3-Chloro-2-(phenylsulfinyl)-1-propene and 3-Chloro-2-(phenylsulfonyl)-1-propene: Preparation and Utility as Reagents for α,α'-Annelation of Cyclic Ketones

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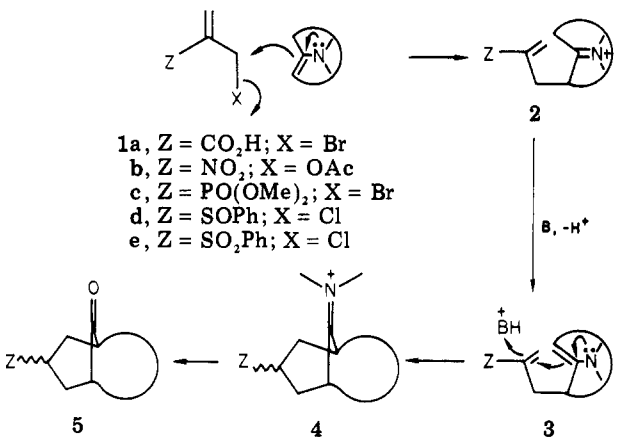
The reaction of allyl chloride (7), at −40 °C to −20 °C, with in situ generated phenylsulfenyl chloride (6) affords exclusively the anti-Markovnikov product 1,3-dichloro-2-(phenylthio)propane (8) in 85–90% yield. Oxidation of 8 with 1 equiv of MCPBA to sulfoxide 9 followed by DBU-catalyzed dehydrochlorination yields 3-chloro-2-(phenylsulfinyl)-1-propene (1d) (70%). Treatment of 8 with 2 equiv of MCPBA yields sulfone 10 which is similarly dehydrochlorinated to 3-chloro-2-(phenylsulfonyl)-1-propene (1e) (81%). The reaction of pyrrolidine enamines of cyclic ketones with 1d and 1.1 equiv of triethylamine in Me_2SO at 95–100 °C affords moderate yields of bicyclic keto thioenol ethers, formed via an α,α'-annelation–Pummerer reaction sequence, together with noncyclized, 2-(phenylsulfinyl)allylated ketone. Similar reactions with 1e provide good yields of bicyclic keto sulfones as approximate 1:1 mixtures of endo and exo isomers, which may be equilibrated to mixtures containing predominantly the exo compounds by treatment with methanolic sodium methoxide.

Any useful annelating agent in Lawton's α,α'-cyclic ketone annelation procedure (Scheme I) must be capable of acting sequentially as an alkylating agent and Michael acceptor.[1] The simplest are substituted propenes, which correspond in structure to the generic 1, wherein X is some leaving group and Z is an electron-withdrawing function. Depending on the nature of Z, quite a variety of bicyclic ketones 5 become available from the reaction.

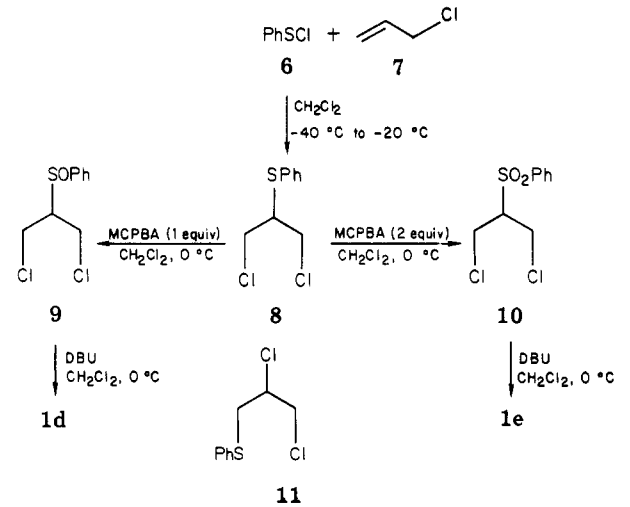
To date, only three Z variants of 1 have been reported: simple esters of α-(bromomethyl)acrylic acid (1a),[2] 3-acetoxy-2-nitro-1-propene (1b),[3] and dimethyl 3-bromo-2-propenylphosphonate (1c).[4] Of these, only the α-(bromomethyl)acrylates have been employed as annelating agents.[1,5] We have recently achieved practical syntheses of two additional Z variants of 1, 3-chloro-2-(phenylsulfinyl)-1-propene (1d) and 3-chloro-2-(phenylsulfonyl)-1-propene (1e), and have examined their utility as annelating agents. Our results are reported herein.

Scheme II outlines our syntheses of 1d and 1e. Since both are prepared from 1,3-dichloro-2-(phenylthio)propane (8), its facile, high-yield preparation was desired. Based on the reported reactions of allylic halides and alcohols with halogens and pseudohalogens, we expected a predominance of 8, the anti-Markovnikov adduct, from the addition of phenylsulfenyl chloride (6) to allyl chloride (7).[6] We found that when a slight excess of 7 is added to a cold (−40 °C) methylene chloride solution of 6, generated in situ from thiophenol and *N*-chlorosuccinimide,[7] and the reaction maintained at −40 °C to −20 °C until complete, the addition proceeds undirectionally, affording only 8 in 85–90% yield. Under these conditions, we have not observed the Markovnikov product 11.[8] Careful oxidation of 8 in methylene chloride at 0 °C with 1 equiv of MCPBA gives sulfoxide 9 which upon DBU-catalyzed dehydrochlorination yields 1d (70%). Treatment of 8 with 2 equiv of MCPBA yields sulfone 10 which is similarly dehydrochlorinated to 1e (81%).

Scheme I



Scheme II



(1) (a) Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 3884. (b) Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. (c) McEuen, J. M.; Nelson, R. P.; Lawton, R. G. *Ibid.* **1970**, *35*, 690.

(2) (a) Ferris, A. F. *J. Org. Chem.* **1955**, *20*, 780. (b) Villieras, J.; Ramboud, M. *Synthesis* **1982**, 924.

(3) (a) Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223. (c) Knochel, P.; Seebach, D. *Ibid.* **1982**, *23*, 3897. (d) Klager, K. *Monatsh Chem.* **1965**, *96*, 1.

(4) Collard, J.; Benezra, C. *Tetrahedron Lett.* **1982**, *23*, 3725.

(5) (a) Speckamp, W. N.; Dijkink, D.; Huisman, H. O. *J. Chem. Soc. D* **1970**, 196. (b) Speckamp, W. N.; Dijkink, J.; Dekkers, A. W. J. D.; Huisman, H. O. *Tetrahedron* **1971**, *27*, 3143.

(6) (a) De la Mare, P. B. D.; Pritchard, J. G. *J. Chem. Soc.* **1954**, 3910. (b) De la Mare, P. B. D.; Naylor, P. G.; Williams, D. L. H. *Ibid.* **1962**, 443. (c) Clarke, C. A.; Williams, D. L. H. *Ibid.* **1966**, 1126. (d) Williams, D. L. H. *J. Chem. Soc. B* **1969**, 421. (e) Hooley, S. R.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1053.

(7) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

(8) G. A. Jones, C. J. M. Stirling, and N. G. Bromby in a recent report (*J. Chem. Soc., Perkin Trans. 2* **1983**, 385) examined the rates of addition of purified phenylsulfenyl chloride (6) to a variety of alkenes which included allyl chloride (7). They report production of both the Markovnikov (11) and anti-Markovnikov (8) adducts. Neither the yield of each nor their product ratio is given.

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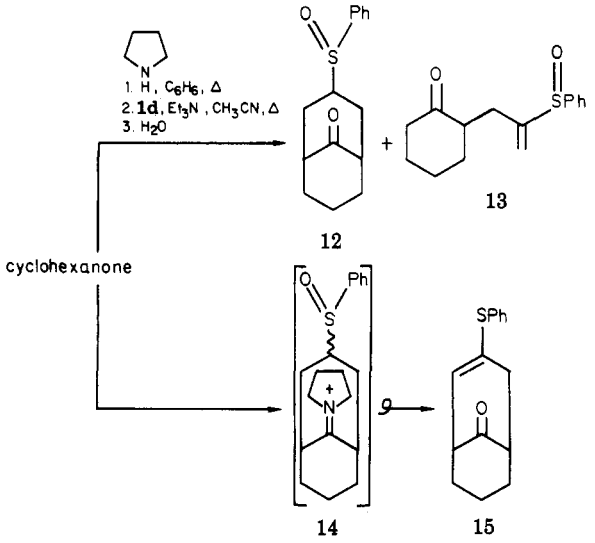
The reaction of sulfoxide **1d** with the pyrrolidine enamine of cyclohexanone and excess triethylamine in refluxing acetonitrile yielded an annelated product, together with noncyclized, (phenylsulfinyl)-allylated product **13**. Upon examination of the spectral characteristics of the annelated product, we learned that we had not obtained the expected keto sulfoxide mixture **12**, but had keto thioenol ether **15**. The (presumed) sulfoxide intermediate **14** had undergone a Pummerer-type reaction under the reaction conditions. In a single step, then, we had succeeded in regiospecifically riveting a masked acetonyl unit to cyclohexanone, a transformation that heretofore has not readily been achieved.



As the results summarized in Table I indicate, our annelation–Pummerer sequence appears quite general. We have never isolated any bicyclic sulfoxides from the reaction.[9] Unfortunately, **1d** is not a particularly effective annelating agent. We list no examples where the yield of thioenol ether is much greater than 40%. Allylation proceeds readily, but subsequent Michael cyclization is difficult. Although we did not routinely quench our reactions once allylation had been achieved, we did obtain a 81% yield of **13** from cyclohexanone after an early workup. Thus, the reaction of enamines with **1d** might well prove a useful route to 1,4-diketones.

For annelation, the following observations are noteworthy. The use of Me_2SO as solvent appears optimum. Annelation does not occur in benzene or ethanol, while only little is observed in dioxane, DMF, and acetonitrile. Either triethylamine or DBU may be used as catalysts. As with

(9) A purely speculative argument for the facility of our Pummerer rearrangement invokes intramolecular reaction of the iminium moiety of **4** (Z = *exo*-phenylsulfinyl) and the easily accessible sulfinyl oxygen, as shown below. Subsequent proton abstraction followed by [1,3]-hydrogen migration would then lead to the Pummerer product.

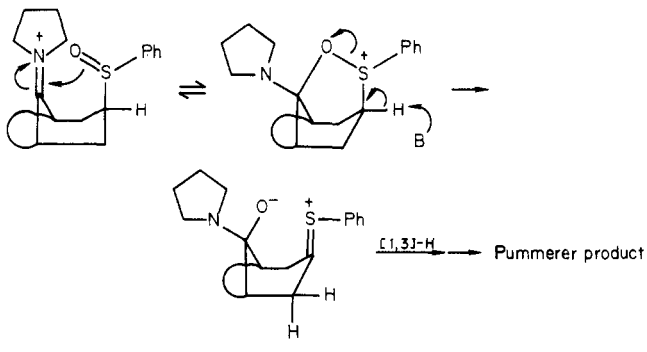
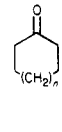
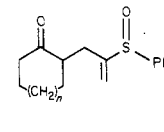
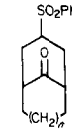
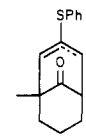
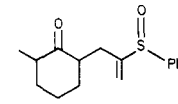
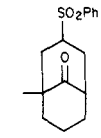
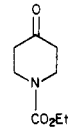
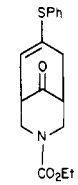
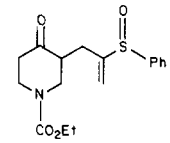
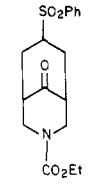


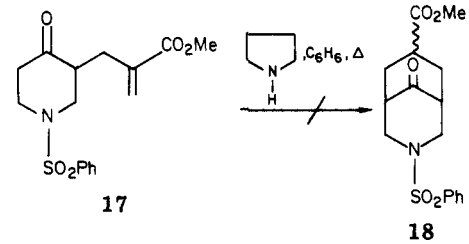
Table I. Keto Thioenol Ethers, (Phenylsulfinyl)allylated Ketones, and Keto Sulfones from Annelations with 1d and 1e

ketone	keto thioenol ether (% yield)[a]	(phenylsulfinyl)-allylated ketone (% yield)[a]	keto sulfone (% yield,[a] endo/exo)
			
$n = 0$	(31)	(19)	(51, 1)
$n = 1$	(41)	(16) (81)[b]	(84, 1)
$n = 2$	(43)	(20)	(75, 1)
			
	(15)[c]	(45)[d]	(78, 1)
			
	(42)	(17)	(83, 2)

[a] Isolated yields; satisfactory analytical data (±0.4% C, H, N, S) were obtained for all new compounds listed. [b] Yield obtained when reaction was quenched after 4 h at 90 °C. [c] A 1:1 mixture of double-bond isomers. [d] The cis to trans ratio was 1:1.

1a, comparable yields of annelation product are obtained if dichloro sulfoxide **9** is substituted for **1d** and the reaction is conducted in the presence of 2.2 equiv of base, thereby generating **1d** in situ. The yields in Table I reflect those obtained by this procedure. The use of 3.3 equiv of base, to account for what may be consumed during the Pummerer reaction, results in no increased annelation yield. Also, conducting the reaction in the presence of activated molecular sieves to remove any water which may be formed during the Pummerer reaction and which conceivably would hydrolyze any allylated enamine intermediate, preventing cyclization, gives no increased yield of annelated product.

Speckamp, in a report on the synthesis of substituted 3-azabicyclo[3.3.1]nonanes, noted that allylated ketone **17**



could not be cyclized to the bicyclic system **18** by repeated treatment with pyrrolidine.[5] When we treated allylated ketone **13** with excess pyrrolidine (3–5 equiv) in refluxing benzene for periods of up to 3 days, we observed no enamine formation and recovered **13** unchanged after distillation of the solvent and amine.

Sulfone **1e** proved quite an effective annelating agent, affording good yields of bicyclic keto sulfones **5** (Z = $PhSO_2$). As was expected, the greater electron-withdrawing character of the sulfone moiety, coupled with its better

ability to stabilize a developing proximate anion, facilitated Michael cyclization once allylation had been achieved. Annelation was usually complete after 2–3 h of heating. As with **1d**, in situ generation of **1e** from **10** was an effective expedient.

Contrary to Lawton's results with **1a**, we saw no endo selectivity in our annelations with **1e**. In all but one of the examples studied, approximately equal mixtures of endo and exo sulfones, as determined by ^1H NMR and/or chromatographic analysis, were afforded. In a model experiment however, the endo/exo sulfone mixture obtained from cyclopentanone was equilibrated to a mixture containg >95% the exo isomer, by refluxing in methanol with 15 mol % of sodium methoxide.

Experimental Section

All melting points were determined on a Thomas Hoover Uni-Melt capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. Proton magnetic resonance spectra were recorded at 60 MHz on a Varian EM360A spectrometer, with tetramethylsilane used as an internal standard. Low-resolution mass spectra were obtained on a Finnigan 4023 GC/MS/DS instrument operated in the chemical ionization mode. Preparative HPLC purifications were performed on a Waters Prep LC/system 500 over Prep Pak 500/silica cartridges. Analytical TLC was performed on Brinkmann, silica gel 60-F254 precoated (0.25 mm) glass plates. Microanalyses were obtained from the Merrell Dow Analytical Dept.

All of the starting ketones, the pyrrolidine enamines of cyclohexanone and cyclopentanone, pyrrolidine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), *m*-chloroperbenzoic acid (MCPBA), thiophenol, allyl chloride, *N*-chlorosuccinimide, and Me_2SO (Gold Label) were obtained from the Aldrich Chemical Co. and used without purification. If the starting pyrrolidine enamine was not available commercially, it was prepared in the usual manner[10] and used as isolated after removal of the solvent and excess pyrrolidine.

1,3-Dichloro-2-(phenylthio)propane (8). The foul odor of thiophenol necessitates that this reaction be conducted in a well-ventilated hood. To a mechanically stirred, nitrogen-blanketed suspension of 6.8 g (0.05 mol) of *N*-chlorosuccinimide in 60 mL of dry methylene chloride at room temperature in a 250-mL flask equipped with a pressure-equalizing dropping funnel, thermometer, and an efficient condenser was added about 0.5 g of a total of 5.5 g (0.05 mol) of thiophenol. The mixture was then gently heated on a steam bath for 1 to 2 min until sulfenyl chloride formation commenced as evidenced by the intense orange coloration of the suspension.[11] Once initiated, the remaining thiophenol was added dropwise at a rate sufficient to maintain the solvent at reflux. Intermittent cooling with an ice bath may be necessary to moderate the vigor of the reaction. When the addition was complete (usually about 30 min were required), the homogeneous orange solution was stirred at room temperature for an additional 30 min. Succinimide precipitates during this time. The suspension was then cooled to −40 °C in a dry ice–acetone bath and 4.2 g (0.055 mol) of allyl chloride was added in one portion. The mixture was then maintained at −40 °C to −20 °C until complete decoloration of the sulfenyl chloride suspension was observed (1 to 2 h). After warming to 0 °C, the cold, colorless suspension was filtered to remove the majority of the succinimide, which was washed with 25 mL of methylene chloride. Concentration of the combined filtrate and wash left a pale yellow oil which was diluted with 30 mL of carbon tetrachloride to precipitate the remainder of the succinimide. This suspension was let stand 1 h and then filtered, and the filtrate was evaporated to dryness, leaving 11.2 g of crude **8** which was sometimes contaminated by a small amount of diphenyl disulfide. Distillation on a Kugelrohr apparatus (90–95 °C, 0.2 mm) afforded 9.5 g (86%) of pure **8** as a pale yellow oil: NMR ($CDCl_3$) δ 7.20–7.60 (m, 5), 3.86 (d, 4, J = 5 Hz), 3.30–3.70 (m, 1); mass spectrum, m/e (relative intensity) 111 (100), 139 (15), 141 (7), 185 (38), 187 (14), 221 (18) 223 (12).

Anal. Calcd for $C_9H_{10}Cl_2S$: C, 48.88; H, 4.56; Cl, 32.06; S, 14.50. Found: C, 48.62; H, 4.36; Cl, 32.00; S, 14.45.

1,3-Dichloro-2-(phenylsulfinyl)propane (9). To a stirred solution of 4.4 g (0.02 mol) of **8** in 25 mL of dry methylene chloride, cooled to 0 °C under nitrogen, a solution of exactly 1 equiv of *m*-chloroperbenzoic acid (4.0 g of 86.9% MCPBA) in 50 mL of methylene chloride was added dropwise at such a rate as to maintain a reaction temperature of 0–5 °C. The addition usually required about 1 h. When the addition was complete, the mixture was stirred an additional 20 min and then filtered to remove the majority of the chlorobenzoic acid, which was washed with 30 mL of methylene chloride. The combined filtrate and wash was diluted with 50 mL of methylene chloride and then washed successively with 10% $NaHCO_3$ (50 mL), 10% $NaHSO_3$ (50 mL), 10% $NaHCO_3$ again (50 mL), and saturated brine and finally dried (Na_2SO_4). Filtration and evaporation of solvent left 4.6 g (97%) of **9** as a pale yellow oil which was pure enough to be used without further purification. Attempted distillation at 0.1 mm led to extensive decomposition. An analytical sample was obtained as a colorless oil after HPLC purification using 2% acetone in methylene chloride as eluent: NMR ($CDCl_3$) δ 7.40–7.90 (m, 5), 3.68–4.10 (m, 4), 2.95–3.50 (m, 1); IR (neat) 1080, 1040 cm^{-1}; mass spectrum, m/e (relative intensity) 109 (13), 125 (100), 126 (32), 127 (20), 237 (53), 239 (36).

Anal. Calcd for $C_9H_{10}Cl_2OS$: C, 45.58; H, 4.25; Cl, 29.90; S, 13.52. Found: C, 45.48; H, 4.23; Cl, 29.81; S, 13.48.

1,3-Dichloro-2-(phenylsulfonyl)propane (10). This compound was prepared from **8** by the same procedure used for the preparation of **9** above, save that 2.1 equiv of MCPBA were employed. From 4.4 g (0.02 mol) of **8** was obtained 4.9 g (98%) of **10** as a colorless oil which solidified on standing. This material was pure enough to be used without further purification. Recrystallization from 9:1 hexane–benzene gave analytically pure material as glistening, colorless plates: mp 70–71 °C; NMR ($CDCl_3$) δ 7.40–8.10 (m, 5), 4.03 (d, 4, J = 5 Hz), 3.40–3.80 (p, 1, J = 5 Hz); IR (CCl_4) 1330, 1150 cm^{-1}; mass spectrum, m/e (relative intensity) 141 (48), 143 (12), 217 (22), 219 (8), 253 (100), 255 (72).

Anal. Calcd for $C_9H_{10}Cl_2O_2S$: C, 42.69; H, 3.98; Cl, 28.03; S, 12.66. Found: C, 42.72; H, 3.92; Cl, 27.95; S, 12.61.

3-Chloro-2-(phenylsulfinyl)-1-propene (1d). A solution of 1.6 g (10.5 mmol) of DBU in 25 mL of dry methylene chloride was added dropwise during 20 min, under a nitrogen atmosphere, to a stirred solution of 2.3 g (10 mmol) of **9** and approximately 25 mg of hydroquinone in 20 mL of methylene chloride. The reaction temperature was maintained at 0–5 °C for an additional 90 min, then diluted while cold with 40 mL of methylene chloride, washed with 25 mL each of chilled 1 N HCl, water, and brine, and finally dried over anhydrous sodium sulfate. Evaporation of solvent in vacuo left 1.6 g (80%) of **1d** as a yellow oil which was pure enough to be used without further purification. An analytical sample was obtained by percolation through a short silica gel column using 2% acetone in methylene chloride as eluent: NMR ($CDCl_3$) δ 7.35–7.90 (m, 5), 6.22 (br s, 1), 6.02 (br s, 1), 3.98 (q, 2, J_{AB} = 14 Hz); mass spectrum, m/e (relative intensity) 125 (32), 201 (100), 203 (40).

Anal. Calcd for C_9H_9ClOS: C, 53.86; H, 4.52; Cl, 17.67; S, 15.98. Found: C, 53.72; H, 4.50; Cl, 17.70; S, 15.92. A sample of **1d** containing 0.1% hydroquinone was unchanged by NMR examination after storage under nitrogen for over 1 month at 10 °C.

3-Chloro-2-(phenylsulfonyl)-1-propene (1e). This compound was prepared from **10** by the same procedure as that used for the preparation of **1d** from **9**. From 2.5 g (0.01 mol) of **10** was obtained 2.0 g (92%) of **1e** as a nearly colorless oil which was used without purification. An analytical sample was obtained by percolation through a short silica gel column using 2% acetone in methylene chloride as eluent: NMR ($CDCl_3$) δ 7.38–8.02 (m, 5), 6.62 (m, 1), 6.23 (m, 1), 4.23 (m, 2); IR (neat) 1320, 1150 cm^{-1}; mass spectrum, m/e (relative intensity) 117 (20), 125 (22), 141 (18), 183 (10), 217 (100), 219 (52).

Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.19; Cl, 16.36; S, 14.80. Found: C, 49.71; H, 4.18; Cl, 16.40; S, 14.74. A sample of **1e** containing 0.1% of hydroquinone was unchanged by NMR ex-

(10) Stork, G.; Brizzolara, A; Landesman, H. L.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(11) As explained in ref 7, the addition of substantially larger amounts of thiophenol at this point invariably results in an uncontrollably exothermic initiation.

amination after storage under nitrogen for 1 month at 10 °C.

Conversion of Ketones into Keto Thioenol Ethers and (Phenylsulfinyl) Allylated Ketones by Reaction with 1d (9). The following procedure for the conversion of cyclohexanone to 3-(phenylthio)-9-oxobicyclo[3.3.1]non-2-ene (**15**) and 2-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone (**13**) is representative. To a stirred, nitrogen-blanketed solution of 1.5 g (0.01 mol) of the pyrrolidine enamine of cyclohexanone, 2.2 g (0.022 mol) of triethylamine, and 20 mg of hydroquinone in 20 mL of dry Me_2SO was added a solution of 2.4 g (0.01 mol) of **9** in 10 mL of Me_2SO dropwise at room temperature during approximately 30 min. The mixture was stirred an additional 1 h (triethylamine hydrochloride precipitates during this time) and then heated to 95–100 °C and maintained in that temperature range for 20 h. After cooling to 40 °C, 8 mL of 2.5 N HCl were added, and the resulting mixture was stirred at 40–50 °C for 20 min. After being cooled to room temperature, the mixture was diluted with 20 mL of saturated brine and exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were then washed with 10% $NaHCO_3$ (2 × 25 mL) and brine and dried (Na_2SO_4). Filtration and evaporation of solvent left 2.2 g of dark, viscous oil which was chromatographed (HPLC) by using 3% acetone in methylene chloride as eluent. Compound **15** (1.0 g, 42%) elutes first, followed by **13** (0.4 g, 16%).

15: mp 69–70 °C (ethyl acetate–hexene, 1:1); NMR ($CDCl_3$) δ 7.13–7.58 (m, 5), 5.74 (br d, 1, J = 6 Hz), 2.40–3.10 (m, 4), 1.47–2.13 (m, 6); IR (CCl_4) 1725 cm^{-1}; mass spectrum, m/e (relative intensity) 111 (12), 167 (7), 245 (100), 246 (19).

Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.52; H, 6.58; S, 13.15.

13: NMR ($CDCl_3$) δ 7.27–7.73 (m, 5), 6.04 (s, 1), 5.68 (br s, 1), 1.20–2.80 (m, 11); IR (neat) 1700, 1040 cm^{-1}; mass spectrum, m/e (relative intensity) 137 (10), 263 (100), 264 (27), 265 (10).

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.80; H, 6.81; S, 12.18.

Conversion of Ketones to Bicyclic Keto Sulfones by Reaction with 1e (10). The following procedure for the conversion of cyclopentanone to 3-(phenylsulfonyl)bicyclo[3.2.1]octan-8-one is representative. A solution of 3.8 g (0.015 mol) of **10** in 15 mL of dry Me_2SO was added dropwise during 30 min, at room temperature under nitrogen, to a stirred solution of 2.0 g (0.015 mol) of the pyrrolidine enamine of cyclopentanone, 3.3 g (0.033 mol) of triethylamine, and 30 mg of hydroquinone in 40 mL of dry Me_2SO. The mixture was stirred an additional 1 h (triethylamine hydrochloride precipitates during this time), and then heated at 90–95 °C for 3 h. After cooling to 40 °C, 20 mL of 1 N HCl were added, and the resulting mixture was stirred at 40–50 °C for 20 min. At room temperature, 40 mL of saturated brine were added, and the mixture then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with two 25-mL portions of 10% $NaHCO_3$ and then brine and dried (Na_2SO_4). Workup left 2.1 g (51%) of a 1:1 mixture of the endo and exo sulfones as a dark viscous oil which solidified on standing. The endo/exo ratio was determined from the NMR spectrum by integration of the C*H*SO_2Ph multiplets at δ 2.72–3.34 (endo) and 3.20–3.90 (exo). Pure samples of each isomer were obtained by preparative HPLC using 2.5% acetone in methylene chloride as eluent. The endo isomer elutes first.

***endo*-3-(Phenylsulfonyl)bicyclo[3.2.1]octan-8-one**: mp 76–78 °C (ethyl acetate–hexane, 1:1); NMR ($CDCl_3$) δ 7.40–7.93 (m, 5), 2.72–3.34 (m, 1), 1.90–2.60 (m, 10); mass spectrum, m/e (relative intensity) 123 (6), 125 (5), 265 (100), 266 (12), 267 (4).

Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.62; H, 6.10; S, 12.11. Found: C, 63.42; H, 6.08; S, 12.08.

***exo*-3-(Phenylsulfonyl)bicyclo[3.2.1]octan-8-one**: mp 129–130 °C (ethyl acetate–hexane, 1:1); NMR ($CDCl_3$) δ 7.35–8.02 (m, 5), 3.20–3.90 (m, 1), 1.52–2.50 (m, 10); mass spectrum, m/e (relative intensity) 123 (3), 125 (3), 265 (100), 266 (18), 267 (7).

Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.62; H, 6.10; S, 12.11. Found: C, 63.50; H, 6.11; S, 12.09.

***exo*-3-(Phenylsulfonyl)bicyclo[3.2.1]octan-8-one.** This was prepared by sodium methoxide equilibration of the 1:1 endo–exo mixture isolated above. To a stirred solution of 0.014 g (0.0006 mol) of sodium in 20 mL of dry methanol was added 1.1 g (0.004 mol) of the 1:1 endo–exo sulfone mixture, as isolated from the above annelation reaction, dissolved in 10 mL of methanol. The resulting solution was heated to reflux under nitrogen and refluxed 20 h, allowed to cool to room temperature, and then acidified with 0.5 mL of glacial acetic acid. The methanol was removed and the residue diluted with 20 mL of water, and the resulting mixture was extracted with chloroform. The combined chloroform extracts were washed with water (5 mL) and then brine and dried (Na_2SO_4). Filtration and evaporation of the chloroform left 1.1 g of oil which solidified. NMR analysis showed that the product was >95% the exo sulfone. Recrystallization (ethyl acetate–hexane, 1:1) yielded pure exo compound.

3-(Phenylthio)-8-oxobicyclo[3.2.1]oct-2-ene: NMR ($CDCl_3$) δ 7.10–7.58 (m, 5), 5.93 (br d, 1, J = 7 Hz), 1.70–3.30 (m, 8); mass spectrum, m/e (relative intensity) 121 (11), 153 (24), 231 (100), 232 (15).

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.02; H, 6.13; S, 13.90. Found: C, 72.90; H, 6.01; S, 13.04.

2-[(Phenylsulfinyl)-2-propenyl]cyclopentanone: NMR ($CDCl_3$) δ 7.30–7.80 (m, 5), 6.13 (s, 1), 5.68 (br s, 1), 1.10–1.80 (m, 9); IR (neat) 1730, 1040 cm^{-1}; mass spectrum, m/e (relative intensity) 123 (17), 233 (10), 249 (100), 250 (25), 251 (12).

Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.73; H, 6.50; S, 12.89. Found: C, 67.56; H, 6.53; S, 12.60.

1-Methyl-3-(phenylthio)-9-oxobicyclo[3.3.1]non-2(3)-ene: obtained as a 1:1 mixture of the 2 and 3 double bond isomers as determined from the NMR spectrum by integration of the two C*H*$_3$ singlets at δ 0.97 and 1.08; NMR ($CDCl_3$) δ 7.07–7.60 (m, 5), 5.48–5.78 (m, 1), 1.40–3.00 (m, 9), 1.08; and 0.97 (two s, total 3); mass spectrum, m/e (relative intensity) 111 (100), 149 (32), 151 (30), 167 (22), 259 (82).

Anal. Calcd for $C_{16}H_{18}OS$: C, 74.39; H, 7.02; S, 12.39. Found: C, 74.09; H, 6.95; S, 12.33.

2-Methyl-6-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone: obtained as an approximate 1:1 mixture of cis and trans isomers as determined from the NMR spectrum by integration of the two sets of C*H*$_3$ doublets at δ 1.00 and 0.90; NMR ($CDCl_3$) δ 7.32–7.72 (m, 5), 6.03 (s, 1), 5.57 (br s, 1), 1.18–2.87 (m, 10), [1.00 (d, J = 2 Hz) and 0.90 (d, J = 2 Hz), total 3]; mass spectrum, m/e (relative intensity) 111 (9), 151 (30), 277 (100), 278 (20).

Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.54; H, 7.30; S, 11.58. Found: C, 69.30; H, 7.28; S, 11.60.

8-(Phenylthio)-10-oxobicyclo[4.3.1]dec-7-ene: NMR ($CDCl_3$) δ 7.13–7.56 (m, 5), 5.64–5.80 (m, 1), 0.94–3.11 (m, 12); mass spectrum, m/e (relative intensity) 121 (20), 149 (25), 181 (30), 241 (40), 259 (100), 260 (25).

Anal. Calcd for $C_{16}H_{18}OS$: C, 74.39; H, 7.02; S, 12.38. Found: C, 74.12; H, 6.99; S, 12.33.

2-[2-(Phenylsulfinyl)-2-propenyl]cycloheptanone: NMR ($CDCl_3$) δ 7.32–7.82 (m, 5), 6.07 (s, 1), 5.60 (br s, 1), 2.03–2.87 (m, 5), 1.00–2.03 (m, 8); mass spectrum, m/e (relative intensity) 111 (41), 151 (98), 277 (100), 278 (25).

Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.54; H, 7.30; S, 11.58. Found: C, 69.25; H, 7.27; S, 11.50.

***N*-(Ethoxycarbonyl)-3-aza-7-(phenylthio)-9-oxobicyclo[3.3.1]non-6-ene**: mp 118–120 °C (isopropyl alcohol–water, 1:1); NMR ($CDCl_3$) δ 7.16–7.50 (m, 5), 5.48–5.76 (m, 1), 4.02–4.70 (m, 4), 2.34–3.34 (m, 6), 1.30 (t, 3, J = 6.5 Hz); IR (KBr) 1728, 1690 cm^{-1}; mass spectrum, m/e (relative intensity) 272 (47), 300 (18), 318 (100), 319 (20).

Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.34; H, 6.04; N, 4.41; S, 10.08. Found: C, 64.28; H, 6.03; N, 4.39; S, 10.09.

***N*-(Ethoxycarbonyl)-3-[2-(phenylsulfinyl)-2-propenyl]-4-piperidone**: NMR ($CDCl_3$) δ 7.38–7.73 (m, 5), 6.14 (s, 1), 5.68 (br s, 1), 4.18 (q, 2, J = 7 Hz), 1.70–3.48 (m, 9), 1.28 (t, 3, J = 7 Hz); IR (KBr) 1690, 1230, 1050 cm^{-1}; mass spectrum, m/e (relative intensity) 210 (15), 247 (22), 290 (32), 336 (100), 337 (23).

Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18; S, 9.54. Found: C, 60.71; H, 6.30; N, 4.16; S, 9.50.

3-(Phenylsulfonyl)bicyclo[3.3.1]nonan-9-one: obtained as a 1:1 mixture of endo and exo sulfone isomers as determined from the NMR spectrum by integration of the C*H*SO_2Ph multiples at δ 3.70–4.33 and 2.60–3.28; mp 116–120 °C (ethyl acetate–hexane, 1:2); NMR ($CDCl_3$) δ 7.37–8.05 (m, 5), 3.70–4.33 and 2.60–3.28 (two m, total 1), 1.34–2.60 (m, 12); mass spectrum, m/e (relative intensity) 125 (13), 137 (36), 279 (100), 280 (16).

Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52; S, 11.50. Found: C, 64.50; H, 6.49; S, 11.46.

1-Methyl-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one: obtained as an approximate 1:1 mixture of endo and exo isomers as determined from the NMR spectrum by integration of the two CH_3 singlets at δ 0.98 and 1.00; mp 103–106 °C (benzene–hexane, 5:2), NMR ($CDCl_3$) δ 7.50–8.08 (m, 5), 3.87–4.52 (m, 0.5), 1.40–3.20 (m, 11.5), 0.98 and 1.00 (two s, total 3); mass spectrum, *m/e* (relative intensity) 123 (15), 133 (45), 143 (30), 151 (100), 152 (25), 293 (42).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.74; H, 6.90; S, 10.95. Found: C, 65.64; H, 6.90; S, 10.97.

8-(Phenylsulfonyl)bicyclo[4.3.1]decan-10-one: obtained as an approximate 1:1 mixture of endo and exo isomers by TLC analysis (2% acetone in methylene chloride); mp 127–129 °C (benzene–hexane, 1:1); NMR ($CDCl_3$) δ 7.52–8.04 (m, 5), 3.38–4.00 (m, 1), 2.62–3.07 (m, 2), 1.25–2.30 (m, 12); mass spectrum, *m/e* (relative intensity) 133 (18), 143 (15), 151 (73), 171 (13), 293 (100), 294 (29).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.74; H, 6.90; S, 10.94. Found: C, 65.55; H, 6.92; S, 10.90.

***N*-(Ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one**: obtained as a 2:1 mixture of endo/exo isomers as determined from the NMR spectrum by integration of the OCH_2 and CH_3 resonances at δ 4.12 and 4.17 (OCH_2) and 1.24 and 1.28 (CH_3); mp 138–144 °C (benzene–hexane, 1:1); NMR ($CDCl_3$) δ 7.50–7.96 (m, 5), 4.40 (br d, 2), [4.12 (q, J = 7 Hz) and 4.17 (q, J = 7 Hz), total 2], 1.82–3.47 (m, 9), [1.24 (t, J = 7 Hz) and 1.28 (t, J = 7 Hz), total 3]; mass spectrum, *m/e* (relative intensity) 210 (100), 306 (50), 352 (70), 353 (13).

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.11; H, 6.02; N, 3.99; S, 9.11. Found: C, 58.04; H, 6.00; N, 3.97; S, 9.08.

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Registry No. **1d**, 90838-29-2; **1e**, 90838-30-5; **6**, 931-59-9; **7**, 107-05-1; **8**, 90838-43-0; **9**, 90838-44-1; **10**, 90838-45-2; **13**, 90838-48-5; **15**, 90838-49-6; PhSH, 108-98-5; 3-(phenylthio)-8-oxobicyclo[3.2.1]oct-2-ene, 90838-31-6; 8-(phenylthio)-10-oxobicyclo[4.3.1]dec-7-ene, 90838-32-7; 1-methyl-3-(phenylthio)-9-oxobicyclo[3.3.1]non-2-ene, 90838-33-8; 1-methyl-3-(phenylthio)-9-oxobicyclo[3.3.1]non-3-ene, 90857-61-7; *N*-(ethoxycarbonyl)-3-aza-7-(phenylthio)-9-oxabicyclo[3.3.1]non-6-ene, 90838-34-9; *endo*-3-(phenylsulfonyl)bicyclo[3.2.1]octan-8-one, 90838-35-0; *exo*-3-(phenylsulfonyl)bicyclo[3.2.1]octan-8-one, 90838-36-1; *endo*-8-(phenylsulfonyl)bicyclo[4.3.1]decan-10-one, 90838-37-2; *exo*-8-(phenylsulfonyl)bicyclo[4.3.1]decan-10-one, 90838-38-3; *endo*-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-39-4; *exo*-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-40-7; *endo*-*N*-(ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)-bicyclo[3.3.1]nonan-9-one, 90838-41-8; *exo*-*N*-(ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-42-9; *endo*-1-methyl-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-46-3; *exo*-1-methyl-3-(phenylsulfonyl)bicyclo-[3.3.1]nonan-9-one, 90838-47-4; 2-[2-(phenylsulfinyl)-2-propenyl]cyclopentanone, 90838-50-9; 2-[2-(phenylsulfinyl)-2-propenyl]cycloheptanone, 90838-51-0; *cis*-2-methyl-6-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone, 90838-52-1; *trans*-2-methyl-6-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone, 90898-46-7; *N*-(ethoxycarbonyl)-3-[2-(phenylsulfinyl)-2-propenyl]-4-piperidone, 90838-53-2; *N*-chlorosuccinimide, 128-09-6; 1-(1-cyclohexenyl)pyrrolidine, 1125-99-1; 1-(1-cyclopentenyl)-pyrrolidine, 7148-07-4; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; 2-methylcyclohexanone, 583-60-8; ethyl 4-oxopiperidine-1-carboxylate, 29976-53-2.

The Synthesis of Isotopically Labeled β-Adrenergic Agents by Reductive Amination: Unexpected Site of Deuterium Incorporation

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The reduction of imines derived from the condensation of (*R*)-norepinephrine and certain methyl ketones with D_2 over a Pt catalyst leads to the formation of deuterium labeled products in which the deuterium is located exclusively in the methyl substituent. The absence of any detectable label at the methine position argues in favor of a "directed" process in which a methyl proton is the source for the methine CH.

A novel route to potential tissue specific β-adrenergic agonists involves the synthesis of N-substituted norepinephrine derivatives in which the catecholamine moiety is connected through an alkyl spacer arm to a carrier group. Compounds **6** and **7** are examples of such agonists which have been tested in both in vitro and in vivo assays with encouraging results.[1-3] As part of our studies designed to evaluate the pharmacological and metabolic properties of these N-substituted norepinephrine derivatives we required tritium labeled products of high specific activity (10 Ci/mmol). Compounds **6** and **7** have been prepared by $NaCNBH_3$ reduction and catalytic hydrogenation of the corresponding imines **4** and **5** which in turn are derived by condensation of norepinephrine (**1**) and the methyl ketones **2** and **3** (Figure 1).[1] Previous attempts to prepare radiolabeled **7** from commercially available tritium labeled norepinephrine (benzyl label, 5–15 Ci/mmol) were only partly successful in our hands since the yields of the desired amines were low (2–22%) due to the small scale reaction conditions that were required.[4]

In an attempt to overcome these problems, we elected to explore the possibility of introducing the label by catalytic tritiation of the imines **4** and **5**. Before proceeding with reductions with carrier free tritium, well defined reaction conditions had to be established. Additionally, since the final labeled products are to be used in pharmacokinetic and metabolic profiling studies, it was important to determine both the specific activity and the location of the

(1) Jacobson, K. A.; Marr-Leisy, D.; Rosenkranz, R. P.; Verlander, M. S.; Melmon, K. L.; Goodman, M. *J. Med. Chem.* **1983**, *26*, 492.
(2) Verlander, M. S.; Jacobson, K. A.; Rosenkranz, R. P.; Melmon, K. L.; Goodman, M. *Biopolymers* **1983**, *22*, 531.
(3) Rosenkranz, R. P.; Jacobson, K. A.; Goodman, M.; Verlander, M.; Melmon, K. L. *Proc. West. Pharmacol. Soc.* **1983**, *25*, 19.
(4) Goodman, M., unpublished results, 1983.

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