Philippine Journal of Science
136 (1): 33-43, June 2007
ISSN 0031 - 7683

Double-bridged Tetrathiafulvalene Macrocycles with m-Xylylene, Trimethylene and Glucose Linkers: Synthesis and Characterization

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The synthesis of novel tetrathiafulvalene (TTF) macrocycles with m-Xylylene, Trimethylene, and Glucose units is reported. The synthesis involves the preparation and stepwise base deprotection of cyanoethyl protected TTF, its reaction with m-xylyldibromide, 1,3-bromopropane and/or acetylated dihaloglucose, followed by deacetylation.

Key Words: Sugar H-bonding, Van der Waal's Interaction

INTRODUCTION

The π-electron donor tetrathiafulvalene (TTF) is redox-active, exhibiting a reversible two-step oxidation. It has desirable characteristics that are exploited to give a variety of uses in molecular, supramolecular, and materials chemistry (Jeppensen et al. 2004; Iyoda et al. 2004; Rovira 2004). When incorporated in a macrocycle, this property can be utilized to influence the complexation of guest molecules. It can also act as a sensor where complexation of ions or molecules is detected by a change in redox property of the host (Jorgensen et al. 1994). Sugars, on the other hand, are polyhydroxylated and capable of forming multiple H-bonding interactions with the guest molecules in a macrocyclic system (Simmonds 1992). They may exhibit high stereospecificity because of the presence of several chiral centers. The macrocycles with TTF and sugar units have potential applications in chemical and pharmaceutical industries, and biological research. For example, they can be used as a valuable tool for drug delivery (Hansen et al. 1992). Molecular systems that are based on host-guest interaction have been synthesized and were found capable of acting as sensors, catalysts, and molecular switches. (Jorgensen et al. 1994; Demiralp & Goddard 1997; Bryce et al. 1998; Jeppensen et al. 2000; Takimiya et al. 2000; Simonsen & Becher 1997; Simonsen et al.1999). Some of these TTF macrocycles are double-bridged type but none so far are with sugar units. In this paper, we describe the synthesis of novel macrocycles containing glucose units.

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MATERIALS AND METHODS

General Methods and Instrumentation

Column chromatography was performed on Camlab silica gel 60 (0.04-0.063 mm/230-400 mesh), and reactions were monitored by thin layer chromatography (Camlab aluminum backed sheets coated with 0.25 mm silica) with UV light, iodine and/or Orcinol monohydrate/sulfuric acid as visualizing agent.

Proton NMR spectra were recorded at 300 MHz on a Bruker AC 300. Peak positions are quoted against the δ scale relative to the residual signal ($CHCl_3$ δ7.27,

DMSO δ2.50) using the following abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad. Carbon-13 NMR spectra were recorded at 75.5 MHz on the Bruker AC 300 and at 67.5 MHz on a Jeol GX 270. The multiplicities of carbon-13 were elucidated using distortionless enhancement by polarization transfer (DEPT) experiments. Two dimensional correlation experiments were obtained on the Bruker AM360.

Infrared spectra were recorded on a Perkin-Elmer 1600 series Fourier Transform Spectrophotometer. Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal Melting Point Apparatus and are uncorrected. Electrospray mass spectra were recorded on a Micromass Platform quadrupole mass analyser. Optical rotations were measured on an Optical Activity AA-100 polarimeter and are calculated according to the following formula: $[\alpha]_D=100\alpha$ /lc where α is the observed rotation, l is the path length (0.5dm), c is the concentration in g 100ml-1. The units of : $[\alpha]_D$ are 10-1 deg cm2 g-1. All optical rotations were obtained using chloroform as solvent.

Syntheses

Bis(tetraethylammonium)-bis(1,3-dithiol-2-thion-4,5-dithiolato)-zinkat (1)
Finely shaved Na metal (46g, 2 mol) were added to anhydrous CS2 (350 mL, 5.8 mol) and cooled in an ice bath (0-5 °C). Dry DMF (400 mL) were added slowly over a period of 6 h. After stirring overnight, the solution was cooled in an ice bath and methanol (100 mL) was slowly added to get rid of unreacted sodium. After diluting the solution with 1:1.5 MeOH/H_20 (2.5L), it was divided into 2 portions and transferred into 2 4-L erlenmeyer flasks. $ZnCl_2$ (20g) in ammonia solution (375 mL) and diluted with methanol (375 mL) was added to each flask. To each of the resulting solutions, Et4NBr (33g) in distilled H_2O (250 mL) was slowly added over a period of 4 h and stirred overnight. Each solution was filtered using a large sintered glass funnel. Solid was washed with distilled H_2O (500 mL), isopropyl alcohol until filtrate was clear and diethyl ether (500 mL). After drying, 1 was obtained as red precipitate (90.07, 50%): mp (202-205°C)

4,5-Bis(2'-cyanoethylthio)-1,3-dithiole-2-thione (2)
To a solution of bis(tetraethylammonium)-bis(1,3-dithiol-2-thion-4,5-dithiolato)-zinkat 1 (10.6g, 14.8 mmol) in acetonitrile (220 mL) was added 3-bromopropionitrile (6.2 ml, 74.7 mmol) and the solution was refluxed for 2 h. The resulting solution was cooled to room temperature and the precipitated salt was suction filtered. The precipitate was concentrated in vacuo. The crude product was dissolved in dichloromethane (250 mL), washed with H_2O (3 x 200 mL), dried with $MgSO_4$, filtered and the solvent removed in vacuo. Recrystallization of product in CH_2Cl_2/EtOH afforded 2 as yellow needles (8.04g, 89%): mp 82-83°C; Rf 0.583 (acetone/dichloromethane/hexane/toluene, 1/1/1/1, v/v);

δ_H (300 MHz, $CDCl_3$) 3.17 (4H, t, J 7Hz, SC$H_2$$CH_2$CN) and 2.82 (4H, t, J 7Hz, SCH_2CH_2CN);

δ_C (75.5 MH∫z, $CDCl_3$) 209.3 (C=S), 136.0 (C=), 117.3 (C≡N), 31.9 (SC$H_2$$CH_2$CN), and 19.2 ($SCH_2CH_2$CN).

4,5-Bis(2'-cyanoethylthio)-1,3-dithiole-2-one (3)
To a solution of 4,5-bis(2'-cyanoethylthio)-1,3-dithiole-2-thione 2 (3.94g, 12.96 mmol) in dichloromethane (150 mL) was added glacial acetic acid (50 mL) and mercuric acetate (4.13g, 12.96 mmol). The mixture was refluxed for 16 h. After cooling to room temperature, the resulting precipitate was filtered using celite and washed thoroughly with dichloromethane. The filtrate was concentrated in vacuo, redissolved in $CHCl_3$, washed with saturated NaHCO3 (2 x 100 mL), dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. Recrystallization of product in absolute EtOH gave 3 as yellow crystals (3.38g, 93%): mp 77-78°C (lit 64-65°C); Rf 0.544 (acetone/dichloromethane/hexane/toluene, 1/1/1/1, v/v);

δ_H (300 MHz, $CDCl_3$) 3.13 (4H,t, J 7Hz, SC$H_2$$CH_2$CN) and 2.79 (4H, t, J 7Hz, SCH_2CH_2CN);

δ_C (75.5 MHz, CDCl3) 188.1 (C=O), 127.6 (C=), 117.6 (C≡N), 31.8 (SC$H_2$$CH_2$CN) and 19.2 ($SCH_2CH_2$CN).

4,5-Bis(ethylenedithio)-1,3-dithiole-2-thione (4)
To a solution of of bis(tetraethylammonium)-bis(1,3-dithiol-2-thion-4,5-dithiolato)-zinkat 1 (11.8g, 16.4 mmol) in acetone (200 mL) was added 1,2-dibromoethane (3.6 mL, 41.7 mmol) and refluxed overnight. After cooling to room temperature, the precipitated salt was suction filtered and thoroughly washed with $CHCl_3$. The combined filtrate was concentrated in vacuo, redissolved in $CHCl_3$, washed with distilled water (2 x 250 mL), dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. Recrystallization of product in $CHCl_3$/MeOH gave 4 as yellow needles (5.65g, 77%): mp 119-120°C (lit 119-120°C); Rf 0.737 (acetone/dichloromethane/hexane/toluene, 1/1/1/1 , v/v);

δ_H (300 MHz, $CDCl_3$) 3.42 (4H, s, SC$H_2$$CH_2$S);

δ_C (75.5 MHz, $CDCl_3$) 208.0 (C=S), 123.0 (C=), and 29.8 (SC$H_2$$CH_2$S).

2,3-Bis(2'-cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene (5)

4,5-bis(2'-cyanoethylthio)-1,3-dithiole-2-one **3** (6.3g, 21.8 mmol) and 4,5-Bis(ethylenedithio)-1,3-dithiole-2-thione 4 (4.9g, 21.8 mmol) were suspended in Triethylphosphite (60 mL). The mixture was heated at 100°C for 3 h under argon with efficient stirring. After cooling to room temperature, the precipitate was thoroughly washed with MeOH and dried in vacuo. The solid was subjected to column chromatography using 100% DCM as eluting solvent affording **5** as orange solid (5.3g, 53%): mp 140-142°C (lit 140-142°C); Rf 0.654 (acetone/DCM/hexane/toluene, 1/1/1/1 , v/v); ES^+ [M+H] 465;

δ_H (300 MHz, DMSO-d6) 3.40 (4H, s, SC$\underline{H}_2$CH$_2$S), 3.15 (4H, t, J 7Hz, SC$\underline{H}_2$CH$_2$CN) and 2.87 (4H, t, J 7Hz, SCH$_2$C$\underline{H}_2$CN).

Methyl 2,3,4,Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside

A mixture of methyl α-D-glucopyranoside (2.00g, 10.3 mmol), triphenylphosphine (4.05g, 15.5 mmol), imidazole (2.10g, 30.9 mmol) and iodine (3.90g, 15.5 mmol) in toluene (200 mL) was vigorously stirred at 700C for 2.5 h. Heating was stopped and resulting mixture was stirred for another 15 h. After water (200 mL) was added, the mixture was vigorously stirred for 20 min and transferred to a separating funnel. The organic phase was extracted with water until no product is left in toluene layer. The combined aqueous phase was concentrated in vacuo. Acetic anhydride (40 mL) and pyridine (52 mL) were added and the solution was stirred overnight. After removing the solvent in vacuo, the residue is dissolved in toluene, washed with water, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Recrystallization in absolute EtOH gave the product as white solid (3.075g, 87%): mp 146-147°C (lit 148-149°C); Rf 0.621 (acetone/dichloromethane/hexane/toluene, 1/1/1/1, v/v); ν_{max} (thin film)/cm^{-1} 1739 ($COOCH_3$);

δ_H (300 MHz, $CDCl_3$) 5.45 (1H, t, J 10Hz, H-3), 4.95 (1H, d, J 4Hz, H-1), 4.83-4.89 (2H, m, H-2, H-4), 3.72-3.81 (1H, m, H-5), 3.47 (3H, s, C$\underline{H}_3$O), 3.29 (1H, dd, J 3Hz, J 11Hz, H-6a), 3.13 (1H, dd, J 8Hz, J 11Hz, H-6b), 2.06, 2.04, 2.00 (9H, 3 s, 3 CH_3COO);

δ_C (75.5 MHz, $CDCl_3$) 170.2, 170.17, and 169.8 (3CH$_3\underline{C}$OO), 96.8 (C-1), 72.6, 71.0, 69.8 and 68.7 (C-2, C-3, C-4, and C-5), 55.9 ($\underline{C}$H$_3$O), 20.9 (2C), and 20.8, (3 CH$_3\underline{C}$OO) and 3.9 (C-6).

1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside

To a solution of Methyl 2,3,4,Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (3.28g, 7.6 mmol) in acetic anhydride (50 mL) and glacial acetic acid (20 mL) was slowly added conc. H_2SO_4 (1.6 mL). After stirring for 24 h, solution was poured into crushed ice (100 g). The precipitate was filtered and thoroughly washed with saturated $NaHCO_3$ and distilled water. The precipitate was dried in a dessicator under high vacuum with silica and P_2O_5 for 2 h. Recrystallization in absolute EtOH gave the product as white crystals (2.8g, 79%): mp 172°C (lit 182°C); Rf 0.657 (acetone/dichloromethane/hexane/toluene, 1/1/1/1, v/v); ν_{max} (thin film)/cm^{-1} 1740 ($COOCH_3$);

δ_H (300 MHz, CDCl3) 6.35 (1H, d, J 4Hz, H-1), 5.48 (1H, t, J 10Hz, H-3), 5.10 (1H, dd, J 4Hz, J 10Hz, H-2), 5.00 (1H, t, J 10Hz, H-4), 3.81-3.87 (1H, m, H-5), 3.33 (1H, dd, J 3Hz, J 11Hz, H-6a), 3.16 (1H, dd, J 6Hz, J 11Hz, H-6b), 2.20, 2.08, 2.04 and 2.03 (12H, 4 s, 4 C$\underline{H}_3$COO);

δ_C (75.5 MHz, $CDCl_3$) 170.0, 169.7, 169.5, and 168.9 (4CH_3COO), 89.0 (C-1), 72.3, 70.7, 69.6 and 69.4 (C-2, C-3, C-4, and C-5), 21.0, 20.8 (2C), and 20.6 (4 $\underline{C}H_3$COO), and 3.52 (C-6).

2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide

To 1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (2.19g, 4.78 mmol), 45% HBr/HOAc (15 mL) was added and stirred for 3 h and 20 min. Solution was diluted with $CHCl_3$ (80 mL) and added to crushed ice (~200g). Organic phase was washed with $NaHCO_3$ (2 x 200 ml) and H_2O (2 x 200 mL), dried with $MgSO_4$, filtered and solvent evaporated in vacuo giving the product as white solid (2.02g, 88%): mp 178-179°C (diethyl-ether); Rf 0.707 (acetone/dichloromethane/hexane/toluene, 1/1/1/1, v/v); ν_{max} (nujol)/cm^{-1} 1742 ($COOCH_3$);

δ_H (300 MHz, $CDCl_3$) 6.62 (1H, d, J 4Hz, H-1), 5.56 (1H, t, J 10Hz, H-3), 5.17 (1H, t, J 10Hz, H-4), 5.05 (1H, t, J 10Hz, H-4), 4.83 (1H, dd, J 4Hz, J 10Hz, H-2), 3.93-4.04 (1H, m, H-5), 3.37 (1H, dd, J 3Hz, J 11Hz, H-6a), 3.22 (1H, dd, J 6Hz, J 11Hz, H-6b), 2.11, 2.08, and 2.04 (9H, 3s, 3 C$\underline{H}_3$COO);

δ_C (75.5 MHz, $CDCl_3$) 170.1, 169.6 and 169.5 (3CH$_3\underline{C}$OO), 86.1 (C-1), 72.5, 71.7, 70.8, and 70.0 (C-2, C-3, C-4 and C-5), 2.67 (C-6), and 20.8 (3C) (3 $\underline{C}$H$_3$COO).

1,6-Bis[3'-(2''-cyanoethylthio)-6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio]-2,3,4-tri-O-acetyl-β-D-glucopyranoside (6b)

Cesium hydroxide ($CsOH.H_2O$) (450mg, 2.68 mmol) in MeOH (5 mL) was injected to 2,3-bis(2'-cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene (1.189 g, 1.56

mmol) in dry and degassed DMF (30 mL) under argon using a syringe pump over a period of 2.5 h. After overnight stirring, 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide (650mg, 1.58 mmol) in DMF (3 mL) was added and solution stirred for 36 hours. After removing the solvent in vacuo, the residue was dissolved in dichloromethane, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was subjected to gradient elution flash column chromatography using 100% dichloromethane and 5% EtOAc/CH_2Cl_2, as eluting solvents affording orange solid (817mg, 65%): mp 126-128°C; Rf 0.330 (acetone/dichloromethane/hexane, 1/1/2, v/v); $[\alpha]_D^{20}$ 31.4 (c1); ν_{max} (thin film)/cm^{-1} 1748.7 ($COOCH_3$), 2249 (CN); ES+ [M+H] 1093, [M+Na] 1115;

δ_H (300 MHz, $CDCl_3$) 5.22 (1H, t, J 10Hz, H-3), 5.01 (2H, dt, J 10Hz, H-2, H-4), 4.77 (1H, d, J 10Hz, H-1), 3.75 (1H, m, H-5), 3.30 (4H, s, $SC\underline{H}_2CH_2S$), 3.29 (4H, s, $SC\underline{H}_2CH_2S$), 3.01-3.13 (5H, m, $SC\underline{H}_2CH_2CN$, H-6a), 2.91 (1H, dd, J 14Hz, J 8Hz, H-6b), 2.08, 2.06, and 2.00 (9H, 3s, $3C\underline{H}_3COO$);

δ_C (75.5 MHz, $CDCl_3$) 170.2, 169.7 and 169.5 (3 $CH_3\underline{C}OO$), 130.5, 128.7, 127.2, 126.1, 114.2, 113.99, 113.93, 113.90, 112.4, 112.2, 111.7, and 111.2 (12 $\underline{C}$=), 117.9 ($\underline{C}\equiv N$), 85.2 (C-1), 77.4, 73.6, 70.7, and 70.0 (C-2, C-3, C-4, and C-5), 37.6 (C-6), 31.8 and 31.6 (2 $S\underline{C}H_2CH_2CN$), 30.4 (SCH_2CH_2S), 20.7 (2C), 20.8 (3 $\underline{C}H_3COO$) and 19.04 and 19.09 (2 $SCH_2\underline{C}H_2CN$).

1.6-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-2,3,4-tri-O-acetyl-β-D-glucopyranosyl]-3'-ylthio]-2,3,4-tri-O-acetyl-β-D-glucopyranoside (7b1) and (7b2)

Cesium hydroxide ($CsOH.H_2O$) (187mg, 1.11 mmol) in MeOH (5 mL) was injected to 1,6-Bis[3'-(2''-cyanoethylthio)-6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio]-2,3,4-tri-O-acetyl-β-D-glucopyranoside (516 mg, 0.53 mmol) in dry and degassed DMF (8 mL) under argon using a syringe pump over a period of 3.5 h. After overnight stirring, 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide (253mg, 0.528 mmol) in DMF (8 mL) was added and solution stirred for 36 h. After removing the solvent in vacuo, the residue was dissolved in DCM, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was subjected to gradient elution flash column chromatography using 100% DCM, 5% EtOAc/CH_2Cl_2 and 10%EtOAc/ CH_2Cl_2 as eluting solvents affording **7b1** (126 mg, 19%) and **7b2** (65 mg, 10%) as orange oil;

7b1:Rf 0.308 (6% EtOAc/CH2Cl2); ν_{max} (thin film)/cm^{-1} 1757 ($COOCH_3$), ES^+ [M+H] 1257;

δ_H (300 MHz, $CDCl_3$) 5.26 (2H, t, J 10Hz, H-3'), 5.02-5.23 (4H, m, H-2', H-4'), 4.72 (2H, d, J 10Hz, H-1'), 3.72 (2H, m, H-5'), 3.18 (2H, dd, J 2Hz, J 12Hz, H-6a'), 2.85 (2H, dd, J 8Hz, J 14Hz, H-6b'), 3.29 (8H, s, $SC\underline{H}_2C\underline{H}_2S$), 2.12, 2.11 and 2.03 (9H, 3s, $3C\underline{H}_3COO$);

δ_C (67.5 MHz, $CDCl_3$) 170.1, 169.5, and 169 (3 $CH_3\underline{C}OO$), 133.5, 122.9, 114.2, 114.0, 112.7, and 110.6 (6 $\underline{C}$=), 87.7 (C-1'), 77.2, 73.5, 70.5, and 70.4 (C-2', C-3', C-4', and C-5'), 37.0 (C-6'), 30.2 ($S\underline{C}H_2\underline{C}H_2S$), 20.74, 20.71, and 20.55 (3 $\underline{C}H_3COO$).

7b2: Rf 0..212 (6% EtOAc/CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 1754 ($COOCH_3$), ES+ [M+H] 1257;

δ_H (300 MHz, $CDCl_3$) 5.25 (2H, t, J 10Hz, H-3'), 4.84-5.00 (6H, m, H-1', H-2', H-4'), 3.53, (2H, m, H-5'), 3.27 (2H, s, $SC\underline{H}_2CH'2S$), 3.29 (2H, s, $SCH_2C\underline{H}'_2S$) 2.12, 2.11 and 2.03 (9H, 3s, $3C\underline{H}_3COO$);

δ_C (75.5MHz, $CDCl_3$) 170.0, 169.8, and 169.7 (3 $CH_3\underline{C}OO$), 115.1, 113.7, 113.4, 113.1, 113.0, and 110.9 (6 C=), 85.5 (C-1a'), 85.3 (C-1b'), 76.9, 73.5, 71.5, and 70.8 (C-2', C-3', C-4', and C-5'), 38.2 (C-6'), 30.17 ($S\underline{C}H_2CH_2S$), 30.12 ($SCH_2\underline{C}'H_2S$), 20.8, 20.7, and 20.6 (3 $\underline{C}H_3COO$).

α,α'-Bis(3'-(2''-cyanoethylthio)-6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-m-xylene (6a)

Twenty five percent (25%) NMe_4OH/MeOH (503 μL, 1.22 mmol) was injected to 2,3-bis(2'-cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene (516 mg, 1.11 mmol) in dry and degassed DMF (20 mL) under argon using a syringe pump over a period of 40 min. After 3 h of stirring, α,α'-dibromo-m-xylene (147mg, 0.555 mmol) was added and solution stirred overnight. After removing the solvent in vacuo, the residue was dissolved in DCM, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was column chromatographed using 100% DCM as eluent affording 6a as orange oil (419 mg, 82%): Rf 0.288 (100% DCM); ν_{max} (thin film)/cm^{-1} 2244 (CN), ES^+ [M+H] 925;

δ_H (300 MHz, $CDCl_3$) 7.35-7.22 (4H, m, Ar-H), 4.01 (4H, s, $C\underline{H}_2ArC\underline{H}_2$), 3.32 (8H, s, $SC\underline{H}_2C\underline{H}_2S$), 2.82 (4H, t, J 7Hz, $SC\underline{H}_2CH_2CN$), and 2.33 (4H, t, J 7Hz, $SCH_2C\underline{H}_2CN$);

δ_C (75.5 MHz, $CDCl_3$) 137.3, 131.93, 130, 129.5, 128.7, 126.4, 113.9, 113.86, 111.8, 112.1, (10 $\underline{C}$=), 117.91 (C≡N), 40.66 ($\underline{C}H_2Ar\underline{C}H_2$), 31.6 ($S\underline{C}H_2CH_2CN$), 30.4 ($S\underline{C}H_2\underline{C}H_2S$), and 18.5 ($SCH_2\underline{C}H_2CN$).

1,6-[α,α'-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-m-xylyl]-3'-ylthio]-2,3,4-tri-O-acetyl-β-D-glucopyranoside (7a)

Cesium hydroxide ($CsOH.H_2O$) (106mg, 0.64 mmol) in MeOH (2 mL) was injected to bis TTF-m-xylyl derivative 6a (275mg, 0.298 mmol) in dry and degassed DMF (30 ml). After 4 h of stirring, 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide (143mg, 0.30 mmol) in DMF (8 mL) was added using a syringe pump over 6 h. After overnight stirring, the solvent was removed in vacuo, the residue was dissolved in DCM, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The residue was column chromatographed using 100% CH_2Cl_2 and 3% EtOAc/CH_2Cl_2 as eluting solvents affording **7a** (203 mg, 63%) as orange oil: Rf 0.0.45 (3% EtOAc/CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 1748 ($COOCH_3$), ES^+ [M+H] 1089;

δ_H (300 MHz, $CDCl_3$) 7.51 (1H, t, J 8Hz, H-1), 7.25 (1H, d, J 8Hz, H-2) 7.15-7.13 (2H, m, H-3, H-6), 5.06 (1H, t, J 10Hz, H-3'), 4.77 (1H, t, J 10Hz), 4.76 (1H, t, J 10 Hz,), 4.14 (1H, m, J 10Hz), 3.87 (1H, d, J 14Hz), 3.73 (1H, d, J 14Hz), 3.37-3.26 (8H, m, $SC\underline{H}_2C\underline{H}_2S$), 2.21, 2.15, and 2.02 (9H, 3s, $C\underline{H}_3COO$);

δ_C (75.5 MHz, $CDCl_3$) 170.2, 120.0, and 169.6 (3 $CH_3\underline{C}OO$), 139.2, 138.3, 133.3, 132.3, 130.1, 129.9, 129.6, 128.7, 127.0, 125.3, 114.1, 113.83, 113.77, 113.2, 112.8, 112.6, and 110.8 (17 $\underline{C}$=), 88.7 (C-1'), 76.9, 73.1, 71.0, and 69.7 (C-2', C-3', C-4', and C-5'), 40.90 ($\underline{C}H_2ArC'H_2$), 40.42 ($CH_2Ar\underline{C}'H_2$), 37.8 (C-6'), 30.3 ($S\underline{C}H_2C'H_2S$), 30.2 ($SCH_2\underline{C}'H_2S$), 21.1 (2C) and 20.8 (3 CH_3COO).

1,3-Bis(3'-(2"-cyanoethylthio)-6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)propane (6c)
Twenty five percent (25%) NMe_4OH/MeOH (490 μL, 1.19 mmol) was injected to 2,3-Bis(2'-cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene (524 mg, 1.13 mmol) in dry and degassed DMF (25 mL) under argon using a syringe pump over a period of 75 minutes. After 11 h of stirring, 1,3 dibromopropane (58 mL, 0.57 mmol) was injected and solution stirred overnight. After removing the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was column chromatographed using 100% CH_2Cl_2 as eluent affording **6c** as orange oil (370 mg, 76%): Rf 0.297 (100% CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 2253 (CN), ES^+ [M+H] 863;

δ_H (300 MHz, $CDCl_3$) 3.29 (8H, s, $SC\underline{H}_2C\underline{H}_2S$), 3.05 (4H, t, J 7Hz, $SC\underline{H}_2CH_2C\underline{H}_2S$ or $SC\underline{H}_2CH_2CN$), 2.99 (4H, t, J 7Hz, $SC\underline{H}_2CH_2C\underline{H}_2S$ or $SC\underline{H}_2CH_2CN$), 2.71 (4H, t, J 7Hz, $SCH_2C\underline{H}_2CN$), and 1.98 (2H, qu, J 7Hz, $SCH_2C\underline{H}_2CH_2S$);

δ_C (75.5 MHz, $CDCl_3$) 131.6, 124.9, 114.02 (2C), 114.05, 112.2, and 111 (6 $\underline{C}$=), 34.8 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 31.7 ($SCH_2CH_2CN$), 30.4 ($SCH_2CH_2S$), 29.7 ($SCH_2\underline{C}H_2CH_2S$), and 19.0 ($SCH_2\underline{C}H_2CN$).

1,6-[1",3"-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-propyl]-3'-ylthio]-2,3,4-tri-O-acetyl-β-D-glucopyranoside (7c)
Cesium hydroxide ($CsOH.H_2O$) (143mg, 0.851 mmol) in MeOH (2 mL) was injected to 1,3-bis(3'-(2''-cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene-2-ylthio)propane (345mg, 0.400 mmol) in dry and degassed DMF (15 mL). After 36 h of stirring, 2,3,4,Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide (192mg, 00.401 mmol) in DMF (7 mL) was added and solution stirred for 36 h. After removing the solvent in vacuo, the residue was dissolved in dichloromethane, washed with H_2O, dried with $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was column chromatographed using 100% CH_2Cl_2 as eluting solvent affording **7c**(148 mg, 36%) as orange solid: mp 222°C; Rf 0.275 (100% CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 1741 ($COOCH_3$), ES^+ [M+H] 1027;

δ_H (300 MHz, $CDCl_3$) 5.21 (2H, t, J 10Hz, H-3'), 5.03 (1H, t, J 10Hz, H-4'), 4.96, t, J 10 Hz, H-2'), 4.80 (1H, d, J 10Hz, H-1'), 3.60 (1H, m, H-5'), 3.31 (8H, s, $SC\underline{H}_2C\underline{H}_2S$), 3.17-2.80 (6H, m, H-6', $SC\underline{H}_2CH_2C\underline{H}_2S$), 2.14, 2.12, and 2.03 (9H, 3s, $3C\underline{H}_3COO$), 2.05-1.97 (2H, m, $SCH_2C\underline{H}_2CH_2S$).

1,6-α,α'-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-m-xylyl]-3'-ylthio]-β-D-glucopyranoside (8a)
Bis –TTF-sugar-xylyl macrocycle was dissolved in 4:1 dioxane/methanol. Sodium methoxide was injected 2.87 mL and the solution was stirred for 5 h. Solution was neutralized with Dowex 50w-x8(H+), filtered and solvent evaporated in vacuo. The residue was washed with DCM then filtered affording 8a as yellowish solid (78mg, 85%). Mp 165°C. ν_{max} (thin film)/cm^{-1} 3390 (OH), ES^+ [M+H] 963.

1,6-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio) -β-D-glucopyranosyl]-3'-ylthio]-2-β-D-glucopyranoside(8b1)
Bis TTF-Sugar Macrocycle **7b1** was dissolved in 6 mL 5:1 DCM/MeOH. 0.1 M NaOMe was injected and solution stirred for 40 min. Solution was neutralized with Dowex 50w-x8(H+), filtered and solvent evaporated in vacuo affording 8b1 as brownish solid (50mg, 98%). ν_{max} (thin film)/cm^{-1} 3300 (OH), ES^+ [M+H] 1005.

1,6-[Bis(6',7'-ethylenedithiotetrathiafulvalene-2'-ylthio)-propyl]-3'-ylthio]-β-D-glucopyranoside (8c)
Bis –TTF-sugar-propyl macrocycle was suspended in 10 mL 1:1 Dioxane/methanol. Sodium methoxide was injected

and solution stirred overnight. . Solution was neutralized with Dowex 50w-x8(H+), filtered and solvent evaporated in vacuo affording 8c as brownish solid.ES^+ [M+H] 901.

RESULTS AND DISCUSSION

The synthesis of the macrocycles requires the preparation of the bis-cyanoethyl protected TTF **5** (Figure 1). Following the procedure of Becher (Becher & Lau 1997), the zinc complex **1** produced from the sodium metal reduction of carbon disulfide in the presence of N,N-dimethylformamide was reacted with 3-bromopropionitrile giving **2**. Transchalcogenation of **2** using mercuric acetate gave the corresponding oxone **3**. Triethylphosphite coupling of **3** with **4** prepared from the reaction of zinc complex and 1,2-dibromoethane gave **5** in 53% yield.

Selective mono-deprotection of **5** by treating it with 0.5 equivalent of cesium hydroxide or NMe_4OH/MeOH (Figure 2) gave the monothiolate anion in-situ¬. Reacting

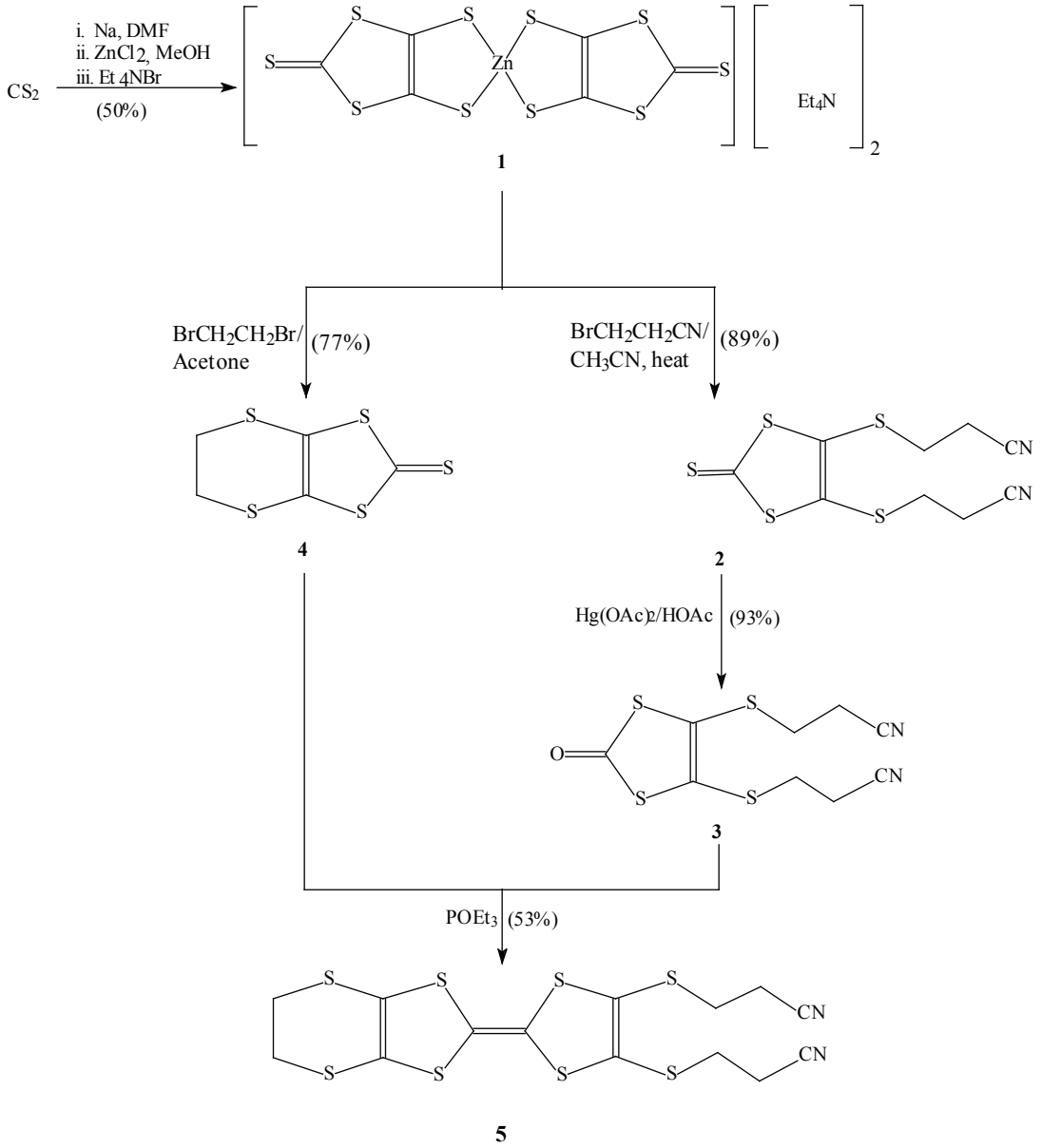


Figure 1. Preparation of Bis-Cyanoethyl protected TTF

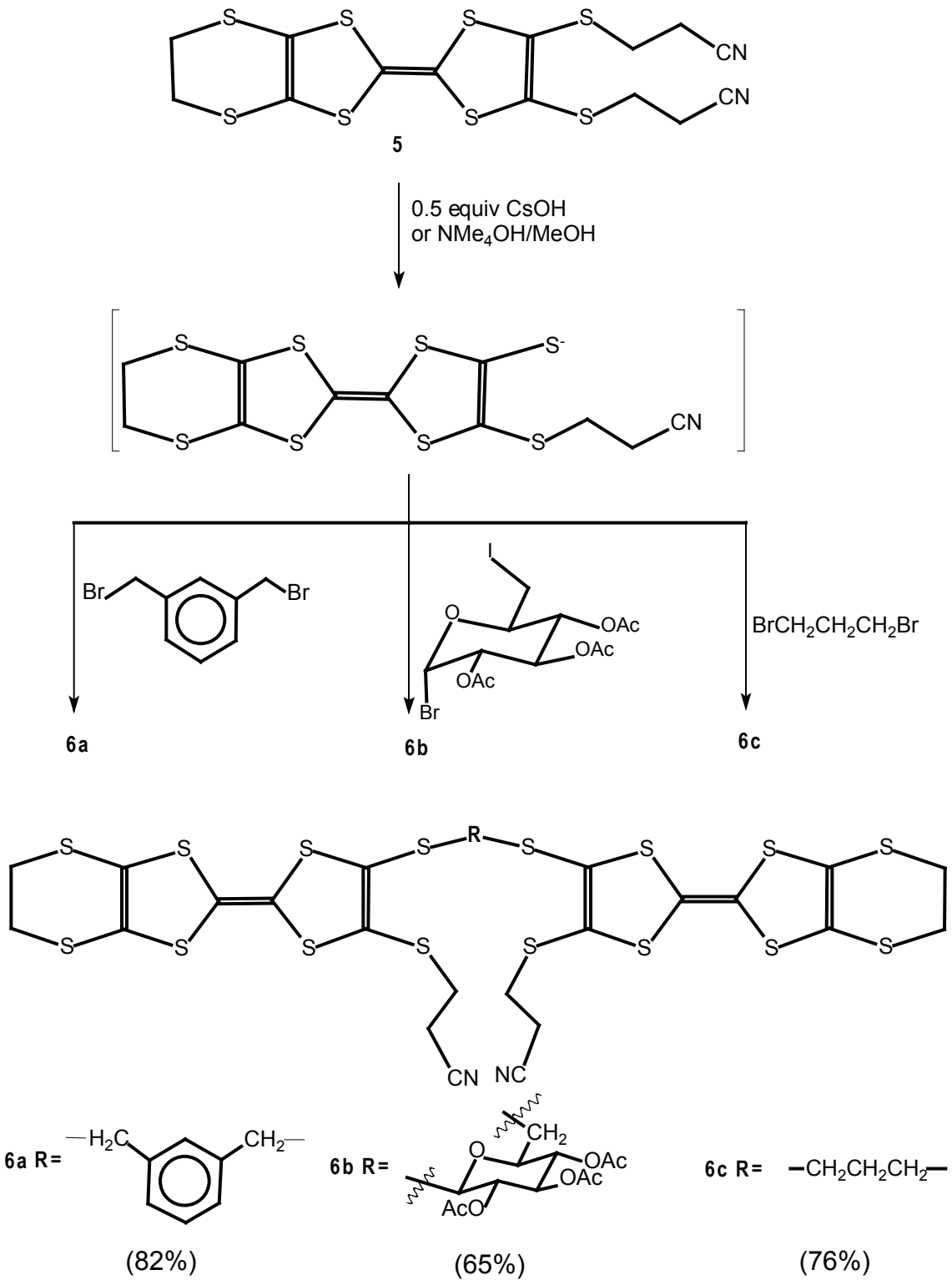


Figure 2. Preparation of bis-TTF derivatives 6a-c

it with 1 equivalent of a linker molecule with 2 leaving groups produced the bis-TTF derivatives **6a**-**6c**.

Compounds **6a** and **6c** are precursor to macrocycles with cavities having a hydrophilic and a hydrophobic part. The phenyl ring and the trimethylene group will provide sites for the π-π interaction and Van der Waals interaction, respectively, between hosts and guests. The sugar moiety, on the other hand, will provide the site for H-bonding. Glucose was chosen as the sugar to be incorporated because it is readily available and inexpensive. Acetate was selected to protect the hydroxyl groups of glucose because of ease in preparation and removal at the latter stages of macrocyle synthesis. The acetylated dihalosugar used contains 2 good leaving groups: a bromide at the anomeric carbon for it to readily undergo a Koenig-Knorr type reaction and an Iodide at position 6. It was prepared in 3 steps (Figure 3).

The anomeric carbon in **6b** has a β-configuration .The 1H-NMR spectrum showed the anomeric proton giving a doublet at δ 4.65 (J 10 Hz). The high coupling constant is consistent with protons that are diaxial with ~ 180° dihedral angle. Vicinal gauche protons have an associated J values of 1-4 Hz. The favored β-configuration can be explained by the participation of the neighboring acetate (Figure 4).

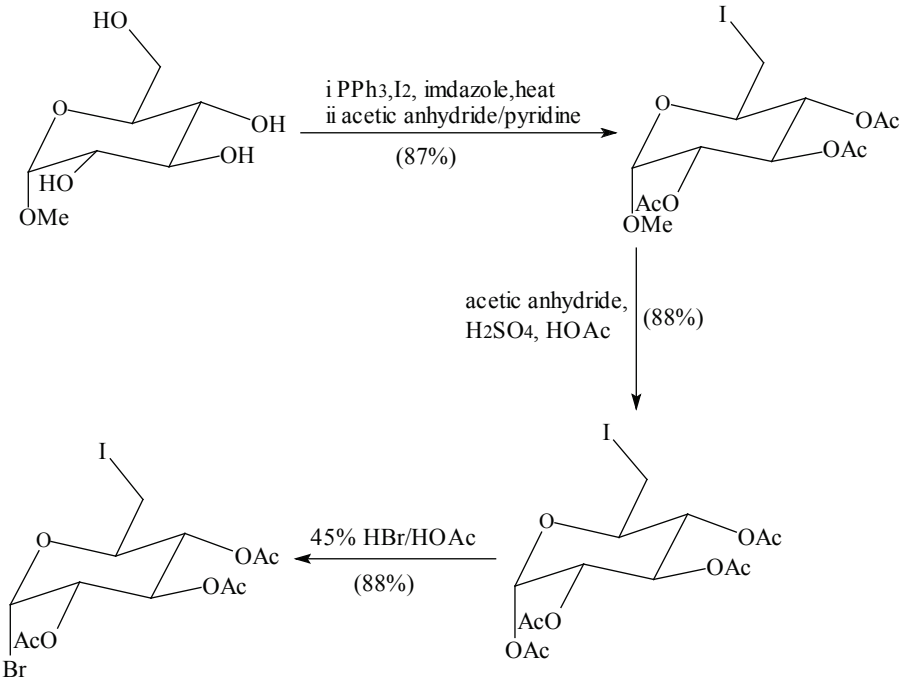


Figure 3. Preparation of glucose derivative with two leaving groups

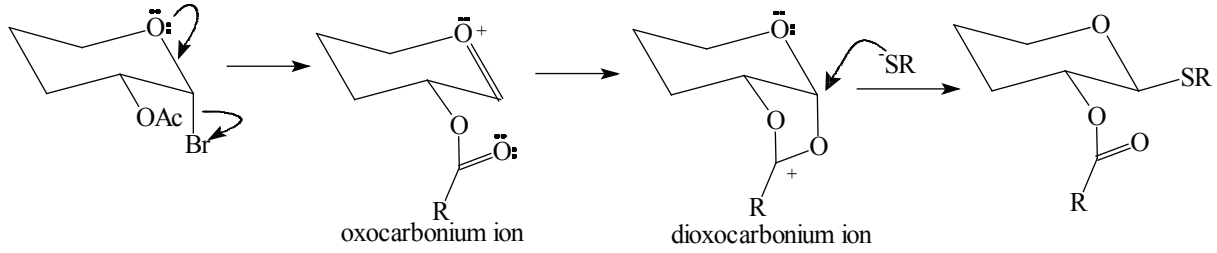


Figure 4. Neighboring group participation in substitution reaction

Once the bromide has departed as encouraged by the cesium or ammonium salts to give the oxocarbonium ion, it reacts with the acetate at the adjacent carbon to give a more stable dioxocarbonium ion. Nucleophilic attack of the thiolate salt results in the ring opening to give a bond trans to participating acetate.

Deprotection of the remaining cyanoethyl groups with cesium hydroxide and treatment with 0.5 equivalent of the acetylated dihaloglucose produced **7a-c** (Figure 5) in reasonable yields. The relatively higher yield of **7a** can be attributed to the rigidness of the phenyl ring, which orients the thiolate groups of **6a** closer to one another, increasing the possibility of reacting with only 1 acetylated dihaloglucose. The lower yield of **7c**, on the other hand, can be due to the flexible rotation around the trimethylene linker forming a mixture of polymeric products. All the products gave a β-configuration for the sugars' anomeric carbon.

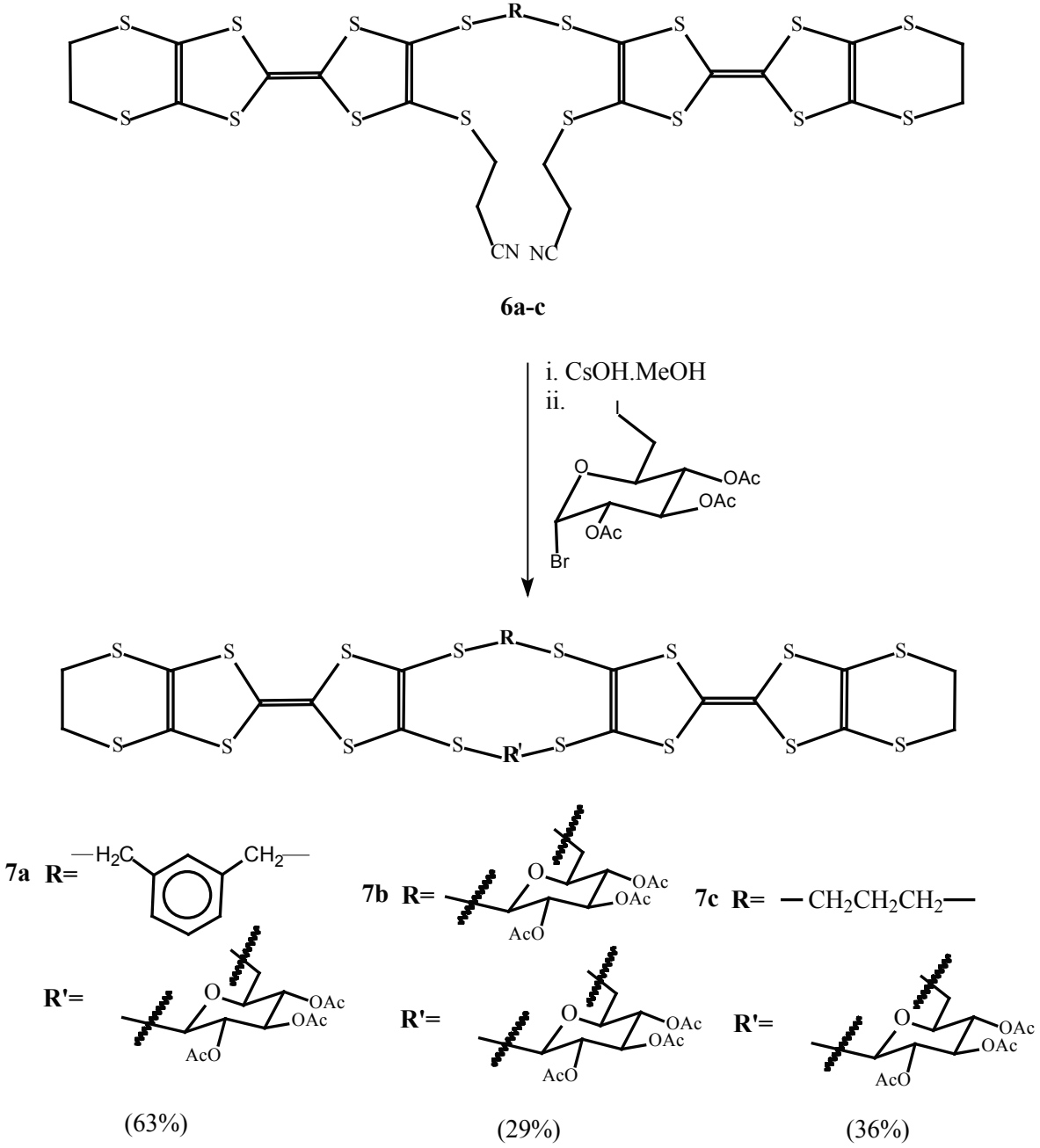
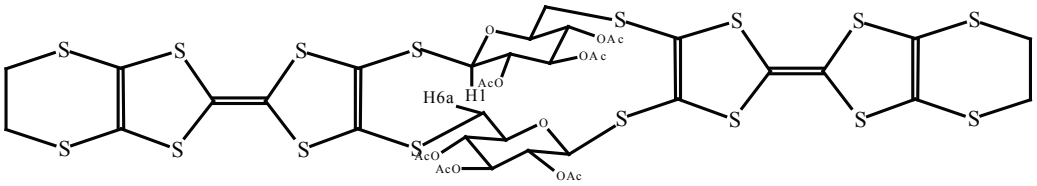
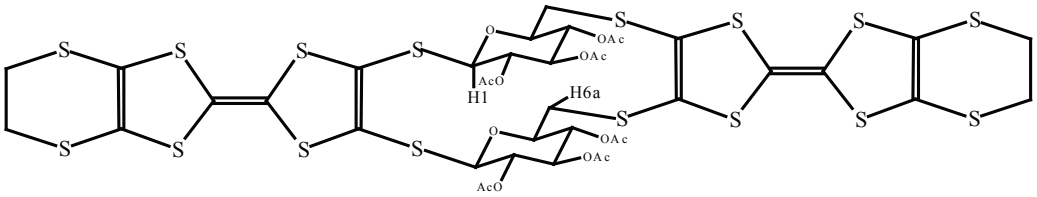


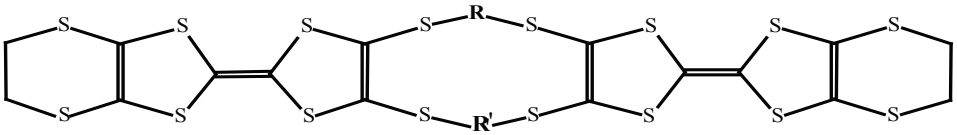
Figure 5. Macrocycle synthesis from bis TTF derivative 6a-c



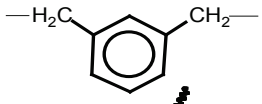
7b1 (19%)



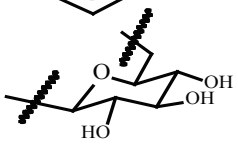
7b2 (10%)



8a R=



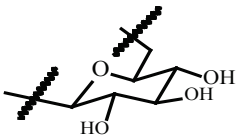
R'=



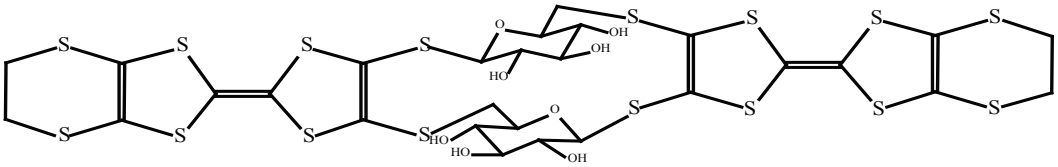
(100%)

8c R= $-CH_2CH_2CH_2-$

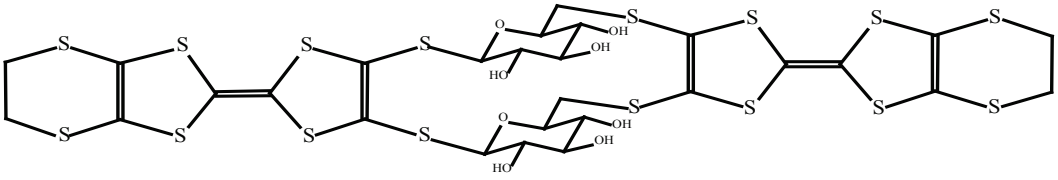
R'=



(100%)



8b1 (100%)



8b2

Compound **7b** was initially obtained as isomeric macrocycle. Flash column chromatography gave the less polar **7b1** (19%) and **7b2** (10%)

The identity of **7b1** and **7b2** were determined using nuclear overhauser (NOE) experiments. When H1 protons of the 2 compounds were irradiated, correlation between H6a and the anomeric proton was observed in the less polar product and none in the other. The only way it would give a correlation is if the attachment of the sugars are 1,6:6,1 where H1and H6a are in close proximity. The less polar product was then assigned as **7b1**.

Deacetylation of **7a-c** using NaOMe/MeOH-dioxane gave the corresponding macrocycles **8a-c** except **8b2**. Due to the limited amount of **8b2** obtained, the desired conversion was not successfully carried out. However, it is expected that deacetylation of **7b2** will give **8b2**.

CONCLUSION

The synthesis of novel TTF macrocycles containing m-xylylene, trimethylene and glucose units was described. This is the first reported Tetrathiafulvalene macrocyle with sugar units.

ACKNOWLEDGMENT

The Department of Science and Technology-Engineering and Science Education Program (ESEP) (Philippines) and De La Salle University for the scholarship grant of GV Alea is sincerely acknowledged. The authors also wish to acknowledge the University Research and Coordination office for partially funding this project.

REFERENCES.

BECHER J and LAU J. 1997. Oligomeric Tetrathiafulvalene Macrocycles. Synthesis 9: 1015-1019.

BRYCE M, DEVONPORT W, GOLDENBERG L and WANG C. 1998. Macromolecular Tetrathiafulvalene Chemistry. Chem Comm p. 9: 945-951.

DEMIRALP E and GODDARD WA III. 1997. Structures and Energetics Study of Tetrathiafulvalene-Based Donors of Organic Superconductors. J Phy Chem 101(43) 8128-8131.

HANSEN TK, JORGENSEN T, STEIN PC and Becher J. 1992. Crown Ether Derivatives of Tetrathiafulvalene. J Org Chem 57: 6403-6409.

IYODA M, HASEGAWA M and MIYAKE Y. 2004. Bi-TTF, Bis-TTF, and Related TTF Oligomers. Chem Rev 104 (11,) 5085-5114.

JEPPENSEN J, NIELSEN B and BECHER J. 2004. Tetrathiafulvalene Cyclophanes and Cage Molecules. Chem Rev 104(11) 5115-5132.

JEPPESEN J, TAKIMIYA K, JENSEN F, BRIMERT T. NIELSEN K THORUP N and BECHER J. 2000. Pyrrolo-Annelated Tetrathiafulvalenes: The Parent Systems. J Org Chem 65(18): 5794-5805.

JORGENSEN T, HANSEN TK and BECHER J. 1994. Tetrathiafulvalenes as Building Blocks in Supramolecular Chemistry. Chem Soci Rev 23: 41-51

ROVIRA C. 2004. Bis(ethylenethio)tetrathiafulvalene (BET-TTF) and Related Dissymmetrical Electron Donors: From the Molecule to Functional Molecular Materials and Devices (OFETs). Chem Rev 104 (11) 5289-5318.

SIMMONDS RJ. 1992. Chemistry of Biomolecules: An introduction. Cambridge: The Royal Society of Chemistry. 276p.

SIMONSEN KB and BECHER J. 1997. Tetrathiafulvalene Thiolates: Important Synthetic Building Blocks for Macrocyclic and Supramolecular Chemistry. Synlett 11: 1211-1220.

SIMONSEN KB, SVENSTRUP NJ. LAU J, THORUP N and BECHER J. 1998. Tetrathiafulvalene Belts with Large Cavities. Angew Chem Int Ed 38(10): 1417-1419.

TAKIMIYA K, THORUP N and BECHER J. 2000. A Flexible Cyclophane: Design, Synthesis, and Structure of a Multibridged Tris-tetrathiafulvalene (TTF) Macrocycle. Chem Eur J 6(11): 1947-1954.