Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3699–3703

Reactivity of 1-phenylsulfinyl-2-phenylsulfanylethylene (SOSE) with *O*-nucleophiles generated by potassium *tert*-butoxide

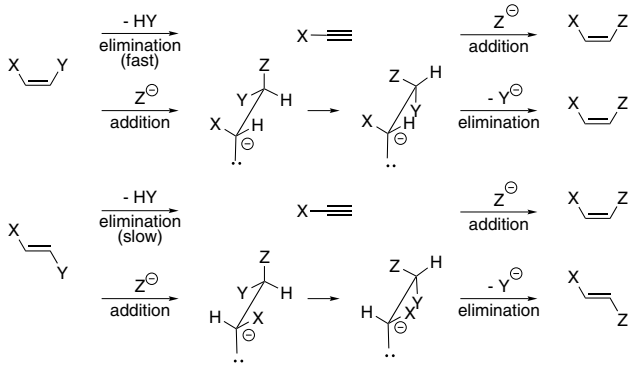
Leonardo Pellizzaro,[a] Elena Cabianca,[a,b] Arnaud Tatibouët,[b] Pierluigi Padovan,[a] Fabrizio Fabris,[a] Patrick Rollin[b,*] and Ottorino De Lucchi[a,*]

[a]*Dipartimento di Chimica, Università Ca' Foscari di Venezia, Dorsoduro 2137, I-30123 Venezia, Italy*
[b]*Institut de Chimie Organique et Analytique, associé au CNRS, Université d'Orléans, B.P. 6759, F-45067 Orléans, France*

Received 6 February 2007; revised 19 March 2007; accepted 21 March 2007
Available online 25 March 2007

Abstract—*E*-1-Phenylsulfinyl-2-phenylsulfanylethylene (*E*-SOSE) reacts with *O*-nucleophiles generated by means of *t*-BuOK via an addition–elimination mechanism, thus affording the product of substitution of the phenylsulfanyl group in a stereo-conservative process. When used alone, the strongly basic and hindered *tert*-butoxide brings about elimination of either the phenylthiolate or phenylsulfinate groups. *Z*-SOSE is much more prone to elimination: either with *t*-BuOK alone or with other *O*-nucleophiles generated by *t*-BuOK, it always leads to products derived from elimination. Other alkaline *tert*-butoxides or other bases appear not as effective in generating species nucleophilic enough to react with *E*-SOSE.

Nucleophilic substitution reactions on vic-disubstituted ethenes may occur either via an elimination–addition (E–Ad_N) or an addition–elimination (Ad_N–E) mechanism. The actual sequence of events depends on a number of features among which the *E* or *Z* stereochemistry of the olefinic substrate, the electrophilicity of the double bond (i.e., the electron withdrawing capacity as well as the nucleofugal ability of the substituents), the nucleophilicity of the incoming nucleophile and the reaction conditions.[1] Customarily, strongly electrophilic alkenes undergo addition of the nucleophile before elimination (i.e., the Ad_N–E mechanism) while less electrophilic alkenes first eliminate the leaving nucleophile before the addition of the incoming nucleophile (i.e., the E–Ad_N mechanism). A simple and direct, though not exhaustive, perception of the implication of either one of the two mechanisms is given by the stereospecificity of the reaction and by the difference in reactivity of the *E*- and *Z*-isomers. Indeed, the E–Ad_N mechanism implies that both *Z* and *E* compounds afford the *Z* product and that the *E* isomer is less reactive, while the Ad_N–E is stereo-conservative with *Z*- and *E*-isomers exhibiting comparable reactivity (Scheme 1).[2]



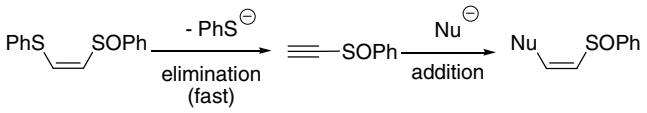
Scheme 1. Elimination–addition versus addition–elimination in nucleophilic substitutions on *vic*-disubstituted ethenes.

For example, either *Z*- or *E*-1,2-bis(phenylsulfonyl)ethylenes (BPSE) react via addition–elimination (affording stereospecifically substitution products with conservation of the stereochemistry),[3] while *Z*- and *E*-dichloroethylenes react via an elimination–addition mechanism: in fact, only the *Z*-isomer reacts whereas the *E* is not reactive because of the unfavourable antiperiplanar alignment of the leaving group in the elimination step.[4]

Because of the low electron withdrawing ability of its substituents, the recently introduced

Keywords: Vinyl sulfoxides; Michael addition; Alkaline *tert*-butoxides.
* Corresponding authors. Tel.: +39 041 234 8546; fax: +39 041 234 8517 (O.D.L.); e-mail: delucchi@unive.it

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.125



Scheme 2. Reactivity of *Z*-SOSE with nucleophiles.

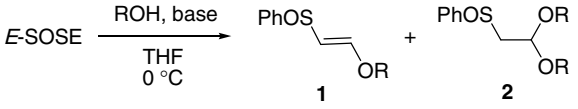
1-phenylsulfinyl-2-phenylsulfanylethylene (SOSE) was expected to behave similarly to dichloroethylene: indeed only the *Z*-isomer was reactive towards oxygen nucleophiles generated by means of LiHMDS (Scheme 2). Both BPSE and SOSE revealed useful for the introduction of robust acetalic protecting groups for carbohydrates.[5,6] Although in the case of BPSE both *Z*- and *E*-isomers can be used, the presence of a sole oxygen atom in the structure of SOSE offers clear advantage in terms of atom economy, and the presence of a stable stereogenic centre in the sulfinyl group is a further synthetic opportunity. In this work, we report the possibility to tune nucleophilicity versus basicity of the oxygen centres of alcohols and diols to such an extent that *E*-SOSE can also be rendered synthetically useful.

In details, it was observed that alkoxides generated by *t*-BuOK in THF react stereospecifically with *E*-SOSE to afford products resulting from a substitution of the phenylsulfanyl group (Table 1). The reaction of *E*-SOSE with methanol was taken as the model reaction where to test the effect of the counterion Li^+ versus Na^+ versus K^+ (entries 1–3). While *t*-BuONa and *t*-BuOK gave similar results, affording nearly quantitative yields of β-phenylsulfinyldimethylacetal **2** (R = Me)[7] under identical reaction conditions, *t*-BuOLi proved less reactive (ca. 40% yield only). The reaction was unsuccessful with amines (entries 4–8), or with stronger bases (entries 9–11). Interestingly, the reaction also proceeded with benzotriazole and imidazole (entries 12 and 13), though in moderate yields.

Application of the *t*-BuOK procedure to diverse alcohols with variable steric hindrance (entries 14–17) furnished the corresponding alkoxyvinyl sulfoxides **1**,[9] whereas the related acetals **2** were only detected as traces. Most likely, the bulkiness of both partners can be taken as responsible for preventing the second Michael addition. In contrast, diols (entries 18 and 19) were converted as expected[5] into the corresponding cyclic acetals: in such cases, the intramolecularity of the reaction helps in driving the reaction to the final product.[10,11]

Contrary to the above results, the reaction of *Z*-SOSE with *O*-nucleophiles generated by *t*-BuOK did not afford the expected substitution products, but led to apparent reduction of the sulfinyl group to produce fair yields of *Z*-1,2-bis(phenylsulfanyl)ethylene **3**.[12] It is therefore not possible to use *t*-BuOK as a base to promote substitution on *Z*-SOSE, whereas LiHMDS has given good results with a number of *O*-nucleophiles, including terpenols reported in Table 1 (entries 14–17).[13] The formation of bis-sulfide **3** is observed when either *Z*-

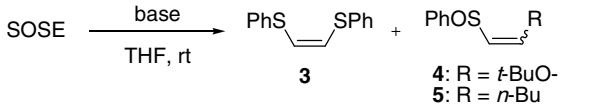
Table 1. Reaction of *E*-SOSE with *O*-nucleophiles generated by different bases



Entry	ROH	Base	Enolether **1**	Acetal **2**
1	MeOH	*t*-BuOK	—	98%
2	MeOH	*t*-BuONa	—	98%
3	MeOH	*t*-BuOLi	—	40%
4	MeOH	Et_3N	—	—
5	MeOH	TMEDA	—	—
6	MeOH	*i*-Pr_2NH	—	—
7	MeOH	HMDS	—	—
8	MeOH	DBU	—	—
9	MeOH	NaH	—	Traces
10	MeOH	*n*-BuLi	—	Traces
11	MeOH	LDA	—	—
12	MeOH	Imidazole	—	50%
13	MeOH	Benzotriazole	—	50%
14	(−)-Menthol	*t*-BuOK	45%	Traces
15	(−)-*endo*-Borneol	*t*-BuOK	40%	Traces
16	(+)-*endo*-Fenchol	*t*-BuOK	20%	Traces
17	(+)-Isopinocampheol	*t*-BuOK	26%	6%
18	1,2:5,6-Di-*O*-isopropylidene-D-mannitol	*t*-BuOK	—	80%
19	1,3:4,6-Di-*O*-benzylidene-D-mannitol[8]	*t*-BuOK	—	50%

General procedure: To a solution of alcohol or diol (10.0 or 5.0 mmol) in dry THF (10 mL) maintained at 0 °C under argon, the base (10.0 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min and a solution of *E*-SOSE (5.0 mmol) in dry THF (2 mL) was added by syringe. The resulting solution was maintained at 0 °C for 5 h then poured into cold water (50 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was analyzed by GC–MS and ^1H NMR and purified by FC. All new compounds gave satisfactory analytical data. Selected spectroscopic data are reported in the references.

Table 2. Reaction of *Z*-SOSE with bases



Entry	SOSE isomer	Base	Bis-sulfide **3**	Sulfoxide
1	*Z*	*t*-BuOK	50%	**4** (12%)
2	*E*	*t*-BuOK	50%	**4** (12%)
3	*Z*	*t*-BuONa	50%	**4** (15%)
4	*Z*	*t*-BuOLi	—	—
5	*Z*	KH	—	—
6	*Z*	NaH	—	—
7	*Z*	LiHMDS	20%	—
8	*Z*	*n*-BuLi	50%	**5** (Traces)

General procedure: To a solution of base (10.0 mmol) in dry THF (10 mL) maintained at 0 °C under argon a solution of *E*-SOSE (5.0 mmol) in dry THF (2 mL) was added by syringe. The mixture was stirred at 0 °C for 15 min then left to rise to rt over 5 h. The mixture was poured into cold water (50 mL) then extracted with diethyl ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was analyzed by GC–MS and ^{1}H NMR and purified by FC. All new compounds gave satisfactory analytical data. Selected spectroscopic data are reported in the references.

or *E*-SOSE is reacted with *t*-BuOK alone (Table 2, entries 1 and 2).

Together with **3** a little amount of the alkoxyvinyl sulfoxide **4**[14] is also produced despite the bulkiness of the *t*-butoxide anion. It should be pointed out that both *t*-BuOK and *t*-BuONa seem to be able to induce this reaction (entries 1–3), whereas *t*-BuOLi (entry 4) is inoperative, as well as other strong bases (entries 5 and 6). While producing minor amounts of **3** (entry 7), LiHMDS was observed to isomerize *Z*-SOSE into *E*-SOSE in relevant amounts. Butyl lithium (entry 8) furnished **3** in good yield together with only traces of the 2-*C*-butyl derivative **5**.[15]

This unexpected conversion of SOSE into **3** prompted us to further investigate[16] the mechanism of formation of the bis-sulfide, a direct 'reduction' of the sulfinyl group appearing highly improbable. When carried out in the presence of cyclohexene or triphenylphosphine, the reaction expectedly revealed no oxidation products. More realistic stands the hypothesis of a scrambling of substituents through formation of the transient alkynyl sulfide **6** via an E–Ad$_N$ process (Scheme 3).

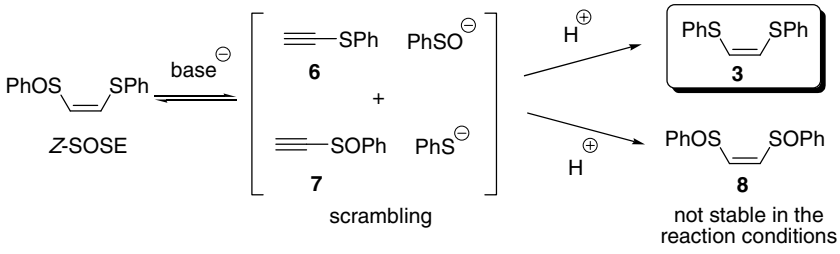
With a view to backing this hypothesis up, the experiment was carried out at a lower temperature, allowing to detect (GC–MS) a high concentration of **6**,[17] which was finally isolated by flash chromatography, together with alkynyl sulfoxide **7**.[18] In addition, the formation of phenylsulfenate ion generated by the elimination process, was corroborated by electrophilic trapping with benzyl chloride (Scheme 4). Under such conditions, the resulting sulfoxide **9**[19] could be isolated in 40% yield.

In addition, the parent sulfide **10** was also isolated in moderate yield, confirming that *t*-BuOK eliminates indifferently both the phenylsulfenate and the phenylthiolate ions, because of the close acidity of the two vinylic hydrogens in SOSE.

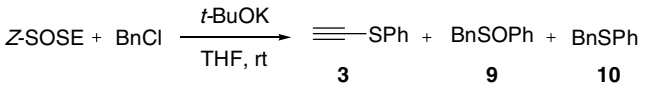
Further confirmation of the process by reacting *t*-BuOK with bicycloolefin **11**,[20] in which elimination is precluded: in such case, no bis-sulfide was formed (Scheme 5).

With those data in hands, it can be assumed that in the presence of *t*-BuOK, *E*- or *Z*-SOSE first eliminates $PhSO^-$ or PhS^- with formation of either alkyne **6** or alkyne **7**, which can undergo counter-addition of the expelled anions, to finally afford bis-sulfide **3** and bis-sulfoxide **8** (Scheme 3). Control experiments have shown that **8** is not stable under the reaction conditions and produces intractable mixtures of polar compounds. It is therefore not detected and **3** appears as the only apparent reaction product.

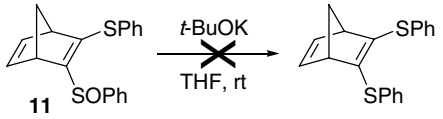
The observation that the *E*-isomer appears as reactive towards *t*-BuOK as the *Z*-isomer implies that despite of the poor electron withdrawing character of its substituents, SOSE reacts via an addition–elimination mechanism, similarly to BPSE and unlike a number of related alkenes (e.g., dichloroalkenes). In order to ascertain that unexpected behaviour, we attempted to evaluate the electrophilic character of the olefin by taking the ^{13}C NMR chemical shifts of the sp^2 carbons as electronic density probes. Even though being aware of the perturbation of the chemical shifts value induced by anisotropy, our aim was to establish some kind of predictive rule for the reactivity of electrophilic alkenes towards nucleophilic substitution (i.e., Ad$_N$–E vs E–Ad$_N$). The hypothesis was partially confirmed by observing that the δ value for *Z*-BPSE (140.5 ppm) is comparable to those of *Z*-SOSE (138.6 ppm for the =CH–SOPh), while systems that react through an elimination–addi-



Scheme 3. Mechanism proposed to explain the formation of **3**.



Scheme 4. Trapping experiment of the transient sulfide and sulfenate.



Scheme 5. Experiment confirming the elimination–addition path for the formation of bis-sulfide **3**.

tion mechanism, typically *Z*-1,2-dichloroethylene, display a much different chemical shift (120.0 ppm).

In summary, the above results highlight a strong dependence on the nature of the base used to generate the nucleophilic species. *Z*-SOSE reacts smoothly with *O*-nucleophiles generated with LiHMDS as base, while *O*-nucleophiles generated by potassium *tert*-butoxide react with *E*-SOSE. Thus the use of SOSE as a simple and advantageous protective reagent in carbohydrate chemistry is general for both isomers when the appropriate reaction conditions are applied.

Acknowledgements

This work was co-funded by MIUR (Rome) within the national PRIN framework. We also thank EGIDE for support.

References and notes

1. Patai, S.; Rappoport, Z. *The Chemistry of Alkenes*; Wiley Interscience: New York, NY, 1964; pp 525–546.
2. Such a rather simplified statement finds exceptions due to the non-stereospecific *syn* addition of nucleophiles to electrophilic alkynes and to *Z* to *E* isomerism under the reaction conditions.
3. (a) Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 985–991; (b) De Lucchi, O.; Pasquato, L.; Rollin, P.; Tatibouët, A. In *e-EROS Enyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2005. doi:10.1002/047084289X.rb183; (c) Cabianca, E.; Chéry, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Synlett* **2001**, 1962–1964; (d) Chéry, F.; Desroses, M.; Tatibouët, A.; Rollin, P.; De Lucchi, O. *Tetrahedron* **2003**, *59*, 4563–4572.
4. Truce, W. E.; Boundakian, M. M.; Heine, R. F.; McManimie, R. J. *J. Am. Chem. Soc.* **1956**, *78*, 2743–2748.
5. Cabianca, E.; Tatibouët, A.; Fabris, F.; De Lucchi, O.; Rollin, P. *Tetrahedron Lett.* **2005**, *46*, 1035–1037.
6. Chéry, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Synthesis* **2001**, 286–292.
7. Selected spectroscopic data for **2** (R=Me): ^{1}H NMR ($CDCl_3$) δ 2.96 (dd, 1H, $J_{gem} = 13.1$, H-1b), 3.12 (dd, 1H, H-1a), 4.76 (dd, 1H, $J_{1a-2} = 4.0$, $J_{1b-2} = 7.3$, H-2), 7.49–7.57 (m, 3H, H–PhSO), 7.6–7.7 (m, 2H, *ortho*-H–PhSO). ^{13}C NMR ($CDCl_3$) δ 53.3, 54.7 (2 Me), 60.9 (C-1), 99.5 (C-2), 123.9 (2*CH–*ortho*-PhSO), 129.4 (2*CH–*meta*-PhSO), 131.3 (CH–*para*-PhSO), 144.0 (C_{IV}–PhSO). MS: *m*/*z* 237 $[M+Na]^+$.
8. Diol prepared according to: Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1123–1126.
9. Selected spectroscopy data for the (*E*)-alkoxyvinyl sulfoxide derived from (−)-menthol (2 epimeric sulfoxides): ^{1}H NMR ($CDCl_3$) δ 0.75, 0.79 (2d, 3H, $J_{8-9} = J_{8-10} = 7.0$, Me), 0.89–0.95 (m, 8H, 2Me, H-4b, H-6b), 0.98–1.13 (m, 1H, H-3b), 1.19–1.45 (m, 2H, H-2, H-5), 1.68 (br d, 2H, H-3a, H-4a), 1.99–2.11 (m, 2H, H-6a, H-8), 3.68–3.80 (m, 1H, H-1), 5.77 (d, 1H, $J_{vic} = 12.7$, H-2_{vinyl}), 7.22, 7.25 (2d, 1H, $J_{vic} = 12.5$, 12.7, H-1_{vinyl}), 7.44–7.50 (m, 3H, H–PhSO), 7.59–7.63 (m, 2H, *ortho*-H–PhSO). ^{13}C NMR ($CDCl_3$) δ 16.4, 20.7 (C-9, C-10), 22.0 (C-7), 23.4 (C-3), 26.0 (C-8), 31.5 (C-5), 34.1 (C-4), 40.5, 40.8 (C-6), 47.5 (C-2), 83.2, 83.6 (C-1), 112,2, 112.3 (C-2_{vinyl}), 124.4 (CH–*ortho*-PhSO), 129.1 (CH–*meta*-PhSO), 130.3 (CH–*para*-PhSO), 145.5 (C_{IV}–PhSO), 158.0 (C-1_{vinyl}). MS: *m*/*z* 329 $[M+Na]^+$.
10. Selected spectroscopy data for the β-phenylsulfinylacetal derived from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2 epimeric sulfoxides): ^{1}H NMR ($CDCl_3$) δ 2.99–3.23 (m, CH_2SOPh), 5.43–5.46 (m, C*H*–CH_2SOPh). ^{13}C NMR ($CDCl_3$) δ 62.2, 62.3 (*C*H_2SOPh), 66.1, 66.6 (C-1, C-6), 99.9 (*C*H–CH_2SOPh), 124.0 (CH–*ortho*-PhSO), 129.3 (CH–*meta*-PhSO), 131.2 (CH–*para*-PhSO), 144.0 (C_{IV}–PhSO). MS: *m*/*z* 435 $[M+Na]^+$.
11. Selected spectroscopy data for the β-phenylsulfinylacetal derived from 1,3:4,6-di-*O*-benzylidene-D-mannitol (2 epimeric sulfoxides): ^{1}H NMR ($CDCl_3$) δ 2.9–3.2 (m, CH_2SOPh), 5.26, 5.36 (2 dd, C*H*–CH_2SOPh), 5.48, 5.52 (2s, C*H*–Ph). ^{13}C NMR ($CDCl_3$) δ 59.9, 61.1 (*C*H_2SOPh), 67.0, 67.1, 68.7, 68.8 (C-1, C-2, C-5, C-6), 81.8 (C-3, C-4), 95.9, 96.0 (*C*H–CH_2SOPh), 100.8, 100.9 (*C*H–Ph), 123.9, 124.0 (CH–*ortho*-PhSO), 129.0, 129.4 (CH–*meta*-PhSO), 131.4 (CH–*para*-PhSO), 143.1, 143.6 (C_{IV}–PhSO). MS: *m*/*z* 531.5 $[M+Na]^+$.
12. (a) Cusa, N. W.; McCombie, H. *J. Chem. Soc.* **1937**, 767–770; (b) Truce, W. E.; Boudakian, M. M.; Heine, R. F.; McManimie, R. J. *J. Am. Chem. Soc.* **1956**, *78*, 2743–2748.
13. Cabianca, E. Ph.D. Thesis, Orléans (**2004**).
14. Selected spectroscopy data for **4**: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H, CMe_3), 5.36 (d, 1H, $J_{vic} = 7.8$, H-2), 6.83 (d, 1H, H-1), 7.6–7.7 (m, 2H, *ortho*-H–PhSO), 7.40–7.55 (m, 3H, H–PhSO). ^{13}C NMR ($CDCl_3$) δ 27.7 (Me), 79.8 (C_{IV}–*t*-Bu), 112.4 (C-1), 123.6 (CH–*ortho*-PhSO), 128.6 (CH–*meta*-PhSO), 129.8 (CH–*para*-PhSO), 145.7 (C_{IV}–PhSO), 148.6 (C-2). MS: *m*/*z* 247.5 $[M+Na]^+$.
15. Cardellicchio, C.; Fiandanese, V.; Naso, F. *J. Org. Chem.* **1992**, *57*, 1718–1722.
16. The reaction furnished the same results using diethyl ether or NMP instead of THF, whereas no reaction took place in dichloromethane.
17. Hunter, G. A.; McNab, H. *Synthesis* **1993**, 1067–1068.
18. Laba, V. I.; Sviridova, A. V.; Prilezhaeva, E. N. *Izv. Akad. Nauk SSSR, Ser. Khim* **1972**, *1*, 212–213, Selected spectroscopy data for **7**: ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 1H, acetylenic H) 7.55-7.59 (m, 3H, H–PhSO), 7.80–7.84 (m, 2H, *ortho*-H–PhSO). ^{13}C NMR ($CDCl_3$) δ 81.8 (acetylenic C_{IV}), 90.5 (acetylenic CH), 125.1 (2*CH–*ortho*-PhSO), 129.8 (2*CH–*meta*-PhSO), 132.2 (CH–*para*-PhSO), 143.2 (C_{IV}–PhSO). MS: *m*/*z* 173 $[M+Na]^+$.
19. Kakarla, R.; Dulina, R. G.; Hatzenbuhler, N. T.; Hui, Y. W.; Sofia, M. J. *J. Org. Chem.* **1996**, *61*, 8347–8349.
20. Cyclopentadiene was added to a crude dichloromethane solution of 1-phenylsulfinyl-2-phenylsulfanylacetylene obtained by controlled *m*-CPBA oxidation of 1,2-bis(phenylsulfanyl)acetylene (see: Pasquato, L.; De Lucchi, O.; Krotz, L. *Tetrahedron Lett.* **1991**, *32*, 2177–2178)

and 12 h refluxing of the mixture; flash-chromatography purification afforded **11** as a 6:4 mixture of stereoisomers. Selected spectroscopic data: ^{1}H NMR ($CDCl_3$) δ 1.92, 2.13 (2 br d, $J = 6.8$, apical H-7), 3.38, 3.61 (2 br s, bridgehead-H-1 and H-4 minor), 3.43, 3.88 (2 br s, bridgehead-H-1 and H-4 major), 5.90 (dd, $J = 4.6$, $J = 3.0$, vinyl-H major), 6.29 (dd, $J = 4.6$, $J = 3.3$, vinyl-H major), 6.56 (dd, $J = 4.9$, $J = 3.0$, vinyl-H minor), 6.82 (dd, $J = 4.9$, $J = 3.7$, vinyl-H minor), 7.28–7.65 (series of m, H-Ar). ^{13}C NMR ($CDCl_3$) δ 48.2, 49.8, 55.7, 56.9, 68.2, 70.4, 124.0, 128.2, 128.3, 128.8, 128.9, 129.2, 129.3, 130.1, 132.0, 132.7, 137.6, 139.8, 140.0, 142.0, 142.2, 143.2, 148.9, 150.0, 156.9, 159.8. MS (EI): m/z 276 [$M^+ - SO$].