# A Multicomponent Coupling Strategy for the Synthesis of the Triene Component of the Oxazolomycin Antibiotics

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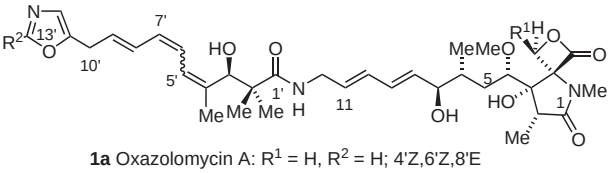
**Abstract:** Concise and versatile routes suitable for the synthesis of three geometric isomers of an analogue of the left hand triene subunit of oxazolomycin are reported, using a Stille coupling strategy.

**Key Words:** Stille reaction, natural products, diastereoselectivity, organometallic reagents

Oxazolomycin A **1a** is the parent member of a class of antibiotics,[1] other members being oxazolomycins B and C **1b**,**c**,[2] 16-methyloxazolomycin **1d**, neooxazolomycin,[3] and the curromycins **1e**,**f**.[4–6] They possess an unusual spiro fused β-lactone/γ-lactam linked via a triene and (*E*,*E*)-diene spacer to an oxazole terminal residue. The phthoxazolins, which are essentially the left hand domain of oxazolomycin, are also known,[7,8] although these have markedly different biological activity.[9–11] The oxazolomycins and curromycins **1a**–**f** (Figure 1) are isolated from *Streptomyces* and exhibit wide ranging and potent antibiotic activity, including inhibition of Gram positive bacteria, antiviral activity against vaccinia, herpes simplex type I, and influenza A, as well as in vivo antitumour activity; notably, this biological activity is coupled with low toxicity. Oxazolomycin **1a** is an effective protonophore at pH < 7.0, but conveys both protons and monovalent cations (e.g. $K^+$) at 7.0 < pH < 7.5,[12] and it is this activity which is thought to be responsible for its antibacterial, antiviral, and cytotoxic properties.

Notwithstanding the potent and wide-ranging but ill-understood biological activity of this class of compounds, the oxazolomycins have received little synthetic attention. There is only one total synthesis of any of these compounds,[13] although we[14] and others[15] have examined routes for the synthesis of the lactam unit, and a synthesis of phthoxazolin[16] has been reported. The synthesis of the required oxazole unit has also received recent attention.[17] We report here a concise and versatile route for the synthesis of the three known geometric isomers of the C1′-C13′ triene subunit of oxazolomycin in racemic form,[18] with the oxazole ring replaced by a phenyl group, conducted as part of a long-term plan to identify the biological action of these compounds.

Our routes made use of regioselective Stille couplings[19,20] in a three-component coupling strategy (Scheme 1). Allylic alcohol **2a** was synthesised by AIBN-catalysed hydrostannylation of propargyl alcohol in a modification of the literature procedure[21] (involving purification by column chromatography rather than distillation followed by preparative HPLC), which gave the product in 67% isolated yield. Swern oxidation then afforded aldehyde **2b** in excellent yield (90%), whereas oxidation with PCC gave only a 40% yield.[22] After several unsuccessful attempts under various conditions, Wadsworth–Emmons olefination with phosphonate **3c**, prepared from β-dicarbonyl **3a** via bromide **3b**, was found to occur using NaH as the base, which gave (*E*,*E*)-diene **4** as the sole product, albeit in moderate yield (50%). The third double-bond was introduced by reaction of vinyl iodide **5**, prepared by Takai homologation[23] of phenylacetaldehyde with $CrCl_2/CHI_3$, with stannane **4** to give (*E*,*E*,*E*)-triene **6a** in 84% isolated yield. Reduction with $NaBH_4$ then gave alcohol **6b** in 92% yield, in which the polyene system had not been shifted into conjugation with the phenyl group.



**1a** Oxazolomycin A: $R^1$ = H, $R^2$ = H; 4′*Z*,6′*Z*,8′*E*
**1b** Oxazolomycin B: $R^1$ = H, $R^2$ = H; 4′*E*,6′*E*,8′*E*
**1c** Oxazolomycin C: $R^1$ = H, $R^2$ = H; 4′*Z*,6′*E*,8′*E*
**1d** 16-Methyloxazolomycin: $R^1$ = Me, $R^2$ = H; 4′*Z*,6′*Z*,8′*E*
**1e** Curromycin A: $R^1$ = $CH_3OCH_2$, $R^2$ = Me; 4′*Z*,6′*Z*,8′*E*
**1f** Curromycin B: $R^1$ = Me, $R^2$ = Me; 4′*Z*,6′*Z*,8′*E*

**Figure 1**

Encouraged by the successful use of a Stille reaction to construct the (*E*,*E*,*E*)-triene system of oxazolomycin B in a mild and stereoselective manner, attention was then focused on the development of an analogous strategy towards the (*Z*,*Z*,*E*)- and (*Z*,*E*,*E*)-triene systems present in oxazolomycin A and oxazolomycin C respectively. It was decided to adopt a strategy involving coupling between a divinyl halide and a vinylstannane in the key step (Scheme 2).

Iodide **7a** was prepared as a single isomer from propargyl alcohol following the literature procedure,[24] and the free hydroxyl group then protected as its TBDMS-ether **7b** in excellent yield (99%). Conversion of this iodide to stannane **7c** was then effected via metal-halogen exchange followed by $Bu_3SnCl$ quench, but the course of this reaction was found to be very solvent dependent: in THF, the major product was in fact vinyl silane **8** whereas in $Et_2O$

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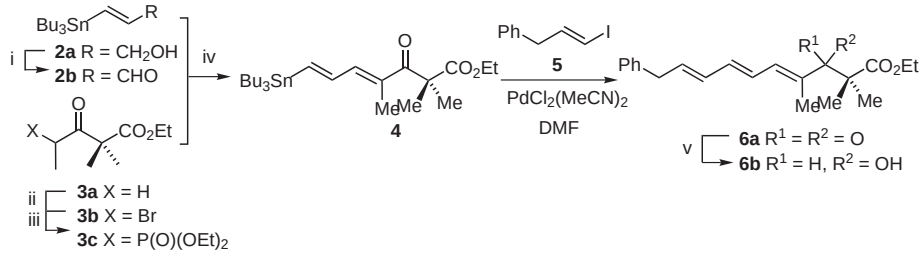



**Scheme 1** (i) PCC or ClCOCOCl, DMSO, $Et_3N$; (ii) $Br_2$/HOAc; (iii) $P(OEt)_3$; (iv) NaH, THF; (v) $NaBH_4$.

the desired stannane **7c** was obtained in excellent yield (90%). Purification of this stannane by column chromatography had to be performed with 1% $Et_3N$ in the eluant in order to prevent protodestannylation. Removal of the silyl protecting group in stannane **7c** using TBAF followed by Swern oxidation of the crude alcohol gave aldehyde **7e**; aldol reaction with ethyl isobutyrate then gave racemic alcohol **9** in good overall yield (65%) over the three steps. The required divinyl halides **10a** were prepared by homologation of aldehyde **11** using the Takai[23] or Wittig procedures[25] (77% of a 3:1 mixture of (*E*,*E*):(*Z*,*E*)-**10a** and 69% yield of a 1:8 mixture of (*E*,*E*):(*Z*,*E*)-**10a** respectively), and 1(*Z*)-bromide **10b** was obtained according to the recent literature protocol (75% yield).[26]

Stannane **9** was reacted under standard Stille coupling conditions with divinyl halides **10a**,**b**. Reaction for 10 hours with excess of (*E*,*E*)-**10a** gave a 72% yield of a 3:1 mixture of (*Z*,*Z*,*E*):(*Z*,*E*,*E*) triene products **12a** and **13a**, dropping to a 1:1 ratio if the reaction time was lengthened to 24 hours. Use of (*Z*,*E*)-iodide **10a** did not improve this ratio, giving a 74% yield of a 1.2:1 mixture of (*Z*,*Z*,*E*):(*Z*,*E*,*E*) triene product **12a** and **13a**. We have not established if this lack of stereospecificity arises from differential reactivities of the (*E*,*E*)- and (*Z*,*E*)-iodide components of **10a**, and/or equilibration of reactants or products under the conditions of the Stille coupling reaction. The stereochemistry of the major (*Z*,*Z*,*E*) product **12a** was established by careful NOE analysis (Figure 2). In an attempt to improve the stereoselectivity of this Stille reaction, isomerically pure bromide (*Z*)-**10b** was investigated, and found to give the product, but the reaction was unreliable, probably due to the lower intrinsic reactivity of vinyl bromides. Hydrolysis of a 3:1 mixture of (*Z*,*Z*,*E*):(*Z*,*E*,*E*) triene product **12a** and **13a** gave acids **12b**:**13b** in 70% yield. These trienes are analogues of oxazolomycins A and C and inthomycins C and B respectively.

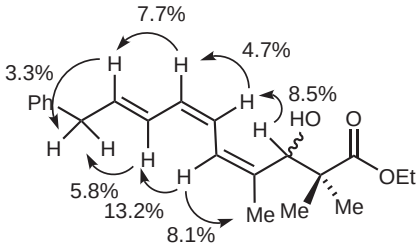
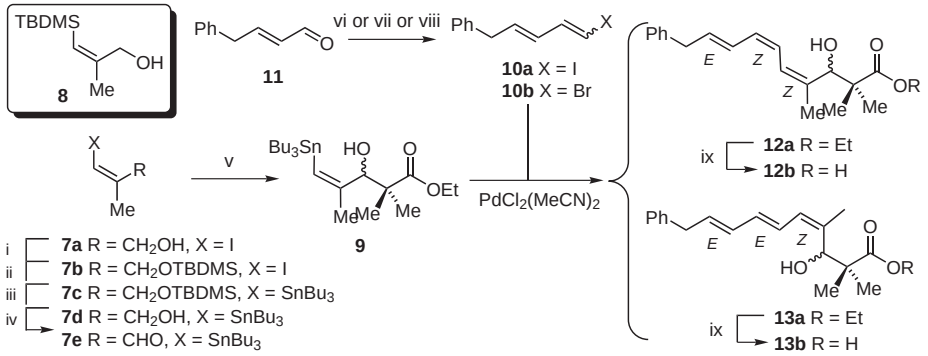



**Figure 2**

In summary, this is a flexible and efficient synthetic route enabling access to each of the three-triene systems present in the oxazolomycin class of antibiotics, and the methodology is potentially applicable to the synthesis of analogues with variation both in the side-chain geometry and in the identity of the terminal aromatic or heteroaromatic residue. Exploitation of this synthetic strategy will enable details of the biological mode of action of these interesting compounds to be unravelled.




**Scheme 2** (i) TBDMSCl, $Et_3N$; (ii) *n*-BuLi, $Bu_3SnCl$; (iii) TBAF/THF; (iv) ClCOCOCl, $Et_3N$, DMSO; (v) $Me_2CHCO_2Et$, LDA; (vi) $CrCl_2$, $CHI_3$; (vii) NaHMDS, $ICH_2PPh_3^+I^-$; (viii) (a) $PPh_3$, $CBr_4$; (b) $Bu_3SnH$, cat. $Pd(PPh_3)_4$; (ix) LiOH, THF, $H_2O$, MeOH (1:1:1), r.t. 24 h.

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