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Polycondensed Heterocycles. IX. Pyrrolo[2,1-*c*][1,4]benzothiazepines. Synthesis of 3-(Dimethylamino)methyl Derivatives.

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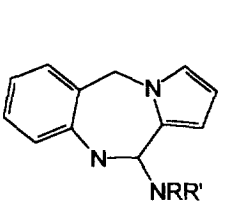
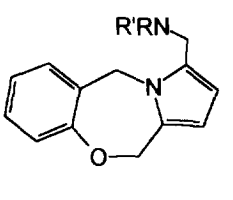
Abstract: The synthesis of 3-(dimethylamino)methyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine derivatives **2a-c**, which might show significant central nervous system (CNS) activity, is described. The basic side chain was introduced by a Mannich condensation with the preformed heterocyclic systems **1a-c**. Synthesis of novel 5-phenyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1c** by a nucleophilic aromatic fluoride displacement-cyclization and an attempted alternative route to **1c** *via* a Pummerer rearrangement-cyclization are also reported. A mechanism for an unexpected formation of a pyrrole-2-carbaldehyde is proposed, as well. Copyright © 1996 Elsevier Science Ltd

Our group has recently reported on the synthesis of pyrrole and sulfur containing heterocycles as precursors of compounds of potential pharmacological interest.[1,2] Their functionalization towards different possible activities is still under investigation and only the preliminary results obtained in the synthesis of potential CNS active agents are reported here. Since numerous heterocyclic aromatic tricyclics, including pyrrolobenzodiazepines **I**[3] and pyrrolobenzoxazepines **II**[4] and **III**[5], bearing a basic side chain have been found to possess psychotropic activity, we aimed at the synthesis of 3-(dimethylamino)methyl derivatives of previously published pyrrolo[2,1-*c*][1,4]benzothiazepine **1a** and 11-(4-fluorophenyl)-pyrrolo[2,1-*c*][1,4]benzothiazepine **1b** and the new 5-phenylpyrrolo[2,1-*c*][1,4]benzothiazepine **1c** (see below) in order to assess if any biological property could be ascribed to this series of compounds. While the functionalization was easily achieved by subjecting such condensed tricyclics to Mannich reaction with paraformaldehyde and dimethylamine hydrochloride (Scheme I) to give rather stable amines **2a-c**, the synthesis of precursor **1c** was found to be somewhat difficult.

The first attempted pathway started from 2-(methylthio)benzaldehyde **3** which was transformed into carbinol **4** by means of phenylmagnesium bromide. Highly hindered corresponding chloride **5** did not succeed in N-alkylating the pyrrole in the successive step under different reaction conditions (for instance: NaH/DMF, potassium/THF, *t*-BuOK/18-crown-6/THF).



I



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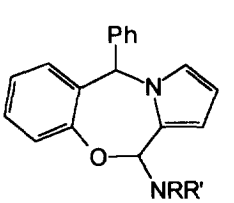
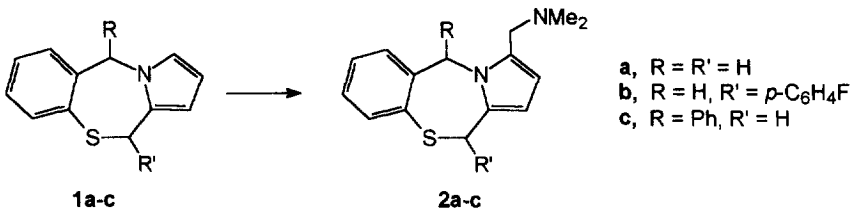
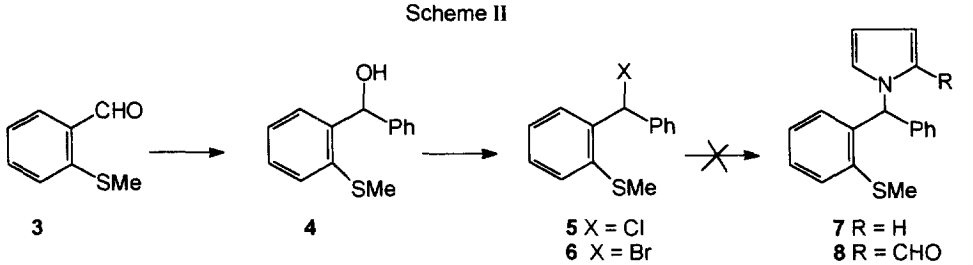


III

Scheme I

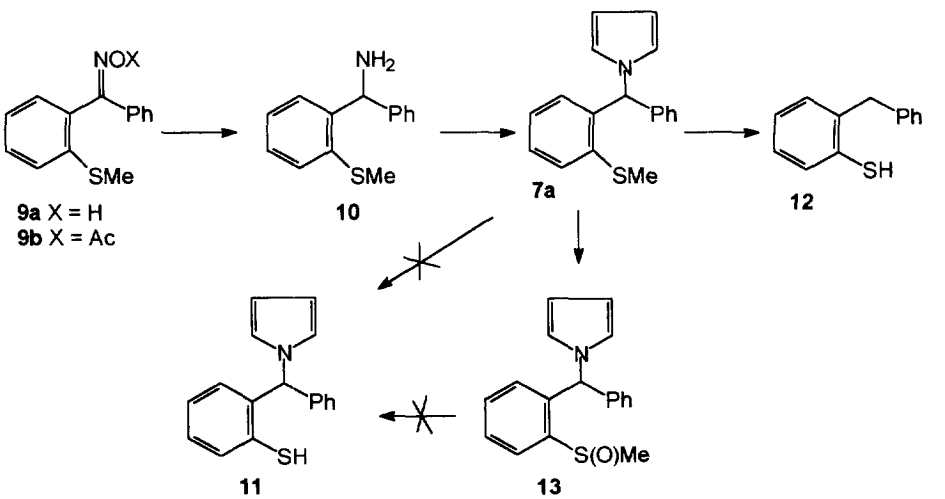


Scheme II



Even the use of more reactive bromide derivative **6** and pyrrole-2-carbaldehyde did not give any satisfactory result (Scheme II).

Scheme III



Therefore an alternative strategy using 2-(methylthio)benzophenone oxime **9a**[6] as a starting material was devised (Scheme III). In the attempt to obtain amine **10**, both $LiAlH_4$ reduction of **9a** and BH_3/THF reduction

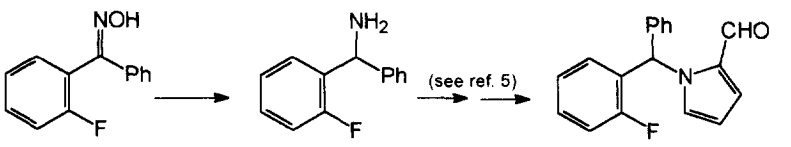
of its O-acetyl derivative **9b** resulted in a complex mixture of products. Contrariwise, Gaehde and Matsueda' procedure[7] using Zn in conc. NH_3/EtOH, applied to **9a**, proved to be successful in providing the required amine in excellent yield. The key 1-[(2-methylthiophenyl)phenylmethyl]pyrrole **7a** was synthesized from the condensation of α-(2-methylthiophenyl)benzenemethanamine **10** with 2,5-dimethoxytetrahydrofuran after the fashion of Clauson-Kaas. Hence, we tried to liberate the sulfur of **7a** from the methyl group in order to obtain key-intermediate **11** which should have been added with a suitable "activated" methylene group (i.e.: CH_2COR) before sulfur mono-oxygenation and subsequent final acid-promoted Pummerer rearrangement-cyclization (see ref. 2).

Somewhat surprisingly, while following a procedure already applied successfully to parent compounds,[8] both demethylation and unwanted C-N bond hydrogenolysis were observed when compound **7a** was treated with a 5-fold excess of Na° in dimethylacetamide at 80 °C, giving rise only to 2-mercaptodiphenylmethane **12**. On the other hand, the use of even an equimolar amount of the metal led to a mixture of unreacted material and **12** in a ratio of almost 1:1.

A second three-step procedure was attempted by transforming compound **7a** into corresponding diastereomeric sulfoxides **13** to be in turn subjected to transposition-elimination reaction using trifluoroacetic anhydride according to Young *et al.*.[9] In fact, when diastereomeric sulfoxides, separable by chromatography, were each reacted with $(CF_3CO)_2O$, complete decomposition was only observed in both cases. Owing to this, such a synthetic approach to **1c** had to be abandoned.

Accordingly, an alternative route following closely the one set up by Kapples and Effland[5] for related pyrrolo[2,1-*c*][1,4]benzoxazepines was undertaken. 2-Fluorobenzophenone oxime **14**, obtained from commercial 2-fluorobenzophenone, was the starting material for the preparation of key intermediate 1-[(2-fluorophenyl)phenylmethyl]pyrrole-2-carboxaldehyde (**16**) (Scheme IV).

Scheme IV



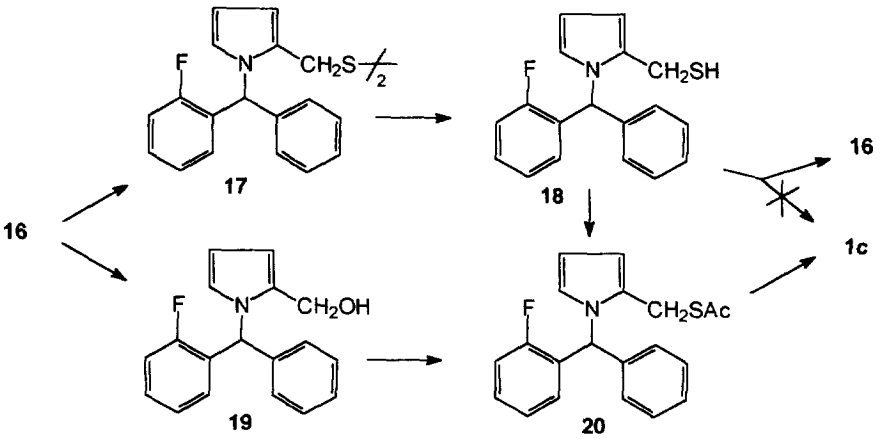
14 **15** **16**

While in the published procedure the intermediate amine **15** had been obtained by a catalytic method requiring high pressure of hydrogen, in our hands the previously-mentioned Zn/NH_3 procedure did work equally well in a less risky way. Compound **16** was then converted into disulfide **17** by means of $(NH_4)_2S$[10] and successive $LiAlH_4$ reduction afforded thiol **18** in good yield. Attempts to cyclize directly thiol **18** to **1c** utilizing a nucleophilic aromatic fluoride displacement with NaH or MeONa in DMF were unsuccessful. The only product which was possible to isolate from such a reaction after chromatography was aldehyde **16** in almost 30% yield, likely due to a preferred sulphur displacement.

A possible explanation for such a reaction behaviour could be proposed by considering that the presence of the negative charge on the thiol group presumably helps to shield the fluorophenyl group from attack by base so obstructing aryne formation. Consequently, a hydride abstraction from the thiolate anion, probably by DMF, produces a somewhat stabilized thioaldehyde (as this one conjugation between -CH=S and the electron-rich aromatic ring would be) which hydrolyzes to aldehyde during work-up (Chart I, path 1). Accordingly, the deep-red colour developed during the reaction would account for the presence of such a thioaldehyde. Alternatively, the thiolate anion could fragment to CH_2=S (which would polymerize spontaneously) and 2-

metalated pyrrole which would then nucleophilically attack DMF as a second molecule of DMF somehow initiates an Oppenauer oxidation of the pyrrolyl alkoxide intermediate (Chart I, path 2).[11]

Scheme V



Accordingly, preliminary acetylation of thiol group followed by the displacement step, using two molar equivalents of MeONa or NaH in DMF/benzene, gave tricyclic **1c** in 25% yield, accounting for the formation of an aryne intermediate, initially attacked by the intact thiolacetate, followed by solvolysis by MeOH (when MeONa was used) or water (during work-up of NaH catalyzed reaction) and final removal of acetyl group (Chart II).

Chart I

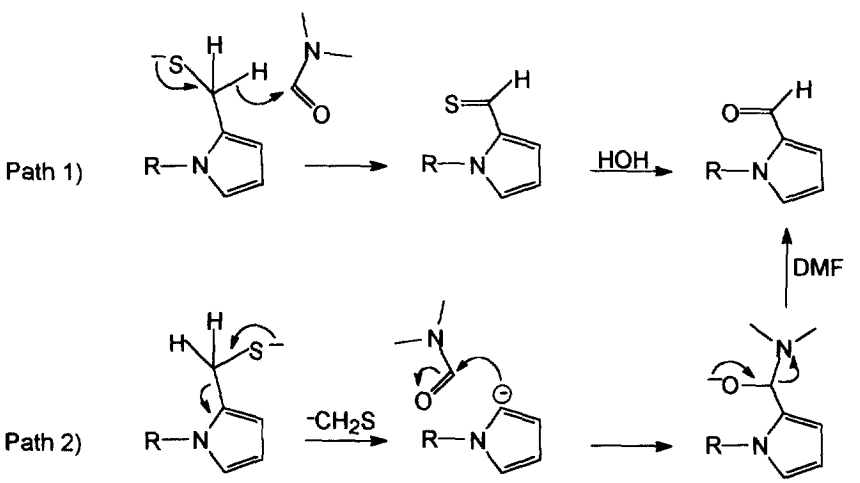
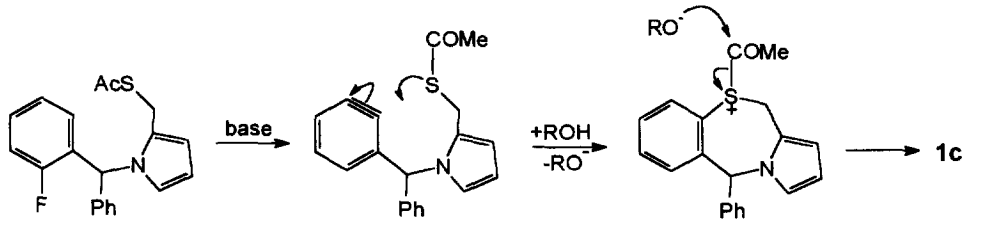


Chart II



Moreover, thiolacetate **20** could be more conveniently achieved by subjecting aldehyde **16** to $NaBH_4$ reduction and transforming the rather unstable resulting alcohol **19** under modified Mitsunobu conditions by means of Ph_3P, DPAD and thiolacetic acid.[12]

Preliminary binding tests performed on a series of CNS receptors with compounds **2a-c** have shown a noteworthy affinity for alpha-1 NA receptor (compared to Phentolamine as the reference ligand) and, to a lesser extent, for 5-HT_2 receptor (with respect to Methysergide). More extensive biological studies are in progress and will be reported in due course.

Experimental

Where necessary, solvents were dried and purified according to the recommended procedures.[13] Extracts were dried over Na_2SO_4 and solvents were removed under reduced pressure. Melting points were determined using an Electrothermal 8103 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 398 using KBr discs and nuclear magnetic resonance spectra were taken on a Bruker 200 instrument. The chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. Flash chromatography separations were performed using Merck 230-400 mesh silica gel as the solid phase. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. All reactions were carried out in an argon atmosphere.

5-Phenyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1c**.

A solution of thiolacetate **19** (3.39 g,10 mmole) in a mixture of dry DMF (10 ml) and dry benzene (40 ml), was added dropwise to a suspension of freshly prepared MeONa (or 50% mineral oil dispersion of NaH) (20 mmole) in dry benzene at -20°. The flask was then immediately immersed in a pre-heated (60°) oil bath and kept at this temperature for 3 hours with stirring. Removal of the solvent gave a residue which was chromatographed (benzene:cyclohexane, 1:2 as an eluant) to give a white solid (0.7 g, 25% yield) which was recrystallized from methanol; mp 107°; ^1H nmr ($CDCl_3$): δ 3.53 (s, 2H), 6.00 (t, 1H), 6.15 (m, 1H), 6.32 (m, 1H), 6.62 (m, 1H), 6.94 (s, 1H), 6.95-7.14 (m, 4H), 7.20-7.40 (m, 4H); ms: m/z 277 (M^+).

Anal. Calcd. for $C_{18}H_{15}OS$: C, 77.94; H, 5.45; N, 5.05. Found: C, 77.99; H, 5.33; N, 4.99.

General procedure for the preparation of compouds **2a-c**.

A mixture of the proper tricyclic **1a-c** (10 mmole), paraformaldehyde (33 mmole) and dimethylamine hydrochloride (11 mmole) was heated to 60° in ethanol (35 ml) (or acetic acid for compd **1c**) until no starting

material could be detected by tlc (8-14 hours). The solvent was then evaporated and the resulting residue was sequentially stirred with water, basified with 10 % sodium hydroxide solution, and extracted with dichloromethane. Removal of the solvent gave an oil which was purified by flash chromatography (methanol:dichloromethane, 1:19). Recrystallization from a suitable solvent yielded white crystals (chemical and physical data of compounds **2a-c** are collected in Table I).

Table I. Physical and chemical data for compounds **2a-c**.

Compd	Mp °C	Yield %	Recryst. Solvent	Molecular Formula and Analysis %. Calcd./Found	^{1}H nmr ($CDCl_3$)	ms:m/z (M^+)
2a	85-87	89	2-propanol	$C_{15}H_{18}N_2S$ C 69.73 H 7.02 N 10.84 C 69.68 H 6.91 N 10.89	2.19 (s, 6H), 3.39 (s, 2H), 4.32 (s, 2H), 5.30 (s, 2H), 5.91 (q, 2H), 6.95-7.28 (m, 4H)	258
2b	175-176	70	2-propanol	$C_{21}H_{21}FN_2S$ C 71.56 H 6.01 N 7.95 C 71.32 H 5.88 N 8.12	2.21 (s, 6H), 3.40 (ABq, 2H), 5.37 (ABq, 2H), 5.49 (d, 1H), 5.85 (d, 1H), 5.98 (s, 1H), 7.03-7.47 (m, 8H)	352
2c	52-53	48	methanol	$C_{21}H_{22}N_2S$ C 75.41 H 6.63 N 8.38 C 75.59 H 6.40 N 8.25	2.12 (s, 6H), 3.08 (ABq, 2H), 3.29 (s, 2H), 6.00 (d, 1H), 6.07 (d, 1H), 6.80 (t, 1H), 6.95-7.13 (m, 4H), 7.15-7.36 (m, 4H), 7.53 (s, 1H)	334

2-(Methylthio)benzhydrol **4**.

To the Grignard reagent generated from the reaction of magnesium turnings (2.2 g, 0.09 g-atom) and bromobenzene (15 g, 0.095 mole) in dry ethyl ether (40 ml), a solution of 2-(methylthio)benzaldehyde (12.6 g, 0.083 mole) in dry ethyl ether (15 ml) was added dropwise with ice-cooling. After the addition was complete, the cooling bath was removed and the solution was stirred for 30 minutes at room temperature. Afterward, an additional 50 ml of ethyl ether and an aqueous solution of ammonium chloride (4.2 g in 13 ml of water) were successively added with cooling. The solution was stirred for 3 hours then weakly acidified with 10% sulphuric acid. The layers were separated extracting further the aqueous fase with ethyl ether. The collected organic phase gave a pale yellow oil which was purified by vacuum distillation (164.5°/0.04 mmHg) to give **4** (18g, 79% yield); ir (neat): υ cm^{-1}, 3390 (b OH); ^{1}H nmr ($CDCl_3$): δ 2.40 (s, 3H), 2.89 (bs, 1H), 6.22 (d, 1H), 7.21-7.53 (m, 9H).

Anal. Calcd. for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 72.99; H, 6.13; S, 13.69.

2-(Methylthio)benzhydryl chloride **5**.

A mixture of 2-(methylthio)benzhydrol **4** (12 g, 0.052 mole) and concentrated hydrochloric acid (100 ml) was stirred for 15 hours to 60°. The cooled mixture was diluted with 150 ml of water before ethyl ether extraction. The separated organic layer was cautiously shaken with sodium bicarbonate saturated solution. Removal of the solvent gave a yellow oil which was distilled under vacuum (134-135°/0.02 mmHg) to give pure **5** (11 g, 85 % yield). ^{1}H nmr ($CDCl_3$): δ 2.47 (s, 3H), 6.79 (s, 1H), 7.27-7.64 (m, 9H).

Anal. Calcd. for $C_{14}H_{13}ClS$: C, 67.59; H, 5.27; Cl, 14.25; S, 12.89. Found: C, 67.76; H, 5.32; Cl, 14.15; S, 12.72.

2-(Methylthio)benzhydryl bromide **6**.

To a solution of 2-(methylthio)benzhydrol **4** (16 g, 0.070 mole) in chloroform (150 ml), a solution of phosphorus tribromide (11.4 g, 0.042 mole) in chloroform (60 ml) was added dropwise in 30 minutes. The mixture was stirred for 24 hours at room temperature and then worked up in the same manner described for compound **5**. Vacuum distillation (136°/0.03mmHg) gave pure compound **6** (16 g, 78% yield). ^{1}H nmr ($CDCl_3$): δ 2.46 (s, 3H), 6.88 (s, 1H), 7.26-7.65 (m, 9H).

Anal. Calcd. for $C_{14}H_{13}BrS$: C, 57.35; H, 4.47; Br, 27.25; S, 10.93. Found: C, 57.59; H, 4.57; Br, 27.15; S, 11.07.

2-(Methylthio)benzophenone O-acetyloxime **9b**.

Acetic anhydride (5 ml) was added portionwise to a stirred solution of oxime **9a** (4.8 g, 0.02 mole) and 4-dimethylaminopyridine (cat.) in dry pyridine (10 ml). After stirring for 45 minutes at 60°, the reaction was poured into ice-water where a solid separated. Filtration, washings with water and subsequent recrystallization of the crude material from 70% ethanol (C°) gave **9b** as a white solid (5 g, 88%), mp 94°; ir (nujol): υ cm^{-1}, 1778 (C=O); ^{1}H nmr ($CDCl_3$): δ 2.07 (s, 3H), 2.37 (s, 3H), 7.11 (m, 1H), 7.20-7.48 (m, 7H), 7.60 (m, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.44; H, 5.38; N, 4.82.

α-[2-(Methylthio)phenyl]benzenemethanamine **10**.

Ammonia gas was bubbled for 20 minutes into a ice-cooled mixture of ethanol (15 ml) and concentrated ammonia (80 ml). To this, oxime **9a** (5 g, 0.023 mole) and zinc dust 325 mesh (4.5 g, 0.069 g-atom) were successively added. After 18 hours stirring to 50° all the starting material disappeared (tlc) and the hot solution was rapidly filtered. The pH of the resulting filtrate was adjusted to 9 by cautious addition of hydrochloric acid at 0°. The solution was then concentrated to 3/4 of the initial volume and extracted with ethyl acetate. Removal of the solvent gave an oil which was chromatographed (ethyl acetate:light petroleum, 3:10) to yield pure amine **10** (4.2 g, 90%). ^{1}H nmr (DMSO): δ 2.43 (s, 3H), 2.48 (t, 2H), 5.77 (s, 1H), 7.32-7.41 (m, 9H).

Anal. Calcd. for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.13; H, 6.38; N, 5.92.

1-{[2-(Methylthio)phenyl]phenylmethyl}pyrrole **7a**.

To chilled acetic acid (35 ml) was added amine **10** (6 g, 0.026 mole). This was followed by the addition of 2,5-dimethoxytetrahydrofuran (3.5 g, 0.026 mole). The mixture was heated at 100° for 30 minutes after which the

solvent was evaporated and the residue was taken up in diethyl ether. The organics were washed sequentially with saturated sodium bicarbonate solution, water and brine. Evaporation of the solvent left a brown oil which was chromatographed (dichloromethane:light petroleum, 4:1) to give **7a** as a solid (5.5 g, 75%). An analytical sample was obtained by crystallization from light petroleum, mp 99-100°; ^{1}H nmr ($CDCl_3$): δ 2.36 (s, 3H), 6.19 (t, 2H), 6.57 (t, 2H), 6.71 (d, 1H), 6.87 (s, 1H), 7.01-7.33 (m, 8H).

Anal. Calcd. for $C_{18}H_{17}NS$: C, 77.38; H, 6.13; N, 5.01. Found: C, 77.60; H, 6.12; N, 4.87.

2-Mercaptodiphenylmethane **12**.

To a solution of compound **7a** (2 g, 7.2 mmole) in N,N-dimethylacetamide (20 ml), small pieces of sodium metal (0.83 g, 0.036 g-atom) were added at room temperature. The mixture was then heated to 80° overnight. After cooling to room temperature, the dark brown resulting solution was cautiously quenched with ice and successively washed with two small portion of ethyl ether. The aqueous layer was then made acidic (ph 3) by addition of concentrated hydrochloric acid at 0°. Diethyl ether extraction followed by recrystallization from light petroleum (C°) gave pure **12** as a colorless solid (1.25 g, 88%); mp 53°; ir (nujol): υ cm^{-1}, 2560 (SH); ^{1}H nmr ($CDCl_3$): δ 3.30 (s, 1H), 4.08 (s, 2H), 7.08-7.41 (m, 9H).

Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.00. Found: C, 78.20; H, 6.04; S, 15.88.

1-{[2-(Methylsulfinyl)phenyl]phenylmethyl}pyrrole **13**.

A solution of commercial 3-chloroperoxybenzoic acid (MCPBA) (2.4 mmole) in dichloromethane (7 ml) was added dropwise at 0° to a solution of compound **7a** (0.65 g, 2.3 mmole) in dichloromethane (7 ml). The mixture was stirred at the same temperature until no starting material could be detected by tlc (~ 6 hours).[14] The suspension was filtered and the resulting solution was shaken with 5% potassium carbonate. After drying, the organic layer gave a gum which was chromatographed (ethyl acetate:light petroleum, 2:1) to give a less polar diastereomer **13'**. Recrystallization of this from ethanol gave a white solid (0.33 g, 48%); mp 142-143°; ir (nujol): υ cm^{-1}, 1055 (SO); ^{1}H nmr ($CDCl_3$): δ 1.97 (s, 3H), 6.18 (t, 2H), 6.55 (t, 2H), 6.92 (m, 4H), 7.32-7.51 (m, 4H), 7.61 (t, 1H), 8.20 (d, 1H).

Anal. Calcd. for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.00; H, 6.20; N, 4.65.

Further elution followed by recrystallization (ethanol) gave a more polar diastereomer **13''** (0.30 g, 44%) as a white solid; mp 133°; ir (nujol): υ cm^{-1}, 1060 (SO); ^{1}H nmr ($CDCl_3$): δ 2.01 (s, 3H), 6.22 (t, 2H), 6.57 (t, 2H), 6.75 (d, 1H), 6.94 (s, 1H), 7.18 (m, 2H), 7.30-7.58 (m, 5H), 8.05 (m, 1H).

Anal. Calcd. for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.29; H, 6.26; N, 4.81

α-(2-Fluorophenyl)benzenemethanamine **15**.

This compound was prepared by applying the same procedure described for compound **10** starting from known oxime **14**[15] in 88% yield. Chemical and physical data of the product were in agreement with those reported in the literature.[5]

Bis{1-[(2-Fluorophenyl)phenylmethyl]-2-pyrrolylmethyl}disulfide **17**.

To a mixture of aldehyde **16** (2.79 g, 10 mmole) in ethanol (40 ml) a 20% solution of ammonium sulfide in water (20 ml, 60 mmole) was added, then it was stirred for 3 days at room temperature. The mixture was

poured into water (200 ml) and extracted with diethyl ether. Removal of the solvent gave **17** as a viscous oil (2.5 g, 85%) which was purified by chromatography (ethyl acetate:light petroleum, 1:19); ^{1}H nmr ($CDCl_3$): δ 3.61 (s, 4H), 6.09 (m, 2H), 6.20 (m, 2H), 6.35 (m, 2H), 6.69 (m, 2H), 6.99 (s, 2H), 7.01-7.20 (m, 8H), 7.24-7.41 (m, 8H).

Anal. Calcd. for $C_{36}H_{30}F_2N_2S_2$: C, 72.95; H, 5.10; N, 4.73. Found: C, 73.09; H, 5.26; N, 4.81

1-[(2-Fluorophenyl)phenylmethyl]-1*H*-pyrrole-2-methanethiol **18**.

$LiAlH_4$ (0.09 g, 2.4 mmole) slurry in dry diethyl ether (50 ml) was added dropwise to a solution of disulfide **17** (0.7 g, 1.18 mmole) in the same solvent (15 ml). After 2 hours stirring at room temperature, the excess of hydride was cautiously destroyed by sequential addition of water and 15% sulfuric acid (pH ≅ 1). Ethyl ether extraction gave pure **18** as an oil (0.6 g, 85%). An analytical sample was purified by chromatography (benzene:cyclohexane, 1:1); ir (neat): υ cm^{-1}, 2585 (SH); ^{1}H nmr ($CDCl_3$): δ 1.76 (t, 1H), 3.62 (m, 2H), 6.06 (m, 1H), 6.14 (m, 1H), 6.33 (m, 1H), 6.70 (m, 1H), 7.07-7.11 (m, 4H), 7.13 (s, 1H), 7.26-7.40 (m, 4H).

Anal. Calcd. for $C_{18}H_{16}FNS$: C, 72.70; H, 5.42; N, 4.71. Found: C, 73.00; H, 5.56; N, 4.91.

1-[(2-Fluorophenyl)phenylmethyl]-1*H*-pyrrole-2-methanol **19**.

To a stirring suspension of $NaBH_4$ (0.14 g, 3.6 mole) in 2-propanol (10 ml) was added dropwise a solution of aldehyde **16** (0.5 g, 1.8 mmole) in 2-propanol (10 ml). The mixture was stirred at reflux for 30 minutes. Removal of the solvent gave a white semi-solid which was stirred with water (20 ml) for 15 minutes, then extracted with dichloromethane. The organic layer was evaporated to dryness to leave a solid (0.44 g, 87%) which was used without purification in the subsequent step; ^{1}H nmr ($CDCl_3$): δ 1.39 (t, 1H), 4.49 (d, 2H), 6.08 (t, 1H), 6.18 (t, 1H), 6.41 (t, 1H), 6.74 (m, 1H), 6.95-7.17 (m, 5H), 7.21-7.43 (m, 4H).

1-[(2-Fluorophenyl)phenylmethyl]-1*H*-pyrrole-2-methanethiolacetate **20**.

Starting from **18**.

Acetic anhydride (5 ml) was added portionwise to a stirred and ice-cooled solution of thiol **18** (6 g, 0.02 mole) and 4-dimethylaminopyridine (cat.) in dry pyridine (10 ml). After stirring for 1 day at room temperature, the evaporation of the volatiles and subsequent chromatography (benzene:hexane, 4:1) gave **20** as a colorless oil (4.5 g, 66%); ir (neat): υ cm^{-1}, 1695 (C=O); ^{1}H nmr ($CDCl_3$): δ 2.27 (s, 3H), 4.12 (s, 2H), 6.08 (m, 1H), 6.19 (m, 1H), 6.35 (m, 1H), 6.70 (m, 1H), 6.77 (s, 1H), 6.95-7.12 (m, 4H), 7.27-7.41 (m, 4H).

Anal. Calcd. for $C_{20}H_{18}FNOS$: C, 70.77; H, 5.35; N, 4.13. Found: C, 70.70; H, 5.56; N, 4.11.

Starting from **19**.

To a well stirred and ice-cooled solution of dry triphenylphosphine (1.84 g, 7 mmole) in dry THF (5 ml), diisopropyl azodicarboxylate (1.41 g, 7 mmole) was added dropwise. After 30 minutes a solution of crude **19** (1 g, 3.5 mmole) and thiolacetic acid (0.5 ml, 7 mmole) in dry THF (5 ml) was added slowly. The mixture was stirred for 30 minutes at 0°, then overnight at room temperature. Removal of the solvent left a residue which was taken up in diethyl ether (~5 ml). The insoluble material was filtered off and the oily residue, obtained after evaporation of the solvent, was chromatographed to afford pure **20** as a colorless oil (1.1 g, 92%).

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References and notes

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