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

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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 B₁⁸ and moenomycin.⁹ Of these compounds, only reductiomycin **2** has succumbed to total synthesis.¹⁰ The O \rightarrow 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 reaction¹² 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 $\mathbf{8}^{13}$ 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 prepared¹⁴ 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 ¹H NMR spectroscopy [7 (n = 2): J 13.5, 15.0 Hz; (n = 3): J 13.2, 14.85, 14.85 Hz].



Scheme 2 Reagents and conditions: i, NaClO₂, 72%; ii, COCl₂, cat. DMF; iii, **11**, DMAP, pyridine, 74% from **9**; iv, (EtO)₂P(O)CH₂CO₂Me, LDA, THF; v, LiOH, aq. THF, heat, 88% from **8**; vi, COCl₂, cat. DMF; vii, **11**, DMAP, pyridine, 63% from **10**; viii, NO₂(gas), Et₂O; ix, H₂, PtO₂, HCl, AcOH (ref. 14)

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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)ethene¹⁵ 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(PPh₃)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 PdCl₂(MeCN)₂ or Pd(PPh₃)₄ gave a complex product mixture but clean transformation was achieved using PdCl₂(PPh₃)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 $R_{\rm f}$, 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 published² 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 D₂O).§



Scheme 3 Reagents and conditions: i, Boc₂O, THF, 5 d, 80%; ii, Me₃SiC=CH, Et₃N, Pd(PPh₃)₂Cl₂; iii, K₂CO₃, MeOH, 92% from 13; iv, Bu₃SnCH=CHSnBu₃, Pd⁰ (see text); v, Bu₃SnH, AlBN, 100 °C, 2 h, 86%; vi, 7 (n = 2), Pd⁰ (see text); vii, TFA, CH₂Cl₂, 60% from 15



Scheme 4 Reagents and conditions: i, Bu₃SnCH=CHSnBu₃ (0.5 equiv.), PdCl₂(PPh₃)₂ (4 mol%), DIBAL-H, THF-DMF, 59%

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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 ¹³C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.

‡ For example: $R_f = 0.36$ (lit.,^{3a} 0.35; CHCl₃–MeOH, 9:1); mp 252 °C (lit.,^{3a} 172 °C; lit.,^{3b} 256 °C); $\delta_{\rm H}$ (CDCl₃, 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, 4-H), 6.01 (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 × CH₂); ¹H and ¹³C NMR in (CD₃)₂SO were consistent with published^{3a} data [Found (EI): 310.1324. C₁₈H₁₈N₂O₃ requires *M*, 310.1317 (2 ppm error)].

§ For example: mp 300 °C (decomp.) [lit., ² 316 °C (decomp.)]; λ_{max} (0.4 M Na₂CO₃)/nm 420, 258 [lit., ² 420, 260]; δ_{H} (D₂O, 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 × CH₂); δ_{C} (100 MHz, D₂O 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. C₂₆H₂₆N₂O₆ requires *M*, 462.179087 (2 ppm error)].

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