g, 2.34 mmol), *N*-(2,5-di-*tert*-butylphenyl)maleimide (1.0 g, 3.5 mmol), and dry NaI (2.1 g, 14 mmol) were reacted in DMF, and the product was worked up in a similar manner as described for **13a**.[9] The crude product was first chromatographed (silica gel, $CHCl_3$) to give 0.82 g of a white solid; 0.67 g of the white solid was recrystallized for EtOH (40 mL), giving 0.41 g (1.05 mmol, 61% yield) as rods. The isolated product is believed to be the endo adduct. ^1H NMR ($CDCl_3$): δ 7.35 (d, J = 8.5 Hz, 1 H), 7.24–7.19 (m, 6 H), 5.31 (d, J = 2.2 Hz, 1 H), 3.47 (m, 2 H), 3.33 (d, J = 14.2 Hz, 2 H), 2.94 (dm, J = 14.2 Hz, 2 H), 1.23 (s, 18 H), 1.05 (s, 18 H). ^1H NMR (C_6D_6): δ 7.27 (d, J = 8.5 Hz, 1 H), 7.14–6.96 (m, 6 H), 5.66 (d, J = 2.2 Hz, 1 H), 3.11 (d, J = 14.1 Hz, 2 H), 2.70 (m, 2 H), 2.29 (dm, J = 13.9 Hz, 2 H), 1.30 (s, 18 H), 1.03 (s, 18 H). ^{13}C NMR ($CDCl_3$): δ 179.82, 150.12, 144.46, 135.44, 130.20, 128.04, 127.85, 127.57, 127.36, 126.51, 40.57, 35.07, 33.97, 31.56, 30.97, 30.17. MS (EI, 70 eV), m/e (relative abundance) 374 (100), 389 (52), 318 (35), 128 (24). Molecular ion calcd for $C_{26}H_{31}NO_2$, $M^{\cdot+}$ 389.2354, found 389.2364.

***N*,*N*′-Bis(4-*tert*-butylphenyl)-9,10-dioxo-2,3,6,7-anthracenetetracarboxylic 2,3:6,7-Diimide (9a).** The CAN oxidation of **6a** to **9a** follows the related procedure for the synthesis of **8**. The reaction was performed in the dark, and solubility limitations required the use of a $CHCl_3$–CH_3CN solvent mixture. During the course of the reaction, the bright yellow color of the reaction mixture turned to a pale yellow color. After 3 days, the solvent was removed under reduced pressure. The product mixture was suspended in H_2O and sonicated for several minutes, and a yellow solid was collected by filtration. The crude product was recrystallized from $CHCl_3$ to give the desired product in 43% yield. ^1H NMR ($CDCl_3$ (0.5 mL) and TFA-*d* (2 drops)): δ 8.99 (s, 4 H), 7.58 (d, J = 8.7 Hz, 4 H), 7.35 (d, J = 8.5 Hz, 4 H), 1.37 (s, 18 H). IR (KBr, cm^{-1}): 2963, 1783, 1724, 1679, 1618, 1518, 1388, 1315, 1209, 1127, 713. HRMS (FAB; H_2SO_4 matrix) calcd for $C_{34}H_{31}N_2O_6$ ($M + H^+$) 611.2182, found 611.2122. UV–vis (CH_2Cl_2) λ_{nm} (log ϵ): 340 (3.79), 276 (4.59), 240 (4.80).

***N*,*N*′-Bis(2,5-di-*tert*-butylphenyl)-9,10-dioxo-2,3,6,7-anthracenetetracarboxylic 2,3:6,7-Diimide (9b).** The CAN oxidation of **6b** to **9b** also follows the related procedure for the synthesis of **8**. The crude product was purified by heating in CCl_4 and allowed to cool, and the pale yellow solid was collected by filtration, 31% yield. R_f = 0.59 (CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 8.98 (s, 4 H), 7.58 (d, J = 8.6 Hz, 2 H), 7.49 (dd, J_1 = 8.6 Hz, J_2 = 2.1 Hz, 2 H), 6.96 (d, J = 2.1 Hz, 2 H), 1.31 (s, 18 H), 1.30 (s, 18 H). IR (KBr, cm^{-1}): 2963, 1786, 1719, 1685, 1675, 1309, 719. HRMS (FAB, MNBA matrix) calcd for $C_{46}h_{46}N_2O_6$ ($M^{\cdot+}$) 722.3356, found 722.3288.

1,4,8,11-Tetramethoxy-2,3,9,10-tetramethyl-6,13-pentacenedione. 3,6-Dimethoxy-4,5-dimethylcyclobuten-1-ol (34 mg, 0.16 mmol)[4,5] was placed in a 25-mL round-bottom flask containing benzoquinone (8.6 mg, 0.08 mmol) and toluene (15 mL). The flask was equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The solution was purged with N_2 and heated to reflux for 4 days. The solution was cooled overnight in a refrigerator and the bright yellow precipitate that formed was collected by filtration, washed several times with toluene, and dried in vacuo. The pentacene quinone (19 mg, 0.04 mmol, 25% yield) can be purified in small quantities by chromatography over silica gel with $CHCl_3$ eluent. ^1H NMR ($CDCl_3$): δ 9.14 (s, 4 H), 3.94 (s, 12 H), 2.44 (s, 12 H). IR (KBr, cm^{-1}): 1674, 1606, 1453, 1424, 1322, 1272. HRMS (EI, 70 eV) calcd for $C_{30}H_{28}O_6$ 484.1878, found 484.1880.

2,3,9,10-Tetramethyl-1,4,6,8,11,13-pentacenehexone (11). **11** was prepared by the CAN oxidation of 1,4,8,11-tetramethoxy-2,3,9,10-tetramethyl-6,13-pentacenedione in a similar procedure as in the formation of **8**. The reaction mixture was stirred for 30 min, and the solution was then added to water and filtered over a small frit. A pale yellow solid was collected and washed with water. The product was dried in vacuo. **11** was obtained in 89% yield and found to be only sparingly soluble in organic solvents. ^1H NMR ($CDCl_3$): δ 9.07 (s, 4 H), 2.27 (s, 12 H). HRMS (EI, 70 eV) calcd for $C_{26}H_{16}O_6$, $M^{\cdot+}$ 424.0958, found 424.0963.

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A [4 + 1] Annulation Approach to Nitrogen Heterocycles Using 2,3-Bis(phenylsulfonyl)-1,3-butadiene and Primary Amines

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The reaction of amines with 2,3-bis(phenylsulfonyl)-1,3-butadiene affords pyrrolidines in high yield. The formation of the nitrogen heterocycle involves initial conjugate addition and this is followed by a 5-*endo*-*trig* cyclization of the resulting amine onto the adjacent vinyl sulfone. Treatment of these pyrrolidines with sodium methoxide induces elimination of benzenesulfinic acid, producing the 3-pyrroline ring system. Heating a sample of the resulting 3-pyrroline in the presence of DDQ smoothly affords 3-(phenylsulfonyl)-substituted pyrroles. Treatment of these pyrroles with *tert*-butyllithium readily generates 2-lithiated pyrroles, which can be quenched with electrophiles such as methyl iodide, benzaldehyde, benzoyl chloride, dimethylformamide, and methyl acrylate. In all cases high yields of *N*-alkyl-2,3-disubstituted-pyrroles were obtained. The ability of these 3-(phenylsulfonyl)-substituted pyrroles to undergo lithiation and subsequent alkylation in high yield was further illustrated by the synthesis of the pyrrolizidine–pyrrole system. Finally, the reaction of 2,3-bis(phenylsulfonyl) diene with *N*,*N*′-dimethylethylenediamine was investigated. The reaction proceeds by two competitive pathways leading to both six- and eight-membered rings under kinetic conditions. Upon stirring for longer periods of time, the eight-membered ring undergoes a ring contraction to give the thermodynamically more stable piperazine system.

The occurrence of five-membered nitrogen heterocycles in many natural products continues to contribute to the development of new synthetic methodologies.[1-3] The preparation of pyrrolidines has received extensive attention from synthetic chemists in recent years, in part due to the

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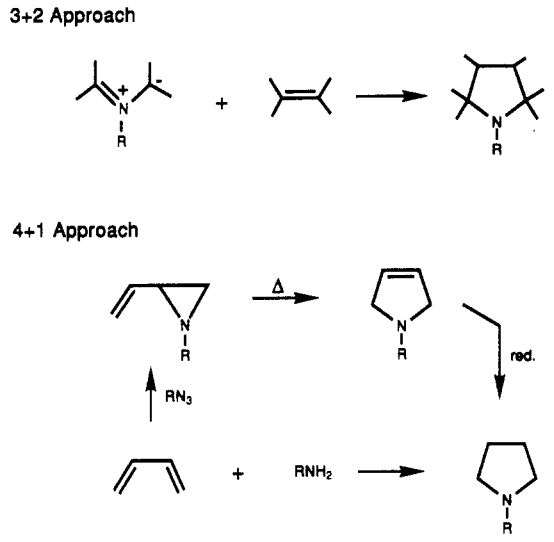
interesting biological activities exhibited by several polysubstituted pyrrolidines.[4-7] Particularly useful general approaches to these five-ring heterocycles are the intramolecular ene strategy developed by Oppolzer,[8] the electrophilic promoted cyclization of unsaturated amine derivatives,[9] the tandem cationic aza-Cope–Mannich cyclization synthesis of Overman,[10] the transition-metal-catalyzed cyclization of unsaturated amines,[11] and the 1,3-dipolar cycloaddition route.[12] The elaboration of pyrrolidines using the [3 + 2] bond disconnection strategy has



attracted a great deal of attention due to its brevity and efficiency.[13] The cycloaddition reaction has been used with a wide range of azomethine ylide precursors[14] as well as with 2-azaallyl anions.[15] An alternative route to simple pyrrolizidine alkaloids that has been realized by both Hudlicky[16] and Pearson[17] is one that uses the intramolecular cyclization of azido dienes. In analogy with similar ring closures of carbenoids,[18] these cyclizations combined with the subsequent thermolysis of vinylaziridines, provide a reliable pyrrolidine annulation technology representing a clever [4 + 1] union of a nitrene with a diene. In connection with our ongoing synthetic program to develop new methods for pyrrolidine synthesis,[19] we thought it worthwhile to examine a route to 3-pyrrolines that involves a different [4 + 1] annulation strategy. The general approach involves the formal 1,4-addition of a primary amine across an activated 1,3-butadiene.[20] Successful application of this reaction to the synthesis of pyrrolidines where the product carries further functionality are rare. In this paper we report on the reaction of 2,3-bis(phenylsulfonyl)-1,3-butadiene (1) with various amines as a method for synthesizing these heterocycles in excellent yield.

Results and Discussion

Conjugated dienes with electron-donating or electron-withdrawing substituents within the diene unit have attracted considerable attention during recent years.[21-24] Sulfur-substituted dienes, in particular, have been widely used in the Diels–Alder reaction.[25] The sulfur atom not only increases the reactivity of the diene but also adds control to the regioselectivity of the cycloaddition. Furthermore, the richness of synthetic transformations involving sulfur functionality make the [4 + 2] adducts very useful in organic synthesis.[25] Recently, Bäckvall and coworkers have shown that the higher oxidized phenylsulfonyl-substituted dienes are extremely versatile synthons that can be used for Diels–Alder chemistry.[26] In connection with our recently reported use of unsaturated sulfones in cycloaddition chemistry,[27] we thought it would be worthwhile to study the reaction of 2,3-bis(phenylsulfonyl)-1,3-butadiene (1)[28] with various primary amines as a method for synthesizing 3-pyrrolines. While the re-

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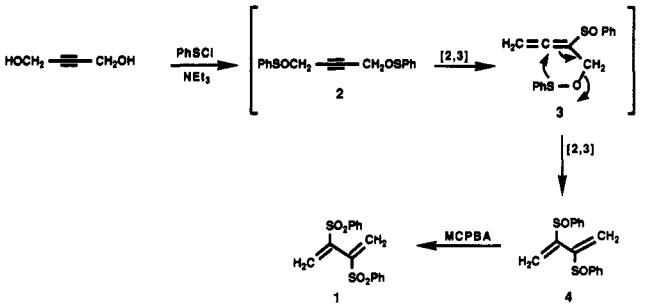
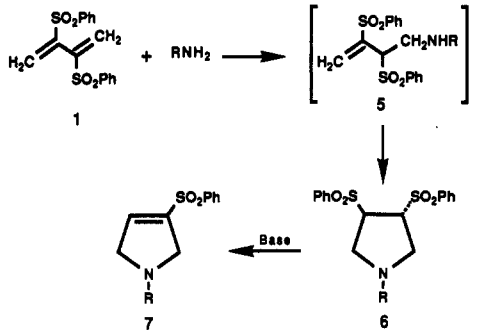
actions of vinyl sulfones with carbon nucleophiles have been well investigated,[29] much less attention has been paid to the nucleophilic addition of amines to phenylsulfonyl-activated dienes. It seemed to us that the 2,3-diactivated diene 1 should be highly reactive toward nucleophilic addition because of its markedly lowered LUMO energy level compared to 1,3-butadiene.[30]

In spite of its simplicity and its obvious potential as an activated diene, 2,3-bis(phenylsulfonyl)-1,3-butadiene (1) has not been extensively utilized for organic synthesis. This reagent was prepared by a modification of the procedure of Okamura and Jeganathan in multigram quantities.[28] Treatment of 2-butyne-1,4-diol with benzenesulfenyl chloride produced the disulfenate ester 2 as a



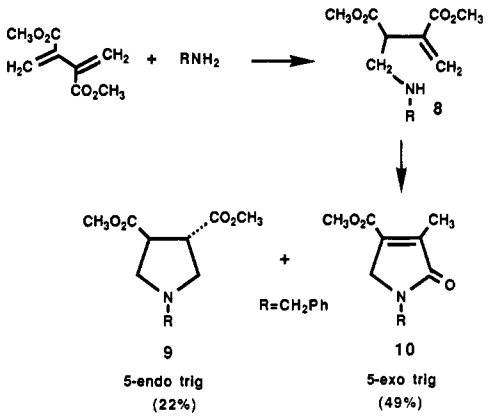
transient species, which rapidly undergoes a series of 2,3-sigmatropic rearrangements to give disulfoxide 4. This material could be readily oxidized to 1 with MCPBA in excellent yield.

We have studied the reaction of 1 with various primary amines using a 1:1 methylene chloride–methanol mixture and found that pyrrolidine 6 could be isolated as the exclusive product. This ring system is somewhat unstable and was readily converted to the corresponding 3-pyrroline 7 by treatment with sodium methoxide. Further heating



entry	R	% yield
a	CH_2Ph	100
b	*n*-Bu	93
c	$(CH_2)_3OH$	92
d	$(CH_2)_2OH$	98
e	$CH_2C_6H_4$(*o*-OMe)	90
f	$(CH_2)_2OMe$	93

of 7 in the presence of DDQ afforded the expected pyrrole 11 in high yield. The formation of the five-membered nitrogen heterocycle proceeds through a two-step sequence. The first step involves initial conjugate addition and this is followed by a 5-*endo-trig* cyclization of the amino group of the initial adduct onto the adjacent vinyl sulfone. The facility of the 5-*endo-trig* cyclization under such mild conditions (25 °C) is particularly surprising in that it is generally considered a disfavored process.[31] Although an examination of molecular models shows that while there is a severe angle strain in the endocyclic cyclization of 5 to 6, little else can happen to the initially formed adduct 5. It should be noted that amine additions to 2,3-dicarbomethoxy-1,3-butadiene also proceeds in part via a 5-*endo-trig* cyclization (22%) even though the alternative 5-exo-trig process is available.[32]



Heteroatom-facilitated ortho lithiation is a very popular and powerful technique that can lead to regiospecific attachment of an electrophile ortho to a heteroatom-containing substituent on an aromatic ring.[33] Recently some significant and creative applications of this methodology to the synthesis of several different classes of pyrroles have been reported.[34] We reasoned that under suitable conditions the sulfonyl group might stabilize an ortho lithium atom, thus facilitating anion formation at the 2-position of the pyrrole ring.[35,36] Indeed, we found that adding 1.2 equiv of *tert*-butyllithium in pentane to 1.0 equiv of pyrrole 11 in tetrahydrofuran readily generated the desired carbanion. Quenching the *N*-butyl-lithiated pyrrole 12 with such electrophiles as methyl iodide, benzaldehyde, benzoyl chloride, dimethylformamide, and methyl methacrylate led to 60–98% yields of isolated 2,3-disubstituted pyrroles 13. One of the reasons why the sulfonyl group is attracting considerable attention as a useful functionality in organic synthesis is that it can behave as a temporary transformer of chemical reactivity in the preparation of eventually sulfur-free compounds.[37] Indeed, the above sequence of reactions allows for the synthesis of 2-substituted pyrroles since the phenylsulfonyl group can be readily removed by reductive methods.[38]

The ability of these 3-(phenylsulfonyl)pyrroles to undergo lithiation and subsequent alkylation in high yield suggested a facile synthesis of the pyrrolizidine–pyrrole ring system. The process we envisioned and its successful

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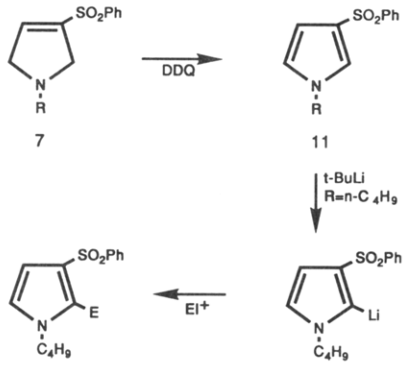
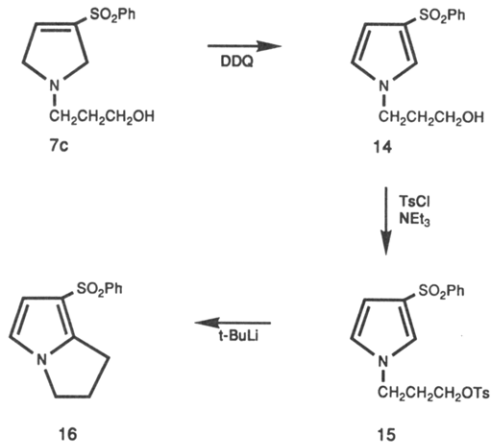
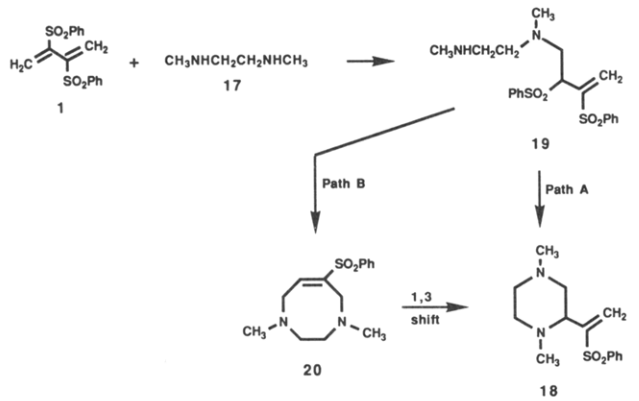


entry	El	E
a	MeI	Me
b	PhCHO	CH(OH)Ph
c	PhCOCl	COPh
d	Me_2NCHO	CHO
e	Methyl Methacrylate	$CO(CH_3)C=CH_2$

implementation is outlined below. The sequence began by treating 3-pyrroline **7c** with DDQ. The resulting pyrrole was converted to the corresponding tosylate, which was subjected to metalation using *tert*-butyllithium to give **16** in 95% yield.



We have also examined the reaction of bis(phenylsulfonyl) diene **1** with *N,N'*-dimethylethylenediamine (**17**) and found that the reaction proceeded smoothly, giving piperazine **18** in 92% isolated yield. Two fundamentally different pathways seem possible to account for the formation of **18**. One path involves conjugate addition to give **19** followed by SN_2 displacement of the sulfonyl group by the neighboring secondary amine (path A). The second



possibility (path B) proceeds by double conjugate addition followed by elimination and then a 1,3-ring contraction reaction. In order to differentiate between the two pathways, we followed the reaction as a function of time by NMR spectroscopy. Interestingly, the resulting data indicate that both pathways are operative. Immediately after mixing (<5 min), the NMR spectrum indicated total consumption of starting material and a 3:2 mixture of diazocyclooctene **20** and piperazine **18**. Structure **20** was assigned on the basis of its characteristic NMR spectrum [($CDCl_3$, 90 MHz) δ 2.25 (s, 3 H), 2.30–2.85 (m, 4 H), 2.45 (s, 3 H), 3.40 (d, 2 H, J = 6.0 Hz), 3.85 (s, 2 H), 7.05 (t, 1 H, J = 6.0 Hz), and 7.25–7.85 (m, 5 H)]. The reaction was further monitored over a period of time and diazacyclooctene **20** was found to slowly rearrange to piperazine **18**. The reaction required an additional 14 to go to completion at 25 °C. That the initial product distribution consists of a 3:2 mixture of structural isomers suggests that the reaction proceeds by both paths A and B. One can infer from the data that piperazine **18** is the thermodynamically more favored product.

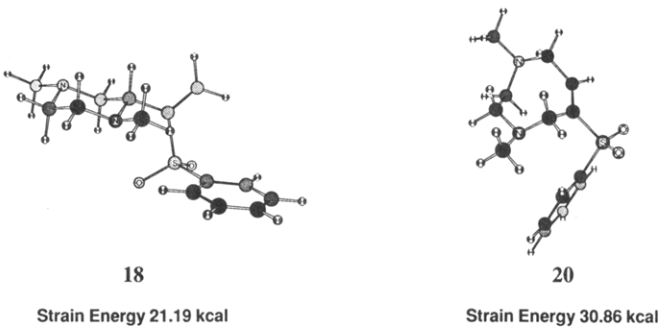


Figure 1. Three-dimensional representations of the lowest energy conformations of piperazine **18** and diazacyclooctene **20**.

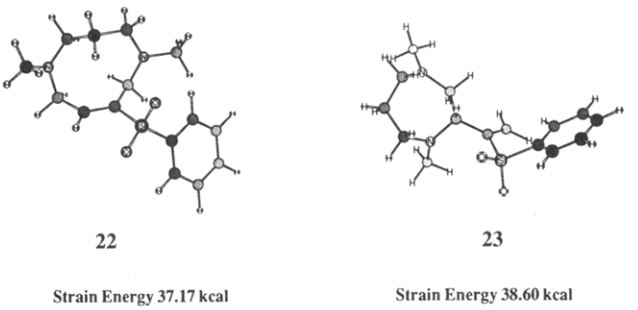


Figure 2. Three-dimensional representations of the lowest energy conformations of diazaclononene **22** and 1,4-diazepine **23**.

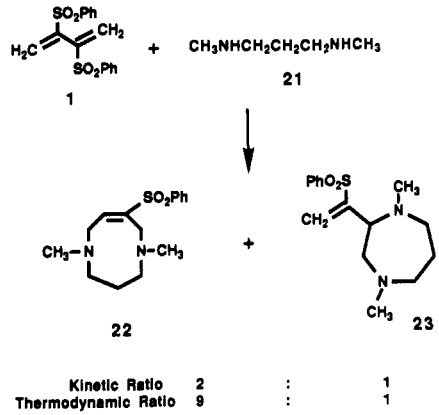
Greater quantitative appreciation of the energy difference between structures **18** and **20** was achieved by subjecting this pair of compounds to energy minimization within the Model KS 2.94 program.[39] The respective global minima (Figure 1) were found by making use of multiconformer generation in Model (TTY, Conf, Statistical, Coordinate) followed by batch minimization using Bakmdl. The resulting lowest energy conformations were then submitted to MMX89 for the calculation of strain energies.[40] The calculations reveal a 9.67-kcal difference in strain energies, thereby accounting for the exclusive formation of piperazine **18** upon treating diene **1** with diamine **17** for extended periods of time.

A related reaction was also observed to occur when bis(phenylsulfonyl) diene **1** was treated with *N,N'*-dimethylpropanediamine (**21**). In this case a mixture of

(39) We thank Professor Kosta Steliou of the University of Montreal for providing a copy of the extensively rewritten Still Model program and for providing a VMS version of the MMX PC modification of MM2.

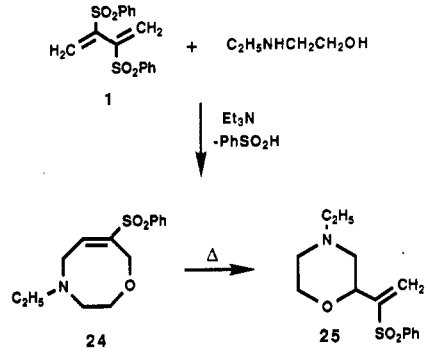
(40) MMX is derived from MM2 (1977 Version QCPE 395) with the VESCF π-subroutines from MMP1 (QCPE 318). The version of MMX used in this study (VMS version) has been updated with improved MM2 parameters for sulfones. Gilbert, K. E.; Gajewski, J. J. Serena Software, P.O. Box 3076, Bloomington, IN 47402–3076.

diazacyclononene **22** and 1,4-diazepine **23** was isolated. The ^1H NMR spectrum taken shortly after mixing showed a 2:1 ratio of **22** to **23**. Heating the mixture for several



hours in benzene at 80 °C enhanced the amount of **22** (9:1 ratio). This observation is consistent with the view that the seven-membered 1,4-diazepine ring undergoes ring enlargement to the thermodynamically more stable isomer (i.e., **22**). The computational results show that the lowest energy conformation of **22** is 1.43 kcal lower in energy than that of **23** (see Figure 2). This is a subtle effect that is not immediately obvious on inspection of molecular models but for which MMX calculations serve well to predict product stabilities.

We also succeeded in extending the cyclization of bis(phenylsulfonyl) diene **1** with *N*-ethylethanolamine. Although our earlier studies indicated that oxygen nucleophiles are generally unreactive toward diene **1**, we felt that an intramolecular reaction might occur. Indeed, when diene **1** was treated with 1-(ethylamino)ethanol in the presence of triethylamine, 1,4-oxazacyclooctene **24** was obtained as the major product. The formation of **24** can be accounted for in terms of a double conjugate addition followed by an elimination step (i.e., path B). When this material was subjected to silica gel chromatography, however, only the ethenylmorpholine isomer **25** was isolated. This same material was also formed in quantitative yield from **24** on extended heating in benzene. Again, MMX calculations clearly indicate that the ground-state strain energy of **25** is significantly less than the kinetic product **24** (i.e., 5.9 kcal).



In conclusion, the work reported herein establishes the utility of bis(phenylsulfonyl)-1,3-diene as a useful synthon for the preparation of various heterocycles. Substituted pyrrolines and pyrroles are available via a [4 + 1] annulation reaction of the diene with various primary amines. Dinucleophilic reagents react with the activated diene to give novel heterocycles via a double conjugate addition–elimination–rearrangement sequence. Other aspects of the [4 + 1] annulation approach and its application to alkaloid synthesis will appear in forthcoming papers.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on Varian EM-390 and General Electric QE 300 spectrometers. ^{13}C NMR spectra were recorded on a GE QE 300 spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

General Procedure for the Preparation of 3-(Phenylsulfonyl)-3-pyrrolines 7. A solution containing 3.0 mmol of 2,3-bis(phenylsulfonyl)-1,3-butadiene (1) and 3.0 mmol of the appropriate amine in 250 mL of a 1:1 methylene chloride–methanol mixture was stirred for 12 h at room temperature. To the clear yellow solution was added 9.0 mmol of sodium methoxide. The bright yellow solution was stirred for 1 h at room temperature and was quenched with 50 mL of a saturated aqueous ammonium chloride solution. The organic layer was separated, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give yellow oil. In the above fashion the following compounds were obtained.

***N*-Benzyl-3-(phenylsulfonyl)-3-pyrroline (7a)**: 100% yield; IR ($CHCl_3$) 3035, 1455, 1315, and 1160 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.68 (m, 2 H), 3.72 (m, 2 H), 3.80 (s, 2 H), 6.78 (m, 1 H), 7.30 (m, 5 H), 7.55 (m, 2 H), 7.70 (m, 1 H), and 6.79 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.2, 59.7, 59.8, 127.2, 127.8, 128.4, 129.2, 133.6, 138.1, 139.0, 139.1, 139.2 and 142.0; HRMS calcd for $C_{17}H_{17}NO_2S$ 299.0980, found 299.0980. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.43; H, 5.65; N, 4.69.

***N*-(*n*-Butyl)-3-(phenylsulfonyl)-3-pyrroline (7b)**: 93% yield; IR (neat) 3070, 2960, 2930, 2870, 2800, 1310, and 1150 cm^{-1}; NMR ($CDCl_3$ 300 MHz) δ 0.78 (t, 3 H, J = 7.2 Hz), 1.15–1.33 (m, 4 H), 2.46 (m, 2 H), 3.51 (m, 2 H), 3.55 (m, 2 H), 6.65 (m, 1 H), 7.45 (m, 2 H), 7.54 (m, 1 H), and 7.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 20.3, 30.9, 55.5, 57.4, 60.0, 127.7, 127.9, 129.3, 133.6, 139.2, and 142.0; HRMS calcd for $C_{14}H_{19}NO_2S$ 265.1136, found 265.1133.

***N*-(3-Hydroxypropyl)-3-(phenylsulfonyl)-3-pyrroline (7c)**: 92% yield; IR (neat) 3400 (br), 3070, 2940, 2880, 1625, 1310, and 1150 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.51 (tt, 2 H, J = 6.5 and 6.0 Hz), 2.67 (t, 2 H, J = 6.5 Hz), 3.53 (m, 4 H), 3.57 (m, 2 H), 3.85 (br s, 1 H), 6.61 (m, 1 H), 7.45 (m, 2 H), 7.55 (m, 1 H), and 7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.8, 54.9, 57.5, 60.0, 62.7, 127.6, 129.2, 133.7, 138.6, 138.7 and 141.6; HRMS calcd for $C_{13}H_{17}NO_3S$ 267.0929, found 267.0927.

***N*-(2-Hydroxyethyl)-3-(phenylsulfonyl)-3-pyrroline (7d)**: 98% yield; IR (neat) 3400 (br), 3070, 2940, 2880, 2810, 1625, 1450, 1310, and 1160 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.65 (br s, 1 H), 2.75 (t, 2 H, J = 6.0 Hz), 3.60 (t, 2 H, J = 5.5 Hz), 3.70 (br s, 4 H), 6.75 (br s, 1 H), 7.65 (m, 3 H), and 7.95 (m, 2 H); HRMS calcd for $C_{12}H_{15}NO_3S$ 253.0773, found 253.0766. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N 5.53. Found: C, 56.71; H, 6.09; N, 5.38.

***N*-(*o*-Methoxybenzyl)-3-(phenylsulfonyl)-3-pyrroline (7e)**: 90% yield; IR (neat) 3065, 2940, 2880, 2840, 1605, 1590, 1495, 1465, 1450, 1310, 1245, and 1155 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.70 (br s, 4 H), 3.75 (s, 3 H), 3.77 (s, 2 H), 6.70 (br s, 1 H), 6.85 (m, 2 H), 7.20 (m, 2 H), 7.55 (m, 3 H), and 7.82 (m, 2 H); HRMS calcd for $C_{18}H_{19}NO_3S$ 329.1086, found 329.1080. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.31; H, 5.71; N, 4.18.

***N*-(2′-Methoxyethyl)-3-(phenylsulfonyl)-3-pyrroline (7f)**: 93% yield; IR (neat) 3070, 2935, 2880, 2820, 1450, 1310, 1150, 1120, 1085, 765, 725, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.80 (t, 2 H, J = 6.0 Hz), 3.30 (s, 3 H), 3.40 (t, 2 H, J = 6.0 Hz), 3.75 (br s, 4 H), 6.75 (br s, 1 H), 7.60 (m, 3 H), and 7.90 (m, 2 H); HRMS calcd for $C_{13}H_{17}NO_3S$ 267.0929, found 267.0931.

General Procedure for the Preparation of 3-(Phenylsulfonyl)pyrroles. A solution containing 4.3 mmol of the 3-(phenylsulfonyl)-3-pyrroline and 4.3 mmol of DDQ in 80 mL of

benzene was stirred for 3 h at room temperature. To the dark red solution was added 150 mL of methylene chloride. The solution was washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to give a black oil. The crude oil was chromatographed on a silica gel column using methylene chloride as the eluent. The major fraction contained the 3-(phenylsulfonyl)pyrrole whose structures was assigned on the basis of its spectral properties. On the basis of the above procedure the following compounds were obtained.

***N*-Benzyl-3-(phenylsulfonyl)pyrrole (11a)**: 65% yield; mp 163–164 °C; IR (KBr) 3140, 1520, 1455, 1305, 1155, 1125, and 735 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 5.10 (s, 2 H), 6.46 (m, 1 H), 6.64 (m, 1 H), 7.12 (m, 2 H), 7.30 (m, 1 H), 7.35 (m, 3 H), 7.45 (m, 3 H), and 7.90 (m, 2 H). Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.40; H, 5.15; N, 4.69.

***N*-(*n*-Butyl)-3-(phenylsulfonyl)pyrrole (11b)**: 88% yield, yellow oil; IR (neat) 3130, 3070, 2960, 2930, 2875, 1520, 1440, 1305, 1160, 1120, and 1080 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.90 (t, 3 H, J = 6.6 Hz), 1.40 (m, 2 H), 1.70 (m, 2 H), 3.90 (t, 2 H, J = 7.0 Hz), 6.50 (m, 1 H), 6.65 (m, 1 H), 7.30 (m, 1 H), 6.75 (m, 3 H), and 8.05 (m, 2 H); HRMS calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0979.

***N*-(3′-Hydroxypropyl)-3-(phenylsulfonyl)pyrrole (11c)**: 88% yield, yellow oil; IR (neat) 3500 (br), 3120, 2950, 2880, 1730, 1515, 1445, 1300, and 1150 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.85 (m, 2 H), 2.40 (br s, 1 H), 3.45 (t, 2 H, J = 6.2 Hz), 3.90 (t, 2 H, J = 7.0 Hz), 6.40 (m, 1 H), 6.60 (m, 1 H), 6.85 (m, 1 H), 7.45 (m, 3 H), and 7.85 (m, 2 H); HRMS calcd for $C_{13}H_{15}NO_3S$ 265.0773, found 265.0771.

General Procedure for the Alkylation Reactions of *N*-Butyl-3-(phenylsulfonyl)pyrrole (11b). A solution containing 0.37 mmol of pyrrole **11b** in 20 mL of tetrahydrofuran was cooled to −78 °C under a nitrogen atmosphere. To this solution was added 0.32 mL of a 1.38 M *tert*-butyllithium solution in pentane. The resulting yellow solution was stirred for 10 min at −78 °C, and this was followed by the addition of 0.37 mmol of the appropriate electrophile. The reaction was warmed to room temperature and was quenched with a saturated ammonium chloride solution. Evaporation of the solvent under reduced pressure left an oil, which was taken up in methylene chloride. The organic layer was washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting crude oil was chromatographed on a silica gel plate, using a 20% ethyl acetate–hexane mixture as the eluent. The major fraction contained the pure alkylated product whose structure was assigned on the basis of its spectral properties.

***N*-(*n*-Butyl)-2-methyl-3-(phenylsulfonyl)pyrrole (13a)**: 95% yield; IR (neat) 3120, 3060, 2955, 2930, 2870, 1505, 1445, 1415, 1300, 1145, and 1090 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3 H, J = 7.3 Hz), 1.30 (m, 2 H), 1.65 (m, 2 H), 2.40 (s, 3 H), 3.75 (t, 2 H, J = 7.3 Hz), 6.51 (d, 1 H, J = 3.0 Hz) 6.54 (d, 1 H, J = 3.0 Hz), 7.40–7.50 (m, 3 H), and 7.90 (m, 2 H); HRMS calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1128.

***N*-(*n*-Butyl)-2-(hydroxybenzyl)-3-(phenylsulfonyl)pyrrole (13b)**: 100% yield; mp 151–152 °C; IR (KBr) 3460 (br), 3130, 2970, 2940, 1505, 1450, 1305, 1290, 1145, 1085, 735, and 620 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3 H, J = 7.3 Hz), 1.15 (m, 2 H), 1.35 (m, 1 H), 1.50 (m, 1 H), 3.75 (t, 2 H, J = 7.6 Hz), 3.95 (d, 1 H, J = 7.6 Hz), 6.40 (d, 1 H, J = 7.6 Hz), 6.62 (s, 2 H), 7.05 (m, 2 H), 7.20 (m, 3 H), 7.35 (m, 2 H), 7.50 (m, 1 H), and 7.65 (m, 2 H); HRMS calcd for $C_{21}H_{23}NO_3S$ 369.1399, found 369.1398.

***N*-(*n*-Butyl)-2-benzoyl-3-(phenylsulfonyl)pyrrole (13c)**: 54% yield; IR (neat) 3060, 2955, 2930, 2870, 1665, 1600, 1580, 1475, 1445, 1410, 1310, 1250, 1185, 1150, 1085, and 915 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3 H, J = 7.3 Hz), 1.20 (m, 2 H), 1.60 (m, 2 H), 3.80 (t, 2 H, J = 7.3 Hz), 6.65 (d, 1 H, J = 2.8 Hz), 6.80 (d, 1 H, J = 2.8 Hz), and 7.40–7.90 (m, 10 H); HRMS calcd for $C_{21}H_{21}NO_3S$ 367.1242, found 367.1228. Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81. Found: C, 68.31; H 5.69; N, 3.65.

***N*-(*n*-Butyl)-2-formyl-3-(phenylsulfonyl)pyrrole (13d)**: 100% yield; IR (neat) 2970, 2940, 2880, 1675, 1485, 1395, 1320, 1310, and 1150 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.90 (t, 3 H, J = 6.6 Hz), 1.30 (m, 2 H), 1.70 (m, 2 H), 4.30 (t, 2 H, J = 7.5 Hz), 6.65 (d, 1 H, J = 3.0 Hz), 6.90 (d, 1 H, J = 3.0 Hz), 7.55 (m, 3 H), 7.95 (m, 2 H), and 10.40 (s, 1 H); HRMS calcd for $C_{15}H_{17}NO_3S$ 291.0929, found 291.0929. Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.76; H, 5.64; N, 4.73.

***N*-(*n*-Butyl)-2-(2′-methyl-1′-oxopropenyl)-3-(phenylsulfonyl)pyrrole (13e)**: 51% yield; IR (neat) 3120, 2960, 2930, 2870, 1660, 1445, 1415, 1305, 1225, 1190, 1155, 1085, 760, 725, 695, and 605 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3 H, J = 7.4 Hz), 1.25 (m, 2 H), 1.60 (m, 2 H), 20.05 (s, 3 H), 3.80 (t, 2 H, J = 7.4 Hz), 5.45 (s, 1 H), 5.85 (s, 1 H), 6.50 (d, 1 H, J = 2.8 Hz), 6.70 (d, 1 H, J = 2.8 Hz), 7.40–7.55 (m, 3 H), and 7.80–7.95 (m, 2 H); HRMS calcd for $C_{18}H_{21}NO_3S$ 331.1242, found 331.1241.

Preparation of 2,3-Dihydro-7-(phenylsulfonyl)-1*H*-pyrrolizine (16). A solution containing 0.65 g of *N*-(3-hydroxypropyl)-3-(phenylsulfonyl)pyrrole **11c** in 15 mL of chloroform was stirred at 0 °C during which time 0.58 g of pyridine was added. To the stirred solution was added 0.93 g of *p*-toluenesulfonyl chloride over a 15-min period of time. The ice bath was removed, and the solution was stirred at room temperature for 10 h and was then washed with a 2.0 N hydrochloric acid solution and a 10% aqueous sodium bicarbonate solution followed by water. The solution was dried over magnesium sulfate and concentrated under reduced pressure to afford a dark brown oil. The crude material was chromatographed on a silica gel column using a 20% ethyl acetate–hexane mixture as the eluent. The major fraction contained 1.02 g (100% yield) of a clear oil whose structure was identified as tosylate **15** on the basis of its NMR spectrum: NMR ($CDCl_3$, 90 MHz) δ 1.95 (m, 2 H), 2.35 (s, 3 H), 3.90 (m, 4 H), 6.35 (m, 1 H), 6.55 (m, 1 H), 7.15 (m, 1 H), and 7.20–7.90 (m, 9 H). This material was used in the next step without further purification.

A solution containing 0.09 g of the above tosylate in 20 mL of tetrahydrofuran was cooled to −78 °C under a nitrogen atmosphere. To this solution was added 0.15 mL of a 1.7 M *tert*-butyllithium solution in pentane. The resulting orange solution was stirred for 10 min at −78 °C and 0.50 g of HMPA was added. The soltuion was stirred for another 10 min at −78 °C and was allowed to warm to room temperature. The reaction was quenched with an aqueous ammonium chloride solution. Evaporation of the solvent under reduced pressure left a white oily solid, which was dissolved in methylene chloride. The organic layer was washed with a 2 N hydrochloric acid solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting white solid was recrystallized from a 1:1 methylene chloride–ether solution to give 0.05 g (96%) of a white crystalline solid, mp 134–135 °C, whose structure was assigned as 2,3-dihydro-7-(phenylsulfonyl)-1*H*-pyrrolizine (**16**) on the basis of its spectral properties: IR (KBr) 3120, 2990, 1540, 1510, 1450, 1430, 1305, 1295, 1195, 1150, and 755 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.50 (m, 2 H), 3.05 (t, 2 H, J = 7.4 Hz), 3.95 (t, 2 *H*, J = 7.4 Hz), 6.48 (d, 1 H, J = 2.9 Hz), 6.55 (d, 1 H, J = 2.9 Hz), 7.40–7.55 (m, 3 H), and 7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 27.0, 47.1, 112.4, 114.8, 115.6, 126.4, 128.8, 132.1, 141.6, and 144.2. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.10; H, 5.29; N, 5.48.

Reaction of 2,3-Bis(phenylsulfonyl)-1,3-butadiene (1) with *N,N′*-Dimethylethylenediamine (17). To a solution containing 250 mg of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) in 20 mL of methylene chloride was added 66 mg of *N,N′*-dimethylethylenediamine (**17**). After stirring for 5 min, 76 mg (0.75 mmol) of triethylamine was added, and the reaction was stirred at 25 °C under a nitrogen atmosphere for an additional 12 h. The reaction mixture was washed once with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography using a 90% chloroform–methanol mixture as the eluent. The major fraction contained 193 mg (92% yield) of a pale yellow solid (mp 105–106 °C) whose structure was assigned as 1,4-dimethyl-2-(1-(phenylsulfonyl)ethenyl)-1,4-piperazine (**18**) on the basis of its spectral properties: IR ($CHCl_3$) 3080, 2960, 2860, 2815, 1450, 1310, 1160, 1085, 1030, 845, and 795 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3 H), 1.67 (t, 1 H, J = 10.3 Hz), 1.98–2.14 (m, 2 H), 2.08 (s, 3 H), 2.55–2.74 (m, 4 H), 6.08 (s, 1 H), 6.52 (s, 1 H), 7.44 (t, 2 H, J = 7.5 Hz), 7.53 (t, 1 H, J = 7.5 Hz), and 7.80 (d, 21 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.4, 44.8, 54.2, 54.5, 61.2, 62.1, 125.6, 128.1, 128.5, 133.1, 137.5, and 149.5. Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C,

59.81; H, 7.03; N, 9.78.

The crude NMR spectrum prior to silica gel chromatography showed the presence of 1,4-dimethyl-6-(phenylsulfonyl)-1,4-diazacyclooct-6-ene (**20**): NMR ($CDCl_3$, 90 MHz) δ 2.25 (s, 3 H), 2.30–2.85 (m, 4 H), 2.45 (s, 3 H), 3.40 (d, 2 H, J = 6.0 Hz), 3.85 (s, 2 H), 7.05 (t, 1 H, J = 6.0 Hz), and 7.25–7.85 (m, 5 H). Unfortunately, all attempts to isolate a pure sample of **20** failed as it readily rearranged to piperazine **18**.

Reaction of 2,3-Bis(phenylsulfonyl)-1,3-butadiene (1) with *N,N'*-Dimethyl-1,3-propanediamine (21). To a solution containing 250 mg of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) in 20 mL of methylene chloride at 0 °C was added 76 mg of *N,N'*-dimethyl-1,3-propanediamine (**21**). After stirring for 5 min, 76 mg of triethylamine was added, and the reaction was stirred at 0 °C under a nitrogen atmosphere for an additional 3 h. The reaction mixture was washed once with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue consisted of a 2:1 mixture of 1,5-dimethyl-7-(phenylsulfonyl)-1,5-diazacyclonon-7-ene (**22**) and 1,4-dimethyl-5-(1-(phenylsulfonyl)ethenyl)-1,4-diazepine (**23**). Heating the reaction mixture in refluxing benzene for 4 h afforded a 9:1 mixture of **22** and **23**. Flash chromatography of the reaction mixture on a silica gel column using a 90% chloroform–methanol mixture as the eluent resulted in the isolation of cyclononene **22** (155 mg (70% yield)) as a pale yellow solid (mp 124–125 °C) whose structure was assigned on the basis of its spectral properties: IR ($CHCl_3$) 3010, 2950, 2930, 2845, 2800, 1450, 1305, 1220, 1150, 1085, and 690 cm^{-1}; NMR ($CDCl_3$), 300 MHz) δ 1.41 (m, 2 H), 1.92 (s, 3 H), 2.08 (t, 2 H, J = 6.5 Hz), 2.19 (s, 3 H), 2.24 (t, 2 H, J = 7.6 Hz), 3.12 (s, 2 H), 3.35 (d, 2 H, J = 5.7 Hz), 7.17 (t, 1 H, J = 5.7 Hz), 7.52 (t, 2 H, J = 7.2 Hz), 7.59 (t, 1 H, J = 7.2), and 7.86 (d, 2 H, J = 7.2 Hz). Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.20; H, 7.53; N, 9.51. Found: C, 61.11; H, 7.39; N, 9.34. Diazepine **23** showed the following NMR characteristics: NMR ($CDCl_3$, 300 MHz) δ 6.18 (s, 1 H) and 6.45 (s, 1 H). Unfortunately, a pure sample of diazepine **23** could not be obtained as it was readily converted to **22** upon silica gel chromatography.

Reaction of 2,3-Bis(phenylsulfonyl)-1,3-butadiene (1) with 2-(Ethylamino)ethanol. To a solution containing 250 mg of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) in 20 mL of methylene chloride at 25 °C was added 67 mg of 2-(ethylamino)ethanol. After stirring for 5 min, 76 mg of triethylamine was added, and the reaction was stirred at 25 °C under a nitrogen atmosphere for an additional 16 h. The reaction mixture was washed once with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography on a silica gel column, using a 90% chloroform–methanol mixture as the eluent. The major fraction contained 151 mg (72% yield) of a yellow oil whose structure was assigned as 4-ethyl-2-(1-(phenylsulfonyl)ethenyl)morpholine (**25**) on the basis of its spectral properties: IR (neat) 3080, 2985, 2880, 2820, 1445, 1310, 1220, 1180, 1155, 1110, 1085, and 970 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3 H, J = 7.2 Hz), 1.84 (dd, 1 H, J = 11.1 and 10.1 Hz), 2.06 (m, 1 H), 2.35 (q, 2 H, J = 7.2 Hz), 2.66 (m, 1 H), 3.02 (m, 1 H), 3.53 (m, 1 H), 3.78 (m, 1 H), 4.18 (m, 1 H), 6.19 (s, 1 H), 6.54 (s, 1 H), 7.45–7.70 (m, 3 H), and 7.87 (d, 2 H, J = 7.4 Hz). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.71; H, 6.59; N, 4.92. The initial crude NMR spectrum showed only the presence of 4-ethyl-7-(phenylsulfonyl)-1,4-oxazacyclooct-6-ene (**24**) whose structure was assigned on the basis of its characteristic NMR spectrum: NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, 3 H, J = 7.2 Hz), 2.25 (q, 2 H, J = 7.2 Hz), 2.37 (t, 2 H, J = 5.0 Hz), 3.33 (s, 2 H), 3.39 (d, 2 H, J = 6.6 Hz), 3.47 (t, 2 H, J = 5.0 Hz), 7.14 (t, 1 H, J = 6.6 Hz), 7.45–7.70 (m, 3 H), and 7.88 (d, 2 H, J = 7.4 Hz). Unfortunately, all attempts to isolate a pure sample of **24** failed as it readily rearranged to **25**.

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Iterative Synthesis of Selectively Substituted α,β-Unsaturated and Saturated Medium-Ring Lactones

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Chloro, chloromethyl, and chlorofluoro carbenoids, generated by reaction of a base on the corresponding halides, were added to trimethylsilyl enol ethers derived from lactones, to give 1-[(trimethylsilyl)oxy]-2-chlorobicyclo-[*n*.1.0]oxanes. Thermal rearrangement of these adducts led to the α,β-ethylenic lactones, corresponding to a one-carbon ring expansion of the starting lactones. After hydrogenation, with the same iterative sequence a new one-carbon ring expansion could be performed. This method allowed the preparation in good yields of hitherto unknown medium-ring lactones. Spectroscopic and physicochemical properties of the isomeric unsaturated lactones were examined. For the 9- and 10-membered series, the trans isomers could be readily isomerized by I_2 into the cis isomers or gave diolides under acidic conditions.

The synthesis of medium-ring lactones has been the subject of active investigation recently, as many of these compounds possess diverse and significant biological activities. In the case of macrolide preparation,[1] the main synthetic methods leading to these compounds begin from either linear or cyclic precursors. Starting with linear precursors, ring closure can be effected by generation of the C(O)–O– moiety;[1] the main drawback of such a process, disfavored on entropy grounds, is the need for dilution in order to avoid intermolecular condensations. However, lactonizations by enzymic methods have been described in a few cases[2]. Ring closure can also be obtained through carbon–carbon bond formation by various methods,[3]

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