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SYNTHESIS OF A PYRENOPHORIN PRECURSOR, 7-HYDROXY-4-OXO-2-OCTENOIC ACID BY THE DIRECT PALLADIUM CATALYZED COUPLING OF AN ACRYLIC TIN REAGENT WITH AN ACID CHLORIDE

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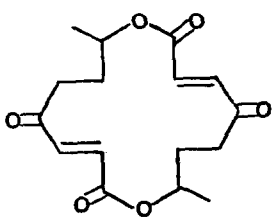
Abstract. A palladium catalyzed coupling reaction of an organotin reagent bearing acrylate functionality with an acid chloride serves as a method to introduce both a ketone and an acrylate functionality into a carbon framework; thus the coupling reaction of 4-t-butyldiphenylsiloxypentanoyl chloride with benzyl 3-tributylstannylacrylate gave a 71% yield of benzyl 7-t-butyldiphenylsiloxy-4-oxo-2-octenoate, which was converted to the ketal of 7-hydroxy-4-oxo-2-octenoic acid, a precursor to the macrolide antibiotic, pyrenophorin.

The β-carboxyvinyl group occurs widely in many natural products, particularly the antibiotic natural macrolides such as pyrenophorin,[1] vermiculin,[2] elaiophylin,[3] colletodiol,[4] grahamimycin A_1[5] and mycinolideIV.[6] For the synthesis of such products the development of a reagent containing an acrylic building block that could be coupled with other carbon frameworks was a particularly desirable objective.

The synthesis of the macrolide antibiotic ( )-pyrenophorin (1)[1] has been achieved by several routes,[7,8] including the dimerization of the ketal or dithiane protected hydroxy acids 2.[9,10] Described herein is the synthesis of 2a utilizing the palladium catalyzed



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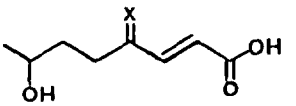


2 a. X= $-OCH_2CH_2O-$

b. X= $-S(CH_2)_3S-$

coupling of an organotin reagent containing the acrylate building block with an acid chloride[11] as the key step in the synthesis of the carbon framework of 2.

The coupling of the appropriately functionalized acid chloride (3) with 3-tributylstannylacrylate reagent (4) to yield ketone 5 was envisaged as a relatively simple, direct route to 2 (Scheme 1). Because the palladium catalyzed ketone synthesis is

mild and will tolerate a wide variety of functional groups on both the acid chloride and organotin coupling partners,[11] this coupling method has the advantage that the acrylate functionality can be introduced directly to yield the 4-keto-2-alkenoate unit with minimal protection.

The acid chloride coupling partner (**3**) was synthesized from -valerolactone through a disilyl hydroxy acid, hydrolysis of which gave the free acid in a 71% yield from -valerolactone. Treatment of the silyl protected acid with oxalyl chloride gave the corresponding acid chloride **3**, which was used without further purification. The t-butyldiphenyl silyl protecting group was required during conversion of the acid to the acid chloride, as other protecting groups such as allyl, t-butyldimethylsilyl, and THP were extruded with concomitant regeneration of -valerolactone.

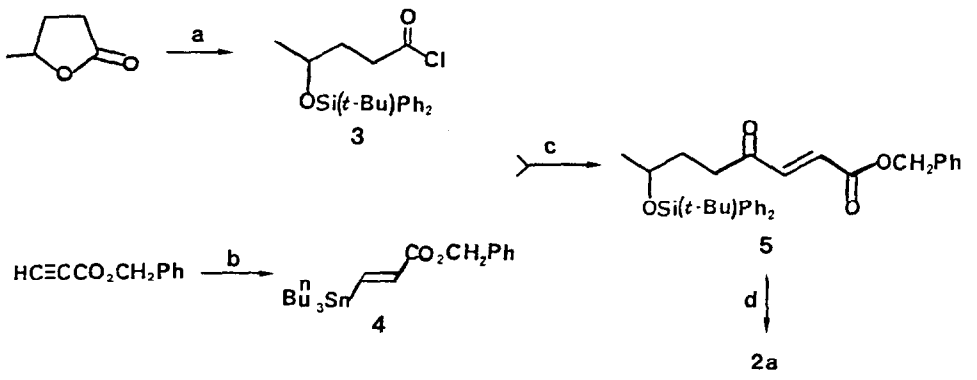
Of a number of available methods[12,13] for the synthesis of the organotin coupling partner, the radical hydrostannation of benzyl propiolate was carried out to give a 1:1 mixture of E- and Z-isomers (**4a**) in 90% yield. Use of the benzyl ester suppressed the polar addition product, 2-tributylstannylacrylate, which is formed in the hydrostannation of methyl propiolate.[14] The E,Z-isomers were separated by medium pressure LC (silica gel, 2% ethyl acetate-hexane).

The coupling of **3** with **4** was carried out as follows: A solution of **3** [prepared from 200 mg (0.561 mmole) of lactone, 253 mg (0.561 mmol) of **4** and 10 mg (1.3×10^{-2} mmol) of benzylchlorobis(triphenylphosphine)palladium(II) in 2 mL of chloroform was flushed with carbon monoxide. The mixture was sealed in a tube and heated to 65°C for 18 h, after which an additional 150 mg (0.330 mmol) of **4** was added, and the reaction was allowed to continue for 12 h. The mixture was poured into ether and washed with an equal volume of aqueous potassium fluoride. The precipitated tributyltin fluoride was removed and the filtrate was concentrated and treated with ethyl acetate to precipitate the remaining tin fluoride. The organic product was purified by medium pressure LC (silica gel, 10% ethyl acetate:hexane) to give 200 mg (71%) of **5**. The carbon monoxide was necessary for the high yield since low yields were obtained under nitrogen or air. Presumably this was due to decarbonylation of the acylpalladium catalytic intermediate prior to coupling, which was suppressed in the presence of carbon monoxide.

The ketalization of **5** gave the ketal in 76% yield. The basic hydrolysis of the ester followed by silyl deprotection with tetrabutylammonium fluoride gave **2**[7] in 70% yield from the ketal.

The overall yield of **2** from -valerolactone was 27%. Since the R- and S-enantiomers of valerolactone are both available,[15] no reactions enroute to **2** involve bond breaking at the chiral center and the Mitsunobu reaction[16] for the dimerization of **2** is highly stereospecific, both enantiomers of **2** and the naturally occurring (R,R)-pyrenophorin should be available by this method.

Scheme I



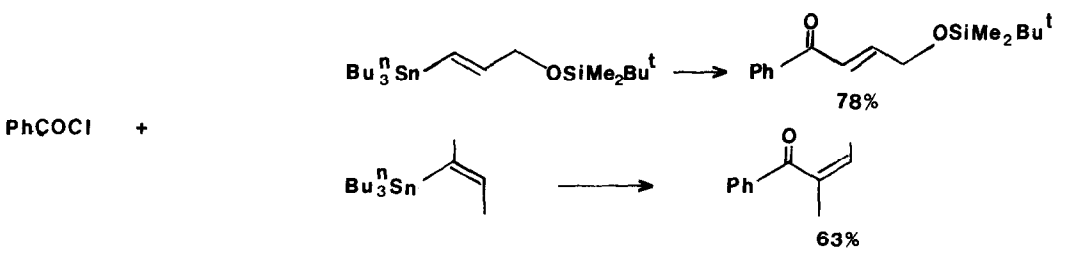
[a](i) 2.4N aq KOH (1 eq), 12 h, 25°C. (ii) Bu^tPh_2SiCl (2.2 eq), imidazole (2.5 eq), 50°C, 24 h (96% i and ii). (iii) 2.4N KOH, Bu^n_4NOH, H_2O, reflux 15 h. (74%). (iv) $C_2O_2Cl_2$ (1.5 eq), CH_2Cl_2, 25°C, 12 h.

[b]Bu^n_4SnH, AIBN, 65°C, 15 h.

[c]1.6 eq 4, 2.4 mole % benzylchlorobis(triphenylphosphine)palladium(II),[6] $CHCl_3$, CO (1 atm), 65°C, 30 h (71%).

[d] (i) $(CH_2OH)_2$ (2.1 eq), $HC(OEt)_3$ (1.9 eq), 0.1 mL $BF_3{\cdot}Et_2O$, C_6H_6, reflux 24 h (76%). (ii) 2.4N KOH, Bu^n_4NOH, THF, (92%). (iii) $Bu^n_4NF{\cdot}3H_2O$ (2.5 eq), THF, reflux 44 h (76%).

Generally, this palladium catalyzed coupling reaction can be carried out with other functionality present in either coupling partner, and with retention of double bond geometry from the vinyl tin reagent.



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