The preparation of thiophene-based azacryptand Mannich bases

Julie D. E. Chaffin,* John M. Barker and Patrick R. Huddleston

Department of Chemistry and Physics, The Nottingham Trent University, Clifton Lane, Nottingham, UK NG11 8NS

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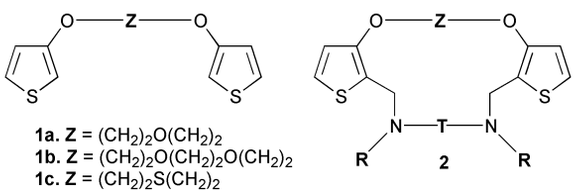
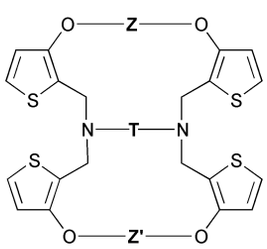
The preparation of cryptand-like structures, incorporating four thiophene rings, was undertaken. A variety of approaches were considered, but a stepwise process commencing from the readily available α,ω-bis(2-formyl-3-thienyloxy)alkanes of the type ArO-**Z**-OAr (where Ar = 2-formyl-3-thienyl and **Z** = heteroalkyl chain) yielded excellent results. A range of open chain and cyclic Mannich bases incorporating one or two macrorings was prepared *via* reduction of open chain and macrocyclic imines derived from the heteroalkyl-bridged bisaldehydes. Tosyl and acetyl derivatives of the reduced products, *viz.* the intermediate secondary amines were prepared; the latter exhibited diastereoisomerism.

The ability of a considerable range of crown compounds to act as hosts for a variety of species is well known and has been reviewed extensively.[1–3] The incorporation of nitrogen into the macroheterocycle has extended the utility of crowns further still, amino groups being useful reactive sites from which additional macrocyclic rings may be introduced. Our earlier publications[4] in this area have described the synthesis of, *inter alia*, a range of thiophene-based Mannich bases of type **2** from appropriate thiophenes **1**. The aim of the present work was to extend the approach to the formation of cryptands of type **3**.





Pastushok *et al.*[5] have prepared benzoazacrown ethers and cryptands by the Mannich condensation of phenols and secondary diamines, but as far as we are aware no thiophene compounds of type **3** have been reported previously. Some thiophene-based macrocycles of a different type are known.[6] Condensation of thiophene-2,5-dialdehyde with trisamines $[H_2N(CH_2)_x]_3N$ (x = 2 and 3) leads to the appropriate bicyclic hexamines; in the case where x = 3 the product could be reduced to the octaamino-compound. Unlike their furan counterparts, these compounds were not obtained in the absence of a silver template.

Results and discussion

In our first approach it was assumed that, with the correct ratio of reagent and substrate, it might be possible to obtain the desired compounds in a one-pot synthesis. In a model reaction to test this theory, 3-methoxythiophene was reacted with 1,2-ethylenediamine–formaldehyde under the conditions that had been successful in our earlier work,[4] but the yield of **4** was disappointingly low (14%). It was then considered that an internal template effect might operate if an ether chain linked the pairs of thiophene rings. Accordingly the ether **1b** was reacted with the stoichiometric quantity of the iminium species derived from 1,2-ethylenediamine or hexane-1,6-diamine and formaldehyde, in the hope of obtaining the bismacrocycles **5a** and **5b**.

In the event a complex mixture of products, which could not be separated, was obtained. Indeed, it would have been very fortunate if the desired substances had been favoured over other, equally likely, condensation products (*e.g.* **6a**,**b**). In order to have some compounds of type **6** to hand, thiophene ether **1b** was reacted with 4-methoxybenzylamine–formaldehyde to give a satisfactory yield (59%) of the cyclic amine **7**. The plan was then to remove the protecting 4-methoxybenzyl group, to give the secondary amine, which could then be used to prepare **6a** and **6b**. Unfortunately all attempts to remove the blocking group failed.

Attention was then turned to the stepwise synthesis of the target cryptand system, the preparation of diamines of general structure **12** (Scheme 1) being the first aim. In principle there are several approaches to such compounds. Firstly, they might be obtained by conversion of the 2,2′-bis(carboxylic acids) that are the immediate precursors of compounds **1** into the bisamides by reaction with α,ω-diamines, followed by reduction. However, our earlier work along these lines with other compounds had not been encouraging so this route was not explored. A second alternative would involve Mannich condensation of *N*-protected α,ω-diamines with **1** and formaldehyde, followed by deprotection. We had considerable difficulty in preparing suitable protected diamines; further, our experiences with compound **7** did not encourage us to pursue this route. The successful synthesis finally adopted had encouraging precedents in the literature for the formation of macrocyclic imines.[7]

Vilsmeier formylation[8] of **1a**–**c** proceeded in excellent yields (85–95%), the bisaldehydes being stable, crystalline compounds. In order that we could gain some experience in the preparation and reduction of imines in these systems the bisaldehydes were condensed with *n*-propylamine; for added interest a single compound derived from *N*-ethanolamine (2-aminoethanol) was also prepared. The formation of the imines **9** and subsequent borohydride reduction of the crude products to give the bisamines **10** proceeded with a good return of material, excellent indications for the preparation of the cyclic products **11**

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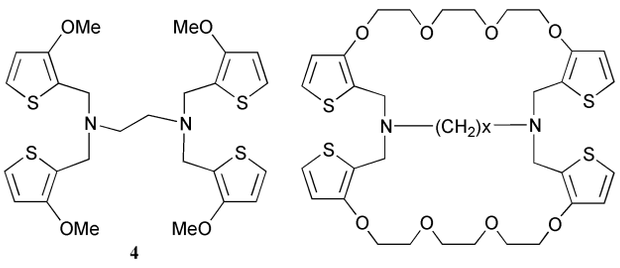

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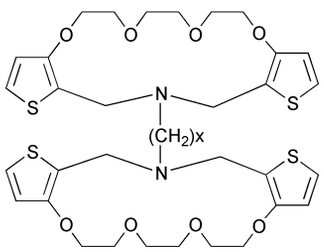
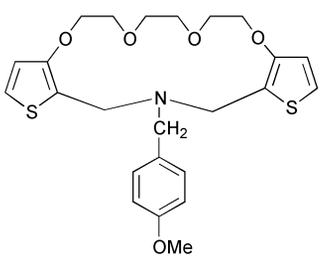
5a, x = 2
5b, x= 6



6a, b



7

and **12**. In the earliest trial experiment **1a** was reacted with methylamine, but the final reduction product was contaminated with 1,5-bis(2-hydroxymethyl-3-thienyloxy)-3-oxapentane **13** arising from direct reduction of the –CHO groups. The identity of the contaminant was confirmed by independent synthesis of **13**. It seems likely that some of the volatile amine had escaped from the reaction mixture before imine formation was complete; no such problem arose when *n*-propylamine or ethanolamine was employed.

We now turned our attention to the reaction of **8** with α,ω-diamines. Ethylenediamine yielded only polymeric residues; hexane-1,6-diamine gave slightly better results, but 2,2′-oxybis(ethylamine) [bis(2-aminoethyl) ether] was the reagent of choice, giving macrocyclic products **11b–d** and **12b–d** of reasonable purity with the added interest that the linking group -**T**- contained an oxygen atom in the chain.

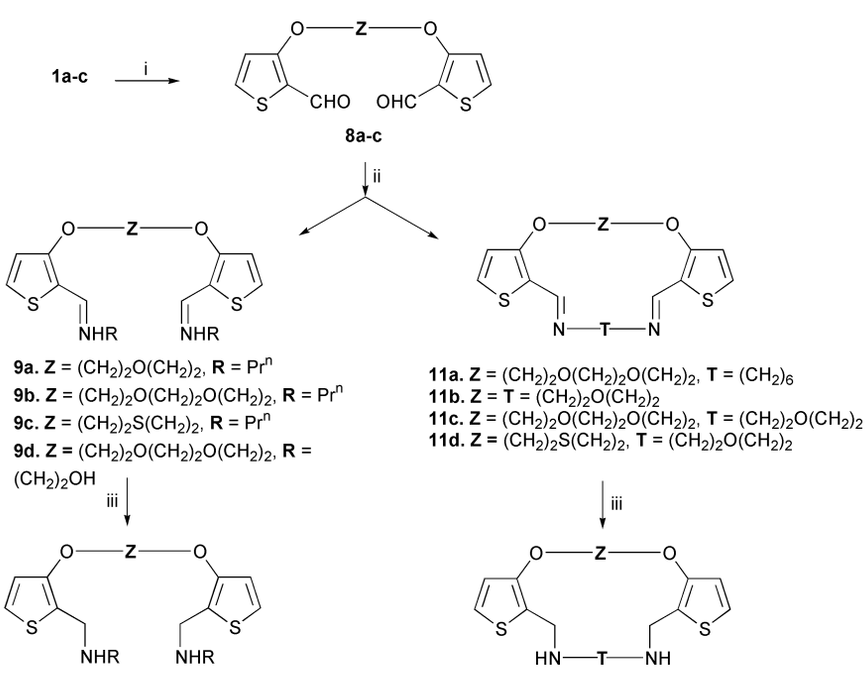
The crude bisimines in both the cyclic and acyclic series were unstable and were reduced without purification. The resulting bisamines could not be purified by the normal methods (*e.g.* acidic extraction, chromatography), and so were characterised through their acetyl and toluene-*p*-sulfonyl derivatives **14** to **17**.

The former derivatives were obtained in *ca.* 100% yield for the open chain compounds **14**, and 50% for the cyclic bisamines **16**–possibly an indication of the purity of the reduction products in both cases. The acetyl derivatives exhibit diastereoisomerism due to restricted rotation about the amide C–N bond (*cf. N*,*N*-dimethylformamide); the carbon-13 spectra of the acyclic compounds show two sets of signals and those of the cyclic compounds show three or four. In each case the signals collapse into a single set when the temperature was raised sufficiently (see Table 1 for typical examples).

The toluene-*p*-sulfonyl derivatives **15** and **17** were obtained in *ca.* 50% yield from the crude reduction mixture in both cyclic and acyclic cases. It is of interest that the cyclic compounds yielded crystalline derivatives with both reagents, whereas those derived from the open chain compounds were oils.

The last major part of the study was the use of the diamines just discussed in Mannich reactions with a variety of oxygenated thiophene derivatives to give a range of macrcocylic products. In trial experiments the acyclic diamines were reacted with 3-methoxythiophene, to give the model acyclic Mannich bases **18** in satisfactory yield (60–70%). Replacement of the methoxythiophene with the ethers **1** led to modest yields (20–29%) of the large ring compounds **19a–d**.

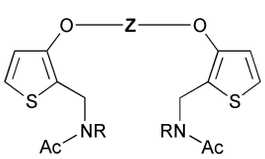
Some optimisation work was carried out, using the formation of compound **19a** as an example. An increase in yield from 28 to 36% took place when the preparation was carried out under "dilution principle" conditions.[9] The effect of the addition of inorganic salts under conditions of normal dilution was also



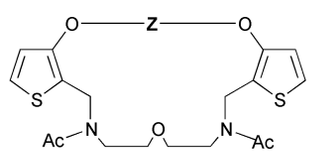
Scheme 1 Preparation of acyclic and cyclic secondary diamines. *Reagents and conditions*: (i) $POCl_3$, DMF, 1,2-dichloroethane, Δ; (ii) $^nPrNH_2$ for **9a–c**, $NH_2(CH_2)_2OH$ for **9d**, $NH_2(CH_2)_6NH_2$ for **11a**, $NH_2(CH_2)_2O(CH_2)_2NH_2 \cdot 2HCl$ and NaOH for **11b–d**, EtOH, Δ; (iii) $NaBH_4$, EtOH, Δ.

Table 1 ^{13}C chemical data for **14c** and **16a** at selected temperatures in d_6-DMSO

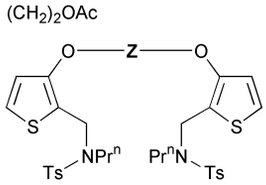
	14c			**16a**			
Carbon atom	20 °C	70 °C	100 °C	20 °C	70 °C	100 °C	150 °C
C=O	170.12, 170.03	169.91	169.24	169.59, 169.74	169.66, 169.74	169.56, 169.61	168.75
Ar 3-C	153.55, 153.78	153.66	153.62	154.25, 154.03	154.32, 154.12	154.28	153.46
Ar 5-C	123.83, 123.20	123.47, 124.43	123.16	124.17, 123.72, 124.00	124.04, 123.88, 123.59, 123.30	123.84, 123.56, 123.99, 123.30	122.75
Ar 2-C	118.24, 116.98	123.25, 123.06		117.68, 117.43	116.96, 117.97,	118.06, 118.47,	117.76
Ar 4-C	116.26, 116.33	116.60, 117.00	116.91	116.78, 117.01, 116.71	117.11, 117.59, 117.37	117.12, 117.25, 118.15, 117.34, 117.45, 117.63, 117.39	116.80
$ArOCH_2$	71.25, 21.02	71.41	71.52	70.94	71.23	71.39	70.80
$ArCH_2NCH_2$	49.76, 47.10	49.71	—	46.18, 43.25,	46.47, 43.63,	46.90, 46.79,	–
$ArCH_2N$	39.23, 39.23,	39.43		46.68, 42.93	46.86, 43.25, 44.13, 44.85, 46.34	46.67, 43.76	
Ar OCH_2CH_2	32.17	32.26	32.34	60.45, 69.27	69.59, 68.53,	69.59	68.93
$ArCH_2NCH_2CH_2$	21.98, 20.85	20.97	21.06	67.98, 67.78	67.96, 69.43, 68.68	68.34	67.77
CO*Me*	21.10, 21.98	21.98	21.58	21.11, 21.62	21.02, 21.44	21.08	20.08
$N(CH_2)_2Me$	11.66, 11.84	11.52	11.41	–	–	–	–



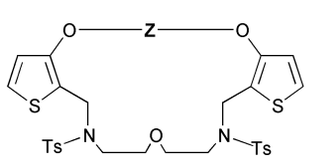
14a. Z = $(CH_2)_2O(CH_2)_2$, **R** = Pr^n
14b. Z = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **R** = Pr^n
14c. Z = $(CH_2)_2S(CH_2)_2$, **R** = Pr^n
14d. Z = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **R** = $(CH_2)_2OAc$



16a. Z = $(CH_2)_2O(CH_2)_2$
16b. Z = $(CH_2)_2O(CH_2)_2O(CH_2)_2$
16c. Z = $(CH_2)_2S(CH_2)_2$



15a. Z = $(CH_2)_2O(CH_2)_2$
15b. Z = $(CH_2)_2O(CH_2)_2O(CH_2)_2$
15c. Z = $(CH_2)_2S(CH_2)_2$

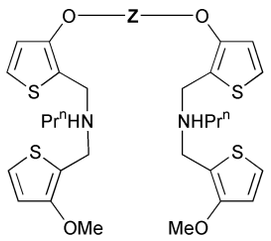


17a. Z = $(CH_2)_2O(CH_2)_2$
17b. Z = $(CH_2)_2O(CH_2)_2O(CH_2)_2$
17c. Z = $(CH_2)_2S(CH_2)_2$

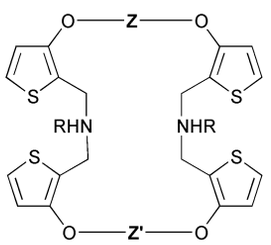
examined, to see if any template effect might apply. A marked improvement was noted (yields in the range 32–35%) in the presence of nickel(II) acetate, lead(II) acetate, sodium acetate and silver nitrate; barium carbonate was most effective, raising the return to 43%.

The utility of this approach for the synthesis of lariat ethers was examined. The Mannich reaction appears to have been successful but compound **19e** could not be purified chromatographically, so it was converted to the diacetate **19f**, which was isolated in very poor yield. It has been previously noted that secondary aminoalcohols react slowly under Mannich reaction conditions so these poor results may be due to a high degree of polymerisation in the macrocyclisation step.

In the final set of experiments the cyclic diamines **12** were employed in Mannich condensations with formaldehyde and a selection of ethers **1**, giving the cryptand-type macrocycles **20**. The yield of **20a** was disappointing (15%); application of dilution principle conditions did not improve results. However results for the compounds derived from 2,2′-oxybis(ethylamine) **20b–e** exhibited a marked improvement (25–35% yield). The

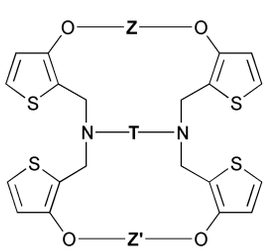


18a. **Z** = $(CH_2)_2O(CH_2)_2$
18b. **Z** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$
18c. **Z** = $(CH_2)_2S(CH_2)_2$



19a. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2$, **R** = Pr^n
19b. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **R** = Pr^n
19c. **Z** = **Z'** = $(CH_2)_2S(CH_2)_2$, **R** = Pr^n
19d. **Z** = $(CH_2)_2O(CH_2)_2$, **Z'** = $(CH_2)_2S(CH_2)_2$, **R** = Pr^n
19e. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **R** = $(CH_2)_2OH$
19f. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **R** = $(CH_2)_2OAc$

evidence is that the bisamines are at best only 50% pure so this suggests that when the linking group **T** was heteroalkyl the final cyclisations are quite effective (*ca.* 50%), better than when the large single ring (as in **19**) was to be the outcome.



20a. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **T** = $(CH_2)_6$
20b. **Z** = **Z'** = **T** = $(CH_2)_2O(CH_2)_2$
20c. **Z** = **Z'** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$, **T** = $(CH_2)_2O(CH_2)_2$
20d. **Z** = **Z'** = $(CH_2)_2S(CH_2)_2$, **T** = $(CH_2)_2O(CH_2)_2$
20e. **Z** = $(CH_2)_2O(CH_2)_2$, **Z'** = $(CH_2)_2O(CH_2)_2$

During the preparation of **19c**, **19f** and **20d**, compounds thought to be the products of incomplete macrocyclisation were eluted from the column after the desired product had been isolated.

In conclusion bismacrocylic Mannich bases can be prepared from readily accessible α,ω-bis(2-formyl-3-thienyloxy)alkanes *via* a stepwise process involving the reduction of macrocyclic imines.

Experimental

Melting points were determined using open capillary tubes in an electrically heated Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 1600 FT-IR spectrometer as potassium bromide discs or thin films between sodium chloride plates. NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B 60 MHz (^{1}H NMR only), a JEOL FX60Q 60 MHz (^{13}C NMR only) or a JEOL EX-270 MHz NMR spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm on the delta scale; *J* values are given in Hz.

Microanalyses for C, H and N were determined by the analytical department of Shell Research Centre, Sittingbourne and the microanalysis unit of the University of Nottingham. Mass spectroscopic determinations (chemical ionisation) were carried out by Shell Research Centre, Sittingbourne. Preparative column chromatography employed 60–120 mesh silica gel (particle size 0.13–0.25 μm) or Brockmann Grade 1 aluminium oxide (activated, neutral) purchased from BDH Ltd. All solvents for chromatographic work were redistilled. 1,2-Dichloroethane was dried over calcium chloride. Ethylenediamine and DMF were distilled and stored over molecular sieves.

Preparation of *N*,*N*,*N*′,*N*′-tetrakis(3-methoxy-2-thienylmethyl)-ethylenediamine 4

A solution of ethylenediamine (0.13 g, 2.2×10^{-3} mol, 0.25 eq.) and formaldehyde (37% aq solution, 0.66 ml, 8.8×10^{-3} mol, 1.0 eq.) in glacial acetic acid (20 ml) was infused at a rate of *ca.* 1 ml h^{-1} by use of a syringe pump into a stirred solution of 3-methoxythiophene (1.0 g, 8.8×10^{-3} mol, 1.0 eq.) in the same solvent (5 ml) at ambient temperature. Twenty-four hours after the start of infusion the reaction mixture was basified with 4 M sodium hydroxide solution and extracted into ether (×2). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brown oil which partly solidified (1.11 g). Recrystallisation of the crude material from ethyl acetate–light petroleum, bp 40–60 °C afforded the *title compound* as a yellow solid (0.17 g, 14%), mp 121–123 °C (Found: C, 54.9; H, 5.7; N, 4.9. $C_{26}H_{32}N_2O_4S_4$ requires C, 55.3; H, 5.7; N, 5.0%); δ_H ($CDCl_3$) 7.05 (4H, d, *J* 5, Ar 5-H), 6.76 (4H, d, *J* 5, Ar 4-H), 3.76 (12H, s, OMe), 3.73 (8H, s, $ArCH_2N$) and 2.70 (4H, s, NCH_2) ppm; δ_C ($CDCl_3$) 154.3 (Ar 3-C), 122.4 (Ar 5-C), 119.8 (Ar 2-C), 116.2 (Ar 4-C), 58.8 (OMe), 51.2 ($ArCH_2N$) and 48.5 (NCH_2) ppm; ν_{max} (KBr) 1563.6s (Ar C=C) cm^{-1}.

Preparation of the macrocycle derived from *p*-methoxybenzylamine 7

The α,ω-bis(3-thienyloxy)alkane **1b** was added to a solution of *p*-methoxybenzylamine (1.1 eq.) and formaldehyde (37% aqueous solution, 2.2 eq.) in glacial acetic acid (25 ml g^{-1} of bisether). The mixture was stirred at room temperature for 24 h, then basified with 4 M sodium hydroxide solution and extracted with ether (×2). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material, obtained in quantitative yield was recrystallised from ethyl acetate to provide the title *Mannich base* (59%), mp 120–123 °C (Found: C, 61.0; H, 6.2; N, 3.2. $C_{24}H_{29}NO_5S_2$ requires C, 60.6; H, 6.2; N, 2.9%); δ_H ($CDCl_3$) 7.39 (2H, d, *J* 9, Ph 2-H), 7.07 (2H, d, *J* 6, Ar 5-H), 6.87 (2H, d, *J* 9, Ph 3-H), 6.73 (2H, d, *J* 6, Ar 4-H), 4.13 (4H, m, $ArOCH_2$), 3.79 (3H, s, OMe), 3.76 (4H, s, $ArOCH_2$), 3.73 (4H, m, $ArOCH_2CH_2$), 3.70 (4H, s, $ArOCH_2CH_2OCH_2$) and 3.57 (2H, s, $PhCH_2N$) ppm; δ_C ($CDCl_3$) 158.5 (Ph 4-C), 153.6 (Ar 3-C), 131.8 (Ph 1-C), 129.8 (Ph 3-C), 122.6 (Ar 5-C), 121.9 (Ar 2-C), 117.2 (Ar 4-C), 113.6 (Ph 2-C), 71.5 ($ArOCH_2$), 70.8 ($ArOCH_2CH_2$), 69.63 ($ArOCH_2CH_2OCH_2$), 56.21 ($PhCH_2N$), 55.22 (OMe) and 48.19 ($ArCH_2N$) ppm; ν_{max} (KBr) 1608.4m (Ph C=C) and 1560.2s (Ar C=C) cm^{-1}.

Preparation of the α,ω-bis(2-formyl-3-thienyloxy)alkanes 8a–c

A solution of the α,ω-bis(3-thienyloxy)alkane **1a**–**c** in the minimum volume of anhydrous 1,2-dichloroethane was added to a stirred solution of anhydrous DMF (2.2 eq.) and phosphorus oxychloride (2.2 eq.) in the same solvent (5 or 10 ml g^{-1} of bisether). The mixture was heated at 95–100 °C for 2 h (oil bath), then poured into an aqueous solution of sodium acetate (10–13%; 4 g g^{-1} of bisether) and stirred for a further 1 h at ambient temperature. The aqueous layer was neutralised with dilute sodium hydroxide solution and, if precipitation was evident, DCM was added to the mixture. The two phases were

Table 2 Analytical data for the bisaldehydes

Compound (Formula)	Yield (%)	Mp/°C	M^+ (M)	Found (required) %C	%H
8a $C_{14}H_{14}O_5S_2$	95	81–82	327 (326.4)	51.4 (51.5)	4.4 (4.3)
8b $C_{16}H_{18}O_6S_2$	90	110–112	371 (370.4)	51.6 (51.9)	4.9 (4.9)
8c $C_{14}H_{14}O_4S_3$	85	96–98	343 (342.5)	49.2 (49.1)	4.3 (4.1)

Table 3 Analytical data for the bisacetamides[a]

Compound (Formula)	Yield (%)	Chromatography system[b]	Mp/°C	Found (required) %C	%H	%N
14a $C_{24}H_{36}N_2O_5S_2$	98	1 : 0	Oil	57.7 (58.0)	7.6 (7.3)	5.3 (5.6)
14b $C_{26}H_{40}N_2O_6S_2$	83	1 : 1	Oil	57.9 (57.8)	7.8 (7.5)	5.0 (5.2)
14c $C_{24}H_{36}N_2O_4S_3$	84	1 : 1	Oil	55.9 (56.2)	7.4 (7.1)	5.3 (5.5)
14d $C_{28}H_{30}N_2O_{10}S_2$	41	1 : 1 ⟶ 2 : 1 ⟶ 1 : 0	Oil	53.2 (53.5)	6.7 (6.4)	4.3 (4.5)
16a $C_{22}H_{30}N_2O_6S_2$	56	2 : 3	141–145	54.7 (54.8)	6.5 (6.3)	5.6 (5.8)
16b $C_{24}H_{34}N_2O_7S_2$	47	1 : 1 ⟶ 1 : 0	80–83	54.4 (54.7)	6.8 (6.5)	5.2 (5.3)
16c $C_{22}H_{30}N_2O_5S_3$	39	1 : 1 ⟶ 2 : 1 ⟶ 1 : 0	154	53.0 (53.0)	6.3 (6.1)	5.3 (5.6)

[a] In all cases a mixture of diastereoisomers was analysed. [b] The crude material was preabsorbed onto alumina and subjected to column chromatography using ethyl acetate–petroleum ether, bp 40–60 °C in the ratio shown.

Table 4 Analytical data for the bistoluenesulfonamides

Compound (Formula)	Yield (%)	Chromatography system[a]	Mp/°C	Found (required) %C	%H	%N
15a $C_{34}H_{44}N_2O_7S_4$	63	1 : 3	Oil	56.3 (56.6)	6.2 (6.2)	3.9 (3.9)
15b $C_{36}H_{48}N_2O_8S_4$	62	1 : 3 ⟶ 1 : 2	Oil	56.5 (56.5)	6.6 (6.3)	4.0 (3.7)
15c $C_{34}H_{44}N_2O_6S_5$	44	1 : 3	Oil	55.1 (55.4)	6.3 (6.0)	3.9 (3.8)
17a $C_{32}H_{38}N_2O_8S_4$	62	1 : 3 ⟶ 1 : 2 ⟶ 1 : 0 ⟶ $CHCl_3$	160–161	54.4 (54.4)	5.7 (5.4)	3.7 (4.0)
17b $C_{34}H_{42}N_2O_9S_4$	31	1 : 3	128–130	54.7 (54.4)	5.9 (5.6)	3.6 (3.7)
17c $C_{32}H_{38}N_2O_7S_5$	44	1 : 3 ⟶ 1 : 2 ⟶ 1 : 1	120–122	53.1 (53.2)	5.5 (5.3)	3.6 (3.9)

[a] In all cases the crude material was preabsorbed onto alumina and subjected to column chromatography using ethyl acetate–petroleum ether, bp 40–60 °C in the ratio shown.

separated and the aqueous layer was extracted with a further portion of DCM. The organic phases were combined, dried ($MgSO_4$) and evaporated to give the crude *bisaldehyde*, which was then recrystallised from ethyl acetate (see Table 2).

Preparation of the open chain bisimines 9a–d

A stirred solution of the α,ω-bis(2-formyl-3-thienyloxy)alkane **1a–c** (1.0 eq.) and 2.5 equivalents of the primary amine (*n*-propylamine for **9a–c** or ethanolamine for **9d**) in anhydrous ethanol (20 ml g^{-1} of bisaldehyde) was boiled under reflux for 1 h. The mixture was cooled and the excess of solvent/reagent was removed *in vacuo* to give the crude *bisimine* in essentially quantitative yield. Analytical data for these compounds are not available, as they were found to be unstable.

Preparation of the macrocyclic bisimines 11a–d

The aliphatic diamine (hexane-1,6-diamine for **11a** or 2,2′-oxybis(ethylamine) dihydrochloride for **11b–d**; 1.1 eq.) was added to a solution of the α,ω-bis(2-formyl-3-thienyloxy)-alkane **1a–c** (1.0 eq.) and sodium hydroxide (for **11b–d** only; 2.2 eq.) in boiling anhydrous ethanol (25 ml g^{-1} of the bisaldehyde). The mixture was boiled under reflux for 1 h. With hexane-1,6-diamine the solvent was removed *in vacuo* to give the crude *bisimine* **11a** in essentially quantitative yield. With 2,2′-oxybis-(ethylamine) the residue was extracted several times with DCM. The DCM extracts were filtered, dried ($MgSO_4$) and evaporated to give the crude *bisimine* **11b–d** in essentially quantitative yield. Analytical and ^{13}C NMR data for these compounds are not available, as they were found to be unstable.

Preparation of the bisamines 10a–d and 12a–d

The crude bisimine was prepared as described earlier but was not isolated. A solution of sodium borohydride (2.5 eq.) in anhydrous ethanol (10 ml g^{-1} of bisaldehyde for the open chain amines, 25 ml g^{-1} for the macrocyclic amines) was added and the mixture was boiled under reflux for 1 h. The solution was cooled and evaporated; the residue was treated with water and extracted into DCM (×2). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield the crude *bisamine* in almost quantitative yield. Analytical data for all, and ^{13}C NMR data for the macrocyclic compounds, are not available as they were found to be difficult to purify; derivatives were prepared (see Tables 3 and 4).

Preparation of 1,5-bis(2-hydroxymethyl-3-thienyloxy)-3-oxapentane 13

A solution of the bisaldehyde **8a** (0.50 g, 1.5×10^{-3} mol, 1.0 eq.) and sodium borohydride (0.15 g, 3.9×10^{-3} mol, 2.6 eq.) in anhydrous ethanol (10 ml) were boiled under reflux for 2 h. The mixture was worked up in the usual way to yield the *title compound* as a colourless oil (0.40 g, 79%), δ_H ($CDCl_3$) 7.08 (2H, d, *J* 6, Ar 5-H), 6.75 (2H, d, *J* 6, Ar 4-H), 4.61 (4H, d, *J* 6, $ArCH_2OH$), 4.11 (4H, m, $ArOCH_2$), 4.05 (2H, t, *J* 6, OH), 3.73 (4H, m, $ArOCH_2CH_2O$) ppm, δ_C ($CDCl_3$) 153.26 (Ar 3-C), 123.02 (Ar 5-C), 122.08 (Ar 2-C), 117.63 (Ar 4-C), 70.91 ($ArOCH_2$), 69.74 ($ArOCH_2CH_2O$), 55.09 ($ArCH_2OH$) ppm.

Table 5 Analytical data for the open chain Mannich bases

Compound (Formula)	Yield (%)	Chromatography system[a]	Found (required) %C	%H	%N
18a $C_{32}H_{44}N_2O_5S_4$	63	1 : 15	57.7 (57.8)	7.0 (6.7)	4.0 (4.2)
18b $C_{34}H_{48}N_2O_6S_4$	60	1 : 12 ⟶ 1 : 8 ⟶ 1 : 4	54.4 (54.6)	7.0 (6.8)	3.8 (4.0)
18c $C_{32}H_{44}N_2O_4S_5$	70	1 : 12 ⟶ 1 : 8	56.4 (56.4)	6.8 (6.5)	3.9 (4.1)

[a] In all cases the crude material was preabsorbed onto alumina and subjected to column chromatography using ethyl acetate–petroleum ether, bp 40–60 °C in the ratio shown.

Table 6 Analytical data for the Mannich bases incorporating one macro-ring[a]

Compound (Formula)	Yield (%)	Chromatography system[b]	Mp/°C	$M^+/2$ (M)[c]	Found (required) %C	%H	%N
19a $C_{34}H_{46}N_2O_6S_4$	23	1 : 12 ⟶ 1 : 8 ⟶ 1 : 5 ⟶ 1 : 8 ⟶ 1 : 5	86–88	354 (707.0)	57.5 (57.8)	6.6 (6.6)	3.8 (4.0)
19b $C_{38}H_{54}N_2O_8S_4$	20	1 : 3 ⟶ 1 : 0 ⟶ $CHCl_3$	115–116 (EtOH)	398 (795.1)	57.4 (57.4)	7.1 (6.8)	3.6 (3.5)
19c $C_{34}H_{46}N_2O_4S_6$	23	1 : 12 ⟶ 1 : 8 ⟶ 1 : 4	97–98	370 (739.1)	55.0 (55.3)	6.2 (6.3)	3.7 (3.8)
19d $C_{34}H_{46}N_2O_5S_5$	29	1 : 8	81–82	354 + 370 (723.1)	56.2 (56.5)	6.6 (6.4)	3.6 (3.9)

[a] Analytical data for **19e**,**f** are not available as samples could not be sufficiently purified. [b] In all cases the crude material was preabsorbed onto alumina and subjected to column chromatography using ethyl acetate–petroleum ether, bp 40–60 °C in the ratio shown. [c] No molecular ion was evident.

Table 7 Analytical data for the bi-macrocyclic Mannich bases

Compound (Formula)	Yield (%)	Chromatography system[a]	Mp/°C	Found (required) %C	%H	%N
20a $C_{38}H_{52}N_2O_8S_4$	15	1 : 2 ⟶ 1 : 1	117–120	57.7 (57.6)	6.8 (6.6)	3.6 (3.5)
20b $C_{32}H_{40}N_2O_7S_4$	32	1 : 3 ⟶ 1 : 2	119–122	55.6 (55.5)	6.0 (5.8)	3.7 (4.0)
20c $C_{34}H_{44}N_2O_9S_4$	25	1 : 3 ⟶ 1 : 0	115–117	55.1 (55.4)	6.5 (6.2)	3.8 (3.6)
20d $C_{32}H_{40}N_2O_5S_6$	35	1 : 4 ⟶ 1 : 3 ⟶ 1 : 2	99–101	52.7 (53.0)	5.7 (5.6)	3.7 (3.9)
20e $C_{32}H_{40}N_2O_6S_5$	28	1 : 3	119 (EtOH)	54.5 (54.2)	6.0 (5.7)	3.8 (4.0)

[a] In all cases the crude material was preabsorbed onto alumina and subjected to column chromatography using ethyl acetate–petroleum ether, bp 40–60 °C in the ratio shown.

Preparation of the Mannich bases incorporating four thiophene rings 18a–c, 19a–e and 20a–e

3-Methoxythiophene (for **18a**–**c**; 2.0 eq.) or the relevant α,ω-bis(3-thienyloxy)alkane (**1a**–**c**; 1.0 eq.) was added to a solution of the crude bisamine (**10a**–**e** or **12a**–**e**; 1.0 eq.) and formaldehyde (37% aq solution, 2.0 eq.) in glacial acetic acid (25 ml g^{-1} of open chain amine, ~20 ml g^{-1} of macrocyclic amine). The solution was stirred at room temperature for 24 h, basified with 4 M sodium hydroxide solution and extracted into DCM (×2). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material was preabsorbed onto alumina and subjected to column chromatography. The *Mannich base* was eluted from the column by the solvent system described in Tables 5–7.

Preparation of the macrocyclic Mannich base 19a by the application of dilution principle and templating techniques

Method A (dilution principle). A solution of formaldehyde (37% aq solution, 2.0 eq.) in glacial acetic acid (10 ml g^{-1} of bisamine) and a solution of 1,5-bis(3-thienyloxy)-3-oxapentane **1a** (1.0 eq.) in the same solvent (10 ml g^{-1} of bisamine) were infused simultaneously *via* use of a syringe pump at a rate of 0.66 ml h^{-1} into a stirred solution of the bisamine **10a** (1.0 eq.) in glacial acetic acid (5 ml g^{-1} of bisamine) at room temperature. Twenty-four hours after the start of infusion the mixture was worked- up in the usual manner.

Method B (template). The crude product was prepared by the general method outlined above with the addition of the metal salt [nickel(II) acetate, silver nitrate, lead(II) acetate, sodium acetate or barium carbonate; 1.0 eq.].

The crude material in all cases was preabsorbed onto alumina and subjected to column chromatography. The title compound was eluted from the column by 1 : 5 ethyl acetate–light petroleum, bp 40–60 °C. Individual yields were as follows: nickel(II) acetate (32%), silver nitrate (32%), lead(II) acetate (33%), sodium acetate (35%), barium carbonate (43%). The mp and ^{13}C NMR spectroscopic data for each product were consistent with the expected structure.

Preparation of the bi-macrocyclic Mannich base 20a by the application of dilution principle techniques

A solution of hexane-1,6-diamine (0.35 g, 3.0×10^{-3} mol, 1.1 eq.) in anhydrous ethanol (20 ml) was infused *via* a syringe pump at a rate of *ca.* 11.5 ml h^{-1} into a stirred, boiling solution of the bisaldehyde **8b** (1.0 g, 2.7×10^{-3} mol, 1.0 eq.) in the same solvent (100 ml). Four hours after commencement of infusion a solution of sodium borohydride (0.26 g, 6.8×10^{-3} mol, 2.5 eq.) in anhydrous ethanol (20 ml) was added. The mixture was boiled under reflux for a further 2 h and then worked-up in the usual manner to give **12a** as an orange oil (1.23 g). This material was used in the next step without further purification.

A solution of 1,8-bis(3-thienyloxy)-3,6-dioxaoctane **1b** (0.85 g, 2.7×10^{-3} mol, 1.0 eq.) in glacial acetic acid (10 ml) and a solution of formaldeyde (37% aq solution, 0.48 ml, 6.4×10^{-3} mol, 2.4 eq.) in the same solvent (10 ml) were infused simultaneously at a rate of 45 ml h^{-1} into a stirred solution of the crude bisamine **12a** (1.23 g) in glacial acetic acid (5 ml), which

Table 8 ^{1}H NMR data ranges for the α,ω-bis(3-thienyloxy)alkanes

Compound	Ar 5-H	Ar 4-H	$ArCH_xN$	$ArCH_xNCH_2$	Other signals[a]
8a–c	7.62–7.65, d, *J* 5–6	6.85–6.87, d, *J* 5–6	–	–	9.98–10.00, s, CH=O
9a–d	7.23–7.25, d, *J* 5–6	6.77–6.80, d, *J* 5–6	8.42–8.45, s, CH=N	3.40–3.62, t, *J* 5–7	1.66, se,[b] *J* 7, CH_2Me + 0.91, t, *J* 7, Me or 3.79, m, CH_2OH + 3.55, t, *J* 7, OH
10a–d	6.96–7.08, d, *J* 5–6	6.71–6.80, d, *J* 5–6	3.78–3.87, s, CH_2N	2.50–2.71, t, *J* 5–7	1.41–1.66, se,[b] *J* 7, CH_2Me + 0.81–0.91, t, *J* 7–8, Me or 3.60, t, *J* 5, CH_2OH + 3.29, s, OH
11a–d	7.24–7.28, d, *J* 5–6	6.73–6.78, d, *J* 5–6	8.41–8.63, s, CH=N	3.52–3.80, s or m	1.44, m, $NCH_2(CH_2)_2$ or 3.64–3.70, m, NCH_2CH_2O
12a–d	6.98–7.05, d, *J* 5–6	6.70–6.75, d, *J* 5–6	3.79–3.87, s, CH_2N	2.55–2.84, s or m	1.32, m, $NCH_2(CH_2)_2$ or 3.51–3.53, m, NCH_2CH_2O
14a–d	7.00–7.14, d, *J* 5–6	6.68–6.84, d, *J* 5–6	4.44–4.66, s, CH_2N	3.13–3.62, t, *J* 6–8	2.01–2.23, s, COMe, 1.49–1.57, m, CH_2Me + 0.79–0.90, t, *J* 7–8, Me or 1.49, m, NCH_2CH_2O
15a–c	7.08–7.11, br s or d, *J* 5–6	6.73, br s or d, *J* 5–6	4.45–4.47, s, CH_2N	2.87–3.07, br s or t, *J* 8	7.29–7.75, d, *J* 7–9, Ph 3-H, 7.27–7.70, d, *J* 8–9, Ph 2-H, 2.39–2.41, s, PhMe, 1.24–1.48, m, CH_2Me, 0.75–0.77, t, *J* 7–8, Me
16a–c	7.12–7.14, m or d, *J* 5–6	6.75–6.81, m or d, *J* 5–6	4.61–4.74, s, CH_2N	3.43–3.48, m	3.58–3.59, m, NCH_2CH_2O, 2.04–2.27, s, COMe
17a–c	7.12–7.13, d, *J* 5–6	6.71–6.72, d, *J* 5–6	4.50–4.51, s, CH_2N	3.22–3.24, t, *J* 6	7.69–7.70, d, *J* 8 Ph 3-H, 7.27–7.28, d, *J* 8–9, Ph 2-H, 2.40–2.41, s, PhMe, 3.38–3.40, t, *J* 6 NCH_2CH_2O
18a–c	7.04–7.07, 2 × d, *J* 5–6	6.72–6.78, 2 × d, *J* 5–6	3.68–3.76, 2 × s, CH_2N	2.42–2.43, t, *J* 7–8	3.68–3.78, s, ArOMe, 1.53–1.54, se, *J* 7, CH_2Me + 0.85–0.86, t, *J* 7, Me
19a–e	7.06–7.12, d, *J* 5–6	6.74–6.79, d, *J* 5–6	3.69–3.82, 2 × s or s, CH_2N	2.44–2.75, m or t, *J* 6–7	1.52–1.54, se, *J* 7, CH_2Me + 0.86–0.87, t, *J* 7–8, Me or 3.74, m, NCH_2CH_2OH + 3.29, br s, OH or 4.18, t, *J* 6, NCH_2CH_2OAc + 2.03, s, MeC=O
20a–e	7.08–7.12, d or 2 × d, *J* 5–6	6.76–6.78, d or 2 × d, *J* 5–6	3.83–3.97, s, CH_2N	2.51–2.81, t, *J* 6	1.53, br s NCH_2CH_2 + 1.22, br s, $N(CH_2)_2CH_2$ or 3.61–3.63, t, *J* 6, NCH_2CH_2O

[a] Additional characteristic NMR signals for bridging group **Z** = $(CH_2)_2O(CH_2)_2$ 4.08–4.35 (4H, m or t, *J* 4–5, 2 × $ArOCH_2$), 3.73–3.92 (4H, m or t, *J* 5–7, 2 × $ArOCH_2CH_2O$); **Z** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$ 4.03–4.31 (4H, br s or m or t, *J* 4–5, 2 × $ArOCH_2$), 3.70–3.90 (4H, br s or m or t, *J* 4–5, 2 × $ArOCH_2CH_2$), 3.62–3.73 (4H, m or s, 2 × $ArOCH_2CH_2OCH_2$); **Z** = $(CH_2)_2S(CH_2)_2$ 4.09–4.37 (4H, br s or m or t, *J* 6–7, 2 × $ArOCH_2$), 2.78–3.07 (4H, br s or m or t, *J* 4–7, 2 × $ArOCH_2CH_2S$). [b] Se = sextet.

Table 9 ^{13}C NMR data ranges for the α,ω-bis(3-thienyloxy)alkanes

Compound	Ar 3-C	Ar 5-C	Ar 2-C	Ar 4-C	$ArCH_xN$	$ArCH_xNCH_2$	Other signals[a]
8a–c	163.4–164.2	134.9–135.2	121.9–122.1	116.3–116.8	–	–	181.1–181.4, C=O
9a–d	151.7–154.2	127.6–128.2	119.4–120.1	116.5–116.9	157.1–158.4 CH=N	61.9–63.3	24.1–24.2 CH_2Me + 11.8 Me or 63.3 NCH_2CH_2O
11a–d	152.8–153.4	121.5–122.3	120.3–121.3	117.1–117.5	43.6–44.1 CH_2N	50.3–50.8	22.8–23.0 CH_2Me + 11.5–11.8 Me or 60.7 NCH_2CH_2O
14a–d	153.3–154.4	122.6–123.9	116.6–118.5	116.0–117.0	38.6–44.0 CH_2N	44.2–49.7	20.4–21.7 CH_2Me + 11.0–11.4 Me, 20.7–21.9 CO*Me* or 61.3–62.1 NCH_2CH_2O
15a–c	154.2–154.7	124.0–124.3	116.3–116.5	116.6	41.7–45.0 CH_2N	48.9–49.1	143.0 Ph 1-C, 137.3–137.5 Ph 4-C, 129.6–129.7 Ph 2-C, 127.1–127.2 Ph 3-C, 21.4–22.9 PhMe, 21.3–21.4 CH_2Me + 11.1–11.2 Me
16a–c	170.5–171.0	152.9–154.3	122.8–124.3	115.8–117.0	38.4–45.6 CH_2N	44.1–47.6	68.3–70.1 NCH_2CH_2O 21.4–22.0 CO*Me*
17a–c	154.4–154.9	124.4–124.6	115.9–116.4	116.2–116.6	41.9–42.6 CH_2N	45.6–46.0	143.0–143.2 Ph 1-C, 137.5–137.6 Ph 4-C, 129.5–129.8 Ph 2-C, 127.1–127.2 Ph 3-C, 21.5 PhMe, 68.3–68.8 NCH_2CH_2O
18a–c	153.1–154.6	122.4–122.6	119.7–121.5	116.2–117.5	48.2–48.4 CH_2N	54.7–54.8	58.7–58.8 ArO*Me*, 20.3 CH_2Me + 11.8 Me
19a–e	153.1–154.6	122.5–124.7	117.1–121.8	117.1–117.4	47.8–48.8 CH_2N	50.9–55.0	20.4 CH_2Me + 11.8 Me or 58.4–58.5 NCH_2CH_2OH or 62.6 NCH_2CH_2OAc + 21.1 *Me*C=O
20a–e	153.2–153.7	122.6–122.9	120.3–121.1	116.9–117.1	48.1–48.4 CH_2N	50.9–51.1	27.7 NCH_2CH_2 + 24.8 $N(CH_2)_2CH_2$ or 68.2–68.5 NCH_2CH_2O

[a] Additional characteristic NMR signals for bridging group **Z** = $(CH_2)_2O(CH_2)_2$ 70.9–71.5 (2 × $ArOCH_2$), 69.8–70.4 (2 × $ArOCH_2CH_2O$); **Z** = $(CH_2)_2O(CH_2)_2O(CH_2)_2$ 70.6–71.5 (2 × $ArOCH_2$), 69.8–71.0 (2 × $ArOCH_2CH_2O$), 69.6–70.9 (2 × $ArOCH_2CH_2OCH_2$); **Z** = $(CH_2)_2S(CH_2)_2$ 70.9–72.1 (2 × $ArOCH_2$), 31.8–33.2 (2 × $ArOCH_2CH_2S$).

was heated in an oil bath at 100 °C. Twenty-five minutes after the start of infusion the mixture was cooled and worked up in the usual manner to yield a brown oil.

The crude material was preabsorbed onto alumina and subjected to column chromatography. The Mannich base (0.25 g, 12%) was eluted firstly with 1 : 1 and then with 1 : 2 ethyl acetate–light petroleum, bp 40–60 °C, mp 114–116 °C (*q.v.* Table 7; mp 117–120 °C).

Infrared spectroscopic data

All of the bridged thiophene compounds exhibited a strong thiophene C=C stretch at 1542.2–1567.7 cm^{-1}. Additional characteristic absorptions include those of the bisaldehydes 1654.3–1624.0 cm^{-1}, s (C=O); the bisimines 1631.9–1642.2 cm^{-1}, s (C=N); the bisamines 3310.0–3358.1 cm^{-1}, s–w (NH); the bisacetamides 1651.2–1628.7 cm^{-1}, s (C=O) and the bistoluenesulfonamides 1597.7–1594.7 cm^{-1}, s–w (C=C). Compounds **9d**, **10d** and **19e** exhibited an O–H stretching absorption at 3471.1–3358.1 m–s cm^{-1}. Compounds **14d** and **19f** exhibited a strong ester C=O absorption at 1738.1–1747.6 cm^{-1}.

NMR data

Listed in Tables 8 and 9 are the NMR data for the α,ω-bis-(3-thienyloxy)alkanes.

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