Tetrahedron Letters,Vol.28,No.2,pp 221-224,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# SYNTHESIS OF A HYDROXY DIHYDROFURAN ACETAL RELATED TO AZADIRACHTIN: A POTENT INSECT ANTIFEEDANT

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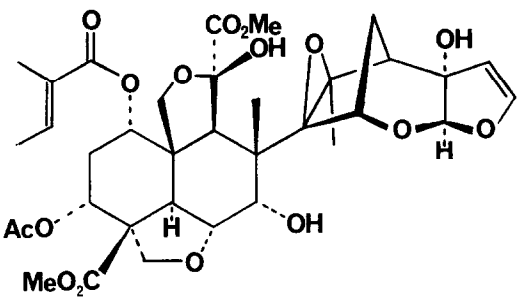
*Summary: The synthesis of novel hydroxy dihydro and tetrahydrofuran acetals modelled on the insect antifeedant azadirachtin is described.*

Azadirachtin (1) is one of a number of insect antifeedants of the limonoid family isolated from the neem tree Azadirachta indica (A. Juss).

(1)

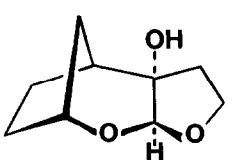



There is a considerable growing interest in neem extracts for possible commercial development as novel pest control agents.

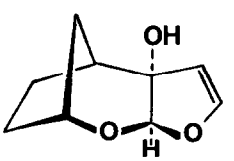
Now that the correct structure of azadirachtin (1) has been determined by X-ray[1] and NMR techniques[2] the stage is set to study the functional groups responsible for activity. In studies directed towards the total synthesis of a natural product, it is important to develop a flexible approach which is applicable, not only to the total synthesis, but also to the preparation of compounds which can be used to probe such relationships. We have already shown in the diterpene area during our work on clerodane antifeedants that synthesis of partial structural units can afford active compounds[3].

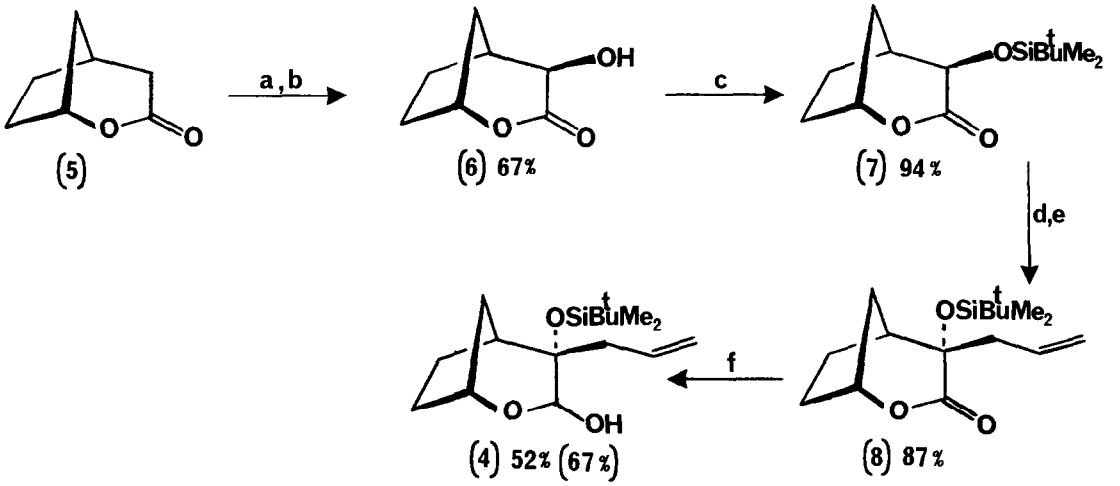
Others have described methods for the preparation of bis-furan acetals as potential antifeedants since these groups are also common to many clerodanes[4-8]. To date however the preparation of simple model compounds based on the hydroxy dihydrofuran acetal fragment of azadirachtin have not been reported. In this letter we describe the stereocontrolled synthesis of compounds (2) and (3) and show that (3) is a potent insect antifeedant.

(2)



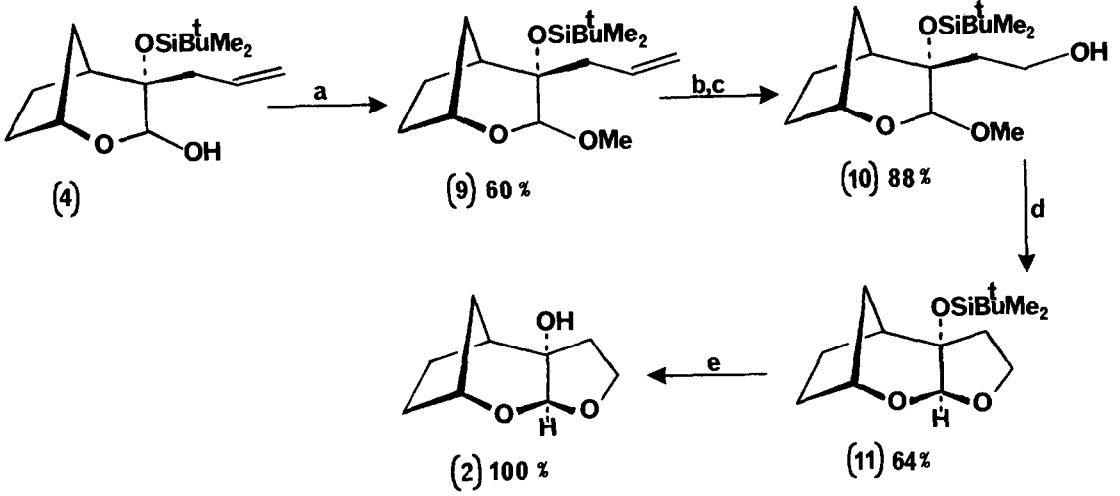

(3)





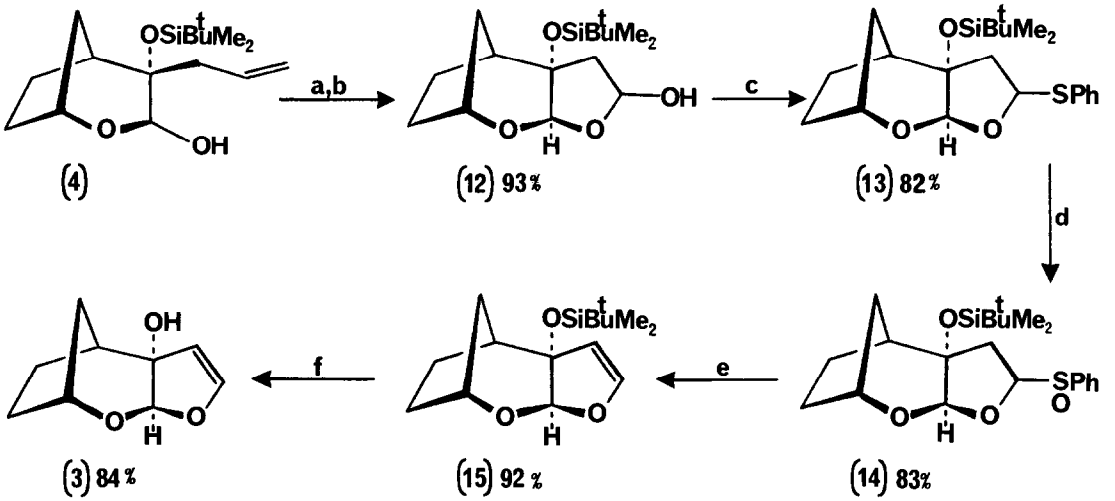

a) 1.1 eq. LDA,THF, -78°C b) 1.2 eq. MoOPH, -78°C to 0°C c) 1.2 eq. TBDMSCl, 4 eq. imidazole, DMF, RT d) 1.1 eq. KDA, -78°C e) 2 eq. allyl bromide, -78°C f) 0.6M DIBAL, toluene, -78°C.

The key intermediate (4) for these syntheses was readily available, on a large scale from the bicyclic lactone (5)[9]. Oxidation of the lithium enolate of (5) with MoOPH complex[10] at -78°C occurred from the least hindered face to give a single isomer (6) as confirmed by X-ray crystallography †. Standard silyl protection of (6) using t-butyldimethylsilyl chloride/imidazole in dimethylformamide followed by treatment with potassium diisopropylamide (potassium t-butoxide, diisopropylamine, n-butyllithium in tetrahydrofuran) at -78°C gave the potassium enolate which quenched from the least hindered face with allyl bromide to give the allyl lactone (8) in 87% yield. No other isomer was apparent by tlc analysis or 250 MHz $^1$H NMR spectroscopy and the relative stereochemistry of (8) was confirmed by single crystal X-ray analysis on a t-butyldimethylsilyl deprotected derivative. Lactone (8) was converted into the lactol (4) (52%, 67% based on recovered starting material) by treatment at -78°C with a 0.6M diisobutylaluminium hydride solution added with the aid of a syringe pump over several hours.




a) MeOH, trace c.$H_2SO_4$ b) $O_3$, MeOH, -78°C c) excess $NaBH_4$, RT d) trace Amberlyst 15, MeCN e) excess TBAF, THF, RT

The labile lactol (4) was protected as its methyl ether (9) in 60% yield by treating a methanolic solution with a trace of conc. sulphuric acid (60%). Subsequent ozonolysis in methanol followed by reductive workup (sodium borohydride) afforded the anomeric alcohols (10) (88%). Compounds (10) were cyclised in acetonitrile, using Amberlyst 15 as the transacetalization catalyst, to give (11) in 64% isolated yield. Deprotection of (11) using an excess of tetra n-butylammonium fluoride in tetrahydrofuran gave (2) quantitatively.




a) $O_3$, DCM, -78°C b) 1.1 eq. $PPh_3$, RT c) 1.4 eq. PhSH, MeCN, trace Amberlyst 15, 4A sieves d) 1.1 eq. m-CPBA, DCM, RT e) Toluene, Δ f) excess TBAF, THF, RT.

Lactol (4) was treated with ozone in dichloromethane at -78°C to give ozonides which were stable to dimethylsulphide, but which decomposed over 2h at RT in the presence of excess triphenylphosphine to give ketal lactol (12) in entirely the closed form††.

Attempted dehydration of lactol (12) directly to the enol (15) using a variety of reagents failed. However, conversion of (12) to the sulphide (13) proceeded smoothly in 82% yield using thiophenol. Oxidation of (13) with m-chloroperbenzoic acid in dichloromethane gave a mixture of three sulphoxides in a combined yield of 83%. Thermolysis of these in boiling toluene gave the enolether ketal (15) (92%) which was cleanly deprotected with tetra n-butylammonium fluoride in tetrahydrofuran to give the required hydroxy enolether ketal (3) (84%).

BIOASSAYS were undertaken on final instar larvae of the lepidopteran Spodoptera littoralis (Boisd) reared on a bean-based diet[11]. Glass fibre discs (Whatman GF/A 2 x 1 cm diameter) were used as the test substrate. The discs were made palatable by the addition of 100µl sucrose solution (0.05M). The test compounds were dissolved in 90% ethanol to give a range of concentrations from 1ppm-100ppm. A 100µl aliquot of the solution containing the test compound was applied to the treated disc (T) and a 100µl aliquot of 90% ethanol applied to the control disc (C). When dried, the weighed discs were presented as a pair (C vs T) to individual larvae in a petri dish for up to 8h so that never more than 50% of any disc was eaten. The discs were reweighed and the Inhibition Index calculated. The Index identifies both phagostimulants (-ve values) and deterrents (+ve values) with a range from +100 to -100. Positive values greater than 75% (1,2,3) indicate

exceptionally potent antifeedants, whereas those between 0-25% are considered to have poor activity (6). These results show that the novel hydroxy dihydrofuran acetal (3), which represents a fragment of azadirachtin, is itself nearly as potent an antifeedant as azadirachtin.

BIOASSAY RESULTS

| | Compound | Inhibition Index (C-T/C+T)% | | |
|---|---|---|---|---|
| | | 100ppm | 10ppm | 1ppm |
| | 6 | 15.8±9.63 | | |
| | 2 | 100.0±0.00 | 69.1±2.24 | 54.8±7.25 |
| | 3 | 100.0±0.00 | 97.7±8.89 | 65.8±2.27 |
| Azadirachtin | 1 | 100.0±0.00 | 100.0±0.00 | 98.8±1.11 |

Clearly these synthetic approaches should also find application in the synthesis of natural products.

*We acknowledge financial support for this work from the SERC and Rohm and Haas Co., Spring House, Pennsylvania, USA. We thank Dr. Zev Lidert (Rohm and Haas Co.) for useful discussions.*

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† We thank Dr. D.J. Williams, Imperial College, for X-ray crystallographic results.

†† No evidence of any open hydroxy aldehyde form was evident by $^1H$ NMR spectroscopy in $CDCl_3$ solution.

(Received in UK 29 October 1986)