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Unsaturated Amides Derived from 2-Amino-3-hydroxycyclopentenone: A Stille Approach to the Synthesis of Asuka-*m*ABA, 2880-II, and Limocrocin‡

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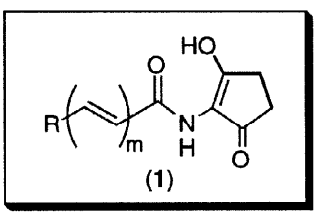
Abstract: A Stille palladium catalysed vinyl halide-vinyl stannane or aryl stannane coupling approach to the title compounds is described. The 2-aminocyclopentanedione-derived vinyl bromides (**12**, n = 1, 2, 3) were prepared and coupled to synthesise 2880-II (**4**), a *Streptomyces* metabolite, asuka-*m*ABA (**6**), obtained during investigations to elucidate the biogenesis of the antibiotic asukamycin, and limocrocin (**10**), a naturally occurring antibiotic and antiviral agent.

Unsaturated 2-amino-3-hydroxycyclopentenone derived amides (**1**) are produced by a large number of *Streptomyces* species, and many possess interesting biological properties.[1-17] In terms of the conjugated acid moiety, a range of different chain lengths (m = 1, 3, 4, 5, 7 *etc.*) are known (Figure 1).[18] The parent (m = 1) group includes the antifungal agent reductiomycin (AM-6201, **2**),[1,2] the related pyrrole reductiline (**3**),[3] substance 2880-II (**4**),[4,5] and more complex members such as bafiliomycin B_1[6] and virustomycin A (**5**).[7] Examples of higher vinylogues are asuka-*m*ABA (**6**),[8] isolated during studies to elucidate the biosynthesis of the antibiotic asukamycin, the *ras* farnesyltransferase inhibitor manumycin A,[9,10] other members of the manumycin family such as alisamycin (**7**)[11,12] and colabomycin (**8**),[13] the antibiotic enopeptin B (**9**),[14,15] and the antiviral agent limocrocin (**10**).[16,17]



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‡*This manuscript is dedicated to Professor Alan Katritzky to mark his 70th birthday, his many contributions to chemistry, and his pioneering work during the establishment of the School of Chemical Sciences at the University of East Anglia, Norwich.*

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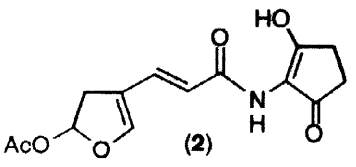
Figure 1



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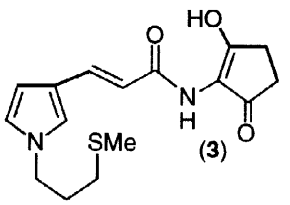

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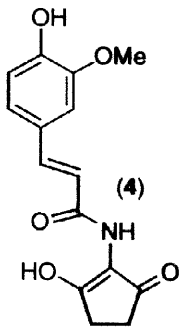

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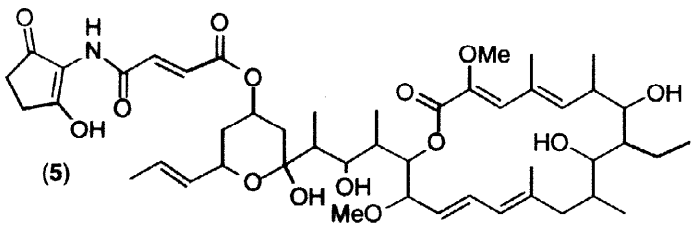

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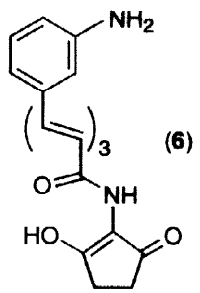

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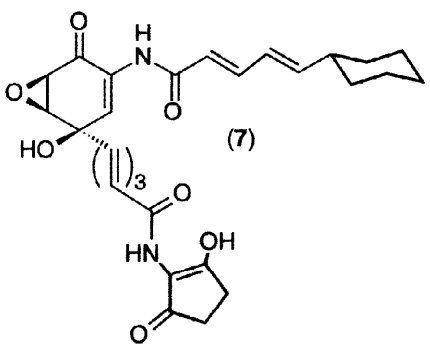

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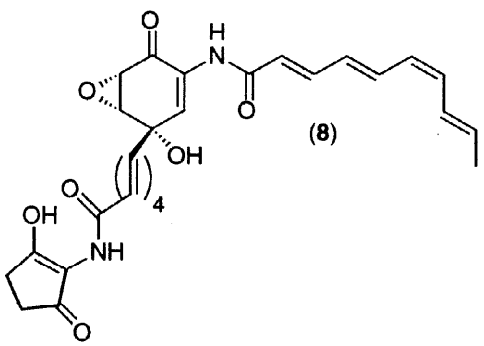
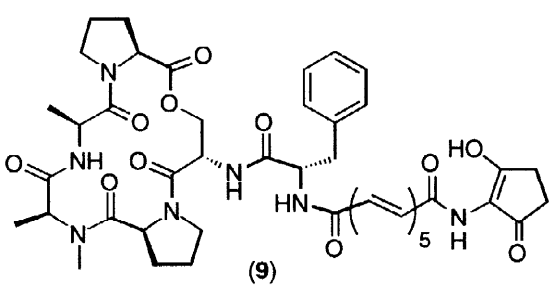


(8)



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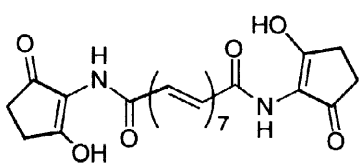
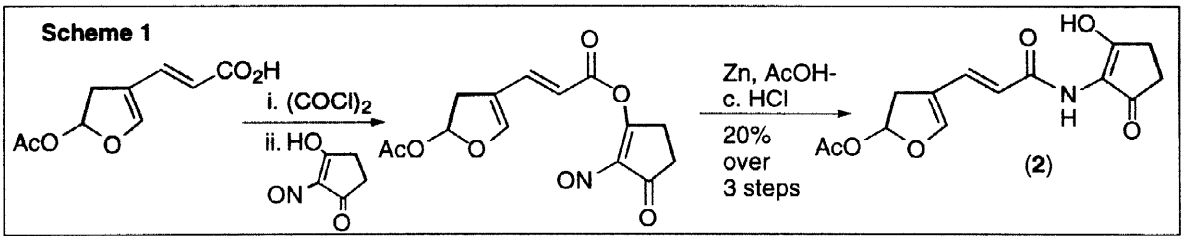


(10)

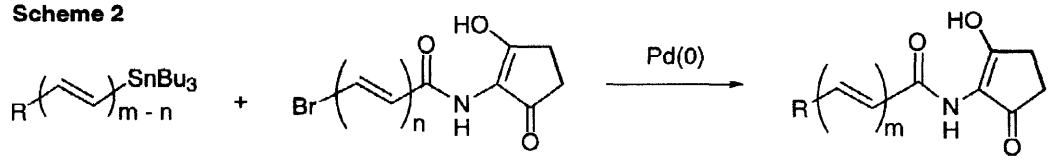
Scheme 1



Before the advent of the programme described herein, only three members of this family had succumbed to total synthesis. Reductiomycin (**2**) and reductiline (**3**) were prepared using a reductive O → N acyl migration procedure for the introduction of the 2-amino-3-hydroxycyclopentenone-derived unit (Scheme 1).[2,3] This sequence is ingenious, but it is low yielding and unsuitable for the more complex polyenes shown in Figure 1. In addition, 2880-II (**4**) was prepared using a direct acid chloride-amine coupling reaction to prepare the key amide bond,[5] and more recently a similar procedure has been employed during the synthesis of enopeptin B (**9**).[15]

We were interested in the development of efficient synthetic routes to compounds of general structure (**1**) and the use of this methodology for the preparation of natural products of biological interest. The synthetic approach we decided to investigate is based on the palladium mediated Stille coupling reaction[19,20] between vinylstannanes and 2-amino-3-hydroxycyclopentenone-derived vinyl halides, as shown in Scheme 2. Here we describe the successful implementation of this approach resulting in the syntheses of 2880-II (**4**), asuka-*m*ABA (**6**) and limocrocin (**10**), the last two for the first time.[21]

Scheme 2

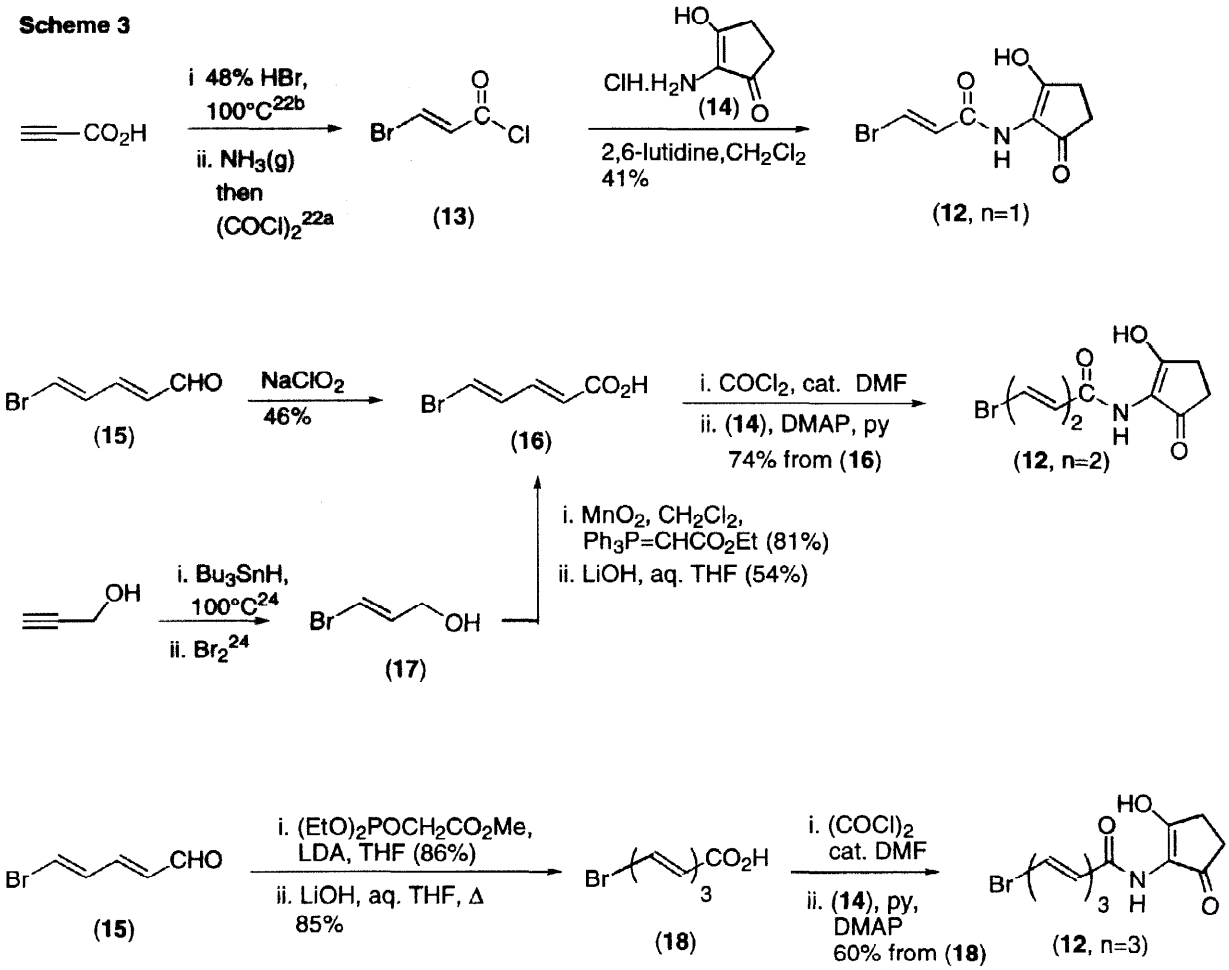


(**11**) (**12**) (**1**)

Preparation of the vinyl bromides (12)

We first set out to prepare the vinyl bromides (**12**, n = 1, 2, 3) using the procedures shown in Scheme 3. The key amine hydrochloride (**14**)[5,18] was prepared from cyclopentanedione using Ebenezer's procedure.[5] Acid chloride (**13**) is also known,[22a] being prepared from the corresponding acid, which can itself be obtained *via* the hydrobromination of propiolic acid.[22b] The coupling of acid chloride (**13**) and amine (**14**) to give the alkenyl bromide (**12**, n = 1) proved difficult but could be achieved by employing lutidine as the base and adding it dropwise to the reaction mixture. When pyridine was employed in place of lutidine, a lower yield of the adduct was obtained. For the two higher vinylogues (**12**, n = 2, 3), the starting material was bromodienal (**15**), readily prepared from potassium glutaconaldehyde.[23] Chlorite oxidation of aldehyde (**15**) gave the novel acid (**16**) as a crystalline solid. Acid (**16**) could also be prepared in four steps from propargyl alcohol *via* vinyl bromide (**17**).[24] The key to the success of this approach was the *in situ* manganese dioxide oxidation-Wittig reaction[25] of alcohol (**17**). Alcohol (**17**) was used as an *E/Z* mixture and further alkene isomerisation was observed during the saponification of the intermediate ester,[26] but the *E,E*-isomer (**16**) could be obtained in pure form by recrystallisation. The propargyl alcohol route to (**16**) was preferred when multi-gram amounts were required. Wadsworth-Emmons homologation-saponification of aldehyde (**15**) gave the trienoic acid (**18**). Acids (**16**) and (**18**) were readily converted into the corresponding amides by acid chloride formation and treatment with amine hydrochloride (**14**) in pyridine with catalytic DMAP. The configurations of vinyl bromides (**12**, n = 1, 2, 3) were established using ^{1}H-NMR spectroscopy [*e.g.* (**12**, n = 3), vinyl *J* values = 13, 15, 15 Hz].

Scheme 3



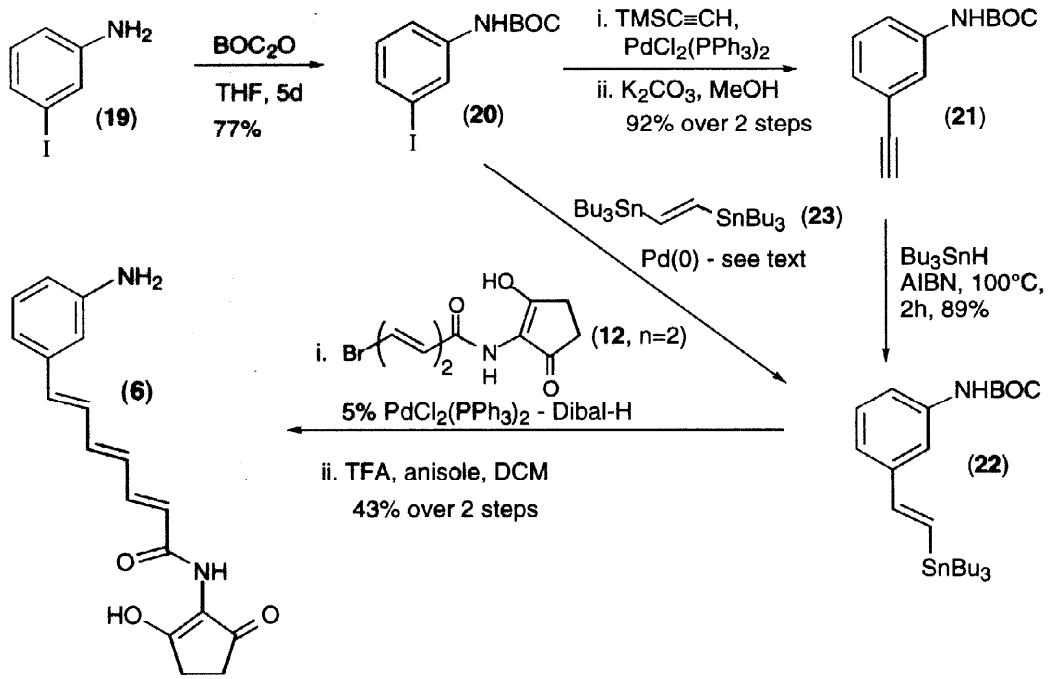
Stille coupling of the vinyl bromides (12)

We next set out to establish the viability of the Stille coupling reaction. The initial target was asuka-*m*ABA (**6**, Scheme 4), first produced by feeding *m*-aminobenzoic acid to *Streptomyces nodosus* ssp. *asukaensis* during studies to elucidate the biosynthesis of the antibiotic asukamycin.[8]

Commercially-available 3-iodoaniline (**19**) was *N*-protected and the resulting BOC derivative (**20**) was converted into alkyne (**21**) *via* a Sonogashira coupling-hydrolysis sequence. Hydrostannylation of alkyne (**21**) gave the requisite *E*-vinylstannane (**22**) in high overall yield. The direct conversion of iodide (**20**) into vinylstannane (**22**) by coupling with *E*-1,2-bis(tributylstannyl)ethene (**23**) was also explored but it was difficult to drive the reaction to completion and mixtures of (**20**) and (**22**) were inseparable by column chromatography. With $Pd(PPh_3)_4$ as catalyst in toluene at 100°C, the reaction did proceed to completion (52%), but the two step sequence was preferred.

The crucial Stille coupling of (**22**) and (**12**, n = 2) was investigated next. Catalysis with $PdCl_2(MeCN)_2$ or $Pd(PPh_3)_4$ was not particularly effective (slow reactions and/or mixtures produced) but the required transformation was efficiently achieved using Negishi's catalyst, $PdCl_2(PPh_3)_2$ (5 mol%) pre-reduced using Dibal-H.[20] Rigorous deoxygenation was required in order to prevent dimerisation of the vinylstannane,[27] but under these conditions efficient coupling yields were obtained. Deprotection of the crude product gave

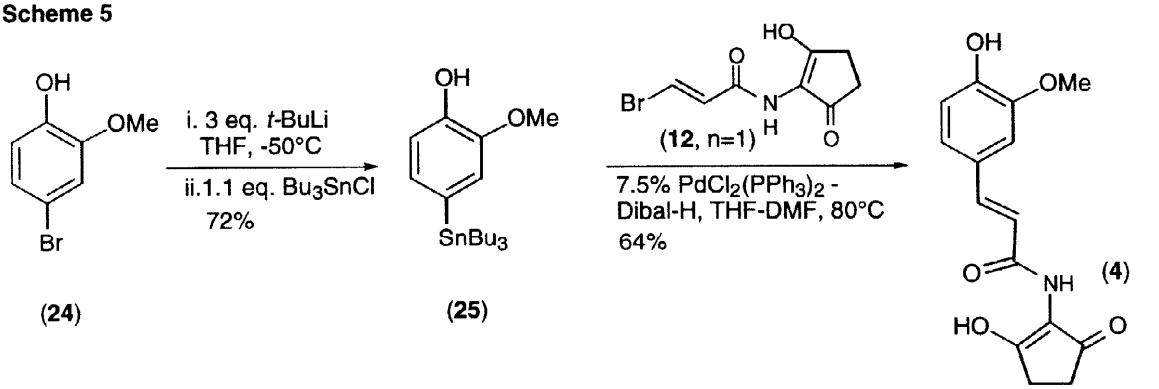
Scheme 4



asuka-*m*ABA (**6**)[8] in 43% yield over the two steps. This is the first chemical synthesis of this compound; the IR and UV data, as well as m.p. (m.p. 252°C, lit.[8b] m.p. 256°C) and R_f, were in accord with published values.[8] The two publications[8a,b] which report NMR data for (**6**) are inconsistent, but our data are in broad accord with the more recent publication.[8a]

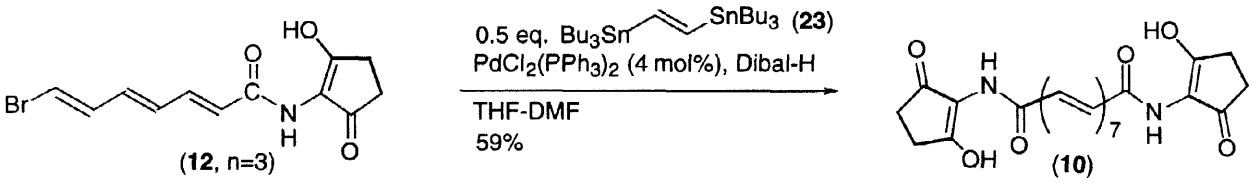
This methodology is also applicable to aryl stannane-vinyl bromide coupling, as shown in Scheme 5 for the preparation of 2880-II (**4**), a compound related to ferulic acid, which has been isolated from *Streptomyces griseoflavus*.[4] Substance 2880-II has been synthesised by Ebenezer[5] using an amide coupling procedure. With Stille coupling methodology the key precursor is aryl stannane (**25**), which was efficiently prepared from commercially available aryl bromide (**24**) *via* a one pot procedure. Thus, lithiation of (**24**) followed by trapping of the resultant dianion with tributyltin chloride gave (**25**) in 72% overall yield. Using the optimum Stille coupling conditions referred to above, at room temperature, the coupling reaction of arylstannane (**25**) with alkenyl bromide (**12**, n = 1) was extremely slow. Increasing the temperature to 80°C, however, gave 2880-II (**4**) in 64% yield with m.p. and NMR data consistent with published[4,5] values.

Scheme 5



Having established the value of the Stille coupling procedure utilising the two lower vinylogues (**12**, n = 1,2), we moved on to investigate the use of (**12**, n = 3). In this case, the target molecule was limocrocin (**10**). This novel 2-amino-3-hydroxycyclopentenone-derived diamide was isolated[16] from *Streptomyces limosus* and subsequently shown to be a specific inhibitor of reverse transcriptase.[17] We envisaged the construction of limocrocin *via* the highly convergent double Stille approach shown in Scheme 6. The double Stille coupling of *E*-1,2-bis(tributylstannyl)ethene (**23**) has also been employed for the preparation of rather more complex natural products.[28] Using a similar procedure to before, bromotrienamide (**12**, n = 3) underwent the required coupling giving limocrocin (**10**) in 59% yield. Once again, it was important to rigorously deoxygenate the reaction mixture in order to minimise by-product formation. This is the first reported synthesis of limocrocin, which was obtained as a highly insoluble red solid. UV and IR data were in accord with published[16] values and high resolution mass spectrometric data and fragmentation patterns were consistent with the assigned structure. In addition, for the first time, NMR data was obtained on limocrocin (as its disodium salt in D_2O).

Scheme 6



In summary, we have established that the Stille coupling reaction of vinyl bromides containing 2-amino-3-hydroxycyclopentenone-derived amides provides an efficient procedure for the preparation of natural products containing this functional group. We have shown that vinyl stannanes and aryl stannanes can be employed as coupling partners and have demonstrated the utility of the procedure by preparing the bioactive natural products 2880-II (**4**), asuka-*m*ABA (**6**), and limocrocin (**10**). We have subsequently employed this methodology to prepare alisamycin (**7**),[12] and are currently exploring its utility for the synthesis of other natural products.

General Directions

NMR spectra were recorded on Jeol GX-270 or Bruker AMX 500 instruments. Tetramethylsilane (TMS) or $CDCl_3/CHCl_3$ was used as the internal standard and *J* values are in Hz. Carbon spectra were verified using DEPT experiments. Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Ultraviolet (UV) spectra were recorded on a Hewlett Packard 8453 instrument. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high resolution mass spectra were recorded on a Micromass Autospec spectrometer. Elemental analyses were carried out at the University of East Anglia, Norwich. Chromatography is medium pressure flash column chromatography and was performed using ICN silica gel (32-63) or Matrex silica gel 60 (70-200) using the eluant specified. Preparative t.l.c. was carried out using pre-prepared plates (Merck silica gel 60 F-254, 5715). PE is petroleum ether (b.p. 40-60°C), DCM is dichloromethane, EtOAc is ethyl

acetate, ether is diethyl ether, THF is tetrahydrofuran, DMF is dimethylformamide. Where necessary, ether and THF were distilled from sodium-benzophenone ketyl, and DCM from calcium hydride, immediately before use. Water is distilled water. Except where specified, all reagents were purchased from commercial sources and were used without further purification. RT is room temperature. Amine hydrochloride (**14**), prepared by a published[5] procedure, was used immediately without purification (estimated 85% pure).

N-(2'-Hydroxy-5-oxocyclopent-1'-en-1'-yl)-3-bromopent-2E-enamide (12, n = 1)

Using a small amount of DCM to complete the transfer, β-bromoacryloyl chloride (**13**)[22a] (200 mg, 1.18 mmol) and dimethylaminopyridine (1mg) were added to a solution of amine hydrochloride (**14**)[5] (144 mg, *ca.* 85% pure, *ca.* 0.82 mmol) in dry dichloromethane (60 ml) at 0°C and under nitrogen atomosphere. A solution of 2,6-lutidine (0.10 ml) in dichloromethane (1 ml) was then added dropwise over about 4 h. The resulting mixture was warmed up to RT, and an additional solution of 2,6-lutidine (0.05 ml) in dichloromethane (0.5 ml) was slowly added over 6 h. The reaction mixture was stirred overnight and then concentrated (*ca.* 1 ml). Purification by column chromatography (DCM-methanol, 95:5) gave compound (**12**, n = 1) (83 mg, 41%) as a white solid, m.p. 223-4°C; R_f 0.30 (DCM-methanol, 10:1); $\nu_{max.}$ (nujol)/cm^{-1} 3240, 3073, 1692, 1595, 1342, 953, 774; δ_H (270 MHz; $CDCl_3$) 13.20 (1 H, s, OH), 8.09 (1 H, br s, NH), 7.65 (1 H, d, *J* 14, 3-H), 6.82 (1 H, d, *J* 14, 2-H), 2.53-2.64 (m, 4 H, 2 x CH_2), ; δ_C (67.5 MHz; $CDCl_3$) 197.5, 174.3, 163.2, 128.4, 126.5, 114.7, 32.1, 25.7; *m/z* (EI) 247 (M^+, 15%), 245 (M^+, 16%), 166 (100%); (Found: M^+, 244.9690. $C_8H_8BrNO_3$ requires 244.9688).

5-Bromopenta-2E,4E-dienoic acid (16)

(a) By oxidation of Dienal (15): A solution of sodium chlorite (622 mg, 6.88 mmol) and potassium dihydrogen orthophosphate (620 mg, 4.56 mmol) in water (2.5 ml) were added to a vigorously stirred solution of 5-bromopenta-2*E*,4*E*-dienal (**15**)[23] (100 mg, 0.62 mmol) and 2-methyl-but-2-ene (2 ml) in *tert*-butanol (7 ml). After stirring at RT overnight, the volatile components were evaporated and the residue extracted with DCM (5 x 30 ml). The combined organic layers were washed with water (50 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give an off-white solid. Purification by column chromatography (Et_2O) gave 5-bromo penta-2*E*,4*E*-dienoic acid (**16**) (51 mg, 46%) as a white solid, m.p. 175-177°C; R_f (Et_2O) 0.37; (Found: C, 34.14; H, 2.73. $C_5H_5BrO_2$ requires C, 33.93; H, 2.85%); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3944, 3691, 3054, 2987, 1724, 1693, 1421, 1267; δ_H (270 MHz; CD_3OD) 7.21 (1 H, dd, *J* 15.3, 10.2, 3-H), 7.03 (1 H, d, *J* 13.3, 5-H), 6.94 (1 H, dd, *J* 10.2, 13.3, 4-H), 5.95 (1 H, d, *J* 15.3, 2-H); δ_C (67.5 MHz; CD_3OD) 169.9, 142.9, 136.6, 123.5, 119.0; *m/z* (EI) 176 (M^+, 60%), 159 (87), 131 (33), 97 (86) (Found: M^+, 175.9474. $C_5H_5BrO_2$ requires 175.9473).

(b)[25] *From 3-Bromoprop-2-enol (17):* At RT and under nitrogen atomosphere, manganese dioxide (Aldrich, activated, 4.35 g, 50 mmol) was added in 5 portions over 5 h to a stirred solution of alcohol (**17**)[24] (*E*:*Z* = 3:1; 680 mg, 5 mmol) and (carboethoxymethylene)triphenylphosphorane (2.09 g, 6 mmol) in DCM (50 ml). The resulting reaction mixture was stirred for *ca.* 24 h until t.l.c. indicated that all of (17) had been consumed. The manganese dioxide was removed by filtration, washed with DCM, and the combined DCM portions were concentrated to *ca.* 1-2 ml. Column chromatography (PE-ether, 10:1) gave a stereoisomeric mixture of ethyl 5-bromopenta-2,4-dienoate[26] (0.82 g, 81%) as a colourless oil, R_f 0.6 (PE-ether, 3:1) which

was used directly. $LiOH{\cdot}H_2O$ (3.4 g, 81 mmol) in water (25 ml) was added in 3 portions over 20 min to a vigorously stirred solution of ethyl 5-bromo-penta-2,4-dienoate (2.05 g, 10 mmol) in THF (70 ml) at RT. The reaction mixture was stirred at 60°C for 1-2 h until no starting material was left (t.l.c.). The THF was removed under reduced pressure, the aqueous layer was neutralised with solid K_2HPO_4 and then extracted with ethyl acetate (5 x 50 ml). The solution was then acidified to *ca.* pH 6 (dil. H_2SO_4) and extracted with ethyl acetate until no further product could be detected by t.l.c (*ca.* 5 x 50 ml). The combined organic layers were dried over sodium sulphate and the solvent evaporated to give a crude product which was recrystallised (chloroform-PE) to give acid (**16**) (0.79 g). The mother liquid contained (**16**) plus stereoisomers; addition of a small piece of iodine to the solution and exposure to light for 10 h, followed by recrystallisation gave a second crop of (**16**) (0.17 g; total yield, 54%) with data as above.

N-(2'-Hydroxy-5-oxocyclopent-1'-en-1'-yl)-5-bromopenta-2E,4E-dienamide (12, n = 2)

A solution of oxalyl chloride (40 mg, 0.32 mmol) in DCM (2 ml) was added dropwise over 30 min to a stirred solution of 5-bromopenta-2*E*,4*E*-dienoic acid (**16**) (53 mg, 0.30 mmol) in DCM (7 ml) containing 3 drops of DMF at 0°C under nitrogen. After being stirred at RT for 1.5 h, this solution was added dropwise over 1 h to a mixture of 2-amino-3-hydroxy-2-cyclopenten-1-one hydrochloride (**14**)[5] (63 mg, *ca.* 85% pure, *ca.* 0.36 mmol) and 4-dimethylaminopyridine (8 mg) in dry pyridine (6 ml) at 0°C under nitrogen. After stirring at RT overnight, the pyridine was evaporated under reduced pressure (azeotroping with toluene). Purification by column chromatography (DCM-MeOH, 95:5) gave *N*-(2'-hydroxy-5-oxocyclopent-1'-en-1'-yl)-5-bromopenta-2*E*,4*E*-dienamide (**12**, n = 2) (60 mg, 74%) as a yellow solid, m.p. 232-233°C; R_f (DCM-MeOH, 95:5) 0.26; (Found: C, 44.29; H, 3.62; N, 5.00. $C_{10}H_{10}NO_3Br$ requires C, 44.14; H, 3.70; N, 5.15%); $\nu_{max.}$ (DCM)/cm^{-1} 3691, 3363, 3058, 2987, 1701, 1635, 1550, 1535, 1423, 1267, 1155; δ_H (270 MHz; $CDCl_3$) 13.37 (1 H, s, OH), 7.64 (1 H, s, NH), 7.16 (1 H, dd, *J* 14.5, 10.9, 3-H), 6.75-6.89 (2 H, m, 4-H, 5-H), 6.02 (1 H, d, *J* 14.5, 2-H), 2.51 (4 H, m, 2 x CH_2); δ_C (67.5 MHz; $CDCl_3$) 197.3, 173.9, 165.0, 141.0, 135.0, 121.2, 119.2, 114.8, 32.1, 25.6; *m/z* (EI) 271 (M^+, 81%), 192 (95), 159 (100) (Found: M^+, 270.9839. $C_{10}H_{10}NO_3Br$ requires 270.9844).

7-Bromohepta-2E,4E,6E-trienoic acid (18)

(i) A solution of methyl diethylphosphonoacetate (256 mg, 1.22 mmol) in THF (10 ml) was added dropwise over 1 h to a stirred solution of lithium diisopropylamide (2.0 *M* in THF, 0.59 ml, 1.18 mmol) in THF (5 ml) at -78°C under nitrogen. The reaction was maintained at -78°C for 1 h before being warmed to 0°C and treated dropwise over 30 min with 5-bromopenta-2*E*,4*E*-dienal (**14**)[23] (150 mg, 0.93 mmol) in THF (5 ml). After stirring at RT overnight, the reaction mixture was quenched with saturated ammonium chloride solution (50 ml) and extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (Et_2O-PE, 1:1) gave methyl 7-bromohepta-2*E*,4*E*,6*E*-trienoate (173 mg, 86%) as a pale yellow oil, R_f (Et_2O-PE, 1:1) which was fully characterised

(ii) A suspension of lithium hydroxide.monohydrate (81.5 mg, 1.94 mmol) in water (3 ml) was added to a stirred solution of methyl 7-bromohepta-2*E*,4*E*,6*E*-trienoate (140 mg, 0.65 mmol) in THF (10 ml) at RT. After heating at reflux for 4 h, THF was evaporated under reduced pressure and the residue diluted with

water (15 ml). The solution was neutralised to pH 7.0 by the portionwise addition of potassium dihydrogen orthophosphate and the product extracted into EtOAc (3 x 50 ml). After drying ($MgSO_4$), the solvent was evaporated under reduced pressure to give an off-white solid. Purification by column chromatography (EtOAc) gave 7-bromohepta-2*E*,4*E*,6*E*-trienoic acid (**18**) (110 mg, 85%) as a white solid, m.p. 199-200°C; R_f (EtOAc) 0.30; (Found: C, 41.59; H, 3.39. $C_7H_7O_2Br$ requires C, 41.41; H, 3.48%); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3693, 3523, 1720, 1691, 1626, 1576, 1415, 1307, 1282, 1109, 989, 933, 773; δ_H (270 MHz; CD_3OD) 7.26 (1 H, dd, *J* 15.2, 10.6, 3-H), 6.76 (1 H, dd, *J* 10.7, 13.5, 6-H), 6.53 (1 H, d, *J* 13.5, 7-H), 6.42 (1 H, dd, *J* 14.8, 10.7, 5-H), 6.36 (1 H, dd, *J* 10.6, 14.8, 4-H), 5.90 (1 H, d, *J* 15.2, 2-H); δ_C (67.5 MHz; CD_3OD) 167.8, 144.6, 138.1, 137.8, 131.9, 123.6, 114.1; *m/z* (EI) 202 (M^+, 30%), 157 (11), 123 (21), 79 (100) (Found: M^+, 201.9629. $C_7H_7O_2Br$ requires 201.9629).

N-(3'-Hydroxy-1'-oxocyclopent-2'-en-2'-yl)-7-bromohept-2E,4E,6E-trienamide (12, n = 3)

A solution of oxalyl chloride (29 mg, 0.23 mmol) in DCM (3 ml) was added dropwise over 30 min to a stirred solution of 7-bromohepta-2*E*,4*E*,6*E*-trienoic acid (43 mg, 0.21 mmol) (**18**) in DCM (7 ml) containing 3 drops of DMF at 0°C under nitrogen. After being stirred at RT for 1.5 h, this solution was added dropwise over 1 h to a mixture of 2-amino-3-hydroxy-2-cyclopenten-1-one hydrochloride (44 mg, *ca.* 85% pure, *ca.* 0.25 mmol) and 4-dimethylaminopyridine (5 mg) in dry pyridine (8 ml) at 0°C under nitrogen. After stirring at RT overnight, the pyridine was evaporated under reduced pressure (azeotroping with toluene). Purification by column chromatography (DCM-MeOH, 95:5) gave N-(3'-hydroxy-1'-oxocyclopent-2'-en-2'-yl)-7-bromohept-2*E*,4*E*,6*E*-trienamide (**12**, n = 3) (38 mg, 60%) as a yellow solid, m.p. 207-209°C; R_f (DCM-MeOH 95:5) 0.45; (Found: C, 48.47; H, 4.02; N, 4.52. $C_{12}H_{12}NO_3Br$ requires C, 48.34; H, 4.06; N, 4.70%); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3693, 3608, 3373, 3284, 3016, 2927, 2854, 1630, 1604, 1566, 1531, 1371, 1227, 999; δ_H [270 MHz; $(CD_3)_2CO$] 13.71 (1 H, s, OH), 8.83 (1 H, s, NH), 7.32 (1 H, dd, *J* 14.9, 11.1, 3-H), 6.97 (1 H, dd, *J* 10.6, 13.2, 6-H), 6.85 (1 H, d, *J* 13.2, 7-H), 6.72 (1 H, dd, *J* 14.9, 10.6, 5-H), 6.67 (1 H, d, *J* 14.9, 2-H), 6.55 (1 H, dd, *J* 11.1, 14.9, 4-H), 2.56 (4 H, br s, 2 x CH_2); δ_C [100 MHz; $(CD_3)_2CO$] 197.3, 174.4, 167.1, 143.5, 138.4, 138.2, 131.9, 123.7, 115.8, 114.5, 32.8, 26.2; *m/z* (EI) 297 (M^+, 31%), 218 (42), 185 (51) (Found: M^+, 296.9999. $C_{12}H_{12}NO_3Br$ requires 297.00005).

N-tert-Butoxycarbonyl-3-iodoaniline (20)

A solution of 3-iodoaniline (**19**) (8.5 g, 0.039 mol) and di-*tert*-butyldicarbonate (10.58 g, 0.048 mol) in THF (60 ml) were stirred at RT under nitrogen for 5 d. On completion, the reaction mixture was diluted with Et_2O (150 ml) and washed with water (60 ml), a 1:1 solution of saturated sodium hydrogencarbonate/water (60 ml), water (60 ml) and brine (50 ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a colourless oil. Purification by column chromatography (Et_2O-PE, 1:2), followed by recrystallisation from Et_2O-PE gave *N-tert*-butoxycarbonyl-3-iodoaniline (**20**)[29] (9.54 g, 77%) as a white crystalline solid, m.p. 74-75°C; R_f (Et_2O-PE 1:4) 0.47; $\nu_{max.}$ (nujol)/cm^{-1} 3293, 2924, 2854, 1712, 1690, 1594, 1531, 1466, 1366, 1284, 1242, 1162, 1053, 773; δ_H (270 MHz; $CDCl_3$) 7.83 (1 H, br s, 2-H), 7.35 (1 H, d, *J* 8.1, 6-H), 7.26 (1 H, d, *J* 8.1, 4-H), 6.98 (1 H, t, *J* 8.1, 5-H), 6.55 (1 H, br s, NH), 1.55 (9 H, s, ^{t}Bu); δ_C (67.5 MHz; $CDCl_3$) 152.4, 139.5, 131.7, 130.2, 127.1, 117.6, 94.2, 80.8, 28.2; *m/z* (CI) 337 (MNH_4^+, 52%), 320 (20) and 264 (50) (Found: M^+, 319.0061. $C_{11}H_{14}NO_2I$ requires 319.0069).

N-tert-Butoxycarbonyl-3-(ethynyl)aniline (21)

(i) (Trimethylsilyl)acetylene (**20**) (0.55 g, 5.60 mmol) was added in one portion to a vigorously stirred solution of *N-tert*-butoxycarbonyl-3-iodoaniline (1.5 g, 4.70 mmol), $Pd(PPh_3)_2Cl_2$ (165 mg, 0.24 mmol) and copper iodide (22 mg, 0.12 mmol) in triethylamine (60 ml) at RT under nitrogen. After heating at 50°C for 2 h, the reaction mixture was allowed to cool to RT, poured into 20% citric acid solution (200 ml) and extracted with Et_2O (3 x 100 ml). The combined organic layers were washed with 20% citric acid solution (80 ml), saturated sodium hydrogencarbonate solution (80 ml) and water (80 ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a brown oil. Purification by column chromatography (Et_2O-PE, 1:8) gave *N-tert*-butoxycarbonyl-3-(2'-trimethylsilylethynyl)aniline (1.25 g, 92%) as a pale brown solid, m.p. 137-139°C which was fully characterised.

(ii) A solution of *N-tert*-butoxycarbonyl-3-(2'-trimethylsilylethynyl)aniline (1.25 g, 4.32 mmol) and potassium carbonate (0.9 g) in MeOH (50 ml) was stirred at RT for 1 h. On completion, the potassium carbonate was removed by filtration and the MeOH evaporated under reduced pressure. The residue was then extracted with EtOAc (3 x 60 ml). The combined organic layers were washed with 20% citric acid solution (40 ml), saturated sodium hydrogencarbonate solution (40 ml) and water (40 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a pale yellow oil. Purification by column chromatography (Et_2O-PE, 1:8) gave *N-tert*-butoxycarbonyl-3-(ethynyl)aniline (**21**) (0.94 g, 100%) as a colourless oil; R_f (Et_2O-PE, 1:4) 0.45; $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3438, 3305, 2981, 2933, 1726, 1585, 1516, 1487, 1431, 1404, 1369, 1273, 1161, 1057, 868; δ_H (270 MHz; $CDCl_3$) 7.53 (1 H, br s, 2-H), 7.35 (1 H, d, *J* 7.7, 6-H), 7.21 (1 H, t, *J* 7.7, 5-H), 7.14 (1 H, d, *J* 7.7, 4-H), 6.69 (1 H, br s, NH), 3.04 (1 H, s, C≡CH) and 1.51 (9 H, s, ^{t}Bu); δ_C (67.5 MHz; $CDCl_3$) 152.6, 138.4, 128.8, 126.6, 121.8, 119.0, 122.6, 83.3, 80.7, 77.1, 28.2; *m/z* (CI) 235 (MNH_4^+, 60%), 218 (MH^+, 10), 117 (25) (Found: MNH_4^+, 235.1449. $C_{13}H_{19}N_2O_2$ requires 235.1446).

N-tert-Butoxycarbonyl-3-(2'-tri-n-butylstannylethenyl)aniline (22)

A solution of tri-*n*-butyltin hydride (0.70 g, 2.41 mmol), azoisobutyronitrile (2 mg) and *N-tert*-butoxycarbonyl-3-(ethynyl)aniline (**21**) (0.35 g, 1.61 mmol) were heated at 100°C for 1 h. On completion, the mixture was cooled to RT and purified directly by column chromatography (Et_2O-PE, 1:8) to give *N-tert*-butoxycarbonyl-3-(2'-tri-*n*-butylstannylethenyl)aniline (**22**) (0.73 g, 89%) as a colourless oil; R_f (Et_2O-PE, 1:8) 0.60; $\nu_{max.}$ (film)/cm^{-1} 3336, 2956, 2925, 2852, 1715, 1705, 1605, 1575, 1527, 1483, 1367, 1235, 1163, 1053, 873; δ_H (400 MHz; $CDCl_3$) 7.48 (1 H, br s, 2-H), 7.25 (1 H, t, *J* 7.9, 5-H), 7.17 (1 H, d, *J* 7.9, 6-H), 7.11 (1 H, d, *J* 7.9, 4-H), 6.88 (1 H, d, *J* 19.4, 1'-H), 6.83 (1 H, d, *J* 19.4, 2'-H), 6.50 (1 H, br s, NH), 1.53 (9 H, s, ^{t}Bu), 0.86-1.63 (27 H, m, Bu_3Sn); δ_C (67.5 MHz; $CDCl_3$) 152.8, 145.7, 139.7, 138.6, 130.2, 129.0, 120.8, 117.6, 116.0, 80.5, 28.4, 29.0, 27.3, 13.7, 9.6; *m/z* (CI) 527 (MNH_4^+, 100%) 508 (MH^+, 75) (Found: M-Bu^+, 450.1599. $C_{21}H_{34}NO_2{}^{118}Sn$ requires 450.1606).

Asuka mABA (6)

(i) A solution of Dibal-H (1.0 *M* in THF; 0.11 ml, 0.11 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (38 mg, 0.05 mmol) in THF (2 ml) at RT under nitrogen. After stirring at RT for 5 min, 0.1 ml of the solution was removed and used immediately in the following coupling reaction.

Solutions of *N-tert*-butoxycarbonyl-3-(2'-tri-*n*-butylstannylethenyl)aniline (34 mg, 0.067 mmol) in DMF (0.5 ml) and dienamide (**12**, n = 2) (20 mg, 0.074 mmol) in DMF (0.5 ml) were added in rapid succession to a vigorously stirred solution of the pre-generated catalyst in THF (0.1 ml) at RT under nitrogen. After stirring at RT for 12 h, the reaction mixture was poured into water (20 ml) and extracted with EtOAc (3 x 40 ml). The combined organic layers were washed with water (30 ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give an oily solid. Purification by preparative t.l.c. (DCM-EtOAc, 4:6) gave *N*-(2'-hydroxy-5'-oxocyclopent-1'-en-1'-yl)-7-(3'-*tert*-butoxycarbonylamidophenyl)hepta-2*E*,4*E*,6*E* -trienamide (19 mg, 70%) as a yellow waxy solid; R_f ($CHCl_3$-MeOH, 9:1) 0.40, which was fully characterised.

(ii) A solution of *N*-(2'-hydroxy-5'-oxocyclopent-1'-en-1'-yl)-7-(3'-*tert*-butoxycarbonylamidophenyl)hepta-2*E*,4*E*,6*E*-trienamide (15 mg, 0.04 mmol) in DCM (1 ml) was added to a stirred solution of anisole (7.5 mg) and DCM-CF_3CO_2H (4:1, 2 ml) at RT under nitrogen. After stirring at RT for 1 h, the reaction mixture was poured into saturated sodium hydrogencarbonate solution (30 ml) and extracted with EtOAc (3 x 40 ml). The combined organic layers were washed with water (30 ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a dull yellow solid. Purification by column chromatography (DCM-MeOH, 9:1) gave asuka-*m*ABA (**6**) (7 mg, 62%) as a yellow solid, m.p. 252°C (lit.[8b] 256°C); R_f ($CHCl_3$-MeOH, 9:1) 0.36; $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3689, 3631, 3374, 2944, 1629, 1602, 1559, 1530, 1373, 1016; $\lambda_{max.}$ (MeOH)/nm 342, 259; δ_H (400 MHz; $CDCl_3$) 13.68 (1 H, s, OH), 7.48 (1 H, br s, NH), 7.41 (1 H, dd, *J* 14.6, 11.5, 3-H), 7.15 (1 H, t, *J* 7.9, 12-H), 6.85 (1 H, m, 11-H), 6.84 (1 H, dd, *J* 10.8, 15.0, 6-H), 6.77 (1 H, br s, 9-H), 6.77 (1 H, dd, *J* 14.2, 10.8, 5-H), 6.69 (1 H, d, *J* 15.0, 7-H), 6.64 (1 H, d, *J* 7.9, 13-H), 6.45 (1 H, dd, *J* 11.5, 14.2, 4-H), 6.01 (1 H, d, *J* 14.6, 2-H), 2.54-2.64 (4 H, m, 2 x CH_2); δ_C (100 MHz; DMSO) 166.0, 148.8, 142.4, 141.2, 137.3, 136.9, 129.8, 129.1, 127.4, 121.2, 114.8 (2 x C), 114.4, 111.9 (as in the literature,[8b] only one hydroxycyclopentenone carbon is observed); *m/z* (EI) 310 (M^+, 24%), 198 (32), 170 (100), 132 (94) (Found: M^+, 310.1324. $C_{18}H_{18}N_2O_3$ requires 310.1317).

2-Methoxy-4-(tributylstannyl)-phenol (25)

tert-Butyllithium (1.7 M in pentane, 4.34 ml, 7.4 mmol) was added to a solution of 4-bromo-2-methoxyphenol (**24**) (500 mg, 2.46 mmol) in THF (12 ml) cooled to -78°C at such a rate that the internal temperature did not exceed -50°C (milky yellow solution). The mixture was stirred at -50°C for an additional 20 min, and then tributyltin chloride (0.74 ml, 2.73 mmol) was added in a single portion. The resulting colourless solution was stirred for 1 h at -50°C, then quenched with 10% aqueous potassium fluoride (7 ml), and the reaction allowed to warm to RT. The mixture was diluted with EtOAc (20 ml), washed with brine (5 ml), dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (PE-Et_2O, 9:1) gave stannane (**25**) (730 mg, 72%) as a colourless liquid, R_f 0.50 (PE-EtOAc, 95:5); $\nu_{max.}$ (NaCl))/cm^{-1} 3421, 2956, 2926, 2872, 2952, 1579, 1500, 1464, 1257, 1222, 1126, 1072, 1036; δ_H (500 MHz, $CDCl_3$) 7.00 (3 H, m, 3-H, 5-H, 6-H), 3.89 (3H, s, OMe), 1.70-1.50 (6 H, m, 3 x CH_2), 1.50-1.30 (6 H, m, 3 x CH_2), 1.15-1.00 (6 H, m, 3 x CH_2), 0.89 (9 H, t, *J* = 7.5, 3 x CH_3); δ_C (125 MHz, $CDCl_3$) 146.5, 145.7, 131.7, 129.7, 117.9, 114.5, 55.8, 29.1, 27.3, 13.6, 9.7 [Found (EI): 353.0866. $C_{15}H_{25}O_2{}^{116}Sn$ (M^+ - Bu) requires 353.0872].

2880-II (4)

A solution of Dibal-H (1.0 *M* in THF, 0.015 ml, 0.015 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (4.20 mg, 0.006 mmol) in tetrahydrofuran (0.2 ml) at RT under nitrogen. After stirring for 10 min, a solution of stannane (**25**) (50.0 mg, 0.13 mmol) followed by a solution of bromodiene (**12**, n = 1) (20.0 mg, 0.081 mmol) respectively in dry and degassed DMF (0.4 ml) were added to the solution of the pre-reduced catalyst at RT. The reaction was stirred for 16 h at 80°C, then the solvent was removed under high vacuum. The crude product was purified by preparative t.l.c. (DCM-MeOH, 95:5) to give product (**4**) (15 mg, 64%) as a yellow powder, m.p. 269-270°C (lit. 272°C,[4] 265-268°C[5]); R_f 0.26 (DCM-MeOH, 95:5); $\nu_{max.}$ ($CHCl_3$)/ cm^{-1} 3234, 2958, 2924, 2852, 1691, 1620, 1605, 1514, 1396, 1273, 1159, 1126, 1032; δ_H (500 MHz, $CDCl_3$) 13.50 (1 H, br s, enol OH), 7.66 (1 H, d, *J* 15.5, 3-H), 7.48 (1 H, br s, NH), 7.11 (1 H, dd, *J* 2.0, 8.0, 6'-H), 7.04 (1 H, d, *J* 2.0, 2'-H), 6.95 (1 H, d, *J* 8.0, 5'-H), 6.39 (1 H, d, *J* 15.5, 2-H), 5.86 (1 H, br s, Ar-OH), 3.96 (3 H, s, OMe), 2.65-2.60 (2 H, m, CH_2), 2.58-2.50 (2 H, m, CH_2); δ_C (125 MHz, $CDCl_3/CD_3OD$, 4:1): 166.3, 148.8, 147.5, 144.2, 126.3, 122.8, 115.1 (2 x C), 114.5, 110.4, 55.6 (as in the literature,[4,5] only one hydroxycyclopentenone carbon is observed); *m/z* (EI) 289 (M^+, 20), 177 (60), 149 (100) (Found: M^+, 289.09566. $C_{15}H_{15}NO_5$ requires: 289.09502).

Limocrocin (10)

A solution of Dibal-H (1.0 *M* in THF; 0.14 ml, 0.14 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) in THF (1 ml) at RT under nitrogen. After stirring at RT for 5 min, 0.1 ml of this solution was removed and used immediately in the following coupling reaction.

A solution of *E*-1,2-*bis*(tri-*n*-butylstannyl)ethene[30] (51 mg, 0.084 mmol) in dry, degassed DMF (0.5 ml) and trienamide (**12**, n = 3) (50 mg, 0.17 mmol) in dry, degassed DMF (0.5 ml) were added in rapid succession to a vigorously stirred solution of the pre-generated catalyst in THF (0.2 ml) at RT under nitrogen. After stirring at RT overnight, the precipitated product was extracted into saturated sodium hydrogencarbonate solution (20 ml). This layer was then washed with EtOAc (3 x 50 ml) and then acidified to pH 6.0 with 1 *M* hydrochloric acid. From this solution, the product precipitated overnight and was isolated by a centrifuge separation. Final purification was achieved by washing the product with acetone (2 x 10 ml). This gave limocrocin (**10**) (23 mg, 59%) as a red solid, m.p. 300°C (dec.) [lit.[10] 316°C (dec.)]; $\lambda_{max.}$ [(0.4 *M* Na_2CO_3)/nm 420, 258 (lit.[16] 420, 260)]; δ_H (400 MHz; D_2O, Na^+ salt) 7.22 (2 H, dd, *J* 15.0, 11.3, 3-H), 6.40-6.73 (10 H, m, 4-H, 5-H, 6-H, 7-H, 8-H), 6.15 (2 H, d, *J* 15.0, 2-H), 2.38 (8 H, s, 4 x CH_2); δ_C (100 MHz; D_2O, Na^+ salt) 203.7, 171.0, 144.4, 143.5, 139.9, 138.2, 136.8, 134.1, 125.6, 114.1, 33.3; *m/z* (EI) 462 (M^+ 31%) (Found: M^+, 462.1802. $C_{26}H_{26}N_2O_6$ requires 462.1791).

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