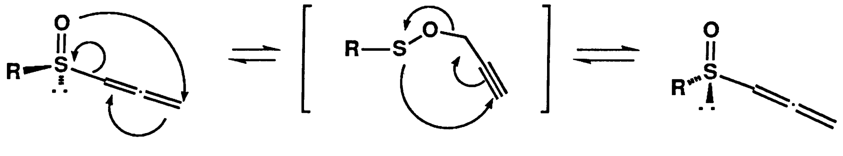
CHEMISTRY LETTERS, pp. 1581-1584, 1990.

The First Synthesis of a Thermally Stable, Chiral Allenic Sulfoxide, (2-*exo*-Hydroxy-10-bornylsulfinyl)propa-1,2-diene

Yoshitsugu ARAI, Masanori TAKADOI, Tohru KONTANI,
Toru KOIZUMI,* and Motoo SHIRO*,†
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01
† Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Sagisu 5-12-4, Fukushima-ku, Osaka 553

The first synthesis of a thermally stable, chiral allenic sulfoxide (2-*exo*-hydroxy-10-bornylsulfinyl)propa-1,2-diene, has been achieved. It was revealed that the sulfoxide would be stabilized to racemization by an intramolecular hydrogen-bond.

As a continuation of our studies on the synthesis of chiral sulfoxides,[1] we were intrigued by synthesis of optically pure allenic sulfoxides. The chemistry of chiral allenic sulfoxides, despite their synthetic potential,[2] has not been developed because the chirality at the sulfur atom has been known to be susceptible to epimerization through a [2,3]-sigmatropic rearrangement (Eq. 1).[3] As the result, all attempts to isolate stable aryl allenic sulfoxides in optically pure form have failed. For example, *p*-tolyl 1,3-dimethylallenyl sulfoxide mutarotates on standing at room temperature in acetone solution.[4]



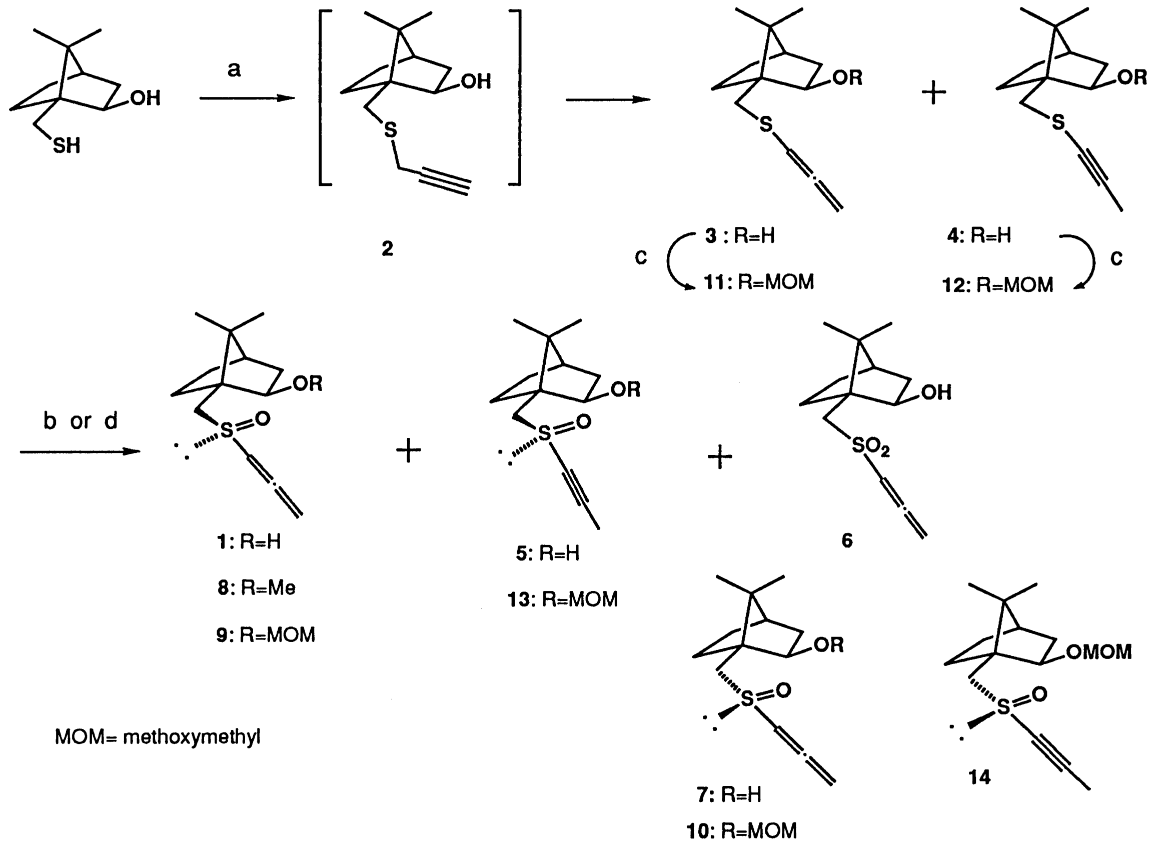
(1)

We considered that the [2,3]-sigmatropic rearrangement could be suppressed by lowering the electron density of the sulfinyl oxygen in allenic sulfoxides by the formation of an intramolecular hydrogen-bond. For this purpose, we devised a synthesis of (2-*exo*-hydroxy-10-bornylsulfinyl)-propa-1,2-diene (**1**), thereby showing that the chiral sulfoxide **1** is quite stable without epimerization on heating (*vide infra*).

The synthetic route to **1** is illustrated in Scheme 1. 10-Mercaptoisoborneol[5)] was treated with propargyl bromide and sodium hydride in tetrahydrofuran at -78 °C. The reaction was complete within a few hours to afford the propargyl sulfide **2**. However, a prolonged reaction period (4 h) at elevated temperature (allowed to rise to 0 °C) produced the allenic sulfide **3** as the major product. The propynyl sulfide **4** was also obtained under these conditions. The formation of **3** could be easily monitored on TLC, in which a UV active spot appeared. Although the major sulfide **3** was separable from **4**, chromatographic separation caused poor yields of **3** because of its unstable character. Therefore, a 6:1 mixture of the sulfides **3** and **4** was subjected to oxidation without separation. Exposure to 3-chloroperoxybenzoic acid gave the sulfoxide **1**, mp 67-68 °C, $[\alpha]_D^{25}$ -80.7°(c 1.02, acetone), in 74% yield from **3**, along with the isomeric sulfoxide **5** and the allenic sulfone **6** (20% combined yield).[6)] The absolute configuration of the sulfur center of **1** was confirmed to be R by the single crystal X-ray analysis.[7)] The OH absorption in the FT-IR spectrum of **1** at 3445 cm^{-1} was observed even in diluted solution (0.005 M in carbon tetrachloride), which suggests the presence of an intramolecular hydrogen-bond.[8)] Next, we examined the thermal stability of **1** in refluxing solvent. Under the conditions no inversion of the sulfinyl center of **1** was observed (Table 1). One explanation of this stability to diastereoisomerization is that the sulfur center can be stabilized through the intramolecular hydrogen-bond between the sulfinyl oxygen and the secondary hydroxyl attached to the bornyl residue. Accordingly, interconversions, i.e. [2,3]-sigmatropic rearrangement or pyramidal inversion, would be impeded by this interaction.

In order to confirm this assumption we undertook to synthesize the compounds **8** and **9** in which such intramolecular hydrogen bond does not exist. Several attempts to protect the hydroxy group in **1** as the methyl ether **8** or as the methoxymethyl ether **9** from **1** were unfruitful. On the other hand, the methoxymethyl ether **9** could be obtained by reaction of **3** with chloromethyl methyl ether and Hünig base,[9)] followed by oxidation of the resulting sulfide **11** with 3-chloroperoxybenzoic acid. The sulfide **11** contaminated with **12** (**11**:**12**=6:1) was subjected to oxidation. The oxidation afforded the sulfoxides **9** and **10** as a 1:1 diastereoisomeric mixture, accompanied by **13** and **14** (17% combined yield). The configuration of the sulfur center in **9** could be assigned as R by identification with the compound that was independently synthesized, though in very poor yield, from **1** through methoxymethylation.

Heating of pure **9** or **10** in refluxing toluene resulted in isomerization giving an approximately equimolar mixture of **9** and **10** (Table 1). It



Scheme 1. a) 1.1 equiv. propargyl bromide, 1.3 equiv. sodium hydride, tetrahydrofuran, -78 – 0 °C, 4 h, 89% of a 6:1 mixture of **3** and **4**. b) **1** (prepared from a 6:1 mixture of **3** and **4**): 1.1 equiv. 3-chloroperoxybenzoic acid, CH_2Cl_2, -78 °C, 3 h, 74% **1**, 10% **5**, 10% **6**. c) **11** and **12** (prepared from a 6:1 mixture of **3** and **4**): 5 equiv. MOMCl, 5 equiv. $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C – r.t., 12 h, 94% of a 3:2.5 mixture of **11** and **12** . d) **9** and **10** (prepared from a 6:1 mixture of **11** and **12**): 1.1 equiv. 3-chloroperoxybenzoic acid, -78 °C, 1 h, 37% **9** , 37% **10**, 17% of a 1:1 mixture of **13** and **14**

Table 1. Thermal stability of the sulfoxides **1**, **9**, and **10**

Compound	Conditions			Proportions	Recovered
	Solvent	Temp	Time/h	**9** : **10**	yield/%[a)]
1	benzene	reflux	240		83[b)]
1	toluene	reflux	72		90[b)]
9	toluene	reflux	1	1 : 1.3[c)]	95
9	toluene	reflux	6	1 : 1.3[c)]	100
10	toluene	reflux	1	1 : 1.3[c)]	91
10	toluene	reflux	6	1 : 1.3[c)]	94

a) Estimated by isolation. b) In each case no diastereoisomeric allenic sulfoxide **7** was detected in the NMR spectrum of the crude product. c) Determined by HPLC analysis.

was revealed that protection of the hydroxyl in the bornyl residue resulted in ready epimerization at the sulfur center.

In summary, our results show that allenic sulfoxides, otherwise unstable, could be self-stabilized by the intramolecular hydrogen-bond between the sulfinyl oxygen and the secondary hydroxy group. Our synthetic methodology would provide a route to various chiral allenic sulfoxides which are reactive enough as dipolarophiles to nitrones and as dienophiles to dienes in Diels-Alder reactions.

This work was supported by the Research Foundation for Pharmaceutical Sciences and TERUMO Life Science Foundation.

References

1) Y. Arai, M. Matsui, and T. Koizumi, Synthesis, 1990, 320.

2) R. S. Brown, S. C. Eyley, and P. J. Parsons, Synth. Commun., 15, 633 (1985); A. Padwa, B. H. Norman, and J. Pereumattam, Tetrahedron Lett., 30, 663 (1989); R.A. Gibbs, K. Bartels, R.W.K. Lee, and W.H. Okamura, J. Am. Chem. Soc., 111, 3717 (1989).

3) D. R. Rayer, A. J. Gordon, and K. Mislow, J. Am. Chem. Soc., 90, 4854, 4869 (1968).

4) M. Cinquini, S. Colonna, and C. J. M. Stirling, J. Chem. Soc., Chem. Commun., 1975, 256; M. Cinquini, S. Colonna, F. Cozzi, and C. J. M. Stirling, J. Chem. Soc., Perkin Trans. 1, 1976, 2061.

5) E. L. Eliel and W. J. Frazee, J. Org. Chem., 44, 3598 (1979).

6) New compounds were chromatographically homogeneous and gave analytical and spectroscopic data in accordance with their structure. No diastereoisomeric sulfoxide **7** was produced in this oxidation reaction. For the diastereoselective oxidation, see: Ref. 1.

7) Crystal data of **1**: orthorhombic crystals, space group $P2_12_12_1$, a=9.615(1), b=20.616(3), c=6.715(1) Å, V=1331.2(4) Å^3, D_c=1.199 g/cm^3, Z=4, $\lambda(\mathrm{Cu}_{K\alpha})$=1.54178 Å, crystal dimensions, 0.35 x 0.35 x 0.35 mm^3. Intensity data were collected on a Rigaku AFC-5 diffractometer using ω-2θ scan technique in the region of $2\theta \leq 130°$. A total of 1337 unique reflections were measured, of which 1221 unique reflections with $|F_0| > 3\delta(F_0)$ were used for structure determination. The structure was solved by direct method (MULTAN 87) and refined by block-diagonal least-squares technique to R=0.039, R_w=0.054.

8) K. Nakanishi and P. H. Solomon, "Infrared Absorption Spectroscopy," 2 ed, Holden-Day, Inc., San Francisco (1977), p. 27.

9) E. J. Corey, J.-L. Gras, and P. Ulrich, Tetrahedron Lett., 1976, 809.

(Received June 15, 1990)