Tetrahedron Letters,Vol.30,No.50,pp 7115-7116,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A NEW ROUTE TO SPIROACETALS AND THE CONSTRUCTION OF A MODEL FOR THE SYNTHESIS OF PHYLLANTHOCIN

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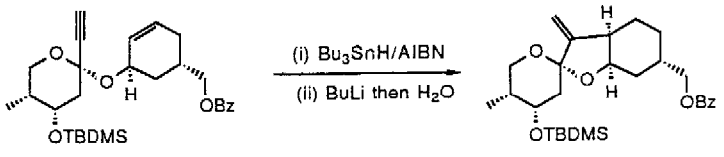
Abstract

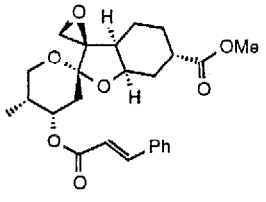
A new route to spiroacetals is presented which relies on a tin mediated radical cyclisation. This reaction has been applied to a model for phyllanthocin construction.

The functionalised spiroacetal unit is widely found in biologically important natural products.[1] The antineoplastic agent phyllanthoside is one such important natural product and its aglycone phyllanthocin (1) is a key target for phyllanthoside synthesis.[2]

We envisaged a rapid route into the phyllanthocin skeleton using a tin mediated radical cyclisation shown in Scheme 1.

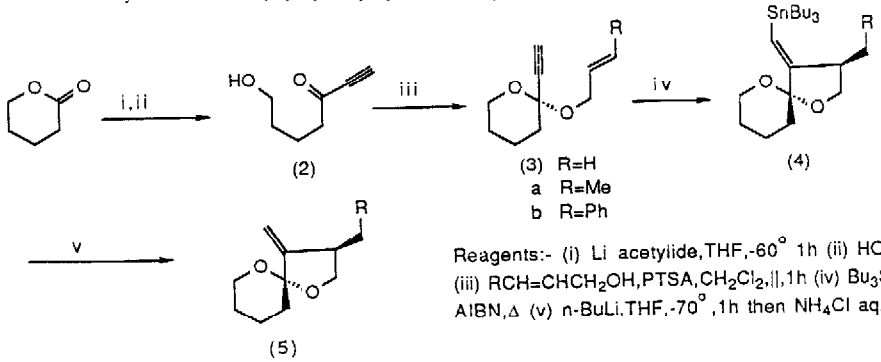


Scheme 1



(1)

Our initial experiments focused on the development of a new spiroacetal synthesis using the idea set out in Scheme 1. Reaction of δ-valerolactone with lithium acetylide gave the acetylenic ketone (2) in 91% yield. Acid catalysed addition of allyl alcohol to the ketone (2) proceeded smoothly yielding the acetal (3) (79% PTSA/CH_2Cl_2/Δ), which on heating with neat tri-n-butyltin hydride[3] in the presence of a catalytic (5 mol%) amount of AIBN gave the alkenylstannane (4) (85%) (Scheme 2).



(2)

(3) R=H
a R=Me
b R=Ph

(4)

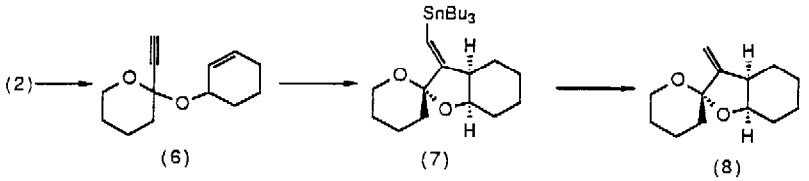
(5)

Reagents:- (i) Li acetylide,THF,-60° 1h (ii) HOAc (iii) RCH=CHCH$_2$OH,PTSA,CH_2Cl_2,||,1h (iv) Bu_3SnH AIBN,Δ (v) n-BuLi,THF,-70°,1h then NH_4Cl aq.

Scheme 2

A number of methods for the removal of the tri-n-butyltin residue from (4) were tried (I_2, RuO_4, SiO_2, HF, Bu_4NF) with no success. Treatment of (4) with n-butyllithium at -78°C however, cleanly removed the tri-n-butyltin group and an aqueous quench gave the spiroacetal (5) in 78% yield.[4] This method offers a rapid entry into spiroacetals with the added advantage that the alkenyl anion derived from the reaction of (4) with n-butyllithium can be intercepted with a range of electrophiles. The possibility of Stille coupling also exists for these versatile intermediates.

Reaction of the keto alcohol (2) with cyclohexenol is particularly interesting as it offers a very flexible and straightforward entry into the phyllanthocin ring system (Scheme 3). The acetal (6) was formed in 69% yield from the acid catalysed addition of cyclohexenol to (2).[5]



Reagents:- (i) 2-cyclohexen-1-ol,PTSA,CH_2Cl_2,1h then K_2CO_3 (69%) (ii) Bu_3SnH,AIBN, Δ (60%) (iii) n-BuLi,THF,-78° 1h then NH_4Cl aq.

Scheme 3

Destannylation of (7) with n-butyllithium gave the spiroacetal (8), a model for the synthesis of phyllanthocin (1). Further results in this area and progress on our total synthesis of phyllanthocin will appear in full at a later date.

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4. 270 MHz($CDCl_3$) δ 5.17(1H,d,J2.8), 5.00(1H,d,J2.8), 4.04(1H,dd,J8.0, 8.0), 3.89(1H, ddd,J11.6, 11.6, 2.7), 3.69(1H,m), 3.45(1H,dd,J8.3, 10.0), 2.81-2.72(1H,m), 1.85-1.45(6H,m) and 1.14(3H,d,J6.7).

5. All new compounds were subjected to full analysis and stereochemical data was determined by nmr analysis.

(Received in UK 29 September 1989)