# The Reaction of N-Magnesium Derivatives of Pyrroles with N-Mesylchloromethylpyrroles: A Synthesis of Dipyrrylmethanes

Andrew D. Abell,*[†] Brent K. Nabbs,[†] and Alan R. Battersby[‡]

*Department of Chemistry, University of Canterbury, Christchurch, New Zealand, and University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.*

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Attachment of an alkyl- or arylsulfonyl group at the nitrogen atom of a pyrrole reduces the aromaticity and electron availability of the system. This is confirmed by the structure of an N-tosylated chloromethylpyrrole determined by X-ray crystallography. In agreement, N-mesylated chloromethylpyrroles are handleable materials which react smoothly with N-magnesium derivatives of pyrroles to provide a novel route for synthesis of dipyrrylmethanes. Several examples of this synthesis are described, including the construction of molecules carrying deuterium at the interpyrrolic methylene group.

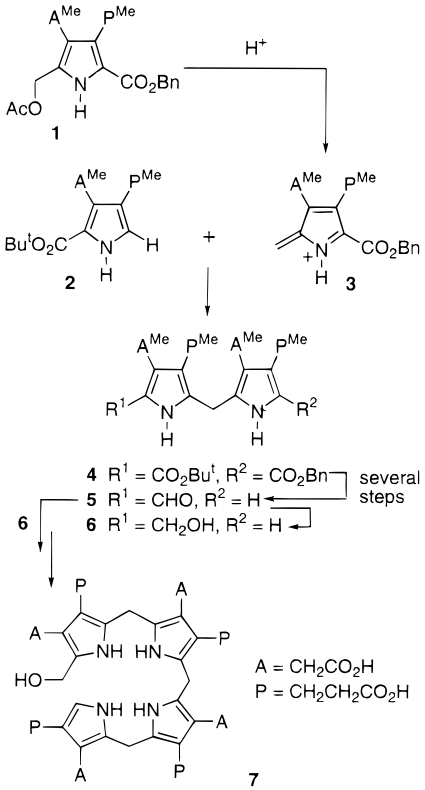
## Introduction

Dipyrrylmethanes, such as **5** and **6**, are commonly prepared by electrophilic attack by an azafulvene on an α-unsubstituted pyrrole, such as **2**, the former being generated from an acetoxymethylpyrrole (e.g., **1**), a hydroxymethylpyrrole, or a chloromethylpyrrole under acidic conditions.[1−5] For a typical sequence see Scheme 1.[2] This approach has also been successfully applied in the synthesis of bilanes, for example, hydroxymethylbilane **7**,[2,3] by coupling together two dipyrrylmethanes (Scheme 1). Alternatively, electrophilic attack by an azafulvene **9** at the substituted α position of a hydroxymethylpyrrole **8**, with subsequent elimination of formaldehyde, can give rise to a symmetrical dipyrrylmethane of the type **10** (Scheme 2).[1,6]

In this paper, we report a synthesis of dipyrrylmethanes based on the coupling of a ring-deactivated chloromethylpyrrole and the N-magnesium derivative of a pyrrole, prepared using methylmagnesium iodide. This method avoids the acidic conditions employed in the coupling procedures discussed above and directs the coupling to give an unsymmetrical dipyrrylmethane (see Schemes 7 and 8 for examples).

Simple N-magnesium derivatives of pyrroles have been reported to react with alkylating agents to produce a mixture of 2(α)- and 3(*β*)-alkylpyrroles, in which the 2 isomer usually predominates.[7−9] To the best of our knowledge, this work is the first report of a synthesis of dipyrrylmethanes based on the use of pyrrolylmagnesium salts. The reaction of an electrophile with a pyrrolyl anion prepared by treatment of the corresponding pyrrole with a base other than methylmagnesium iodide is reported to give products of reaction at nitrogen.[9,10] Such N-alkylation is avoided by using the N-magnesium derivatives.

**Scheme 1**




[†] University of Canterbury.
[‡] University Chemical Laboratory.

(1) (a) *The Chemistry of Pyrroles*; Jones, A. R., Bean, G. P., Eds.; Academic Press: London, 1977; pp 356−357. (b) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4.
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(9) Reference 1a; Chapter 4.
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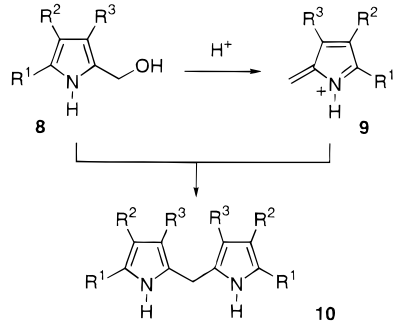
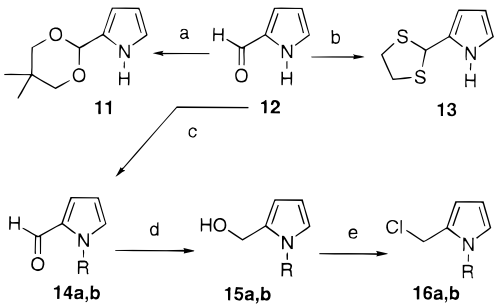
**Scheme 2**



**Scheme 3**[a]



**a** R = $SO_2Me$
**b** R = $SO_2C_6H_4Me$

[a]Key: (a) $CMe_2(CH_2OH)_2$, 1,2-DCE, reflux (ref 18); (b) $HSCH_2CH_2SH$, MeOH (ref 4); (c) NaH, THF, followed by $MeSO_2Cl$ or $MeC_6H_4SO_2Cl$; (d) $Zn(BH_4)_2$, diethyl ether, 0 °C; (e) $MeSO_2Cl$, $CH_2Cl_2$, $iPr_2NEt$, 0 °C.

## Results and Discussion

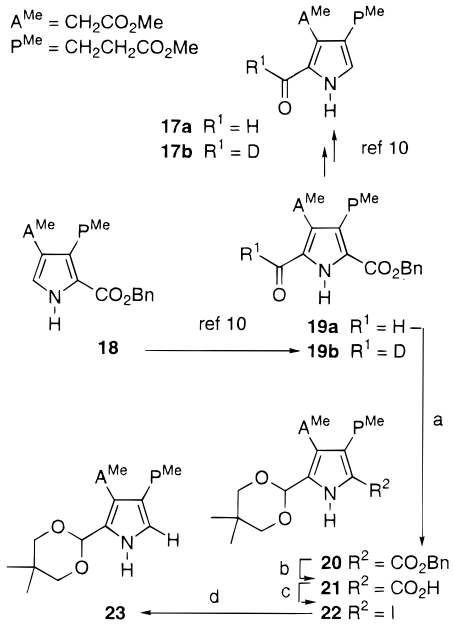
α-Formyldipyrrylmethanes of the type **5** (for specific examples see **32** and **34**) were selected for synthesis because the 2-formyl group provides a suitable site for elaboration into biologically important bilanes such as the type **7**, as shown in Scheme 1.[2,3]

**Synthesis of Starting Materials.** The key starting materials, **11** and **13**, were conveniently prepared from pyrrole-2-carboxaldehyde (**12**; Scheme 3). The N-methanesulfonyl-2-chloromethylpyrrole **16a** was also prepared from **12** by N-mesylation, reduction, and introduction of the chloro group (Scheme 3). Compound **16b** was similarly prepared from pyrrole-2-carboxaldehyde (Scheme 3).

The α-benzyloxycarbonyl-α-formylpyrroles **19a**[10] and **19b**[10] provided access to the acetal **23**, the chloromethylpyrrole **26a**, and its deuterated analogue **26b** (see Schemes 4 and 5). The deuterated analogue **19b** was itself prepared by Vilsmeier formylation of pyrrole **18**[10] using dimethylformamide-$d_6$ (Scheme 4). The acetal **23** was prepared from **19a** as illustrated in Scheme 4. In a key step, the benzyloxycarbonyl group of **19a** served to deactivate the pyrrole and hence facilitate the introduction of the acetal (conditions a in Scheme 4) to yield **20**. The benzyloxycarbonyl group was then removed by standard sequence **20** to **23**.

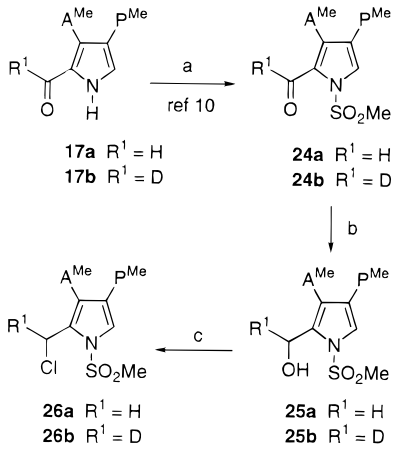
A similar debenzylation and decarboxylation sequence on separate samples of **19a** and **19b** was used[10] to prepare the α-formylpyrroles **17a** and **17b** (Scheme 4).[10] These aldehydes were then used in the preparation of **26a** and **26b** (Scheme 5). The synthetic sequence employed here was analogous to that used in the synthesis

**Scheme 4**[a]



[a]Key: (a) $CMe_2(CH_2OH)_2$, PTSA, 1,2-DCE, reflux; (b) $H_2$, Pd on C; (c) $NaHCO_3$, $H_2O$, KI, $I_2$, reflux; (d) $PtO_2$, MeOH, $H_2$.

**Scheme 5**[a]

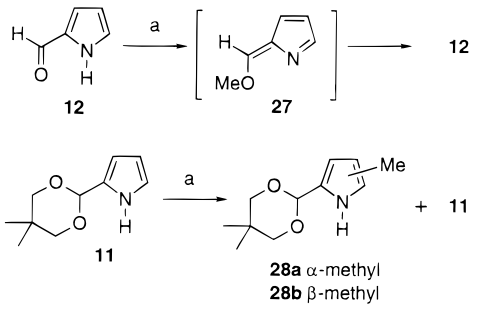


[a]Key: (a) NaH, THF, followed by $MeSO_2Cl$; (b) $NaBH_4$,$CH_2Cl_2$, MeOH, 0 °C; (c) $MeSO_2Cl$, $CH_2Cl_2$, $iPr_2NEt$, 0 °C.

of **16**, i.e., N-mesylation and reduction to give the hydroxymethylpyrroles **25a** and **25b**, which were converted into the chloromethyl analogues by reaction with methanesulfonyl (mesyl) chloride (Scheme 5). An *O*-mesyl derivative of **25a** is the probable intermediate for **26a** but was not isolated due to its rapid reaction with ionic chloride. However, the *O*-mesylate was detected by $^1H$ NMR spectroscopy in a reaction of **25a** with methanesulfonic anhydride in an NMR tube at −30 °C.

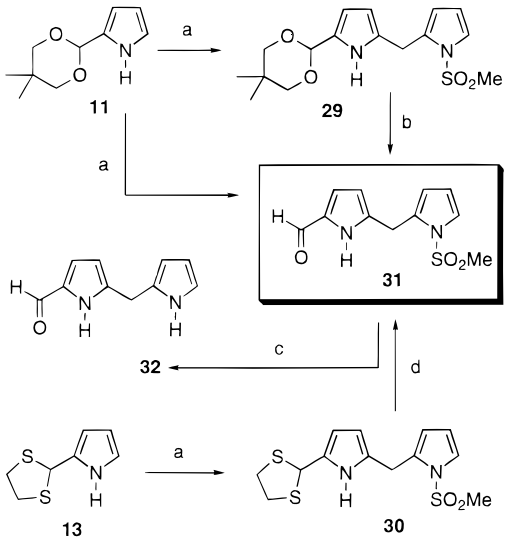
**Synthesis of Dipyrrylmethanes.** In an initial experiment, **12** was deprotonated with methylmagnesium iodide to give the corresponding N-magnesium salt which precipitated from the reaction mixture (Scheme 6). Excess methyl iodide was added, and after the mixture was stirred for 3 h, a homogeneous solution was obtained; however, workup gave recovered starting material **12**. We reasoned that methylation had taken place on the

**Scheme 6**[a]




[a]Key: (a) MeMgI, THF, -10 °C then MeI then $H_2O$.

**Scheme 7**[a]




[a]Key: (a) MeMgI, THF, -10 °C then **16a**, -10 °C to rt then either dilute aqueous acetic acid (**29**) or $NH_4Cl$ (**30**) or dilute aqueous HCl (**31**); (b) pyridinium tosylate, $H_2O$/acetone (1:1), reflux; (c) NaOH, MeOH, reflux; (d) $HgCl_2$, $CaCO_3$, MeCN/$H_2O$ (4:1), rt.

formyl oxygen, rather than on a carbon of the pyrrole, to give **27**. This had then hydrolyzed to **12** on workup (Scheme 6). In contrast, the treatment of **12** with sodium hydride and then with mesyl chloride gave **14a**, the product of reaction at the pyrrolic nitrogen (Scheme 3). The foregoing complication is not possible with the acetal **11**. Indeed, reaction of **11** with methylmagnesium iodide, followed by the addition of an excess of methyl iodide, gave an inseparable mixture of the α- and *β*-methylated pyrroles **28** and starting material **12** in a ratio of 2:5 (Scheme 6).

Next, we turned our attention to the coupling of **11** with the chloromethylpyrrole **16a** (Scheme 7) bearing an N-mesyl group to stabilize the system. Hydroxymethyl- and chloromethylpyrroles, lacking an N-mesyl or related group, are reactive and labile,[10] whereas **16a** and its synthetic precursor **15a** were stable compounds. The effect of an electron-withdrawing group (EWG) on the nitrogen of a chloromethylpyrrole was shown by determining the structure of the N-*p*-toluenesulfonyl (tosyl) derivative **16b** by X-ray analysis (see Figure 1 and later for a discussion).

The N-magnesium salt derived from **11** was reacted with the N-mesylchloromethylpyrrole **16a** (Scheme 7). Workup with acetic acid gave the doubly protected

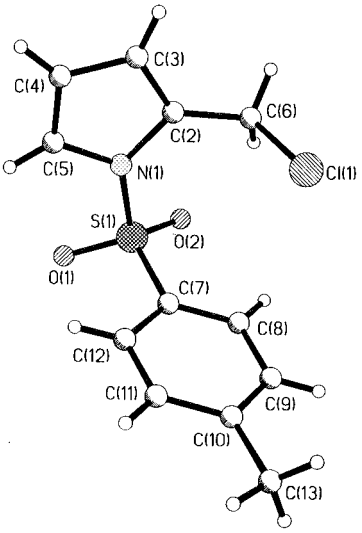



**Figure 1.** ORTEP diagram of **16b** showing the crystallographic numbering scheme.

dipyrrylmethane **29** in admixture with **12**. The coupling appeared to proceed exclusively at the α position, with none of the alternative *β*-coupled product being isolated. Treatment of **29** with pyridinium tosylate gave the dipyrrylmethane **31** (60% over both steps), which was fully characterized. A reaction of the N-magnesium salt of **11** with **16a**, followed by the addition of aqueous hydrochloric acid, gave **31** directly in 63% yield (Scheme 7) from which **32** was obtained in 85% yield by heating with aqueous sodium hydroxide. The dipyrrylmethane **32** has previously been prepared, in modest yield, by formylation of 2,2′-dipyrrylmethane, itself prepared by sodium borohydride reduction of 2,2′-dipyrryl ketone.[11]

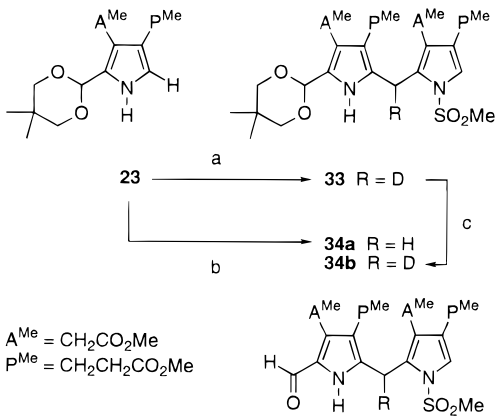
The thioacetal **13** was similarly treated with methylmagnesium iodide, and the product was coupled with **16a** to give the protected dipyrrylmethane **30** (Scheme 7). Again, no *β*-coupled product was evident by $^1$H NMR spectroscopy. Reaction of **30** with mercuric chloride then gave **31** in 40% overall yield (two steps).

This approach to dipyrrylmethanes was further extended with the preparation of **34a** and its deuterated analogue **34b** (Scheme 8). Compounds **34** are useful synthetic precursors to biologically important bilanes,[3,12] and the deuterium label in **34b** provides a potentially useful marker for biosynthetic studies. To this end, the pyrrole **23** was reacted first with methylmagnesium iodide and then with the N-mesylchloromethylpyrrole **26a**, followed by acidic hydrolysis to give **34a** in 75% yield (Scheme 8). An analogous sequence using the deuterated analogue **26b**, but worked up with acetic acid, gave the doubly protected dipyrrylmethane **33**, which was hydrolyzed with aqueous hydrochloric acid to the dipyrrylmethane **34b** in good yield.

**X-ray Structure Determination.** The structure of **16b** was determined to show the preferred conformation in the solid state and to measure the effect of an electron-withdrawing substituent (e.g., tosyl) on the nitrogen of the pyrrole ring. A search of the Cambridge Crystallographic Data Base revealed few reported structures of N-tosyl- and N-mesylpyrroles.[13]

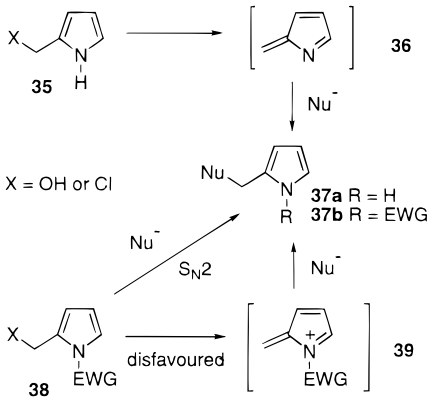
(11) Clezy P. S.; Liepa, A. J.; Webb, N. W. *Aust. J. Chem.* **1972**, *25*, 1991.
(12) Abell, A. D., unpublished data.

**Scheme 8**[a]




[a]Key: (a) MeMgI, THF, -10 °C then **26b**, -10 °C to rt then AcOH; (b) MeMgI, THF, -10 °C then **26a**, -10 °C to rt then dilute aqueous HCl; (c) dilute aqueous HCl.

**Scheme 9**




A perspective drawing of **16b**, with atomic labeling, is presented in Figure 1. The first point to note regarding this structure is that the N(1)−C(2) and N(1)−C(5) bond lengths are relatively long [1.412(3) and 1.392(3) Å, respectively] as compared to pyrroles without an electron-withdrawing substituent on nitrogen.[14] In addition, the C(2)−C(3) and C(4)−C(5) bond lengths are relatively short [1.353(4) and 1.342(4) Å, respectively]. These observations show that the aromaticity of the pyrrole ring is significantly reduced by introduction of an EWG (e.g., tosyl) on nitrogen. The result is that derivatives of the general type **38** (see Scheme 9 and **16b** for a specific example) are stable entities which are suitable for controlled reaction with a nucleophile (a pyrrolyl-N-magnesium salt in this study) to give **37b** (compounds **31** and **34** in this study). This is in agreement with our recent report[10] that an electron-withdrawing substituent on nitrogen of an hydroxymethyl- or chloromethylpyrrole of the general type **38** suppresses formation of a highly reactive azafulvenium species (e.g., **39** in Scheme 9). Related azafulvenes of the type **36** have been postulated to account for the increased reactivity of pyrroles of the type **35** with a nucleophile to give **37a** (Scheme 9).

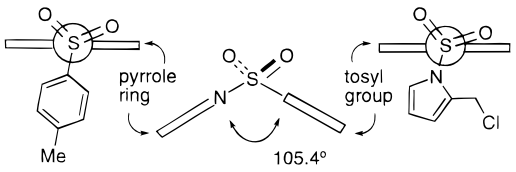



**Figure 2.** X-ray crystallographic conformation of **16b**.

The second point to note regarding the crystal structure of **16b** is that the tosyl group adopts the expected tetrahedral geometry about S(1) [O(2)−S(1)−O(1) 120.7°, N(1)−S(1)−C(7) 105.4°, N(1)−S(1)−O(1) 104.2°, N(1)−S(1)−O(2) 106.9°, C(7)−S(1)−O(1) 109.3°, and C(7)−S(1)−O(2) 109.2°]. The X-ray structures of related N-mesyl- and N-tosylpyrroles reveal that the sulfonyl group adopts a pseudostaggered orientation with respect to the pyrrole ring,[13c,14] where the *S*-methyl or aryl vector is almost perpendicular to the pyrrole ring plane. The structure of **16b** reported here displays a significant deviation from this staggered geometry as depicted in Figure 2, left-hand structure [C(7)−S(1)−N(1)−C(2) 78.9° and C(7)−S(1)−N(1)−C(5) −102.5°]. The equivalent conformation adopted by the *S*-pyrrole vector shows an even greater deviation from a staggered geometry as depicted in Figure 2, right-hand structure [C(12)−C(7)−S(1)−N(1) 71.8° and C(12)−C(7)−S(1)−N(1) −108.2°]. Finally, the sum of the angles at nitrogen [C(2)−N(1)−S(1) 129.1°, C(2)−N(1)−C(5) 107.7°, and C(5)−N(1)−S(1) 123.3°] is 360.1°, which is consistent with a planar nitrogen.

In summary, we have developed a short, convenient, and versatile synthetic route to dipyrrylmethanes which involves the coupling of a pyrrolyl-N-magnesium salt (derived from either an oxygen acetal or a thioacetal of pyrrole-2-carboxaldehyde) with a ring-deactivated chloromethylpyrrole. The coupling occurs at the α position of the pyrrolyl nucleus, with none of the alternative *β*-coupled products being isolated. The reaction sequence has also been used to incorporate a deuterium label into the dipyrrylmethane to build useful biological probes for the study of the biosynthesis of natural porphyrins and related pigments.[12] Finally, the influence of an N-tosyl group on the aromaticity of the pyrrole ring was examined by determination of the crystal structure of N-tosylchloromethylpyrrole **16b**.

## Experimental Section

**General Methods.** Melting points are uncorrected. NMR spectra were recorded at 250, 300, or 400 MHz ($^1$H) and at 63 or 75 MHz ($^{13}$C) in the specified solvent and at a probe temperature of 23 °C, unless otherwise specified. Light petroleum refers to a hydrocarbon fraction of bp 60−70 °C. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone, and all reactions were carried out under an atmosphere of nitrogen. Solutions were dried with $MgSO_4$ prior to evaporation under reduced pressure, unless otherwise specified.

**[1-(Methanesulfonyl)pyrrol-2-yl]methanol (15a).** A solution of **12** (200 mg, 2.10 mmol) in dry THF (2 mL) was added to a stirred suspension of sodium hydride (76 mg of an 80% suspension in oil washed twice with dry light petroleum, 2.52 mmol, 1.2 equiv) in THF (6 mL). The resulting mixture was stirred at room temperature for 15 min. A solution of mesyl chloride (236 μL, 2.94 mmol, 1.4 equiv) in dry THF (2 mL) was slowly added, and the mixture was stirred for 60 min at room temperature. Water (10 mL) was added, the THF was removed, and the resulting mixture was extracted with dichlo-

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(14) Chadwick, D. J. In *Pyrroles*; Jones, R. A., Ed.; John Wiley & Sons: New York, 1990; Vol. 48, Part 1, pp 22−30.

romethane (10 mL). The aqueous phase was re-extracted with dichloromethane (3 × 15 mL), and the combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (10 mL), water (10 mL), and brine (10 mL), dried, and evaporated to give **14a** as a pale yellow oil which solidified on standing: mp 41−42 °C (lit.[15] 43−44 °C).

This sample was dissolved in dry diethyl ether (10 mL) at 0 °C, zinc borohydride (15.0 mL of a 0.14 M solution in dry diethyl ether, 2.10 mmol) was added, and the mixture was stirred at 0 °C for 30 min. Water (2 mL) and glacial acetic acid (2 mL, 10% solution in water) were carefully added. The separated aqueous phase was re-extracted with dichloromethane (2 × 10 mL), and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL), dried, and evaporated. The resultant oil was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:1.6) to give **15a** as a pink solid (317 mg, 86% overall) which was further purified by sublimation under reduced pressure: mp 67−68 °C (lit.[10] 67−68 °C); IR ($CHCl_3$) 3587, 1178, 1142 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.30 (s, 3H), 4.77 (s, 2H), 6.25 (m, 1H), 6.31 (m, 1H), 7.16 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 42.8, 56.3, 111.1, 115.2, 123.1, 133.4. Anal. Calcd for $C_6H_9NO_3S$: C, 41.13; H, 5.18; N, 7.99. Found: C, 41.11; H, 5.24; N, 8.30.

**[1-(4-Methylphenylsulfonyl)pyrrol-2-yl]methanol (15b).** **12** (105 mg, 1.11 mmol) was treated with tosyl chloride (306 mg, 1.60 mmol, 1.4 equiv) as described for the preparation of **14a**. The resulting oil was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:2) to give **14b** (272 mg, 99%) as a pink solid: mp 92−94 °C (lit.[16] 94 °C).

A sample of **14b** (82 mg, 0.33 mmol) was reduced with zinc borohydride (2.35 mL of a 0.14 M solution in dry diethyl ether, 0.33 mmol) using the method described for **15a**. Purification of the product by flash chromatography on silica (ethyl acetate/light petroleum, 1:2) gave **15b** as a pale pink solid (75 mg, 91%): mp 94−96 °C (lit.[16] 97 °C); IR ($CHCl_3$) 3582, 1367, 1175, 1150 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.38 (s, 3H), 2.95 (br s, 1H), 4.59 (s, 2H), 6.21−6.25 (m, 2H), 7.25−7.29 (m, 3H), 7.70 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.4, 56.6, 111.7, 114.9, 123.3, 126.5, 130.0, 134.4, 135.8, 145.1; HRMS calcd for $C_{12}H_{13}NO_3S$ 251.0616, found 251.0615.

**2-Chloromethyl-1-methanesulfonylpyrrole (16a).** Mesyl chloride (46 $\mu$L, 0.58 mmol, 1.5 equiv) was added to an ice-cooled and stirred solution of **15a** (67 mg, 0.38 mmol) and *N*,*N*-diisopropylethylamine (100 $\mu$L, 0.58 mmol, 1.5 equiv) in dichloromethane (2 mL). After it was stirred for 20 min, the solution was warmed to room temperature over 30 min, then diluted with dichloromethane (10 mL), and washed with iced water (10 mL), cold aqueous hydrochloric acid (10%, 10 mL), and saturated aqueous sodium hydrogen carbonate (10 mL). The organic phase was dried and evaporated to give **16a** as an orange oil (65 mg, 87%), which was subsequently used without purification: IR ($CHCl_3$) 1369, 1180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.40 (s, 3H), 4.94 (s, 2H), 6.27 (m, 1H), 6.43 (m, 1H), 7.21 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 37.8, 43.2, 111.5, 117.1, 124.2, 130.0; HRMS calcd for $C_6H_8NO_2S$ (M − Cl) 158.0276, found 158.0276.

**2-Chloromethyl-1-(4-methylphenylsulfonyl)pyrrole (16b).** The *N*-tosylhydroxymethylpyrrole **15b** (70 mg, 0.28 mmol) was treated with mesyl chloride (33 $\mu$L, 0.42 mmol, 1.5 equiv) under the conditions used for the preparation of **16a**. The resulting oil was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:2) to give **16b** as a pale pink solid (62 mg, 83%). This was recrystallized from ethyl acetate/light petroleum to give pale yellow crystals: mp 84 °C; IR ($CHCl_3$) 1371, 1190, 1175, 1150, 1123 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.39 (s, 3H), 4.83 (s, 2H), 6.24 (m, 1H), 6.36 (m, 1H), 7.27−7.33 (m, 3H), 7.78 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.5, 37.2, 111.6, 116.9, 124.3, 127.1, 129.8, 130.3, 135.7, 145.2. Anal. Calcd for $C_{12}H_{12}ClNO_2S$: C, 53.43; H, 4.48; N, 5.19. Found: C, 53.88; H, 4.65; N, 5.00.

**Benzyl 5-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-methoxycarbonylethyl-4-methoxycarbonylmethylpyrrol-2-ylcarboxylate (20).** The formylpyrrole **19a**[17] (6 g), 2,2-dimethylpropane-1,3-diol (22.6 g), and *p*-toluenesulfonic acid (500 mg) were heated under reflux in 1,2-dichloroethane (20 mL) in a modified Dean−Stark apparatus in which the solvent passed through 4 Å sieves before returning to the flask. After 45 min, the solution was shaken with saturated aqueous sodium hydrogen carbonate (30 mL), and the organic layer was separated, washed with water (20 mL), dried, and evaporated. The residue was chromatographed on silica (diethyl ether/hexane, 0:1−1:1) to give a solid which was recrystallized from diethyl ether/hexane to give **20** as a colorless solid (6.38 g, 82%): mp 96−97 °C; IR ($CHCl_3$) 3440, 2955, 2850, 1725, 1695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.76 (s, 3H), 1.20 (s, 3H), 2.50 (m, 2H), 2.98 (m, 2H), 3.55 (s, 2H), 3.60 (s, 3H), 3.65 (s, 3H), 3.59 and 3.69 (ABq, $J$ = 11.3 Hz, 4H), 5.29 (s, 2H), 5.50 (s, 1H), 7.37 (m, 5H), 9.17 (br s, 1H). Anal. Calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60; N, 2.98. Found: C, 63.49; H, 6.53; N, 2.98.

**5-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-methoxycarbonylethyl-4-methoxycarbonylmethylpyrrol-2-ylmethanoic acid (21).** A solution of **20** (1.5 g, 3.2 mmol) in THF (40 mL), containing triethylamine (3 drops), was stirred with 10% Pd on C (175 mg), under an atmosphere of hydrogen, for 1.25 h. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. The residue was recrystallized from dichloromethane/hexane to give **21** (1.16 g, 96%): mp 130−133 °C; IR ($CHCl_3$) 3430, 3250, 2940, 1725, 1660 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.77 (s, 3H), 1.21 (s, 3H), 2.59 (t, $J$ = 8 Hz, 2H), 3.02 (t, $J$ = 8 Hz, 2H), 3.57 (s, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.60 and 3.70 (ABq, $J$ = 11 Hz, 4H), 5.52 (s, 1H), 9.30 (br s, 1H). Anal. Calcd for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57; N, 3.65. Found: C, 56.09; H, 6.73; N, 3.58.

**2-(5,5-Dimethyl-1,3-dioxan-2-yl)-4-methoxycarbonylethyl-3-methoxycarbonylmethylpyrrole (23).** To a stirred solution of **21** (1.0 g, 2.6 mmol) in methanol (30 mL) was added a solution of sodium hydrogen carbonate (570 mg) in water (7 mL). An aqueous solution of iodine and potassium iodide (5.5 mL, 0.5 M $I_2$ and 1.0 M KI) was then added over 30 min, and the resultant solution was stirred at room temperature for a further 1 h. Aqueous 10% sodium thiosulfate was added to remove the excess iodine, and the resultant mixture was partitioned between water (80 mL) and dichloromethane (50 mL). The organic layer was separated, and the aqueous phase was re-extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (30 mL), dried, and evaporated to give the iodopyrrole **22** as a pale yellow oil, which crystallized on standing (909 mg, 75%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.76 (s, 3H), 1.22 (s, 3H), 2.45 (m, 2H), 2.67 (m, 2H), 3.53 (s, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 3.59 and 3.67 (ABq, $J$ = 10.9 Hz, 4H), 5.48 (s, 1H), 8.38 (br s, 1H); HRMS calcd for $C_{17}H_{24}NO_6I$ 465.0648, found 465.0674.

Adams catalyst (50 mg) was stirred in methanol (15 mL) under hydrogen for 2 h. A solution of the preceding iodopyrrole **22** (820 mg, 1.76 mmol) in methanol (15 mL) containing triethylamine (400 $\mu$L) was added and the mixture was stirred under hydrogen for 15 h at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness. Water (20 mL) and dichloromethane (25 mL) were added, and the organic phase was separated, washed with water, dried, and evaporated to give **23** as an unstable pale yellow oil, which was used quickly without further purification (539 mg, 90%): IR ($CHCl_3$) 3430, 2940, 1720, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.75 (s, 3H), 1.21 (s, 3H), 2.53 (t, $J$ = 8 Hz, 2H), 2.72 (t, $J$ = 8 Hz, 2H), 3.50 (s, 2H), 3.64 (s, 6H), 3.61 and 3.67 (ABq, $J$ = 11 Hz, 4H), 5.50 (s, 1H), 6.46 (d, $J$ = 2.4 Hz, 1H), 8.24 (br s, 1H); HRMS calcd for $C_{17}H_{25}NO_6$ 339.1682, found 339.1676.

**[*formyl*-$^2$H]-2-Formyl-1-methanesulfonyl-4-methoxycarbonylethyl-3-methoxycarbonylmethylpyrrole (24b)**

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**and Its Unlabeled Analogue 24a.** The deuterated formylpyrrole **17b**[10] (500 mg, 1.96 mmol) was added portionwise to a stirred suspension of sodium hydride (170 mg, 60% dispersion in oil washed three times with hexane) in THF (30 mL). After 45 min of stirring at room temperature, mesyl chloride (500 $\mu$L, 6.46 mmol) was added, and the THF was evaporated. Water (150 mL) was added and shaken with dichloromethane (4 × 50 mL), the organic layer was washed with sodium hydrogen carbonate (50 mL, 10% aqueous) and water (50 mL), dried, and evaporated. Chromatography on silica using diethyl ether and recrystallization of the product from dichloromethane/diethyl ether/hexane gave the pyrrole **24b** (608 mg, 93%) as colorless needles: mp 62−64 °C; HRMS calcd for $C_{13}H_{16}DNO_7S$ 332.0792, found 332.0792.

The unlabeled formylpyrrole **24a** was similarly prepared from **17a**. Recrystallization from dichloromethane/diethyl ether/hexane gave **24a** as colorless needles: mp 64−65 °C; IR ($CHCl_3$) 3000, 2950, 1725, 1640 $cm^{-1}$; $\lambda_{max}$ 290, 258 nm; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.59 (t, $J$ = 7.5 Hz, 2H), 2.75 (t, $J$ = 7.5 Hz, 2H), 3.52 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 3.84 (s, 2H), 7.31 (s, 1H), 9.95 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 19.6, 30.2, 33.6, 43.5, 51.8, 52.4, 126.0, 126.4, 129.9, 133.1, 170.1, 172.6, 178.7. Anal. Calcd for $C_{13}H_{17}NO_7S$: C, 47.12; H, 5.17; N, 4.23. Found: C, 47.20; H, 5.45; N, 4.20.

**[*methylene*-$^2H_1$]-2-Hydroxymethyl-1-methanesulfonyl-4-methoxycarbonylethyl-3-methoxycarbonylmethylpyrrole (25b) and Its Unlabeled Analogue 25a.** The formylpyrrole **24a** (400 mg, 1.21 mmol) in dichloromethane (20 mL) and methanol (10 mL) was stirred at 0 °C. Sodium borohydride (70 mg) was added, and after a further 10 min at 0 °C, dichloromethane (75 mL) was added. The solution was washed with aqueous oxalic acid (15 mL, 5%) and water (15 mL), dried, and evaporated. Recrystallization of the residue from dichloromethane/diethyl ether/hexane gave **25a** (392 mg, 97%), as needles: mp 95−96.5 °C; IR ($CHCl_3$) 3350, 2910, 1720, 1350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.56 (m, 2H), 2.70 (m, 2H), 3.10 (t, $J$ = 6.6 Hz, 1H), 3.35 (s, 3H), 3.49 (s, 2H), 3.67 (s, 3H), 3.73 (s, 3H), 4.76 (d, $J$ = 6.6 Hz, 2H), 6.94 (s, 1H); $^{13}C$ NMR $\delta$ ($CDCl_3$, 63 MHz) 20.3, 29.7, 33.9, 43.1, 51.6, 52.6, 53.8, 119.2, 120.2, 124.5, 132.1, 172.5, 173.0. Anal. Calcd for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.74; N, 4.20. Found: C, 46.90; H, 5.85; N, 4.20.

Sodium borodeuteride reduction of **24b** as described above gave the deuterated hydroxymethylpyrroles **25b**. Its $^1H$ NMR spectrum was identical to that of **25a** except for $\delta$ 3.10 (d, $J$ = 6.6 Hz, 1H), 4.74 (d, $J$ = 6.6 Hz, 1H); HRMS calcd for $C_{13}H_{18}DNO_7S$ 334.0945, found 334.0948.

**5-(1,3-Dithiolan-2-yl)-1′-methanesulfonyl-2,2′-dipyrrylmethane (30).** Methylmagnesium iodide (0.55 mL of a 2.0 M solution in dry diethyl ether, 1.10 mmol) was added to a stirred solution of **13**[4] (200 mg, 1.17 mmol) in THF (3 mL) cooled in an ice−sodium chloride bath (−10 °C). This orange suspension was stirred at −10 °C for 30 min and then at room temperature for a further 30 min before being lowered to −10 °C in preparation for rapid addition of the chloromethylpyrrole **16a** (65 mg, 0.33 mmol) in dry THF (2 mL). The cooling bath was removed, and after the reaction mixture had been stirred at room temperature for 2 h, diethyl ether and excess saturated aqueous ammonium chloride were added. The organic phase was separated, washed with saturated aqueous ammonium chloride, dried, and evaporated. Flash chromatography on silica (ethyl acetate/light petroleum, 1:8) of the resulting oil gave recovered **13** (134 mg) and **30** which crystallized at 0 °C (55 mg, 50%) and was recrystallized from methanol: mp 108 °C; IR ($CHCl_3$) 3441, 3009, 2932, 1364, 1180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.57 (s, 3H), 3.36 (m, 4H), 4.11 (s, 2H), 5.73 (s, 1H), 5.81 (m, 1H), 6.04 (m, 1H), 6.17 (m, 1H), 6.21 (m, 1H), 7.08 (m, 1H), 8.52 (br s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 26.0, 39.8, 42.0, 49.2, 107.3, 108.5, 111.1, 113.6, 122.2, 127.7, 129.1, 132.5. Anal. Calcd for $C_{13}H_{16}N_2O_2S_3$: C, 47.54; H, 4.91; N, 8.53; S, 29.28. Found: C, 47.28; H, 4.88, N, 8.74; S, 29.37.

**5-Formyl-1′-methanesulfonyl-2,2′-dipyrrylmethane (31). Method A.** A solution of **30** (12 mg, 0.04 mmol) in 80% aqueous acetonitrile (1.5 mL) was added to a stirred mixture of mercury(II) chloride (20 mg, 0.07 mmol) and powdered calcium carbonate (11 mg, 0.11 mmol) in 80% aqueous acetonitrile (1.5 mL). The mixture was stirred at room temperature for 1 h, then dichloromethane (20 mL) was added, and the mixture was filtered. The organic phase was separated, and the aqueous phase was re-extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried, and evaporated. Flash chromatography of the residue on silica (ethyl acetate/light petroleum, 1:2) gave **31** (8 mg, 83%), which was recrystallized from methanol to give pale orange needles: mp 141−142 °C; IR ($CHCl_3$) 3431, 1651, 1367, 1191 $cm^{-1}$; $^1H$ NMR (acetone-$d_6$, 300 MHz) $\delta$ 3.00 (s, 3H), 4.15 (s, 2H), 5.93 (m, 1H), 6.00 (dd, $J$ = 3.9 and 2.4 Hz, 1H), 6.11 (m, 1H), 6.80 (dd, $J$ = 3.9 and 2.4 Hz, 1H), 7.00 (m, 1H), 9.31 (s, 1H), 10.86 (br s, 1H); $^{13}C$ NMR (acetone-$d_6$, 75 MHz) $\delta$ 25.9, 42.1, 110.4, 111.3, 113.9, 121.1, 122.5, 131.9, 133.1, 138.4, 178.3. Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.52; H, 4.86; N, 11.09.

**Method B.** Methylmagnesium iodide (0.52 mL of a 2.0 M solution in dry diethyl ether, 1.04 mmol) was added to a stirred solution of **11**[18] (201 mg, 1.11 mmol) in THF (3 mL) under the conditions used above for **13** to generate the *N*-magnesium derivative. This was reacted with the chloromethylpyrrole **16a** (61 mg, 0.32 mmol), again exactly as for the preparation of **30**. After 2 h of stirring, water (1 mL) was added followed by aqueous glacial acetic acid (10%, 5 mL), and the mixture was stirred for 10 min. Dichloromethane (10 mL) was added, and the separated organic phase, together with subsequent dichloromethane washings (2 × 10 mL) of the aqueous phase, was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried, and evaporated. Flash chromatography of the residue on silica (ethyl acetate/light petroleum, 1:6) gave **11** (104 mg) and an inseparable mixture of **12** and **29** (1:3 by $^1H$ NMR), which was used in the next step without further purification. **29** (as assigned from the mixture): $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.77 (s, 3H), 1.23 (s, 3H), 2.58 (s, 3H), 3.63 (m, 4H), 4.13 (s, 2H), 5.39 (s, 1H), 5.91 (m, 1H), 6.10 (m, 1H), 6.16 (m, 1H), 6.20 (m, 1H), 7.08 (m, 1H), 8.51 (br s, 1H).

A solution of the crude **29** (81 mg, 0.24 mmol) and PPTS (6.0 mg, 0.02 mmol, 0.1 equiv) in 50% aqueous acetone (4 mL) was stirred at reflux for 45 min. Dichloromethane (10 mL) was added, and the separated organic phase, together with subsequent dichloromethane washings (2 × 5 mL) of the aqueous phase, was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried, and evaporated. Purification of the residue by flash chromatography on silica (ethyl acetate/light petroleum, 2:3) gave **31** (48 mg, 60% overall for both steps) showing spectroscopic data identical to those above.

**Method C.** The *N*-magnesium salt of **11** was reacted with **16a** as described in method B. The preparation was worked up by the addition of water (1 mL) followed by dilute aqueous hydrochloric acid (5 mL). The mixture was then stirred for 10 min and extracted with dichloromethane as described in method B. Purification of the resulting oil by flash chromatography on silica (ethyl acetate/light petroleum, 1:2) gave **31** (24 mg, 63%) showing $^1H$ NMR data as above.

**5-Formyl-2,2′-dipyrrylmethane (32).** Aqueous sodium hydroxide (5 M, 1 mL) was added to a stirred solution of **31** (23 mg, 0.09 mmol) in methanol (4 mL), and the mixture was heated at reflux for 3 h. Saturated aqueous ammonium chloride was added, the mixture was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were washed with water (2 × 10 mL), dried, and evaporated. The resulting oil was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:2) to give **32** (13 mg, 85%) which was recrystallized from ethyl acetate/light petroleum: mp 118 °C (lit.[11] 120−121 °C); IR ($CHCl_3$) 3470, 3433, 3292, 3032, 3013, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.02 (s, 2H), 6.03 (m, 1H), 6.11 (m, 1H), 6.16 (dd, $J$ = 3.9 and 2.4 Hz, 1H), 6.67 (m, 1H), 6.95 (dd, $J$ = 3.9 and 2.4 Hz, 1H), 9.18 (br

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s, 1H), 9.30 (s, 1H), 11.10 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 26.5, 106.6, 108.3, 110.6, 117.6, 124.6, 127.4, 132.0, 142.2, 178.7; HRMS calcd for $C_{10}H_{10}N_2O$ 174.0793, found 174.0796.

**3,4′-Dimethoxycarbonylethyl-3′,4-dimethoxycarbonylmethyl-5-formyl-1′-methanesulfonyl-2,2′-dipyrrylmethane (34a) and Its [$^2H_1$]-Analogue 34b.** Mesyl chloride (40 $\mu$L, 1.5 equiv) was added to an ice-cooled solution of **25a** (110 mg) in dichloromethane (2 mL) containing *N*,*N*-diisopropylethylamine (92 $\mu$L, 1.5 equiv). Stirring was continued at 0 °C for 20 min and for a further 30 min at room temperature. The solution was diluted with dichloromethane (10 mL) and washed successively with ice water, cold dilute aqueous hydrochloric acid, and saturated aqueous sodium hydrogen carbonate. The organic phase was dried and evaporated, to give the chloromethylpyrrole **26a** (91 mg, 86%): $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 2.56 (m, 2H), 2.70 (m, 2H), 3.32 (s, 3H), 3.49 (s, 2H), 3.67 (s, 3H), 3.69 (s, 3H), 4.97 (s, 2H), 6.98 (s, 1H); $^{13}$C NMR ($CDCl_3$, 63 MHz) $\delta$ 20.3, 29.9, 33.6, 35.4, 43.2, 51.7, 52.3, 120.4, 122.5, 125.6, 127.7, 172.9, 170.5; *m*/*z* (FD) 353 ($M^+ - {}^{37}$Cl), 351 ($M^+ - {}^{35}$Cl).

Methylmagnesium iodide (250 $\mu$L, 1.2 M in diethyl ether, 1.2 equiv) was added to a stirred solution of the pyrrole **23** (100 mg, 0.30 mmol) in THF (4 mL), and the resultant heterogeneous mixture was stirred at room temperature under argon for 1 h. The above chloromethylpyrrole **26a** (in 1.5 mL of THF) was added dropwise, and the mixture was stirred at room temperature for 20 h. Water (1 mL) was added followed by dilute aqueous hydrochloric acid (5 mL), and the mixture was stirred for 10 min. Dichloromethane (20 mL) was added, and the organic phase, together with subsequent dichloromethane washings (2 × 10 mL) of the aqueous phase, was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL), dried, and evaporated. Preparative TLC (ethyl acetate/diethyl ether, 1:2) gave the formylpyrrole **17a** (13 mg, 15%) and the *N*-mesyldipyrrylmethane **34a** as a pale yellow oil (141 mg, 75% based on **23**): IR (film) 2950, 1730, 1640 cm$^{-1}$; $\lambda_{max}$ 306 nm; $^1$H NMR ($CD_2Cl_2$, 400 MHz) $\delta$ 2.41 (s, 3H), 2.52 (m, 2H), 2.57 (m, 2H), 2.69 (m, 2H), 2.87 (m, 2H), 3.57 (s, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 3.81 (s, 3H), 3.77 (s, 2H), 4.15 (s, 2H), 6.91 (s, 1H), 9.51 (s, 1H), 10.10 (br s, 1H); HRMS calcd for $C_{25}H_{32}N_2O_{11}S$ 568.1727, found 568.1731.

The above sequence was repeated using the deuterated hydroxymethylpyrrole **25b** in place of **25a**. The resulting labeled chloromethylpyrrole **26b** was then reacted with the *N*-magnesium salt of **23**, prepared as described above, for 48 h. The addition of excess water and acetic acid followed by preparative TLC (ethyl acetate/diethyl ether, 1:2) gave recovered starting material **23** (26%) and the labeled dipyrrylmethane **33b** as a labile pale yellow oil (70%): $^1$H NMR ($CD_2Cl_2$, 400 MHz) $\delta$ 1.24 (s, 3H), 1.37 (s, 3H), 2.33 (s, 3H), 2.43 (m, 2H), 2.56 (m, 2H), 2.67 (m, 2H), 2.78 (m, 2H), 3.47 (s, 2H), 3.55 (s, 2H), 3.62 (s, 3H), 3.64 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 4.04 (s, 1H), 5.34 (s, 1H), 6.90 (s, 1H), 9.36 (br s, 1H); $^{13}$C NMR ($CD_2Cl_2$, 63 MHz) $\delta$ 19.5, 20.8, 21.5 (t, CHD), 22.0, 23.0, 29.9, 30.1, 33.8, 35.7, 41.7, 51.8, 51.9, 52.0, 52.5, 71.7, 77.8, 96.3, 113.1, 118.9, 119.5, 123.8, 124.7, 126.4, 130.2, 172.9, 173.0, 173.8, 173.9.

The preceding dipyrrylmethane **33** in dichloromethane was shaken with dilute aqueous hydrochloric acid for 10 min. The organic phase was separated, dried, and evaporated to give the labeled dipyrrylmethane **34b** as an oil: $^1$H NMR ($CD_2Cl_2$, 400 MHz) $\delta$ 4.13 (s, 1H), otherwise identical to the spectrum of **34a**; $^{13}$C NMR ($CDCl_3$, 63 MHz) $\delta$ 18.7, 20.4, 21.4 (t, CHD), 29.5, 30.8, 33.4, 34.7, 41.9, 51.6, 51.8, 52.2, 53.1, 119.1, 119.9, 122.7, 124.8, 128.0, 129.1, 133.6, 171.3, 172.9, 173.0, 173.2, 177.3.

**Crystallographic Structure Determination for Compound 16b by X-ray Analysis.** $C_{12}H_{12}ClNO_2S$: MW 269.74, mp 84 °C, crystal dimensions 1.02 × 0.32 × 0.25 mm, monoclinic, $a$ = 7.645(2) Å, $b$ = 15.689(5) Å, $c$ = 10.543(3) Å, $\beta$ = 105.20(2)°, $V$ = 1220.3(6) Å$^3$, space group $P2_1/n$, $Z$ = 4, $F(000)$ = 560, $D_{calc}$ = 1.468 mg/m$^3$, absorption coefficient 0.472 mm$^{-1}$, $\theta$ range for data collection 2.39−22.50, index ranges $-8 \le h \le 0$, $0 \le k \le 16$, $-10 \le l \le 11$, maximum and minimum transmissions 0.3008 and 0.3345, data/restraints/parameters 1593/0/155, goodness of fit on $F^2$ = 1.097, final $R$ indices [$I > 2\sigma(I)$] $R_1$ = 0.0330 and $wR_2$ = 0.0849, $R$ indices (all data) $R_1$ = 0.0378 and $wR_2$ = 0.0883, and largest difference peak and hole 0.284 and −0.207 eÅ$^{-3}$.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 19 reflections with 4.25° ≤ 2$\theta$ ≤ 16.5° from a Siemens four-circle diffractometer. A unique data set was measured at 293(2) K within a $2\theta_{max}$ = 45° limit ($\omega$ scans). Of the 1611 reflections obtained, 1593 were unique ($R_{int}$ = 0.0051) and were used in the full-matrix least-squares refinement.[19] The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed only 3.97% decay. The structure was solved by direct methods.[20] Hydrogen atoms were fixed in idealized positions. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton.[21] Full details of the X-ray structural determination of **16b** have been deposited with the Cambridge Crystallographic Data Centre (CCDC).

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**Supporting Information Available:** Tables of crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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