Intramolecular Palladium-catalysed Cross Coupling; a Route to γ-Oxo-α,β-unsaturated Macrocycles

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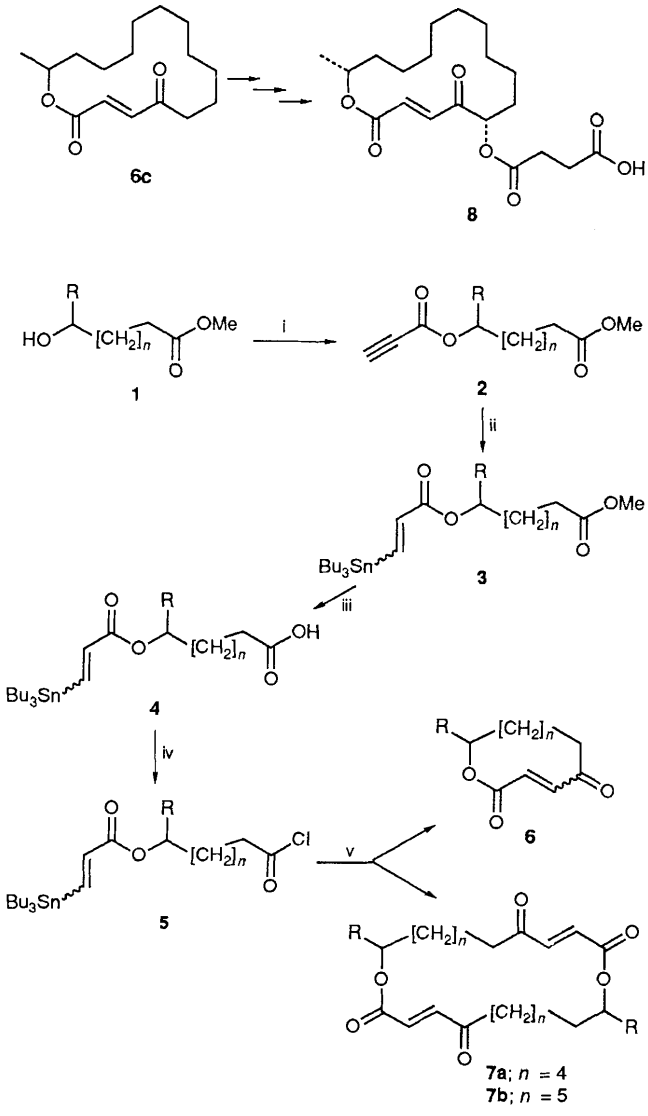
A new and relatively simple method involving Pd^0-catalysed cross coupling of acid chlorides and β-stannyl alkenoates provides an efficient route to γ-oxo-α,β-unsaturated macrolides.

γ-Oxo-α,β-unsaturated esters are common to many naturally occurring macrocyclic antibiotics.[1] Most of the numerous methods for incorporating this functionality demand relatively delicate macrocyclisation techniques and extensive use of protecting groups.[2] A relatively mild and facile intermolecular Stille cross coupling followed by traditional macrolactonisation to such compounds has been reported[3a] but the potential for direct macrocyclisation by the Stille reaction was not described. We now report that by employing high temperature (100 °C) in toluene and high dilution (4 mmol dm^{-3}) macrocyclisation *via* intramolecular Stille cross coupling leads to highly functionalised macrocycles of ring sizes 11 to 20.

Suitable precursors **5** were readily obtained as follows. Mitsunobu esterification[4] of propiolic acid and ω-hydroxy methyl esters **1**† (82–94%), followed by Et_3B-induced hydrostannylation[5] with Bu^n_3SnH in benzene afforded quantitatively the β-stannyl alkenoates **3** as a roughly 1 : 1 mixture of *Z*- and *E*-isomers which were cleanly separated by column

† ω-Hydroxy methyl esters were synthesised from their corresponding commercially available β-hydroxy acids except for **1f** and **1g** which were formed by Baeyer–Villiger oxidation of cyclooctanone and cycloheptanone to their lactones followed by BF_3-mediated ester cleavage in methanol.



Scheme 1. *Reagents and conditions*: i, propiolic acid (2 equiv.) diethyl azodicarboxylate (DEAD) (2 equiv.), PPh_3 (2 equiv.), tetrahydrofuran (THF), room temp.; ii, Bu^n_3SnH (1.2 equiv.), BEt_3 (0.1 equiv.), benzene, 0.5 h, room temp.; iii, LiOH (1 equiv.), THF–H_2O (9 : 1), 14 h then acidified to pH 4; iv, $(COCl)_2$, catalytic DMF, toluene, −5 → 10 °C with degassing; v, $PhCH_2Pd(PPh_3)_2Cl$ (5 mol%), toluene, 3 atmospheres CO, 100 °C, 4 mmol dm^{-3} dilution, 7–14 h

chromatography. Regioselective saponification of the methyl esters **3** with 1 equiv. of LiOH (THF–H_2O) and acidification to pH 4 gave the free acid **4** in excellent yields (>90%) from **3**. These were smoothly converted to the corresponding acid chlorides **5** in almost quantitative yield with little or no destannylation by treatment of a 10 mmol dm^{-3} solution in toluene at −5 °C with $(COCl)_2$–cat. dimethylformamide (DMF) followed by degassing the reaction mixture at 10 °C with argon prior to solvent evaporation.

Intramolecular Stille couplings were performed in a glass Fisher–Porter pressure bottle. The vessel was charged with the palladium catalyst benzylchlorobis(triphenylphosphine)palladium(II) (5 mol %) in toluene and flushed several times with carbon monoxide. The substrate (0.2 mmol) was then added dissolved in toluene to a 4 mmol dm^{-3} dilution. The bottle was pressurised to 3 atmospheres of carbon monoxide, transferred quickly to a preheated oil bath at 100 °C and heated for 7–14 h. Precipitation of a metallic deposit signalled the reaction to be complete; the mixture was then cooled, vented, diluted with diethyl ether and filtered through Celite. The filtrate was concentrated and the residue purified by column chromatography [SiO_2 diethyl ether–hexanes (1 : 5 gradient)] to afford the macrocyclic products **6** (32–70%) (Table 1).

Table 1 Preparation of γ-oxo-α,β-unsaturated macrolides **6** and **7**

β-Stannyl-alkenoate	R	*n*	Ring size	Product	Yield (%)
E-**5a**	H	13	20	*E*-**6a**	48
E-**5b**	H	9	16	*E*-**6b**	53
E-**5c**	Me	9	16	*E*-**6c**	70
Z-**5d**	C_6H_{11}	9	16	*E*-**6d**	58
E-**5e**	H	7	14	*E*-**6e**	55
E-**5f**	H	5	12	*Z*-**6f**	41
E-**5g**	H	4	11	*Z*-**6h**, *E*-**7a**	32, 30
E-**5h**	H	3	20 (dimer)	*E*-**7b**	58

Amongst the plethora of naturally occurring γ-oxo-α,β-unsaturated macrolides many are 12-, 14- or 16-membered and hence this direct method of preparation is attractive. This is exemplified by *E*-**6c**[6]‡ (70%), whose transformation into macrolide antibiotic (±)-A 26771B **8** has already been described,[7] and by the direct synthesis of the patulolide B[8] framework, *e.g.* *Z*-**6f** (41%). Substituents larger than methyl can also be accommodated to provide macrocyclic products in comparable yields to products obtained from the unsubstituted precursors, *e.g.* *E*-**6d** (58%). The amount of monomeric species was found to decrease considerably when the reaction was applied to smaller ring sizes (*n* = 4 and 3, Table 1), and resulted in the formation of dimers **7a** and **7b**. This offers a potential route to macrolide dilactone antibiotics, *e.g.* pyrenophorins.[9] Another interesting feature was that only *E*-geometry products were obtained for products of ring sizes 14 to 20 (Table 1) despite the fact that either *E*- or *Z*-precursors could be used for macrocyclisation, *e.g.* *E*-**5c** → *E*-**6c**; *Z*-**5d** → *E*-**6d**. This can be attributed to the fact that although the vinyl group transfers with retention of stereochemistry at the double bond from tin to palladium,[3b] isomerisation of the α,β-unsaturated ketone product takes place rapidly under the reaction conditions and ultimately the thermodynamic *transoid* configuration is observed in the coupled product. Further evidence supporting the formation of the thermodynamic product was seen with ring sizes 11 and 12 where *Z*-double bond geometry was obtained in the product (**5f** and **5g**) from their corresponding *E*-precursors.

The mechanism of the cross coupling can be described as 'template driven' by the palladium catalyst, but also of prime importance is the 'effective molarity' as lower yields were obtained both at high concentrations (50–10 mmol dm^{-3}) due to intermolecular products, and at low concentrations (2 mmol dm^{-3}) where protodestannylation was predominant.

The optimal temperature and solvent found for intramolecular macrocyclisation to γ-oxo-α,β-unsaturated esters differs from that reported for intermolecular coupling of acid chlorides to organotins where polar solvents have been argued to play an important role in electrophilic cleavages of carbon–tin bonds.[3c] Indeed attempted intramolecular coupling of *E*-**5b** under the optimised intermolecular conditions[3b] (65 °C, 30 h, $CHCl_3$, 1 atm CO) resulted in intermolecular coupling and destannylation reactions with poor yields (<20%) of macrocyclised product *E*-**6b**. This points to an important feature for successful Stille macrocyclisation reactions where intermolecular processes effectively compete that *entropic factors should be maximised and enthalpic factors minimised.*

In conclusion, we have found a facile and versatile route to γ-oxo-α,β-unsaturated macrolides of ring sizes 11–20 employing palladium-mediated cross coupling and have exploited it to the synthesis of natural products.

‡ **6c**, 4-Oxohexadec-2-en-15-olide, ^1H NMR (200 MHz): δ 1.30 (3H, d, *J* 6.5 Hz, 15-Me), 1.18–1.80 (18H, br, m), 2.43–2.70 (m, 5-H_2), 5.01–5.16 (m, 15-H), 6.66, 7.20 (AB, *J* 16 Hz, 2-H, 3-H).

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