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Studies in Macrolide Synthesis: A Novel Cyclodimerisation Approach to the Synthesis of Elaiophylin Using a Double Stille Cross-Coupling Reaction.

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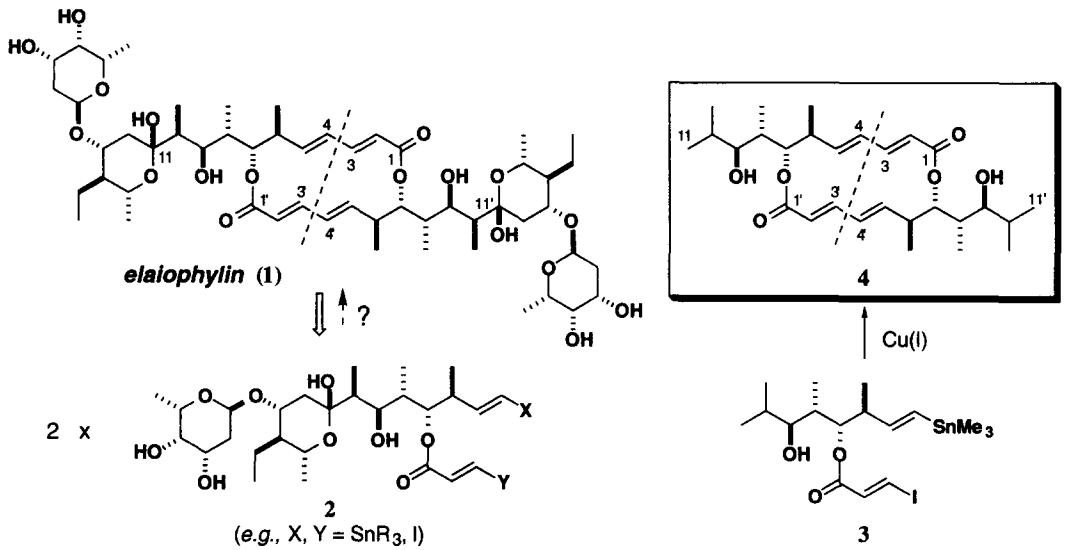
Abstract: The 16-membered macrodiolide **4**, corresponding to the macrocyclic core of elaiophylin (**1**), was prepared *via* the copper-mediated cyclodimerisation of stannane **3**.

Elaiophylin (**1**) is a 16-membered macrolide antibiotic, isolated from cultures of *Streptomyces melanosporus*, which was first reported by Arcamone *et al.*[1a] and shortly after by Arai.[1b] The C_2-symmetric, macrodiolide structure was determined by spectroscopic methods and chemical degradation,[2a-d] where the full absolute configuration was elucidated by X-ray crystallographic analysis.[2e,f] Elaiophylin (**1**) is structurally related (having similar stereochemistry in its secoacid) to several other 16- and 18-membered monomeric macrolides, particularly the bafilomycins and concanamycins.[3]



Scheme 1

Previous synthetic efforts[4] directed towards elaiophylin (**1**) have constructed the macrodiolide core by a conventional esterification / lactonisation strategy, which has enabled its total synthesis[4a,b] as well as that of various aglycone derivatives.[4c-f] As part of our studies in macrolide synthesis,[5] we considered an alternative approach to this unsaturated, 16-membered macrocycle by a novel cyclodimerisation process based on a double Stille cross-coupling reaction. In our most ambitious plan, as shown in **Scheme 1**, this would be the final step of the total synthesis. In practice, this would require the stereocontrolled formation of the C_3–C_4 and $C_{3'}$–$C_{4'}$ bonds (avoiding competing oligomerisation) in **1** from a monomeric unit **2** having both acid- and base-sensitive functionality and multiple hydroxyl groups. We now report a copper-mediated, double cross-coupling reaction performed on the stannane **3**, which leads to an efficient synthesis of the C_2-symmetric macrodiolide **4**, corresponding to a truncated version of elaiophylin.

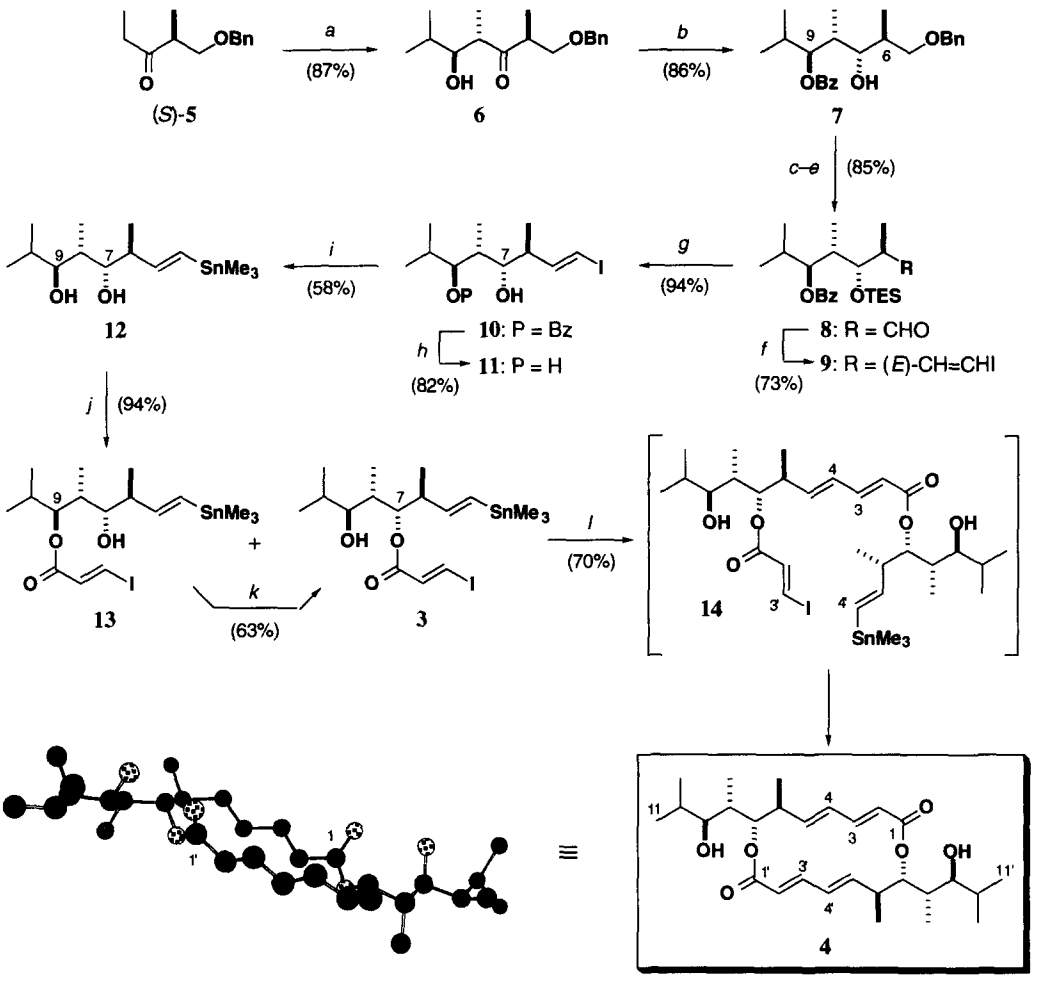
The C_2-symmetry of elaiophylin lends itself well to a cyclodimerisation synthetic strategy, where the two (*E*,*E*)-diene units (which preclude formation of an 8-membered ring) would be introduced upon macrocycle formation. Advantages of the Stille cross-coupling approach are that the use of hydroxyl protecting groups is minimised (possibly avoided altogether) and otherwise sensitive functionality may be tolerated.[6] Moreover, good precedent for the use of one-pot, *double* Stille coupling reactions[7] in the construction of macrocycles are included *inter alia* in Baldwin's synthesis of pyrenophorin,[7a] Nicolaou's synthesis of rapamycin[7b,c] and Danishefsky's synthesis of dynemycin A.[7d,e]

The monomeric unit **3** was chosen as a suitable model substrate (incorporating the C_1–C_{11} part structure of elaiophylin with the associated four contiguous stereocentres) for **2** to test the viability of this cyclodimerisation strategy. As shown in **Scheme 2**,[8] this stannane **3** was prepared from the ketone (*S*)-**5**[9] which has been used extensively as a dipropionate building block for the expedient synthesis of a wide range of polypropionate natural products.[10] Using our standard conditions,[9] a boron-mediated *anti* aldol reaction between (*S*)-**5** and isobutyraldehyde proceeded with high diastereoselectivity (≥97% ds) to give adduct **6** in 87% yield. This was followed by an Evans-Tishchenko *anti* reduction,[11] performed in the presence of benzaldehyde, which afforded an 86% yield of the benzoate **7** with similarly high levels of diastereoselectivity. In these two steps, we had correctly set up the *anti-syn-anti* stereotetrad spanning C_6–C_9 in elaiophylin.

The stepwise introduction of the two functionalised double bonds in **3** was now required. Thus, benzoate **7** was first converted into the aldehyde **8** by a straightforward, 3-step sequence of TES hydroxyl protection, debenzylation and Swern oxidation (85%). Using CHI_3 and $CrCl_2$ in THF, a Takai olefination reaction[12] selectively converted **8** into the corresponding (*E*)-alkenyl iodide **9** (*E* : *Z* = ≥95 : 5) in 73% yield. After removal of the TES protecting group to give **10**, esterification of the free C_7-OH was first attempted with (*E*)-3-iodopropenoic acid[13] under a variety of conditions. However, presumably due to the steric congestion experienced in this alcohol from the neighbouring benzoate, these reactions proved fruitless. The benzoate ester was therefore cleaved by hydrolysis to give the diol **11**. Next, a Pd(0)-catalysed, iodine–tin exchange reaction[14] was performed on **11** using $(Me_3Sn)_2$ in the presence of Li_2CO_3 to generate the corresponding stannane **12** in 58% yield. Esterification of diol **12** with (*E*)-3-iodopropenoic acid (DCC, DMAP, CH_2Cl_2, –20 °C)[15] then provided a 94 : 6 mixture of the regioisomers **13** and **3** in 94% yield. Under these kinetic conditions, reaction at the C_9-OH was greatly preferred over the presumably more hindered C_7-OH. Subsequently, equilibration of this mixture was achieved (retaining the acid-labile stannane) under mild conditions[16] using $Ti(O^iPr)_4$ (CH_2Cl_2, 20 °C, 16 h) to provide a 69 : 31 mixture now in favour of the C_7 ester **3**. After careful chromatographic purification (SiO_2 pre-treated with Et_3N, 1% Et_2O in CH_2Cl_2), the desired monomeric unit **3** was isolated in 44% yield.

The key cyclodimerisation reaction was performed with copper (I) thiophene-2-carboxylate (CuTC), a new Cu(I) reagent introduced by Allred and Liebeskind[17] to promote Stille cross-coupling reactions under mild conditions (NB: in the absence of Pd catalysis). Gratifyingly, treatment of a 0.01 M solution of monomer **3** in *N*-methylpyrrolidinone with CuTC (10 equiv) at room temperature produced the required 16-membered macrocycle **4** in an unoptimised 70% yield. The reaction showed clean formation of **4** without any isolation of the open-chain intermediate **14**, suggesting the occurrence of a rapid Cu(I)-mediated cyclisation without competing oligomerisation. The macrodiolide **4** (FAB-MS, m/z = 477), $[\alpha]_D^{20}$ +78.5 (*c* = 0.48, $CHCl_3$), displayed characteristically simple ^1H and ^{13}C NMR spectra[8] as expected from its C_2-symmetry and in accordance with that reported[18] for the corresponding portion of the aglycone of elaiophylin (**1**).

In summary, the efficient cyclodimerisation, 2 x **3** → **4**, further demonstrates the power of the Stille cross-coupling reaction in the synthesis of structurally complex macrocycles.[6,7] Moreover, the Liebeskind CuTC protocol[17] appears to be an excellent new method for achieving Stille couplings under extremely mild conditions in both inter- and intramolecular situations. Studies are currently underway to apply this cyclodimerisation strategy to the total synthesis of elaiophylin itself, as well as to access other ring sizes.



Scheme 2: (*a*) $^{c}Hex_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; $^{i}PrCHO$, 0 °C, 2 h; –20 °C, 16 h; H_2O_2, pH7 buffer-MeOH, 0 °C, 1 h; (*b*) SmI_2, PhCHO, THF, 3 °C, 16 h; (*c*) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 40 min; (*d*) H_2, $Pd(OH)_2$, THF, 20 °C, 16 h; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 90 min; Et_3N, –78 °C, 30 min; (*f*) $CrCl_2$, CHI_3, THF, 3 °C, 16 h; (*g*) PPTS, MeOH, 20 °C, 48 h; (*h*) K_2CO_3, MeOH, 20 °C, 48 h; (*i*) $Pd(PPh_3)_2Cl_2$, $(Me_3Sn)_2$, Li_2CO_3, THF, 55 °C, 16 h; (*j*) (*E*)-$ICH{=}CHCO_2H$, DCC, DMAP, CH_2Cl_2, –20 °C, 16 h; (*k*) $Ti(O^{i}Pr)_4$, CH_2Cl_2, 20 °C, 16 h; (*l*) CuTC, NMP, 20 °C, 16 h.

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8. All new compounds gave spectroscopic data in agreement with the assigned structures. Stannane **3** had: $[\alpha]_D^{20}$ –38.9 (c = 0.71, $CHCl_3$); ν_{max}(thin film) 3532, 1704, 1592; ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.85 (1H, d, J = 14.8 Hz, $H_{3'}$), 6.84 (1H, d, J = 14.8 Hz, $H_{2'}$), 5.97 (1H, d, J = 18.7 Hz, H_4), 5.72 (1H, dd, J = 18.7, 7.9 Hz, H_5), 5.14 (1H, d, J = 19.8 Hz, H_7), 2.99 - 2.96 (1H, m, H_9), 2.72 (1H, d, J = 4.8 Hz, OH), 2.54 - 2.47 (1H, m, H_6), 1.86 - 1.80 (2H, m, H_8 and H_{10}), 1.01 (3H, d, J = 7.3 Hz, Me), 0.99 (3H, d, J = 7.3 Hz, Me), 0.844 (3H, d, J = 6.7 Hz, Me), 0.840 (3H, d, J = 7.0 Hz, Me), 0.07 (9H, s, $J_{Sn\text{-}H}$ = 27.1 Hz, 3 x SnMe); ^{13}C NMR δ (100 MHz, $CDCl_3$) 165.0, 150.4, 136.3, 130.1, 100.1, 77.8, 75.5, 44.2, 37.3, 28.9, 20.8, 16.5, 13.8, 9.3, –9.7; Macrodiolide **4** (m.p. 226–228 °C) had: ν_{max}(thin film) 3500, 1694, 1644, 1614; ^{1}H NMR δ (500 MHz, $CDCl_3$) 6.97 (2H, dd, J = 15.3, 11.1 Hz, $H_{3,3'}$), 6.09 (2H, dd, J = 15.1, 11.1 Hz, $H_{4,4'}$), 5.66 (2H, d, J = 15.3 Hz, $H_{2,2'}$), 5.65 (2H, dd, J = 15.1, 11.2 Hz, $H_{5,5'}$), 4.97 (2H, dd, J = 10.2, 1.5 Hz, $H_{7,7'}$), 3.14 - 3.10 (2H, m, $H_{9,9'}$), 2.92 (2H, d, J = 4.8 Hz, 2 x OH), 2.55 - 2.49 (2H, m, $H_{6,6'}$), 1.91 - 1.82 (4H, m, $H_{8,8'}$ and $H_{10,10'}$), 1.04 (6H, d, J = 6.7 Hz, 2 x Me), 1.00 (6H, d, J = 6.8 Hz, 2 x Me), 0.867 (6H, d, J = 7.1 Hz, 2 x Me), 0.865 (6H, d, J = 6.5 Hz, 2 x Me); ^{13}C NMR δ (100 MHz, $CDCl_3$) 169.2, 145.0, 144.5, 131.6, 121.2, 78.0, 75.5, 41.2, 36.4, 28.9, 20.8, 15.1, 13.9, 9.1; HRMS (FAB^+) $[M+H]^+$ found 477.3233, $C_{28}H_{45}O_6$ requires 477.3216.

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