1 H, each br s, OH × 2); MS, m/z 178 (M^+). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.80; H, 7.85.

X-ray Results. Crystal data of compound **33**: $C_{15}H_{18}O_4$, MW = 262.3, monoclinic, space group $P2_1/c$, a = 10.924 (7) Å, b = 8.125 (5) Å, c = 17.187 (9) Å, β = 112.82 (5)°, V = 1406 (1) Å^3, Z = 4, D_c = 1.239 g cm^{-3}. The structure was solved by direct methods and refined by a block-diagonal least-squares technique to R = 0.048 for 2076 reflections, excluding the hydrogen atoms of one of the methyl groups.

Supplementary Material Available: Perspective view, tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for compound **33** (5 pages). Ordering information is given on any current masthead page.

Notes

Regiochemistry of Formation, Stereochemistry, and Interconversion of α-*tert*-Butyl(4- or 5-nitro-*N*-methyl-2-pyrrolyl)methyl Sulfones and Sulfinates[1]

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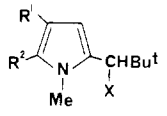
In a recent paper we reported that the chlorides **1** and **2** reacted with nucleophiles or with methanol to give substitution products by an S_N1 process.[2] When we treated the above chlorides with sodium *p*-toluenesulfinate (**3**), complex reaction products resulted, and it appeared that simple substitution reactions were not taking place. We now report the results of the reaction of **1** and **2** with the salt **3**.

Results and Discussion

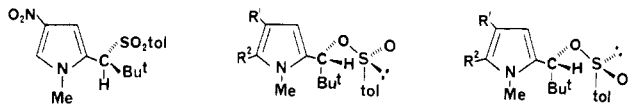
Reaction of the Chlorides 1 and 2 with Sodium *p*-Toluenesulfinate (3). Treatment of the chloride **1** with the salt **3** in DMF at 60 °C for 15 min gave a mixture of four compounds, as judged from the *N*-methyl and *tert*-butyl resonances in the ^{1}H NMR spectrum of the crude reaction mixture, in ca. 92% yield [estimated by reference to added TNT (2,4,6-trinitrotoluene)]. On the basis of



	R^1	R^2	X
1	NO_2	H	Cl
2	H	NO_2	Cl
4	NO_2	H	OH
5	NO_2	H	*p*-$MeC_6H_4SO_2$
7	NO_2	H	*p*-MeC_6H_4S
8	H	NO_2	*p*-$MeC_6H_4SO_2$
10	H	NO_2	OH
11	H	NO_2	OCHO

spectroscopic and chemical evidence presented below these products were assigned as the alcohol **4** (6%), the sulfone **5** (28%), and the two diastereomeric sulfinic esters **6a** (36%) and **6b** (22%). Duplicate reactions varied slightly

Na$^+$ *p*-$MeC_6H_4SO_2^-$
3



5a

	R^1	R^2
6a	NO_2	H
9a	H	NO_2

	R^1	R^2
6b	NO_2	H
9b	H	NO_2

in the relative proportion of these products (±4%). The benzylic and aromatic region of the ^{1}H NMR spectrum obtained from a typical mixture resulting from this reaction is given in Figure 1a. The reaction products on standing for ca. 17 h in $CDCl_3$ at room temperature changed into a simple mixture of the alcohol **4** (20%) and the sulfone **5** (71%). The sulfone **5** could be isolated readily from any reaction mixture resulting from treatment of **1** with **3** so long as the mixture was left for 15–20 h before recrystallization. Sulfone **5** had the required elemental composition and was unambiguously prepared from the sulfide **7** (previously isolated from the reaction of chloride **1** with *p*-toluenethiolate ion)[2] by oxidation with *m*-chloroperbenzoic acid in dichloromethane. The ^{1}H NMR spectrum of **5** is given in Figure 1b. In previous studies in our laboratories, it has been found that sulfones of the type Ar′CH-*t*-$BuSO_2$Ar exhibit dynamic ^{1}H NMR phenomena around the Ar′–CH bond.[3-5] This sulfone did not exhibit DNMR effects, and it appeared reasonable that it was "locked" into the less hindered conformation **5a**, in which the *N*-methyl group was remote from the bulky substituents on the benzylic carbon. This conclusion was confirmed by NOE experiments. Irradiation of the benzylic proton (H1) gave significant enhancement of the signals from the *N*-methyl group (9.7%), the *tert*-butyl group (10.6%), and also the signal from the two protons on the benzene ring ortho to the SO_2 group (6.1%). Irradiation of the *N*-Me group gave a 3.7% enhancement of H1, a 3.3% of H5′ and a 0.8% enhancement of the signal for the two ring protons ortho to the sulfonyl group respectively. Irradiation of the *tert*-butyl group enhancement of the signal for H1 (2.2%) and H3′ (2.3%). The significant interactions of H1 and the *N*-Me group with

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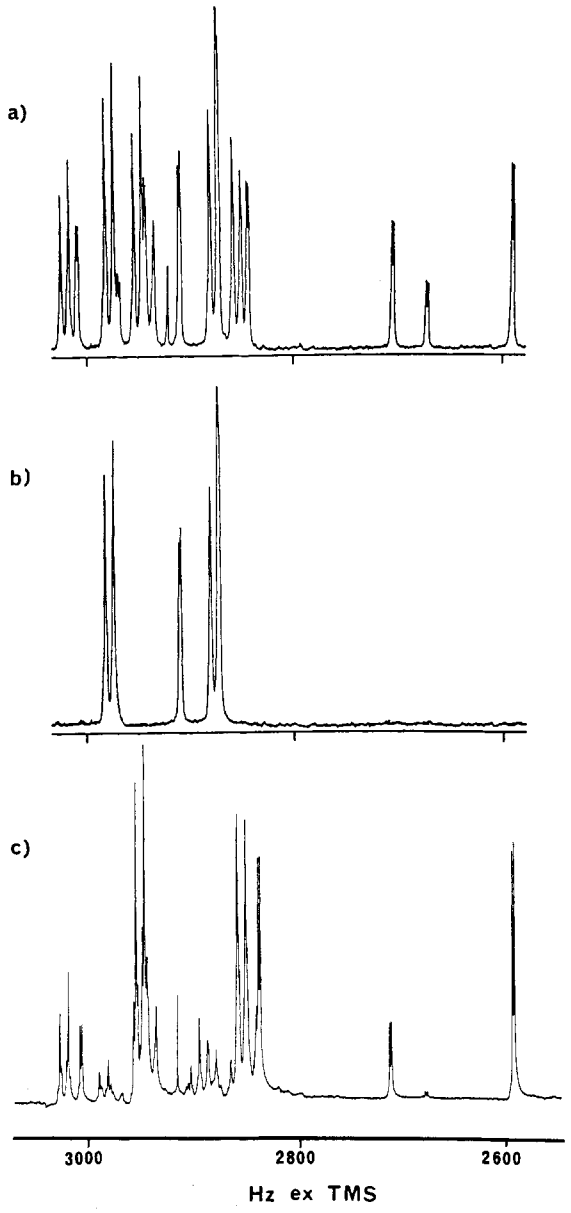


Figure 1. 400-MHz ^{1}H NMR spectrum of (a) reaction mixture from reaction of chloride **1** with salt **3**, (b) compound **5**, and (c) reaction mixture from *p*-toluenesulfinylation of alcohol **4**.

the protons on the *p*-tolyl ring confirm the "folded back" conformation adopted by this group.[3-5]

Preparation of the sulfinate esters **6a** and **6b** was attempted by treatment of the alcohol **4** with *p*-toluenesulfinyl chloride in pyridine at room temperature. The ^{1}H NMR spectrum of the crude product from this reaction (see Figure 1c) consisted of signals which were coincident with those from **6a** and **6b** formed in the reaction of **1** with **3**, but in a different ratio (**6a**:**6b** = ca. 3:1), and much weaker signals from sulfone **5**. Attempts to purify or separate the mixture of sulfinic esters by chromatography led to formation of the alcohol **4** and/or conversion into the sulfone **5**. When mixtures from the *p*-toluenesulfinylation reaction were kept at 20 °C in $CDCl_3$ for 20 h, all signals from **6a** and **6b** disappeared and were replaced by those from **5** together with signals from small amounts of the alcohol **4**.

When any mixture of the isomers **5**, **6a**, and **6b** in $CDCl_3$ were shaken with 3 M hydrochloric acid, the ^{1}H NMR signals from the esters **6a** and **6b** (and any contaminating alcohol **4**) disappeared and were replaced by those from the chloride **1**, whereas signals from the sulfone **5** were

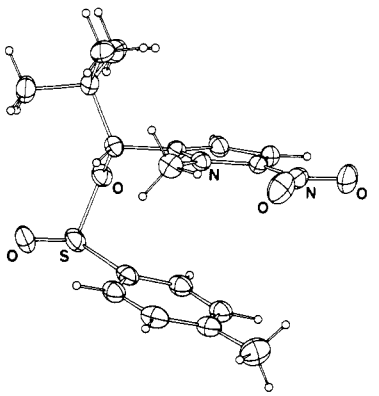


Figure 2. ORTEP representation of the X-ray structure of compound **9a**.

unaffected. By the use of internal TNT in these ^{1}H NMR experiments it could readily be shown that all the conversions were taking place quantitatively.

The chemical shift data for **5**, **6a**, and **6b** confirm the assigned structures. For example, the chemical shifts for the benzylic protons in **6a** and **6b** (δ 4.83 and 4.85, respectively) are consistent with the sulfinic ester structures and differ in the expected fashion from the chemical shift for the benzylic proton in the sulfone **5** (δ 3.94). Despite the large chemical shift differences between corresponding protons (e.g., *N*-Me groups at δ 3.25 and 3.74, respectively) in the diastereomers **6a** and **6b**, assignment of the relative configuration at the benzylic carbon and at sulfur cannot be made in absence of other data.[6]

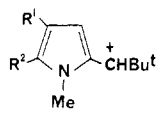
The reaction of the 5-nitro chloride **2** with *p*-toluenesulfinate ion in DMF at 60 °C proceeded more slowly than the reaction involving **1**, consistent with the operation of an S_N1 mechanism,[2] and after 3.5 and 5.5 h respectively gave the following identifiable products (proportions estimated after 3.5 and 5.5 h respectively by ^{1}H NMR): unchanged starting material **2** (15, 4%), sulfone **8** (20, 22%), the sulfinic esters **9a** (12, 14%) and **9b** (7, 8%), the alcohol **10** (8, 9%), and the formate ester **11** (11, 13%). The constitution of the latter compound was confirmed by independent preparation by formylation of the alcohol **10**. The isomerization of the esters **9a**/**b** into the sulfone **8** was relatively slow. Consequently it was not surprising that the esters **9a** and **9b**, independently prepared by *p*-toluenesulfinylation of the alcohol **10** (estimated yields 64% and 30%, respectively) could be separated by fractional crystallization and PLC and were characterized in the normal fashion. The major ester **9a** formed well-defined crystals, and its structure, determined by X-ray crystallography, is given in Figure 2. It can be seen that the configurations at the benzylic carbon (C1) and the sulfoxide sulfur are $1RS,S_{SR}$. The *N*-Me and pyrrole ring protons in **9a** (and also **6a**) were upfield of the corresponding protons in **9b** (**6b**) and the $\Delta\delta$ values for the *N*-Me, H3′, and H4′(H5′) resonances were −0.60 (−0.49), −0.16 (−0.28) and −0.26 (−0.44) ppm, respectively. The methyl resonances in the *p*-tolyl ring also exhibit this same trend and for **9a** (**6a**) and **9b** (**6b**) were at δ 2.33 (2.32) and 2.43 (2.43), respectively. It would appear that the preferred conformation found for **9a** *in solution* is similar to that

(6) Based on the similarity of chemical shift patterns in the pairs **6a**/**b** and **9a**/**b** and the fact that **6a** and **9a** are the major products not only in the *p*-toluenesulfinylation reactions of alcohols **4** and **10**, respectively, but also in the substitution reactions of **1** and **2**, respectively, with **3** it would seem reasonable to assume that **6a** and **9a** have the same relative stereochemistries. On the basis of X-ray determined structure of **9a**, the esters **6a** and **6b** can be assigned as the $1RS,S_{SR}$ and $1RS,S_{RS}$ isomers, respectively.

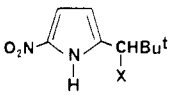
exhibited in the solid state, wherein the *p*-toluenesulfinyloxy group lies immediately over the pyrrole ring (see Figure 2). It is well-known that such an arrangement causes significant shielding of protons.[7] The minor isomer **9b** did not form sharp melting crystals, although it was isomerically pure (by ^{1}H NMR) (see Experimental Section).

The formation of products from treatment of the chlorides **1** and **2** is readily rationalized in terms of an S_N1 mechanism in which either α-*tert*-butyl(*N*-methyl-4-nitro-2-pyrrolyl)methyl or -5-nitro-2-pyrrolyl)methyl cations, **12** and **13**, respectively, are trapped by the ambident *p*-toluenesulfinate ion. The formation of the alcohols **4** and **10** can be rationalized as arising from trapping of these cations by adventitious water and/or by hydrolysis of the sulfinic esters. The formation of the formate ester **11**, presumably through trapping of the intermediate cation by the solvent (DMF), has an analogy in related thienyl derivatives.[8]

What is unusual in the reactions of **1** or **2** with **3**, is the substantial formation of sulfinic esters. Stirling, in a review of sulfinic acid chemistry,[9] reported that "in all but a few instances, nucleophilic attack by sulfinate ion yields sulfonyl derivatives." Among the exceptions noted, which gave sulfinic esters, were the reaction of silver arenesulfinates with methyl iodide, the reaction of sulfinate ions with alkyl chloroformates (an S_Ni reaction), and the reaction of sulfinate ions with chlorocarbonates and related compounds, involving mixed anhydrides. In what appears to be the only other example of significant sulfinic ester formation in an alkylation reaction, the treatment of arenesulfinate ions with triethyloxonium tetrafluoroborate gives high proportions of the ethyl arenesulfinates.[10] It was concluded[10] that with a highly reactive alkylating agent, the attack on the sulfinate ion proceeds in a kinetically controlled manner to give a sulfinic ester, while in the reaction with weak alkylating agents a thermodynamically controlled attack gives more stable isomeric sulfones. In the reactions of **1** or **2** with **3**, it is clear that the product distribution is that arising from kinetic control and that the sulfones **5** and **8** are the thermodynamically stable products. The origin of the kinetic preference for the sulfinic esters may well lie in the high reactivity of the pyrrolylmethyl cations **12** and **13**, but it is also possible



	R^1	R^2
12	NO_2	H
13	H	NO_2



14 X = Cl
15 X = *p*-$MeC_6H_4SO_2$

that the regiochemistry of attack of the *p*-toluenesulfinate ion on **12** and **13** is sterically controlled. The benzylic carbons, bearing the positive charge, in **12** and **13** not only form part of a neopentyl system but also are ortho to a methyl group. This very hindered environment may well be inducing departure from the normally preferred S-alkylation pathway. As limited support of this explanation, the chloride **14**, without the ortho *N*-methyl group, on treatment with the salt **3** in DMF at 20 °C for 5 min, gives a good yield (71%) of the sulfone **15**. No detectable amounts of sulfinic esters were found. The rapidity of this reaction (compared with the conditions needed for the reaction of **2** with **3**; >5.5 h at 60 °C) would indicate, however, that a more reactive system is involved, and so rapid isomerization of sulfinic ester intermediates into the sulfone **15** cannot be ruled out. One final point of note in these reactions is the contrast between the reactions of the chlorides **1** and **2** and the analogous 4- and 5-nitro derivatives in the thiophene[11] and furan[12] systems and the analogous substrates in the *p*-nitrophenyl[3] and *m*-nitrophenyl[4] series. All of these compounds give the S-alkylation products, namely, the corresponding *p*-tolyl sulfones, by either $S_{RN}1$ or S_N(AEAE) reactions.

Experimental Section

Melting points were determined thermoelectrically on a Reichert hot stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined on a Varian Associates EM-390 or a Bruker WM-400 spectrometer on 5–10% w/v solutions in $CDCl_3$. ^{1}H chemical shifts are quoted in ppm downfield of internal $SiMe_4$. Infrared spectra were recorded on a Perkin-Elmer 221 or a BIO-RAD FTS-20 FTIR spectrophotometer, and ultraviolet spectra were recorded on Perkin-Elmer 402 and Hitachi 150-20 spectrophotometers. Mass spectra were recorded on an A.E.I. MS-902 spectrometer at 70 eV. Analyses were carried out at AMDEL, Melbourne. Thin-layer chromatography (TLC) was performed on Merck Kieselgel $HF_{254+366}$ (type 60). Preparative-layer chromatography (PLC) was performed on Merck Kieselgel $PF_{254+366}$. Flash chromatography[13] was performed on Merck silica gel 60 (230–240 mesh). Light petroleum refers to the fraction of bp 65–70 °C. Reaction mixtures were worked up by dilution with water followed by threefold extraction with ether, washing the ether layer with water and brine, drying ($MgSO_4$), and removal of the ether under reduced pressure to give the crude product.

Reaction of the 4-Nitro Chloride 1 with Sodium *p*-Toluenesulfinate (3). Sodium *p*-toluenesulfinate (**3**) (150 mg, 0.83 mmol) was added to a solution of 2-(1′-chloro-2′,2′-dimethylpropyl)-1-methyl-4-nitro-1*H*-pyrrole **1** (97 mg, 0.42 mmol) in DMF (1.7 mL) at 60 °C under nitrogen. The reaction mixture was quenched after 15 min and worked up in the usual manner. The crude product was allowed to stand in chloroform for 17 h and the solvent removed and recrystallized to yield **2,2-dimethyl-1-(1′-methyl-4′-nitro-2′-pyrrolyl)propyl *p*-tolyl sulfone (5)**: while crystals, mp 181–182 °C (chloroform/light petroleum); 79 mg (54%); ^{1}H NMR δ 1.29 (s, 9 H, *t*-Bu), 2.39 (s, 3 H, ArMe), 3.01 (s, 3 H, *N*-Me), 3.94 (s, 1 H, H1), 7.18 (d, 1 H, $J_{3',5'}$ = 2.0 Hz, H3′), [AA′XX′ pattern] 7.20 (m, 2 H), 7.44 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.4 Hz), 7.24 (d, 1 H, $J_{3',5'}$ = 2.0 Hz, H5′); NOE experiments were preformed and gave the following results, irradiation of H1 (9.7% to *N*-Me, 10.6% to *t*-Bu, 6.1% to 2 H meta to Me), irradiation of *N*-Me (3.7% to H1, 3.3% to H5′, 0.8% to 2H meta to Me), irradiation of *t*-Bu (2.2% to H1, 2.3% to H3′); IR ($CHCl_3$) 1602, 1507, 1361, 1183, 1142, 1122, 859 cm^{-1}; UV (EtOH) 275 (ϵ 7.1 × 10^3), 320 nm (4.5 × 10^3); mass spectrum, *m/z* (relative intensity) 350 (M^+, 0.1), 196 (16), 195 (100), 139 (8), 127 (8), 91 (9), 69 (12), 42 (9), 41 (11).

Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.3; H, 6.3; N, 8.0. Found: C, 58.1; H, 6.4; N, 7.9.

The sulfinic esters **(1*RS*,*S*$_{SR}$)-** and **(1*RS*,*S*$_{RS}$)-2,2-dimethyl-1-(1′-methyl-4′-nitro-2′-pyrrolyl)propyl *p*-toluenesulfinate (6a** and **6b**, respectively) were not isolated but were identified by their ^{1}H NMR spectra and their formation from the alcohol **4** on *p*-toluenesulfinylation (see below). The following ^{1}H NMR data were obtained for **6a**: δ 0.95 (s, 9 H, *t*-Bu), 2.32 (s, 3 H, ArMe), 3.25 (s, 3 H, *N*-Me), 4.83 (s, 1 H, H1), 6.48 (d, $J_{3',5'}$

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= 1.9 Hz, H3'), 7.08 (d, 1 H, $J_{3',5'}$ = 1.9 Hz, H5'), [AA'XX' system] 7.14 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.4 Hz, 2 H ortho to Me), 7.37 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.4 Hz, 2 H meta to Me). The following ^{1}H NMR data were obtained for **6b**: δ 0.97 (s, 9 H, *t*-Bu), 2.43 (s, 3 H, ArMe), 3.74 (s, 3 H, *N*-Me), 4.85 (s, 1 H, H1), 6.76 (d, $J_{3',5'}$ = 1.9 Hz, H3'), [AA'XX' pattern] 7.35 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.4 Hz, 2 H ortho to Me), 7.56 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.4 Hz, 2 H meta to Me), 7.52 (d, $J_{3',5'}$ = 1.9 Hz, H5').

When mixtures containing the sulfinic esters **6a** and **6b** in $CDCl_3$ were treated with hydrochloric acid (3 M), the signals from the esters in the ^{1}H NMR spectra slowly disappeared and were replaced by those from the chloride **1**. The signals from the sulfone **5** were unaffected.

Independent Preparation of Sulfone 5. *m*-Chloroperbenzoic acid (41 mg, 0.24 mmol) was added to a solution of the sulfide **7**[2] (40 mg, 0.12 mmol) in chloroform (10 mL) at 20 °C. After 5 min the reaction mixture was worked up in the usual manner to yield the sulfone **5** (81%) identical with the sample prepared above.

Reaction of the Alcohol 4 with *p*-Toluenesulfinyl Chloride. Freshly prepared *p*-toluenesulfinyl chloride[14] (100 mg, 0.57 mmol) was added dropwise to the alcohol **4** (31 mg, 0.15 mmol) dissolved in pyridine (1 mL) cooled to 5 °C and the reaction mixture allowed to stir at room temperature for 35 min. The reaction mixture was quenched with 5% ammonium chloride solution and extracted with ether in the usual manner. The ^{1}H NMR spectrum showed a 3:1 mixture of the sulfinic esters **6a** and **6b** (identical resonances with those above), together with small amounts of the sulfone **5**. When the NMR sample was allowed to stand for 20 h only the stable sulfone **5** remained.

Reaction of the 5-Nitro Chloride 2 with Sodium *p*-Toluenesulfinate (3). Sodium *p*-toluenesulfinate (**3**) (75 mg, 0.45 mmol) was added to a solution of the chloride **2** (49 mg, 0.21 mmol) in dimethylformamide (0.9 mL) at 60 °C under nitrogen. Two such reaction mixtures were quenched after 3.5 and 5.5 h and worked up in the usual manner. Analysis of the reaction mixture by ^{1}H NMR spectroscopy with 2,4,6-trinitrotoluene as internal standard gave the following product distributions after 3.5 and 5.5 h, respectively: **2** (15, 4%); sulfone **8** (20, 22%); sulfinate **9a** (12, 14%); sulfinate **9b** (7, 8%); alcohol **10** (8, 9%); and formate **11** (11, 13%). The combined crude products from several reactions were allowed to stand in chloroform for several days, the solvent was removed, and the crude product was recrystallized from chloroform/light petroleum to give **2,2-dimethyl-1-(1'-methyl-5'-nitro-2'-pyrrolyl)propyl *p*-tolyl sulfone (8)**: white plates, mp 135–137 °C (chloroform/light petroleum); ^{1}H NMR δ 1.31 (s, 9 H, *t*-Bu), 2.37 (s, 3 H, ArMe), 3.29 (s, 3 H, *N*-Me), 4.06 (s, 1 H, H1), 6.76 (d, 1 H, $J_{3',4'}$ = 4.6 Hz, H3'), [AA'XX' pattern] 7.18 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.3 Hz, 2 H ortho to Me), 7.41 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.3 Hz, 2 H meta to Me), 7.22 (d, 1 H, $J_{3',4'}$ = 4.6 Hz, H4'); IR ($CHCl_3$) 1609, 1466, 1419, 1374, 1338, 1184, 1119 cm^{-1}; UV (EtOH) 346 nm (ε 9.0 × 10^3); mass spectrum, *m/z* (relative intensity) 350 (M$^+$, 1), 289 (0.5), 196 (13), 195 (100), 178 (7), 92 (9), 91 (9), 69 (17).

Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.3; H, 6.3; N, 8.0. Found: C, 58.2; H, 6.4; N, 7.7.

Reaction of Alcohol 10 with *p*-Toluenesulfinyl Chloride. The 5-nitro alcohol **10** (0.197 g, 0.93 mmol) was dissolved in pyridine (10 mL) and cooled to 5 °C. Freshly prepared *p*-toluenesulfinyl chloride[14] (315 mg, 1.8 mmol) was added dropwise, and the reaction mixture was allowed to stir for 1.5 h. The reaction mixture was poured onto ice–water and extracted with ether to give a crude product (369 mg) which consisted of a mixture of **9a** and **9b** in a ca. 2:1 ratio (estimated yields, 64% and 30%, respectively). The crude product was recrystallized to give **(1*RS*,*S*$_{SR}$)-2,2-dimethyl-1-(1'-methyl-5'-nitro-2'-pyrrolyl)propyl *p*-toluenesulfinate (9a)**: yellow prisms, mp 95–97 °C (ether); 102 mg (31%); ^{1}H NMR δ 0.96 (s, 9 H, *t*-Bu), 2.33 (s, 3 H, ArMe), 3.38 (s, 3 H, *N*-Me), 4.90 (s, 1 H, H1'), 6.10 (d, 1 H, $J_{3,4}$ = 4.4 Hz, H3), 7.03 (d, 1 H, $J_{3,4}$ = 4.4 Hz, H4), [AA'XX' pattern] 7.11 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.1 Hz, 2 H ortho to Me); 7.35 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.1 Hz, 2 H meta to Me); IR ($CHCl_3$) 1453, 1356, 1286, 1146, 1131, 1113, 924 cm^{-1}; UV (EtOH) 259 (ε 3.1 × 10^3), 352 nm (5.7 × 10^3); mass spectrum, *m/z* (relative intensity) 350 (M$^+$, 3), 289 (2), 195 (100), 165 (14), 150 (33), 139 (19), 91 (30); see below for X-ray structure determination.

Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.3; H, 6.3; N, 8.0. Found: C, 58.1; H, 6.5; N, 8.3.

After recrystallization of **9a**, the mother liquors were evaporated, and the residue was separated into components by flash chromatography on silica gel with 30% ethyl acetate/light petroleum as eluent to give a further sample of **9a** (83 mg) [total yield 185 mg (57%)] and **(1*RS*,*S*$_{RS}$)-2,2-dimethyl-1-(1'-methyl-5'-nitro-2'-pyrrolyl)propyl *p*-toluenesulfinate (9b)**: white needles from light petroleum (87 mg, 27%), softens at 64–67 °C and melts at 85–88 °C; ^{1}H NMR δ 0.94 (s, 9 H, *t*-Bu), 2.43 (s, 3 H, ArMe), 3.98 (s, 3 H, *N*-Me), 4.93 (s, 1 H, H1'), 6.26 (d, 1 H, $J_{3,4}$ = 4.4 Hz, H3), 7.28 (d, 1 H, $J_{3,4}$ = 4.4 Hz, H4), [AA'XX' pattern] 7.35 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.1 Hz, 2 H ortho to Me); 7.61 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.1 Hz, 2 H meta to Me); IR ($CHCl_3$) 1459, 1370, 1292, 1285, 1148 cm^{-1}; UV (EtOH) 224 (ε 1.5 × 10^4), 349 nm (1.3 × 10^4); mass spectrum, *m/z* (relative intensity) 350 (M$^+$, 3), 304 (9), 196 (30), 195, (100), 91 (30).

Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.3; H, 6.3; N, 8.0. Found: C, 58.1; H, 6.4; N, 7.8.

1-(1'-Methyl-4'-nitro-2'-pyrrolyl)-2,2-dimethylpropyl Formate (11). This compound was formed only in small amounts in the reaction of **2** with **3** and was independently prepared as follows. Acetic formic anhydride (500 mg) was added to the alcohol **10** (224 mg, 1.06 mmol) at room temperature, and the reaction mixture was allowed to stand for 2 days. The reaction mixture was purified by PLC with 15% ethyl acetate/light petroleum as eluent to yield **11** (174 mg, 68%): a yellow oil; ^{1}H NMR δ 1.03 (s, 9 H, *t*-Bu), 4.04 (s, 3 H, *N*-Me), 5.58 (br s, 1 H, H1'), 6.19 (d, 1 H, $J_{3,4}$ = 4.5 Hz, H3), 7.20 (d, 1 H, $J_{3,4}$ = 4.5 Hz, H4), 8.07 (d, 1 H, $J_{CHO,1'}$ = 1.2 Hz, OCOH); IR ($CHCl_3$) 1725, 1456, 1360, 1285, 1161, 1149, 741 cm^{-1}; UV (EtOH) 344 nm (ε 1.3 × 10^4); mass spectrum, *m/z* (relative intensity) 240 (M$^+$, 26), 224 (3), 195 (10), 184 (80), 167 (17), 155 (41), 139 (60), 109 (26), 57 (100), 29 (32); high-resolution mass spectrum calcd for $C_{11}H_{16}N_2O_4$ 240.1110, found M$^+$ 240.1109.

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.9; H, 6.7; N, 11.7. Found: C, 55.2; H, 6.6; N, 12.0.

Reaction of 2-(1-Chloro-2,2-dimethylpropyl)-5-nitropyrrole (14) with Sodium *p*-Toluenesulfinate (3). Sodium *p*-toluenesulfinate 320 mg, 1.8 mmol) was added to a solution of the chloride **14** (191 mg, 0.88 mmol) in DMF (3.4 mL) at 20 °C under nitrogen. The reaction mixture was quenched after 5 min and worked up to the usual manner. The crude product was recrystallized from chloroform/light petroleum to yield **2,2-dimethyl-1-(5'-nitro-2'-pyrrolyl)propyl *p*-tolyl sulfone (15)**: a white powder, mp 185–186 °C; 210 mg (71%); ^{1}H NMR δ 1.31 (s, 9 H, *t*-Bu), 2.36 (s, 3 H, ArMe), 3.99 (s, 1 H, H1), 5.91 (dd, 1 H, $J_{3',4'}$ = 4.2 Hz, $J_{1',3'}$ = 2.8 Hz, H3'), 6.89 (dd, 1 H, $J_{3',4'}$ = 4.2 Hz, $J_{1',4'}$ = 2.6 Hz, H4'), [AA'XX' pattern] 7.18 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.3 Hz, 2 H ortho to Me), 7.42 (m, 2 H, $J_{AX} + J_{AX'}$ = 8.3 Hz, 2 H meta to Me), 8.90 (br s, 1 H, NH); IR ($CHCl_3$) 3406, 1599, 1508, 1467, 1417, 1302, 1176, 1110, 1066 cm^{-1}; UV (EtOH) 351 nm (ε 1.4 × 10^4); mass spectrum, *m/z* (relative intensity) 280 (M$^+$ − *t*-Bu, 2), 181 (100), 164 (22), 139 (25), 133 (18), 119 (26), 118 (22), 92 (39), 91 (63), 65 (46), 51 (17), 41 (33), 39 (37).

Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.1; H, 6.0; N, 8.3. Found: C, 56.8; H, 6.1; N, 8.3.

Structure Determination for Sulfinate Ester 9a. Crystal data: Formula $C_{17}H_{22}N_2O_4S$; M_r 350.4, orthorhombic, space group *Fdd*2, *a* = 10.434 (4) Å, *b* = 22.528 (6) Å, *c* = 30.387 (7) Å; *V* 7140.9 Å^3, *Z* 16, D_c 1.303 g cm^{-3}, μ(Mo Kα) 1.62 cm^{-1}, λ(Mo Kα) 0.7107 Å, *F*(000) 2976 electrons.

Intensity data were collected on an Enraf-Nonius diffractometer in the range $1 < \theta < 25°$ using an ω–θ scan. The scan width and horizontal counter apertures employed were $(1.40 + 0.35 \tan \theta)°$ and $(2.40 + \tan \theta)$ mm, respectively. Data reduction and application of Lorentz, polarization, and decomposition (<3%) corrections were applied by using program SUSCAD.[15] Of the 1590 independent reflections collected, 1412 with $I > 2.5\sigma(I)$ were considered observed and used in the calculations.

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The structure was solved by direct methods using SHELX-76.[16] Hydrogen atoms were included at calculated sites (C–H, 0.97 Å). Full-matrix least-squares refinement of an overall scale factor, positional and thermal (anisotropic non-hydrogen, isotropic hydrogen) parameters converged (all shifts $< 0.02\sigma$ with R^* 0.033, R_w 0.039 and $w = 1.11/(\sigma^2(F_o) + 0.00037F_o^2)$. Maximum excursions in a final difference map were +0.20 e Å^{-3} and −0.20 e Å^{-3}. Scattering factors and anomalous dispersion terms used were those supplied in SHELX-76.[16] All calculations were carried out by using SHELX-76, and plots were drawn using ORTEP.[17]

Registry No. 1, 114563-22-3; 2, 114550-77-5; 3, 824-79-3; 4, 114550-78-6; 5, 114550-79-7; 6a, 114550-80-0; 6b, 114550-81-1; 7, 114550-82-2; 8, 114550-83-3; 9a, 114550-84-4; 9b, 114550-85-5; 10, 114550-86-6; 11, 114550-87-7; 14, 114550-88-8; 15, 114550-89-9; *p*-toluenesulfinyl chloride, 10439-23-3; acetic formic anhydride, 2258-42-6.

Supplementary Material Available: X-ray crystallographic data for compound **9a** including positional parameters, anisotropic thermal parameters, and complete listings of bond distances and angles (5 pages). Ordering information is given on any current masthead page.

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Reagents for the Stepwise Functionalization of Spermine

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Introduction

In recent years, there has been growing interest in the polyamines putrescine, spermidine, and spermine. These amines are widespread in nature and are implicated in the control of proliferative processes.[1-3] This latter role is largely responsible for the recent surge in the synthesis of polyamine derived compounds. We have, in recent years, synthesized a number of polyamine analogues which have demonstrated potent antineoplastic activity[4] and have proven useful in studies both of the polyamine cellular uptake apparatus[5] and polyamine metabolism.[6] Although not as widely distributed in nature as putrescine and spermidine, the tetraamine spermine forms the backbone of many alkaloids.[7] Further, there is much interest currently in the biological activity of synthetic analogues[8] of spermine, as spermine analogues have proven to be the most potent antineoplastics of all the polyamine derivatives.[4]

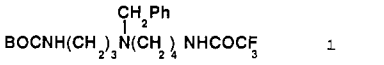
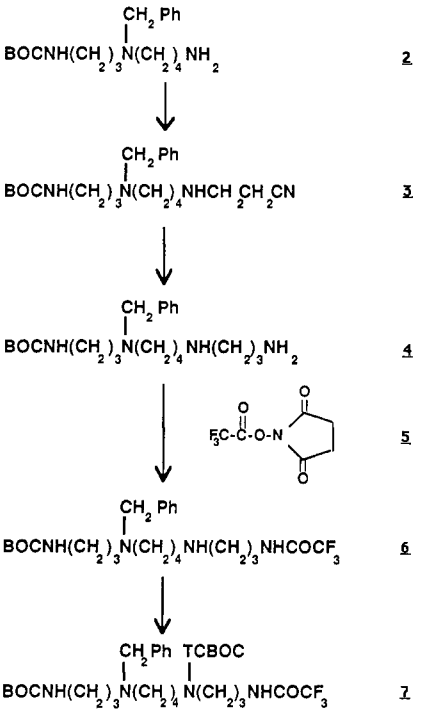


Figure 1.

Scheme I. Synthesis of Tetraprotected Spermine[a]



[a] BOC = $CO_2C(CH_3)_3$; TCBOC = $CO_2C(CH_3)_2CCl_3$.

Although several partially functionalized spermidine reagents have been developed,[9,10] only two such spermine reagents have been prepared.[11,12] Specifically, spermine has been selectively modified as the bis(hexahydropyrimidine) using formaldehyde[11] and as its N^1,N^{12}-bis(phthalimide) derivative.[12] However, these reagents do not allow differentiation between the two primary or two secondary nitrogens.

In a previous paper, we reported the synthesis of a triprotected spermidine reagent **1** (Figure 1), containing three independently removable, or orthogonal,[13] *N*-protecting groups.[10] This same reagent was utilized in the production of a spermine reagent with four independent amine-protecting groups. These protecting groups include benzyl, *tert*-butoxycarbonyl (BOC), trifluoroacetyl, and the

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