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Synthesis of (+)-Squamostanal-A : a Bioactive Acetogenin of Annonaceae

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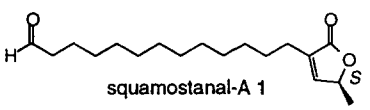
Key words: butenolides; acetogenins of Annonaceae.

Abstract: Squamostanal-A (5*S*-3-(12-formyldodecyl)-5-methyl-2,5-dihydrofuran-2-one) was synthesized in 4 steps from a commercially available starting material. This *pseudo*-natural compound, probably an oxidation product of acetogenins of Annonaceae, may serve as a useful synthon for the total synthesis of solamin or squamocin.

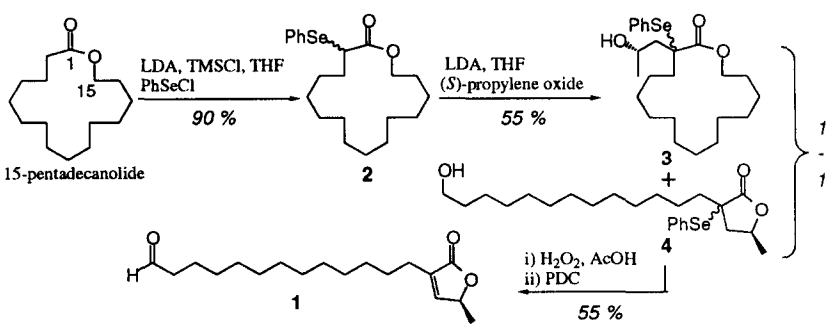
Squamostanal-A **1** was isolated from the seeds of *Annona squamosa* and characterized, by usual spectroscopic methods (NMR, mass spectrometry, and circular dichroism), as (5*S*)-3-(12-formyldodecyl)-5-methyl-2,5-dihydrofuran-2-one[1]. **1** is probably an oxidation product of squamocin, also isolated from the same plant material. Furthermore, such degradative products (aldehyde or the corresponding carboxylic acid) are easily obtained by oxidative processes from other acetogenins[2,3].



squamostanal-A 1

Eventhough it is probably an artifact of isolation and purification steps, like muricatacin[4], **1** may serve as a very useful chiral building block for the total synthesis of acetogenins of Annonaceae[5]. Therefore we wish to report its total synthesis in a very few steps and high overall yield from an inexpensive starting material, 15-pentadecanolide (Scheme 1).

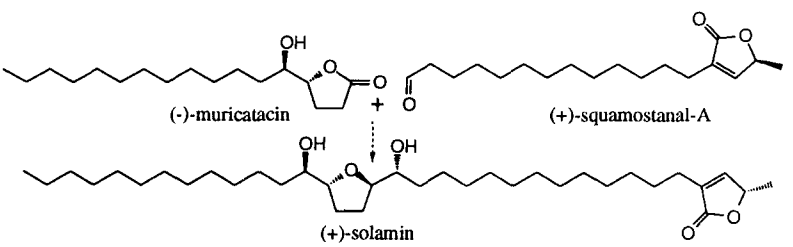
Scheme 1



15-pentadecanolide, in the presence of 1 eq. of TMSCl, was enolized with one equivalent of LDA at -78 °C, and then 1 eq. of phenylselenium chloride was added. After usual work up the seleno derivative **2** was obtained in 90 % yield after purification by flash chromatography on silica gel. Then, **2** was enolized at -78°C with 1 eq. of LDA and 2.5 eq. of (*S*)-propylene oxide were added and then temperature was allowed to reach 20 °C and stirring was maintained 12 hours. It was expected that the macrolactone **3** should give rise to the trans-lactonized product, namely the butyrolactone **4**, the supposed most stable lactone ring. However, surprisingly, a 1:1 mixture of lactones **3** and **4** was obtained. Indeed, the thermodynamic equilibrium between **3** and **4** shows clearly a small difference of stability between the two compounds. After separation, **4** was first oxidized with H_2O_2 in acidic medium leading to the selenoxide derivative which afforded directly the corresponding butenolide by *syn* elimination at 0 °C. The hydroxy butenolide was then treated with PDC to afford the desired product **1** with $[\alpha]_D$ = + 27 (c = 0.67, $CHCl_3$). Spectroscopic data of **1** are in accord with those of natural squamostanal-A. Of course, the use of (*R*)-propylene oxide would eventually lead to (-)-squamostanal-A. Therefore, this strategy allows the access of both enantiomers of the natural product.

In conclusion, **1** is easily accessible from a commercially available starting material in four steps and 10 % overall yield (not optimized), and will be a useful building block[6] for the synthesis of solamin, through a cross coupling reaction with muricatacin (Scheme 2).

Scheme 2



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References and notes

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