A Stille approach to unsaturated amides derived from 2-amino-3-hydroxycyclopentenone: the synthesis of asuka-mABA and limocrocin

Gregor Macdonald,[a] Norman J. Lewis[b] and Richard J. K. Taylor[a]*

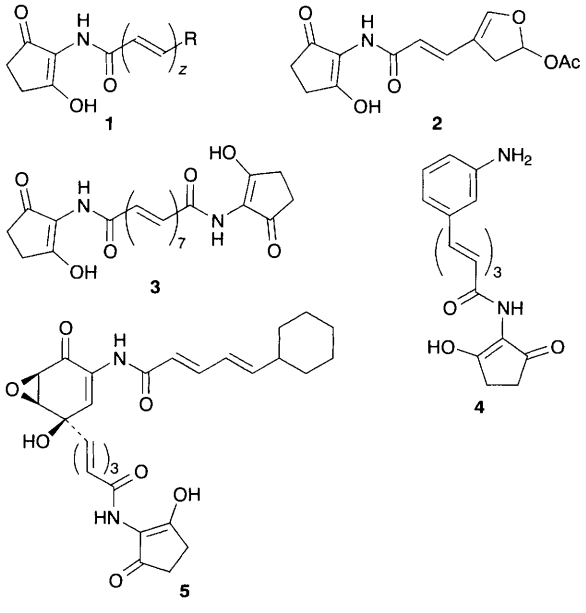
[a] *Department of Chemistry, University of York, Heslington, York, UK YO1 5DD*
[b] *SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge, Kent, UK TN11 9AN*

A Stille palladium-catalysed vinyl halide–vinyl stannane coupling approach to the title compounds is described.

The structural unit **1** is common to a range of biologically active natural products. These include the antifungal agent reductiomycin **2**,[1] the antiviral antibiotic limocrocin **3**,[2] the biosynthetic antibiotic precursor asuka-mABA **4**,[3] the antibiotic colabomycin,[4] the *ras* farnesyltransferase inhibitor manumycin A[5] and other members of the manumycin family such as alisamycin **5**,[6] as well as more complex antibiotics such as virustomycin A,[7] bafilomycin B_1[8] and moenomycin.[9] Of these compounds, only reductiomycin **2** has succumbed to total synthesis.[10] The O→N acyl migration procedure used for the introduction of the 2-amino-3-hydroxycyclopentenone-derived unit in the successful synthesis is ingenious but it is low yielding and unsuitable for the more complex, acid-labile polyenes **3**–**5**.

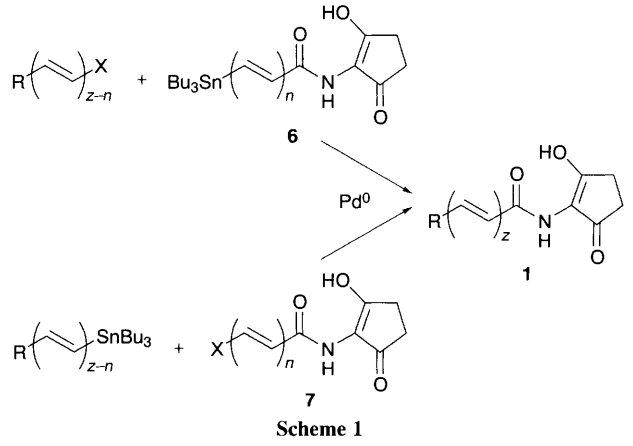
We were interested in the development of efficient synthetic routes to compounds of general structure **1** and the use of this methodology to prepare natural products of biological interest. Here we describe the successful implementation of this aim resulting in the first chemical syntheses of asuka-mABA **4** and limocrocin **3**. We have also recently utilised this methodology in the first total synthesis of alisamycin **5**.[11] The synthetic approach we decided to investigate is based on the Stille palladium-catalysed coupling reaction[12] between vinyl halides and vinyl stannanes, as shown in Scheme 1.

Initial studies were directed towards the synthesis of the aminocyclopentanedione-derived vinyltin reagent **6** (n = 3), but these were problematic and so we concentrated on the preparation of the complementary vinyl bromide systems **7**.

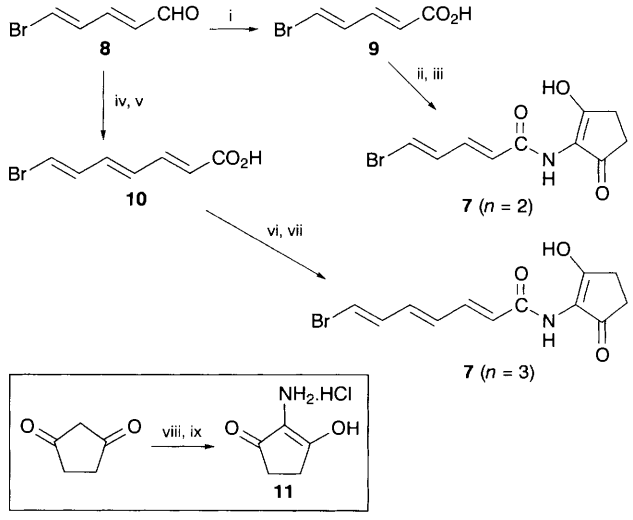


In view of the accessibility of bromodienal **8**,[13] we initially targeted amide **7** in the n = 2 series (Scheme 2).†

Oxidation of aldehyde **8** using sodium chlorite proceeded efficiently to give acid **9**. This acid was converted into the corresponding acid chloride, which was treated *in situ* with amine hydrochloride **11**, readily prepared[14] from cyclopentane-1,3-dione, as shown. This sequence produced the required bromide **7** (n = 2). Wittig homologation–saponification of **8** gave triene acid **10**, which was elaborated to the higher vinylogue **7** (n = 3). The all-*trans* structures of compounds **7** were confirmed by ^{1}H NMR spectroscopy [**7** (n = 2): J 13.5, 15.0 Hz; (n = 3): J 13.2, 14.85, 14.85 Hz].



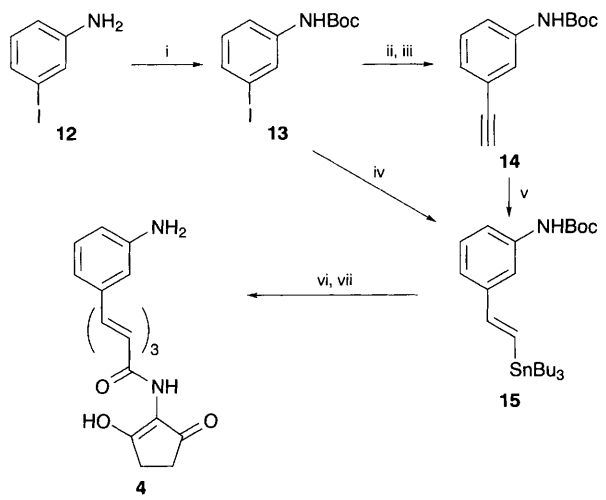
Scheme 1



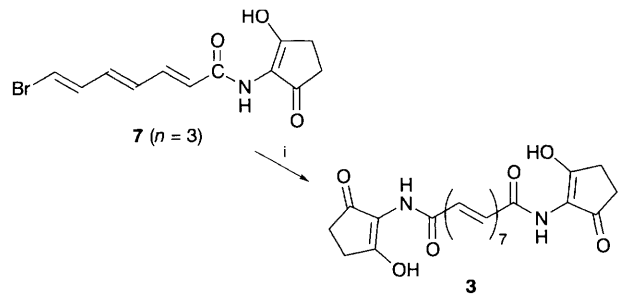
Scheme 2 *Reagents and conditions*: i, $NaClO_2$, 72%; ii, $COCl_2$, cat. DMF; iii, **11**, DMAP, pyridine, 74% from **9**; iv, $(EtO)_2P(O)CH_2CO_2Me$, LDA, THF; v, LiOH, aq. THF, heat, 88% from **8**; vi, $COCl_2$, cat. DMF; vii, **11**, DMAP, pyridine, 63% from **10**; viii, NO_2(gas), Et_2O; ix, H_2, PtO_2, HCl, AcOH (ref. 14)

In order to establish the viability of the Stille coupling approach outlined in Scheme 1, we first looked at the synthesis of asuka-mABA **4** as shown in Scheme 3. Commercially available 3-iodoaniline **12** was N-protected and the resulting Boc derivative **13** converted into alkyne **14** *via* a Sonogashira coupling-hydrolysis sequence. Hydrostannylation of alkyne **14** gave the requisite *E*-vinylstannane **15** in high overall yield. The direct conversion of iodide **13** into vinylstannane **15** by coupling with (*E*)-1,2-bis(tributylstannyl)ethene[15] was also explored but it was difficult to drive the reaction to completion and mixtures of **13** and **15** were inseparable by column chromatography [the use of $Pd(PPh_3)_4$, toluene, 100 °C did produce **15** in 52% yield but the 2 step sequence was preferred]. The Stille coupling of **15** and **7** (n = 2) was investigated next. Coupling using $PdCl_2(MeCN)_2$ or $Pd(PPh_3)_4$ gave a complex product mixture but clean transformation was achieved using $PdCl_2(PPh_3)_2$ (4 mol%) which was pre-reduced using DIBAL-H.[16] Deprotection of the adduct gave asuka-mABA **4**, the biosynthetic precursor of the antibiotic asukamycin.[3] This is the first chemical synthesis of this compound; the NMR, IR, UV and mass spectral data, as well as mp and R_f, were in accord with published values.‡

Using a similar procedure, the higher vinylogue **7** (n = 3) was utilised in a double coupling with (*E*)-1,2-bis(tributylstannyl)ethene as shown in Scheme 4. This provides a very convenient method for the preparation of the antiviral antibiotic limocrocin **3**.[2] 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[2] 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 the disodium salt in D_2O).§



Scheme 3 *Reagents and conditions*: i, Boc_2O, THF, 5 d, 80%; ii, $Me_3SiC{\equiv}CH$, Et_3N, $Pd(PPh_3)_2Cl_2$; iii, K_2CO_3, MeOH, 92% from **13**; iv, $Bu_3SnCH{=}CHSnBu_3$, Pd^0 (see text); v, Bu_3SnH, AIBN, 100 °C, 2 h, 86%; vi, **7** (n = 2), Pd^0 (see text); vii, TFA, CH_2Cl_2, 60% from **15**



Scheme 4 *Reagents and conditions*: i, $Bu_3SnCH{=}CHSnBu_3$ (0.5 equiv.), $PdCl_2(PPh_3)_2$ (4 mol%), DIBAL-H, THF–DMF, 59%

We are currently exploring the utility of the methodology for the synthesis of manumycin A and related compounds.[11]

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Footnotes

† All new compounds were fully characterised by ^1H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.

‡ For example: R_f = 0.36 (lit.,[3a] 0.35; $CHCl_3$–MeOH, 9 : 1); mp 252 °C (lit.,[3a] 172 °C; lit.,[3b] 256 °C); $\delta_H(CDCl_3$, 400 MHz) 13.68 (1 H, s, enol-OH), 7.48 (1 H, br s, NH), 7.41 (1 H, dd, J 14.6, 11.5 Hz, 3-H), 7.15 (1 H, t, J 7.9 Hz, Ar-H), 6.85 (1 H, m, Ar-H), 6.84 (1 H, dd, J 10.8, 15.0 Hz, 6-H), 6.77 (1 H, br s, Ar-H), 6.77 (1 H, dd, J 10.8, 14.2 Hz, H-5), 6.69 (1 H, d, J 15.0 Hz, H-7), 6.64 (1 H, d, J 7.9 Hz, Ar-H), 6.45 (1 H, dd, J 11.5, 14.2 Hz, 4-H), 6.01 (1 H, d, J 14.6 Hz, 2-H), 2.54–2.64 (4 H, m, 2 × CH_2); ^1H and ^{13}C NMR in $(CD_3)_2SO$ were consistent with published[3a] data [Found (EI): 310.1324. $C_{18}H_{18}N_2O_3$ requires M, 310.1317 (2 ppm error)].

§ For example: mp 300 °C (decomp.) [lit.,[2] 316 °C (decomp.)]; λ_{max} (0.4 M Na_2CO_3)/nm 420, 258 [lit.,[2] 420, 260]; $\delta_H(D_2O$, 400 MHz, sodium salt) 6.15 (2 H, d, J 15.0 Hz, 2-H), 7.22 (2 H, dd, J 15.0, 11.25 Hz, 3-H), 6.40–6.73 (10 H, m), 2.38 (8 H, s, 4 × CH_2); δ_C(100 MHz, D_2O sodium salt) 203.7, 171.0, 144.4, 143.5, 139.9, 138.2, 136.8, 134.1, 125.6, 114.1, 33.3 [Found (EI): 462.180219. $C_{26}H_{26}N_2O_6$ requires M, 462.179087 (2 ppm error)].

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