The preparation of novel thiophene-based macrocyclic Mannich bases

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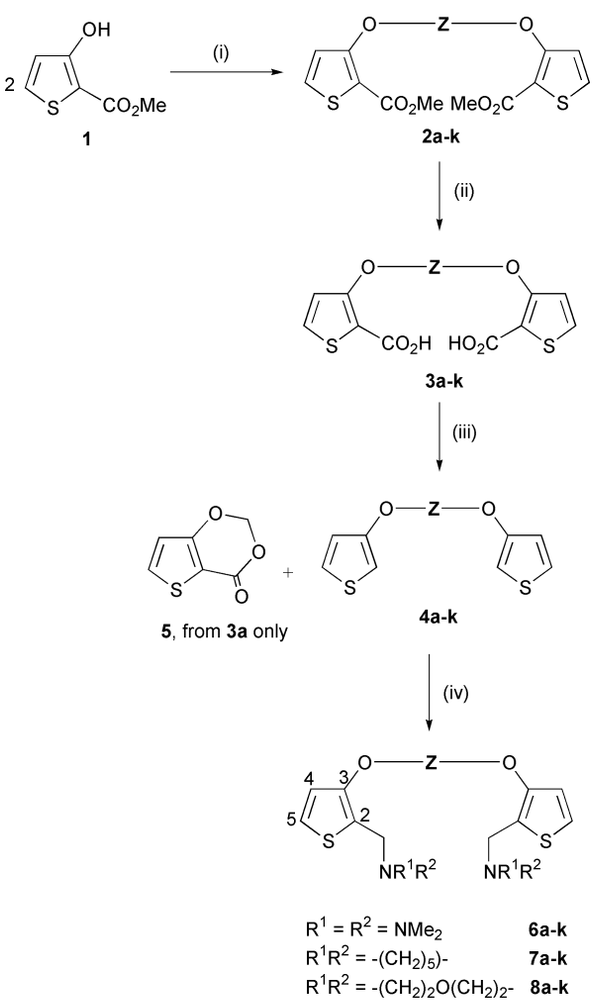
A range of macrocyclic thiophene-based Mannich bases containing 10–22-membered rings has been prepared. The starting materials for the synthesis were substances of the type ArO–**Z**–OAr (where Ar = 2-methoxycarbonyl-3-thienyl and **Z** = alkyl or heteroalkyl), which were made by the reaction of α,ω-dihalides or -bis(toluene-*p*-sulfonate)s with two moles of methyl 3-hydroxythiophene-2-carboxylate. Saponification and subsequent decarboxylation of these compounds afforded the corresponding α,ω-bis(3-thienyloxy)alkanes. Macrocyclic Mannich bases were prepared from these ethers by aminomethylation. High dilution conditions were not required in many cases and, in the case of the heteroalkyl-bridged ethers, this is believed to be due to an internal template effect enhancing the yield.

Thiophene-based macrocycles of the crown ether type have not been widely reported, probably due to the poor donor properties of the thiophene sulfur atom and the inaccessibility of dihydroxythiophenes of the type that would be necessary for the crown ether syntheses. However, thiophene does have some advantages over its oxygen and nitrogen counterparts. Thiophene derivatives are generally more stable and their reactivity is comparable to that of their benzene analogues; the possibility of desulfurisation adds further interest. A useful summary of this area of work was written by Russell and Press in 1996;[1] prior to this there had been no major reviews since Meth-Cohn[2] and Newkome *et al.*[3] published their reports in the 1970's. More recently there has been interest in the synthesis and complexation properties of tetraimines, as precursors to cyclic amines.[4–6] A number of papers have described the preparation of thiophene-based crown esters and amides;[7–9] generally, there is a significant decrease in complexation ability when ester groups replace ether oxygens in the crown. Thiacrown transition metal complexes are of interest due to their similarity to systems of biological importance. A range of examples has been prepared by the action of a dithiol on a bis(halomethyl)-thiophene derivative under conditions of high dilution.[10] Several groups have described the synthesis of thiophene-based macrocycles incorporating polyethereal linkages.[11–15] Use of the (modified) Mannich reaction to prepare macrocycles (but not in the macrocyclisation step) has been widely documented[16] but as far as we are aware, its use in thiophene-based systems is novel and there have been no reports of thiophene-based lariat ether systems. A preliminary account of the present work has been published.[17]

Results and discussion

Initial work was concentrated on the preparation of thiophene derivatives which were only substituted in the 2- and 3-positions. The preparation of the necessary intermediates and of the open chain bis Mannich bases derived from them is shown in Scheme 1.

A range of compounds with the formula ArO–**Z**–OAr (where Ar = 2-methoxycarbonyl-3-thienyl) was prepared by the coupling of α,ω-dihalides (**Z** = alkyl) or selected bis(toluene-*p*-



$R^1 = R^2 = NMe_2$ **6a-k**
$R^1R^2 = -(CH_2)_5-$ **7a-k**
$R^1R^2 = -(CH_2)_2O(CH_2)_2-$ **8a-k**

Scheme 1 Preparation and modification of α,ω-bis(2-methoxycarbonyl-3-thienyloxy)alkanes. For the nature of **Z**, see Table 1. *Reagents and conditions*: (i) Br–**Z**–Br or TsO–**Z**–OTs (Ts = *p*-tolylsulfonyl), K_2CO_3, DMF, 95–100 °C or Me_2CO–Δ; (ii) KOH, EtOH (aq.), Δ then H^+; (iii) Cu_2O, C_5H_5N (py), Δ; (iv) R^1R^2NH, HCHO, glacial AcOH, Δ or RT.

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Table 1 Classification of and abbreviations for **Z**

Class	**Z**	Abbreviation
a	CH_2	C_1
b	$(CH_2)_2$	C_2
c	$(CH_2)_3$	C_3
d	$(CH_2)_4$	C_4
e	$(CH_2)_6$	C_6
f	$(CH_2)_8$	C_8
g	$(CH_2)_{10}$	C_{10}
h	$(CH_2)_2O(CH_2)_2$	C_2OC_2
i	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	$C_2OC_2OC_2$
j	$(CH_2)_2S(CH_2)_2$	C_2SC_2
k	$(CH_2)_2NTs(CH_2)_2$	C_2NTsC_2

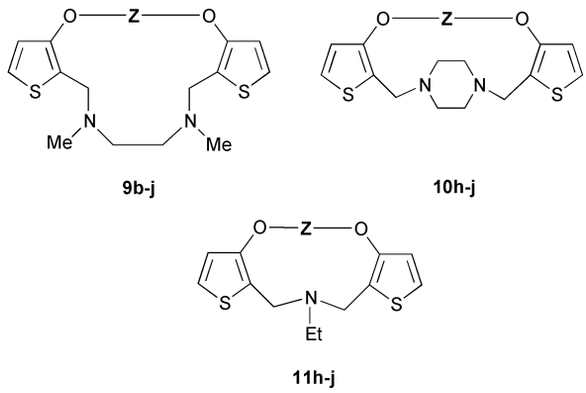

Fig. 1 Macrocyclic Mannich bases derived from *N*,*N*′-dimethylethylenediamine, piperazine, or ethylamine (see Table 1 for **Z**).

sulfonate)s (**Z** = heteroalkyl) with two equivalents of methyl 3-hydroxythiophene-2-carboxylate[18] **1**. The ester groups were saponified and the resulting acids were decarboxylated, in high yield, to give the corresponding α,ω-bis(3-thienyloxy)alkanes **4a**–**k** (Ar = 3-thienyl). Decarboxylation of the C_1-linked compound **3a** was atypical (a consequence of its acetal-like nature) and, in this case, the product was contaminated with the lactone **5** resulting from intramolecular displacement of a hydroxythiophene moiety. This by-product could be removed by an alkaline wash. The lactone was the major product when the bis acid **3a** was treated with copper(0). Approaches to macrocyclic compounds were hampered by the fact that the bis ethers **4a**–**k** (Ar = 3-thienyl) degrade under all but the mildest of reaction conditions.

The bis acids **3a**–**k** had some potential for macrocyclisation *via* the carboxy functions but generally this class of compounds exhibited limited solubility in solvents which would have been appropriate for cyclisation procedures. More active intermediates, *viz.* acid chlorides and anhydrides, could be isolated *via* treatment of the bis acid with thionyl chloride or acetic anhydride respectively, but these compounds proved to be overly sensitive to hydrolysis and/or decomposition.

The reagents commonly used to halogenate (*e.g.* iodine–nitric acid or *N*-bromosuccinimide) or nitrate (*e.g.* nitric acid–acetic acid–acetic anhydride or copper(II) nitrate–acetic anhydride) thiophene derivatives proved to be too acidic for use on the α,ω-bis(thienyloxy)alkanes **4a**–**k**. Various reagents were also employed to induce acylation, *viz.* acetic anhydride–phosphoric acid, acetyl chloride–titanium tetrachloride, acetic anhydride–boron trifluoride–diethyl ether or acetic acid–trifluoroacetic anhydride–phosphoric acid,[19] but yields were, at best, poor.

It was through the formation of the Mannich bases[20] (**6a**–**k**, **7a**–**k** and **8a**–**k**) that entry into macrocyclic systems was achieved. These bases were readily accessible from the bis ethers *via* reaction with mild, imine-like electrophilic species; they could also be obtained by decarboxylative substitution of the related bis acids, but in poorer overall yields. Amino alcohols, such as *N*-methyl-2-aminoethanol, could also be used to prepare the pre-formed iminium species utilised in the Mannich reaction, but in this case aminomethylation was slow and its products were difficult to purify. Compounds **4a**–**k** were particularly reactive towards mildly electrophilic species; in the absence of a base they would condense with formaldehyde alone under the Mannich reaction conditions, to give the appropriate 2,2′-methylene-bridged compounds.

Extension of these facile Mannich base preparations gave macrocyclic compounds in what may be considered to be very good yields for such processes. The bis ethers **4a**–**k**, on treatment with one equivalent of an α,ω-bis-secondary alkylamine of the type RNH—NHR, under conditions of normal dilution, gave the cyclic structures shown in Fig. 1. Mass spectroscopic and TLC data indicated that the products were monomeric; dimers and higher polymers were formed to some extent, but they could be removed by chromatography. Macrocyclisation of the C_2NTsC_2-linked compounds was not undertaken since trial attempts to effect detosylation of intermediates were unsuccessful.

The C_1-linked compound **4a** failed to give a cyclic product on reaction with *N*,*N*′-dimethylethylenediamine (presumably due to the steric constraints involved in the ring formation), but compounds in which the linking alkyl chain was longer did undergo macrocyclisation. It is significant that use of high dilution techniques resulted in only a modest increase in the return of [1 + 1] cyclic product, *e.g.* 46 to 62% yield in a typical case. Interestingly, the yield of cyclic product decreased as the linking chain length increased [69% for C_2 (**9b**); 45% for C_4 (**9d**); 23% for C_{10} **9g**], *i.e.* as the number of degrees of freedom in the intermediate increased. The yields of the macrocyclic bases were noticeably higher when the linking group between the aryl rings was heteroalkyl rather than alkyl [53% for C_2OC_2 (**9h**); 77% for $C_2OC_2OC_2$ (**9i**); 42% for C_2SC_2 (**9j**)]. This is thought to be due to a template effect, *i.e.* the electrophile is coordinated to a heteroatom and thus delivered to the reactive site. We suggest that there is a dipole–dipole interaction between the negative end of the carbon–heteroatom bond in the bridge and the positive end of the dipole in the $CH_2{=}N^+$ of the attacking cation. This effect was increasingly marked in the sterically congested macrocycles derived from piperazine: alkyl-bridged compounds could not be isolated as extensive polymerisation was evident. It is interesting to note that the yield of the C_2-bridged macrocycle **9b** is high in relation to that of the remaining compounds in this class (69%; as opposed to the next highest recovery for C_3 which is 46%). Chain length is such that it is likely that the oxygen atom at position 3′ could act as an internal template in this case.

Our data indicated that the C_2OC_2- and C_2SC_2-linked macrocyclic Mannich bases derived from piperazine and ethylamine consisted in each case of a mixture of closely related substances. When **Z** = C_2OC_2 the major (slower eluting) component could be isolated chromatographically; in the case of **10h** this was analysed separately, the remaining three compounds were analysed as mixtures. In all cases the correct microanalytical data were obtained and the ^{13}C NMR data showed a doubling of the peaks, neither fewer nor more, so the compounds must be very closely related (see Table 2). A likely explanation would be that they must be either two forms of the same compound with different spatial arrangements or a mixture of the monomer and dimer. The following observations suggest that the former explanation is likely. 1. The major component exhibited an R_f value comparable to that of an acyclic analogue, which suggested that it is monomeric. However, the minor component eluted further on TLC, which would not be expected of a higher oligomer. 2. Mass spectroscopic analysis

Table 2 ^{13}C chemical data for **10h** and **10j**, **11h** and **11j**

Carbon atom	Piperazine[a]		*N*-Ethylamine[a]	
	C_2OC_2 **10h**	C_2SC_2 **10j**	C_2OC_2 **11h**	C_2SC_2 **11j**
Ar 3-C	154.77 (154.16)	154.09 (153.71)	152.74 (153.55)	153.17 (153.22)
Ar 5-C	123.34 (122.66)	123.34 (122.78)	122.21 (122.53)	122.28 (122.84)
Ar 2-C	115.61 (118.18)	118.43 (118.33)	121.67 (121.36)	117.81 (117.07)
Ar 4-C	114.95 (117.36)	116.28 (117.09)	117.77 (117.36)	117.81 (116.96)
$ArOCH_2$	69.95 (71.43)	70.76 (71.79)	70.96 (70.22)	72.52 (71.75)
$ArOCH_2CH_2$	69.86 (70.22)	32.38 (32.08)	69.24 (70.22)	31.28 (32.09)
$ArCH_2N$	48.27 (52.13)	52.40 (52.24)	48.18 (47.91)	47.62 (47.94)
$ArCH_2NCH_2$	47.49 (52.29)	47.89 (48.70)	46.59 (46.77)	47.69 (46.76)
CH_2CH_3	—	—	13.37 (12.15)	12.74 (12.00)

[a] Figures in parentheses indicate the shifts of the minor component.

of the mixtures gave the correct molecular weight for a [1 + 1] macrocycle.

Molecular modelling has shown that the molecule is not planar and the smaller ring size of these macrocycles, in contrast to the $C_2OC_2OC_2$-linked compounds may restrict rotation of, for example, the *N*-ethyl group; hence a form of atropisomerism could exist. This phenomenon was increasingly marked in the corresponding C_2SC_2-linked compounds **10j** and **11j**, which suggested that the presence of a larger heteroatom in the bridge is significant. Dynamic ^{13}C NMR studies on the C_2SC_2-linked compounds indicated that the barrier to interconversion of these compounds could not be overcome below 150 °C and that individually they are very stable. It is suggested that the reaction products are mixtures of stereoisomers but this cannot be proved from the data available at present.

In order to extend the scope of this work we decided to undertake the preparation of lariat ethers *via* substitution at the 4- or 5-positions of the thiophene ring. Two general approaches were examined, namely electrophilic substitution of the thiophene ring itself, and ring closure of intermediates carrying the desired substituents. The first approach failed because conditions vigorous enough to bring about electrophilic substitution were generally harsh enough to bring about decomposition (*e.g.* bromination, lithiation). It was possible to introduce the nitro group but reductive methods leading to synthetically useful intermediates (*e.g.* amines or acetamides) failed for the most part. Moderate success was achieved *via* the ring closure approach,[21] but sterically bulky groups (*e.g.* 5-*p*-methoxybenzyl) interfered with the Mannich reaction and a 2,2′-methylene-bridged compound was isolated. The 5-methyl group could be incorporated using this methodology and would undergo benzylic bromination, but the alkoxymethyl side chain was not accessible *via* nucleophilic substitution. The 5-methoxy group was introduced[22] but it was found to destabilise the system and the Mannich reaction failed.

In summary, [1 + 1] macrocyclic Mannich bases are readily accessible from α,ω-bis(3-thienyloxy)alkanes, but efforts to prepare lariat ethers *via* the corresponding 4- or 5-substituted derivatives were not successful.

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 δ 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. Pyridine was distilled over potassium hydroxide and stored over sodium hydroxide pellets. The bis(toluene-*p*-sulfonate)s were obtained by methods adapted from the literature.

Preparation of the α,ω-bis(2-methoxycarbonyl-3-thienyloxy)-alkanes 2a–k

A stirred solution of the methyl 3-hydroxythiophene-2-carboxylate **1**, anhydrous potassium carbonate (0.55 eq.) and the coupling agent (the corresponding α,ω-dibromoalkane for **2a**–**g** or the corresponding α,ω-bis(toluene-*p*-sulfonate) for **2h**–**k**; 0.55 eq.) in anhydrous *N*,*N*-dimethylformamide (DMF) (for **2a**–**i** and **2k**; 5 ml g^{-1} of thiophene ester) was heated on an oil bath maintained at 95–100 °C or boiled under reflux in acetone (for **2j**; 5 ml g^{-1} of thiophene ester) for **5h**, and then poured into ice. The *alkyl-bridged* **2a**–**g** and the *C_2OC_2- and C_2SC_2-linked bis esters* (**2h** and **2j**, respectively) precipitated out and were filtered off. The *$C_2OC_2OC_2$- and C_2NTsC_2-linked esters* (**2i** and **2k**, respectively) were isolated by extraction with dichloromethane (DCM). The crude products were either digested in hot solvent (ethyl acetate, ethanol, methanol or acetone) or recrystallised. The results of the individual preparations are presented in Table 3.

Preparation of the α,ω-bis(2-carboxy-3-thienyloxy)alkanes 3a–k

A stirred solution of the α,ω-bis(2-methoxycarbonyl-3-thienyloxy)alkane **2a**–**k** and potassium hydroxide (4.0 eq.) in 50% (when **Z** = alkyl) or 80% (when **Z** = heteroalkyl) aqueous ethanol (16 or 20 ml g^{-1} respectively) was boiled under reflux for 1–2 h. The solution was filtered through glass wool into a stirred mixture of ice and a slight excess of hydrochloric acid. Compounds **3a**–**h**,**j**,**k** precipitated out and were filtered off, washed with water and dried under vacuum at 60 °C. *1,8-Bis(2-carboxy-3-thienyloxy)-3,6-dioxaoctane* **3i** was deposited as a gum, which solidified on trituration. The solid was filtered off, washed with water and dissolved in acetone. The solution was dried ($MgSO_4$) and evaporated at room temperature to give a solid which was triturated in ether. Compound **3i** was filtered off, washed with ether and dried under vacuum at ambient temperature. A summary of the results is presented in Table 4.

Preparation of the α,ω-bis(3-thienyloxy)alkanes 4a–k

A mixture of the α,ω-bis(2-carboxy-3-thienyloxy)alkane **3a**–**k** and copper(I) oxide (1.2 wt eq.) in pyridine (10 ml g^{-1} of bis acid) was boiled under reflux for 1 h. The solvent was removed under reduced pressure and the residue was extracted repeatedly with DCM. The combined organic extracts were washed with dilute hydrochloric acid, then with dilute sodium hydroxide or saturated sodium hydrogen carbonate solution, dried ($MgSO_4$ or K_2CO_3) and evaporated to give the crude *bis ether*. Compounds **4b**–**k** were recrystallised. An ethereal solution of the liquid containing *bis(3-thienyloxy)methane* **4a** was treated with several portions of concentrated sodium

Table 3 Analytical data for the bis esters

Compound	Yield (%)	Mp/°C (solvent)	M^+ (*M*)	Found (required) %C	%H
2a $C_{13}H_{12}O_6S_2$	71	174–176 (DMF)	n/a (328.4)	47.6 (47.6)	3.7 (3.7)
2b $C_{14}H_{14}O_6S_2$	89	189–190 (MeCN)	343 (342.4)	49.1 (49.1)	4.3 (4.1)
2c $C_{15}H_{16}O_6S_2$	80	138–140 (Me_2CO)	357 (356.4)	50.9 (50.6)	4.6 (4.5)
2d $C_{16}H_{18}O_6S_2$	83	190–192 (MeCN)	371 (370.5)	51.7 (51.7)	4.9 (4.9)
2e $C_{18}H_{22}O_6S_2$	90	166–167 (MeCN)	n/a (398.5)	54.2 (54.3)	5.6 (5.6)
2f $C_{20}H_{26}O_6S_2$	93	150–152 (Me_2CO)	427 (426.6)	56.5 (56.3)	6.1 (6.1)
2g $C_{22}H_{30}O_6S_2$	90	141–143 (Me_2CO)	455 (454.6)	58.1 (58.1)	6.7 (6.7)
2h $C_{16}H_{22}O_7S_2$	86	76 (aq MeOH)	387 (386.5)	49.9 (49.7)	4.7 (4.7)
2i $C_{18}H_{22}O_8S_2$	98	67–69 (1 : 1 EA–PE)[a]	431 (430.5)	49.6 (50.2)	5.1 (5.1)
2j $C_{16}H_{18}O_6S_3$	70	118 (EtOH)	n/a (402.5)	47.7 (47.7)	47.7 (47.7)
2k $C_{23}H_{25}NO_8S$	96	99–100 (1 : 1 EA–PE)[a]	No M^+ (539.7)	n/a[b]	n/a[b]

[a] 1 : 1 ethyl acetate–petroleum ether. [b] Unsatisfactory microanalytical data were obtained for the C_2NTsC_2-linked compound **2k** on three occasions, although the spectroscopic properties were as expected and the subsequent bis acid **3k** could be analysed correctly (see Table 4).

Table 4 Analytical data for the bis acids

Compound	Yield (%)	Mp/°C	$M^+ - 43$(*M*)	Found (required) %C	%H
3a $C_{11}H_8O_6S_2$	99	211–212	n/a (300.3)	44.0 (44.0)	2.7 (2.7)
3b $C_{12}H_{10}O_6S_2$	93	219–220	271 (314.3)	45.8 (45.9)	3.3 (3.2)
3c $C_{13}H_{12}O_6S_2$	100	207–208	285 (328.4)	47.6 (47.6)	3.7 (3.7)
3d $C_{14}H_{14}O_6S_2$	100	228–229	No M^+ (342.4)	48.9 (49.1)	4.3 (4.1)
3e $C_{16}H_{18}O_6S_2$	85	184–186	n/a (370.4)	52.1 (51.9)	5.1 (4.9)
3f $C_{18}H_{22}O_6S_2$	100	170–171	355 (398.5)	53.9 (54.3)	5.8 (5.6)
3g $C_{20}H_{26}O_6S_2$	98	172–174	383 (426.6)	55.9 (56.3)	6.5 (6.1)
3h $C_{14}H_{14}O_7S_2$	100	189	315 (358.4)	46.6 (46.9)	3.9 (3.9)
3i $C_{16}H_{28}O_8S_2$	88	91–99	359 (402.5)	n/a[a]	n/a[a]
3j $C_{14}H_{14}O_6S_3$	91	178–179	331 (374.5)	45.2 (44.9)	4.0 (3.8)
3k[b] $C_{21}H_{21}NO_8S_3$	99	168	No M^+ (511.6)	49.1 (49.3)	4.3 (4.1)

[a] Unsatisfactory microanalytical data were obtained for the $C_2OC_2OC_2$-linked compound **3i** on two occasions, although the spectroscopic properties were as expected and the subsequent decarboxylated material **4i** could be analysed correctly (see Table 5). [b] %N Found 2.7%, required 2.7%.

hydroxide solution. The organic solution was dried ($MgSO_4$) and evaporated and the liquid was distilled under vacuum. See Table 5 for results of individual preparations.

Preparation of the lactone 5

α,ω-Bis(2-carboxy-3-thienyloxy)methane **3a** (5.0 g, 0.017 mol, 1.0 eq.) and copper bronze (5.0 g, 1.0 wt eq.) were thoroughly mixed in a Claisen distillation flask. The solid was sealed with a glass wool plug and the mixture was distilled (free flame) at *ca.* 15 mmHg. An orange liquid (bp *ca.* 200 °C) was collected; distillation was halted when the distillate began to darken. The product solidified on cooling; it was subjected to chromatography on silica (gravity column) using chloroform as the eluent. After a fore-run the *title compound* (1.24 g) was eluted from the column, this material was recrystallised from 50% aq. MeOH (0.81 g, 31%); mp 74–75 °C (Found: C, 45.7; H, 2.4. $C_6H_4O_3S$ requires C, 46.2; H, 2.6%); δ_H ($CDCl_3$) 7.72 (1H, d, $J = 5.5$ Hz, Ar(5)H), 6.83 (1H, d, J 6, Ar 4-H) and 5.69 (2H, s, ArOCH_2) ppm; δ_C ($CDCl_3$) 163.11 (C=O), 157.58 (Ar 3-H), 135.97 (Ar 5-H), 116.93 (Ar 4-H), 108.87 (Ar 2-H) and 92.33 (ArOCH_2); ν_{max} (film) 1737.0s (C=O) and 1545.2m (C=C) cm^{-1}; *m*/*z* (CI, CH_4) 157 (100%, M + 1).

Table 5 Analytical data for the bis ethers

Compound (Formula)	Yield (%)	Mp/°C	M^+ (*M*)	Found (required) %C	%H
4a $C_{11}H_8O_6S_2$	52	[a]	213 (212.3)	51.6 (51.3)	4.0 (3.8)
4b $C_{12}H_{10}O_6S_2$	73	156–159	227 (226.3)	52.9 (53.1)	4.6 (4.5)
4c $C_{13}H_{12}O_6S_2$	85	65–66	241 (240.4)	54.7 (55.0)	5.1 (5.0)
4d $C_{14}H_{14}O_6S_2$	88	104–106	255 (254.4)	56.9 (56.7)	5.5 (5.6)
4e $C_{16}H_{18}O_6S_2$	90	117–119 (EtOH)	n/a (282.4)	59.7 (59.5)	6.7 (6.4)
4f $C_{18}H_{22}O_6S_2$	98	73–74 (EtOH)	311 (310.5)	62.2 (61.9)	7.0 (7.1)
4g $C_{20}H_{26}O_6S_2$	73	98	339 (338.5)	64.1 (63.9)	7.7 (7.7)
4h $C_{14}H_{14}O_7S_2$	98	58–60 (MeOH)	271 (270.4)	53.5 (53.3)	5.2 (5.2)
4i $C_{16}H_{28}O_8S_2$	96	54–57 (EtOH)	315 (314.4)	53.7 (53.5)	5.7 (5.8)
4j $C_{14}H_{14}O_6S_3$	81	94–97 (EtOH)	287 (286.4)	50.1 (50.3)	4.9 (4.9)
4k [b] $C_{21}H_{21}NO_8S_3$	94	81–83 (MeOH)	[M^+ − Ts 270] (423.6)	53.9 (53.9)	5.0 (5.0)

[a] Bp = 134–138 °C/0.4 mmHg. [b] %N Found 3.3%, required 3.1%.

Table 6 Analytical data for the bis(dimethylaminomethyl) Mannich bases

Compound	Yield (%, crude)	Mp/°C	M^+ (*M*)	Found (required) %C	%H	%N
6a $C_{15}H_{22}N_2O_2S_2$	88	Oil	327 (326.5)	54.9 (55.2)	6.5 (6.8)	8.4 (8.6)
6b $C_{16}H_{24}N_2O_2S_2$	96	45–48 [a]	341 (340.5)	56.2 (56.4)	6.9 (7.1)	7.7 (8.2)
6c $C_{17}H_{26}N_2O_2S_2$	100	Oil	355 (354.5)	57.9 (57.6)	7.5 (7.4)	7.7 (7.9)
6d $C_{18}H_{28}N_2O_2S_2$	90	63–64 [b]	369 (368.6)	58.4 (58.7)	7.8 (7.7)	7.8 (7.6)
6e $C_{20}H_{32}N_2O_2S_2$	85	42–44	n/a (396.6)	60.2 (60.6)	8.0 (8.1)	7.4 (7.1)
6f $C_{22}H_{36}N_2O_2S_2$	94	Oil	n/a (424.7)	62.4 (62.2)	8.9 (8.6)	6.6 (6.6)
6g $C_{24}H_{40}N_2O_2S_2$	93	Oil	453 (452.7)	63.2 (63.7)	8.8 (8.9)	6.0 (6.2)
6h $C_{18}H_{28}N_2O_3S_2$	98	Oil	385 (384.6)	56.2 (56.2)	7.3 (7.3)	7.0 (7.3)
6i $C_{20}H_{32}N_2O_4S_2$	100	Oil	429 (428.6)	56.1 (56.1)	7.8 (7.5)	6.7 (6.5)
6j $C_{18}H_{28}N_2O_2S_3$	87	Oil	n/a (400.6)	53.7 (54.0)	7.3 (7.0)	6.8 (7.0)
6k $C_{25}H_{35}N_3O_4S_3$	97	Oil	538 (537.8)	55.7 (55.8)	6.7 (6.6)	7.9 (7.8)

[a] Trituration. [b] MeOH.

Preparation of the open chain Mannich bases 6a–k, 7a–k and 8a–k

The α,ω-bis(3-thienyloxy)alkane **4a**–**k** was added to a stirred solution of 2.2 equivalents of the secondary amine (40% aqueous solution of dimethylamine for **8a**–**k**, piperidine for **9a**–**k** or morpholine for **10a**–**k**) and formaldehyde (37% aqueous solution; 2.2 eq.) in glacial acetic acid (25 ml g^{-1} of bis ether). When **Z** was C_1 alkyl, the mixture was boiled under reflux for 1 h, and then cooled. When **Z** was C_2–C_{10} alkyl, the mixture was heated to reflux until the bis ether had just dissolved and was then cooled. When **Z** was heteroalkyl, the mixture was stirred at ambient temperature for 48 h. The solution was then basified with 4 M sodium hydroxide solution and extracted with DCM (×2). The combined organic extracts were dried (K_2CO_3 or $MgSO_4$) and evaporated to give the *Mannich base*. The products were essentially analytically pure as obtained. The solids were purified either by recrystallisation or by trituration with light petroleum, bp 40–60 °C. The oils could be purified by extraction into dilute acid, where necessary. See Tables 6, 7 and 8 for results of individual preparations.

Preparation of the macrocyclic Mannich bases 9b–j, 10h–j and 11h–j

The α,ω-bis(3-thienyloxy)alkane **4b**–**j** was added to a solution

Table 7 Analytical data for the bis(piperidinomethyl) Mannich bases

Compound	Yield (%, crude)	Mp/°C	M^+ (*M*)	Found (required) %C	%H	%N
7a $C_{21}H_{30}N_2O_2S_2$	99	Oil	407 (406.6)	61.7 (62.0)	7.2 (7.4)	6.6 (6.9)
7b $C_{22}H_{32}N_2O_2S_2$	100	48–51[a]	421 (420.6)	62.8 (62.8)	8.0 (7.7)	6.5 (6.7)
7c $C_{23}H_{34}N_2O_2S_2$	98	Oil	435 (434.7)	63.9 (63.6)	7.7 (7.9)	6.6 (6.4)
7d $C_{24}H_{36}N_2O_2S_2$	100	78–79[b]	n/a (448.7)	64.3 (64.3)	8.4 (8.1)	6.2 (6.2)
7e $C_{26}H_{40}N_2O_2S_2$	92	67–69	n/a (476.8)	65.5 (65.5)	8.5 (8.5)	5.9 (5.9)
7f $C_{28}H_{44}N_2O_2S_2$	92	Oil	505 (504.8)	66.2 (66.6)	8.9 (8.8)	5.5 (5.6)
7g $C_{30}H_{48}N_2O_2S_2$	91	Oil	533 (532.9)	67.8 (67.6)	9.4 (9.4)	5.4 (5.3)
7h $C_{24}H_{36}N_2O_3S_2$	97	Oil	465 (464.7)	62.3 (62.0)	7.7 (7.8)	6.2 (6.0)
7i $C_{26}H_{40}N_2O_4S_2$	100	Oil	509 (508.8)	61.1 (61.4)	8.0 (7.9)	5.5 (5.5)
7j $C_{24}H_{36}N_2O_2S_3$	96	Oil	n/a (480.8)	59.7 (60.0)	7.9 (7.6)	5.9 (5.8)
7k $C_{31}H_{43}N_3O_4S_3$	97	Oil	[M^+ − Ts 464] (617.9)	60.2 (60.3)	7.2 (7.0)	6.7 (6.8)

[a] Trituration. [b] MeOH.

Table 8 Analytical data for the bis(morpholinomethyl) Mannich bases

Compound (Formula)	Yield (%, crude)	Mp/°C	M^+ (*M*)	Found (required) %C	%H	%N
8a $C_{15}H_{22}N_2O_2S_2$	99	70–72	411 (410.6)	55.8 (55.6)	6.7 (6.4)	6.5 (6.8)
8b $C_{16}H_{24}N_2O_2S_2$	100	113–115[a]	425 (424.6)	56.3 (56.6)	6.7 (6.7)	6.5 (6.6)
8c $C_{17}H_{26}N_2O_2S_2$	98	85–87[a]	439 (438.6)	57.6 (57.5)	7.1 (6.9)	6.4 (6.4)
8d $C_{18}H_{28}N_2O_2S_2$	95	146–147[a]	453 (452.6)	58.2 (58.4)	6.9 (7.1)	6.2 (6.2)
8e $C_{20}H_{32}N_2O_2S_2$	93	58–61	n/a (480.7)	59.8 (60.0)	7.6 (7.6)	5.5 (5.8)
8f $C_{22}H_{36}N_2O_2S_2$	100	49–50[b]	509 (508.8)	61.4 (61.4)	7.9 (7.9)	5.3 (5.5)
8g $C_{24}H_{40}N_2O_2S_2$	100	56–60[b]	537 (536.8)	43.6 (43.9)	6.1 (6.1)	3.2 (3.4)
8h $C_{15}H_{22}N_2O_2S_2$	99	Oil	469 (468.6)	56.0 (56.4)	6.5 (6.9)	6.1 (6.0)
8i $C_{15}H_{22}N_2O_2S_2$	98	Oil	513 (512.7)	56.0 (56.2)	7.3 (7.1)	5.4 (5.5)
8j $C_{15}H_{22}N_2O_2S_2$	97	71–73[a]	n/a (484.7)	54.4 (54.5)	6.8 (6.7)	5.9 (5.8)
8k $C_{15}H_{22}N_2O_2S_2$	100	Oil	No M^+ (621.8)	56.3 (56.0)	6.4 (6.3)	6.7 (6.8)

[a] MeOH. [b] Trituration.

of 1.1 equivalents of the amine (*N*,*N*′-dimethylethylenediamine for **9b–j**, piperazine for **10h–j**, ethylamine for **11h–j**) and formaldehyde (37% aqueous solution, 2.2 eq.) in glacial acetic acid (25 ml g^{-1} of bis ether). The mixture was stirred at room temperature for 24 h, then basified with 4 M sodium hydroxide solution and extracted into ether (for **9b–j**) or DCM (for **10h–j**, and **11h–j**) (×2). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude material was preabsorbed onto alumina and subjected to column chromatography (gravity column). The *macrocyclic Mannich bases* **9b–j**, **10h–j** and **11h–j** were eluted with 1 : 1 chloroform–toluene. Details of the individual preparations are described in Tables 9, 10 and 11.

Infrared data

All of the bridged thiophene compounds exhibited a strong thiophene C=C stretch at 1566–1535 cm^{-1}. Additional characteristic absorptions include those of the bis esters 1718–1678 cm^{-1}, s (C=O); the bis acids 2928–2604 cm^{-1}, s (CO*OH*) and 1698–1629 cm^{-1}, s (C=O); and the tosyl compounds 1600–1595 cm^{-1}, m–w (C=C).

Table 9 Analytical data for the macrocyclic Mannich bases derived from *N*,*N*′-dimethylethylenediamine

Compound	Yield (%)	Mp/°C[a]	M^+ (*M*)	Found (required) %C	%H	%N
9b $C_{16}H_{22}N_2O_2S_2$	69	Oil	339 (338.5)	56.6 (56.8)	6.4 (6.6)	8.4 (8.3)
9c $C_{17}H_{24}N_2O_2S_2$	46	Oil	353 (352.5)	57.6 (57.9)	6.8 (6.9)	7.6 (8.0)
9d $C_{18}H_{26}N_2O_2S_2$	45	Oil	367 (366.6)	58.8 (59.0)	7.1 (7.2)	7.6 (7.6)
9e $C_{20}H_{30}N_2O_2S_2$	37	Oil	395 (394.6)	61.2 (60.9)	7.6 (7.7)	7.1 (7.1)
9f $C_{22}H_{34}N_2O_2S_2$	30	Oil	423 (422.6)	62.5 (62.5)	7.9 (8.1)	6.9 (6.6)
9g $C_{24}H_{38}N_2O_2S_2$	23	Oil	451 (450.7)	63.8 (64.0)	8.2 (8.5)	6.6 (6.2)
9h $C_{18}H_{26}N_2O_3S_2$	47	Oil	383 (382.6)	56.2 (56.6)	6.9 (6.9)	7.0 (7.3)
9i $C_{20}H_{30}N_2O_4S_2$	54	90–92	n/a (426.6)	56.4 (56.3)	7.3 (7.1)	6.5 (6.6)
9j $C_{18}H_{26}N_2O_2S_3$	51	87–89	399 (398.6)	53.9 (54.2)	6.5 (6.6)	6.7 (7.0)

[a] Chromatography.

Table 10 Analytical data for the macrocyclic Mannich bases derived from piperazine

Compound	Yield (%)	Mp/°C[a]	M^+ (*M*)	Found (required) %C	%H	%N
10h $C_{15}H_{22}N_2O_2S_2$	53	131–168	381 (380.5)	56.8 (56.8)	6.3 (6.4)	7.3 (7.4)
10i $C_{15}H_{22}N_2O_2S_2$	77	101	425 (424.6)	56.7 (56.6)	6.6 (6.7)	6.6 (6.6)
10j $C_{15}H_{22}N_2O_2S_2$	42	116–122	397 (396.6)	54.9 (54.5)	6.2 (6.1)	6.9 (7.1)

[a] Chromatography.

Table 11 Analytical data for the macrocyclic Mannich bases derived from ethylamine

Compound	Yield (%)	Mp/°C[a]	M^+ (*M*)	Found (required) %C	%H	%N
11h $C_{15}H_{22}N_2O_2S_2$	84	87–94	340 (339.5)	56.3 (56.6)	6.2 (6.2)	4.2 (4.1)
11i $C_{15}H_{22}N_2O_2S_2$	80	102–104	384 (383.5)	56.3 (56.4)	6.5 (6.6)	3.6 (3.7)
11j $C_{15}H_{22}N_2O_2S_2$	64	Oil	356 (355.5)	53.7 (54.1)	5.9 (6.0)	3.9 (3.9)

[a] Chromatography.

NMR data

Listed in Tables 12 and 13 are the NMR data for the α,ω-bis-(3-thienyloxy)alkanes.

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Table 12 ^{1}H NMR data ranges for the α,ω-bis(3-thienyloxy)alkanes

Compound	Ar 5-H	Ar 4-H	$ArCH_2N$	$ArCH_2NCH_x$	Other signals[a]
2a–k	7.35–7.81 (d, *J* 5–6)	6.84–7.18 (d, *J* 6)	—	—	3.70–3.88 (s, CO_2Me)
3a–k	7.52–7.79 (d, *J* 5–6)	6.90–7.18 (d, *J* 5–6)	—	—	br, variable, CO_2H
4a–k	7.07–7.26 (m)	6.64–6.80 (m)	—	—	6.15–6.62 (m, Ar 2-H)
6a–k	7.02–7.16 (d, *J* 5–6)	6.76–6.97 (d, *J* 5–6)	3.48–3.67 (s)	2.20–2.32 (s, NMe)	—
7a–k	6.99–7.10 (d, *J* 5–6)	6.70–6.92 (d, *J* 5–6)	3.53–3.65 (s)	2.37–2.44 (m or t, *J* 5, NCH_2)	1.39–1.57 (m, $NCH_2(CH_2)_3$)
8a–k	7.02–7.22 (d, *J* 4–6)	6.66–6.99 (d, *J* 5–6)	3.54–3.69 (s)	2.38–2.50 (m or t, *J* 5, NCH_2)	3.62–3.71 (m or t, *J* 5, NCH_2CH_2O)
9b–j	7.02–7.17 (d, *J* 5–6)	6.76–6.87 (d, *J* 5–6)	3.56–3.80 (s)	2.41–2.69 (s, NCH_2) 2.28–2.44 (s, NMe)	—
10h–j	7.05–7.14 (d, *J* 5)	6.73–6.77 (d, *J* 5–8)	3.49–3.85 (s)	2.44–2.85 (s, NCH_2)	—
11h–j	7.05–7.08 (d, *J* 4–6)	6.73–6.78 (d, *J* 5–7)	3.76–3.96 (s)	2.57–2.67 (t or q, *J* 5–7, NCH_2Me)	1.08–1.14 (t, *J* 7–8, Me)

[a] Additional characteristic NMR signals for bridging group **Z** (*cf.* Table 1): C_1 (**a**) 5.50–5.81 (2H, s, $ArOCH_2$); C_2 (**b**) 4.20–4.48 (4H, s, 2 × $ArOCH_2$); C_3 (**c**) 4.08–4.36 (4H, t, *J* 6–7, 2 × $ArOCH_2$), 2.10–2.20 (2H, m, $ArOCH_2CH_2$); C_4 (**d**) 3.97–4.16 (4H, m or t, *J* 4–7, $ArOCH_2$), 1.87–1.94 (4H, m, 2 × $ArOCH_2CH_2$); C_6 (**e**) 3.95–4.15 (4H, m or t, *J* 6–7, 2 × $ArOCH_2$), 1.87–1.94 (8H, m and m or br s, 2 × $ArOCH_2(CH_2)_2$); C_8 (**f**) 3.94–4.12 (4H, t, *J* 6–7, 2 × $ArOCH_2$), 1.36–1.72 (12H, m and m or br s, 2 × $ArOCH_2(CH_2)_3$); C_{10} (**g**) 3.88–4.14 (4H, t, *J* 5–7, 2 × $ArOCH_2$), 1.29–1.73 (16H, m and m or br s, 2 × $ArOCH_2(CH_2)_4$); C_2OC_2 (**h**) 4.07–4.37 (4H, m or t, *J* 5, 2 × $ArOCH_2$), 3.67–3.99 (4H, m or t, *J* 5, 2 × $ArOCH_2CH_2O$); $C_2OC_2OC_2$ (**i**) 4.05–4.33 (4H, m or t, *J* 4–6, 2 × $ArOCH_2$), 3.60–3.84 (8H, m or m and s, 2 × $ArOCH_2CH_2OCH_2$); C_2SC_2 (**j**) 4.12–4.34 (4H, t, *J* 6–7, 2 × $ArOCH_2$), 2.85–3.10 (4H, t, *J* 6–7, 2 × $ArOCH_2CH_2S$); $C_2N(Ts)C_2$ (**k**) 7.70–7.74 (2H, d, *J* 7–9, Ph 2-H and Ph 6-H; *i.e. ortho* to SO_2), 7.19–7.29 (2H, d, *J* 6–9, Ph 3-H and Ph 5-H; *i.e. meta* to SO_2), 4.16–4.33 (4H, m or t, *J* 6, 2 × $ArOCH_2$), 3.59–3.76 (4H, m or t, *J* 6, 2 × $ArOCH_2CH_2N$), 2.23–2.42 (3H, s, Ph*Me*).

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

Compound	Ar 3-C	Ar 5-C	Ar 4-C	Ar 2-C	$ArCH_2N$	$ArCH_2N(CH_2)_x$	Others[a]
2a–k	156.0–161.4	130.3–131.5	116.9–119.5	108.0–112.7	—	—	161.0–162.2 (C=O) 51.1–51.6 (CO_2Me)
3a–k	157.3–160.6	128.9–130.8	116.1–119.8	109.2–113.8	—	—	161.0–162.9 (C=O)
4a–k	154.8–158.1	124.5–124.9	119.2–119.8	97.0–102.5	—	—	—
6a–k	151.4–154.6	122.3–123.3	115.9–118.4	117.3–121.6	53.2–53.6	44.1–45.0 (NMe)	—
7a–k	151.4–154.4	122.3–123.5	116.7–118.5	118.2–121.4	53.1–53.2	53.8–54.0 (NCH_2)	26.0, 24.3 ($NCH_2(CH_2)_3$)
8a–k	151.5–154.6	122.7–123.9	116.7–118.3	120.4–117.1	52.1–53.2	52.8–53.2 (NCH_2)	67.0–67.1 (NCH_2CH_2O)
9b–j	150.6–154.5	122.5–123.8	116.2–117.3	116.6–123.3	52.1–54.3	49.9–51.9 (NCH_2) 42.3–44.7 (NMe)	—
10h–j	154.1–154.8	122.4–123.3	115.0–117.4	115.6–118.4	48.3–52.2	47.5–52.3 (NCH_2)	—
11h–j	152.7–153.6	122.2–122.8	117.0–117.8	117.1–121.7	47.6–48.2	46.6–47.7 (NCH_2Me)	12.0–13.4 (Me)

[a] Additional characteristic NMR signals for bridging group **Z** (*cf.* Table 1): C_1 (**a**) 93.9–94.7 ($ArOCH_2$); C_2 (**b**) 68.6–70.8 (2 × $ArOCH_2$); C_3 (**c**) 66.7–68.4 (2 × $ArOCH_2$), 29.1–30.2 ($ArOCH_2CH_2$); C_4 (**d**) 69.7–71.4 (2 × $ArOCH_2$), 25.6–26.4 (2 × $ArOCH_2CH_2$); C_6 (**e**) 70.0–71.5 (2 × $ArOCH_2$), 25.1–29.6 (2 × $ArOCH_2(CH_2)_2$); C_8 (**f**) 70.3–72.0 (2 × $ArOCH_2$), 23.4–29.7 (2 × $ArOCH_2(CH_2)_3$); C_{10} (**g**) 70.3–71.8 (2 × $ArOCH_2$), 25.3–29.7 (2 × $ArOCH_2(CH_2)_4$) C_2OC_2 (**h**) 69.7–71.7 (2 × $ArOCH_2$), 67.8–70.3 (2 × $ArOCH_2CH_2O$); $C_2OC_2OC_2$ (**i**) 70.8–71.8 (2 × $ArOCH_2$), 69.67–71.16 (2 × $ArOCH_2CH_2OCH_2$); C_2SC_2 (**j**) 70.0–72.5 (2 × $ArOCH_2$), 29.4–32.4 (2 × $ArOCH_2CH_2S$); $C_2N(Ts)C_2$ (**k**) 143.4–143.7 (Ph 4-C; *i.e. para* to SO_2), 136.4–136.8 (Ph 1-C; *i.e.* adjacent to SO_2), 129.6–129.9 (Ph 3-C and Ph 5-C; *i.e. meta* to SO_2), 126.3–127.2 (Ph 2-C and Ph 6-C; *i.e. ortho* to SO_2), 69.2–71.0 (2 × $ArOCH_2$), 48.7–49.3 (2 × $ArOCH_2CH_2N$), 21.3–21.5 (Ph*Me*).

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