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Synthesis of new crown analogs derived from bisphenol

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Synthesis of hexaoxa **5**, octaoxa **6** and tetradiaza macrocycle **7** has been accomplished by reacting bisphenol **1** with tosylates **2, 3** and **4** respectively, under basic conditions. Dithia-bridged macrocycles **10** and **13** are prepared by reacting key-intermediates, ditosylate **9** and diiodo compound **12**, respectively with $Na_2S.9H_2O$. Attempted metal ion complexation and two phase extraction with macrocycles **5, 6, 10** and **13** was unsuccessful probably due to insufficient ligating potential available with these macrocycles.

The chemistry of crown ethers initiated by ingenious studies of Pedersen[1a] and later developed by Cram[1b], Lehn[1c], Stoddart and others has been quite prosperous for the past 40 years and as a result valuable contributions were made to various fields of chemistry[1,2]. Synthetic organic chemists have played a pivotal role in designing and synthesising crown ethers and macrocycles of all possible structural types to study the relationship between their structures and physical properties[3].

During the past 10 years, bisphenol **1** has been extensively used to develop a number of macrocycles for the investigation of molecular recognition, host-guest interaction and as models to mimic enzyme active sites[4]. In the present investigation, we have exploited bisphenol **1** as a building block to synthesise hitherto unknown crown type macrocycles to study their potential in metal ion complexation.

Synthesis of hexaoxa 5, octaoxa 6 and tetraoxa-diazatosyl 7 macrocycles. The strategy employed for the synthesis of macrocycles **5,6** and **7** entailed the coupling of bisphenol **1** with bis alkylating compounds **2, 3** or **4**, respectively under basic conditions. For the preparation of **5**, bisintramolecular alkylation of **1** with diethylene glycol ditosylate **2**[5] was performed in dry THF using solid KOH as the base under high dilution conditions (Scheme I). A small amount of 18-crown-6 was also added as the phase transfer catalyst. The crude product after column chromatography and crystallisation from ethanol gave **5** as colourless solid, m.p. 175-76°C (yield 12%).

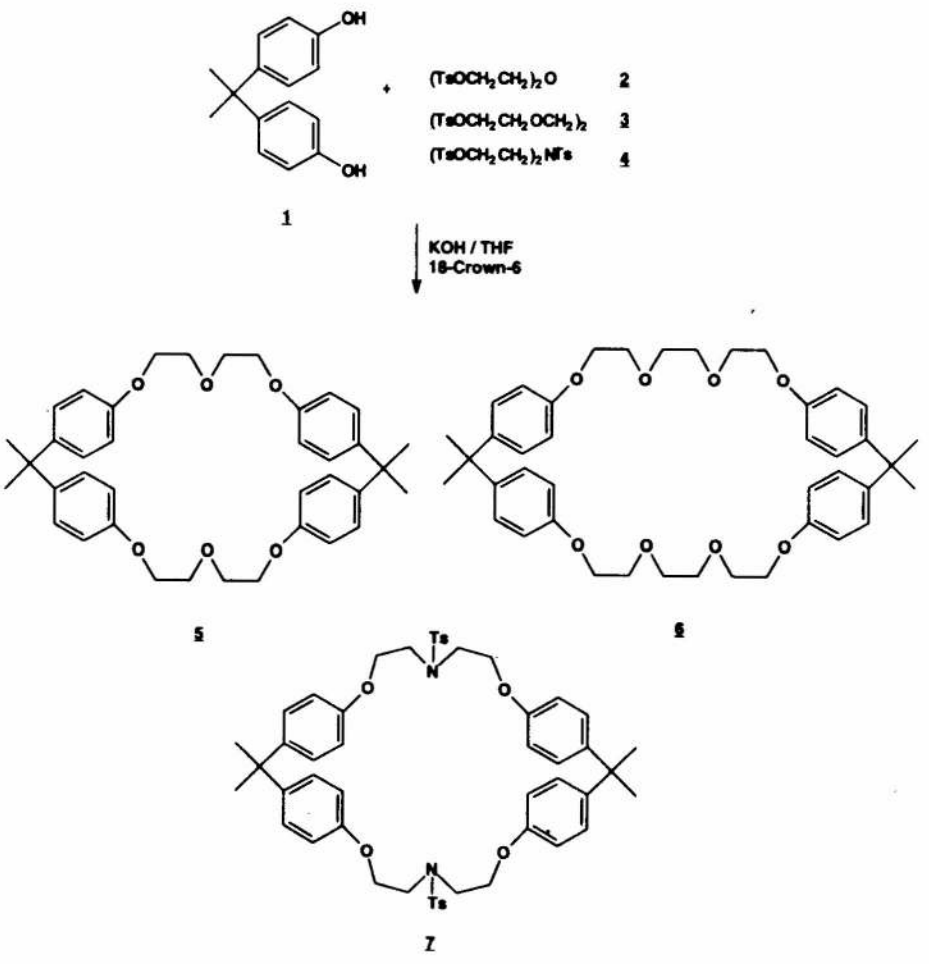
The compound was analysed satisfactorily for $(C_{19}H_{22}O_3)_n$ and its mass spectrum showed molecular ion peak M^+ at m/z 596 which corresponds to 2:2 macrocyclisation (i.e. n=2) involving two molecules each of bisphenol **1** and ditosylate **2**.

Similarly, condensation of **1** with ditosylate **3** and tritosylate **4**, gave respective 2:2 stoichiometric macrocycles, **6** (27%), m.p. 125-26°C, M^+ m/z 684 and **7** (14%), m.p. 217-18°C, M^+ m/z 902.

It was of much interest to us to convert tetraoxa-diazatosyl macrocycle **7** into its detosylated analog (-NH instead of N-Ts in structure **7**) for the ultimate purpose of metal ion complexation studies. However, attempts to effect N-detosylation under different conditions as reported in the literature (conc. H_2SO_4, HBr-phenol[8], as well as LAH[9] in refluxing THF) either failed or gave only partial conversion as indicated by TLC analysis of the reaction mixture.

Synthesis of tetraoxa-dithia macrocycles 10 and 13. Synthesis of tetraoxa-dithia macrocycles **10** and **13** was carried out by employing the sequences shown in Scheme II. The synthesis of diol **8** required as an intermediate for macrocycle **10** has been reported via alkylation of bisphenol **1** with ethyleneoxide in the presence of anion exchange resin at 150°C under autoclave conditions[10]. Since the reported conditions are too drastic and rather impractical, we sought to suitably modify the reaction so as to achieve the above conversion under milder conditions.

Our attempt to react bisphenol **1** with cheaply available 2- chloroethanol in K_2CO_3-DMF condition showed practically no conversion and with NaH as the base, only 10-15% yield of **8** could be realised. Subsequently, we found that the above reaction in aqueous NaOH, initially at 0-5°C for 4 hr and then at room temperature for 40 hr proceeded smoothly and resulted in the direct precipitation of the product **8**. Further purification was achieved by repeated crys-



Scheme I

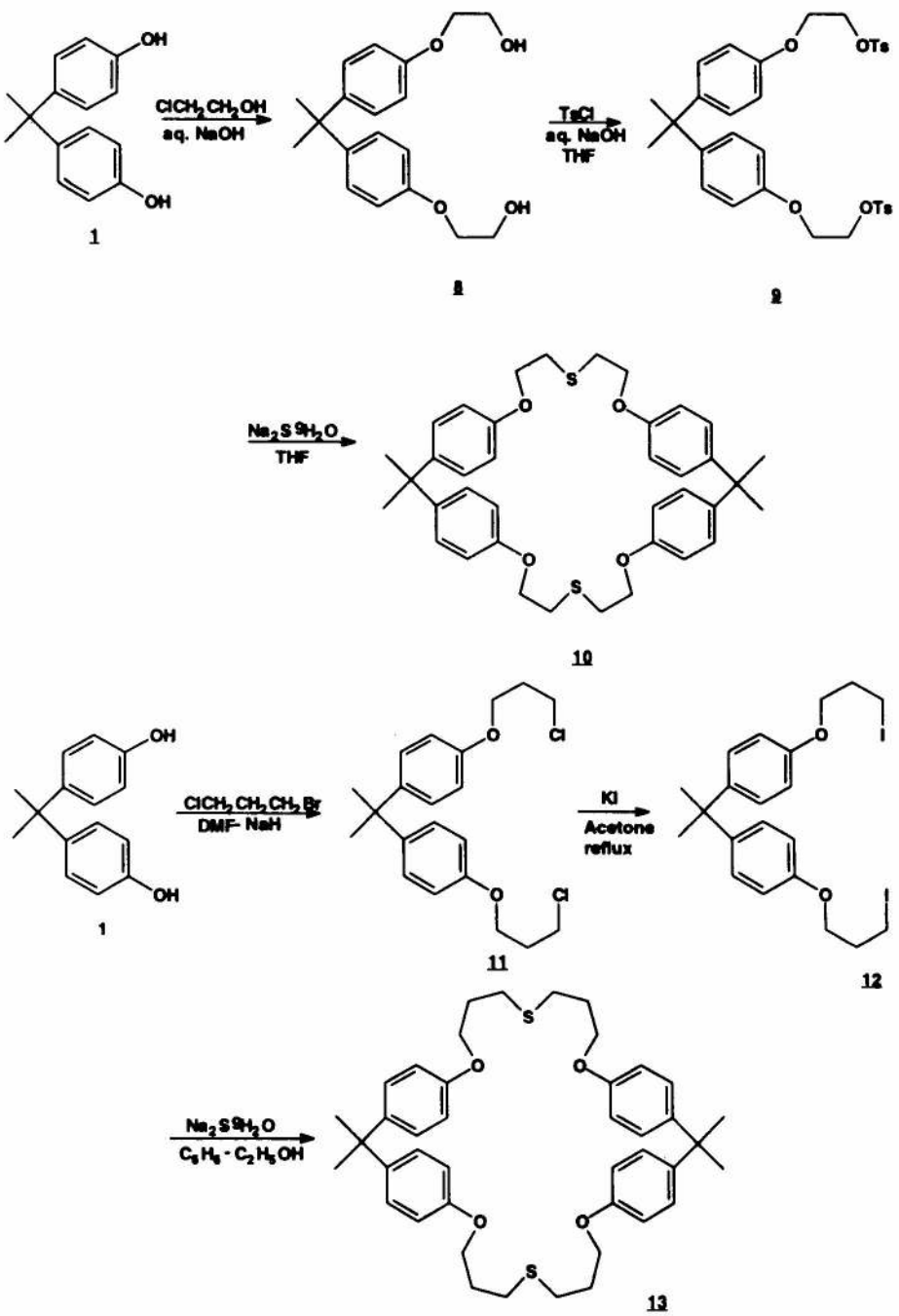
Further purification was achieved by repeated crystallisation from ethanol to give pure diol **8** in 65% yield, m.p. 103-5°C. Thus our procedure for the preparation **8** is an improvement over the literature procedure[10].

The reaction of **8** with 2.5 equivalent of *p*-toluene sulphonyl chloride in pyridine or NaOH gave ditosylate **9**, as a thick syrup (a major single spot on TLC) which was used as such for the reactions without further purification (purity *ca* 90% from ^{1}H NMR). Ditosylate **9** was reacted with $Na_2S.9H_2O$ in THF - methanol solvent system under high dilution conditions to yield **10**, m.p. 173-75°C, M^+ m/z 628.

The synthesis of tetraoxa - dithia macrocycle **13** containing propyl spacers was carried out as shown in Scheme II. Bisphenol **1** was reacted with an excess of 1-bromo-3-chloropropane in DMF- NaH system. The crude product was purified by SiO_2 (essentially to remove the excess of 1-bromo-3-chloropropane) to afford the required dichloride **11** as a colourless oil in 85% yield. The compound **11** was subjected to the dithiabridge formation with $Na_2S.9H_2O$ in benzene - ethanol solvent system under reflux conditions. However, most of the starting **11** was recovered unchanged without any indication of the product formation. The lack of reactivity of **11** may be attributed to the poor nucleofugicity of chloride ion in S_N2 reaction. To enhance the reactivity, diiodide **12** was prepared by heating **11** with excess of **KI** in dry acetone. A quantitative conversion of **12** was achieved as judged by TLC and NMR analysis (-CH_2-I appeared as expected upfield at δ3.8; the absorption for CH_2Cl appears at δ4.0 in compound **11**).

The diiodide **12** underwent thia macrocyclization with $Na_2S.9H_2O$ in benzene - ethanol solvent system to give colourless crystals of **13**, m.p. 166-68°C (35% yield), M^+ m/z 684.

It is worth noting that all the presently synthesised bisphenol macrocycles correspond to 2:2 condensation. The absence of 1:1 cyclisation mode can be



Scheme II

explained on the ground that the resulting macrocycles would be more strained (relative to 2:2 macrocycles) due to smaller cavity dimensions. Consequently, the final intramolecular ring closure might be rendered energetically unfavourable to avoid the formation of strained 1:1 macrocycles. This observation is also in keeping with the literature where bisphenol reportedly forms only 2:2 condensed macrocycles[4].

Attempted complexation with macrocycles 5, 6, 10 and 13. The complexation studies on macrocycles polyethers towards metal ions and primary alkyl ammonium salts are of interest from the point of view of ion selective complexation, ion transport and phase transfer catalysis. Thus crystalline metal and ammonium ion complexation were studied for the above macrocycles which encompass sufficient

number of oxygen or oxygen - sulphur ligands required for complexation.

Macrocycles **5, 6, 10** and **13** were individually dissolved in hot methanol or methanol-$CHCl_3$ and treated with 2-4 fold excess of KSCN, NaSCN or NH_4SCN. The clear solution on keeping at room temperature, deposited colourless crystals of starting macrocycles only. Also, the $CHCl_3$ solutions of macrocycles ($1\times M^{-3}$) show virtually zero extraction of Li^+, Na^+, K^+ and Cs^+ picrates from their aqueous solutions ($5\times M^{-3}$).

One of the most important conditions for effective metal ion complexation by crown systems is the ability of most, if not all ligating atoms (O, S etc) to be able to interact through their lone pairs with the metal ions. The failure of our macrocycles to participate in complexation may be due to the presence of large biphenyl spacers which tend to keep two ligating bridges sufficiently far apart so as to disallow effective convergent binding of oxygen (or oxygen-sulphur) ligands with the metal ions.

Experimental Section

Melting points were determined using apparatus employing electrical heating and are uncorrected. IR spectra were recorded either in a neat liquid or in KBr pellet on a Shimadzu FTIR- 4200; NMR spectra on a varian EM-360L at 60 MHz or Varian VR- 300S at 300 MHz with TMS as internal standard. TLC was carried out on a manually coated silica gel plates (3×10 cm) using Acme TLC silica gel. Bisphenol was a commercial product from S.D. Fine Chemicals, India and was used as such.

Macrocyclization of 5, 6 and 7. General procedure. Bisphenol **1** (10 mmoles) and appropriate bis alkylating agent **2, 3** or **4** (10 mmoles each) were dissolved in dry THF (200 mL) and added dropwise to the stirred THF (150 mL) containing solid KOH (50 mmoles) and 18-crown-6 (50 mg) at 55-60°C over a period of 8 hr. The reaction was refluxed further for 10 hr, cooled to room temperature and filtered through a pad of celite. The crude product obtained on solvent removal was chromatographed on silica gel to obtain the macrocycles **5, 6** or **7**, respectively.

Hexaoxa macrocycle 5; m.p. 175-76°C (12% yield) (Found: C, 76.38; H, 7.14. $C_{38}H_{44}O_6$ requires C, 76.51; H, 7.38%); IR(KBr): 3000, 2900, 1600, 1550, 1240, 1175, 1120, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.6 (s, 6H, $(CH_3)_2C<$), 3.9 (t, 2H, *J*=6Hz, -O-C*H*$_2$-CH_2-O-Ph), 4.1 (t, 2H, *J*=6Hz, Ph-O-C*H*$_2$-CH_2-O), 6.8 (d, 1H, *J*=8 Hz, Ar-H), 7.1 (d, 1H, *J*=8 Hz, Ar-H); MS: m/z 596 (M^+), 582 (100%), 581, 213 and 136.

Octaoxa macrocycle 6; m.p. 125-26°C (yield 27%). (Found: C, 74.32; H, 7.21. $C_{42}H_{52}O_8$ requires C, 73.68; H, 7.60%); IR (KBr): 3000, 1600, 1550, 1275, 1150, 910, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.6 (s, 6H, $(CH_3)_2C$), 3.7 (s, 4H, -O-*CH*$_2$-*CH*$_2$-O-), 3.8 (t, 2H, *J*=6Hz, Ph-O-CH_2-C*H*$_2$-O-), 4.1 (t, 2H, *J*=6Hz, Ph-O-*CH*$_2$-CH_2-O-), 6.7 (d, 1H, *J*=8 Hz, Ar-H), 7.0 (d, 1H, *J*=8 Hz, Ar-H); MS: m/z 684 (M^+), 669 (100%), 327, 213 and 135.

Tetraoxa-diazatosyl macrocycle 7; m.p. 217-18°C (yield 14%) (Found: C, 69.47; H, 6.24; N, 3.23; S, 7.59. $C_{52}H_{58}N_2O_8S_2$ requires C, 69.18; H, 6.43; N, 3.10; S, 7.09%); IR (KBr): 3000, 1610, 1550, 1360, 1200, 990, 830 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$ + DMSO-d_6): 1.8 (s, 6H, $(CH_3)_2C<$), 2.65 (s, 3H, C*H*$_3$-Ph), 3.75 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 4.25 (t, 2H, *J*= 7 Hz, -C*H*$_2$-N<), 6.75 (d, 1H, *J*=8 Hz, Ar-H), 7.20 (d, 1H, *J*=8 Hz, Ar-H), 7.50 (d, 1H, *J*=8 J=*8 Hz*, proton ortho to methyl in *p*-methylsulphonamide, 7.90 (d, 1H, *J*=8 Hz, proton meta to methyl in *p*-methylsulphonamide; MS: m/z 902 (M^+), 890, 700, 309 and 205 (100%).

Preparation of diol 8.To a solution of bisphenol 1 (4.56 g, 20 mmoles) in 5% NaOH (100 mL) was added 2-chloroethanol (6.68 mL, 100 mmoles) at 0-5°C and the reaction flask was sealed with a rubber septum. The reaction was stirred at this temperature for 5 hr and further at room temperature for 40 hr. The resultant white solid was filtered, washed with water and dried. The solid was crystallised twice from ethanol to provide colourless crystals, m.p.102-5°C (lit.[10], m.p. 103°C), yield 65% (4.108 g); IR (KBr): 3450, 3000, 1500, 1250, 1200, 1150, 900, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): 1.8 (s, 6H, $(CH_3)_2C<$), 3.7 (t, 2H, -C*H*$_2$-O-H), 3.9 (t, 2H, Ph-O-C*H*$_2$-), 6.5-7.5 (m, 4H, Ar-H).

Preparation of ditosylate 9. To a solution of diol **8** (3.16 g, 10 mmole) was added 30% NaOH (20 mL) while stirring at 0-5°C. To this stirred solution, *p*-toluene sulphonyl chloride (4.75 g, 25 mmole) dissolved in THF (50 mL) was added dropwise over a period of 1 hr and the mixture stirred further for 2 hr. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×50 mL). The combined extract was washed with water and dried (anhyd. Na_2SO_4). The removal of solvent gave a thick syrup

(a major single spot on TLC) which was used as such for the next reaction. IR (Nujol): 3000, 1600, 1510, 1480, 1380, 1300, 1240, 1180, 1010, 940, 820 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): 1.8 (s, 6H, $(CH_3)_2C<$). 2.6 (s, 3H, C*H*$_3$-Ph), 4.2 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 4.5 (t, 2H, *J*=7 Hz, -C*H*$_2$-O-SO_2-), 6.5-7.5 (m, 8H, Ar-H).

Preparation of tetraoxa-dithia macrocycle 10. The crude ditosylate **9**, (*ca*, purity 90%) was dissolved in THF (150 mL) and added dropwise to a stirred solution of methanol - THF (1:2, 200 mL) containing $Na_2S.9H_2O$ (2.5 g) over a period of 6 hr. After the addition was complete, the reaction mixture was refluxed for about 8 hr. It was then cooled and filtered through a pad of celite and concentrated. The crude product was purified by chromatography (benzene as eluent) on silica gel and further recrystallised from benzene to give fibrous needles, m.p. 174-75 C, yield 13% (Found: C, 72.93; H, 6.94, S, 10.43. $C_{38}H_{44}O_4S_2$ requires C, 72.61; H, 7.00; S, 10.19%); IR (KBr): 3000, 1600, 1500, 1240, 1020, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.6 (s, 6H, $(CH_3)_2C<$), 2.9 (t, 2H, *J*=7 Hz, S-C*H*$_2$-CH_2-), 4.1 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 6.5 (d, 2H, *J*=7 Hz, Ar-H), 7.05 (d, 2H, *J*=7 Hz, Ar-H); MS:m/z 628 (M+), 309, 302, 126, 117 (100%).

Preparation of dichloride 11. Biphenol **1** (2.28 g, 10 mmoles) was dissolved in dry DMF (25 mL) and NaH (1.2 g, 55-60% oil dispersion) was added under N_2 atmosphere. The mixture was stirred at room temperature and 1-bromo-3-chloropropane (2.45 mL, 25 mmoles) was added slowly during 15 min and the mixture was stirred further for 2 hr at room temperature. The reaction was decomposed with aq. NH_4Cl solution and extracted with ethyl acetate (2×50 mL). The organic extract was washed with water, dried (anhyd. Na_2SO_4) and the solvent distilled out. The crude product was subjected to SiO_2 column chromatography and eluted with pet. ether to remove the excess of 1-bromo-3- chloropropane. Subsequent elution with pet. ether: ethyl acetate (95:5) gave **11** as colourless oil (3.23 g) in 85% yield; IR (liquid film): 3000, 1610, 1510, 1480, 1380, 1240, 1180, 1040, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): 1.9 (s, 6H, $(CH_3)_2C<$), 2.5 (m, 2H, -CH_2-C*H*$_2$-CH_2-), 4.0 (t, 2H, *J*=7 Hz, C*H*$_2$-Cl), 4.35 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 6.5-7.05 (m, 4H, Ar-*H*).

Preparation of diiodide compound 12. A mixture of dichloride **11** (1.2 g, 3.15 mmoles), KI (2.0 g) and dry acetone (150 mL) was stirred and refluxed for 6 hr. The complete conversion was confirmed by TLC. The reaction mixture was then cooled, filtered and the solvent removed to give **12** as a colourless oil in quantitative yield. IR (liquid film): 3000, 1610, 1510, 1480, 1300, 1250, 1180, 960 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): 1.6 (s, 6H, $(CH_3)_2C<$), 2.3 (m, 2H, CH_2-C*H*$_2$-CH_2), 3.8 (t, 2H, *J*=7 Hz, C*H*$_2$-I), 4.2 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 6.6-7.3 (m, 4H, Ar-H).

Preparation of tetraoxa-dithia macrocycle 13. Diiodo compound **11** (1.0 g, 1.77 mmoles) was reacted with $Na_2S.9H_2O$ (2.5 g) in benzene-ethanol (1:1, 300 mL). The crude product was subjected to SiO_2 column chromatography (benzene-pet. ether; 30:70 as eluent) and a single low polar product was isolated as a white solid. Crystallisation from ethanol provided white crystals, m.p. 166- 68°C (215 mg, 35% yield) (Found: C, 73.25: H, 8.23, S, 9.58. $C_{42}H_{52}O_4S_2$ requires C, 73.68; H, 7.60; S, 9.36%); IR(KBr): 3000, 1610, 1505, 1250, 1050, 940, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): 1.59 (s, 6H, $(CH_3)_2C<$), 2.0 (m, central, -C*H*$_2$-), 2.68 (t, 2H, *J*=7 Hz, -S-C*H*$_2$-), 3.98 (t, 2H, *J*=7 Hz, Ph-O-C*H*$_2$-), 6.74 (d, 2H, *J*=7 Hz, Ar-H);, 7.05 (d, 2H, *J*=7 Hz, Ar-H); MS: m/z 684 (M^+), 301, 216, 165, 117 (100%).

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