A general route to the *Streptomyces*-derived inthomycin family: the first synthesis of (+)-inthomycin B

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Abstract—A concise, convergent and stereocontrolled synthesis of (+)-inthomycin B, based on the Stille coupling of a stannyl-diene with an oxazole vinyl iodide unit, is described. The asymmetric centre was introduced using the Kiyooka ketene acetal/amino acid-derived oxazaborolidinone procedure.
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The methylene-interrupted oxazolyl-triene motif is found in a number of bioactive natural products including the oxazolomycins and neooxazolomycin,[1] triedimicin B,[2] the curromycins,[3] and the phthoxazolin/inthomycins.[4–6] Phthoxazolin (1) was first isolated by Omura's group from *Streptomyces* in 1990 and shown to possess useful levels of antimicrobial and herbicidal activity, via specific inhibition of cellulose biosynthesis.[4] Subsequent studies[5] confirmed the potent herbicidal activity (e.g., against radish seedlings and velvet leaf in pre- and post-emergence treatments) and demonstrated low cytotoxicity to animal cells. In 1991, Henkel and Zeeck isolated three isomeric compounds, which they named inthomycins A–C (1–3), inthomycin A being identical to phthoxazolin.[6]

The inthomycins have attracted considerable synthetic attention, with a number of analogues being made[7] (including some with the oxazole moiety replaced by a phenyl ring[7b]). However, to date there has only been one reported synthesis of inthomycin A (1), in racemic form, by Hénaff and Whiting,[8] although the acid corresponding to inthomycin A has been prepared by Kende et al. as part of their ground-breaking enantioselective total synthesis of neooxazolomycin.[9]

As part of our programme to prepare members of the oxazolomycin family, together with synthetic analogues,[10] we required an efficient and stereocontrolled procedure to prepare all of the inthomycins. After considerable experimentation,[11] the convergent route shown in retrosynthetic form in Figure 1 was investigated. Thus, the aim was to employ Stille coupling of the vinyl iodide 4 and the dienylstannane 5 to construct the requisite triene unit, on the assumption that iodide 4 would be easily obtained from the known[9] oxazole 6. We felt that the coupling partner 5 would be accessible in enantioenriched form via reaction of a dienal 7, formed in a stereocontrolled manner, with ketene acetal 8 in the presence of a chiral Lewis acid (see later).[12] Herein, we
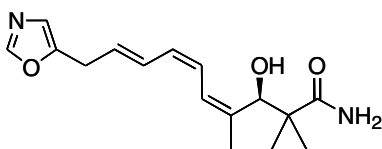
Inthomycin A (1)
(Phthoxazolin)
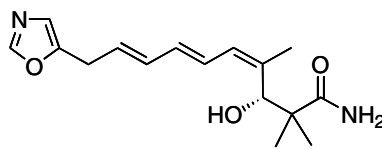
Inthomycin B (2)
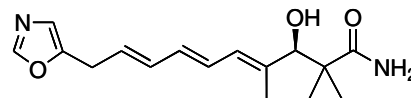
Inthomycin C (3)

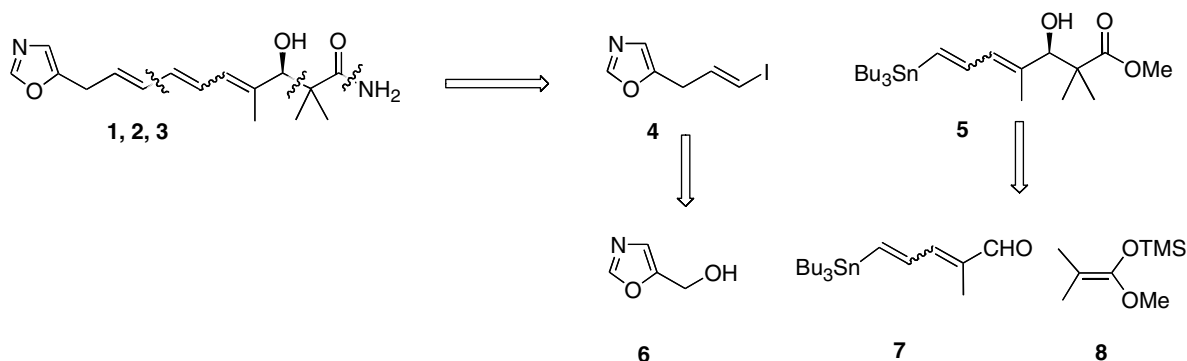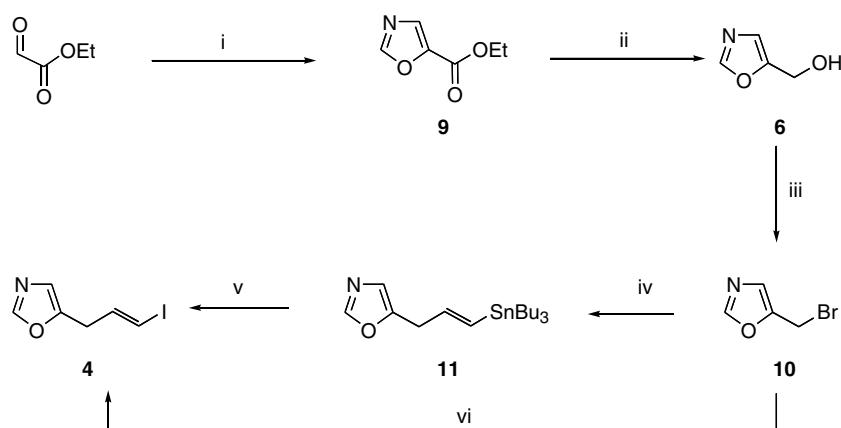*Corresponding author. Fax: +44 (0)1904 434523; e-mail: rjkt1@york.ac.uk

Figure 1.

**Scheme 1.** Reagents and conditions: (i) TOSMIC, K_2CO_3, EtOH, 80 °C, 86%; (ii) $NaBH_4$, EtOH, rt, 60 h, 85%; (iii) NBS, PPh_3, CH_2Cl_2, 0 °C, 1 h, 94%; (iv) Pd_2dba_3 (5 mol %), *E*-$Bu_3SnCH=CHSnBu_3$, THF, 80 °C, 4 h, 51%; (v) I_2, CH_2Cl_2, 0 °C, 20 min, 86%; (vi) Pd_2dba_3 (5 mol %), THF, 80 °C, 4 h, then I_2 at 0 °C, o/n, 46%.

describe the successful implementation of this route as exemplified by the first asymmetric synthesis of any member of the inthomycin family in the form of (+)-inthomycin B (**2**).

The route to vinyl iodide **4** is shown in Scheme 1.[13] Oxazole **9**[14] was prepared in good yield (86%) by treating ethyl glyoxylate with tosyl methyl isocyanate (TOSMIC) provided rigorously anhydrous conditions were employed. Reduction of the ethyl ester with $NaBH_4$ then afforded the primary alcohol **6**[9] in 85% yield. Using a published procedure (NBS/PPh_3),[9] alcohol **6** was converted into the highly unstable bromide **10**,[9] which was immediately coupled to *E*-1,2-bis-(tri-*n*-butylstannyl)ethene. A range of catalysts and reaction conditions were screened to optimise the yield of the 'mono-Stille' coupled product **11**;[8,9] eventually the use of catalytic Pd_2dba_3 in refluxing THF was chosen in view of the reproducible yield (>50%), although the high temperature required did result in degradation of the starting bromide. Tin–iodine exchange then proceeded uneventfully to give the novel vinyl iodide **4**. The final two steps could be telescoped in a one-pot process, which gave iodide **4** in 46% overall yield from bromide **10** and which could be carried out on a multi-gram scale (producing **4** in >3.5 g in a single operation).

Coupling partner *Z,E*-**5** was prepared from the known[15] *E*-3-(tributylstannyl)propenal **12** as shown in Scheme 2. As we have previously reported,[16] reaction of aldehyde **12** with the Still-Gennari bis-trifluoroethoxy phosphonate reagent **13** proceeds in excellent yield (94%) and with complete stereoselectivity to give ester **14**. Subsequent reduction of ester **14** using Dibal-H and TPAP oxidation afforded aldehyde *Z,E*-**7** as a single isomer (δ 10.35, s, 1H, CHO), which underwent isomerisation on silica gel and hence was purified on deactivated alumina, in 83% yield over two steps.

With aldehyde *Z,E*-**7** in hand, we explored asymmetric directed aldol reactions using ketene acetal **8**. Kiyooka's group, and others, have carried out extensive studies using **8** with a range of amino acid-derived oxazaborolidinones.[12] In our studies, we concentrated on the use of the oxazaborolidinone derived from *N*-tosyl-L-valine and BH_3·THF. In initial studies, oxazaborolidinone formation was carried out for the recommended[12a] 1 h period, and extensive reduction of the aldehyde was observed. However, this could be minimised by allowing the oxazaborolidinone to form over 16 h and by using a defined ratio of amino acid/BH_3·THF/aldehyde (2:1.2:1). Optimisation of the reaction conditions in terms of solvent, concentration and temperature
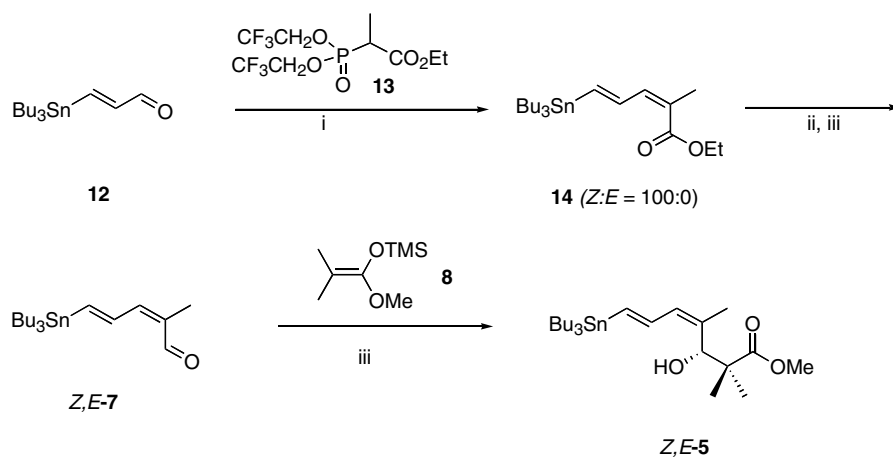
Scheme 2. Reagents and conditions: (i) KHMDS, 18-crown-6, THF, −78 °C to rt, 16 h, 94%; (ii) Dibal-H, CH$_2$Cl$_2$, −10 to 5 °C, 90 min, 85%; (iii) TPAP (5 mol %), NMO, 4 Å molecular sieves, rt, 4 h, 97%; (iv) *N*-tosyl-L-valine, BH$_3$·THF, CH$_2$Cl$_2$, 0 °C to rt slowly, 16 h then at −78 °C add **7** and after 5 min **8**, 2 h, 74%, 64% ee.

resulted in a gratifying 74% yield of *Z,E*-**5** (Scheme 2). The diene stereochemistry was retained as demonstrated by the isolation of a single product. The product was optically enriched {[α]$_D$ +5.4 (*c* 1.07, CHCl$_3$)} and an enantiomeric excess of 64% was established after the next reaction. Literature precedent suggested that the use of *N*-tosyl-L-valine should produce a predominance of the required *R*-*Z,E*-**5** (as shown); this was also confirmed at the next stage.

We were now in a position to investigate the crucial Stille coupling reaction between iodide **4** and enantiomerically enriched *R*-*Z,E*-**5**. The coupling was found to proceed in high yield with a range of catalysts/conditions but initial problems were encountered concerning isomerisation of the *Z,E,E*-triene unit during the course of the reaction. Experimentation revealed that isomerisation was mostly dependent on the catalyst loading rather than the type of palladium catalyst or the nature of reaction solvent/additives. Moving from 5 (ca. 20%

isomerisation) to 1% palladium bis-acetonitrile bis-chloride in DMF completely precluded isomerisation[13] giving the required triene **15** in quantitative yield.[17] Alcohol **15** was converted into diastereomeric *R*- and *S*-Mosher ester derivatives and analysis of the resulting high field ^{1}H NMR spectra[18] confirmed the predominance of the expected *R*-stereochemistry in 64% ee (also confirmed by HPLC studies[19]).

The final transformation required the conversion of methyl ester **15** into the corresponding primary amide **2**. Many unsuccessful attempts at the direct conversion were followed by similar disappointments with the derived carboxylic acid **16**. Success was eventually achieved by the initial formation of acetate **17** followed by formation of the corresponding acid chloride; subsequent in situ treatment with ammonium hydroxide gave amide formation and deprotection leading to inthomycin B **2** in reasonable isolated yield (Scheme 3). The spectral data were consistent with those previously
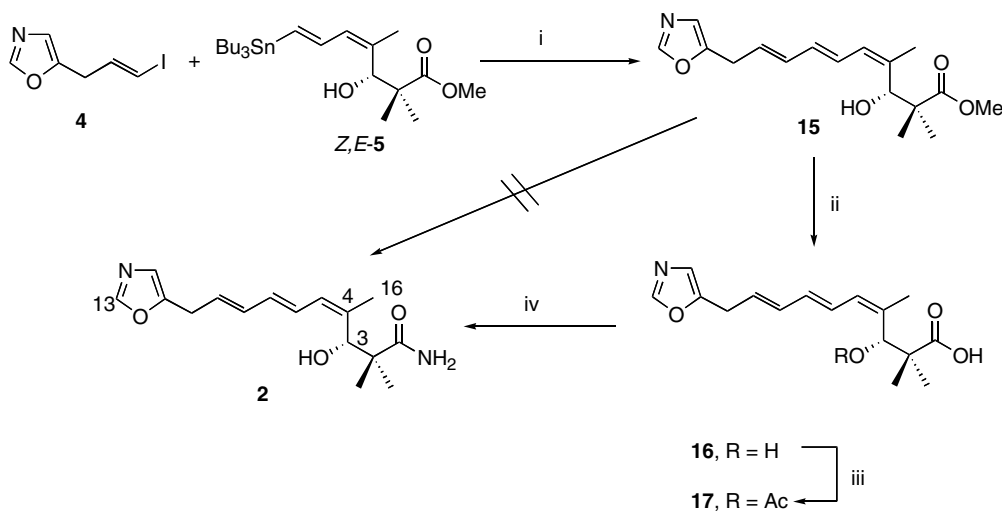
Scheme 3. Reagents and conditions: (i) 1 mol % Pd(CH$_3$CN)$_2$Cl$_2$, DMF, 50 °C, 5 d, quant.; (ii) LiOH, THF/MeOH/H$_2$O (3:1:1), 4.5 h, 73%; (iii) (a) Ac$_2$O, py, rt, 14 h, (b) NaHCO$_3$ (aq), CH$_2$Cl$_2$, 8 h, rt, 62%; (iv) (a) (COCl)$_2$, DMF, CH$_2$Cl$_2$, 0 °C, 3.5 h, (b) NH$_4$OH, rt, o/n, 50%.

reported [e.g., δ_C 19.6 (C-16), 75.9 (C-3), 139.9 (C-4), 151.7 (C-13); lit.[6] δ_C 19.6 (C-16), 75.8 (C-3), 139.9 (C-4), 151.6 (C-13)] and compound **2** was completely characterised {HRMS [found (CI): MH$^+$: 291.1706. $C_{16}H_{23}N_2O_3$ requires MH$^+$: 291.1709, 1.1 ppm error]; λ_{max} (MeOH) 286 nm (27,400), 275 nm (33,600), 266 nm (27,000); $[\alpha]_D$ +19.3 (*c* 1.0, CHCl$_3$); no $[\alpha]_D$ reported in the literature}.

In summary, we have completed the first synthesis of (+)-inthomycin B using a concise, convergent and stereocontrolled route with the Stille coupling of a stannyl-diene with an oxazole vinyl iodide unit, and a Kiyooka ketene acetal/amino acid-derived oxazaborolidinone procedure as its cornerstones. We are currently optimising this route, particularly the Kiyooka step, and we will then use it to prepare inthomycins A and C.

Acknowledgements

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17. Experimental procedure: To a stirred solution of iodide **4** (63 mg, 0.27 mmol) in anhydrous degassed DMF (1 mL) at rt, was added stannane *Z,E*-**5** (119 mg, 0.24 mmol), followed by a solution of dichloro bis(acetonitrile) palladium (0.63 mg, 2.4 μmol) in anhydrous degassed DMF (1 mL). The reaction mixture was heated at 55 °C for 5 d in the dark, and then concentrated in vacuo. The residue was partitioned between ethyl acetate (10 mL) and ammonium hydroxide (0.880 sg (35% ammonia), 10 mL), and the aqueous layer was extracted once more with ethyl acetate (20 mL). The combined organic fractions were washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash silica chromatography (petroleum ether/diethyl ether, 1:1) gave *adduct* **15** (75 mg, quant.) as a yellow oil, $[\alpha]_D^{21}$ +57.9 (*c* 0.80, CHCl$_3$); R_f 0.34 (petroleum ether/ethyl acetate, 1:1); ν_{max} (film) 3419, 3136, 2981, 2951, 1726, 1511, 1471, 1435, 1260, 1192, 1140, 1055, 912 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 1.15 (3H, s, *H*-14/15), 1.27 (3H, s, *H*-14/15), 1.75 (3H, s, *H*-16), 3.48 (2H, d, *J* 7.0, *H*-10), 3.72 (3H, s, *H*-17), 4.71 (1H, s, *H*-3), 5.73 (1H, dt, *J* 14.5, 7.0, *H*-9), 6.03 (1H, d, *J* 11.5, *H*-5), 6.10–6.23 (2H, m, *H*-7 and *H*-8), 6.43 (1H, dd, *J* 11.5, 13.5, *H*-6), 6.79 (1H, s, *H*-12), 7.79 (1H, s, *H*-13); δ_C (100 MHz, CDCl$_3$) 19.6 (*C*-16), 21.1 (*C*-14/15), 24.5 (*C*-14/15), 29.0 (*C*-10), 46.9 (*C*-2), 52.4 (*C*-17), 75.2 (*C*-3), 122.6 (*C*-12), 127.3 (*C*-9), 128.0 (*C*-6), 130.3 (*C*-5), 131.8 (*C*-7/8), 133.5 (*C*-7/8), 137.0 (*C*-4), 150.6 (*C*-13), 150.9 (*C*-11), 178.5 (*C*-1); *m/z* (EI) 305 (M$^+$, 1), 269 (8), 204 (100), 102 (29), 82 (39), 57 (22), 41 (32); [found (EI): M$^+$ 305.1637; $C_{17}H_{23}NO_4$ requires *M* 305.1627, 3.4 ppm error].

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19. HPLC analyses were conducted on the *S*-Mosher's ester derivative of alcohol **15** having established a protocol using the *S*-Mosher's ester derivative of racemic **15**. The HPLC conditions were: Daicel Chiralpak AD, hexane/isopropanol (9:1), 1.0 mL min^{-1}, 254 nm, 13.2 min (*S,S*-**15**), 15.0 min (*R,S*-**15**).