A model synthetic approach towards the furanacetal component of azadirachtin: a potent insect antifeedant

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Dedicated with respect to Professor Sukh Dev on his 80th birthday
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Abstract
In this article, a model synthetic approach towards the furanacetal component of azadirachtin has been described from α-D-glucose. Tandem radical cyclization was the key step for the formation of the desired tricyclic system. The reaction provided a bicyclic system instead of the desired tricyclic molecule. The reason for the unsuccessful tandem cyclization was proposed to be mainly energy factors.

Keywords: α-D-glucose, azadirachtin, tandem radical cyclization

Introduction
The fused cyclic acetal moiety is embodied in a large number of natural products many of which display interesting biological properties, ranging from the highly toxic and carcinogenic aflatoxins\(^1\) to insect antifeedants such as clerodin\(^2\) and azadirachtin \(^1\). The furo[2,3b]pyran unit is conserved in the azadirachtin, whilst several clerodanes and aflaxtoxins contain the more common furo[2,3b]furan moiety. Many methods exist for the synthesis of the furo[2,3b]furans.\(^3\) In contrast, relatively few synthesis of the homologous furo[2,3b]pyrans have been reported.\(^4\)

We wished to develop and work out a much more flexible and relatively shorter route of the bioactive portion of the most potent insect antifeedant azadirachtin. Azadirachtin\(^5\) belongs to the C-seco-limonoid group of triterpinoids and is found in neem tree, or Indian lilac, *Azadirachta indica*. Although the first synthesis of the \(^1\) is yet to be accomplished, nevertheless the biological testing has so far relied upon the natural azadirachtin, their chemically modified fragments, and a few synthetic analogs. The simple compounds \(^2\) and \(^3\), components of the \(^1\), have been synthesized and screened for antifeedant activity.\(^6\) Both of these compounds were found to be active against African leaf worm *Spodoptera lottoralis*. The compound \(^3\) was found to be as potent as the natural product \(^1\) itself at 10 ppm and 1 ppm concentrations. This finding suggested that the
dihydrofuranacetal moiety of the azadirachtin is mainly responsible for its biological activity and therefore stimulated synthesis of both the racemic and enantiomerically pure dihydrofuranacetal analogs.

Shibasaki and coworkers have synthesized an intermediate which closely resembles the dihydrofuranacetal portion of 1 during their efforts directed towards its total synthesis starting from (S)-(-) ethyl lactate. The contribution of Ley and coworkers in the structure determination of azadiractin, synthesis of important intermediates and analogs, and their bioevaluation is unsurmountable. Starting from a 3,4-O-isopropylidenegalactal, Fraser-Reid and coworkers have been able to synthesize a dihydrofuranacetal analog in 7.7% overall yield in 17 steps. In this paper, we discuss full details of model synthetic studies on the tricyclic dihydrofuranacetal moiety of azadirachtin from α-D-glucose.

**Results and Discussion**

Ley’s report that the structural fragment 3 is as active an insect antifeedant as azadirachtin itself prompted us to design a flexible synthetic route to this portion so that simpler analogs could be synthesized. With this aim, a strategy based on an α, β-unsaturated lactone and the corresponding lactol of the required number of carbon atoms as important intermediates was conceived. In retrosynthetic analysis, as shown in scheme I, the key step would be a tandem radical cyclization in which the tricyclic framework would be formed in one step and provide a handle for the synthesis of analogs. The internal carbon of the propargyl function would act as a nucleophilic radical for the tandem cyclization. Another important feature is the recognition of a partially-hidden carbohydrate symmetry in the target molecule, paving the way for a potential synthesis of the enantiomerically pure material. For the model study, we chose X₁=H in structure 4. α-D-glucose as the starting material for the synthesis of optically active target molecule 4 was identified.
Scheme 1. Retrosynthetic analysis.

Over the years carbohydrates have been recognized as naturally occurring organic molecules that are relatively cheap and replenishable source of cyclic and acyclic forms, chain lengths and oxidation or reduction states. They are endowed with a wealth of stereochemical attributes and contain a plethora of functional groups available for chemical exploitation.\(^\text{13}\) \(\alpha\)-D-Glucose 9 is one of the simplest and cheapest carbohydrates used in innumerable syntheses. \(\alpha\)-D-glucose was recognized as an ideal starting material for the synthesis because of several reasons. Firstly, the chirality of anomeric center and C-5 carbon atom of the 9 is preserved in the final molecule. Secondly, the possibility of generation of an olefin in the ring as it is in the molecule 7 from the hydroxyl groups at C-2 and C-3. And thirdly, the advantage offered by the hydroxyl group at C-4 of the 9, which can either be dehydroxylated or preserved for analog preparation. In the compound 7, exchange of anomeric center with propargyl alcohol and one carbon extension in the side chain via \(S_n2\) displacement by cyanide anion at C-6 offered a simple strategy for the synthesis of the 6, a substrate for tandem radical cyclization.

For the synthesis of the 2,3-unsaturated propargyl glucoside 13 or its acetate derivative, we required tri-\(O\)-acetyl-D-glucal in large quantities. Tri-\(O\)-acetyl-D-glucal 10, which is inexpensively and readily available from \(\alpha\)-D-glucose, was prepared according to the literature procedure.\(^\text{14}\) \(\alpha\)-D-glucose was peracetylated to penta-\(O\)-acetyl-\(\alpha\)-D-glucose which was, then, converted to the corresponding tetra- \(O\)-acetyl-\(\alpha\)-D-glucosyl bromide using red phosphorus and bromine. Glycosyl bromide was reduced, in situ to tri- \(O\)-acetyl-\(\alpha\)-D-glucal 10 which was hydrolysed to glucal 11 using a catalytic amount of sodium methoxide in methanol. The primary hydroxyl group in the glucal 11 was selectively tosylated and the secondary hydroxyl groups were, then, acetylated to obtain a new glucal 12 in one pot.\(^\text{14b,15}\) Then the glucal 12 was treated with propargyl alcohol in the presence of \(BF_3\cdot Et_2O\) in chloroform at a low temperature to obtain propargyl glucoside 13. The tosylate group of the 13 was displaced by cyanide ion by heating it with sodium cyanide in DMSO at a moderate temperature. During this process, the acetate group also hydrolyzed. The compound 14, thus obtained, was reacetylated to afford 15. The framework of the 15 was of the type 6, and was ready for tandem free radical cyclization (Scheme II).
Scheme 2

At this stage, the substrate 15 was to be subjected to tributyltin hydride mediated radical cyclization to obtain the desired tricyclic product of the type 4 as planned in the retrosynthetic scheme. The reaction was expected to undergo tandem cyclization. The addition of the tributyltin radical onto the terminal triple bond would result in the generation of a vinylic radical, which could cyclise to form the C-C bond. Similar kind of reactions are well known in the literature. Although nitriles are not efficient radical acceptors, there are examples in the literature where radical species have been added to nitriles to produce iminium radicals, which then are hydrolyzed to the corresponding ketones. However, the drawback of the reaction is that the intermediate iminium radical easily reverts back if the molecular strain demands and, also, they can rearrange to nitrile stabilized carbon radicals which then react further. With the above background we treated the substrate 15 with tributyltin hydride in the presence of a catalytic amount of AIBN in degassed benzene at reflux for 5 h. Unfortunately, the cyclization stopped at a bicyclic stage and a compound 16 (furo-pyran) was obtained as the sole product (scheme II). The radical cyclization from ring to the nitrile group could not be realized to obtain the desired tricyclic system.

The possible reason for the failure of tricyclic product formation was thought to be a considerable energy difference between the intermediate depicted by 17a and 17b in scheme III. The conformation necessary for the reacting centers to come in to close proximity for the C-C
bond formation is 17b, and a small portion of it in this equilibrium would have been sufficient for the tandem cyclization. But the presence of all equatorial substituents and the anomeric stabilization in the representation 17a prevented the ring flip to attain the conformation 17b to an extent that no

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\begin{align*}
\text{17a} & \quad \leftrightarrow \quad \text{17b}
\end{align*}
\]

Scheme 3
double cyclization resulted. Further modifications of the schemes are continuing in our laboratory and will be disclosed elsewhere in future.

In conclusion, we have analysed the retrosynthesis of the biologically active portion of the most potent insect antifeedant \textit{viz}. azadirachtin in a conceptually different manner based on the tandem radical cyclization reactions leading to the relatively simple routes for the analog preparation in optically pure form from \(\alpha\)-D-glucose.

**Experimental Section**

3,4,6-Tri-\(O\)-acetyl-D-glucal (10). \(\alpha\)-D-Glucose (60 g, 0.33 mol) was added to a mixture of acetic anhydride (200 g, 1.96 mol) and 70\% perchloric acid (1.2 mL) at 35 °C during 1 h. After addition of red phosphorus (15 g, 0.48 mol), the vessel was cooled in ice-salt mixture, and bromine (90 g, 0.56 mol) was added dropwise with continued stirring at such a rate as to keep the internal temperature below 20 °C. Subsequently in the same way, 15 mL of water was added during a course of 30 min with careful control of temperature. The mixture was filtered and the filter paper washed with little acetic acid. The filtrate contained tetra-\(O\)-acetyl-\(\alpha\)-D-glucopyranosyl bromide. Meanwhile a solution of sodium acetate (160 g, 1.95 mol) in water (250 mL) and glacial acetic acid (200 mL) was prepared. After the solution was cooled in an ice-salt mixture, zinc dust (110 g, 1.68 mol) and cupric sulfate (11 g, 0.04 mol) in water (40 mL) were added to this solution. When the blue color had disappeared, the solution of above-mentioned bromide was added gradually during 1 h keeping the temperature between -10 and -20 °C. Efficient stirring was necessary and was continued for 3 h at 0 °C. The mixture was filtered, and the filter paper was washed with 50\% acetic acid. Water (500 mL) was added to the combined filtrates at 0 °C and the solution was extracted with chloroform (5 x 100 mL). The combined chloroform extracts were washed with iced-water, saturated sodium carbonate solution, and again with cold-water. The solution was dried by addition of calcium chloride, decanted, and evaporated under reduced pressure. The resulting syrup was dissolved in diethyl
ether and petroleum ether was added to the solution to opalescence. Seed aided crystallization provided pure 10 (45 g, 40%); mp 55 °C, lit. 20 53 - 55 °C; [α] D 25 -12.0 (c 2, EtOH); IR (film) 1740, 1640 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ 1.6 - 2.26 (m, 9H), 4.03 - 4.57 (m, 3H), 4.73 - 4.97 (m, 1H), 5.07 - 5.50 (m, 2H), 6.47 (d, J = 6 Hz, 1H).

**Glucal (11).** To a stirred solution of 10 (10 g, 36.73 mmol) in dry methanol (100 mL) was added methanolic solution of sodium methoxide (prepared by dissolving 50 mg of sodium in 2 mL methanol), and the solution was left at room temperature for 2 days. Evaporation of the solvent gave crystalline 11 in quantitative yield, which was used as such for subsequent steps; mp 56 - 58 °C, lit. 14 57-59 °C; [α] D 25 -8.3 (c 2, H₂O), lit. 14 [α] D 25 - 8 (c 1.9, H₂O); IR (film) 3290 cm⁻¹; ¹H NMR (60 MHz, CD₃OD) δ 3.23 - 3.46 (m, 1H), 3.73 - 4.13 (m, 3H), 4.23 - 4.50 (m, 1H), 4.60 - 5.0 (m, 4H), 6.23 - 6.50 (m, 1H).

**3,4-Di-O-acetyl-6-O-(p-toluenesulfonyl)-D-glucal (12).** The α-D-Glucal 11 (5 g, 34.2 mmol) was dissolved in a mixture of pyridine (20 mL) and dichloromethane (10 mL) and cooled to -50 °C. To this, a solution of p-toluenesulfonyl chloride (7.82 g, 41 mmol) dissolved in dichloromethane (20 mL) was added in a dropwise fashion. The solution was stored at -20 °C for 15 h. Acetic anhydride (10.5 g, 102.8 mmol) was added to the same pot at 0 °C and then allowed to stand at rt for 12 h. The reaction mixture was then poured in ice-cold 2N HCl (100 mL) and extracted quickly with chloroform (5 x 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, water and brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The silica gel chromatography provided 12 (10.5 g, 80%) as a solid and approximately 10% of 10 as a side product; Rf 0.38 (ethyl acetate in petroleum ether, 1: 3); mp 100 °C, lit. 15 100 - 101 °C; [α] D 25 +15.8 (c 0.945, CHCl₃); IR (film) 3030, 1740, 1640, 1590 cm⁻¹; ¹H NMR (60 MHz, CD₃OD) δ 2.00 (s, 6H, OAc), 2.47 (s, 3H, benzylic), 4.03 - 4.50 (m, 3H), 4.83 (dd, J = 6, 3 Hz, 1H), 5.00 - 5.50 (m, 2H), 6.37 (d, J = 6 Hz, 1H), 7.33 (d, J = 8 Hz, 2H, aromatic), 7.83 (d, J = 8 Hz, 2H, aromatic).

**Ethynemethyl 4-O-acetyl-2,3-dIDEOxy-6-(p-toluenesulfonyl)-α-D-erythro-hex-2-enopyranoside (13).** To a solution of 12 (1 g, 2.6 mmol) in chloroform (10 mL) at 0 °C were added propargyl alcohol (250 mg, 4.46 mmol) followed by BF₃·Et₂O (180 mg, 1.27 mmol) and allowed to warm to 10 °C over a period of 5 min. A saturated solution of sodium bicarbonate was added and stirring continued for 5 min. Extraction of the reaction mixture with chloroform (3 x 25 mL), drying of the organic layers over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure provided the crude product which was purified by silica gel chromatography to yield 13 (890 mg, 90%) as a liquid; Rf 0.21 (ethyl acetate in petrolenum ether, 1:4); [α] D 25 +100.8 (c 0.60, CHCl₃); IR (film) 3248, 2910, 2120, 1720 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ 2.00 (s, 6H, OAc), 2.37 (t, J = 3.5 Hz, 1H), 2.44 (s, 3H, benzylic), 3.83 - 4.43 (m, 5H), 4.93 - 5.40 (m, 2H), 5.70 - 6.10 (m, 2H, olefinic), 7.36 (d, J = 8 Hz, 2H, aromatics), 7.80 (d, J = 8 Hz, 2H, aromatics).
Ethynemethyl 6-cyano-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside (14). The tosylate 13 (800 mg, 2.1 mmol) was dissolved in DMSO (1 mL) in a dry flask fitted with a guard-tube and dry sodium cyanide (257 mg, 5.25 mmol) was added to it. The contents were stirred at 60 °C for 3 h, poured into cold water, and extracted with ethyl acetate (5 x 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed by silica gel column chromatography to provide pure 14 (284 mg, 70%) as a liquid; $R_f$ 0.18 (ethyl acetate in petroleum ether, 1: 3); IR (film) 3440, 3300, 2930, 2260, 2124 cm$^{-1}$; $^1$H NMR (60 MHz, CDCl$_3$) δ 2.52 (t, $J$ = 2.2 Hz, 1H), 2.67 - 3.03 (m, 2H), 3.40 (bs, 1H, O$_H$), 3.60 - 4.23 (m, 2H), 4.33 (d, $J$ = 2.2 Hz, 2H), 5.20 (d, $J$ = 1 Hz, 1H), 5.60 - 6.20 (m, 2H, olefinic).

Ethynemethyl 4-acetyl-6-cyano-2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside (15). The cyanoalcohol 14 (250 mg, 1.29 mmol) was dissolved in dichloromethane (1 mL) and pyridine (200 mg, 2.53 mmol) was added to it. After cooling to 0 °C, acetic anhydride (170 mg, 1.67 mmol) and a crystal of DMAP were added. The temperature was allowed to rise to rt and stirring continued for 12 h. The contents of the flask were poured into cold dilute HCl and extracted into dichloromethane (5 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, and evaporated to dryness under reduced pressure. The purification over silica gel column provided pure 15 (280 mg, 92%) as a liquid; $R_f$ 0.26 (ethyl acetate in petroleum ether, 1:9); [α]$^25$D +150.9 (c 0.80, CHCl$_3$); IR (film) 3270, 3420, 2240, 2105, 1730 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.06 (s, 3H, OAc), 2.40 (t, $J$ = 2.4 Hz, 1H), 2.50 - 2.77 (m, 2H), 5.20 - 4.28 (m, 1H), 4.33 (d, $J$ = 2.4 Hz, 2H), 5.00 - 5.37 (m, 1H), 5.80 (s, 2H, olefinic). Anal. Calcd. for C$_{12}$H$_{13}$NO$_4$: C, 61.27; H, 5.53; N, 5.95. Found: C, 61.40; H, 5.64; N, 5.84.

Cyclisation of 15 using n-Bu$_3$SnH. The nitrile 15 (100 mg, 0.425 mmol) was placed in benzene (40 mL) in a dry round-bottomed flask under an atmosphere of nitrogen and the reaction mixture was saturated with nitrogen. While refluxing, a solution of tributyltin hydride (250 mg, 0.85 mmol) and AIBN (10 mg, catalytic), dissolved in benzene (10 ml), was added to it using a syringe pump during a period of 5 h. After the addition was complete, the reflux was continued for 1 h. The solvent was evaporated under reduced pressure and the mixture was chromatographed on silica gel to give pure 16 as a liquid (129 mg, 56 %; a mixture of α- and β-isomers with E- and Z-olefin α : β 4: 1; E: Z = 4:1); $R_f$ 0.67 (ethyl acetate in petroleum ether, 1:9); IR (film) 2240, 1730 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.87 - 0.96 (m, 15H), 1.24 - 1.34 (m, 6H), 1.45 - 1.56 (m, 6H), 1.62 - 1.70 (m, 1H), 2.06 - 2.10 (m, 3H), 2.23 - 2.33 (m, 1H), 2.62 - 2.71 (dd, $J$ = 5.4, 3.3 Hz, 2H), 2.73 - 2.84 (m, 1H), 4.00 - 4.17 (m, 1H), 4.19 - 4.32 (m, 1H), 4.51 - 4.63 (m, 1H), 4.65 - 4.75 (m, 1H), 5.28 (d, $J$ = 3.9 Hz, 0.2H, β-anomeric), 5.34 (d, $J$ = 4.5 Hz, 0.8H, α-anomeric), 5.58 - 5.74 (m, 0.2H, E-olefinic), 5.82 - 6.00 (m, 0.8H, Z-olefinic); MS (Fab, m/z): 528 (M$^+$+1), 526 (M$^+$+1), 524 (M$^+$+1).
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References


