (d, *J* 3.0 Hz, 1H), 4.45 (d, *J* 3.0 Hz, 1H), 4.48 (s, 2H), 4.66 (m, 1H), 6.24 (dd, *J* 5.4, 15.9 Hz, 1H), 6.63 (dd, *J* 0.9, 15.9 Hz, 1H), 6.87-6.92 (m, 2H), 7.19-7.41 (m, 5H); ^{13}C NMR (75.5 MHz) δ 11.7, 14.1, 35.4, 39.7, 55.2, 72.9, 73.3, 75.0, 81.6, 113.9, 126.3, 127.2, 128.4, 129.3, 129.4, 129.7, 130.9, 137.1, 159.4; HR-MS (ESI) calc. for $C_{23}H_{30}NaO_4$ $[M+Na^+]$: 393.2042. Found: 393.2047. Further elution gave *syn*-diol (8.2mg, 3%) as a yellow oil: R_f 0.31 (petrol:EtOAc, 2:1); $[\alpha]^{17}_D$ –13.5 (*c* 0.505, CH_2Cl_2); IR υ_{max} (film) 3402, 2968, 2934, 2912, 2876, 1613,1514, 1248 cm^{-1}; ^1H NMR (300 MHz) δ 0.97 (d, *J* 7.2 Hz, 3H), 1.07 (d, *J* 6.9 Hz, 3H), 1.80 (m, 1H), 1.98 (m, 1H) 2.82 (br s, 2H), 3.42 (d, *J* 4.8 Hz, 1H), 3.78 (s, 3H), 3.86 (dd, *J* 3.0, 6.6 Hz, 1H), 4.41 (d, *J* 4.5 Hz, 2H), 4.45 (m, 1H), 6.20 (dd, *J* 5.4, 15.9 Hz, 1H), 6.61 (d, *J* 15.9 Hz, 1H), 6.86 (m, 2H), 7.21-7.26 (m, 2H), 7.32 (t, *J* 7.5 Hz, 2H), 7.37-7.40 (m, 1H); ^{13}C NMR (75.5 MHz) δ 6.4, 13.4, 36.9, 40.2, 55.2, 72.9, 73.4, 76.7, 78.1, 113.8, 126.4, 127.5, 128.5, 129.2, 129.9, 130.2, 131.1, 136.8, 159.2; HRMS (ESI) calc. for $C_{23}H_{30}NaO_4$ $[M+Na^+]$: 393.2042. Found: 393.2050.



11

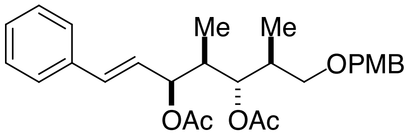
Dimethyl ether 11. To a rapidly stirred suspension of KH (15.8mg, 0.394mmol) in THF (1.0mL) at 0°C under argon was added a solution of diol **10** (29.2mg, 0.079mmol) in THF (2mL) *via* cannula then methyl iodide (25μL, 0.394) was added dropwise and the reaction mixture was warmed to rt and stirred for 1h. The reaction mixture was cooled to 0°C and H_2O was cautiously added followed by CH_2Cl_2 (10mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried then concentrated. The crude product was purified with silica using petrol then petrol:EtOAc (20:1) as eluant to give the dimethyl ether **11** (22.0mg, 70%) as a yellow oil: R_f 0.27 (petrol:EtOAc, 20:1); $[\alpha]^{18}_D$ −1.87 (*c* 1.67, CH_2Cl_2); IR υ_{max} (film) cm^{-1}; ^{1}H NMR (400 MHz) δ 0.90 (d, *J* 6.8 Hz, 3H), 1.11 (d, *J* 6.8 Hz, 3H), 1.79 (m, 1H), 2.09(m, 1H) 3.18 (dd, *J* 2.4, 9.6 Hz, 1H), 3.29 (t, *J* 9.2 Hz, 1H) 3.31 (s, 3H), 3.49 (s, 3H), 3.56 (dd, *J* 4.8, 9.2 Hz, 1H), 3.76 (s, 3H), 4.04 (dd, *J* 2.4, 7.6 Hz, 1H), 4.39 (d, *J* 5.2 Hz, 1H), 6.17 (dd, *J* 7.6, 16.4 Hz, 1H), 6.56 (d, *J* 16.4 Hz, 1H), 6.80-6.84 (m, 2H), 7.20-7.25 (m, 3H), 7.30-7.34 (m, 2H), 7.34-7.41 (m, 2H); ^{13}C NMR (75.5 MHz) δ 10.4, 16.5, 35.7, 41.9, 55.2, 56.4, 61.4, 71.3, 72.7, 81.3, 85.8, 113.6, 126.4, 127.5, 128.6, 129.0, 129.6, 130.8, 131.8, 136.8, 158.9; HRMS (ESI) calc. for $C_{25}H_{34}NaO_4$ [*M*+Na$^+$]: 421.2355. Found: 421.2353.

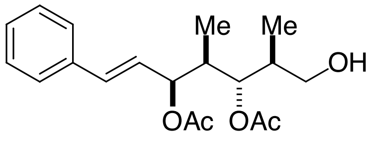


12

Ketone 12. To a stirred solution of the dimethyl ether **11** (22.1mg, 0.056mmol) in CH_2Cl_2 (1.0mL) containing water (56μL) was added 2,3-dichloro-4,5-dicyanoquinone (13.8mg, 0.061mmol) at rt and the solution was stirred for 30min. The reaction mixture was filtered through celite, diluted with CH_2Cl_2 (30mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified on silica with petrol:EtOAc (20:1 then 9:1) as eluant to give the ketone **12** (15.3mg, 72%) as a yellow oil: R_f 0.33 (petrol:EtOAc, 9:1); $[\alpha]^{16}_D$ +47.3 (*c* 0.72, CH_2Cl_2); IR υ_{max} (film) 2964, 2933, 2977, 1687, 1660, 1610. 1514, 1248 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.06 (d, *J* 7.2 Hz, 3H), 1.10 (d, *J* 6.9 Hz, 3H), 2.10 (m, 1H), 3.25 (m, 1H) 3.34 (s, 3H), 3.36 (dd, *J* 6.3, 9.0 Hz, 1H), 3.46 (dd, *J* 3.6, 8.1 Hz, 1H) 3.63 (dd, *J* 8.7, 9.0 Hz, 1H), 3.80 (s, 3H), 4.46 (s, 2H), 6.84 (d, *J* 16.8 Hz, 1H), 6.87-6.91 (m, 2H), 7.26-7.29 (m, 2H), 7.37-7.39 (m, 3H), 7.52-7.58 (m, 3H); ^{13}C NMR (75.5 MHz) δ 14.1, 15.7, 35.9, 47.3, 55.2, 60.9, 71.5, 72.8, 86.4, 113.7, 126.2, 128.4, 128.8, 129.0, 130.3, 130.8, 134.7, 142.4, 159.0, 203.4; HRMS (ESI) calc. for $C_{24}H_{30}NaO_4$ [*M*+Na$^+$]: 405.2042. Found: 405.2032.

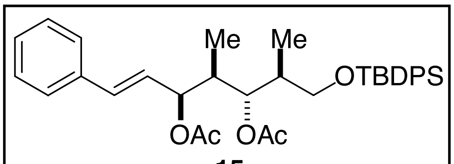
Diacetate 13. To a stirred solution of the *anti*-diol **10** (246mg, 0.663mmol) in CH_2Cl_2 (4.0mL) at rt under argon was added pyridine (804μL), Ac_2O (470μL) and DMAP (10mg) and stirring was continued for 1.5h. The reaction mixture was partitioned between Et_2O and H_2O and the organic layer was washed with saturated aqueous $CuSO_4$, H_2O, saturated aqueous $NaHCO_3$ and brine, then dried. Purification of the crude product by flash chromatography with petrol:EtOAc (10:1, 5:1 then 2:1) as eluant gave the diacetate **13** (46.9mg, 84%) as a yellow oil: R_f 0.80 (petrol:EtOAc, 2:1); $[\alpha]^{21}_D$ +13.9 (*c* 0.92, CH_2Cl_2); IR υ_{max}(film) 2969, 1737, 1613, 1586, 1496, 1373, 1245, 1092, 958, 820, 751 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.96 (d, *J* 7.2 Hz, 3H), 1.03 (d, *J* 7.2 Hz, 3H), 2.04 (s, 3H), 2.08 (s, 3H) 2.20-2.27 (m, 2H), 3.24 (dd, *J* 6.6, 9.3 Hz, 1H), 3.58 (dd, J 5.7, 9.3 Hz, 1H) 3.78 *(*s, 3H), 4.42 (s, 2H), 4.95 (dd, J 3.*3*, 9.3 Hz, 1H), 5.53 (m, 1H$^{)}$, 6.12 (dd, J 6.0, 15.9 Hz, 1H), 6.49 (d, J 15.9 Hz, 1H), 6.85-6.88 (m, 2H), 7.23-7.38 (m, 7H); 13C NMR (75.5 MHz) δ 10.9, 15.6, 20.9, 21.1, 34.6, 38.7, 55.2, 70.9, 72.7, 72.8, 113.7, 126.4, 126.7, 127.7, 128.5, 129.0, 130.4, 131.6, 136.3, 159.0, 170.4, 170.6; HRMS (EI) calc. for $C_{27}H_{34}O_6$ [*M*+]: 454.2355. Found: 454.2367.


13


14

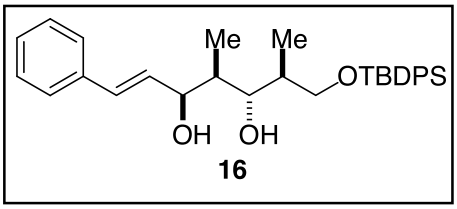
Alcohol 14. To a stirred solution of the diacetate **13** (274mg, 0.603mmol) in CH_2Cl_2 (8.0mL) containing H_2O (448μL) was added 2,3-dichloro-4,5-dicyanoquinone (164mg, 0.724mmol) and the solution was stirred for 1h under argon at rt. The reaction mixture was filtered through celite, diluted with CH_2Cl_2 (50mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography with petrol:EtOAc (2:1 then 1:1) as eluant to give the alcohol **14** (164mg, 81%) as a yellow oil: R_f 0.23 (petrol:EtOAc, 2:1); $[\alpha]^{19}_D$ +1.2 (*c* 1.98, CH_2Cl_2); IR υ_{max} (film) 3452, 2974, 2941, 1733, 1717, 1653, 1372, 1244, 1022 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.02 (d, *J* 6.9 Hz, 3H), 1.05 (d, *J* 7.2 Hz, 3H), 1.86 (br s, 1H), 2.08 (s, 3H), 2.08, (m, 1H), 2.09 (s, 3H), 2.20 (m, 1H), 3.56 (dd, *J* 5.1, 12 Hz, 1H) 3.63 (dd, *J* 4.5, 12 Hz, 1H), 4.93 (dd, *J* 5.4, 7.8 Hz, 1H), 5.62 (ddd, *J* 1.2, 1.2, 6.0 Hz, 1H), 6.14 (dd, J 6.0, 15.9 Hz, 1H) 6.52 (d, J 15.9 Hz, 1H), 7.20-7.38 (m, 5H); ^{13}C NMR (75.5 MHz) δ 11.4, 14.7, 20.9, 21.2, 36.5, 38.5, 63.6, 72.6, 76.8, 126.4, 126.5, 127.9, 128.5, 131.9, 136.2, 170.3, 171.1; HRMS (EI) calc. for $C_{19}H_{26}O_5$ [*M*+]: 334.1780. Found: 334.1788.

Silyl ether 15. To a stirred solution of the alcohol **14** (160mg, 0.479mmol) in DMF (4.0mL) at rt



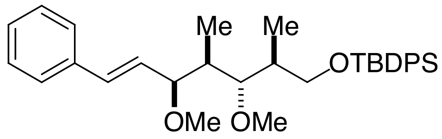
15

under argon was added imidazole (196mg, 2.87mmol) and tert-butyldiphenylsilylchloride (196mg, 1.44mmol) and stirring was continued for 17h. The reaction mixture was partitioned betweeen EtOAc and H_2O then the organic layer was washed with brine, dried, filtered and evaporated. Purification of the crude product on silica gel with petrol:EtOAc (20:1, 10:1 then 5:1) as eluant gave the silyl ether **15** (239mg, 87%) as a yellow oil: R_f 0.10 (petrol:EtOAc, 20:1); $[\alpha]^{20}_D$ +0.88 (*c* 1.79, CH_2Cl_2); IR υ_{max} (film) 3072, 2963, 2933, 2859, 1741, 1240, 1112 cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (d, *J* 6.6 Hz, 3H), 0.96 (d, *J* 6.6 Hz, 3H), 1.05 (s, 9H), 2.00 (s, 3H), 2.08 (s, 3H), 2.18 (ddq, *J* 3.3, 6.6, 6.6 Hz, 1H), 2.29 (m, 1H), 3.48 (dd, *J* 6.6, 10.2 Hz, 1H), 3.76 (dd, *J* 6.0, 10.2 Hz, 1H), 4.94 (dd, *J* 3.3, 9.9 Hz, 1H), 5.52 (m, 1H), 6.07 (dd, *J* 5.7, 15.9 Hz, 1H) 6.47 (d, *J* 15.9 Hz, 1H), 7.21-7.46 (m, 11H), 7.66-7.74 (m, 4H); ^{13}C NMR (75.5 MHz) δ 10.9, 15.2, 19.1, 20.8, 21.1, 26.5, 26.8, 36.5, 38.6, 64.4, 72.8, 76.1,98.5, 126.4, 126.7, 127.6, 127.7, 128.5, 129.6, 131.5, 133.4, 133.5, 134.8, 135.6, 136.3, 170.5, 170.6; HRMS (ESI) calc. for $C_{35}H_{44}NaO_5Si$ [*M*+Na$^+$]: 595.2856. Found: 595.2842.



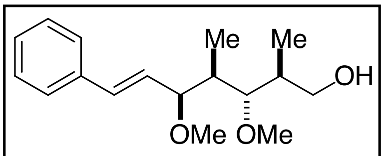
16

Diol 16. To a stirred solution of ether **15** (232mg, 0.405mmol) in CH_2Cl_2 (13.0mL) at –78°C under argon was added a solution of DIBALH in toluene (1.0M, 2.83mL, 2.83mmol). Aqueous sodium tartrate (0.5M, 10mL) was added the solution was warmed to rt and stirred for 30min. Additional sodium tartrate (0.5M, 10mL) was added and the organic layer was diluted with CH_2Cl_2 (10mL). The aqueous layer was further extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O, brine, then dried. The crude product was purified by flash chromatography with petrol:EtOAc (10:1, 5:1 then 1:1) as eluant to give the diol **16** (173.3mg, 88%) as a yellow oil: R_f 0.30 (petrol:EtOAc, 5:1); $[\alpha]^{20}_D$ +10.1 (*c* 1.35, CH_2Cl_2); IR υ_{max} (film) 3417, 3072, 2963, 2932, 2859, 1428, 1113 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (d, *J* 6.9 Hz, 3H), 1.05 (d, *J* 7.2 Hz, 3H), 1.07 (s, 9H), 1.94 (m, 1H), 2.08 (dq, *J* 3.8, 7.2 Hz, 1H), 3.67 (dd, *J* 7.5, 10.2 Hz, 1H), 3.73 (m 1H), 3.87 (dd, *J* 3.9, 10.2 Hz, 1H), 4.32 (d, *J* 3.0Hz, 1H), 4.71 (m, 1H), 4.79 (d, *J* 3.0 Hz, 1H) 6.27 (dd, *J* 5.4, 15.9 Hz, 1H), 6.66 (d, *J* 15.9 Hz, 1H), 7.19-7.34 (m, 4H), 7.40-7.50 (m, 7H), 7.67-7.71 (m, 4H); ^{13}C NMR (75.5 MHz) δ 11.7, 13.7, 19.0, 26.8, 36.7, 39.7, 69.4, 72.8, 82.1, 126.4, 127.2, 127.8, 127.9, 128.5, 129.7, 130.0, 130.1, 131.0, 132.2, 132.3, 135.5, 135.6, 137.2; HRMS (EI) calc. for $C_{31}H_{40}O_3Si$ [M^+]: 488.2747. Found: 488.2740.



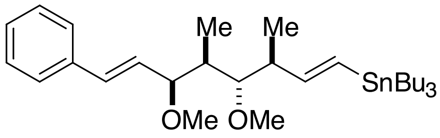
17

Dimethyl ether 17. To a rapidly stirred suspension of KH (85.0mg, 2.12mmol) in THF (5.0mL) at 0°C under argon was added a solution of diol **16** (173mg, 0.354mmol) in THF (6.0mL) *via* cannula, then MeI (132μL, 2.12) was added dropwise and the reaction mixture was warmed to rt and stirred for 1.5h. The mixture was cooled to 0°C and H_2O was cautiously added followed by Et_2O. The aqueous layer was further extracted with Et_2O and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified on silica using petrol then petrol:EtOAc (50:1 then 20:1) as eluant to give the dimethyl ether **17** (178mg, 97%) as a yellow oil: R_f 0.82 (petrol:EtOAc, 5:1); $[\alpha]^{21}_D$ –17.6 (*c* 1.14, CH_2Cl_2); IR υ_{max} (film) 3072, 2964, 2932, 2858, 1472, 1428, 1083 cm^{-1} ; ^{1}H NMR (300 MHz) δ 0.84 (d, *J* 6.9 Hz, 3H), 1.06 (s, 9H), 1.15 (d, *J* 6.6 Hz, 3H), 1.78 (m, 1H), 2.05 (m, 1H), 3.22 (dd, *J* 2.7, 9.3 Hz, 1H), 3.34 (s, 3H), 3.49 (s, 3H), 3.60 (dd, *J* 7.8, 9.9 Hz, 1H), 3.79 (dd, *J* 5.1, 9.6 Hz, 1H), 4.04 (dd, *J* 2.7, 7.2 Hz, 1H), 6.16 (dd, *J* 7.2, 16.2 Hz, 1H), 6.55 (d, *J* 16.2 Hz, 1H), 7.23-7.45 (m, 11H), 7.67-7.71 (m, 4H); ^{13}C NMR (75.5 MHz) δ 10.3, 15.9, 19.2, 26.8, 37.9, 41.6, 56.4, 61.0, 64.7, 81.3, 85.4, 126.3, 127.4, 127.5, 128.5, 129.4, 129.5, 129.6, 131.7, 131.9, 133.93, 133.94, 135.5, 135.6, 136.8; HRMS (ESI) calc. for $C_{33}H_{44}NaO_3Si$ [M+Na^+]: 539.2957. Found: 539.2960.



18

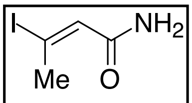
Alcohol 18. To a stirred solution of dimethyl ether **17** (178mg, 0.344mmol) in THF (2.0mL) at rt under argon was added TBAF•3H_2O (217mg, 0.688mmol) and the solution was stirred for 2h. The reaction mixture was partitioned between Et_2O and brine and the aqueous layer was extracted further with Et_2O then the combined organic layers were dried. The crude product was purified on silica with petrol:EtOAc (10:1, 5:1 then 2:1) as eluant to give the alcohol (95.9mg, 100%) as a yellow oil: R_f 0.17 (petrol:EtOAc, 5:1); $[\alpha]^{20}_D$ –4.16 (*c* 1.87, CH_2Cl_2); IR υ_{max} (film) 3438, 2972, 2936, 2828, 1496, 1450, 1094 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.90 (d, *J* 6.9 Hz, 3H), 1.20 (d, *J* 7.2 Hz, 3H), 1.83-1.98 (m, 2H), 2.98 (br s, 1H), 3.28 (dd, *J* 2.4, 9.3 Hz, 1H), 3.32 (s, 3H), 3.53 (s, 3H), 3.55 (m, 1H), 3.84 (m, 1H), 4.07 (dd, *J* 2.4, 7.2 Hz, 1H), 6.19 (dd, *J* 7.2, 15.9 Hz, 1H), 6.58 (d, *J* 15.9 Hz, 1H), 7.22-7.27 (m, 1H), 7.30-7.35 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR (75.5 MHz) δ 10.3, 16.1, 35.7, 42.2, 56.3, 61.5, 64.3, 81.0, 88.2, 126.3, 127.5, 128.5, 129.2, 132.1, 136.6; HRMS (ESI) calc. for $C_{17}H_{26}NaO_3$ [*M*+Na$^+$]: 301.1779. Found: 301.1767.



5

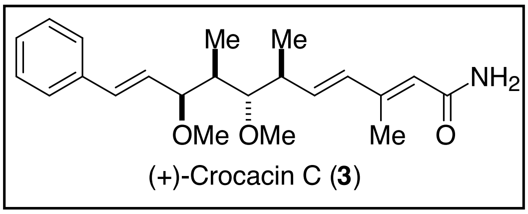
Stannane 5. To a stirred solution of the alcohol **18** (48.7mg, 0.175mmol) in CH_2Cl_2 (3.0mL) at rt under argon was added Dess-Martin periodinane (149mg, 0.350mmol) and stirring was continued for 15min. Saturated aqueous $NaHCO_3$ (2.0mL), and aqueous $Na_2S_2O_3$ (1.5M, 2.0mL) and Et_2O (5mL) were added and stirring was continued for 15min at rt. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried, filtered and concentrated. $CrCl_2$ (215mg, 1.75mmol) was gently flame dried under vacuum (0.1mmHg) then cooled to 0°C and suspended in freeze/thaw degassed DMF (3.0mL) under argon and excluded from light. To the vigorously stirred suspension was added *via* cannula a solution of the crude aldehyde (52.7mg, ~0.175mmol) in freeze/thaw degassed DMF (1.0mL) containing freshly prepared diiodomethyltributyltin (115μL, 0.350mmol). The reaction mixture was allowed to warm to rt over 6h. The reaction mixture was partitioned between Et_2O and water and the aqueous layer was further extracted with Et_2O. The combined organic layers were washed with brine, dried and concentrated. Purification of the crude product by fast vacuum filtration on silica gel using petrol:EtOAc (9:1, 1% NEt_3) as eluant to give the stannane **5** (71.9mg, 75% from the alcohol) as a yellow oil: R_f 0.50 (petrol:EtOAc, 40:1, 1% NEt_3); $[\alpha]^{20}_D$ +19.4 (*c* 1.16, CH_2Cl_2); IR υ_{max} (film) 2958, 1597, 1456, 1377, 1095, 998, 967 cm^{-1} ; ^{1}H NMR (300 MHz) δ 0.84 (t, *J* 7.2 Hz, 12H), 0.85 (d, *J* 7.2 Hz, 3H), 1.15 (d, *J* 6.6 Hz, 3H), 1.21-1.33 (m, 12H), 1.41-1.51 (m, 6H), 1.63 (m, 1H), 2.46 (m, 1H), 3.14 (dd, *J* 2.4, 10.2 Hz, 1H), 3.34 (s, 3H), 3.53 (s, 3H), 4.11 (br d, *J* 7.2 Hz, 1H), 5.86 (d, *J* 19.2 Hz, 1H), 5.96 (dd, *J* 7.2, 19.2 Hz, 1H), 6.17 (dd, *J* 6.9, 16.2 Hz, 1H), 6.57 (d, *J* 16.2 Hz, 1H), 7.21-7.40 (m, 5H); ^{13}C NMR (75.5 MHz) δ 9.42, 9.61, 13.7, 18.3, 27.2, 29.1, 42.5, 44.8, 56.5, 61.2, 81.2, 86.2, 126.3, 127.4, 127.9, 128.5, 129.5, 131.6, 136.9, 150.3; HRMS (ESI) calc. for $C_{30}H_{52}NaO_2{}^{118}Sn$ [*M*+Na$^+$]: 585.2887. Found: 585.2910.

(*E*)-3-Iodo-2-butenamide (6) Tetrolic acid (3.10g, 36.5mmol) was combined with hydroiodic acid (55% aq., 43.8mmol) and the resulting solution was heated to 90°C and stirred for 4h. Cold water



6

(26mL) was added and the product was isolated by filtration and washed with cold water then dried under vacuum for 24h (0.1mmHg) to give *Z*-3-iodo-2-butenoic acid as pale yellow needles (6.04g, 78%). The (*Z*)-acid was heated to 135˚C in a sealed tube for 24h to provide a mixture of (*Z*)-3-iodo-2-butenoic acid and (*E*)-3-iodo-2-butenoic acid (*Z*:*E* ~1:4, 6.04g, 100%). A solution of the crude mixture (2.172g, 10.2mmol) in CH_2Cl_2 (100mL) was treated with excess diazomethane and the solvent was evaporated. The crude mixture of methyl esters was purified on silica gel with petrol:EtOAc (50:1 then 20:1) as eluant to give methyl (*E*)-3-iodo-2-butenoate (**19**) (1.53g, 66%) and methyl (*Z*)-3-iodo-2-butenoate (0.368g, 16%). To a suspension of NH_4Cl (196.2mg, 3.7mmol) under argon at 0°C was added dropwise a solution of $AlMe_3$ in toluene (2.0M, 1.85mL, 3.7mmol). The resulting solution was allowed to warm to rt then recooled to 0°C and a solution of methyl *E*-3-iodo-2-butenoate in toluene (3mL) was added and the mixture was heated to 50°C for 16h. The reaction mixture was then cooled to 0°C and treated with EtOAc (15mL) followed by 10% HCl in saturated NaCl and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and the dried solvent was removed. The crude product was crystallized from CH_2Cl_2/hexane to afford the iodide **6** (136mg, 52%) as colorless prisms; m.p. 124-125°C; υ_{max} 3365, 3188, 1662, 1599, 965 cm^{-1}; ^1H NMR (300 MHz) δ 2.97 (d, *J* 1.2 Hz, 3H), 5.44 (br s, 1H), 5.69 (br s, 1H), 6.58 (q, *J* 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 30.6, 117.4, 132.6, 166.0; HRMS (ESI) calc. for C_4H_6INO [M+Na^+]: 233.9392. Found: 233.9384. Anal. calc. for C_4H_6INO: C, 22.77; H, 2.87; N, 6.64; I, 60.14. Found: C, 23.06; H, 2.70; N, 6.45; I, 60.26.



(+)-Crocacin C (**3**)

(+)-Crocacin C (3). To a stirred soution of the stannane **5** (73.7mg, 0.131mmol) and iodide **6** (41.4mg, 1.96mmol) in freeze/thaw degassed NMP (4.0mL) was added tris-(dibenzylideneacetone)dipalladium(0) (5.9mg, 6.5μmol) and tri-2-furylphosphine (3.0mg, 0.013mmol) and the resutant yellow solution was warmed to 60˚C and stirred for 6h. The reaction mixture was partitioned between EtOAc and H_2O and the organic layer was washed with H_2O then brine and dried. The crude product was first purified on silica gel with petrol:EtOAc (7:3, 1:1 then 1:3) as eluant then by preparative reverse phase HPLC (Spherex 5 C18, 250x10mm, mobile phase H_2O/MeOH 1:4, R_t 14.5 mins) to give crocacin C (**3**) (24.1mg, 51%)

as a white powder: R_f 0.50 (petrol:EtOAc, 1:1); $[\alpha]^{19}_{D}$ +61.3 (*c* 0.30, MeOH), lit.[1] $[\alpha]^{22}_{D}$ +52.2 (*c* 0.3, MeOH); IR υ_{max} (film) 3477, 3398, 3341, 3189, 2976, 2933, 1663, 1602, 1449, 1369, 1266, 1089, 973 cm^{-1}; UV λ_{max} (MeOH) 253 nm (ε 3.50×10^4 $Lmol^{-1}cm^{-1}$); ^{1}H NMR (400 MHz, d_6-acetone) δ 0.83 (d, *J* 6.8 Hz, 3H), 1.15 (d, *J* 7.2 Hz, 3H), 1.54 (m, 1H), 2.20 (d, *J* 1.2 Hz, 3H), 2.57 (m, 1H), 3.15 (dd, *J* 1.5, 9.6 Hz, 1H), 3.28 (s, 3H), 3.51 (s, 3H), 4.06-4.08 (m, 1H), 5.79 (s, 1H), 6.02-6.12 (m, 2H), 6.12 (br s, 1H), 6.24 (dd, *J* 7.2, 16.0 Hz, 1H), 6.57 (d, *J* 16.0 Hz, 1H), 6.70, (br s, 1H), 7.20-7.24 (m, 1H), 7.29-7.33 (m, 2H), 7.45-7.47 (m, 2H); ^{13}C NMR (100 MHz, d_6-acetone) δ 10.1, 13.4, 19.3, 40.8, 43.4, 56.4, 61.5, 81.7, 87.1, 122.0, 127.2, 128.2, 129.4, 130.4, 132.5, 135.0, 137.0, 137.8, 148.1, 169.0; HRMS (ESI) calc. for $C_{22}H_{31}NNaO_3$ [M+Na$^+$]: 380.2202. Found: 380.2201.

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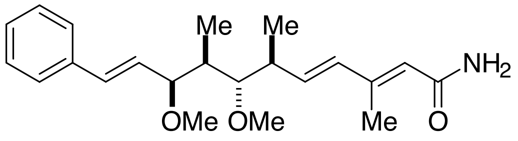
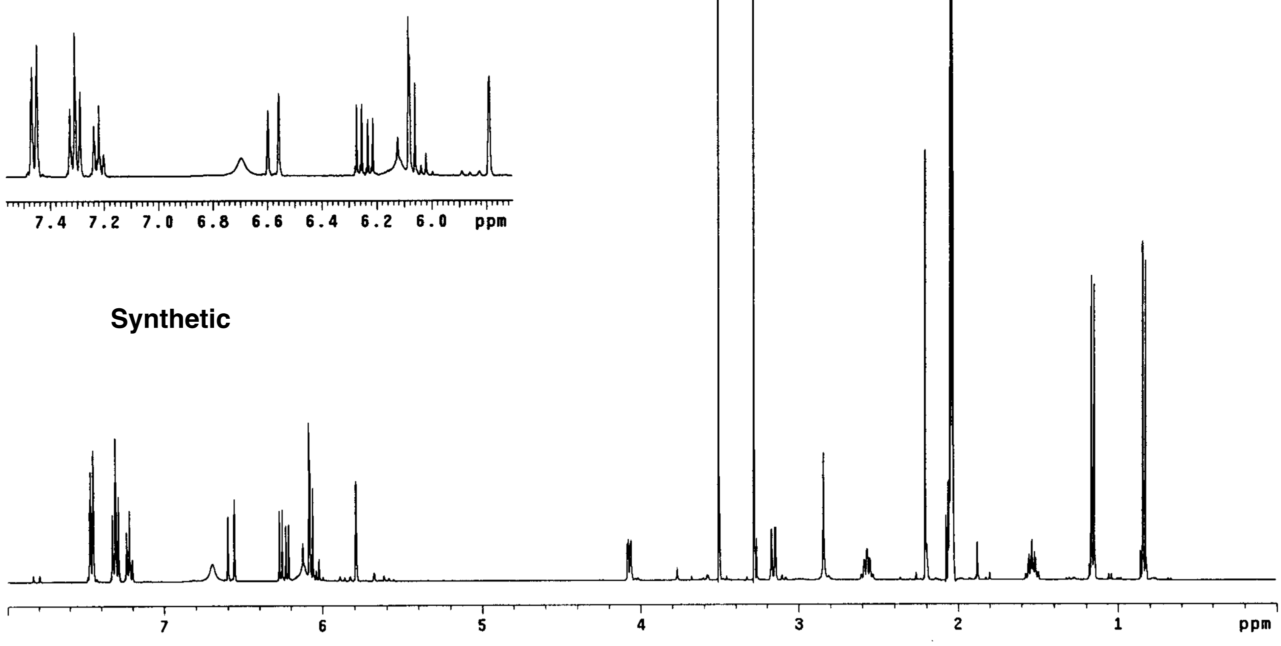
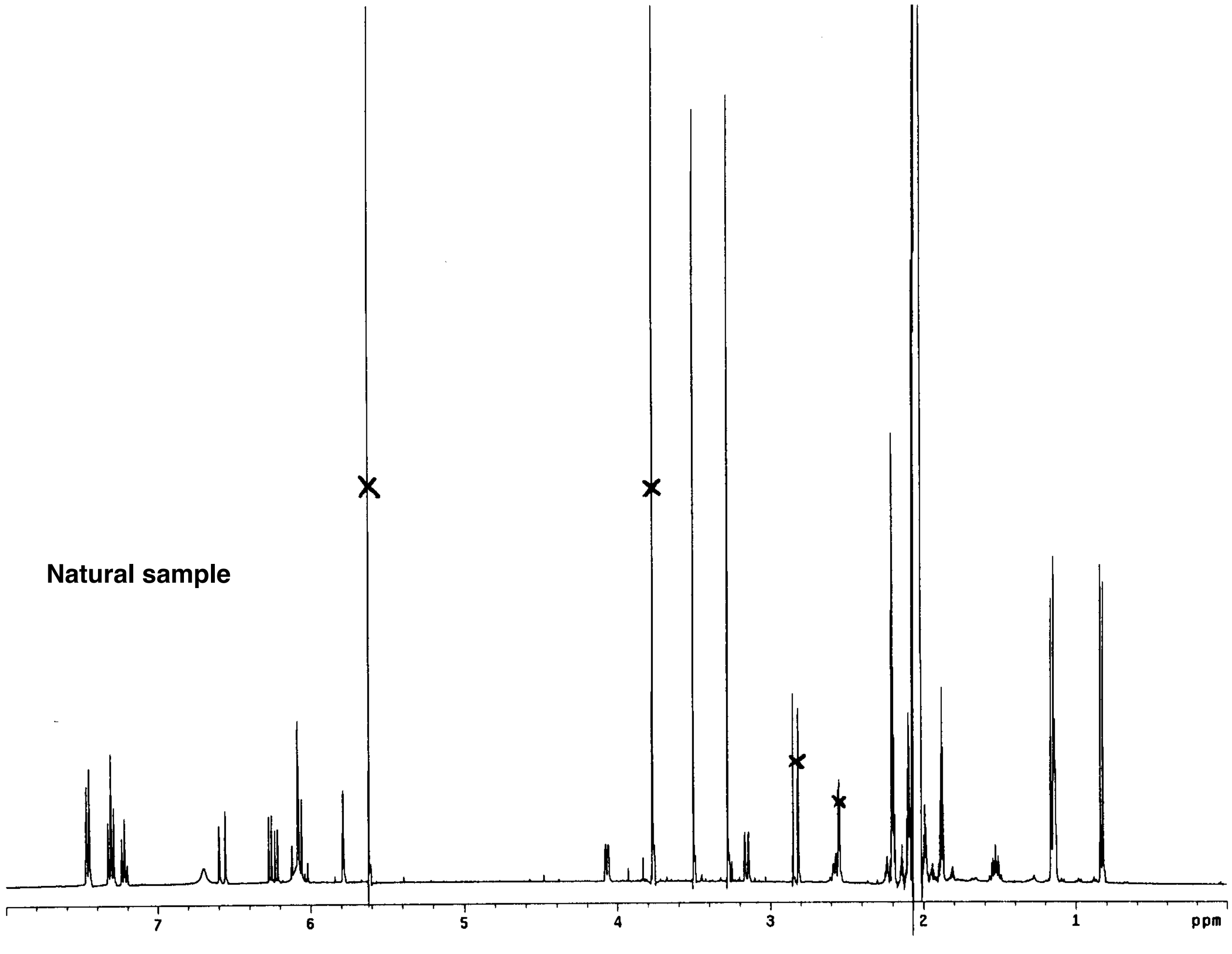
(1) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085-1089.

^{1}H NMR spectra (400 MHz, d_6-acetone)

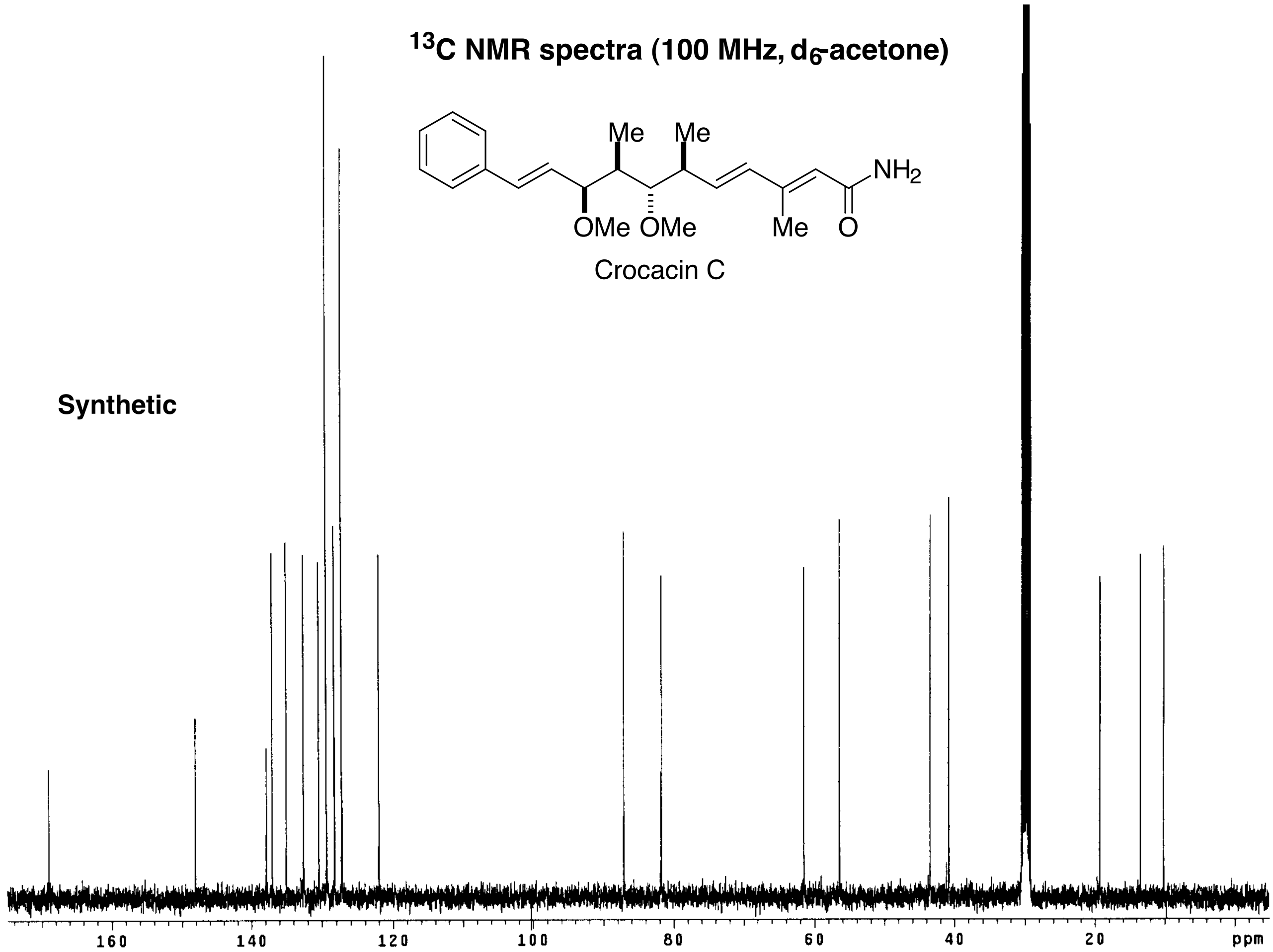


Crocacin C





^{13}C NMR spectra (100 MHz, d_6-acetone)


Crocacin C