A stereoselective carbohydrate route to optically active furo[2,3-b]benzofuran ring system

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Dedicated to Professor Sukh Dev on his 80th anniversary

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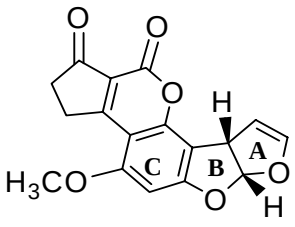
Abstract

A stereoselective synthesis of the furo[2,3-b]benzofuran ring system **8**, commonly encountered in aflatoxins has been achieved by exploiting the inherent chirality of D-glucose. Ozonolysis of **4**, followed by selective hydrolysis of the formate ester intermediate **6**, yielded directly the target ring system **8**, in good over all yields leading to the right stereochemistry at the ring junction corresponding to the naturally occurring isomer of aflatoxin.

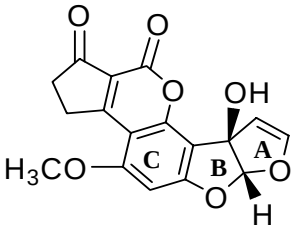
Keywords: Aflatoxin, furo[2,3-b]benzofuran, stereoselective synthesis, tri-*O*-acetyl-D-glucal, Ferrier rearrangement, Claisen rearrangement

Introduction

Carbohydrates are being increasingly employed as starting materials for natural product syntheses, the driving force being the availability of *chiral* centers which are inherent to sugar molecules[1]. Fungal metabolite aflatoxins (Figure 1) are a group of structurally related compounds, having the furo[2,3,b]benzofuran ring system in common. Although several elegant routes have been reported for the synthesis of this ring system and for total synthesis of aflatoxins,[2] there have only been a few reports on the enantioselective synthesis[3] and there has been no report on the synthesis of this framework starting from carbohydrates.



Aflatoxin B_1



Aflatoxin M_1

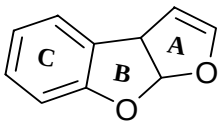


Figure 1. Aflatoxins.

Results and Discussion

Herein**,** we report the stereoselective synthesis of the ABC ring framework of aflatoxin from a carbohydrate precursor. A retrosynthetic analysis of the furo[2,3,b]benzofuran, ABC ring framework (Figure 2) shows that it can be readily obtained starting from a sugar derivative, i.e. a 3-*C*-arylglycal, possessing a defined stereochemistry at C-3 (carbohydrate numbering) and readily synthesized from tri-*O*-acetyl-D-glucal. Thus, we envisaged an enantioselective synthetic route to the furo[2,3,b]benzofuran ring system.

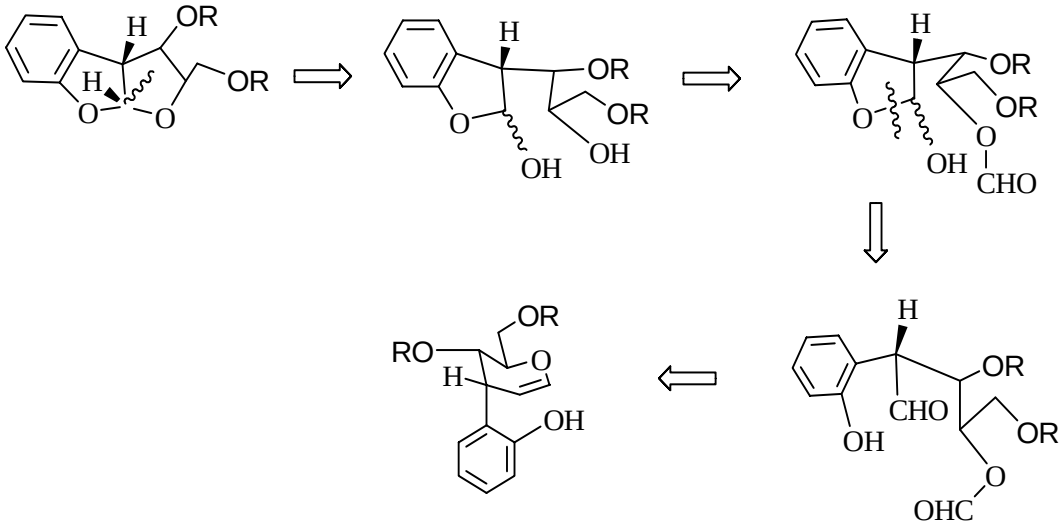
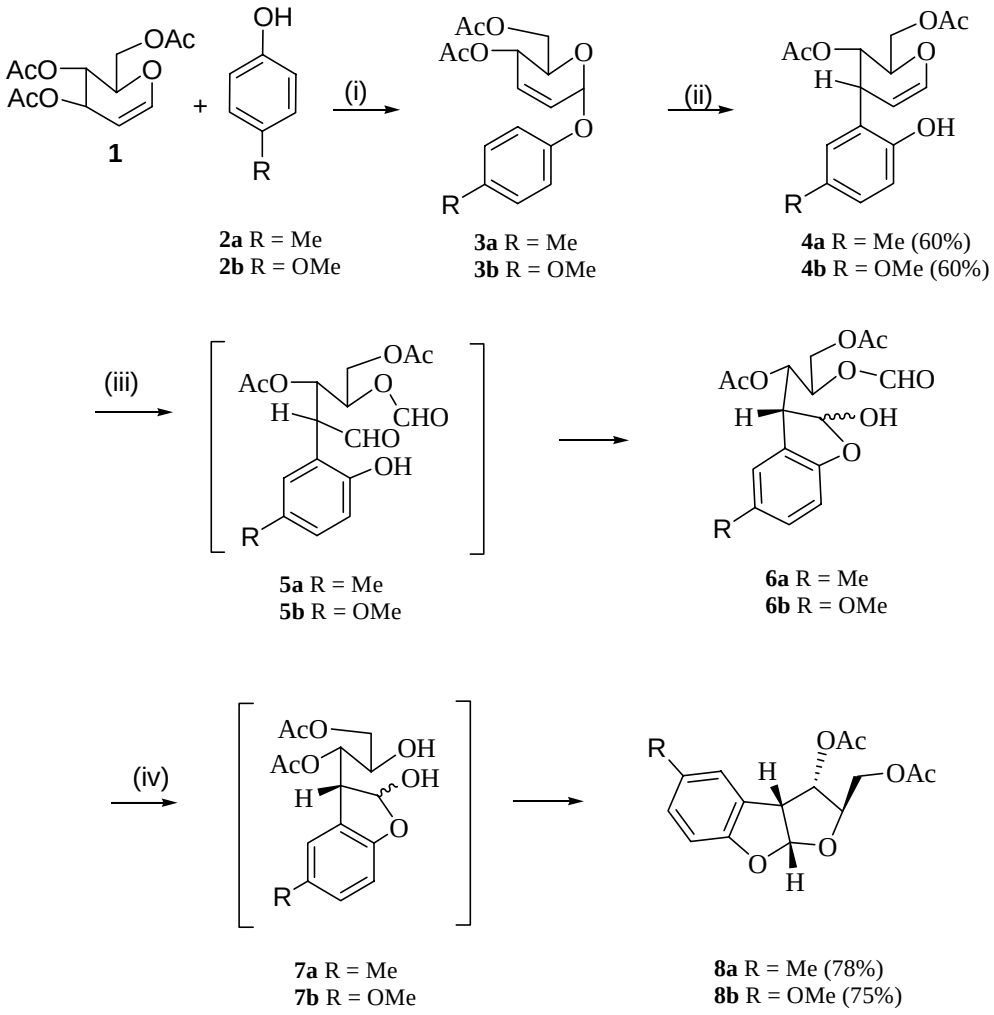


Figure 2. Retrosynthetic analysis of ABC ring framework.

The synthesis of the envisaged starting material, viz. 3-*C*-arylglycal **4**, with well established stereochemistry at the benzylic carbon, has been reported earlier from our laboratory[4] starting from commercially available tri-*O*-acetyl-D-glucal **1**, making use of Ferrier and Claisen rearrangements (Scheme 1).

Glycal **4a,** was ozonized to yield directly the hemiacetal **6a**, without any trace of the intermediate aldehyde **5a,** thereby precluding the possibility of epimerization at the α carbon of aldehyde **5a**. Since the crude ozonized product was pure enough (NMR), the formate ester was hydrolysed immediately so as to avoid any epimerization during purification. The selective hydrolysis of the formate by the literature method[5] of refluxing in AcOH-MeOH mixture did not stop at the alcohol stage **7a,** but led directly to the acetal **8a** thereby generating the ABC ring framework of aflatoxin in good yields (Scheme 1).



Scheme 1. Synthesis of ABC ring framework. (i) chlorobenzene, reflux, 5h (ii) N,N-diethylaniline, reflux, 36h, (iii) O_3, dichloromethane, -78^o C (>95%), (iv) AcOH:MeOH (2:3), reflux, 5h.

By unambiguously setting-up the stereochemistry at C-3 during the earlier "carbohydrate stage" of the molecular metamorphosis, the stereochemistry at the ultimate AB ring junction gets automatically fixed due to the 5-5 *cis* fusion as established by the coupling constants of the relevant protons. Hence, this route leads to the synthesis of the optically active furo[2,3-b]benzofuran ring system with stereochemistry identical to that of the natural isomer of aflatoxin.

Experimental Section

General Procedures. IR spectra were recorded on Shimadzu IR spectrophotometer either as neat or in chloroform solution. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra were recorded on a Jeol 400 MHz NMR spectometer and the chemical shifts are reported with reference to the

internal tetramethysilane (^{1}H) and the central line of $CDCl_3$ (^{13}C). In the ^{13}C NMR the nature of the carbons were determined by recording the off resonance spectra. Optical rotations were recorded on a JASCO polarimeter and the high resolution mass spectrum was recorded on Finnigan mat 8230 spectrometer.

General procedure for ozonolysis.

In a two-necked round bottom flask fitted with a gas inlet on one neck and a gas outlet on the other, the substrate **4** was taken in dichloromethane (25 mL). The gas outlet was connected to a bubble bath containing potassium iodide solution to monitor the completion of reaction. The reaction mixture was cooled to – 78^o C in an acetone/liquid nitrogen bath. Ozone was passed from the ozonizer until a pale blue colour remained in the reaction mixture i.e until the potassium iodide solution in the bubble bath became yellow. The reaction was quenched by injecting in 0.5 mL of dimethylsulphide and then warmed to room temperature. The dichloromethane was removed over vacuum pump before analyzing the crude formate ester **6**. The crude product **6** obtained was immediately used for the next step.

3*R*-2,3-dihydro-2-hydroxy-3-[1'*S*,2'*R*,-1'-acetoxy-2'-formyloxy-3'-acetyloxy]-propyl-5-methyl-benzo[b]furan (6a). Yield : > 95 %, IR (ν, cm $^{-1}$) : 3380, 3010, 1730, ^{1}H NMR spectrum (400 MHz $CDCl_3$) δ (ppm) : 1.93 (s, 3H), 2.08 (s, 3H), 2.28 (s, 3H), 2.62 (s, 1H), ,3.51 (bs, 1H), 4.25 (m, 2H), 5.36 (m, 1H), 5.48 (m, 1H), 5.97 (s, 1H), 6.69 (d, $J_{7,6}$ = 8.0 Hz, 1H), 6.97 (d, $J_{6,7}$ = 8 Hz, 1H), 7.04 (s, 1H), 8.04 (s, 1H).

3*R*-2,3-dihydro-2-hydroxy-3-[1'*S*,2'*R*,-1'-acetoxy-2'-formyloxy-3'-acetyloxy]-propyl-5-methoxy-benzo[b]furan (6b). Yield : > 95 %, IR (ν, cm $^{-1}$) : 3376, 2998, 1737, ^{1}H NMR spectrum (400 MHz $CDCl_3$) δ (ppm) : 1.99 (s, 3H), 2.1 (s, 3H), 2.72 (s, 1H), 3.48 (bs, 1H), 3.75 (s, 3H), 4.2 – 4.3 (m, 2H), 5.23 (m, 1H) 5.48 (m, 1H), 5.86 (s, 1H), 6.66 (d, $J_{7,6}$ = 8.0 Hz, 1H), 6.87 (d, $J_{6,7}$ = 8 Hz, 1H), 7.00 (s,1H, H-4), 8.02 (s, 1H).

General procedure for the selective hydrolysis of formate ester.

The crude formate ester **6** was taken in a single neck RB flask and dissolved in a solution of acetic acid : methanol (3:2). The reaction mixture was refluxed in an oil bath for 5 hours until complete disappearence of the formate ester 6 was observed. The solvents were evaporated using a rotary evaporator. The residue was dissolved in dichloromethane and washed with saturated sodium bicarbonate solution, then with water, dried over anhydrous sodium sulphate and filtered. The solvent was removed under low pressure in rotary evaporator and the product purified by column chromatography over silica using a mixture of hexane and ethyl acetate (9:1) as the eluant to obtain **8**.

2*R*,3*S*,3a*R*,8a*R*-5-methyl-2-acetoxymethyl-3-acetoxy-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran (8a). Yield : 70%, $^{32}[\alpha]_D$: + 64.96 (c = 1.1, CH_2Cl_2), IR (ν, cm $^{-1}$) : 2994, 1734, 1630, ^{1}H NMR spectrum (400 MHz $CDCl_3$) δ (ppm) : 2.09 (s, 3H), 2.11 (s, 3H), 2.27 (s, 3H), 4.05 (m, 1H), 4.15 (dd, *J* = 4.88 Hz, *J* = 12.2 Hz, 1H), 4.28 (dd, *J* = 8.8 Hz, *J* = 5.85Hz, 1H), 4.38 (dd, *J* =12.2 Hz, *J* = 2.44 Hz, 1H), 5 15 (t, *J* = 8.8 Hz, 1H), 6.32 (d, *J* = 5.85 Hz, 1H), 6.76 (m, 2H), 7.00 (m, 1H), The structure of **8a** was further established by a double irradiation study. ^{13}C NMR

spectrum (50.33 MHz) δ (ppm) : 20.81 (q), 20.902 (q), 48.118 (d), 62.371 (t), 73.649 (d), 76.59 (d), 109.07 (d), 109.88 (d), 121.92 (s), 126.52 (d), 130.00 (d), 130.37 (s), 158.03 (s), 170.58 (s), 170.73 (s), HRMS: 306.107854 (obs), 306.11034(cal).

2*R*,3*S*,3a*R*,8a*R*-5-methyl-2-acetoxymethyl-3-acetoxy-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran (8b). Yield : 65 %, $^{32}[\alpha]_D$: 69.46 (c = 1.3 CH_2Cl_2), IR (ν, cm $^{-1}$) : 3007, 1727, 1610, ^{1}H NMR spectrum (400 MHz $CDCl_3$) δ (ppm): 2.09 (s, 3H), 2.11 (s, 3H), 3.73 (s, 3H), 4.05- 4.15 (m, 2H), 4.28 (dd, *J* = 8.6 Hz, *J* = 5.85 Hz, 1H), 4.33 (dd, *J* =12.2 Hz, *J* = 2.44 Hz, 1H), 5.15 (t, *J* = 8.6 Hz, 1H), 6.33 (d, *J* = 5.85 Hz, 1H), 6.56 (m, 1H), 6.73 (m, 2H), ^{13}C NMR spectrum (50.33 MHz) δ (ppm) : 20.1 (q), 20.5 (q), 48.38 (d), 53.43 (q), 62.52 (t), 73.66 (d), 75.99 (d), 108.07 (d), 110.08 (d), 117.52 (d), 119.83 (d), 128.78 (s), 153.07 (s), 158.03 (s), 170.58 (s), 170.73 (s).

Conclusions

Thus, a simple and concise route to the optically active furo[2,3,b]benzofuran ring system (incorporating additional functionality in the A ring, with the possibility of further manipulation) has been achieved starting from a readily available glycal.

Acknowledgements

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