Stereoselective Alkylation of Sulfoxides and Sulfones Derived from (*R*)-Cysteine

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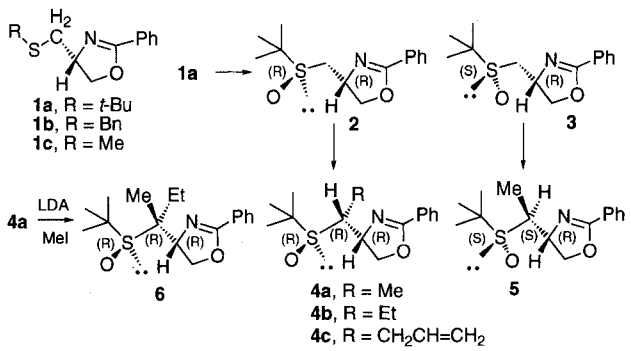
(*R*)-Cysteinol was protected as its oxazoline derivatives **1a–c** and oxidized to the sulfoxides **2**, **3** and the sulfone **7**. These compounds could be alkylated under chelate control to give tertiary and quaternary stereogenic centers in a highly stereoselective manner to yield **4a–c**,**5**, **8a–c**, **11** and **12**. Starting with the sulfone **7**, both configurations at the new chiral center can be constructed.

Natural amino acids are being applied as convenient chiral substrates for syntheses. In this context, we wondered whether (*R*)-cysteinol could serve as a starting material for the elaboration of a defined stereogenic center at C(3) *via* alkylation of appropriate sulfoxides and sulfones. Chiral sulfonyl-stabilized carbanions tend to be configurationally labile, unless special substitution patterns are present or special reaction conditions are used[1]. It is known that the proportions of diastereomers produced from carbanions adjacent to sulfoxides are generally dependent on a number of factors including the nature of the solvent, base and electrophile, the presence of salts, and the method of quenching[2]. Sulfinyl-stabilized anions of benzyl *tert*-butyl sulfoxides, however, are formed by deprotonation of the CH *anti* to the oxygen of the sulfoxide and these can be methylated under inversion[3,4]. With this in mind, we wondered whether the same could be achieved in a purely aliphatic situation, and further, whether a second alkylation would also be highly stereoselective.

We envisaged controlled formation of both configurations of a quaternary center by consecutive alkylations and therefore sought conditions for chelate stabilization of the intermediate anion. We chose *tert*-butyl as S protection for cysteinol and converted the appropriate compound into the 2-phenyl-2-oxazoline **1a** using the method described in ref.[5]. Preliminary experiments were also performed with the benzyl and methyl compounds **1b** and **1c**, but the respective sulfoxides and sulfones could not be deprotonated with sufficient selectivity. Oxidation of **1a** with *m*-CPBA gave 95% of a 2:1 diastereomeric mixture of (*R*,*R*)-**2** and (*S*,*R*)-**3**. The isomers were readily differentiated by their ^{1}H-NMR spectra and could be separated by chromatography. (For the assignment of configurations see below). Oxidations with a number of chiral oxidants produced disappointing chemical yields and only moderate diastereoselectivities[6].

Scheme 1



When **2** was deprotonated by LDA at −78 °C and alkylated with methyl iodide, a single product **4a** (within the limits of NMR detection) was obtained in 78% yield. As indicated by the ^{1}H-NMR spectra, similar treatment of **3** also led to the formation of a diastereomerically pure product **5**, although in this case the reaction was much slower and only a 29% yield was achieved. If the 2:1 mixture of **2** and **3** was alkylated directly, conditions could be found under which only the faster reacting **2** was converted. Thus, one separation step can be avoided.

The relative and absolute configuration (*R*,*R*,*R*) of **4a** was evident from its X-ray structure determination[7] and the fact that (*R*)-cysteine was used as the starting material. Accordingly, the configurations of **2** and **3** are confirmed. The (*S*,*S*,*R*) stereochemistry of **5** is supported above all by mechanistic analogy. In addition, inspection of the ^{1}H-NMR data (Table 1) shows that the different stereochemistry at sulfur produces only slight differences in chemical shifts of **2** and **3**. Furthermore, the two resonances for the ring CH_2 group of **4a** (and the respective couplings) are similar to each other and to those of **2** and **3**, indicating an

[+] X-ray analyses.

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essentially unchanged conformational environment. There are, however, sizeable chemical shift differences between **4a** and **5** for the methyl groups and the two vicinal ring protons. The methyl resonance of **4a** is 0.23 ppm further upfield than that of **5**, whereas the two mentioned ring protons are shifted upfield in **5**. These observations can be taken as circumstantial evidence that the configuration at the methyl-bearing C atom in **5** is actually inverted compared to that in **4a**.

Table 1. ^{1}H-NMR data of compounds **1a**, **2**, **3**, **4a**, **5**

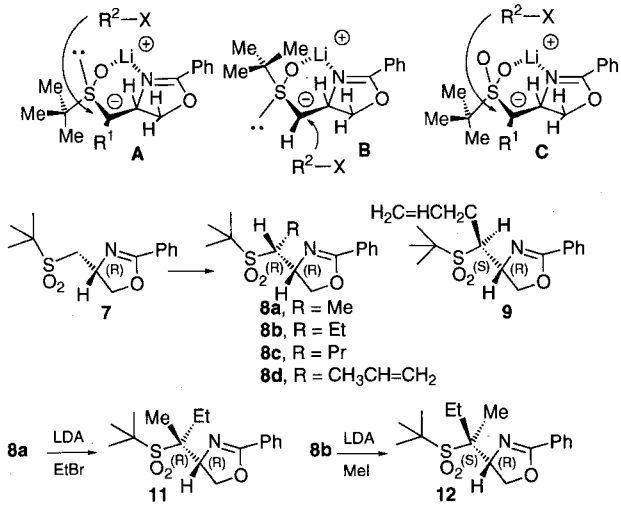
Assignment/ Compound	δ [ppm; 300 MHz], (J; Hz) 1a	2	3	4a	5
t-Bu	1.35	1.28	1.21	1.32	1.32
-CH_3				1.21(d) (7.3)	1.44(d) (6.8)
-S-CH_2-	2.44-3.08(m)				
-SO-CH_2- or -SO-CH-		2.63(dd) (13; 9.9) 3.09(dd) (13; 3.5)	2.69(dd) (13; 8.4) 3.01(dd) (13; 5.2)	3.54(m)	3.01(m)
O-CH_2-		4.46(dd) (9; 7.2)	4.39(dd) (9; 7.7)	4.45(dd) (9.7; 7.3)	4.23(m)
	4.24-4.35 (m; 3 H)	4.65(dd) (9; small)	4.67(dd) (9; small)	4.54(dd) (9.7; small)	4.60(m)
=N-CH-Ph		4.85 (m)	4.84 (m)	4.78 (m)	4.66(m)
	7.32-7.5 (m; 3 H) 7.86-8.01 (m; 2 H)	7.88 (m; 3 H) 7.95 (m; 2 H)	7.39 (m; 3 H) 7.94 (m; 2 H)	7.45 (m; 3 H) 7.95 (m; 2 H)	7.43 (m; 3 H) 7.97 (m; 2H)

Sulfoxide **2** was similarly alkylated with ethyl iodide and allyl bromide, giving **4b** and **4c**, respectively, although the yields were somewhat lower at 68 and 59%. Again, single diastereomers of (*R*,*R*,*R*) configuration were obtained. It was not possible to introduce larger groups such as butyl, apparently because of steric overcrowding.

We then evaluated the possibility of a second alkylation. Deprotonated **4a** could be ethylated as described above to give **6**, albeit only in low yield. Deprotonated **4b**, however, was only decomposed on attempted methylation, and no useful further reaction of **5** could be performed either. Nevertheless, the formation of diastereomerically pure **6** (within the limits of NMR detection) demonstrates that the second alkylation step is also highly stereoselective. Unfortunately, the crystals of **6** were not suitable for an X-ray analysis. However, on the grounds of mechanistic analogy, i.e. inversion at the methyl-bearing C atom, **6** is assigned the (*R*,*R*,*R*) configuration. This assignment is further supported by the ^{1}H-NMR spectrum: The methyl and *tert*-butyl signals are shifted to lower field compared to those in **4a**, whereas the ring protons are largely unaffected. This indicates that the methyl group of **6** occupies the area in space occupied by the −CH-Me hydrogen in **4a**.

The intermediate anions in these alkylations must contain twisted 6-membered chelate rings. In the case of **2** (and **4a**, **b**), anion **A** contains the *tert*-butyl group in a *pseudo*-equatorial orientation. Attack of methyl iodide from the convex upper side is hindered only moderately whereas alkylation from the concave side is not favored. Thus, this model makes formation of (*R*,*R*,*R*)-**4a** quite plausible and explains the increasing difficulty in the second alkylation step of **4a**, **b**, and that even the first alkylation is difficult with bulky reagents. In the alkylation of **3**, anion **B** is formed, in which the *tert*-butyl group occupies a *pseudo*-axial position and shields the upper side, so that the principally unfavored attack from the concave side occurs slowly and inefficiently to yield (*S*,*S*,*R*) compound **5**.

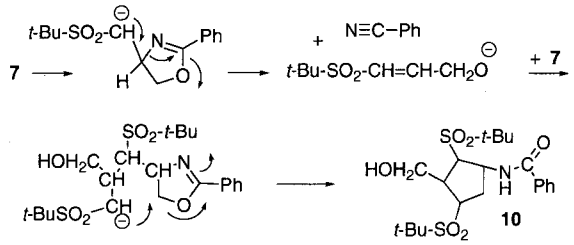
Scheme 2



These findings show that the first and second alkylations of the sulfoxides are highly stereoselective, but steric bulk prohibits versatile applications of the reactions. We also investigated the alkylation of the related sulfone **7**. Although the SO_2 group of **7** is not chiral, the structure of the respective anion should be similar to **A**, with the *tert*-butyl group in a *pseudo*-equatorial position (**C**), and therefore stereoselective alkylation was anticipated. Indeed, the methylation of **7** gave only one product, (*R*,*R*)-**8a**, in 72% yield. The absolute stereochemistry of this compound was again ascertained by X-ray analysis[7]. Analogous conversions of **7** with ethyl and propyl bromides were also highly diastereoselective within the limits of NMR detection, but the yields of **8b** and **8c** decreased to 65 and 14%, respectively. Configurations follow *inter alia* from the closely similar chemical shifts of the SO_2CH-R protons in the NMR spectra to those of **7** and **8a**. No product was obtained with butyl bromide. Instead, a base-catalyzed condensation of starting material **7** (also possible in the absence of butyl bromide; 62% yield) gave compound **10** ($C_{21}H_{33}NO_6S_2$) and benzonitrile. The formation of **10** can be rationalized as shown in Scheme 3. Its structure is consistent with the H−H- and C−H-COSY spectra. Compound **10** is optically active: the original stereocenter of one of the educt molecules is not involved in the reaction. It is not possible, however, to assign relative configurations to the other centers on the basis of the NMR spectra. No crystals suitable for X-ray analysis were obtained. The unexpected formation of this product demonstrates that steric crowding can make alkylation so inefficient that a side reaction becomes predominant.

Returning to the alkylations of **7**, allyl bromide also behaved somewhat irregularly. It led to a chromatographically separable mixture of diastereomers **8d** (major; 24% yield)

Scheme 3



and **9** (minor; 13% yield). Thus, this reagent attacks carbanion **C** from both faces.

Finally, twofold alkylations of **7** with different reagents were tested in the hope of constructing both possible configurations at the new asymmetric carbon atom. When **8a** was ethylated (EtBr; 59% yield) a single isomer **11** was obtained, and when **8b** was methylated (MeI; 27% yield) its epimer **12** was formed, again without noticeable traces of the isomer **11**. The configurations as (*R,R*)-**11** and (*S,R*)-**12** could be deduced from comparison of NMR chemical shifts of the methyl and ethyl signals of **8a**, **8b**, **11** and **12** (cf. Table 2). They are again consistent with the model concept outlined above.

Table 2. ^{1}H-NMR data of compounds **8a**, **b**, **11**, **12**

Assignment/			δ [ppm; 300 MHz], (J; Hz)	
Compound	**8a**	**8b**	**11**	**12**
-CH_2-CH_3	-	1.10 (t)	1.06 (t)	1.25 (t)
***t*-Bu**	1.46 (s)	1.47 (s)	1.57 (s)	1.57 (s)
C-**Me**	1.30 (d)	-	1.72 (s)	1.38 (s)
-CH_2-CH_3	-	2.05 (m)	1.72 (q); 1.88 (q)	2.14 (q); 2.23 (q)
-SO_2-**CH**-	3.94 (dq)	3.69 (dt)	-	-
ring-**CH**	4.98 (dt)	4.89 (m)	4.93 (dd)	5.03 (dd)
ring-CH_2	4.54 (d)	4.45 (dd); 4.58 ("t")	4.54 (dd); 4.66 (dd)	4.52 (dd); 4.68 (dd)
Ph	7.39-7.54 7.92-7.96	7.40-7.52 7.92-7.96	7.45 (m); 7.94 (m)	7.45 (m); 7.95 (m)

A more general application of the procedures evaluated here would require the consecutive removal of the sulfur functions. However, desulfuration of the more interesting derivatives turned out to be difficult. The sulfoxides **2/3** without branching in the side chain and that with a methyl substituent (**4a**) could be desulfurized with Raney nickel in boiling acetone (1.5 and 20 h, respectively). To test for possible racemizations during desulfuration, authentic (*S*)-4-methyl-2-phenyl-2-oxazoline was prepared from L-alanine following the general procedure as described in the Experimental Section. A product with $[\alpha]_D^{25} = -79$ ($c = 1$, EtOH) was obtained. Taking this as a standard, the desulfuration product of **2** had an e.e. of 96%. Sterically more congested **6** and non-substituted sulfone **7**, however, were totally inert towards desulfuration. Other reduction methods such as sodium/liquid NH_3, NaH/*tert*-amyl alcohol/$Ni(OAc)_2$[8] and $NiBr_2$/DME/PPh_3/$LiAlH_4$[9] also failed in these cases.

Conclusions

We have demonstrated that suitable chelation allows the controlled construction of a stereogenic center adjacent to both sulfoxide and sulfone functions in oxazoline derivatives, at least in principle. There are, however, two problems to be overcome, both of which seem to be due to the *tert*-butyl group used for *S* protection: (1) Alkylating agents bulkier than propyl cannot be applied, and (2) desulfuration of sterically demanding reaction products does not proceed. Nevertheless, there seem to be good chances for extending the scope of the method by selecting other protecting groups. Work along this line is to be continued.

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Experimental Section

General: Boiling points relate to the air bath of a kugelrohr distillation apparatus, values are not corrected. – IR-Spectra: Acculab 8 (Beckman) and FT-IR (Mattson Genesis Series). – ^{1}H-NMR Spectra: EM 360 (Varian), AM 300 (Bruker, 300 MHz) or AC-250-P (Bruker, 250 MHz); TMS as internal standard in $CDCl_3$ unless stated otherwise. – ^{13}C-NMR Spectra: AM 300 (Bruker, 75.45 MHz) or AC-250-P (Bruker, 62.9 MHz). – MS: MAT-311 A (Varian; 70 eV). – Polarimetry: DIP-360 (Jasco). – Chromatotron: Model 8924 (Harrison).

Preparation of the Oxazolines (General Procedure)[5]: 100 mmol of the *S*-protected amino alcohol, 21 ml (200 mmol) of benzonitrile and 500 mg of zinc bromide were heated to 130 °C and stirred at this temperature for 4 d. The mixture turned deep-red, and the evolution of ammonia was monitored by a bubble vent. On completion of the reaction, excess benzonitrile was distilled off under aspirator vacuum, and the residue was distilled in a kugelrohr apparatus. Yields: 90–95%.

(R)-4-(tert-Butylthiomethyl)-2-phenyl-2-oxazoline (**1a**): B.p. 105–110 °C/0.5 Torr; $[\alpha]_D^{25} = -1.2$ ($c = 1.7$, EtOH). – IR (NaCl): $\tilde{\nu}$ [cm^{-1}] = 3230, 1630 (–C=N–), 1440, 1350, 1230, 1150, 1050, 1040, 690. – ^{1}H NMR (60 MHz): See Table 1. – $C_{14}H_{19}NOS$ (249.4): calcd. 67.43, H 7.68, N 5.62; found C 67.12, H 7.53, N 5.75.

(R)-4-(Benzylthiomethyl)-2-phenyl-2-oxazoline (**1b**): B.p. 125–130 °C/0.5 Torr; $[\alpha]_D^{25} = -1.6$ ($c = 1$, EtOH). – IR (NaCl): $\tilde{\nu}$ [cm^{-1}] = 3380, 3240, 3060, 3020, 2950, 1630 (–C=N–), 1480, 1440, 1350, 1260, 1060, 965, 690. – ^{1}H NMR (60 MHz): δ = 2.43–3.03 (m, 2H, –S–CH_2–), 3.60–3.85 (m, 2H, C_6H_5–CH_2–), 4.15–4.56 (m, 3H, oxazoline), 7.28 (s, 5H, –CH_2–C_6H_5), 7.38–7.75 (m, 3H, phenyl), 7.85–8.03 (m, 2H, phenyl). – $C_{17}H_{17}NOS$ (283.4): calcd. C 72.05, H 6.04, N 4.94; found C 72.11, H 6.18, N 5.03.

(R)-4-(Methylthiomethyl)-2-phenyl-2-oxazoline (**1c**): B.p. 100–102 °C/0.5 Torr; $[\alpha]_D^{25} = -5.8$ ($c = 1$, EtOH). – IR (NaCl): $\tilde{\nu}$ [cm^{-1}] = 3340, 2920, 1630 (–C=N–), 1520, 1440, 1350, 1250, 1070, 960, 690. – ^{1}H NMR (60 MHz): δ = 2.18 (s, 3H, Me), 2.45–3.08 (m, 2H, –S–CH_2–), 4.20–4.69 (m, 3H, oxazoline), 7.25–7.45 (m, 3H, phenyl), 7.85–8.08 (m, 2H, phenyl). – $C_{11}H_{13}NOS$ (207.3): calcd. C 63.74, H 6.32, N 6.76; found C 63.78, H 6.36, N 6.92.

Oxidation of **1a**: 5.0 g (20 mmol) of **1a** was dissolved in 250 ml of CH_2Cl_2 and the solution was cooled to 0 °C. At this temperature, a solution of 4.93 g (20 mmol) *m*-chloroperbenzoic acid in 250 ml of CH_2Cl_2 was added over a period of 4–5 h. Stirring was continued for about 12 h at room temp., and then the solution was washed with three 500 ml portions of saturated aq. $NaHCO_3$ solu-

tion. The organic phase was dried (Na_2SO_4) and concentrated. The colorless residue (5 g, 95%) of the 2:1 diastereomeric mixture had m.p. 131–132 °C. – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3300, 2920, 1640 (C=N), 1530, 1360, 1280, 1100 (S=O), 1020. – MS (EI; *m/z* (rel. int.)): 266 (5.58) $(M + H)^+$, 209 (92.7), 146 (39.3), 77 (42.1), 57 (100), 41 (47.5). – $C_{14}H_{19}NO_2S$ (265.4): calcd. C 63.36, H 7.22, N 5.28; found C 63.39, H 7.15, N 5.16. – Crystallization from EtOAc enriched the crystals in **2**, but full separation was only effected by chromatography (silica gel, EtOAc/EtOH, 12:1).

First eluted minor isomer:

(4R)-tert-Butyl (2-Phenyl-2-oxazolin-4-yl)methyl (S)-Sulfoxide (**3**), $[\alpha]_D^{25}$ = −116 (*c* = 1.9, CH_2Cl_2). – ^1H NMR (250 MHz): See Table 1.

Later eluted major isomer:

(4R)-tert-Butyl (2-Phenyl-2-oxazolin-4-yl)methyl (S)-Sulfoxide (**2**): $[\alpha]_D^{25}$ = +84.4° (*c* = 1, CH_2Cl_2). – ^1H NMR (250 MHz): See Table 1.

(4R)-tert-Butyl (2-Phenyl-2-oxazolin-4-yl)methyl Sulfone (**7**): 5.0 g (20 mmol) of **1a** and 7.0 g (82 mmol) of $NaHCO_3$ were dissolved/suspended in 50 ml of CH_2Cl_2 and cooled in an ice bath. 10 g (40 mmol) *m*-chloroperbenzoic acid in 250 ml of CH_2Cl_2 was dropped in rapidly and the mixture was stirred for 3 h at room temp., resulting in the voluminous precipitation of *m*-chlorobenzoic acid. The reaction mixture was then poured into 200 ml of 25% aq. ammonia, the organic phase was separated and washed twice with dilute aq. NH_3 solution and twice with saturated aq. NaCl. Drying (Na_2SO_4) and evaporation of the solvent left the sulfone as a colorless solid, which was crystallized from ethanol. Yield: 4.5 g (80%). – m.p. 142 °C; $[\alpha]_D^{25}$ = +18.8 (*c* = 1.08, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2915, 2364, 2341, 1644 (C=N), 1577, 1475, 1365, 1284, 1116, 1062, 1020, 956, 692. – MS (Cl; *m/z* (rel. int.)): 282 (41.5) $(M + H)^+$, 226 (39.5), 209 (83.7), 159 (89.4), 105 (75.3), 91 (15.4), 77 (39.3), 57 (100), 41 (41.3). – ^1H NMR (250 MHz): δ = 1.44 (s, 9H, *t*-Bu), 2.99 (dd, *J* = 13 Hz, 11 Hz, 1H, SO_2-CH_2), 3.62 (dd, *J* = 13 Hz, 2.8 Hz, 1H, SO_2-CH_2), 4.48 (dd, *J* = 9.3 Hz, 7.6 Hz, 1H, $-O-CH_2$), 4.70 ("t", *J* = 9.3 Hz, 1H, $-O-CH_2$), 4.85–4.97 (m, 1H, =N−CH−), 7.38–7.53 (m, 3H, phenyl), 7.91–7.96 (m, 2H, phenyl). – $C_{14}H_{19}NO_3S$ (281.4): calcd. C 59.76, H 6.81, N 4.98; found C 59.65, H 6.64, N 4.86.

Alkylations of the Sulfoxides and Sulfones (General Procedure): 15 mmol of the sulfoxide (or sulfone) was dissolved in 120 ml of absol. THF and cooled to −80 °C with stirring. A freshly prepared solution of LDA (22 mmol) in dry THF was transferred *via* a syringe and septum to a dropping funnel, and added slowly such that the inner vessel temperature did not exceed −70 °C. An intense yellow coloration of the solution was observable at the point of mixing. When the addition was complete, stirring at −78 °C was continued for a further 1 h. At this stage the mixture was deep-orange in color. Then, 30 mmol of the alkylating agent in 100 ml of THF was dropped in, resulting in a slow discoloration. Stirring was continued for 4 h at low temperature, and then for 12 h at room temp. The mixture (now of turbid yellow color) was diluted with 300 ml of CH_2Cl_2 and washed with 300 ml of a half-saturated aq. NH_4Cl solution. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic extracts were washed three times with dil. aq. NaCl solution, dried (Na_2SO_4) and concentrated. Crude products were obtained as oils which subsequently crystallized. Purification was achieved by crystallization or chromatography.

(1R,(Sulfur)R,4'R)-1-tert-Butylsulfinyl-1-(2'-phenyl-2'-oxazolin-4'-yl)ethane (**4a**): 0.75 g (2.8 mmol) of pure **2** were treated with 4 mmol of LDA and 0.3 ml (4.8 mmol) of methyl iodide. DC control indicated that only a polar decomposition product of unknown composition (R_f = 0.59) and **4a** (R_f = 0.41) were present. Chromatography (silica gel, EtOAc/EtOH, 12:1) furnished pure **4a**, yield 0.58 g (78%), m.p. 140 °C; $[\alpha]_D^{25}$ = +137 (*c* = 1.1, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3567, 3471, 3397, 2966, 2908, 2869, 1643, 1492, 1450, 1361, 1249, 1172, 1029, 694. – ^1H NMR (250 MHz): see Table 1. – $C_{15}H_{21}NO_2S$ (279.4): calcd. C 64.48, H 7.58, N 5.01; found C 64.20, H 7.53, N 4.90.

(1S,(Sulfur)S,4'R)-1-tert-Butylsulfinyl-1-(2'-phenyl-2'-oxazolin-4'-yl)ethane (**5**): Prepared in a similar manner as above from 0.5 g (1.9 mmol) of pure **3**, 3 mmol of LDA and 0.2 ml (3.2 mmol) of methyl iodide. DC control showed that only starting material (R_f = 0.28), the polar decomposition product mentioned above (R_f = 0.59) and **5** (R_f = 0.39) were present. Chromatography as before gave 0.15 g (29%) of **5**, m.p. 139 °C, $[\alpha]_D^{25}$ = −35.7 (*c* = 0.8, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3568, 3470, 3398, 2965, 2909, 2868, 1643 (−C=N−), 1493, 1449, 1362, 1248, 1173, 1028, 695. – ^1H NMR (250 MHz): see Table 1. – $C_{15}H_{21}NO_2S$ (279.4): calcd. C 64.48, H 7.58, N 5.01; found C 64.35, H 7.40, N 4.90.

(1R,(Sulfur)R,4'R)-1-tert-Butylsulfinyl-1-(2'-phenyl-2'-oxazolin-4'-yl)propane (**4b**): 4.0 g (15.1 mmol) of the diastereomeric 2:1 mixture **2/3** was treated with 22 mmol LDA and 3.12 g (20 mmol) ethyl iodide according to the general procedure. DC control showed that only unreacted **3**, the usual polar decomposition product (R_f = 0.59) and one new compound were present. Chromatography (silica gel, EtOAc/EtOH, 12:1) furnished a yield of 2.0 g (68% based on **2**); m.p. 80–82 °C; $[\alpha]_D^{25}$ = +165 (*c* = 0.24, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3463, 3436, 2962, 2931, 2873, 1643 (−C=N−), 1465, 1357, 1299, 1238, 1172, 1025, 952, 698. – ^1H NMR (250 MHz): δ = 1.00 (t, *J* = 7.4 Hz, 3H, Me), 1.34 (s, 9H, *t*-Bu), 1.71 (m, 2H), 3.22 (m, 1H), 4.40 (dd, *J* = 9.8 Hz, 7.4 Hz, 1H, $-O-CH_2-$), 4.52 ("t", *J* = 9.9 Hz, 1H, $-O-CH_2-$), 4.76 (m, 1H, =N−CH), 7.54 (m, 3H, phenyl), 7.94 (m, 2H, phenyl). – $C_{16}H_{23}NO_2S$ (293.4): calcd. C 65.49, H 7.90, N 4.77; found C 65.07, H 7.94, N 4.53.

(1R,(Sulfur)R,4'R)-4-tert-Butylsulfinyl-4-(2'-phenyl-2'-oxazolin-4'-yl)-1-butene (**4c**): 4.0 g (15.1 mmol) of the diastereomeric 2:1 mixture **2/3** was treated with 22 mmol of LDA and 4 ml (46 mmol) of allyl bromide according to the general procedure. DC control indicated that only **2** had been converted to a new product. This was separated by chromatography as before to yield 1.8 g (59% based on **2**); m.p. 95–96 °C; $[\alpha]_D^{25}$ = +149 (*c* = 0.91, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3505, 3401, 3066, 2966, 2908, 1639 (−C=N−), 1577, 1492, 1473, 1361, 1295, 1245, 1172, 1068, 1029, 952, 921, 786, 698, 624. – ^1H NMR (250 MHz): δ = 1.31 (s, 9H, *t*-butyl), 2.46 (m, 2H), 3.43 (m, 1H), 4.42 (dd, *J* = 9.8 Hz, 7.3 Hz, 1H, $-O-CH_2-$), 4.54 ("t", *J* = 9.9 Hz, 1H, $-O-CH_2$), 4.77 (m, 1H, =N−CH), 5.09 (m, 2H), 5.70 (m, 1H), 7.45 (m, 3H, phenyl), 7.94 (m, 2H, phenyl). – $C_{17}H_{23}NO_2S$ (305.4): calcd. C 66.85, H 7.59, N 4.59; found C 66.75, H 7.53, N 4.47.

(1R,(Sulfur)R,4'R)-1-t-Butylsulfinyl-1-methyl-1-(2'-phenyl-2'-oxazolin-4'-yl)propane (**6**): Following the general procedure, 3 g (10.7 mmol) of **4a** was treated with 22 mmol of LDA and 1.25 ml (20 mmol) of methyl iodide. As a result, 1.87 g of an orange-colored oil was obtained. DC indicated the formation of several decomposition products, and the strong odor of benzonitrile made a partial destruction of the oxazoline ring seem likely. Chromatography (silica gel, EtOAc/EtOH, 12:1) allowed the isolation of 164 mg (5%), m.p. 142–143 °C. – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3552, 3428, 3363, 2962, 2915, 1646 (−C=N−), 1454, 1365, 1261, 1091, 1018, 952, 798, 698, 674. – MS (EI, *m/z* (rel. int.)): 202 (92.8) (M − SO-*t*-Bu), 146 (100), 105 (97.2), 91 (25.8), 77 (52.9), 57 (82.2), 41 (66.9). – ^1H

NMR (250 MHz): δ = 1.06 (t, *J* = 7.5 Hz, 3H), 1.57 (s, 9H, *t*-Bu), 1.71 (s, 3H), 1.84 and 2.04 (2 q, *J* = 7.5 Hz, 1H each), 4.53 ("t", *J* = 10 Hz, 1H, $-O-CH_2-$), 4.65 (dd, *J* = 10 Hz, 8.7 Hz, 1H, $-O-CH_2-$), 4.92 (dd, *J* = 10 Hz, 8.7 Hz, 1H, =N−CH), 7.46 (m, 3H, phenyl), 7.93 (m, 2H, phenyl). – No correct C, H, N analysis could be obtained.

(1R,4'R)-1-tert-Butylsulfonyl-1-(2'-phenyl-2'-oxazolin-4'-yl)-ethane (**8a**): From 4.0 g (14.2 mmol) of **7** and 4.26 g (30 mmol) of methyl iodide, following the general procedure. Yield 3.02 g (72%); m.p. 155−156°C. – $[\alpha]_D^{25}$ = +10.1 (*c* = 0.7, CH_2Cl_2). – IR (KBr): ṽ [cm^{-1}] = 3532, 3374, 2973, 2935, 2877, 1635 (−C=N−), 1461, 1280, 1110, 1022, 956, 698. – ^1H NMR (300 MHz): δ = 1.30 (d, *J* = 7.2 Hz, 3H, Me), 1.46 (s, 9H, *t*-Bu), 3.94 (dq, *J* = 7.2 Hz, 3.3 Hz, 1H, $-SO_2-CH=$), 4.54 (d, *J* = 8.6 Hz, 2H, $-O-CH_2-$), 4.98 (dt, *J* = 8.6 Hz, 3.3 Hz, 1H, =N−CH), 7.39−7.54 (m, 3H, phenyl), 7.92−7.96 (m, 2H, phenyl). – $C_{15}H_{21}NO_3S$ (295.4): calcd. C 60.99, H 7.17, N 4.74; found C 60.73, H 7.38, N 4.70.

(1R,4'R)-1-tert-Butylsulfonyl-(2'-phenyl-2'-oxazolin-4'-yl)-propane (**8b**): From 4.0 g (14.2 mmol) of **7** and 4.68 g (30 mmol) of ethyl iodide, after chromatography (silica gel/Et_2O), a yield of 2.86 g (65%) was obtained; m.p. 129−130°C, $[\alpha]_D^{25}$ = +19.7 (*c* = 0.51, CH_2Cl_2). – IR (KBr): ṽ [cm^{-1}] = 3525, 3413, 2962, 2927, 2877, 1643 (−C=N−), 1473, 1454, 1369, 1280, 960, 782, 698. – ^1H NMR (250 MHz): δ = 1.10 (t, *J* = 7.3 Hz, 3H, Me), 1.47 (s, 9H, *t*-Bu), 2.05 (m, 2H, $-CH_2-CH_3$), 3.69 (dt, *J* = 3.3 Hz, 8.2 Hz, 1H, $SO_2-CH=$), 4.45 (dd, *J* = 10 Hz, 7.6 Hz, 1H, $-O-CH_2-$), 4.58 ("t", *J* = 10 Hz, 1H, $-O-CH_2-$), 4.89 (m, 1H, =N−CH), 7.40−7.52 (m, 3H, phenyl), 7.92−7.96 (m, 2H, phenyl). – $C_{16}H_{23}NO_3S$ (309.4): calcd. C 62.11, H 7.49, N 4.53; found C 61.87, H 7.26, N 4.43.

(1R,4'R)-1-tert-Butylsulfonyl-1-(2'-phenyl-2'-oxazolin-4'-yl)-butane (**8c**): From 2.0 g (7.1 mmol) of **7** and 0.8 ml (9 mmol) of 1-iodopropane, 2.1 g of crude material was obtained. When this was taken up in EtOAc/petroleum ether (3:7), a brown insoluble material (0.5 g) could be filtered off. Flash chromatography of the soluble part with this solvent mixture furnished first 0.46 g (23%) of unreacted **7**, then 0.32 g (14%) of product **8c**, m.p. 91°C. – $[\alpha]_D^{25}$ = +9.0 (*c* = 0.86, $CHCl_3$). – IR (KBr): ṽ [cm^{-1}] = 2961, 2925, 2871, 1643 (−C=N−), 1577, 1364, 1270, 1261, 1105, 1066, 953, 802, 692. – MS (CI; *m/z* (rel. int.)): 324 $(M + H)^+$, 296 (12.7), 268 (100), 201 (58.8), 172 (43.3), 146 (31.1), 105 (27.9), 91 (6.78), 57 (24.2). – ^1H NMR (250 MHz): δ = 0.87 (t, *J* = 7.2 Hz, 3H, Me), 1.42 (m, 2H, $-CH_2-CH_3$), 1.47 (s, 9H, *t*-Bu), 1.59 (m, 1H), 2.03 (m, 1H), 3.76 (dt, *J* = 3.2 Hz, 7.1 Hz, 1H), 4.45 (dd, *J* = 9.8 Hz, 7.7 Hz, 1H, $-O-CH_2-$), 4.58 ("t", *J* = 9.9 Hz, 1H, $-O-CH_2-$), 4.89 (m, 1H, =N−CH), 7.45 (m, 3H, phenyl), 7.92 (m, 2H, phenyl). – $C_{17}H_{25}NO_3S$ (323.5): calcd. C 63.13, H 4.33, N 7.79; found C 63.10, H 4.12, H 7.51.

(4R,4'R)-4-tert-Butylsulfonyl-4-(2'-phenyl-2'-oxazolin-4'-yl)-1-butene (**8d**) and *(4S,4'R)-4-tert-Butylsulfonyl-4-(2'-phenyl-2'-oxazolin-4'-yl)-1-butene* (**9**): 4.0 g (14.2 mmol) of **7** was treated with 2.57 g (21.3 mmol) of allyl bromide according to the general procedure. 4.47 g of a brownish crude material was obtained. DC (silica gel, EtOAc/petroleum ether, 3:7) indicated the presence of starting material and two new products, which were separated by flash chromatography. Compound **9** was eluted first; 0.6 g (13%) yield, m.p. 93°C. – $[\alpha]_D^{25}$ = +4.22 (*c* = 0.72, $CHCl_3$). – IR (KBr): ṽ [cm^{-1}] = 3074, 2971, 2919, 1650 (−C=N), 1471, 1450, 1357, 1277, 1113, 957. – MS (CI, *m/z* (rel. int.)): 322 $(M + H)^+$, 294 (15.0), 266 (100), 200 (15.5), 147 (7.34), 105 (10.2), 57 (3.97), 41 (17.0). – ^1H NMR (250 MHz): δ = 1.44 (s, 9H, *t*-Bu), 2.86 (m, 2H), 3.36 (m, 1H), 4.33 (dd, *J* = 8.9 Hz, 7.7 Hz, 1H, $-O-CH_2-$), 4.68 (m, 1H, $-O-CH_2-$), 4.78 (m, 1H, =N−CH), 5.13 (m, 2H, $-CH=CH_2$), 6.05 (m, 1H, $-CH=CH_2$), 7.41 (m, 3H, phenyl), 7.93 (m, 2H, phenyl). – $C_{17}H_{23}NO_3S$ (321.4): calcd. C 63.52, H 7.21, N 4.36; found C 63.22, H 7.48, N 4.29.

Compound **8d** was eluted subsequently: 1.1 g (24%) yield, m.p. 98°C; $[\alpha]_D^{25}$ = +13.5 (*c* = 1, $CHCl_3$). – IR (KBr): ṽ [cm^{-1}] = 2972, 2909, 1638 (−C=N−), 1474, 1361, 1282, 1250, 1112, 1066, 1026, 959. – MS (CI, *m/z* (rel. int.)): 322 $(M + H)^+$ (96.2), 294 (15.1), 200 (52.6), 147 (17.0), 105 (51.5), 91 (7.61), 57 (23.2), 41 (15.3). – ^1H NMR (250 MHz): δ = 1.45 (s, 9H, *t*-Bu), 2.35 (m, 1H), 2.75 (m, 1H), 3.87 (m, 1H), 4.49 (dd, *J* = 9.9 Hz, 7.6 Hz, 1H, $-O-CH_2$), 4.59 ("t", *J* = 9.9 Hz, 1H, $-O-CH_2$), 4.93 (m, 1H, =N−CH), 5.02 (m, 2H), 5.92 (m, 1H), 7.43 (m, 3H, phenyl), 7.92 (m, 2H, phenyl). – $C_{17}H_{23}NO_3S$ (321.4): calcd. C 63.52, H 7.21, N 4.36; found C 63.34, H 7.13, N 4.43.

1-Benzoylamino-2,4-bis(tert-butylsulfonyl)-3-hydroxymethylcyclopentane (**10**): 4.0 g (14.2 mmol) of **7** was dissolved in 120 ml of THF and treated with 22 mmol of an LDA solution at −78°C. The mixture was stirred for 3 h at this temperature, and then for about 12 h at room temp. The mixture was worked-up by slow, dropwise addition of methanol, pouring into 300 ml of CH_2Cl_2, washing with aq. NH_4Cl solution, drying (Na_2SO_4) and concentration. The residue was crystallized from diethyl ether/petroleum ether. Yield: 2.02 g (62%); m.p. 252°C. – $[\alpha]_D^{25}$ = −39 (*c* = 0.2, DMSO), (large variations in measurements). – IR (KBr): ṽ [cm^{-1}] = 3405 (−OH, −NH), 3356 (−OH, −NH), 2985, 2940, 2890, 1659 (−C=O), 1540, 1489, 1302, 1121, 1057, 713. – MS (CI, *m/z* (rel. int.)): 460 $(M + H)^+$ (65.0), 404 (78.4), 386 (100), 339 (8.31), 246 (20.0), 216 (7.49), 122 (16.7), 105 (9.57). – ^1H NMR (250 MHz, [D_6]DMSO): δ = 1.34 (s, 9H, *t*-Bu), 1.37 (s, 9H, *t*-Bu), 2.21 (m, 1H), 2.35 (m, 1H), 3.31 (m, 1H), 3.60 (m, 2H), 4.03 (m, 2H), 4.75 (m, 1H), 5.29 (t, *J* = 5.2 Hz, 1H, −O−H), 7.50 (m, 3H, phenyl), 7.78 (m, 2H, phenyl), 8.42 (d, *J* = 7.2 Hz, 1H, N−H). – ^{13}C NMR ([D_6]DMSO): δ = 22.86 (prim., *t*-Bu), 23.08 (prim., *t*-Bu), 35.69 (sec.), 42.21 (tert), 52.88 (tert), 54.02 (tert), 59.65 (tert), 60.44 (quat., *t*-Bu), 61.25 (sec.), 127.4 (tert, phenyl), 128.3 (tert, phenyl), 131.3 (tert, phenyl), 134.5 (quat., phenyl), 166.2 (quat., −C=O). – $C_{21}H_{33}NO_6S_2$ (459.6): calcd. C 54.88, H 7.24, N 3.05; found C 54.63, H 7.13, N 3.06.

(1R,4'R)-1-tert-Butylsulfonyl-1-methyl-1-(2'-phenyl-2'-oxazolin-4'-yl)propane (**11**): 4.43 g (15 mmol) of **8a** was treated with 20 mmol of LDA and 2.5 ml (30 mmol) of ethyl iodide. DC control indicated that a mixture of starting material and one product was present. Purification by column chromatography (silica gel, EtOAc/EtOH, 12:1) furnished 2.86 g (59%), m.p. 128−130°C; $[\alpha]_D^{25}$ = −18.5 (*c* = 0.5, CH_2Cl_2). – IR (KBr): ṽ [cm^{-1}] = 3544, 3440, 2969, 2919, 1646 (−C=N−), 1477, 1454, 1365, 1272, 1145, 1091, 952, 698, 674. – ^1H NMR (300 MHz): δ = 1.06 (t, *J* = 7.5 Hz, 3H, Me), 1.57 (s, 9H, *t*-Bu), 1.72 (s, 3H, Me), 1.72 and 1.88 (AB-q, 2H), 4.54 ("t", *J* = 10 Hz, 1H, $-O-CH_2$), 4.66 (dd, *J* = 7.6 Hz, 10 Hz, 1H, $-O-CH_2$), 4.93 (dd, *J* = 7.6 Hz, 10 Hz, 1H, =N−CH), 7.45 (m, 3H, phenyl), 7.94 (m, 2H, phenyl). – $C_{17}H_{25}NO_3S$ (323.5): calcd. C 63.13, H 7.79, N 4.33; found C 62.99, H 7.69, N 4.33.

(1S,4'R)-1-tert-Butylsulfonyl-1-methyl-1-(2'-phenyl-2'-oxazolin-4'-yl)propane (**12**): 1.0 g (3.2 mmol) of **8b** was treated as described above with 7 mmol of LDA and 0.5 ml (6.4 mmol) of methyl iodide. DC control showed only the presence of **8b** and **12**, which were separated by chromatography as before. Yield 0.28 g (27%); m.p. 103−131°C; $[\alpha]_D^{25}$ = −21.0 (*c* = 0.7, CH_2Cl_2). – IR (KBr): ṽ [cm^{-1}] = 3545, 3439, 2970, 2918, 1645 (−C=N−), 1478, 1453, 1366, 1271, 1146, 1090, 953, 699, 673. – ^1H NMR (300 MHz): δ =

1.25 (t, J = 7.5 Hz, 3H, Me), 1.38 (s, 3H, Me), 1.57 (s, 9H, *t*-Bu), 2.14 and 2.23 (AB-q, 2H, CH_2), 4.52 ("t", J = 10 Hz, 1H, $-O-CH_2-$), 4.68 (dd, J = 10 Hz, 8.8 Hz, 1H, $-O-CH_2-$), 5.03 (dd, J = 10 Hz, 8.8 Hz, 1H, =N−CH), 7.45 (m, 3H, phenyl), 7.95 (m, 2H, phenyl). − $C_{17}H_{25}NO_3S$ (323.5): calcd. C 63.13, H 7.79, N 4.33; found C 63.00, H 7.96, N 4.32.

Desulfuration of **2** *to give (S)-4-Methyl-2-phenyl-2-oxazoline:* 1.0 g (3.8 mmol) of **2** was dissolved in 50 ml of acetone, and 3 spatula measures of Raney nickel W-2 were added. The mixture was refluxed for 1.5 h under argon, then filtered and concentrated in vacuo. The residue was distilled in a kugelrohr apparatus, b.p. 50−60°C/0.1 Torr. Yield: 0.42 g (69%); $[\alpha]_D^{25}$ = −79.8 (c = 1, EtOH). − Authentic material (prepared according to ref.[5]) had $[\alpha]_D^{25}$ = −83.5 (c = 1, EtOH).

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[6] Oxidation of **1c** under Sharpless conditions (*t*-BuOOH/Ti(O-*i*Pr)$_4$/(+)-DET) gave a d.e. of 92%, but again only a poor chemical yield.
[7] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1220-100162. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: internat. (+)44 1223 336-033; e-mail: deposit@chemcrys.cam.ac.uk).
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