Total synthesis of the virginiamycin antibiotic 14,15-anhydropristinamycin II_B

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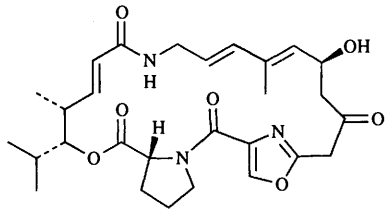
1 PERKIN COMMUNICATION

A total synthesis of the virginiamycin 14,15-anhydropristinamycin II_B 16 has been achieved from chiral, non-racemic starting materials, and using a route which features an intramolecular Stille coupling reaction, *viz.* 14→15, as the key stratagem. The virginiamycin 16 was identical with an authentic sample produced from a *Streptomyces* fermentation process.

The virginiamycins are a novel family of potent antibiotics produced by *Streptomyces*.[1] Structurally they are assigned to one of two groups: (i) Group A virginiamycins, which have a common 23-membered macrolide accommodating an oxazole ring, an (*E*,*E*)-1,3-diene, an acrylamide unit, and an amino acid residue, *e.g.* **1** (virginiamycin M2)[2] and **2**, and (ii) Group B virginiamycins, which are cyclic hexadepsipeptides. Virginiamycin antibiotics have been used as food additives to improve growth of cattle for several years. More recently, formulations involving a number of Group A virginiamycins, like **1** and **2**, have been recognised as cholecystokinin (CCK) antagonists, for treating panic, anxiety and cancer withdrawal.[3] In spite of the biological significance of these compounds, and in spite of considerable effort over many years,[4] a total synthesis of a Group A virginiamycin has not been reported.[5] Our complementary interests in naturally occurring oxazole/thiazoline-based macrocyclic ionophores,[6] and in developing the scope for intramolecular sp^2–sp^2 vinyl coupling reactions in macrocycle constructions,[7] had led us to examine the use of the Stille reaction[8] as the key stratagem in the synthesis of members of the Group A virginiamycins. In this communication we describe a total synthesis of the virginiamycin 14,15-anhydropristinamycin II_B **16**.

The strategy we followed to the virginiamycin **16** was based on the Stille sp^2–sp^2 macrocyclisation **14**→**15**, and required the substituted proline **7** and the 4-oxazole carboxylic acid **13** as central intermediates. The proline-based vinylstannane **7** was produced from the known crystalline *syn*-diastereoisomer (>98% pure) of the (*E*)-unsaturated **3**,[9] as shown in Scheme 1. After protection of **3** as its MOM† ether, reaction with propargylamine in the presence of trimethylaluminium[10] first gave the amide **4a** in 67% yield. Deprotection of the secondary alcohol group in **4a**, followed by acetylation next gave the corresponding acetate **4b**. Treatment of **4b** with the stannylcuprate produced by the addition of Bu_3SnH to a mixture of BuLi and Cu^ICN at −78 °C,[11] then gave the *E*-vinylstannane **5** in 75% yield. The synthesis of **7** from **5** was finally completed following saponification (to **6a**), treatment with proline trifluoroamide,[12] leading to **6b**, and hydrolysis.

The oxazole carboxylic acid **13** required for coupling to the amine **7** was produced *via* a condensation reaction between the carbanion derived from 2-methyl-4-hydroxymethyloxazole **11**, and the bromodienal **10** prepared from the 3-bromobut-2-enol



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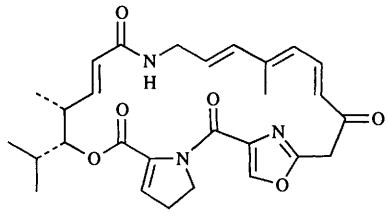

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8,[13] *via* **9** (Scheme 2). Thus treatment of **11**[14] with two equiv. of BuLi in THF at −78 °C followed by addition of the (*E*,*E*)-bromoaldehyde **10** led to the substituted oxazole **12a** in 35% yield. Oxidation of **12a** with MnO_2 next provided the aldehyde (**12b**; 50%),[15] which on further oxidation with buffered sodium chlorite gave the corresponding oxazole carboxylic acid (**13**; 85%).

A coupling reaction between the vinylstannane-substituted amine **7** and the vinyl bromide-substituted oxazole carboxylic acid **13**, in the presence of EDC‡ and HOBT,§ next gave the key intermediate **14** (65%). When this intermediate was treated with triphenylarsine and palladium(0) dibenzylideneacetone dimer in DMF at 100 °C for 16 h, it underwent Stille coupling to produce the virginiamycin **15** as a 1:1 mixture of *sec*-hydroxy group epimers in an unoptimised 30% yield. Oxidation of **15** using Dess–Martin periodinane then gave the virginiamycin **16** which was identical (mixed chromatography, matching ^1H and ^{13}C NMR data) with an authentic sample produced from a *Streptomyces* fermentation process.

Thus, a novel strategy towards the oxazole–proline–acrylamide–polyene 23-membered macrolide-based family of virginiamycins has been realised, and this should be applicable to the synthesis of a range of related virginiamycins. These further studies are in progress.

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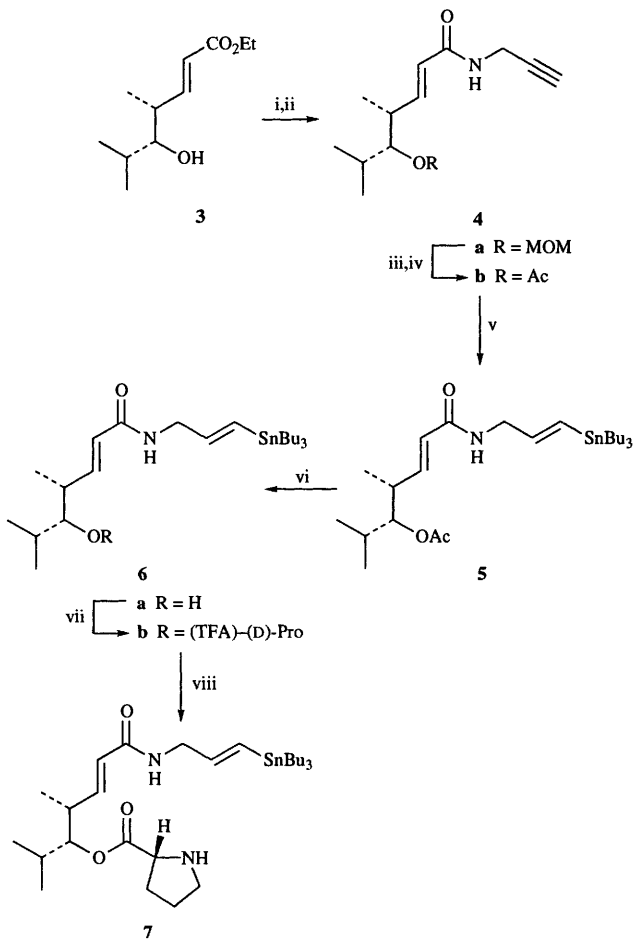
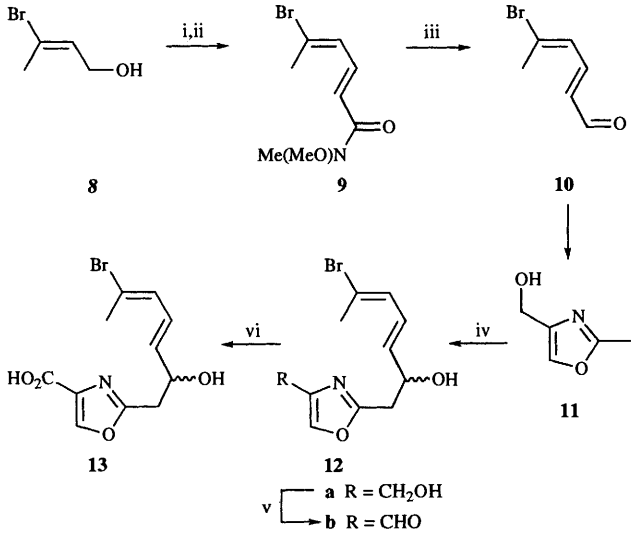
† MOM = Methoxymethyl.

‡ EDC = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

§ HOBT = 1-Hydroxybenzotriazole hydrate.



Scheme 1 *Reagents:* i, MOMCl, DIPEA (80%); ii, $H_2NCH_2C{\equiv}CH$, Me_3Al (67%); iii, TMSBr (92%); iv, AcCl, Et_3N (90%); v, BuLi, CuCN, Bu_3SnH (75%); vi, KOH H_2O (85%); vii, (TFA)-(D)-Pro-OH, DCC, DMAP (76%); viii, K_2CO_3, H_2O (64%)



Scheme 2 *Reagents:* i, MnO_2 (95%); ii, $(EtO)_2POCH_2CONMe(OMe)$, $KOBu^t$ (80%); iii, DIBAL (90%); iv, 2 equiv. BuLi, **10** (34%); v, MnO_2 (50%); vi, $NaClO_2$, KH_2PO_4, 2-methylpent-2-ene (85%)

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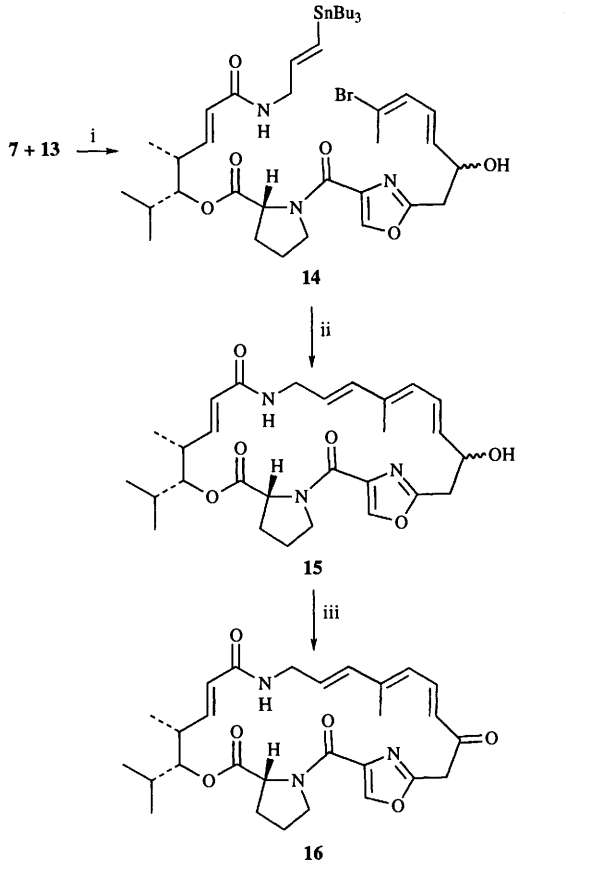

Scheme 3 *Reagents:* i, EDC, HOBT, Et_3N (60%); ii, $Pd_2(dba)_3$, Ph_3As (30%); iii, Dess–Martin periodinane, 58%

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15 The controlled oxidation of **12a** to the corresponding 4-formyloxazole **12b** in the presence of MnO_2 was somewhat fortuitous. The use of many other conventional oxidants instead led to complex mixtures of products in poor yields.

¶ Diisobutylaluminium hydride.

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