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Efficient Synthesis of the Left-Hand Subunit of Milbemycin β3 Using a Suzuki Coupling Reaction.¥

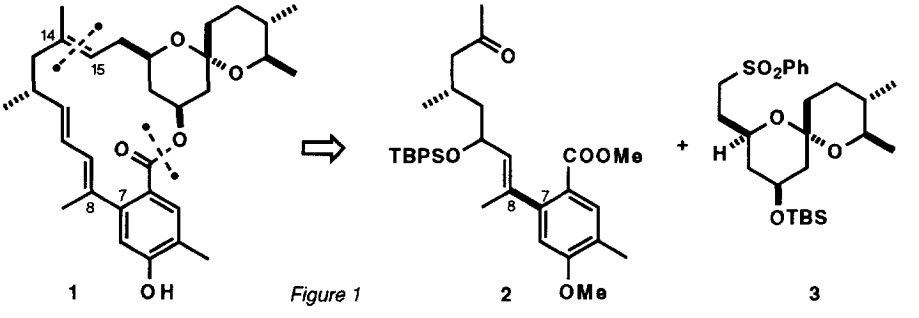
István E Markó,*[a] Fiona Murphy[a] and Simon Dolan[b]

[a]*Université Catholique de Louvain, Département de Chimie, Laboratoire de Chimie Organique, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium.* [b]*Glaxo-Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.*

¥ Dedicated with deep respect to Professor Akira Suzuki

Abstract: The efficient synthesis of the left-hand subunit of the antiparasitic agent milbemycin β3 using a Suzuki coupling is described. The unique role played by thallium carbonate in this palladium-catalysed reaction is discussed.

Milbemycin β3 (MBβ3) **1** is one of the simplest members of the potent milbemycin/avermectin family of antiparasitic agents.[1] As part of a research programme aimed at the profound *de novo* modification of the structure of these anthelmintic agents, with the ultimate aim of using combinatorial chemistry techniques, we required an efficient synthesis of milbemycins and avermectins and selected milbemycin β3 as our test substrate.



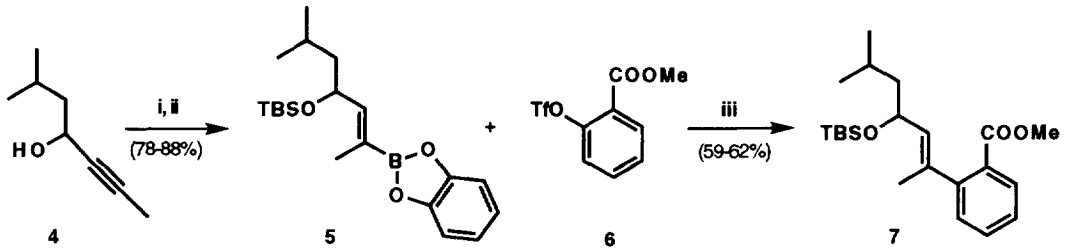
1 *Figure 1* 2 3

Although several elegant syntheses of this natural product have been reported,[2] the shortest route still requires ~25 steps[3] and is clearly unsuitable for our purpose. Therefore, more concise avenues towards MBβ3 **1**, based on the Intramolecular Silyl Modified Sakurai methodology that we reported previously,[4] were explored. In this Letter, we describe our successful endeavour in preparing the fully functionalised fragment **2** ready to be appended to spiroketal **3** (Figure 1).

Retrosynthetic analysis of MBβ3 **1** suggested obvious disconnections at the lactone function as well as at the C_{14}-C_{15} double bond, generating the two subunits **2** and **3**.[5] It was then recognised that fragment **2** could be assembled via a Suzuki coupling[6] (formation of bond C_7-C_8) of a tetrasubstituted aromatic and an *E*-vinylborane. However, before embarking on the synthesis

of **2**, we decided to perform a model study to verify the feasibility of this strategy (Figure 2).

The requisite starting material, propargylic alcohol **4**, was readily prepared by addition of 1-propynylmagnesium bromide to 3-methylbutanal (74-79% yield). Regioselective hydroboration necessitated the discrimination between the alkyne termini and was achieved by adjusting the steric hindrance around C_3 of the acetylene. Thus, alcohol protection using the bulky *tert*-butyldimethylsilyl (TBS) group followed by hydroboration with neat catecholborane smoothly gave regio- and stereo-isomerically pure *E*-vinylborane **5**. The crucial Suzuki coupling between **5** and triflate **6** was then attempted using standard conditions and the desired functionalised styrene derivative **7** was isolated in good yield. Reassured by this incursion into the model study, we then tackled the synthesis of fragment **2**.



i = TBSCl, Et_3N, DMAP, CH_2Cl_2, 20°C; ii = catecholborane, 70°C; iii = 5%$Pd(PPh_3)_4$, K_3PO_4 (1.5 eq), dioxane, 85°C.

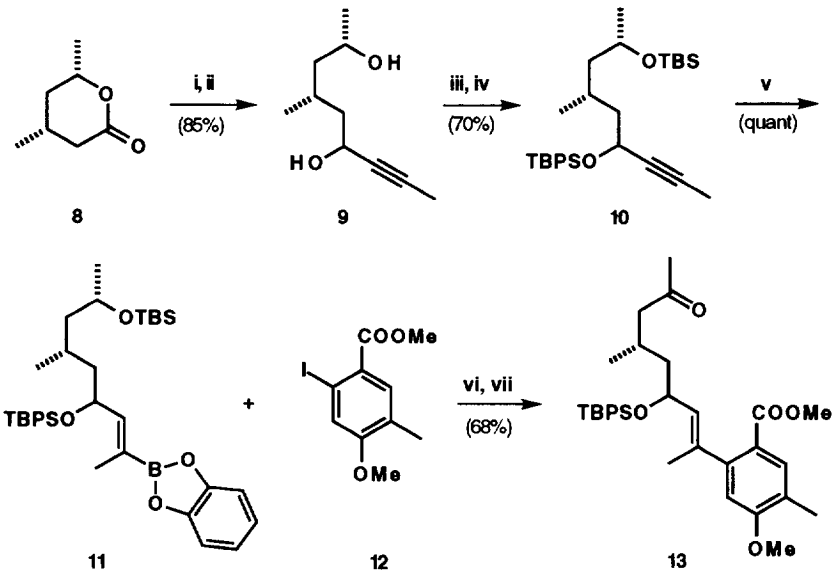
Figure 2

Partial reduction of the lactone function of 4,6-dimethylvalerolactone **8**[7] into the corresponding lactol followed by subsequent addition of 1-propynylmagnesium bromide afforded diol **9** in 85% overall yield. Selective protection of the propargylic alcohol function was achieved by reacting diol **9** with *t*-butyldiphenylsilyl chloride, in the presence of 4-DMAP (5 mol%). Further silylation of the secondary alcohol with TBSCl afforded the *bis*-silylated derivative **10** in 60% overall yield from lactone **8**. Hydroboration (catecholborane, neat, 70°C) resulted in essentially quantitative formation of the *E*-vinylborane **11**. The crucial Suzuki coupling was next attempted employing the previous conditions and totally failed to afford the desired coupling product. Surprised by this unexpected misfortune, we altered systematically various parameters of this reaction. However, extensive modification of the solvent, additives, palladium catalysts and ligands[8] only resulted in the recovery of the unreacted aromatic iodide **12** accompanied by variable amounts of reduction product. This observation suggested that the oxidative addition of the palladium catalyst did indeed take place but that transfer of the vinyl group was the unsuccessful step in the catalytic cycle.

Whilst Kishi showed that resilient couplings of this type could be brought to fruition using TlOH,[9] Suzuki utilised the corresponding Tl_2CO_3 to promote some alkyl-aryl/alkyl-vinyl coupling reactions.[10] The presence of an ester function in aromatic fragment **12** precluded the use of TlOH and we decided to initially study the effect of TlOEt. Disappointingly, mediocre

yields of product **13** (12% yield) were obtained.

However, in the presence of Tl_2CO_3, a smooth reaction took place giving, after simple filtration of the insoluble greenish-yellow TlI, the desired styrene derivative in repeatedly high yield. Jones oxidation in the presence of KF[11] chemoselectively produced the methyl ketone **13** in 68-70% overall yield from vinylborane **11** (Figure 3).



i = Dibal, toluene, -70°C; **ii** = $BrMgCCCH_3$ (3.3 eq), THF, 35°C; **iii** = TBPSCl, Et_3N, DMAP, CH_2Cl_2, -10°C to 20°C; **iv** = TBSCl, Et_3N, DMAP, CH_2Cl_2, 20°C; **v** = neat catecholborane,70°C; **vi** = 10%$Pd(OAc)_2$, 20%PPh_3, Tl_2CO_3 (1.8 eq), CH_3CN, 80°C; **vii** = CrO_3, H_2SO_4, H_2O, acetone, KF, 0°C.

Figure 3

The unique ability of Tl_2CO_3 in successfully promoting this reaction is noteworthy. It is well-known that Suzuki couplings between vinylboranes and arylpalladium iodide species can be difficult and that activation of either or both the Pd(II) salt (by removal of the halogen atom) and the vinylborane (by formation of an ate complex) is sometimes required. This reasoning formed the basis for the use of NaOEt by Suzuki[12] and TlOH by Kishi.[9] The superiority of Tl_2CO_3 over other thallium salts may originate from the generation of the supernucleophilic borate-thallium complex **14** produced by decarboxylation of carbonate adduct **15** (Figure 4). Alternatively, transfer of the thallium carbonate onto cationic palladium (II) salt **16**, followed by loss of CO_2 would also generate a highly reactive ion pair **19** which will recombine to afford the coupling product **13**.

In summary, an efficient and flexible synthesis (5 operations, 7 steps, 40% overall yield) of the fully functionalised left-hand subunit of milbemycin β3 has been achieved, using as the key-step a Suzuki coupling reaction. Thallium carbonate has been found to play a decisive role in this coupling process, the intimate details of which are still a matter of speculation. Further work

towards the coupling of fragment **2** with spiroketal **3**, and completion of the total synthesis of MBβ3, as well as the study of the mechanism of action of thallium carbonate in this and related Suzuki couplings are currently underway in our laboratory. The result of these investigations will be reported in due course.

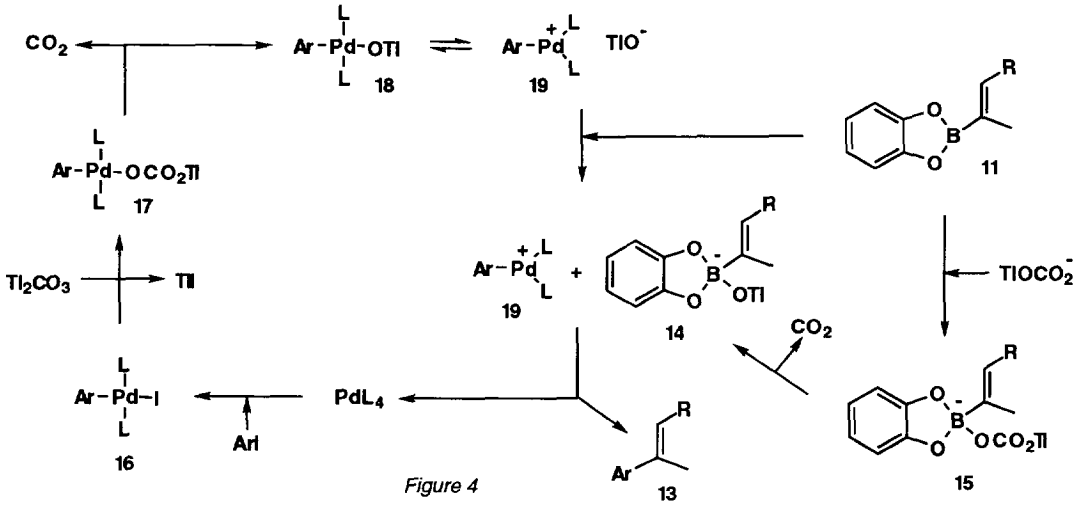


Figure 4

Acknowledgment

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