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# SYNTHESIS OF FLUORINE-CONTAINING NATURAL GASTRODIN AND ITS ANALOGUES

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## SUMMARY

Reactions of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**2**) with p-hydroxybenzaldehyde, trifluoromethyl and fluoro substituted aniline and 2-amino-6-fluorobenzoic acid gave 1-O-(P-formylphenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**3**), 1-N-(m-trifluoromethylphenylamino)-2,3.4.6-tetra-O-acetyl-β-D-glucopyranoside (**4a**), 1-N-(2-carboxyl-3-fluorophenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**4b**) and 1-N-(p-fluorophenyl)-N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**4c**) respectively. 1-O-(perfluoro-2-propoxypropionyl)-O-benzyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**7**) and 1-O-(m-trifluoromethylphenylaminobenzylidene)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**8**) were also prepared in subsequent reactions. Conversion of the acetyl group to the hydroxyl group yielded the corresponding deprotected product. The compounds formed have been characterized by analysis, IR, $^{1}H$ and $^{19}F$ NMR and mass spectroscopy. The influence of phase-transfer catalysts on the reactions is discussed.

## INTRODUCTION

Gastrodin is isolated from the Gastrodin elata. It has been used clinically in treatment of psychoses, schizophrenia, paranoia and manic-depression, showing good sedative and hypnotic activity without side effects. Zhou has totally synthesized gastrodin [1]. Clin-

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ical tests demonstrate that the synthetic gastrodin posseses similar pharmacological effects to natural gastrodin. Fluorine alters electronic effects, imparts increased oxidative and thermal stability, and leads to increased lipid solubility in membranes. Fluorine-containing steroids have proven invaluable as adrenocortical and anti-inflammatory drugs. Huang et al. first synthesized fluorinated gastrodin [4]. Our major interests are to synthesize fluorine-containing derivatives of gastrodin and its analogues to obtain novel biologically active compounds.

## RESULTS AND DISCUSSION

α,β-Glucose was treated in water at 45-47°C for two hours to get α-glucose (**1**), m.p.146-148°C. **1** was treated according to the procedure described by F.Korosy [3] to obtain 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**2**). Reaction of **2** with p-hydroxybenzaldehyde afforded p-formylphenyl-β-D-glucopyranoside (**3**), which further reacted with m-trifluoromethylaniline, resulting in 1-O-(m-trifluoromethylphenylaminobenzylidene)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**8**). Treatment of **2** with fluoro or trifluoromethyl-substituted aniline gave 1-N-(m-trifluoromethyl (or fluoro) phenylamino)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**4**). Deprotection of **4** furnished 1-N-(m-trifluoromethylphenylamino)-β-D-glucopyranoside (**5**).

All of the products mentioned above were prepared in aqueous homogeneous systems in low yield, because the desired products crystallize with difficulty from the viscous slurry. We found that when those reactions were carried out in a two phase system using chloroform as solvent and adding about 0.01% of a fluorine-containing phase-transfer catalyst such as trimethyl-3-(perfluoro-2-propoxypropionylamino)-propylammonium bromide the yield of products was increased significantly (to about 10-20%) and the reactions are relatively clean. The fluorine-containing phase-transfer catalyst provides a facile method to prepare aryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosides.

The $^{19}F$ NMR of **4a**(Rf=m-$CF_3$) and **4c**(Rf=P-F) each showed two sets of signals at 15.6, 16.0, and 50.1, 50.4 ppm respectively, demonstrating the presence of two configurations of each compound.

Reduction of **3** with $NaBH_4$ gave p-hydroxymethylphenyl-2,3,4,6-

tetra-O-acetyl-β-D-glucopyranoside (**6**) which reacted further with perfluoro-2-propoxypropionyl fluoride (ppF) in the presence of sodium hydroxide to give **7**. Reaction of **6** with ppF did not occur when using $Et_3N$.

## EXPERIMENTAL

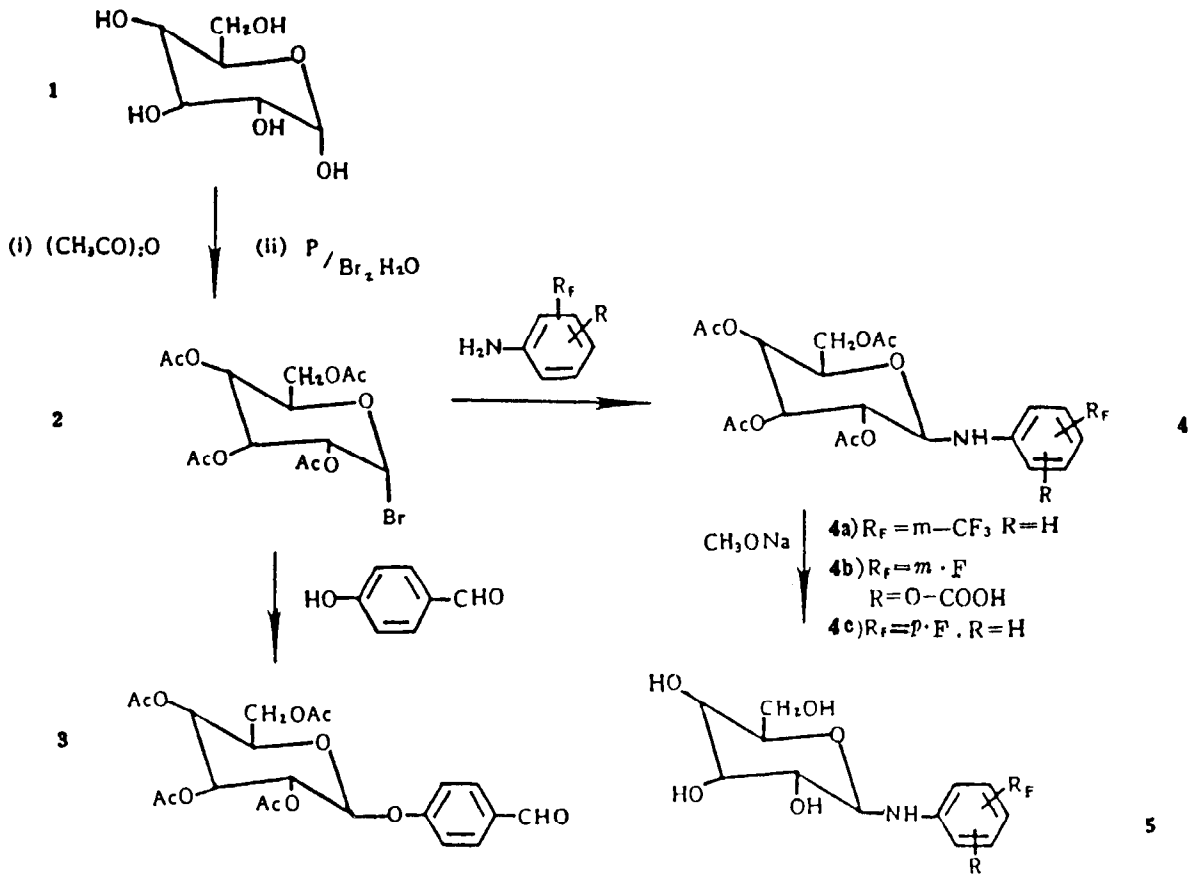
Melting points were taken in open glass capillaries and are uncorrected. $^1H$ NMR and $^{19}F$ NMR spectra in $CDCl_3$ or DMSO-d6 were taken on a Varian XL-200 NMR spectrometer. The chemical shifts are reported in ppm, using TMS or $CF_3COOH$ (positive up field) as internal references. Infrared spectra were obtained with a Zeiss-Specord 75-IR spectrophotometer.

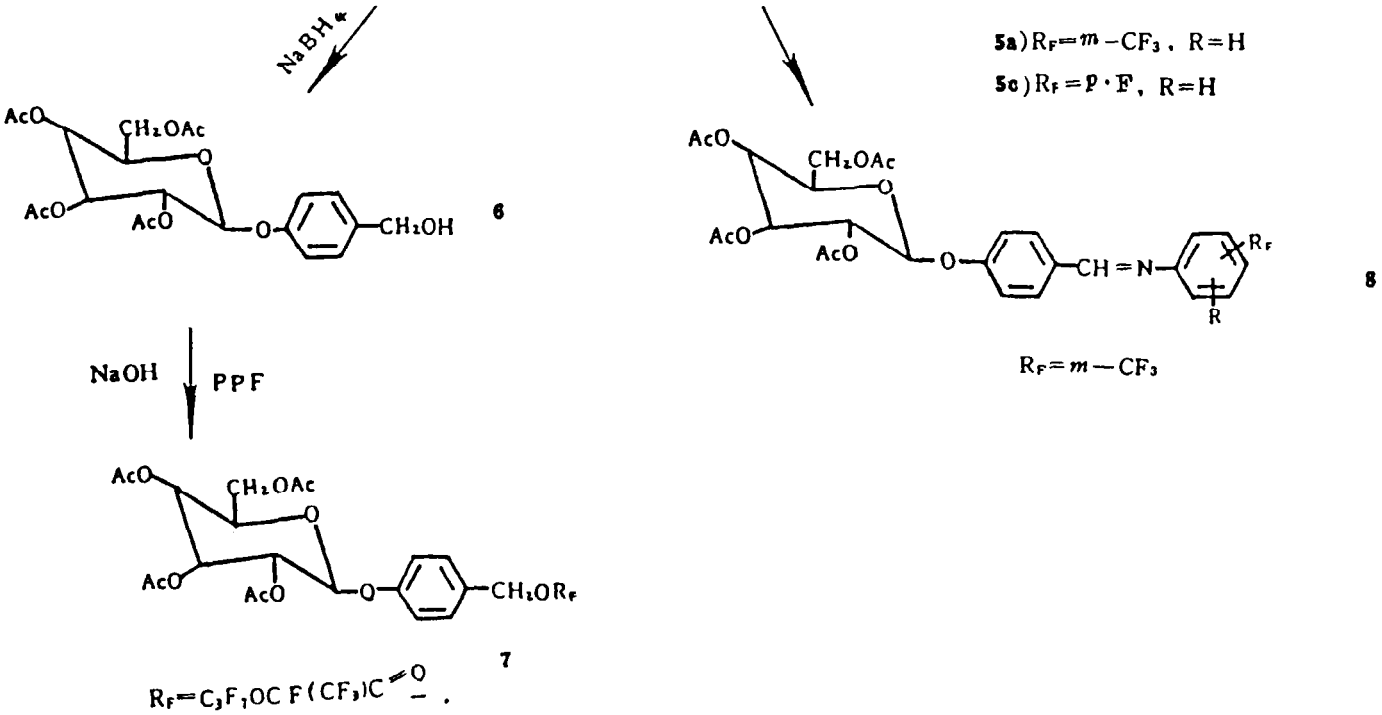
### 2,3,4,6-Tetra-O-Acetyl-α-D-Glucopyranosyl Bromide (2)

40.0ml acetic anhydride was mixed with 0.5g perchloric acid, and 10.0g α-glucose was added in the course of half an hour, taking care that the temperature did not rise above 40 °C. 3.0 g of amorphous phosphorus was added and the flask cooled in an ice-bath. 18.0g bromine was then added gradually, and 36ml water was added dropwise keeping the temperature below 20°C. Chloroform (300ml) was added and the mixture was poured into about 800ml of ice-water and separated and washed with ice-water. The yellow solution was dried with calcium chloride, evaporated in vacuo at 60°C and dissolved in dry ether from which it crystallized on cooling. 17.6g of product was obtained in 85% yield. The m.p 87°C is consistent with that of an authentic example [3].

### 1-O-(perfluoro-2-propoxypropionyl-O-benzyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosides (7)

Treatment of a solution containing 23g (0.056mol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (**2**) in acetone with 10g (0.082mol) of p-hydroxybenzaldehyde gave 8.0g 1-O-(p-formylphenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**3**) according to the procedure described by Zhou et al. [1]. To a stirred solution of 5.6g (0.012mol) **3** in 400ml iso-propanol at 30°C, 0.25g(6.5mmol) $NaBH_4$ was then added stepwise. The reaction mixture was stirred at


1
(i) (CH3CO)2O
(ii) P / Br2 H2O
2
3
4
4a) RF = m–CF3 R=H
4b) RF = m · F
R=O–COOH
4c) RF = p · F , R = H
CH3ONa
5




Reaction Scheme

25-30°C for 3.5 hours, evaporated in vacuo, and crystallized from ethanol. 4.1g of colorless p-hydroxymethylbenzyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**6**) was obtained in 73% yield, m.p. 106-107°C [1].

To the stirred mixture of 0.65g (1.43mmol) of **6** and 0.66g (2.0 mmol) of perfluoro-2-propoxypropionyl fluoride was added about 0.6g of sodium hydroxide. Stirring was continued for 5 hours. A solution of dilute sodium hydroxide was added to the reaction mixture dropwise until basic to litmus and the solution was evaporated in vacuo. The residue obtained was chromatographed on silica gel using acetone as eluant. 0.7g of pure colorless solid **7** was obtained in 62.5% yield. m.p. 90-91°C, IR(KBr): 3480(m. OH), 1750(S, C=O), 1060(S,C-O-)$cm^{-1}$. $^1H$ NMR ($CDCl_3$): 2.0(12H, m, 4 $CH_3COO$), 3.90(2H, m, $ArCH_2$-), 4.20(2H, m, $-CH_2$-), 4.63(1H, m, 5-H), 5.06-5.26(4H, m, 1-4H), 7.10-7.45(2H, d, Ar-H). $^{19}F$ NMR ($CDCl_3$): 4.0(3F, t, $CF_3$), 4.7(3F, s, $CF_3$), 5.20(4F, m, $CF_2$), 54.0(1F, s, C-F). Anal. calcd for $C_{27}H_{25}F_{11}O_{13}$. $H_2O$. C, 41.34; H, 3.47; F, 26.64. Found C, 41.59; H, 3.09; F, 26.37.

**1-O-(m-trifluoromethylplenylaminobenzylidene)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (8)**

To a stirred suspension containing 1.0g (0.002mol) 1-O-(p-formylphenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**3**) in 25ml ethanol was added 1.8g (0.012mol) m-trifluoromethylaniline. The mixture was refluxed for 3 hours and evaporated in vacuo, giving a yellow viscous liquid which was crystallized from alcohol, 1.25g crystalline product **8** was obtained (95.4% yield) m.p. 110-111°C, IR (KBr): 1750(S,C=O), 1060(S,C-O-), 1610(W,C=N)$cm^{-1}$. $^1H$ NMR (DMSO-$d_6$):1.49-2.50(12H, m, 4 $CH_3CO$), 3.30-3.90(3H, m, 5, 6, 6-H), 4.40-5.20(4H, m, 1-4H), 6.40(4H, m, Ar-H), 7.16-7.60(3H, m, Ar-H), $^{19}F$ NMR (DMSO-$d_6$): -17.0(S, $CF_3$), Anal. calcd. for $C_{28}H_{28}F_3NO_{10}$: C, 56.47; H, 4.74; N, 2.35; $M^+$, 595, Found: C, 56.36; H, 4.82; N, 2.53, $M^+$+1, 596.

**1-N-(m-trifluoromethylphenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (4a)**

To a solution comprising 4.11g(0.01mol) 2,3,4,6-tetra-O-acetyl -α-D-glucopyranosyl bromide in chloroform at room temperature was

added 1.47g(0.01mol) of m-trifluoromethylaniline and 10ml of 10% sodium hydroxide solution. An exothermic reaction set in causing a temperature rise from 16-22°C and the stirring was continued for 3 hours. The reaction mixture was evaporated to remove chloroform. The residue was extracted with ethyl acetate. The extracts were washed with water and dried with sodium sulfate and the solvent evaporated to give 3g of crude viscous product (60% yield). After standing the crude product at room temperature for several days, colorless crystals (**4a**) were obtained. m.p. 113-114°C. IR(KBr): 3350(m, NH), 1750(S, C=O), 1250(S, C-F), $^1$H NMR ($CDCl_3$): 1.90-2.06(12H, m, 4 $CH_3CO$), 4.00-4.20(3H, m, 5, 6, 6-H); 4.25(1H, m, NH), 4.50-4.65(4H, m, 1-4H), 6.50-7.50(4H, m, Ar-H). $^{19}$F NMR ($CDCl_3$): -15.6(S, $CF_3$), -16.0(S, $CF_3$). Anal. calcd. for $C_{21}H_{24}F_3NO_9$: C, 51.32; H, 4.92; N, 2.85; F, 11.60; $M^+$, 491; Found: C, 51.18; H, 5.12; N, 2.87; F, 11.39; $M^+$+1, 492.

**1-N-(2-carboxyl-3-fluorophenyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (4b)**

To a solution containing 0.85g(0.007mol) 2-amino-6-fluorobenzoic acid in 15ml chloroform at room temperature was added 1.10g (0.01mol) triethylamine. The 2.87g(0.007mol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in 10ml chloroform was then added dropwise. The reaction mixture was stirred at reflux temperature for 8 hours. Evaporation of the solvent furnished a viscous product which was crystallized from acetone. The crystallized product (**4b**) was obtained (30.9% yield) m.p. 141-142°C. IR(KBr): 3500(w, OH), 3400(W, NH), 1720(S, C=O), 1215(S, C-F). 1080(S, C-O-)cm-1, $^1$H NMR ($CDCl_3$): 2.30-2.90(9H, m, 3 $CH_3CO$), 3.40-3.90 (3H, m, $CH_3CO$), 4.20-5.00(3H, m, 5,6,6-H), 5.32-6.32(4H, m, 1-4H), 6.42-7.02(3H, m, Ar-H). $^{19}$F NMR ($CDCl_3$): 29.0(1F, S, Ar-F). Anal. calcd. for $C_{21}H_{24}FNO_{11}$: C, 51.96; H, 4.98; N, 2.88; F, 3.92. $M^+$, 485 Found: C, 51.78; H, 4.88; N; 3.15; F, 4.20. $M^+$, 485.

**1-N-(p-fluorophenyl)-N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (4c)**

Treatment of **2** with p-fluoroaniline according to the procedure described above, gave 1.60g **4c** (52% yield) m.p. 120-121°C, IR

(KBr): 3400(m, NH), 1725(S, C=O), 1040(S, C-O-), 1240(S, C-F)$cm^{-1}$. $^1H$ NMR ($CDCl_3$): 2.02-2.20(12H, m, 4 $CH_3CO$), 4.06-4.28(3H, m, 5,6, 6-H), 4.32(m, NH), 4.67-5.36(4H, m, 1-4H), 6.57-6.04(2H, m, Ar-H), 6.64-6.93(2H, m, Ar-H), $^{19}F$ NMR ($CD_3Cl$):50.1(S, Ar-F), 50.4(S, Ar-F). Anal. calcd. for $C_{20}H_{24}FNO9$: C, 54.42; H, 5.48; N, 3.17; $M^+$, 441. Found: C, 54.55; H, 5.63; N, 3.14; $M^+$+1, 442.

**1-N-(m-trifluoromethylphenylamino)-β-D-glucopyranoside (5a)**

**4a** and **4c** were treated in methanol with sodium methoxide at 40-45°C. **5a** and **5c** were obtained in near quantitative yield. **5a**. m.p. 102-104°C. Anal. calcd. for $C_{13}H_{16}F_3NO_5$. $H_2O$: C, 45.75; H, 5.32; N, 4.10; F, 16.70; $M^+$, 323. Found: C, 45.60; H, 4.75; N, 3.95; F, 16.71; $M^+$-2, 321: IR(KBr), 3450-3500$cm^{-1}$(S, OH). **5c**: m.p. 147-148°C, Anal. calcd. for $C_{12}H_{16}FNO_5.H_2O$: C, 49.48; H, 6.23; N, 4.81; F, 6.52. $M^+$, 273. Found: C, 49.63; H, 5.98; N, 4.88; F, 5.99. $M^+$, 273; IR(KBr) 3300(b, OH, NH).

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