Stereoselective addition reactions with chalcogen electrophiles

Franz W. Bürgler,[a] Gianfranco Fragale,[a] and Thomas Wirth[a,b]*

[a]Universität Basel, Department Chemie, St. Johanns-Ring 19, 4056 Basel, Switzerland
[b]Cardiff University, School of Chemistry, Park Place, Cardiff CF10 3AT, United Kingdom
E-mail: wirth@cf.ac.uk

Dedicated to Professor Alain Krief on the occasion of his 65th birthday

Abstract
The addition of chalcogen electrophiles to alkenes is investigated using sulfur and tellurium electrophiles. These reagents have been prepared in analogy to the known and well-investigated selenium counterparts.

Keywords: Addition reactions, alkenes, chalcogens, electrophiles, sulfur reagents

Introduction

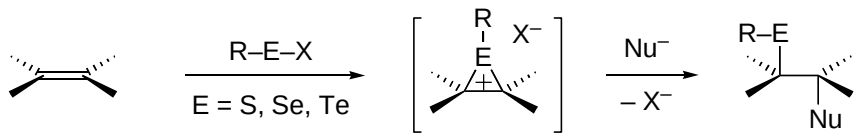
Electrophilic addition reactions to alkenes are known for a long time as key transformations in organic chemistry. Halogen- as well as chalcogen-based methods are widely explored and are now very useful tools in the hands of synthetic chemists.

Before organoselenium reagents became important reagents it was discovered that electrophilic selenium compounds can add stereospecifically to alkenes.[1] Since that time this reaction has been an important tool in the portfolio of organic chemists and is now routinely used even for the synthesis of complex target compounds. Comprehensive reviews on this chemistry have appeared[2,3,4,5,6] and recently the synthesis of chiral selenium electrophiles and their application in asymmetric synthesis has emerged. Herein we describe the synthesis and use of enantiomerically pure sulfur- and tellurium-electrophiles and compare these reagents to the known chiral electrophilic selenium reagents.

Results and Discussion

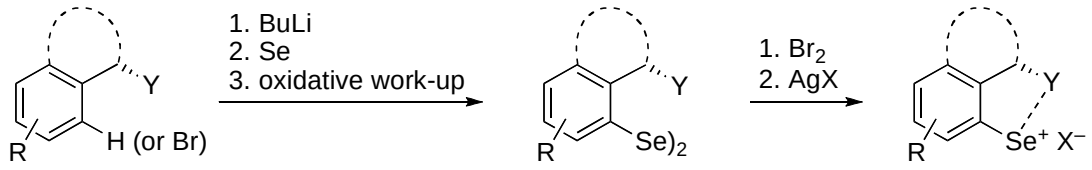
The addition of chalcogen electrophiles to alkenes are usually stereospecific *anti*-additions. The additions proceed via the formation of a chalcogeniranium ion of type **1**, which are opened in the

presence of external nucleophiles to addition products **2**. Internal nucleophiles can lead to cyclic products via an *endo* or via an *exo* pathway.



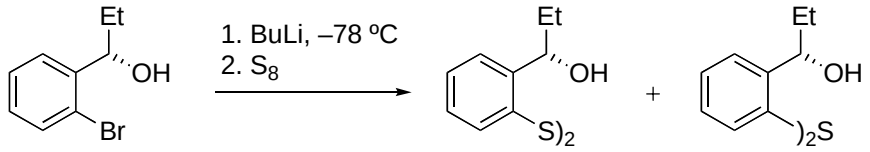
1 **2**

We have investigated various enantiomerically pure selenium electrophiles of the general structure **5** and employed these in stereoselective addition reactions of alkenes. Common precursor molecules are the corresponding diselenides **4** which are easily transferred into the aryl selenenyl halides or into other selenium electrophiles with exchanged counterions. Under certain reaction conditions selectivities of up to 98:2 can be obtained. The right choice of the heteroatom Y and of the counterion X^- is important for obtaining high selectivities and some systematic studies of their influence have been published.[7,8] The diselenides are usually obtained from the enantiomerically pure precursors **3** using either an *ortho*-metallation or a bromine – lithium exchange depending on the substitution pattern and on other functional groups R. The aryllithium compound is obtained for the subsequent reaction with elemental selenium to yield the diselenides **4** after oxidative work-up. An electron lone pair of the heteroatom Y coordinates to the σ* orbital of the selenium atom as shown in **5**.[9,10]



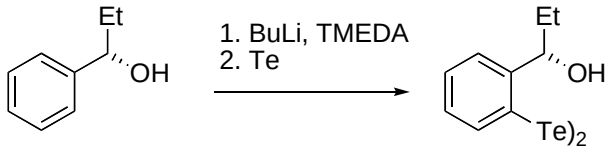
3 **4** **5**

The synthetic route to the corresponding sulfur- and tellurium-electrophiles with a stereogenic center in a benzylic position is similar to the selenium electrophiles mentioned above. The bromine containing precursor **6** could be converted into the disulfide **7** using the method of Pfaltz et al.,[11] but the main product in this reaction was the monosulfide **8**. The ratio of **7**:**8** was 1:5 with 90% combined yield. The two compounds were separated by MPLC. Other methods[12] describing the addition of elemental sulfur to the aryllithium reagent at 0 ºC and not at –78 ºC were not successful in this reaction.



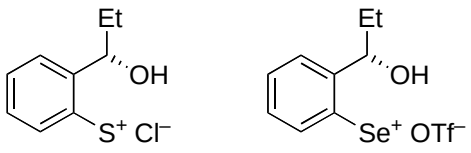
6 **7** **8**

The corresponding tellurium compound was obtained by *ortho*-deprotonation of (*S*)-phenylethanol **9**, but the ditelluride **10** was obtained in only 7% yield. This compound is light-sensitive and all operations have to be performed in the dark. An addition reaction using the tellurium electrophile generated from **10** was performed but the reaction mixture decomposed rapidly and no addition product could be isolated.



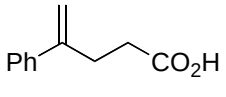
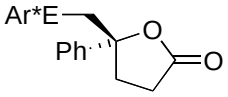
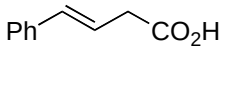
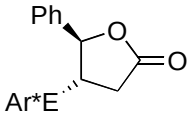
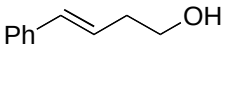
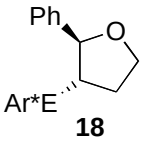
9 **10**

The sulfur electrophile **11** was generated from disulfide **7** by reaction with sulfuryl chloride in THF. Reaction of **11** with alkenes **13** – **15** yielded cyclization products **16** – **18** as shown in Table 1. The yields of the cyclization products were much lower than using the corresponding selenium electrophile, although in the case of the unsaturated carboxylic acid **13** almost similar selectivities were obtained. The strong intramolecular coordination has been proven in the case of selenium electrophiles, its presence in the sulfur electrophiles such as **11** might also be a reason for the low yields in these cyclizations. Although the selectivity in the *exo*-cyclisation of **13** are almost identical for the sulfur electrophile **11** and the selenium electrophile **12**, the results differ in the *endo*-cyclisation of **14**, where a lower selectivitiy is observed with **11**. Unoptimized reaction conditions might be one reason, but the smaller size of the sulfur atom versus the selenium atom might lead to a less efficient interaction of the oxygen lone-pair with the σ*-orbital of the sulfur atom and, therefore, to lower selectivity as this interaction is crucial for an efficient stereoselective reaction.[9,10]



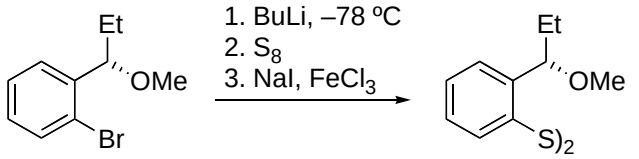
11 **12**

Table 1. Electrophilic cyclizations with electrophiles **11** and **12**

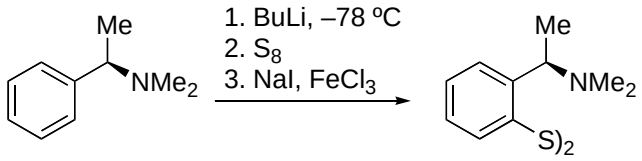
Alkene	Product	Sulfur electrophile **11** (E = S) Yield / *d.r.*	Selenium electrophile **12**[13] (E = Se) Yield / *d.r.*
 **13**	 **16**	38% / 89:11 [a]	58% / 92:8
 **14**	 **17**	5% / 70:30 [a]	41% / 86:14
 **15**	 **18**	4% / n.d. [b]	87% / 92:8

[a]Determined by NMR. [b]Not determined.

The intramolecular coordination of the hydroxy-group with the sulfur electrophile should be weakened by protecting the free hydroxy-group. In addition to disulfide **20**, synthesized from the precursor **19** in 30% yield, we also prepared the nitrogen-based disulfide **22** starting from (*R*)-*N*,*N*-dimethyl-1-phenylethylamine **21** (9% yield).[12] The synthesis yields the free thiols which have then been oxidized to the disulfides using sodium iodide and iron trichloride.[14]



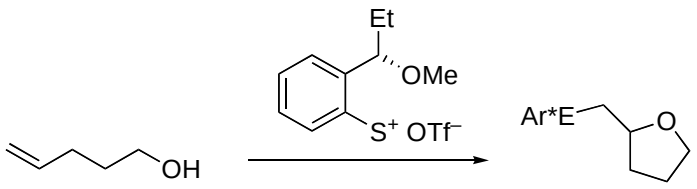
19 **20**



21 **22**

After generation of the sulfur electrophile using elemental bromine / silver triflate, only product mixtures were obtained with the alkenes **13** – **15**. Only the cyclisation of 4-pentenol led to the tetrahydrofuran derivative **23** although in only 10% yield but with a remarkable

diasteromeric ratio of 65:35. The corresponding selenium electrophile only generates a 1:1 diastereomeric ratio with this type of substrate.[13]



23

The nitrogen based sulfur electrophile generated from **22** did, however, not react at all with the alkenes shown in Table 1 under the reaction conditions. The corresponding selenium electrophile has already been proven to be difficult to react.[15]

In conclusion, we have shown that disulfides and a ditelluride could be prepared in analogy to the diselenides investigated earlier. The generation of the corresponding electrophiles is possible using the disulfide precursors, although the reaction yields as well as the observed selectivities are disappointingly low. Optimization of reaction conditions and reagents is required to obtain higher yields and selectivities using sulfur-based electrophilic reagents of the structures mentioned above.

Experimental Section

(*S*,*S*)-Bis[2-(1-hydroxypropyl)phenyl] disulfide (7) and (*S*,*S*)-Bis[2-(1-hydroxypropyl) phenyl] sulfide (8)

(*S*)-1-(2-Bromophenyl)propanol **6** (25.4 mmol, 5.48 g) was dissolved in THF (25 mL) and cooled to –78 ºC. *n*-Butyllithium (76.2 mmol, 1.6M in hexane, 47.6 mL) was added and the solution stirred at room temperature for 30 min. After cooling to –78 ºC a suspension of freshly sublimed sulfur (25.4 mmol, 813 mg) in THF (25 mL) was added and stirred for 3 h at –78 ºC. Addition of 2M HCl (35 mL) was followed by extraction with methyl *tert*-butyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The products **7** and **8** were separated by MPLC.

Compound 7. Colorless solid; (650 mg, 1.95 mmol, 15%); m.p.: 98-100 ºC; $[\alpha]_D^{25}$ = +250.5 (c = 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85 (t, *J* = 7.4 Hz, 6H, CH_3), 1.62-1.68 (m, 4H, CH_2CH_3), 2.08 (s, 2H, OH), 4.88 (t, *J* = 6.2 Hz, 2H, CHOH), 7.24 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 2H, arom. CH), 7.34 (td, *J* = 7.5 Hz, *J* = 1.6 Hz, 2H, arom. CH), 7.45 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 2H, arom. CH), 7.61 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 2H, arom. CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.1 (q), 31.3 (t), 72.2 (d), 126.4 (d), 128.2 (d), 129.1 (d), 132.8 (d), 134.5 (s), 146.1 (s); MS (EI): *m/z* (%) 334 (19) [M^+], 166 (38), 149 (71), 137 (100), 109 (34), 91 (13), 77 (33), 65 (17); IR ($CHCl_3$): ν = 3448, 3007, 2976, 2933, 2400, 1773, 1521, 1477, 1423, 1391, 1046, 928, 877 cm^{-1}.

Compound 8. Colorless solid; (2.94 g, 9.75 mmol, 75%); m.p.: 78-80 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.97 (t, *J* = 7.4 Hz, 6H, CH_3), 1.71-1.82 (m, 4H, CH_2CH_3), 2.2 (s br, 2H, OH), 5.13 (t, *J* = 6.2 Hz, 2H, CHOH), 7.06 (dd, *J* = 7.8 Hz, *J* = 1.1 Hz, 2H, arom. CH), 7.16 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 2H, arom. CH), 7.26-7.33 (m, 2H, arom. CH), 7.57 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 2H, arom. CH); MS (EI): *m/z* (%) = 302 (31) [M^+], 284 (33), 255 (84), 237 (32), 197 (31), 165 (29), 150 (27), 137 (100), 109 (26), 91 (36), 77 (31), 65 (10); IR ($CHCl_3$): ν = 3426, 3063, 3005, 2967, 2934, 2877, 1589, 1464, 1437, 1136, 1051, 1034, 972 cm^{-1}.

(*S*,*S*)-Bis[2-(1-hydroxypropyl)phenyl] ditelluride (10). Dark oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4, 6H), 1.75 (m, 4H), 3.00 (s, 2H), 4.71 (t, *J* = 6.6 Hz, 2H), 7.02 (m, 2H), 7.18-7.35 (m, 4H), 7.97 (d, *J* = 7.8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 10.4 (q), 30.7 (t), 78.6 (d), 108.9 (s), 126.0 (d), 128.4 (d), 128.6 (d), 140.8 (d), 147.3 (s); MS (EI, 70 eV): 526 (10%, M^+), 369 (16), 264 (50), 235 (85), 206 (15), 117 (23), 105 (100), 77 (90), 51 (34); HMRS for $C_{18}H_{22}O_2Te_2$: calc.: 529.9759, found: 529.9746.

General procedure for cyclizations with 11

Disulfide **7** (60 mg, 0.18 mmol) was dissolved in THF (5 mL) and sulfurylchloride (49 mg, 0.36 mmol) was added. After stirring at room temperature for 1 h the alkene (0.36 mmol) in THF (3 mL) was added. After additional 4 h stirring, the reaction mixture was neutralized with phosphate buffer and diisopropylethylamine. After extraction with methyl *tert*-butyl ether (3 x 10 mL) the combined organic extracts were dried ($MgSO_4$), the solvent removed under reduced pressure and the reaction mixture purified by column chromatography.

(*R*)-5-({2-[(*S*)-1-Hydroxypropyl]phenylthio}methyl)-5-phenyldihydrofuran-2(3*H*)-one (16). Colorless oil; (45 mg, 0.13 mmol, 38 %); $[\alpha]_D^{25}$ = – 95.8 (c = 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.98 (t, *J* = 7.4 Hz, 3H, CH_3), 1.78-1.92 (m, 2H, CH_2CH_3), 2.10-2.26 (m, 1H, OH), 2.52-2.61 (m, 2H, CH_2), 2.75-2.88 (m, 2H, CH_2), 3.72 (dd, *J* = 16.6 Hz, *J* = 11.3 Hz, 2H, CH_2S), 6.16-6.20 (m, 1H), 7.34-7.42 (m, 6H, arom. CH), 7.48-7.62 (m, 2H, arom. CH), 7.73-7.76 (d, *J* = 7.5 Hz, 1H, arom. CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 8.6 (q), 27.3 (t), 29.0 (t), 32.33 (t), 41.0 (t), 86.4 (s), 91.4 (d), 122.1 (d), 123.4 (d), 124.9 (d, 2C), 128.6 (d), 128.8 (d, 2C), 129.3 (d), 140.7, 140.8, 147.5 (s), 175.5 (s); IR ($CHCl_3$): ν = 3062, 2970, 2361, 2343, 1784, 1496, 1448, 1418, 1294, 1160, 1125, 1035, 932, 888 cm^{-1}.

(*S*)-2-(1-Methoxypropyl)benzenethiol (19). (2.1 g, 9.2 mmol) was converted according to the procedure described for **7**/**8** into (*S*)-2-(1-methoxypropyl)benzenethiol (252 mg, 1.38 mmol, 30%).

Yellow oil; $[\alpha]_D^{25}$ = – 106.8 (c = 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3H, CH_3), 1.73-1.85 (m, 2H, CH_2CH_3), 3.24 (s, 3H, OCH_3), 3.58 (s, 1H, SH), 4.39 (t, *J* = 6.3 Hz, 1H, CH), 7.10 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H, arom. CH), 7.18 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H, arom. CH), 7.26 (dd, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H, arom. CH), 7.31 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H, arom. CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 10.2 (q), 29.1 (t), 56.7 (q), 83.1 (d), 126.0 (d), 127.4 (d), 127.6 (d), 129.9 (s), 131.1 (d), 139.9 (s); MS (EI): *m/z* (%) 182 (7) [M^+], 150 (86),

135 (100), 121 (14), 109 (17), 91(17), 77 (9); IR ($CHCl_3$): ν = 3061, 2932, 2875, 2822, 2543, 2360, 1591, 1569, 1464, 1437, 1204, 1121, 1081, 751 cm^{-1}.

(*S*,*S*)-Bis-[2-(1-methoxypropyl)phenyl] disulfide (20). (*S*)-2-(1-Methoxypropyl)benzenethiol (252 mg, 1.38 mmol) was dissolved in acetonitrile (10 mL) and stirred with sodium iodide (41 mg, 0.28 mmol) and iron(III)chloride (21 mg, 0.14 mmol) for 45 min. The solvent was removed under reduct pressure and the residue washed with aq. sodium thiosulfate solution (1%, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure yielding **20** (243 mg, 1.33 mmol, 97%).

Yellow oil; $[\alpha]_D^{25}$ = + 51.8 (c = 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (t, *J* = 7.4 Hz, 6H, CH_3), 1.62-1.77 (m, 4H, CH_2CH_3), 3.10 (s, 6H, OCH_3), 4.88 (dd, *J* = 7.3 Hz, *J* = 5.5 Hz, 2H, CH), 7.20 (td, *J* = 7.4 Hz, *J* = 1.7 Hz, 2H, arom. CH), 7.34 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 2H, arom. CH), 7.37 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 2H, arom. CH), 7.60 (dd, *J* = 7.7 Hz, *J* = 1.3 Hz, 2H, arom. CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.2 (q), 30.5 (t), 56.7 (q), 81.5 (d), 126.5 (d), 127.9 (d), 128.1 (d), 130.5 (d), 135.1 (s), 142.6 (s); MS (EI): *m/z* (%) 362 (50) [M^+], 301 (10), 181 (43), 149 (100), 134 (38), 109 (14), 91 (11), 77 (6); IR ($CHCl_3$): ν = 3058, 2964, 2931, 2875, 2360, 1588, 1567, 1462, 1435, 1121, 1080, 936, 909, 754 cm^{-1}.

(*R*)-2-(1-(Dimethylamino)ethyl)benzenethiol (21). (1.63 g, 10.9 mmol) was converted according to the procedure described for **7**/**8** into (*R*)-2-(1-(dimethylamino)ethyl)benzenethiol (220 mg, 1.2 mmol, 11%).

Colorless crystals; m.p.: 135-137 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.62 (d, *J* = 7.1 Hz, 3H, CH_3), 2.58 (s, 6H, $N(CH_3)_2$), 4.46 (q, 1H, CH), 6.86 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H, arom. CH), 6.97-6.99 (m, 2H, arom. CH), 7.03 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H, arom. CH), *7.55* (dd, *J* = 7.8 Hz, *J* = 1.3 Hz, 1H, arom. CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 10.0 (q), 37.3 (q, 2C), 65.2 (d), 120.7 (d), 126.2 (d), 128.1 (d), 132.4 (s), 135.7 (d), 150.0 (s); MS (EI): *m/z* (%) 181 (54) [M^+], 166 (100), 135 (91), 121 (14), 103 (15), 91(42), 72 (63), 65 (7), 44 (46).

(*R*,*R*)-Bis-{2-[1-(Dimethylamino)ethyl]phenyl) disulfide (22). (*R*)-2-(1-(Dimethylamino) ethyl)benzenethiol (153 mg, 0.85 mmol) was converted according to the procedure described for **20** into **22** (131 mg, 0.36 mmol, 86%).

Light yellow oil; $[\alpha]_D^{25}$ = + 99.0 (c = 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (d, *J* = 6.7 Hz, 6H, CH_3), 2.24 (s, 12H, $N(CH_3)_2$), 3.90 (q, *J* = 6.7 Hz, 4H, CH), 7.15- 7.18 (m, 4H, arom. CH), 7.37-7.39 (m, 2H, arom. CH), 7.67-7.70 (m, 2H, arom. CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.1 (q), 31.3 (t), 72.2 (d), 126.4 (d), 128.2 (d), 129.1 (d), 132.8 (d), 134.5 (s), 146.1 (s); MS (FAB, NBA): *m/z* (%) 361 (10) [$(M+H)^+$], 180 (100), 135 (10), 72 (12); IR ($CHCl_3$): ν = 3057, 2973, 2957, 2774, 2360, 2341, 1587, 1567, 1456, 1436, 1368, 1256, 1081, 1036, 953, 747 cm^{-1}.

2-({2-[(S)-1-Methoxypropyl]phenylthio}methyl)tetrahydrofuran (23). 20 (40 mg, 0.11 mmol) in CH_2C1_2 (5 mL) and 4-pentenol (19 mg, 0.22 mmol) yielded **23** (6 mg, 0.02 mmol, 10%) with 65:35 *d.r.* (determined by NMR).

Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3H, CH_3), 1.64-1.75 (m, 2H, CH_2), 1.88-1.95 (m, 2H, CH_2), 2.00-2.39 (m, 2H, CH_2CH_3), 2.90-3.00 (m, 1H, CH_2S), 3.09-3.16

(m, 1H, CH_2S), 3.23 (s, 3H, OCH_3), 3.73-3.81 (m, 1H, CH_2O), 3.89-3.96 (m, 1H, CH_2O), 4.02-4.09 (m, 1H, CH), 4.68-4.74 (m, 1H, CHOMe), 7.20-7.59 (m, 4H, arom. CH); MS (EI): *m/z* (%) 266 (8) [M^+], 235 (23), 205 (5), 165 (8), 149 (41), 135 (25), 115 (6), 91(8), 71(100).

Acknowledgements

Funding by the Schweizer Nationalfonds is gratefully acknowledged.

References

1. Hölzle, G.; Jenny, W. *Helv. Chim. Acta* **1958**, *41*, 593.
2. Beaulieu, P. L.; Déziel, R. In *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; pp 35–66.
3. Wirth, T. *Tetrahedron* **1999**, *55*, 1.
4. Tiecco, M. In *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; *Top. Curr. Chem.*; Springer: Berlin, 2000; Vol. 208, pp 7–54.
5. Wirth, T. *Angew. Chem.* **2000**, *112*, 3890; *Angew. Chem. Int. Ed.* **2000**, *39*, 3740.
6. Browne, D. M.; Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893.
7. Khokhar, S. S.; Wirth, T. *Angew. Chem.* **2004**, *116*, 641; *Angew. Chem. Int. Ed.* **2004**, *43*, 631.
8. Khokhar, S. S.; Wirth, T. *Eur. J. Org. Chem.* **2004**, 4567.
9. Wirth, T.; Fragale, G.; Spichty, M. *J. Am. Chem. Soc.* **1998**, *120*, 3376.
10. Spichty, M.; Fragale, G.; Wirth, T. *J. Am. Chem. Soc.* **2000**, *122*, 10914.
11. Zhou, Q.; Pfaltz, A. *Tetrahedron* **1996**, *50*, 4467.
12. Wipf, P; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.
13. Fragale, G.; Wirth, T. *Eur. J. Org. Chem.* **1998**, 1361.
14. Iranpoor, N.; Zeynizadeh, B. *Synthesis* **1999**, 49.
15. Wirth, T.; Fragale, G. *Chem. Eur. J.* **1997**, *3*, 1894.

