Convenient Synthesis of 3-[1-(Phenylthio)alkyl]- and 3-Alkyl-Substituted 3-Sulfolenes

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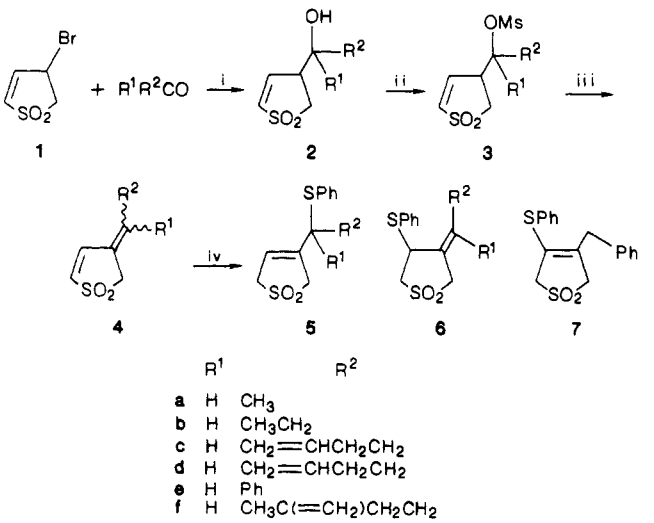
3-[1-(Phenylthio)alkyl]-3-sulfolenes (**5**) were conveniently synthesized by a sequence of mesylation, elimination, and Michael addition reactions of 4-hydroxyalkylated 2-sulfolenes (**2**), which were prepared regioselectively via ultrasound-promoted allylzincation of 4-bromo-2-sulfolene (**1**). 3-Alkyl-3-sulfolenes were synthesized from desulfurization of **5**. The application of the sequence was exemplified with the simple synthesis of α-myrcene.

During our studies of the synthetic application of the direct deprotonation–substitution reactions of 3-sulfolenes,[1] we have successfully prepared alkylated,[1a-c] acylated,[1d] and silylated[1e] derivatives, which are stable precursors of the corresponding substituted 1,3-butadienes. However, these reactions are limited to attaching electrophiles regioselectively to the α-position of the sulfolene ring so that only 2-substituted 3-sulfolenes can be prepared via this route. 3-Substituted 3-sulfolenes, on the other hand, can be prepared from 4-bromo-2-sulfolenes (**1**) by nucleophilic substitution followed by base induced double bond isomerization reactions.[2] However, since the nature of the nucleophiles has a marked influence on the regioselectivity of the substitution reactions, 3-alkylated and 3-acylated 3-sulfolenes cannot be prepared by this sequence. Therefore, it is desirable to have an improved procedure by which the regioselective preparation of these 3-substituted 3-sulfolenes can be accomplished. In fact, there is some progress toward this end recently. We have discovered that compound **1** undergoes regioselective γ-hydroxyalkylation with carbonyl compounds via an allylzincation process. The γ-hydroxyalkylated intermediates **2** can be smoothly converted to 3-acylated 3-sulfolenes by oxidation.[3] We now report that compounds **2** are also useful for the preparation of 3-thioalkylated and 3-alkylated 3-sulfolenes.

4-Hydroxyalkylated 2-sulfolenes (**2a–g**) were prepared from **1** in excellent yields by sonication with a carbonyl compound and Zn–Ag in dry THF in a laboratory cleaning bath (Scheme I and Table I).[3] It is noteworthy that the allylzincation reaction leads to the γ-substituted product exclusively. In no case was an α-substituted product detected. Compounds **2a–g** are easily purified by column chromatography. The HPLC (LiChrosorb column, EtOAc) analyses of these purified products showed the existence of only a single peak. The purity was estimated to exceed 99%. Although we were unable to obtain satisfactory microanalytical data for these products due to their hydroscopic character, all the spectral data (^{1}H NMR, IR, and MS) of **2** and their subsequent chemical transformations into 3-acylated[3] and 3-thioalkylated 3-sulfolenes (see below) confirm the structural assignments.

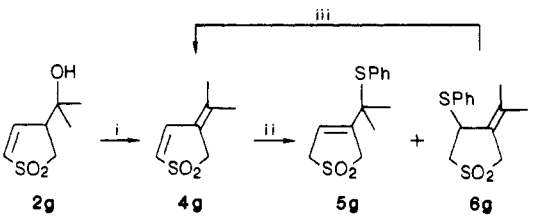
Julia[4] recently found that soft nucleophile adds to 1,3-butadienyl sulfones regioselectively in a 1,4-addition mode to give allylic sulfones. We therefore anticipated that compounds **2** could be converted to 3-substituted 3-sulfolenes via a sequence of dehydration followed by the conjugate addition of the intermediates **4** with a soft nucleophile (Scheme I). Formation of the dienyl sulfone **4a** was accomplished by mesylation of **2a** followed by elimination of the mesylate **3a** with LiOH. The ^{1}H NMR spectrum of **4a** indicated that it is a mixture of *Z* and *E* stereoisomers.[5] Immediate treatment of the relatively unstable compound **4a** with sodium thiophenoxide gave the expected 1,4-adduct **5a** cleanly in 67% overall yield from **3a**. The 1,2-adduct **6a** was not detected (Scheme I). In fact, compound **5a** could be prepared in one pot and

Scheme I[a]



[a] (i) Zn–Ag, ultrasound; (ii) MsCl, Et_3N; (iii) LiOH; (iv) NaSPh.

Scheme II[a]



[a] (i) $SOCl_2$, pyridine; (ii) NaSPh; (iii) LiOH.

(1) (a) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 515. (b) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1323. (c) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 236. (d) Chou, T. S.; Tso, H. H.; Lin, L. C. *J. Org. Chem.* **1986**, *51*, 1000. (e) Chou, T. S.; Tso, H. H.; Tao, Y. T.; Lin, L. C. *Ibid.* **1987**, *52*, 244.

(2) Chou, T. S.; Hung, S. C.; Tso, H. H. *J. Org. Chem.* **1987**, *52*, 3394.

(3) Tso, H. H.; Chou, T. S.; Hung, S. C. *J. Chem. Soc., Chem. Commun.* **1987**, 1552.

(4) Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron* **1986**, *42*, 5321 and reference cited therein.

(5) ^{1}H NMR spectral data of **4a**: δ 1.80, 1.88 (2 d, 3 H), 3.80 (s, 2 H), 5.92 (m, 1 H), 6.52, 6.63 (2 d, 1 H), 6.88, 7.25 (2 d, 1 H). Compared with the ^{1}H NMR spectrum of **4g** (see Experimental Section), compound **4a** has two different kinds of vinyl protons at δ 6.88 and 7.25 corresponding to the β-C hydrogen of the *Z*/*E* isomers. The area ratio of these two peaks showed that the ratio of the *Z*/*E* isomers is about 1:1. Compound **4a** darkens upon storage in a refrigerator overnight.

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Table I. Reactions of the Sulfone 1 with Carbonyl Compounds and the Subsequent Conjugate Addition Products

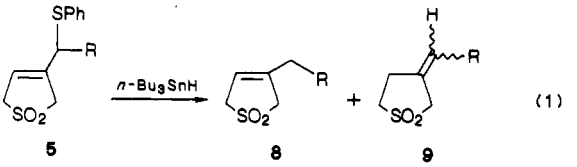
carbonyl compounds	γ-hydroxyalkylated products 2				conjugate addition adducts (yield,[a] %)
		R^1	R^2	yield, %	
CH_3CHO	**2a**	H	Me	97.5	**5a** (76.2)
CH_3CH_2CHO	**2b**	H	Et	85.4	**5b** (77.3)
$CH_2{=}CHCH_2CH_2CHO$	**2c**	H	$CH_2{=}CHCH_2CH_2$	87.5	**5c** (75.6)
$CH_2{=}CHCH_2CH_2CH_2CHO$	**2d**	H	$CH_2{=}CHCH_2CH_2CH_2$	91.7	**5d** (72.4)
PhCHO	**2e**	H	Ph	86.7	**5e** (56.1), **7** (22.5)
$CH_3C(=CH_2)CH_2CH_2CHO$	**2f**	H	$CH_3C(=CH_2)CH_2CH_2$	90.2	**5f** (79.8)
$(CH_3)_2CO$	**2g**	Me	Me	88.9	**5g** (45.8), **6g** (27.3)

[a] Yields are overall yields based on **2**.

in a better yield (76% from **2a**) by a sequantial addition of 1.5 equiv of LiOH and 3.6 equiv of thiophenol to the crude mesylate **3a**. Thus, isolation of the unstable intermediate **4a** is not necessary. Similarly, compounds **2b–d** were also converted cleanly to **5b–d** in good overall yields (Table I). However, when compound **2e** (R^1 = H, R^2 = Ph) was subjected to the reaction sequence, two adducts, **5e** and **7**, were produced in a 5:2 ratio. Compound **7** is presumably formed via a 1,2-addition reaction accompanied by a rapid double-bond migration under the reaction conditions. The concurrence of 1,2-addition was also observed in the reaction of **4g** with the sodium thiophenoxide (Scheme II). Treatment of the diene **4g**, formed by the dehydration of **2g** with thionyl chloride and pyridine, with sodium thiophenoxide gave **5g** and **6g** in a 7:4 ratio. The regioselectivity of the conjugate addition of benzenethiolate to the dienyl sulfone **4** is apparently influenced by the nature of the substituents attached to the terminal carbon. For **4e** and **4g**, where a phenyl group or two methyl groups are attached, the steric crowdedness and/or the electronic effects of these substituents somewhat disfavor 1,4-addition so as to cause the formation of some 1,2-adducts as side products. Attempted isomerization of **6g** to the corresponding 3-sulfolene with LiOH resulted in an elimination reaction to regenerate the diene **4g** in 60% yield (Scheme II). The recycled **4g** can be treated again with thiophenoxide to afford the desired 3-sulfolene **5g**.

It has been reported recently that the thermolysis of 3-[(phenylthio)methyl]-3-sulfolene (**5**, $R^1 = R^2 = H$) produces 2-[(phenylthio)methyl]-1,3-butadiene in excellent yield.[6] Therefore, it is reasonable to believe that compounds **5a–f** should give the corresponding 2-thioalkylated 1,3-butadienes in the same manner. In this respect, the above reaction sequence provides a convenient route for the preparation of precursors of 2-thioalkylated 1,3-butadienes which are potentially useful enophiles in Diels–Alder reactions.[6]

Further transformation of **5** to 3-alkylated 3-sulfolenes by a desulfurization reaction is expected to be easy since the ring-sulfone functionality is known to be inert toward a wide variety of reduction conditions.[7] Indeed, the reaction of compound **5a** with Raney nickel showed that the phenylthio group can be removed smoothly, leaving the ring sulfone untouched. In this reaction, 3-ethyl-3-sulfolene (**8a**) was produced (58.7%) along with the double-bond isomer **9a** as the minor poduct (29.3%). When tri-*n*-butyltin hydride[8] was used for desulfurization, the selectivity of the preferential formation of **8a** over **9a** was slightly improved to 2.5:1 (eq 1). Treatment of **5b** with tri-*n*-butyltin hydride resulted in a similar selectivity so that compounds **8b** and **9b** were also produced in a 2.5:1 ratio. The HPLC analysis indicates that products **9a** and **9b** are mixtures of *Z* and *E* stereoisomers and not separated.

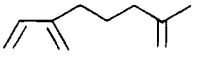


(1)

5 **8** **9**

a, R = CH_3; **b**, R = CH_3CH_2; **c**, R = $CH_3C(=CH_2)CH_2CH_2$

Since it is established that 3-alkyl-substituted 3-sulfolenes can be thermalized to extrude SO_2 to give the corresponding 2-alkyl-substituted 1,3-butadienes,[2,9] the combination of the described reaction sequence for the preparation of 3-alkylated 3-sulfolene from compound **1** and the thermal extrusion of sulfur dioxide thus provides a useful route for the synthesis of 2-alkylated 1,3-butadienes. The application of this strategy can be exemplified with a simple synthesis of α-myrcene. Ultrasonic irradiation of **1** with 4-methylenepentanal in the presence of Zn–Ag gave the product **2f** in 90% yield. Subsequent mesylation, elimination, and benzenethiolate addition produced compound **5f** in 80% overall yield from **2f**. Desulfurization of **5f** with tri-*n*-butyltin hydride yielded **8c** [R = $CH_3(=CH_2)CH_2CH_2$] and **9c** in 60.9% and 24% yields, respectively. Thermolysis of **8c** by preparative GC yielded α-myrcene (**10**) as a single product.



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In summary, with the readily available starting material **1** and the simple reaction conditions, the reaction sequence we described herein provides a convenient route for the preparation of 3-thioalkylated and 3-alkylated 3-sulfolenes which are otherwise not easy to prepare.

Experimental Section

^1H NMR spectra were determined on a Bruker AW-80 spectrometer with $CDCl_3$ as solvent. IR spectra were determined on a Perkin-Elmer 882 spectrometer. Mass spectra were recorded on a Hewlett-Packard 5995B mass spectrometer. Elemental analyses were taken with a Perkin-Elmer 240C analyzer. Melting points were obtained with a Mel-Temp apparatus and were uncorrected. All anhydrous solvents were freshly distilled before use.

Preparation of 4-Hydroxyalkylated 2-Sulfolenes 2a–g. Under a nitrogen atmosphere, a mixture of **1** (0.5 mmol), carbonyl compound (0.7 mmol), and Zn–Ag (0.6 mmol) in 3.5 mL of dry THF was sonicated in a laboratory cleaning bath (Branson, 50–60 Hz) at room temperature for 5 h. After addition of EtOAc (10 mL), the reaction mixture was filtered through a pad of silica gel, concentrated under reduced pressure, and purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to obtain the pure

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(7) Chou, T. S.; You, M. L. *Tetrahedron Lett.* **1985**, *26*, 4495.
(8) Gutierrez, C. G.; Summerhays, L. R. *J. Org. Chem.* **1984**, *49*, 5206.
(9) (a) Isaacs, N. S.; Laila, A. A. R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1470. (b) Mock, W. L. *J. Am. Chem. Soc.* **1975**, *97*, 3673. (c) Grummitt, O.; Leaver, H. *J. Am. Chem. Soc.* **1952**, *74*, 1595.

products. Yields are listed in Table I.

4-(1-Hydroxyethyl)-2-sulfolene (2a): oil; IR (neat) 3493 (OH), 1600, 1301 and 1140 (SO_2), 884, 748 cm^{-1}; ^1H NMR δ 1.25 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.66 (br s, 1 H, OH), 3.26 (m, 3 H, SO_2CH_2CH), 3.96 (m, 1 H, CH_3CHOH), 6.68 (m, 2 H, two vinyl protons on the ring); MS m/z 147, 118 (100), 89, 72, 70, 53, 45, 43.

4-(1-Hydroxypropyl)-2-sulfolene (2b): oil; IR (neat) 3500 (OH), 1605, 1300 and 1140 (SO_2), 890, 736 cm^{-1}; ^1H NMR δ 0.98 (t, J = 8 Hz, 3 H, CH_3CH_2), 1.51 (m, 2 H, CH_3CH_2CH), 2.32 (br s, 1 H, OH), 3.28 (m, 3 H, SO_2CH_2CH), 3.7 (m, 1 H, CHOH), 6.66 (m, 2 H, two vinyl protons on the ring); MS m/z 147, 118 (100%), 89, 72, 70, 59, 57, 55, 53, 43, 41.

4-(1-Hydroxy-4-pentenyl)-2-sulfolene (2c): oil; IR (neat) 3500 (OH), 1642 (C=C), 1600, 1290 and 1140 (SO_2), 920 and 890 (CH_2=CH), 745 cm^{-1}; ^1H NMR δ 1.6 (m, 2 H, CH_2=$CHCH_2CH_2$), 2.22 (m, 2 H, CH_2=$CHCH_2CH_2$), 2.85 (br s, 1 H, OH), 3.26 (m, 3 H, SO_2CH_2CH), 3.73 (m, 1 H, CHOH), 4.92–5.14 (m, 2 H, CH_2=CH), 5.53–6.08 (m, 1 H, CH_2=CH), 6.67 (m, 2 H, two vinyl protons on the ring); MS m/z 147, 118 (100), 85, 72, 70, 67, 57, 55, 53, 43, 41.

4-(1-Hydroxy-5-hexenyl)-2-sulfolene (2d): oil; IR (neat) 3500 (OH), 1641 (C=C), 1600, 1300 and 1140 (SO_2), 890 and 915 (CH_2=CH), 758 cm^{-1}; ^1H NMR δ 1.47 (m, 4 H, CH_2=$CHCH_2CH_2CH_2$), 2.08 (m, 2 H, CH_2=$CHCH_2$), 2.82 (br s, 1 H, OH), 3.26 (m, 3 H, SO_2CH_2CH), 3.73 (m, 1 H, CHOH), 4.88–5.11 (m, 2 H, CH_2=CH), 5.55–6.16 (m, 1 H, CH_2=CH), 6.66 (m, 2 H, two vinyl protons on the ring); MS m/z 147, 118, 99, 89, 81 (100%), 72, 70, 57, 55, 53, 43, 41.

4-(Hydroxybenzyl)-2-sulfolene (2e): solid; mp 106–107 °C; IR (KBr) 3520 (OH), 1605, 1230, 1295 and 1140 (SO_2), 1100, 890, 740, 705 (Ph), 650 cm^{-1}; ^1H NMR δ 2.79 (br s, 1 H, OH), 3.16 (m, 3 H, SO_2CH_2CH), 4.73 (m, 1 H, CHOH), 6.25–6.66 (m, 2 H, two vinyl protons on the ring), 7.32 (s, 5 H, Ph); MS m/z 107 (100), 79, 77, 53, 51.

4-(1-Hydroxy-4-methyl-4-pentenyl)-2-sulfolene (2f): oil; IR (neat) 3490 (OH), 1645 (C=C), 1294 and 1138 (SO_2), 889 (CH_2=C) cm^{-1}; ^1H NMR δ 1.72 [br s, 5 H, $CH_3C(=CH_2)CH_2CH_2$], 2.16 [br t, J = 7 Hz, 3 H, $CH_3C(=CH_2)CH_2$ and OH], 3.26 (br s, 3 H, SO_2CH_2CH), 3.77 (m, 1 H, CHOH), 4.73 (s, 2 H, CH_2=CH), 6.66 (m, 2 H, two vinyl protons on the ring); MS m/z 198, 160, 147, 119, 118, 81 (100), 79, 72, 70, 55, 53, 43, 41.

4-(1-Hydroxy-1-methylethyl)-2-sulfolene (2g): oil; IR (neat) 3500 (OH), 1601, 1295 and 1140 (SO_2), 890, 763 cm^{-1}; ^1H NMR δ 1.24 [s, 6 H, $(CH_3)_2COH$], 2.67 (br s, 1 H, OH), 3.23 (m, 3 H, SO_2CH_2CH), 6.59–6.86 (m, 2 H, two vinyl protons on the ring); MS m/z 88, 70, 61, 45, 43 (100).

Conjugate Addition Reaction for the Preparation of 5a–f and 7. To a mixture of **2** (0.32 mmol) and MsCl (0.62 mmol) in dry THF (6 mL) was added NEt_3 (0.9 mmol) dropwise at 0 °C. The solution was then stirred at room temperature overnight. An excess of EtOAc (20 mL) was added to the reaction mixture, and the precipitate was filtered through a pad of silica gel. The crude mesylate **3**, which was obtained after the filtrate was concentrated in vacuo, was directly used for the next step without purification. A mixture of crude **3** and LiOH (0.48 mmol) in methanol (2 mL) was stirred at room temperature for 2 h. The reaction mixture was cooled in an ice bath, and thiophenol (1.15 mmol) was added dropwise. When the addition was completed, an excess of ethanol (15 mL) was added and the resulting solution was stirred for 15 min in the ice bath followed by overnight at reflux. Concentration in vacuo followed by chromatographic separation (SiO_2, n-hexane/EtOAc) afforded the pure products **5a–d** and **5f**. Compounds **5e** and **7** were separated by HPLC (LiChrosorb, n-hexane/EtOAc, 2:1). Yields are listed in Table I.

3-[1-(Phenylthio)ethyl]-3-sulfolene (5a): oil; IR (neat) 1639, 1582, 1477, 1402, 1233, 1318 and 1122 (SO_2), 751 and 696 (Ph) cm^{-1}; ^1H NMR δ 1.4 (d, J = 7.2 Hz, 3 H, CH_3CH), 3.63, 3.86 (2 br s, 5 H, 2 SO_2CH_2 and CHSPh), 5.39 (s, 1 H, vinyl proton on the ring), 7.29 (s, 5 H, Ph); MS m/z 254 (M^+), 190, 110 (100), 109, 81, 79, 65, 53, 41. Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.52; H, 5.61.

3-[1-(Phenylthio)propyl]-3-sulfolene (5b): oil; IR (neat) 1623, 1582, 1476, 1440, 1402, 1245, 1308 and 1127 (SO_2), 913, 750 and 695 (Ph) cm^{-1}; ^1H NMR δ 1.0 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.69 (m, 2 H, CH_3CH_2CH), 3.5 (t, J = 8 Hz, 1 H, CHSPhCH_2), 3.64 (s, 2 H, SO_2CH_2C), 3.8 (d, J = 3.2 Hz, 2 H, SO_2CH_2CH), 5.36 (br s, 1 H, vinyl proton on the ring), 7.3 (s, 5 H, Ph); MS m/z 268 (M^+), 204, 110 (100), 109, 95, 79, 67, 55, 41. Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.18; H, 6.01. Found: C, 58.31; H, 6.04.

3-[1-(Phenylthio)-4-pentenyl]-3-sulfolene (5c): oil; IR (neat) 1639 (C=C), 1581, 1556, 1476, 1438, 1404, 1240, 1315 and 1127 (SO_2), 999 and 915 (C=C), 750 and 695 (Ph) cm^{-1}; ^1H NMR δ 1.76 (m, 2 H, CH_2=$CHCH_2CH_2$), 2.22 (m, 2 H, CH_2=$CHCH_2$), 3.63 (m, 3 H, SO_2CH_2C and CHSPh), 3.82 (d, J = 3.2 Hz, 2 H, SO_2CH_2CH), 4.93–5.14 (m, 2 H, CH_2=CH), 5.33 (br s, 1 H, vinyl proton on the ring), 5.51–6.04 (m, 1 H, CH_2=CH), 7.28 (s, 5 H, Ph); MS m/z 294 (M^+), 230, 160, 110 (100), 109, 91, 79, 77, 67, 65, 41. Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.19; H, 6.16. Found: C, 61.01; H, 6.25.

3-[1-(Phenylthio)-5-hexenyl]-3-sulfolene (5d): solid; mp 81–82 °C; IR (KBr) 1642 (C=C), 1580, 1465, 1441, 1243, 1311 and 1129 (SO_2), 991 and 909 (C=C), 750 and 692 (Ph) cm^{-1}; ^1H NMR δ 1.56 (m, 4 H, CH_2=$CHCH_2CH_2CH_2$), 2.07 (m, 2 H, CH_2=$CHCH_2$), 3.63 (m, 3 H, SO_2CH_2C and CHSPh), 3.82 (d, J = 4 Hz, 2 H, SO_2CH_2CH), 4.89–5.11 (m, 2 H, CH_2=CH), 5.31 (br s, 1 H, vinyl proton on the ring), 5.6–6.05 (m, 1 H, CH_2=CH), 7.3 (s, 5 H, Ph); MS m/z 308 (M^+), 244, 198, 167, 135, 134, 133, 110 (100), 109, 105, 93, 91, 79, 77, 67, 65, 55, 41. Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.30; H, 6.54. Found: C, 62.02; H, 6.48.

3-[(Phenylthio)benzyl]-3-sulfolene (5e): oil; IR (neat) 1580, 1556, 1482, 1443, 1402, 1249, 1227, 1319 and 1135 (SO_2), 1027, 1003, 914, 751 and 696 (Ph) cm^{-1}; ^1H NMR δ 3.69 (br s, 4 H, 2 SO_2CH_2), 4983 (s, 1 H, CH), 5.72 (s, 1 H, vinyl proton on the ring), 7.27 (s, 10 H, Ph); MS m/z 316 (M^+), 207, 143, 141 (100), 128, 115. Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.53; H, 5.10. Found: C, 64.62; H, 5.31.

3-[1-(Phenylthio)-4-methyl-4-pentenyl]-3-sulfolene (5f): oil; IR (neat) 1650 (C=C), 1239, 1309 and 1125 (SO_2), 893 (C=CH_2), 750 and 695 (Ph) cm^{-1}; ^1H NMR δ 1.69 [s, 3 H, $CH_3C(=CH_2)CH_2$], 1.83 [m, 2 H, $CH_3C(=CH_2)CH_2CH_2$], 2.14 [m, 2 H, $CH_3C(=CH_2)CH_2$], 3.64 (br s, 3 H, SO_2CH_2C), 3.78 (br s, 2 H, SO_2CH_2CH), 4.74 (s, 2 H, CH_2=C), 5.31 (br s, 1 H, vinyl proton on the ring), 7.28 (s, 5 H, Ph); MS m/z 308 (M^+), 239, 175, 135, 134, 133, 119, 110 (100), 109, 105, 93, 91, 79, 77, 65, 55, 41. Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.30; H, 6.54. Found: C, 62.07; H, 6.63.

3-(Phenylthio)-4-benzyl-3-sulfolene (7): oil; IR (neat) 1601, 1528, 1535, 1494, 1477, 1438, 1241, 1322 and 1132 (SO_2), 1071, 1026, 977, 750 and 699 (Ph) cm^{-1}; ^1H NMR δ 3.71, 3.82 (2 s, 6 H, 2 SO_2CH_2 and CH_2Ph), 7.15–7.33 (m, 10 H, Ph); MS m/z 316 (M^+), 252, 161, 143 (100), 142, 141, 128, 127, 115, 110, 91, 77, 65, 51. Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.53; H, 5.10. Found: C, 64.47; H, 5.06.

Preparation of 5g and 6g from 2g. To a solution of **2g** (0.85 mmol) in dry pyridine (6 mL) cooled in an ice bath was added dropwise freshly distilled thionyl chloride (3.36 mmol). The reaction mixture was stirred for 1 h in the ice bath and for another hour at room temperature. The reaction mixture was concentrated and eluted through a silica column (CH_2Cl_2) to remove the excess pyridine. The crude diene sulfone **4g** was obtained in 78.4% yield after the filtrate was concentrated under reduced pressure: ^1H NMR δ 1.82, 1.92 (2 s, 6 H, 2 CH_3), 3.79 (s, 2 H, SO_2CH_2), 6.53 (d, J = 8 Hz, 1 H, SO_2CH=CH), 7.22 (d, J = 8 Hz, 1 H, SO_2CH=CH); IR 1657, 1550, 1280 and 1140 (SO_2) cm^{-1}. To a solution of NaSPh (0.64 mmol) in ethanol (10 mL) at room temperature was added the solution of the crude **4g** in 5 mL of ethanol, and the mixture was heated to reflux overnight. After concentration in vacuo, the two products **5g** and **6g** were separated by HPLC (Lichrosorb, n-hexane/EtOAc, 2:1).

3-[1-(Phenylthio)-1-methylethyl]-3-sulfolene (5g): solid; mp 110–111 °C; IR (KBr) 1418, 1291 and 1136 (SO_2), 755 and 699 (Ph) cm^{-1}; ^1H NMR δ 1.36 (s, 6 H, 2 CH_3), 3.68, 4.02 (2 s, 4 H, 2 SO_2CH_2), 5.18 (s, 1 H, vinyl proton on the ring), 7.33 (s, 5 H, Ph); MS m/z 268 (M^+), 110 (100), 109, 95, 67. Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.18; H, 6.01. Found: C, 58.44; H, 6.15.

3-(Phenylthio)-4-isopropylidenesulfolane (6g): oil; IR (neat) 1584, 1480, 1440, 1400, 1317 and 1122 (SO_2), 920, 754 and 694 (Ph) cm^{-1}; ^1H NMR δ 1.61, 1.69 (2 s, 6 H, 2 CH_3), 3.36 (m, 2 H, SO_2CH_2CH), 3.79 (s, 2 H, SO_2CH_2C), 4.70 (m, 1 H, CHSPh), 7.32 (s, 5 H, Ph); MS m/z 268 (M^+), 110 (100), 109, 95, 67. Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.18; H, 6.01. Found: C, 58.26; H, 5.97.

Desulfurization of 5 for Preparation of 8 and 9. A mixture of **5** (0.25 mmol) and Raney nickel (1.35 g) in ethanol (20 mL)

was heated at 70 °C for 1 h. After filtration through a filter paper to remove the excess of Raney nickel, the filtrate was eluted through a silica gel column (*n*-hexane/EtOAc, 1:1) and concentrated under reduced pressure. The products **8** and **9** were separated by HPLC (LiChrosorb, *n*-hexane/EtOAc, 2:1). Compounds **8** and **9** can be obtained alternatively by treating **5** (0.26 mmol), *n*-Bu_3SnH (1.04 mmol), and AIBN (0.034 mmol) in dry benzene (8 mL) at reflux overnight. The resulting solution was concentrated under reduced pressure, eluted through a silica gel column, and separated by HPLC to obtain the desulfurized products **8** and **9**.

3-Ethyl-3-sulfolene (8a): solid; mp 60–61 °C; IR (KBr) 1295 and 1250 (SO_2), 1110, 778 cm^{-1}; ^1H NMR δ 1.06 (t, J = 8 Hz, 3 H, CH_3CH_2), 2.16 (m, 2 H, CH_3CH_2), 3.65, 3.77 (2 s, 4 H, SO_2CH_2), 5.67 (s, 1 H, vinyl proton on the ring). This compound is now commercially available. The ^1H NMR spectrum is identical with that reported in the *Aldrich Library of NMR Spectra*, 2nd ed., Vol. 2, 786c.

3-Ethylidenesulfolane (9a): oil; IR (neat) 2955, 1642, 1405, 1310 and 1130 (SO_2), 882 cm^{-1}; ^1H NMR δ 1.62 (d, J = 8 Hz, 3 H, CH_3CH=C), 2.81–3.4 (m, 4 H, $SO_2CH_2CH_2$), 3.66 (s, 2 H, SO_2CH_2C), 5.6 (q, J = 8 Hz, 1 H, vinyl proton); MS m/z 146 (M^+), 81, 67 (100), 54, 53, 41. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.3; H, 6.9. Found: C, 49.4; H, 6.8.

3-Propyl-3-sulfolene (8b): solid; mp 88–89 °C; IR (KBr) 2961, 1649, 1294 and 1117 (SO_2), 923, 814, 781 cm^{-1}; ^1H NMR δ 0.89 (t, J = 6.4 Hz, 3 H, CH_3CH_2), 1.44 (m, 2 H, CH_3CH_2), 2.14 (t, J = 7.2 Hz, 2 H, $CH_3CH_2CH_2$), 3.66, 3.75 (2 s, 4 H, 2 SO_2CH_2), 5.68 (s, 1 H, vinyl proton on the ring); MS m/z 160 (M^+), 131, 96, 81, 68 (100), 67, 41. Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55. Found: C, 52.49; H, 7.60.

3-Propylidenesulfolane (9b): oil; IR (neat) 2963, 1640, 1458, 1400, 1312 and 1128 (SO_2), 911, 885; ^1H NMR δ 0.95 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.98 (m, 2 H, CH_3CH_2), 2.8–3.24 (m, 4 H, $SO_2CH_2CH_2$), 3.66 (s, 2 H, SO_2CH_2C), 5.58 (m, 1 H, vinyl proton); MS m/z 160 (M^+), 95, 81, 68, 67, 55, 54, 53, 41. Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55. Found: C, 52.31; H, 7.74.

3-(4-Methyl-4-pentenyl)-3-sulfolene (8c): oil; IR (neat) 1648 (C=C), 1237, 1317 and 1122 (SO_2), 891 cm^{-1}; ^1H NMR δ 1.60 [m, 2 H, $CH_3C(=CH_2)CH_2CH_2$], 1.69 [s, 3 H, $CH_3C(=CH_2)CH_2$], 2.12 [m, 4 H, $CH_3C(=CH_2)CH_2CH_2CH_2C$], 3.66, 3.76 (2 s, 4 H, 2 SO_2CH_2), 4.72 (s, 2 H, C=CH_2), 5.68 (s, 1 H, vinyl proton on the ring); MS m/z 136 (M - 64), 135, 107, 93, 81, 79, 69, 68, 67, 55, 53, 41 (100). Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05. Found: C, 59.86; H, 8.01.

3-(4-Methyl-4-pentenylidene)sulfolane (9c): oil; IR (neat) 2968, 1647, 1311 and 1129 (SO_2), 901, 818, 773 cm^{-1}; ^1H NMR δ 1.7 [s, 3 H, $CH_3C(=CH_2)CH_2$], 2.11 [br s, 4 H, $CH_3C(=CH_2)CH_2CH_2$], 2.75–3.3 (m, 4 H, $SO_2CH_2CH_2$), 3.67 (s, 2 H, SO_2CH_2C), 4.71 (br s, 2 H, C=CH_2), 5.61 (br s, 1 H, C=$CHCH_2$); MS (m/z 200 (M^+), 199, 145, 136, 135, 134, 133, 131, 121, 119, 117, 108, 107, 105, 93, 91, 81, 79, 77, 55 (100), 41. Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05. Found: C, 59.73; H, 8.14.

Synthesis of α-Myrcene (10). Thermolysis of **8c** to give α-myrcene was carried out by injecting **8c** on a preparative GC (injection temperature 240 °C, oven temperature 100 °C) with a SE-30 (3-m) column. The chromatogram showed the existence of only a single product, **10**, which was collected with a dry-ice trap. The ^1H NMR and IR spectra of **10** are identical with those in the literature.[10]

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Palladium-Catalyzed Reactions in the Synthesis of 3- and 4-Substituted Indoles. 4

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4-Bromo-1-tosylindole (**1**) was converted to tricyclic indole enone **11**, a potential intermediate in the synthesis of tetracyclic ergot alkaloids, by a series of palladium-catalyzed processes. Attempts to construct the ergot D ring by the hetero-Diels–Alder reaction of enone **11** and 1-azabutadiene **12** produced not the expected [4 + 2] adduct **13** but the benz[*cd*]indoline derivative **14** resulting from attack of the aza diene at the indole 2-position. The thermodynamic stability of the naphthol nucleus makes enone **11** generally susceptible to attack at the indole 2-position, as evidenced by the attack of hydride and methyl cuprate nucleophiles at this position forming indolines **16** and **17**, respectively.

Introduction

A general approach to the synthesis of 3,4-disubstituted indoles involving palladium(II)-catalyzed formation of 4-bromoindole and sequential introduction of carbon side chains at the 3- and 4-positions using palladium(0) catalysis has recently been developed in these laboratories[1] and has been applied to the synthesis of (±)-clavicipitic acid methyl ester[2] and (±)-aurantioclavine.[3] Herein is presented the use of related methodology to append the C ring of the tetracyclic ergot alkaloids,[4] as well as the results of attempts to annulate the D ring by aza diene cycloaddition chemistry[5] (eq 1).

Results and Discussion

4-Bromo-1-tosylindole, **1**, prepared by the palladium(II)-catalyzed cyclization of *N*-tosyl-2-ethenyl-3-bromoaniline,[1] is a versatile starting material for ergot alkaloid

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