Lithiated γ-Tosyl-Substituted Benzylmethallylamine: New γ-Amino Methallyl Sulfone Anions in Organic Synthesis†

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The mono- and dilithiation of benzyl[2-(tosylmethyl)-2-propenyl]amine (**9**) with *n*-butyllithium at −78 °C leads to the new allyl sulfone monoanion **10a** and dianion **10b**, respectively. The intermediate **10a** reacts regioselectively at the α-position with respect to the sulfone group with different electrophilic reagents (deuterium oxide, alkyl halides, propanal, phenyl isocyanate, and electrophilic olefins) to give the corresponding derivatives **11**. In the case of ethyl propiolate, double Michael addition took place, and the *trans*-substituted methylenepyrrolidine **13** was stereoselectively obtained. Dianion **10b** also reacts at the nitrogen atom when alkyl halides and ethyl propiolate are used as electrophiles. These intermediates **10** are appropriate dinucleophiles in annelation reactions with dielectrophiles to afford six-, seven-, and eight-membered ring nitrogen heterocycles **20**. When 1,3-dichloroacetone, (*Z*)-1,4-dichloro-2-butene, and epibromohydrin were used as electrophiles the cyclization process was stereoselective. Studies on the configuration and conformation of prepared heterocycles **20** have been carried out by means of ^{1}H NMR experiments and X-ray analysis, which have been confirmed by Molecular Mechanics calculations. Base-induced dehydrosulfinylation, reductive desulfonylation, and methylenation reactions have been studied with representative derivatives.

Introduction

Functionalized allyl sulfones with isobutene structure **1** are very useful multicoupling reagents for methylenecyclopentane formations through transition-metal-catalyzed reactions (**1**, X = OCO_2Et,[1a] Cl;[1b] Chart 1) or *via* an organolithium derivative (**1**, X = Br)[2] acting as 1,3-dipole synthon **2** in a [3 + 2] annulation process with electrophilic olefins. The dilithium derivative[3] of 2-(chloromethyl)-3-tosylpropene (**1**, X = Cl)[4] has also been used in cycloannulation reactions as synthons **4**, **5**, or **6** reacting with alkyl bromides, aldehydes, and electrophilic olefins or ketones to afford tosyl-substituted methylenecyclopropanes, 2,5-dihydrofurans, and cyclopentenes or tetrahydrofurans, respectively. On the other hand, intermediate **7** [the monolithium derivative of 2-(cloromethyl)-3-tosylpropene (**1**, X = Cl)] is also a useful intermediate for the general synthesis of 2-substituted 1,3-dienes.[5] When this type of sulfone has an alcohol as functional group (**1**, X = OH) the lithiated intermediate **8**[6] affords 6- and 7-membered ring lactones[6b] and functionalized dienic esters.[6b]

According to the ability of this type of sulfone to be used in cycloannulation reactions, the corresponding γ-aminated methallyl sulfone[7] of the type **1** (X = $NHCH_2$-Ph) should be an appropriate precursor of the corresponding dianion, which could act as a 1,4-dinucleophile[8] for the preparation of nitrogen-containing heterocycles by reaction with dielectrophiles. Amine-containing dianions[7] have been scarcely used in the preparation of saturated heterocycles by reaction with dielectrophiles. We describe in the present paper the mono- and dilithiation of the amino sulfone **9**[9] and their synthetic applications, especially in the preparation of 5−8-membered saturated nitrogen heterocycles (Chart 1).[10]

Results and Discussion

Benzyl[2-(tosylmethyl)-2-propenyl]amine (**9**) was prepared[4] by successive allylic substitution of 3-chloro-2-(chloromethyl)propene with sodium *p*-toluenesulfinate and benzylamine in 60% overall yield. The treatment of this methallylamine **9** with 1 or 2 equiv of *n*-butyllithium at −78 °C in THF in the presence of *N*,*N*′-dimethylpro-

† This paper is dedicated to Mary Fieser for her outstanding dedication to Organic Chemistry.

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(1) (a) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5183−5186. (b) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1988**, *29*, 201−204.

(2) (a) Ghera, E.; Yechezkel, T.; Hassner, A. *Tetrahedron Lett.* **1990**, *31*, 3653−3656. (b) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1993**, *58*, 6716−6724. (c) Yechezkel, T.; Ghera, E.; Ostercamp, D.; Hassner, A. *J. Org. Chem.* **1995**, *60*, 5135−5142.

(3) (a) Nájera, C.; Sansano, J. M. *Tetrahedron Lett.* **1992**, *33*, 6543−6546. (b) Nájera, C.; Sansano, J. M. *Tetrahedron* **1994**, *50*, 3491−3508.

(4) For preparation and applications of this intermediate to the synthesis of γ-functionalized methallyl sulfones, see: Nájera, C.; Sansano, J. M. *Tetrahedron* **1992**, *48*, 5179−5190.

(5) (a) Nájera, C.; Sansano, J. M. *Tetrahedron Lett.* **1993**, *34*, 3781−3784. (b) Nájera, C.; Sansano, J. M. *Tetrahedron* **1994**, *50*, 5829−5844.

(6) (a) Ghera, E.; Ben-Yaakov, E.; Yechezkel, T.; Hassner, A. *Tetrahedron Lett.* **1992**, *33*, 2741−2744. (b) Alonso, D. A.; Nájera, C.; Sansano, J. M. *Tetrahedron* **1994**, *50*, 6603−6620.

(7) For the corresponding unsubstituted allyl organolithium compounds derived from methallylamines see: (a) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1981**, *46*, 3349−3352. (b) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 1135−1136. (c) Barluenga, J.; González, R.; Fañanás, F. J. *Tetrahedron Lett.* **1992**, *33*, 7573−7574. (d) Foubelo, F. Ph.D. Thesis, University of Oviedo, 1989.

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(9) For a preliminary communication, see: Alonso, D. A.; Nájera, C. *Tetrahedron Lett.* **1994**, *35*, 8867−8870.

(10) For a recent review of saturated nitrogen heterocycles see: Steele, J. *Contemp. Org. Synth.* **1994**, 95−112.

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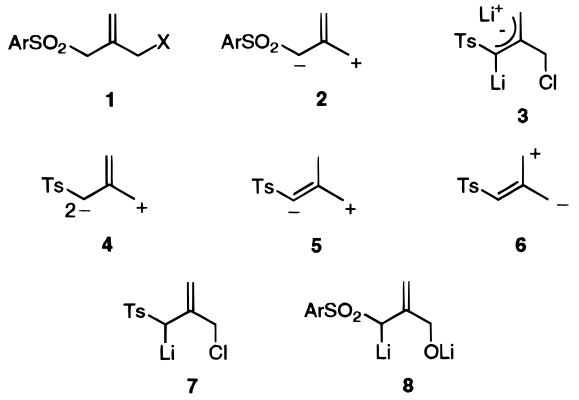
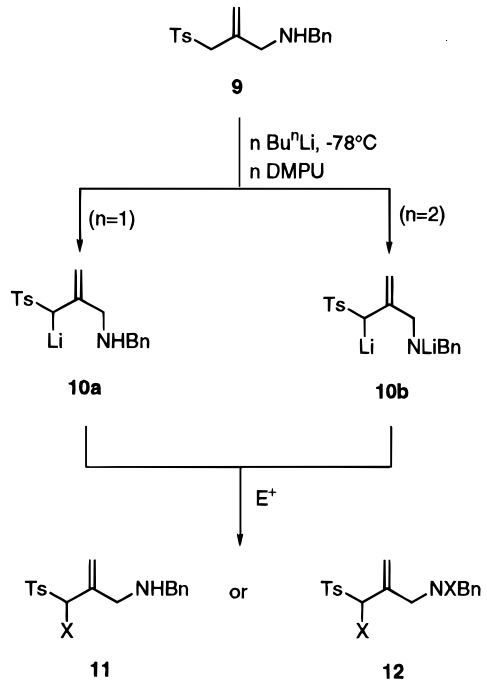
Chart 1



Scheme 1



pyleneurea (DMPU, 1 or 2 equiv) for 15 min gave the allyl sulfone anions **10a** or **10b**, respectively. Both intermediates were chemically characterized by deuterolysis with deuterium oxide to afford compound **11a** (Scheme 1 and Table 1, entries 1 and 2). The reaction of monolithium derivative **10a** with different electrophiles such as alkyl halides, propanal, phenyl isocyanate, and electrophilic olefins took place regioselectively at the α-position with respect to the sulfonyl group to provide compounds **11** (Scheme 1 and Table 1). In the case of dilithium intermediate **10b** the same results were obtained except in the alkylation reaction, which also took place at the nitrogen atom to give compounds **12** (Table 1, entries 4 and 8). Only some differences have been found between the two anions in the diastereomeric ratios obtained in the addition to propanal and methyl crotonate leading to compounds **11f** and **11i**, respectively (Table 1, entries 9, 10, 14, and 15). The *erythro*/*threo* ratio for the hydroxy sulfone **11f** was determined by ^{1}H NMR and assigned according to the coupling constant values.[11]

The behavior of dianion **10b** in the reaction with deuterium oxide as electrophile was rather surprising, because at −78 °C only the monodeuterated compound **11a** was formed; however, when the temperature was allowed to rise to 0 °C, mono- and dideuterated products **11a** and **11a′** (*ca.* 1/1 mixture; 90% yield and 98% of deuterium incorporation by ^{1}H and ^{13}C NMR) were obtained (Scheme 2). Monoanion **10a′** was probably formed by intramolecular lithiation in intermediate **11a**. The existence of monoanions **10a** and **10a′** is a consequence of the pK_a values[12] for hydrogen atoms at the α-position respect to the sulfone group and at the nitrogen atom.

The addition of monoanion **10a** to methyl crotonate was stereoselective, and compound **11i** was obtained with the *threo* configuration,[13] which was determined by ^{1}H NMR on the corresponding *trans*-lactam **16**, obtained by reaction of **11i** with *n*-butyllithium in 48% yield (Scheme 3). Moreover, the same *trans*-lactam **16** was also obtained when the 1/1 mixture of *erythro*/*threo*-**11i** (see Table 1, entry 15) was treated with *n*-butyllithium, probably due to an isomerization process at the α-position with respect to the sulfone group under the basic reaction conditions. Caprolactam **16** showed a small coupling constant (2.8 Hz) between the two methine protons, which is consistent with a *trans*-diaxial conformation of the tosyl and methyl substituents. The axial position of the methyl group was established on the basis of the coupling constants (6.4 and 1.5 Hz) between its geminal methine proton and the methylene at the α-position with respect to the carbonyl group. Moreover, no NOE effects were observed when the methyl or the tolyl group was irradiated. Calculated coupling constants are also in agreement with the proposed structure.[14]

The reaction with ethyl propiolate occurred stereoselectively to provide the thermodynamically most stable *trans*-pyrrolidine derivative **13** resulting from a Michael addition of intermediates **10** to the triple bond to provide intermediate **15**, which after a second intramolecular addition afforded the most stable *trans*-diastereomer **13**. In the case of the dilithiated intermediate **10b** a *ca.* 1/1 mixture of pyrrolidine **13** and the β-enamino ester **14** was obtained due to a concomitant nitrogen attack at the triple bond (Scheme 4 and Table 1, entries 16 and 17). The *trans*-configuration and the conformation of pyrrolidine **13** were determined by ^{1}H−^{1}H COSY and NOE experiments.

Following Kocienski's methodology,[15] the synthesis of the 2-(benzylaminomethyl)-1,3-butadiene (**17**) was carried out in 49% overall yield. The preparation of β-silyl sulfone **11c**, by reaction of monoanion **10a** with iodomethyltrimethylsilane, followed by fluoride induced β-elimination of tosyltrimethylsilane with tetrabutylammonium fluoride in THF[16] provided compound **17** (Scheme 5).

(11) Truce, W. E.; Klinger, T. C. *J. Org. Chem.* **1970**, *35*, 1834−1838.

(12) The pK_a values of dimethylsulfone and diethylamine are 23 and 36, respectively: Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1980**, *45*, 4536−4538.

(13) The same stereochemical outcome was observed by reaction of monolithium derivatives of the bromide **1** (R = Ph, X = Br),[2a] methallyl sulfone,[2c] and alcoholate **8**[6b] with ethyl crotonate.

(14) Torsion angles for the most stable conformer were determined using Molecular Mechanics calculations: Hyperchem V3.0 from Hypercube, Inc., and Autodesk, Inc., using the MM+ force field. Coupling constants values were calculated using the program Altona developed by C. M. Cerdá-García-Rojas, L. Gerardo, and P. Joseph-Nathan.

(15) (a) Kocienski, P. J. *Tetrahedron Lett.* **1979**, 2649−2650. (b) Kocienski, P. J. *J. Org. Chem.* **1980**, *45*, 2037−2039.

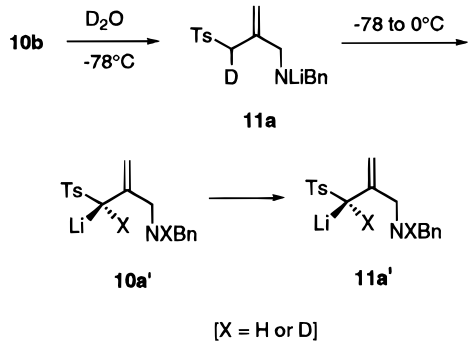
(16) The synthesis of this type of diene has been carried out by reaction of organolithium **7** with (iodomethyl)trimethylsilane followed by amine−chlorine nucleophilic substitution and final TBAF-induced elimination.[5]

Table 1. Reaction of Intermediates 10 with Electrophiles

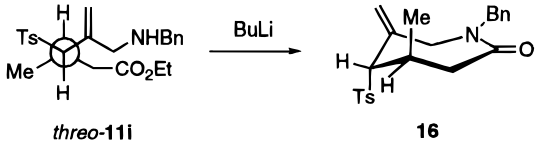
			product			
entry	intermediate	electrophile	no.	X	yield,[a] (%)	R_f[b] or mp,[c] (°C)
1	**10a**	D_2O	**11a**	D	77[d]	45−46
2	**10b**		**11a**		70[e]	
3	**10a**	CH_2=$CHCH_2Br$	**11b**	CH_2=$CHCH_2$	75[e]	0.44[f]
4	**10b**		**12b**		71[g]	0.70[h]
5	**10a**	Me_3SiCH_2I	**11c**	Me_3SiCH_2	61	0.83
6	**10a**	$NCCH_2I$	**11d**	$NCCH_2$	44	0.62
7	**10a**	$Bu^tO_2CCH_2Br$	**11e**	$Bu^tO_2CCH_2$	60	0.77[f]
8	**10b**		**12e**		50	0.36[i]
9	**10a**	EtCHO	**11f**	EtCHOH	72[j]	0.39,[c,k] 0.48[c,l]
10	**10b**		**11f**		56[m]	
11	**10a**	PhNCO	**11g**	PhNHCO	63	0.69
12	**10a**	$CH_2CHCOCH_3$	**11h**	$CH_2CH_2COCH_3$	30	0.64[n]
13	**10b**		**11h**		58	
14	**10a**	(*E*)-$CH_3CHCHCO_2CH_3$	**11i**	$CH_3CHCH_2CO_2CH_3$	61[l]	0.64
15	**10b**		**11i**		60[o]	
16	**10a**	$HCCCO_2Et$	**13**[p]		56	0.78
17	**10b**		**13**[p]		25[q]	

[a] Isolated yield based on starting sulfone **9**, after flash chromatography; silica gel. [b] For oils, in hexane/ether: 3/7. [c] Ether. [d] With a 67% of deuterium incorporation (^{1}H NMR). [e] With a 98% of deuterium incorporation (^{1}H NMR). [f] Hexane/ether: 3/7. [g] Two equiv of electrophile was added. [h] Hexane/ether: 1/1. [i] Hexane/ether: 2/1. [j] *Erythro/threo*: 1/2 (^{1}H NMR). [k] *Erythro*. [l] *Threo*. [m] *Erythro/threo*: 1/6 (^{1}H NMR). [n] EtOAc. [o] *Erythro/threo*: 1/1 (^{1}H NMR). [p] See Scheme 4. [q] 29% of compound **14** [R_f 0.50 (ether)] was also obtained.

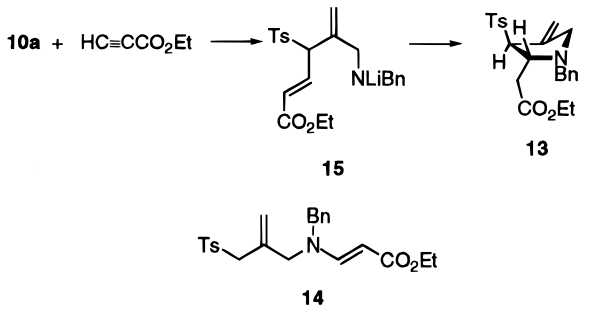
Scheme 2



Scheme 3



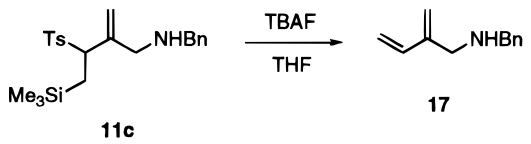
Scheme 4



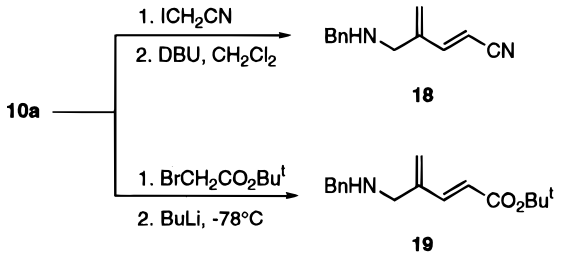
The base-induced dehydrosulfinylation was carried out with compounds **11d** and **11e** derived from the alkylation of monoanion **10a** with iodoacetonitrile and *tert*-butyl bromoacetate, respectively. In the first case crude compound **11d** was treated with DBU in CH_2Cl_2 at room temperature for 3 h to give the dienic aminonitrile **18** in 38% overall yield. The corresponding ester **11e** was treated *in situ* at −78 °C with 1 equiv of *n*-butyllithium[17]

(17) This type of elimination has been also carried out with NaOMe[6b] or TBAF.[18]

Scheme 5



Scheme 6

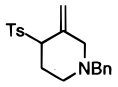
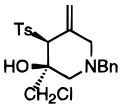
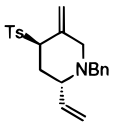
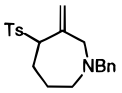
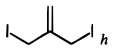
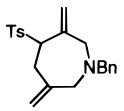
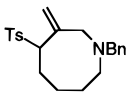
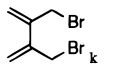
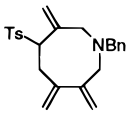
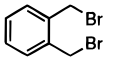
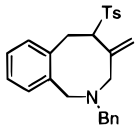


for 1 h to afford the dienic aminoester **19** in 43% overall yield (Scheme 6). In both cases the most stable *trans*-diastereomer was the only one isolated.

The use of intermediates **10** as 1,4-dinucleophiles in annulation reactions in order to prepare different nitrogen-containing saturated heterocycles[10] was first studied with dianion **10b**;[9] however, we found that monolithium derivative **10a** gave in some cases better results. In the case of 1,2-, 1,3-, and 1,4-dihaloalkanes the corresponding 6-, 7-, and 8-membered rings **20a**, **20d**, and **20g** were obtained, respectively (Table 2, entries 1, 2, 6, 7, 10, and 11). However, in the reaction of mono- and dianions **10a** and **10b** with 1,5-diiodopentane the mono- and dialkylated products **11j** and **12j**[20] were obtained in different ratios and the cyclization reaction failed (Chart 2). The reaction with 1,2-dibromoethane gave also the isomerized piperidine **21a** and the cyclopropyl derivative **22** in 10% and 5% yield, respectively. The dialkylation process at the α-position respect to the sulfone group was also observed in the case of the reaction of 1,4-diiodobutane with dianion **10b** to provide mainly compound **23**

(18) Ghera, E.; Ramesh, N. G.; Laxer, A.; Hassner, A. *Tetrahedron Lett.* **1995**, *36*, 1333−1336.
(19) Gaoni, Y.; Sadeh, S. *J. Org. Chem.* **1980**, *45*, 870−881.
(20) These compounds were very unstable and decomposed on standing.

Table 2. Reaction of Intermediates 10 with Dielectrophiles

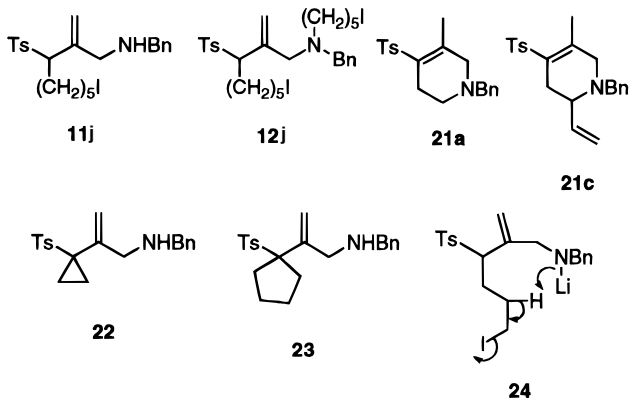
			product			
entry	intermediate	electrophile	no.	structure	yield,[a] (%)	mp,[b] (°C) or R_f[c]
1	**10a**	$Br(CH_2)_2Br$	**20a**		30[d]	144-145
2	**10b**		**20a**		30[d]	
3	**10a**	$(ClCH_2)_2CO$	**20b**		50[e]	0.80
4	**10a**		**20c**		22[f]	122-123
5	**10b**		**20c**		22[f]	
6	**10a**	$I(CH_2)_3I$	**20d**		52	107-108
7	**10b**		**20d**		43[g]	
8	**10b**	 [h]	**20e**		43	112-113
10	**10a**	$I(CH_2)_4I$	**20g**		25[i]	123-124
11	**10b**		**20g**		21[j]	
12	**10a**	 [k]	**20h**		35	135-136
13	**10a**		**20i**		20	206-207
14	**10b**		**20i**		32	

[a] Isolated yield based on sulfone **9**, after flash chromatography; silica gel. [b] Hexane/ether. [c] Ether. [d] Compound **21a** (R_f 0.83) and **22** (R_f 0.66) were also obtained in 10 and 5% yield, respectively. [e] For the major diastereomer. [f] Compound **21c** [R_f 0.68 (hexane/ether: 3/7)] was also obtained in 22% yield. [g] Compound **11b** was also obtained in 22% yield. [h] The reaction of organolithium intermediate **10a** with this electrophile failed. [i] A 12% of unstable monoalkylated product was also obtained. [j] A 42% of compound **23** (R_f 0.59) was also obtained. [k] Prepared according to ref 19.

(Table 2, entry 11). Compounds **22** and **23** were formed through an intra- or intermolecular lithiation of monoalkylated derivatives at the carbon atom at the α-position respect to the sulfone followed by intramolecular C-alkylation (see text above and Scheme 2). 1,3-Diiodopropane gave **11b** as a byproduct due, probably, to the intramolecular dehydroiodination of intermediate **24** (Table 2, entry 7).

Reaction of monolithium **10a** with 1,3-dichloroacetone provided stereoselectively the *trans*-piperidine derivative **20b**, which probably arises from the addition of the carbanion to the carbonyl group followed by intramolecular S_N reaction of the amine at one of the chloromethyl groups. The reaction of mono- or dianions **10a** or **10b** with (*Z*)-1,4-dichloro-2-butene also furnished stereoselectively the *trans*-2,4-disubstituted piperidine **20c** and its isomer **21c** according to a 1,2-substitution process (Table 2, entries 4 and 5). As in the case of compound **20b**, due to the axial position of the tosyl group to avoid allylic strain, the diastereomer obtained (with the vinyl group at the equatorial position) is also the most thermodynamically stable one. The configuration and con-

Chart 2



formation of compounds **20b,c** were established by ^{1}H NMR and NOE measurements.[14]

Perhydroazepines **20e** and **20f** were obtained by reaction of dianion **10b** with 3-iodo-2-(iodomethyl)propene and epibromohydrin, respectively (Table 2, entries 8 and 9). The chair conformation of compound **20e** and the *cis* configuration of the azepine derivative **20f** (Table 2 entry 9) were deduced from ^{1}H NMR studies. In these seven-membered rings the tosyl group is at the equatorial position.[14]

When 1,4-diiodobutane and α,α′-dibromo-*o*-xylene were allowed to react either with monoanion **10a** or dianion **10b** the corresponding perhydroazocines **20g** and **20i** were obtained, respectively (Table 2, entries 10, 11, 13, and 14). In the case of **20g** it was not possible to study its conformation by ^{1}H NMR; only a ^{1}H−^{1}H COSY allowed the assignments of the different protons. In both cases X-ray analysis was carried out, indicating that compound **20g** is in a boat−chair and **20i** in a twist-boat−chair conformation[21] (Figure 1). In the case of compound **20i** difference NOE measurements also confirmed this structure in solution.[14] The perhydroazocine **20h** was prepared by reaction of monoanion **10a** with 2,3-bis-(bromomethyl)-1,3-butadiene:[19] its conformation was tentatively established as twist-chair by NMR and Molecular Mechanics calculations; this seems to be the most stable one.[14]

Reductive treatment of pyrrolidine **13** and perhydroazepine **20d** with sodium amalgam[22] in methanol afforded mainly the corresponding desulfonylated heterocycles **25b** and **26b** together with **25a** and **26a** in 5/1 and 2.5/1 molar ratios (GC), respectively, as a result of isomerization of the double bonds. In the case of compound **13** transesterification with the solvent (MeOH) was also observed, affording the corresponding methyl esters **25** (Scheme 7).

Concerning perhydroazepine **20d**, when we applied Kocienski's methodology[5,15] to the substitution of the tosyl by a methylene group (see text above and Scheme 5), the intermediate allyllithium **27** reacted with (iodomethyl)trimethylsilane at the γ-position to provide compound **28**. However, when intermediate **27** was allowed to react with (chloromethyl)magnesium chloride[23] as electrophile at temperatures ranging from −78 to −30 °C, electrophilic substitution followed by spontaneous β-elimination took place to lead to the corresponding outer ring diene **29** in good yield (90%) (Scheme 8). Julia's methodology[23] seems to be an excellent one for the methylenation of α-sulfonyl carbanions. In addition, dienic compounds **20h** and **29** have promising structures to give Diels−Alder-type reactions in order to built nitrogen-containing polycyclic compounds.

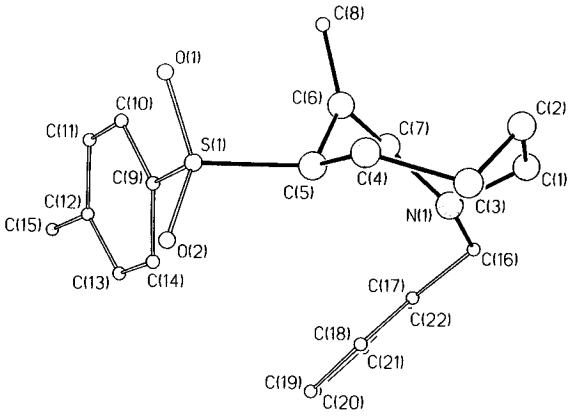
In conclusion, it has been demonstrated that the organolithium compounds derived from tosyl-substituted *N*-benzylmethallylamine are versatile intermediates in synthesis, especially for the preparation in moderate yields of nitrogen-containing heterocycles of different size (5- to 8-membered rings) in a regio- and stereoselective manner, acting as 1,4-dinucleophiles. The presence of the sulfone group in these heterocycles allows configurational and conformational studies by ^{1}H NMR. The possibilty of carrying out dehydrosulfinylation, reductive desulfonylation, and methylenation reactions with the sulfone-containing products augments the synthetic applicability of these reagents. This methodology could be applied, for instance, to the synthesis of other hexahydroazepines or heptahydroazocines, heterocycles that are present in balanol[24] and manzamine A.[25]

Experimental Section

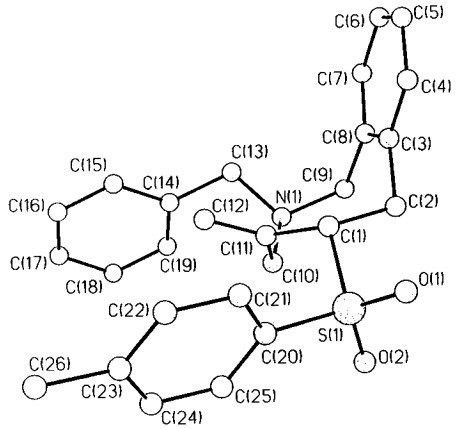
General Procedures. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. IR spectra were obtained as films as neat liquids. ^{1}H and ^{13}C spectra were recorded at 300 and 75 MHz, respectively, with $SiMe_4$ as internal standard using $CDCl_3$ as solvent. ^{13}C-NMR assignments were made on the basis of DEPT experiments. MS spectra were measured mainly by DIP injection (EI, 70eV). High-resolution mass spectra were measured in the corresponding instrument at the University of Valencia. Elemental analyses were performed by the Microanalyses Service of the University of Alicante. X-ray data were collected using a Mo Kα radiation (graphite crystal monochromator, $\lambda = 0.710\ 73$ Å), $\mu = 0.72$ cm^{-1}, $T = 22-25 \pm 1$ °C. The atomic coordinates and other data for compounds **20g** and **20i** were deposited in the Cambridge Crystallographic Data Centre.[30] Chromatographic analyses (GLC) were determined with a 25 m WCOT capillary column (0.22 mm diameters, 0.2 μm film thickness OV-101 stationary phase) using nitrogen (2 mL/min) as the carrier gas, $T_{injector} = 270$ °C, $T_{column} = 60$ °C, and 60−270 (15 °C/min). Thin layer chromatography (TLC) was carried out on plates coated with a 0.2 mm layer of silica gel, using a mixture of hexane/ethyl acetate as eluant, and revealed with iodine. Column chromatography was performed using silica gel 60 of 70−240 mesh and hexane/ether as eluant. All starting materials were commercially available of the best grade and were used without further purification. THF was dried with $LiAlH_4$ under an argon atmosphere and MeOH with magnesium turnings.

Synthesis of Benzyl[2-(tosylmethyl)-2-propenyl]amine (9). To a solution of 2-(chloromethyl)-3-tosylpropene (2.00 g, 8.18 mmol) in THF (20 mL) was added benzylamine (3.07 mL, 20.45 mmol), and the resulting mixture was stirred at 80 °C for 1 d. Then, a saturated aqueous solution of NaCl (20mL) was added, and the resulting mixture was extracted with ether (3 × 20mL), dried (Na_2SO_4), and evaporated (15 Torr), yielding crude compound **9** that was purified by column chromatography (silica gel, hexane/ether: 7/3) to afford 1.98 g (77%) of pure compound: mp 45−46 °C (hexane/ether); R_f 0.55 (ether); IR (KBr) 3320, 3070, 1630, 1300, 1130 cm^{-1}; ^{1}H NMR δ 1.45 (br s, 1H), 2.42 (s, 3H), 3.27 (s, 2H), 3.67 (s, 2H), 3.91 (s, 2H), 4.94, 5.27 (2s, 2H), 7.23−7.33 (m, 7H), 7.73 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR δ 21.5, 52.9, 53.2, 60.2, 120.6, 126.9, 128.0, 128.3, 128.4, 129.5, 135.6, 136.0, 140.1, 144.5; MS *m/e* 315 (M^+, <1), 224

(21) For a recent review about eight-membered rings see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821.
(22) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477−3478.
(23) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133−134.
(24) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402−8403.
(25) Li, S.; Kosemura, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 8217−8220.



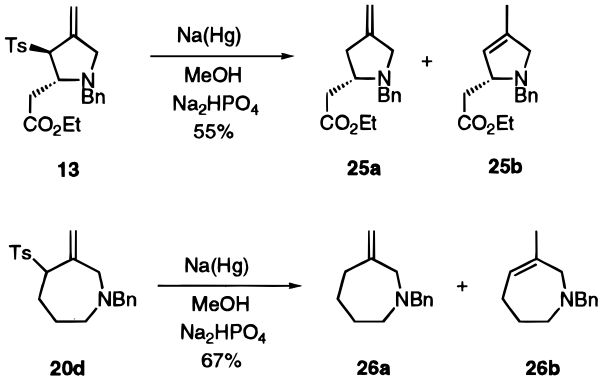
20g



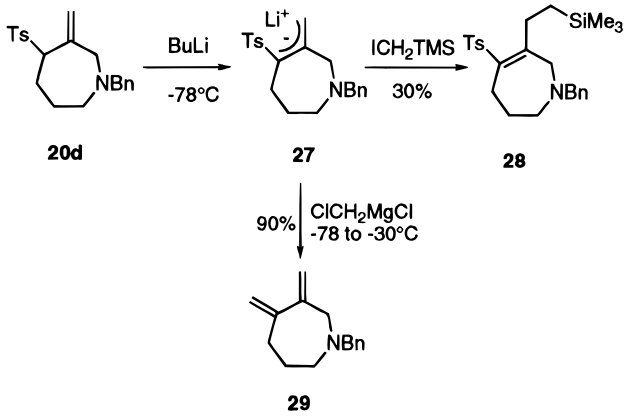
20i

Figure 1. Structures of **20g** and **20i**.

Scheme 7



Scheme 8



(5), 160 (32), 159 (12), 106 (17), 92 (10), 91 (100), 65 (19). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.57; H, 6.67; N, 4.44; S, 10.16. Found: C, 68.59; H, 7.00; N, 4.52; S, 9.48.

Mono- or Dilithiation of Benzyl[2-(tosylmethyl)-2-propenyl]amine. Reaction with Electrophiles. Synthesis of Compounds 11−14 and 20−23. General Procedure. To a solution of benzyl[2-(tosylmethyl)-2-propenyl]amine (**9**) (100 mg, 0.32 mmol) and DMPU (0.046 mL, 0.35 mmol or 0.092 mL, 0.70 mmol) in dry THF (3 or 10 mL) cooled at −78 °C was added a 1.6 M solution of *n*-butyllithium (0.218 mL, 0.35 mmol or 0.437 mL, 0.70 mmol) in hexanes. After 15 min of stirring, the corresponding electrophile was added (0.35 mmol) and the reaction mixture was warmed to room temperature (in the case of alkyl halides and carbonyl compounds, the reaction was warmed to −70 and −60 °C, respectively). The reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether (3 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (silica gel, hexane/ether) and/or recrystallization to afford compounds **11**−**14** and **20**−**23**. Yields and physical data are included in Tables 1 and 2; spectral and analytical data for representative compounds follow.

Benzyl(3-deuterio-2-methylene-3-tosylpropyl)amine (11a): R_f 0.55 (ether); IR (KBr) 3320, 3070,1630, 1300, 1130 cm^{-1}; ^{1}H NMR δ 1.6 (br s, 1H), 2.43 (s, 3H), 3.28 (s, 2H), 3.69 (s, 2H), 3.91 (s, 1H), 4.95, 5.28 (2s, 2H), 7.24−7.34 (m, 7H) 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 21.6, 53.0, 53.3, 60.0 (t, J = 21.2 Hz), 120.7, 127.0, 128.0, 128.4, 128.5, 129.6, 135.7, 136.0, 140.1, 144.6; MS *m/e* 316 (M$^+$, <1), 162 (12), 161 (15), 160 (12), 106 (31), 92 (11), 91 (100), 65 (18). Anal. Calcd for $C_{18}H_{20}DNO_2S$: C, 68.36; H/D,[26] 6.33; N, 4.43; S, 10.17. Found: C, 68.40; H/D, 6.40; N, 4.40; S, 10.18.

***tert*-Butyl 4-[(Benzylamino)methyl]-3-tosyl-4-pentenoate (11e):** IR (neat) 3700−3200, 1720, 1300, 1140 cm^{-1}; ^{1}H NMR δ 1.37 (s, 9H), 2.42 (s with m, 4H), 2.77 (dd, J = 16.2, 10.8 Hz, 1H), 3.01 (dd, J = 16.2, 4.6 Hz, 1H), 3.19, 3.26 (2d, J = 15.0 Hz, 2H), 3.65, 3.73 (2d, J = 13.3 Hz, 2H), 4.27 (dd, J = 10.8, 4.5 Hz, 1H), 5.10, 5.40 (2s, 2H), 7.21−7.34 (m, 7H), 7.70 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 21.6, 27.9, 35.0, 53.1, 54.0, 64.1, 81.6, 118.2, 126.9, 128.1, 128.3, 128.4, 129.5, 133.9, 139.9, 140.3, 144.8, 168.8; MS *m/e* 428 (M$^+$ − 1, <1), 218 (23), 172 (14), 139 (12), 129 (11), 120 (11), 106 (20), 92 (12), 91 (100), 85 (27), 83 (48), 65 (14), 57 (33), 47 (13), 41 (14).

***erythro/threo*-5-[(Benzylamino)methyl]-4-tosyl-5-hexen-3-ol (11f):** IR (neat) 3500, 3300, 3040, 1640, 870,1290, 1140 cm^{-1}; ^{1}H NMR δ (*erythro*) 0.87 (t, J = 6.1Hz, 3H), 1.14, 1.50 (2m, 2H), 1.96 (br s, 1H), 2.34 (s, 3H), 3.10, 3.18 (2d, J = 12.8 Hz, 2H), 3.20 (br s, 1H), 3.56, 3.64 (2d, J = 12.5 Hz, 2H), 3.73 (d, J = 4 Hz, 1H), 4.09 (m,1H), 5.06, 5.22 (2s, 2H), 7.15−7.25 (m, 7H), 7.64 (d, J = 8.3 Hz, 2H); ^{1}H NMR δ (*threo*) 0.91 (t, J = 7.3 Hz, 3H), 1.36, 1.69 (2m, 2H), 2.33 (m with s, 4H), 2.92, 3.01 (2d, J = 13.7 Hz, 2H), 3.52, 3.61 (2d, J = 13.1 Hz, 2H), 3.64 (br s, 1H), 3.84 (d, J = 7.6 Hz, 1H), 4.11 (ddd, J = 9.2, 7.6, 2.7 Hz, 1H), 5.12, 5.27 (2s, 2H), 7.15−7.25 (m, 7H), 7.61 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ (*erythro*) 10.3, 21.6, 28.9, 52.8, 53.0, 69.2, 75.1, 120.8, 127.4, 128.0, 128.2, 128.8, 135.4, 136.9, 138.5, 139.9, 144.5; ^{13}C NMR δ (*threo*) 10.0, 21.6, 27.3, 52.92, 53.1, 71.3, 73.2, 120.2, 127.1, 128.1, 128.4, 129.1, 129.4, 135.2, 138.1, 139.4, 144.7; MS *m/e* 372 (M$^+$ − 1, <1), 344 (M$^+$ − Et, <1), 218 (13), 106 (21), 91 (100), 65 (16); HRMS calcd for $C_{21}H_{25}NO_3S$ 372.1633, found M$^+$ − 1 372.1627.

***N*-Phenyl-3-[(benzylamino)methyl]-3-tosyl-3-butenamide (11g):** IR (neat) 3720−3200, 1640, 1300, 1140 cm^{-1}; ^{1}H

(26) The microanalysis method (sample weighted but D_2O + H_2O content measured gas chromatographically) does not allow the determination of %D content. Thus, calculated %H/D values are corrected considering this fact.

NMR δ (for the major rotamer) 1.98 (br s, 1H), 2.38 (s, 3H), 4.04 (br s, 2H), 4.35, 4.68 (2d, J = 15.9 Hz, 2H), 4.87 (s, 1H), 5.39, 5.45 (2s, 2H), 6.93−7.72 (m, 14H,), 9.16 (br s, 1H); ^{13}C NMR δ (for the major rotamer) 21.6, 50.3, 51.2, 72.6, 119.7, 120.3, 125.0, 127.6, 128.7, 128.8, 128.9, 129.5, 129.7, 133.1, 137.0, 139.3, 145.9, 156.0, 160.9; MS *m/e* 434 (M^+, <1), 279 (13), 264 (16), 186 (12), 173 (11), 130 (10), 106 (13), 93 (23), 92 (13), 91 (100), 77 (16), 65 (19).

Methyl *threo*-5-[(Benzylamino)methyl]-3-methyl-4-tosyl-5-hexenoate (11i): IR (neat) 3344, 3085, 1645, 816, 1735, 1313, 1302, 1288, 1144 cm^{-1}; ^{1}H NMR δ 1.20 (d, J = 6.7 Hz, 3H), 1.35 (br s, 1H), 2.25 (dd, J = 15.3, 9.2 Hz, 1H), 2.38 (s, 3H), 2.80−2.99 (m with dd at 2.91, J = 15.3, 3.7 Hz, 4H), 3.53, 3.59 (2d, J = 14.0 Hz, 2H), 3.65 (s, 3H), 3.86 (d, J = 6.7 Hz, 1H), 5.42, 5.49 (2s, 2H), 7.20−7.35 (m, 7H), 7.67 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 19.0, 21.5, 31.0, 38.4, 51.8, 53.0, 55.1, 70.6, 119.2, 127.0, 128.0, 128.3, 129.2, 129.3, 136.0, 139.3, 139.9, 144.3, 172.7; MS *m/e* 415 (M^+, <1), 260 (18), 186 (10), 106 (12), 92 (10), 91 (100), 65 (14); HRMS calcd for $C_{23}H_{29}NO_4S$ 415.1817, found M^+ 415.1810.

Methyl *erythro*-5-[(Benzylamino)methyl]-3-methyl-4-tosyl-5-hexenoate (11i): IR (neat) 3344, 3085, 1645, 816, 1735, 1313, 1302, 1288, 1144 cm^{-1}; ^{1}H NMR δ 1.15 (d, J = 6.8 Hz, 3H), 1.40 (br s, 1H), 2.37 (s, 3H), 2.50 (dd, J = 16.1, 7.6 Hz,1H), 2.81−2.94 (m, 4H), 3.54, 3.60 (2d, J = 14.0 Hz, 2H), 3.65 (s, 3H), 4.00 (d, J = 7.0 Hz, 1H), 5.41, 5.45 (2s, 2H), 7.19−7.34 (m, 7H), 7.65 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 17.5, 21.5, 30.3, 39.2, 51.5, 53.1, 53.2, 69.5, 119.4, 126.9, 127.9, 128.4, 129.3, 135.8, 138.9, 139.4, 140.0, 144.3, 172.3; MS *m/e* 415 (M^+, <1), 260 (27), 186 (10), 106 (28), 91 (100), 65 (17), 55 (10); HRMS calcd for $C_{23}H_{29}NO_4S$ 415.1817, found M^+ 415.1810.

***tert*-Butyl4-[[*N*-Benzyl-*N*-[(*tert*-butoxycarbonyl)methyl]-amino]methyl]-3-tosyl-4-pentenoate (12e):** IR (neat) 3030, 1630, 880, 1720, 1300, 1140 cm^{-1}; ^{1}H NMR δ 1.35, 1.45 (2s, 18H), 2.41 (s, 3H), 2.69 (dd, J = 16.2, 9.5 Hz, 1H), 2.94 (dd, J = 16.2, 5.5 Hz, 1H), 3.09, 3.18 (2d, J = 17.1 Hz, 2H), 3.25, 3.36 (2d, J = 15.0 Hz, 2H), 3.68, 3.80 (2d, J = 13.4 Hz, 2H), 4.35 (dd, J = 9.5, 5.5 Hz, 1H), 5.09, 5.51 (2s, 2H), 7.24−7.33 (m, 7H), 7.62 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.6, 27.9, 28.2, 35.1, 54.0, 57.8, 58.9, 63.5, 80.6, 81.4, 119.5, 127.0, 128.2, 128.9, 129.3, 129.4, 133.9, 139.0, 139.2, 144.6, 168.6, 170.6; MS *m/e* 452 (M^+ − Bn, 2), 442 (39), 386 (23), 172 (11), 91 (100), 57 (20).

***trans*-*N*-Benzyl-2-[(ethoxycarbonyl)methyl]-4-methylene-3-tosylpyrrolidine (13):** IR (neat) 3080, 1650, 880, 1720, 1300, 1150 cm^{-1}; ^{1}H NMR δ 1.24 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 2.58 (dd, J = 14.6, 4.0 Hz, 1H), 2.66 (dd, J = 14.6, 5.6 Hz, 1H), 2.80 (dq, J = 12.5, 2.1Hz, 1H), 3.22 (d, J = 12.5 Hz, 1H), 3.28, 3.98 (2d, J = 12.8 Hz, 2H), 3.62 (td, J = 5.5, 4.0 Hz, 1H), 4.14 (m, 2H), 4.08−4.20 (m, 2H), 4.40 (dq, J = 5.5, 1.8 Hz, 1H), 5.02, 5.12 (2br s, 2H), 7.17−7.34 (m, 7H), 7.76 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 14.1, 21.6, 37.5, 57.6, 58.0, 60.5, 61.5, 71.4, 113.8, 127.1, 128.1, 128.5, 129.5, 129.6, 134.0, 138.1, 139.0, 144.8, 170.7; MS *m/e* 326 (M^+ − CH_2CO_2Et, 2), 171 (10), 170 (26), 166 (15), 91 (100), 65 (20); HRMS calcd for $C_{16}H_{20}NO_4S$ 322.1113, found, M^+ − Bn 322.1114.

Ethyl (*E*)-3-[*N*-Benzyl-*N*-[2-(tosylmethyl)-2-propenyl]-amino]propenoate (14): mp 134−135 °C (hexane/ether); R_f 0.50 (ether); IR (KBr) 3040, 880, 1620, 1300, 1140 cm^{-1}; ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 3.69 (s, 2H), 3.83 (br s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.32 (br s, 2H), 4.73, 7.61 (2d, J = 13.1 Hz, 2H), 4.99, 5.17 (2s, 2H), 7.18−7.35 (m, 7H), 7.73 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 14.6, 21.6, 53.2, 59.1, 60.0, 61.5, 86.8, 152.0, 122.2, 127.4, 128.1, 128.4, 128.5, 128.8, 129.6, 129.8, 135.1, 145.0, 169.5; MS *m/e* 368 (M^+ − OEt, <1), 258 (62), 91 (100), 65 (11). Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.83; H, 6.54; N, 3.39; S, 7.7. Found: C, 66.88; H, 6.53; N, 3.41; S, 7.76.

***cis*-*N*-Benzyl-3-(chloromethyl)-3-hydroxy-5-methylene-4-tosylpiperidine (20b):** IR (neat) 3467, 1314, 1302, 1289, 1142 cm^{-1}; ^{1}H NMR δ 2.45 (s, 3H), 2.75 (dt, J = 11.9, 1.2 Hz, 1H), 3.17 (d, J = 11.9 Hz, 1H), 3.19, 3.32 (2br d, J = 12.3 Hz, 2H), 3.48, 3.98 (2d, J = 11.6 Hz, 2H), 3.54, 3.63 (2d, J = 13.1 Hz, 2H), 4.17 (br s, 1H), 4.39 (s, 1H), 4.52, 5.03 (2s, 2H), 7.23−7.34 (m, 7H), 7.74 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.7, 53.2, 55.7, 57.5, 61.9, 71.0, 73.8, 122.0, 127.3, 128.4, 128.7, 128.9, 129.5, 135.2, 135.6, 137.7, 145.1; MS *m/e* 376 (M^+ − 18, <1), 250 (19), 92 (10), 91 (100), 65 (20); HRMS calcd for $C_{14}H_{17}ClNO_3S$ 314.0618, found m^+ − Bn 314.0628.

***N*-Benzyl-3-methylene-4-tosylperhydroazepine (20d):** R_f 0.62 (ether); IR (KBr) 3060, 1630, 880, 1300, 1140 cm^{-1}; ^{1}H NMR δ 1.49−1.61, 1.67−1.76 (2m, 2H), 1.92−2.04, 2.26−2.35 (2m, 2H), 2.41−2.49 (m with s at 2.45, 4H), 2.95−3.00 (m, 1H), 3.04, 3.18 (2d, J = 13.4 Hz, 2H), 3.46, 3.65 (2d, J = 13.7 Hz, 2H), 3.86−3.92 (m, 1H), 5.04, 5.10 (2s, 2H), 7.20−7.34 (m, 7H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.5, 24.3, 26.3, 56.2, 57.2, 59.2, 70.4, 125.4, 127.0, 128.2, 128.8, 129.3, 129.4, 134.2, 137.4, 138.7, 144.4; MS *m/e* 355 (M^+, 1), 200 (27), 108 (27), 91 (100), 65 (17). Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.99; H, 7.04; N, 3.94; S, 9.01. Found: C, 71.03; H, 7.08; N, 3.90; S, 8.99.

***N*-Benzyl-3,6,7-trimethylene-4-tosylperhydroazocine (20h):** R_f 0.90 (ether); IR (KBr) 3030, 3020, 1630, 1300, 1140 cm^{-1}; ^{1}H NMR δ 2.38 (s, 3H), 2.88 (br d, J = 14.6Hz, 1H), 3.13 (m, 2H), 3.15 (d, J = 14.6, 1H), 3.24 (d, J = 13.7Hz, 1H), 3.36 (br d, J = 13.7 Hz, 1H), 3.38, 3.64 (2d, J = 13.4Hz, 2H), 3.91 (m, 1H), 4.77−4.80, 4.94−4.99 (2m, 4H), 5.07, 5.16 (2s, 2H), 7.15−7.36 (m, 7H), 7.54 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 21.6, 36.2, 60.8, 60.9, 62.1, 68.6, 113.5, 114.1, 120.8, 127.1, 128.2, 128.7, 129.0, 129.3, 134.9, 138.9, 139.8, 144.0, 147.3, 148.6; MS *m/e* 393 (M^+, <1), 238 (51), 92 (11), 91 (100), 65 (21). Anal. Calcd for $C_{24}H_{27}NO_2S$: C, 73.25; H, 6.92; N, 3.56; S, 8.13. Found: C, 73.21; H, 6.90; N, 3.60; S, 8.14.

Synthesis of *trans*-*N*-Benzyl-4-methyl-6-methylene-5-tosylheptanelactam (16). To a solution of compound **11i** (125 mg, 0.30 mmol) in dry THF (3mL) cooled at 0 °C was added a 1.6 M solution of n-BuLi (0.19 mL, 0.30 mmol) in hexanes. After 16 h of stirring at room temperature, the reaction mixture was poured into NH_4Cl and extracted with ether (3 × 15 mL). The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) to give crude product **16**, which was purified by column chromatography (silica gel, hexane/ether) to afford 50 mg (45%) of lactam **16** as an oil: R_f 0.42 (ether); IR (neat) 1676, 1314, 1302, 1289, 1146 cm^{-1}; ^{1}H NMR δ 1.07 (d, J = 7.2 Hz, 3H), 2.42 (s, 3H), 2.55 (dd, J = 14.5, 6.4 Hz, 1H), 3.05 (m, 1H), 3.43 (d, J = 2.8 Hz, 1H), 3.73 (dd, J = 14.5, 1.5 Hz, 1H), 3.41, 4.81 (2d, J = 15.3 Hz, 2H), 4.39, 4.76 (2d, J = 14.7 Hz, 2H), 4.50, 4.80 (2s, 2H), 7.25−7.30 (m, 7H), 7.62 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 18.4, 21.6, 26.3, 38.4, 48.8, 49.5, 75.1, 126.2, 127.5, 128.5, 128.5, 128.8, 129.5, 133.5, 134.0, 137.1, 144.9, 172.1; MS *m/e* 383 (M^+, <1), 228 (13), 106(11), 92 (11), 91 (100), 66 (19), 41 (10); HRMS calcd for $C_{22}H_{25}NO_3S$ 383.1555, found M^+ 383.1550.

Synthesis of Benzyl[(2-methylene)-3-butenyl]amine (17). To a solution of the silyl sulfone **11c** (255 mg, 0.63 mmol) in THF (5 mL) at 0 °C was added a 1.0 M solution of TBAF (1.9 mL, 1.9 mmol) in THF. After 1 h of stirring at 0 °C, the reaction mixture was hydrolyzed with water and extracted with ether (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (silica gel, hexane/ether) to afford 88 mg (80%) of compound **17**: t_R 10.61; IR (neat) 3347, 3085, 3062, 1614, 860, 1146 cm^{-1}; ^{1}H NMR δ 2.39 (br s, 1H), 3.47, 3.84 (2s, 4H), 5.12 (d, J = 11 Hz, 1H), 5.19, 5.25 (2 br s, 2H), 5.29 (d, J = 17.7 Hz, 1H), 6.43 (dd, J = 17.7, 11 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR δ 49.7, 53.4, 113.7, 116.4, 127.0, 128.2, 128.4, 137.6, 140.2, 143.9; *m/e* 173 (M^+, 12%), 120 (22), 91 (100), 65 (18), 41 (16).

Synthesis of (*E*)-4-[(Benzylamino)methyl]-2,4-pentadienenitrile (18). Crude compound **11d**, prepared from **9** (0.32 mmol) by monolithiation in THF at −78 °C (see before), was dissolved in dry CH_2Cl_2 (4 mL) at 0 °C, and then DBU was added (0.06 mL, 0.38 mmol). After 4 h of stirring at room temperature the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (silica gel, hexane/ether) to afford 24.1 mg (38% from **9**) of compound **18**: R_f 0.30 (hexane/ether 1/2); IR (neat) 3338, 3085, 3061, 1624, 2217 cm^{-1}; ^{1}H NMR δ 1.5 (br s, 1H), 3.41, 3.77 (2s, 4H), 5.45, 5.56 (2s, 2H), 5.66, 7.04 (2d, J = 16.5 Hz, 2H), 7.29−7.37 (m, 5H); ^{13}C NMR δ 49.8, 53.3, 97.8, 118.2, 124.9, 127.2, 128.1, 128.5, 139.7, 142.0, 150.9; MS *m/e* 198 (M^+,

6), 120 (19), 92 (11), 91 (100), 65 (22), 51 (10); HRMS calcd for $C_{13}H_{14}N_2$ 198.1157; found M^+ 198.1157.

Synthesis of *tert*-Butyl (*E*)-4-[(Benzylamino)methyl]-2,4-pentadienoate (19). To a solution of (**9**) (100 mg, 0.32 mmol) in dry THF (3 mL) cooled at −78 °C was added a 1.6 M solution of *n*-BuLi (0.21 mL, 0.33 mmol) in hexanes. After 15 min of stirring, *tert*-butyl bromoacetate was added (0.50 mL, 0.33 mmol) and the reaction mixture was warmed to −70 °C. Then, additional 1.6 M solution of *n*-BuLi (0.21 mL, 0.33 mmol) in hexanes was added. After 1 h of stirring at −70 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with ether (3 × 10 mL). The organic layer was dried (Na_2SO_4) evaporated, and the residue was purified by column chromatography (silica gel, hexane/ether) to afford 37.5 mg (43% from **9**) of compound **19**: R_f 0.63 (ether); IR (neat) 3339, 3085, 3063, 3027, 982, 1708, 1152 cm^{-1}; ^1H NMR δ 1.49 (s, 9H), 1.55 (br s, 1H), 3.42 (m, 2H), 3.80 (s, 2H), 5.46, 5.51 (m, 2H), 5.91, 7.24 (2d, J = 16.2 Hz, 2H), 7.33 (s, 5H); ^{13}C NMR δ 28.1, 49.7, 53.3, 80.3, 120.3, 144.0, 122.9, 127.0, 128.1, 128.4, 140.0, 142.5, 166.3; MS *m/e* 217 (M^+ − Bu^t, 28), 172 (18), 120 (29), 92 (10), 91 (100), 65 (12), 57 (15), 41 (45); HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found M^+ 273.1734.

Reduction of Compounds 13 and 20d with Sodium Amalgam. General Procedure. To a suspension of anhydrous NaH_2PO_4 (251mg, 1.75 mmol) in *ca*. 6% sodium amalgam (1.70 g, 4.4 mmol) in dry methanol (5 mL) was added dropwise at 0 °C the corresponding sulfone (0.44 mmol) in methanol (1.5 mL). The reaction mixture was stirred at room temperature until the reduction was complete (monitored by TLC, GLC). Then, the reaction mixture was hydrolyzed with water and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo (15 Torr), and the residue was purified by column chromatography (silica gel, hexane/ether) to yield compounds **25** and **26**.

Δ³-*N*-Benzyl-2-[(methoxycarbonyl)methyl]-4-methylpyrrolenine (25b): yield 55% (main product); R_f 0.31 (hexane/ether: 7/3); IR (neat) 1730 cm^{-1}; ^1H NMR δ 1.68 (s, 3H), 2.43 (dd, J = 15.0, 8.0 Hz, 1H), 2.57 (dd, J = 15.0, 5.3 Hz, 1H), 3.11−3.19 (m, 1H), 3.58, 4.02 (2d, J = 13.1 Hz, 2H), 3.66 (s, 3H), 3.68 (s, 2H), 5.38 (dq, J = 5.5, 1.5 Hz, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR δ 14.3, 40.9, 51.4, 59.0, 63.7, 67.8, 124.3, 126.9, 128.3, 128.6, 137.5, 139.8, 172.6; MS *m/e* 245 (M^+, <1), 172 (29), 91 (100), 65 (11), 41 (14); HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found M^+ 245.1413.

***N*-Benzyl-3-methyleneperhydroazepine and Δ³-*N*-Benzyl-3-methyl-1,2,5,6,7-pentahydroazepine (26a, 26b):** yield 67%; R_f 0.90 (ether); IR (neat) 3060, 3020, 1650, 900 cm^{-1}; ^1H NMR δ 1.43 (s, 3H), 2.20−2.43, 2.62−2.87 (2m, 6H), 2.17 (m, 2H), 2.39, 2.64 (2m, 4H), 2.85 (t, J = 6.0 Hz, 2H), 3.15 (s, 2H), 3.32 (s, 2H), 3.66, 3.67 (2s, 4H), 4.71, 4.79 (2 br s, 2H), 5.64 (m, 1H), 6.98−7.34 (m, 10H); ^{13}C NMR δ 24.7, 27.2, 28.4, 29.3, 34.9, 55.5, 57.9, 58.3, 60.2, 61.3, 111.5, 126.8, 126.9, 127.1, 128.1, 128.2, 128.8, 128.9, 132.6, 137.1, 139.8, 149.8; MS *m/e* 201 (M^+, 13), 186 (10), 120 (48), 92 (10), 91 (100), 65 (17), 41 (14); HRMS calcd for $C_{14}H_{19}N$, 201.1518, found M^+ 201.1520.

Synthesis of *N*-Benzyl-4-tosyl-3-[(trimethylsilyl)ethyl]-1,2,5,6,7-pentahydroazepine (28). To a solution of compound **20d** (92 mg, 0.26 mmol) in dry THF (3 mL) cooled at −78 °C was added a 1.6 M solution of n-BuLi (0.211 mL, 0.33 mmol) in hexanes. After 15 min of stirring, iodotrimethylsilane was added (0.050 mL, 0.33 mmol), and the reaction mixture was warmed to room temperature. The reaction mixture was hydrolyzed with water and extracted with ether (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated (15 Torr), and the residue was purified by column chromatography (silica gel, hexane/ether) to afford 34 mg (30%) of compound **28**: R_f 0.67 (ether/hexane: 3/1); IR (neat) 1308, 1300, 1289, 1143, 1248, 833, 740 cm^{-1}; ^1H NMR δ −0.14 (s, 9H), 0.26−0.33 (m, 2H), 1.49−1.57 (m, 2H), 2.32−2.38 (m, 2H), 2.41 (s, 3H), 2.62 (m, 2H), 2.77 (t, J = 5.8Hz, 2H), 3.16 (s, 2H), 3.55 (s, 2H), 7.18−7.31 (m, 7H), 7.71 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ −2.1, 15.0, 21.5, 25.8, 28.6, 28.7, 58.7, 59.1, 61.5, 127.1, 127.3, 128.3, 129.0, 129.6, 136.8, 138.8, 139.3, 143.5, 157.6; MS *m/e* 441 (M^+, 3), 286 (34), 120 (64), 92 (10), 91 (100), 73 (30).

Synthesis of *N*-Benzyl-3,4-dimethyleneperhydroazepine (29). To a solution of (chloromethyl)magnesium chloride at −78 °C in THF (0.42 mmol) [prepared from reaction of chloroiodomethane (32 μL, 0.42 mmol) and isopropylmagnesium chloride (212 μL, 0.42 mmol) at −78 °C] was transferred with a cannula a solution of lithiated sulfone **20d** (75 mg, 0.21 mmol) at −78 °C, and the reaction mixture was allowed to warm to −30 °C. Then, the reaction was hydrolyzed with water and extracted with ether (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) to give 58 mg (74% CG) of crude product **29**, which was purified by column chromatography (silica gel, hexane/ether) to afford 40.5 mg (90%) of pure title product: R_f 0.82 (ether/hexane: 3/1); IR (neat) 3081, 894 cm^{-1}; ^1H NMR δ 1.66−1.73 (m, 2H), 2.39−2.43 (m, 2H), 2.86 (t, J = 5.3 Hz, 2H), 3.47 (s, 2H), 3.65 (s, 2H), 4.67, 4.81 (2s, 2H), 5.27, 5.30 (2br s, 2H), 7.21−7.31 (m, 5H); ^{13}C NMR δ 28.5, 35.7, 57.2, 57.3, 59.1, 110.5, 111.9, 126.7, 128.1, 128.8, 139.4, 148.1, 150.3; MS *m/e* 213 (M^+, 22), 212 (24), 198 (11), 122 (12), 92 (12), 91 (100), 79 (13), 65 (20), 42 (18), 41 (16); HRMS calcd for $C_{15}H_{19}N$ 213.1518, found M^+ 213.1508.

X-ray Structure Determination. Colorless crystals used for the X-ray diffraction analyses were obtained by slow evaporation of solutions of compounds **20g** (in ether) and **20i** (in a mixture of CH_2Cl_2 and hexane). Crystal data and a summary of data collection parameters and refinement results have been deposited with the Cambridge Crystallographic Data Centre.[30] Crystals of both compounds were found to be weak scatterers. For both examples, the unit cell parameters were refined to the positions of 25 well-centered reflections[27] in the 2θ range 22.1−31.7° for **20g** and 18.2−20.1° for **20i**. During the collection of intensity data, three monitor reflections were remeasured at regular intervals and did not show any significant change in intensity for either crystal. For both data sets, empirical absorption corrections were based on azimutal scans of several scattering vectors, giving correction factors in the range of 0.86−0.92 for **20g** and 0.90−0.95 for **20i**.[28] The structures were solved by direct methods and refined to F_o2 using full-matrix least-squares calculations.[29] All non-hydrogen atoms were refined with anisotropic displacement parameters for both structures. For **20g**, 25 of the 27 hydrogen atoms were located in a difference Fourier map at the end of the anisotropic refinement of the other atoms. Those hydrogen atoms that behaved well in the refinement were allowed to refine freely. The others were placed at idealized positions and treated as riding atoms. All data with $F_o2 > -\sigma(F_o2)$—that is, all positive data and small negative data—were used in the refinement. For the structure of **20i**, for which the diffraction pattern was very weak and measurements of negative data suspect, all positive data were used in the refinement. At the end of the anisotropic refinement of the non-hydrogen atoms, 26 of the 27 hydrogen atoms were found in a difference map. Because most of these behaved poorly in the last-squares refinement, all were placed at idealized positions. All hydrogen atoms except those of the terminal methylene and methyl groups were treated as riding atoms. For the terminal methylene group, the two C−H distances were loosely restrained to equality. The methyl group was treated as a variable metric rigid group—a rigid group that can expand or contract but that does not change

(27) Diffractometer control program. For **20g**: CAD4-PC, Delft Instruments X-ray Diffraction bv, Delft, The Netherlands, 1993. For **20i**: CAD4-PC V 1.5c, Delft Instruments X-ray Diffraction bv, Delft, The Netherlands, 1994.

(28) Data processed on a Local Area VAXcluster (VMS V5.5-2), with programs of the commercial package SHELXTL-PLUS Release 4.21/V: Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990. Least-squares calculations[29] were done on a Hewlett-Packard 715/50 (HP-UX V9.01).

(29) (a) Sheldrick, G. M. Shelxl-93: FORTRAN-77 program for the refinement of crystal structures from diffraction data. University of Göttingen, 1993. (b) Sheldrick, G. M. *J. Appl. Chem*. Manuscript in preparation.

(30) The author has deposited atomic coordinates for **20g**,**i** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

shape—with a variable torsion angle about the adjacent C—C bond. Each hydrogen atom was assigned an anisotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom.

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Supporting Information Available: Configurational and conformational assignments (**13**, **20b**,**c**,**e**,**f**,**h**,**i**). Spectral and analytical data (**11a′**,**b**—**d**,**h**, **12b**, **20a**,**c**,**e**—**g**,**i**, **21a**,**c**, **22**, and **23**). Copies of ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of new compounds lacking microanalyses (**11e**,**g**,**h**, **12e**, **17**, **20c**, **23**, and **28**) (24 pages). This material is contained in libraries on microfiche, inmediately 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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