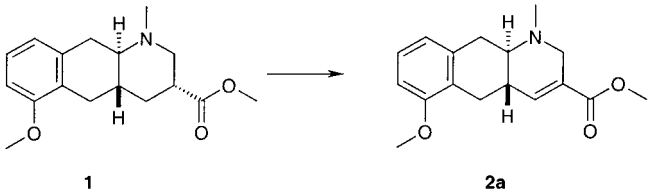
Intriguing Influence of the Solvent on the Regioselectivity of Sulfoxide Thermolysis in β-Amino-α-sulfinyl Esters

by **Markus Bänziger***[a]), **Solange Klein**[a]), and **Grety Rihs**[b])
[a]) Chemical & Analytical Development, *Novartis Pharma AG*, CH-4002 Basel
(Phone: (41) 61 696 45 93; fax: (41) 61 696 27 11; e-mail: markus.baenziger@pharma.novartis.com)
[b]) Preclinical Research Core Technology, *Novartis Pharma AG*, CH-4002 Basel

The sulfoxide thermolysis of the diastereoisomeric methyl (3*R*,4a*S*,10a*R*)-6-methoxy-1-methyl-3-(phenylsulfinyl)-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylates **3a** and **3′b** in toluene yields, by loss of benzenesulfenic acid, an almost 1:1 mixture of the vinylogous urethane **2b** and the isomeric α-aminomethyl enoate **2a**. When this elimination is performed in acetic acid, the enoate **2a** is formed rather selectively. The same solvent effects on the regioselectivity of the elimination of benzenesulfenic acid are observed with a simple sulfoxide of ethyl piperidine-3-carboxylate (**7**).

Introduction. – In the course of new product developments, we were interested in the conversion of methyl (3*R*,4a*R*,10a*R*)-6-methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylate (**1**) [1] to the corresponding unsaturated methyl (4a*S*,10a*R*)-6-methoxy-1-methyl-1,2,4a,5,10,10a-hexahydrobenzo[*g*]quinoline-3-carboxylate (**2a**) [2] (*Scheme 1*).

Scheme 1



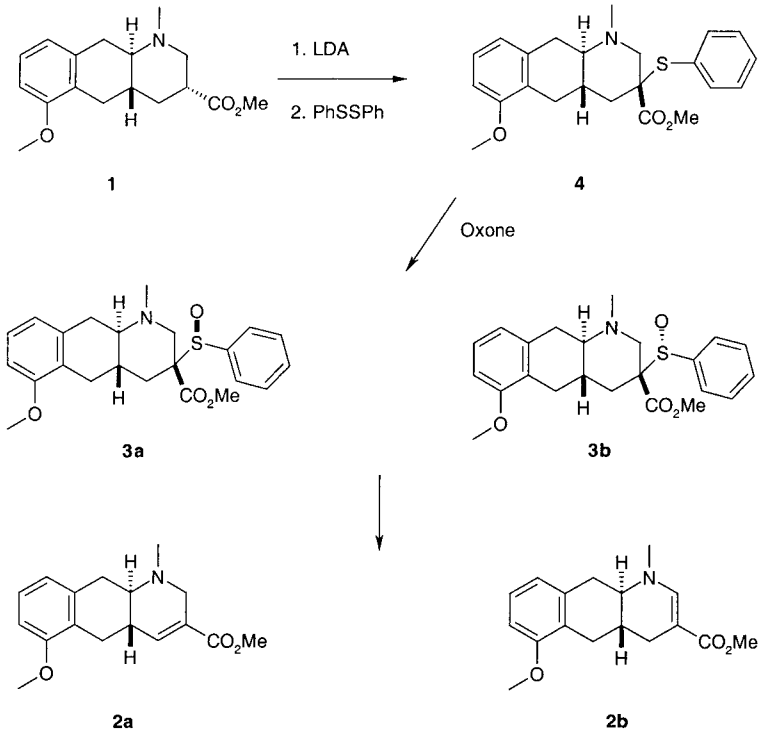
1 **2a**

Compounds of type **1** and **2a** are building blocks of pharmaceutically active compounds, and we decided to introduce the C=C bond by benzenesulfenic acid elimination [3] of the corresponding 3-(phenylsulfinyl)-substituted compound **3**.

Synthesis. – To accomplish the synthesis, the β-amino ester **1** was deprotonated with LDA and reacted with diphenyl disulfide [4] to yield intermediate **4** as a single diastereoisomer in 76% yield after recrystallization. The sulfenylated compound **4** bears the ester group in the axial position, as established by ^{1}H-NMR experiments (NOE).

The sulfide **4** was oxidized with oxone (potassium hydrogen peroxysulfate) [5] in acetone to give a *ca.* 2:1 mixture of the diastereoisomers **3a** and **3b** (*Scheme 2*).

Scheme 2



The two diastereoisomers can be separated by column chromatography; their structures were determined by X-ray crystallography (see *Figs. 1* and *2*).

When the diastereoisomer **3a** or **3b**, or a mixture of both, is heated in toluene or in toluene containing DBU (=1,8-diazabicyclo[5.4.0]undec-7-ene), a mixture of the two elimination products **2a** and **2b** is formed (*Scheme 2*). The ratio of the regioisomers **2a** and **2b** varies from 1:1 to 1:3 in favor of **2b**, depending upon the precursor **3** and upon the reaction temperature. In one series of experiments, we also performed the elimination in AcOH as the solvent. We discovered that **3a** is converted at 80° in AcOH to a 27:1 mixture **2a**/**2b**, while the diastereoisomeric compound **3b** is transformed to a 12:1 mixture **2a**/**2b** under these conditions. Thus, the desired compound **2a** becomes the major product, irrespective of the configuration at the S-atom of the starting material.

To the best of our knowledge, the 3-sulfinylpiperidine-3-carboxylic acid system has only been described once [6], and only one other example of a fused-ring system is known in the literature [7]. However, the thermolysis of such sulfoxides of six-membered ring systems is new. An analogous regioselective sulfenic acid elimination has been described for β-lactams [8].

The thermal instability of sulfoxides is known for a very long time [9]. Sulfoxides undergo thermal *syn*-elimination by the E_i mechanism [10]. We had expected to obtain a mixture of regioisomers **2a** and **2b** in the thermal sulfenic-acid elimination, with **2b** prevailing, because this elimination product (a vinylogous urethane) should be

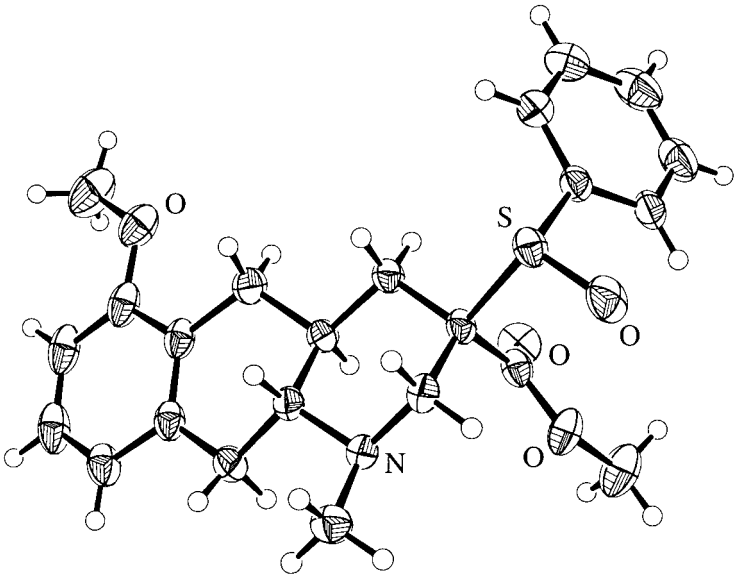


Fig. 1. *ORTEP Drawing of compound* **3a**

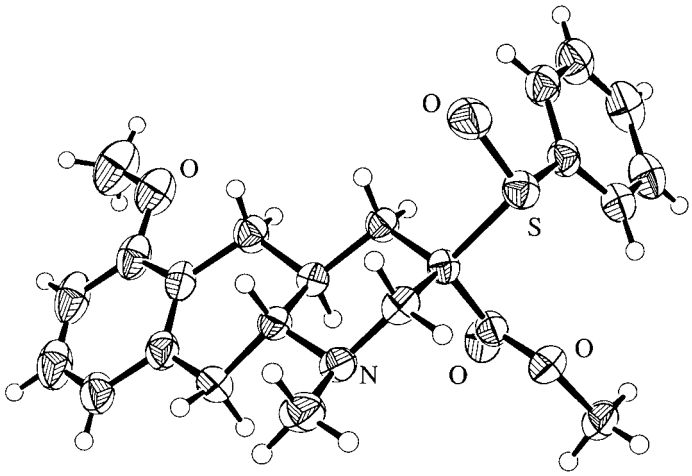
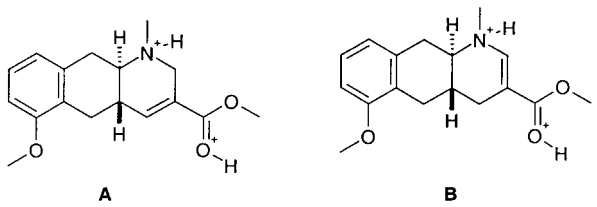


Fig. 2. *ORTEP Drawing of compound* **3b**

thermodynamically more stable than the desired compound **2a**. Thus, the dramatic increase of the regioselectivity of the elimination reaction in favor of compound **2a**, when the reaction is conducted in AcOH, is most surprising. A possible explanation for this effect of AcOH may be that the precursor **3** is doubly protonated in glacial AcOH at 80° – 100°, when the elimination occurs, and that the transition state leading to **A** is more favorable then the one generating **B**.

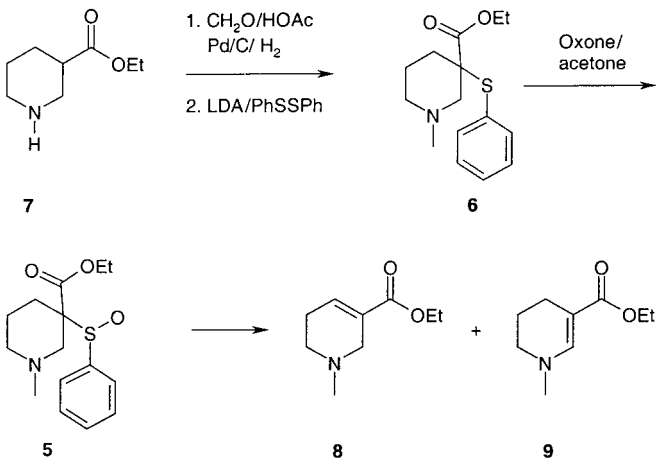


A B

Investigations (HPLC) of the course of the sulfoxide thermolysis with both diastereoisomers **3a** and **3b** in AcOH or toluene/DBU showed that the ratio with which the products **2a** and **2b** are formed remains almost exactly the same during the reaction. An epimerization at the stereogenic S-center was not observed. The elimination products **2a** or **2b** can not be equilibrated with each other by heating in toluene in the presence of DBU or in AcOH. The addition of 2 equiv. of AcONa to a solution of **3a** or **3b** in AcOH has no significant influence on the rate of the elimination reaction and product ratio of **2a**/**2b**.

The same elimination sequence was also performed with ethyl 1-methyl-3-(phenylsulfinyl)piperidine-3-carboxylate (**5**) (*Scheme 3*). The sulfide precursor **6** was prepared in 52% yield from commercially available ethyl piperidine-3-carboxylate (**7**) by *N*-methylation with aqueous CH_2O in MeOH/AcOH under hydrogenation conditions, followed by treatment of the enolate with diphenyl disulfide. The oxidation of the sulfide **6** to the sulfoxide **5** (to give a 2:3 mixture of racemic diastereoisomers) was carried out with oxone in a similar way as with compound **4**. The elimination experiments with **5** were again performed in toluene/DBU or in AcOH directly with the mixture of the diastereoisomers. When the sulfoxide **5** was heated at 80° in AcOH, the ratio in which **8** and **9** are formed was 98:2 (GC analysis), while it was 2:3 after heating in a 1:2 mixture of toluene/DBU at 110°. Thus, similar results were obtained with the sulfoxide mixture of **5**, and with **3a** or **3b** (*Scheme 3*).

Scheme 3



Conclusions. – The 'acetic-acid method' described herein might be a general and selective way to prepare 1,2,5,6-tetrahydropyridine-3-carboxylates from piperidine-3-carboxylates *via* thermolysis of corresponding sulfoxides.

Experimental Part

General. Solvents and reagents were purchased from *Fluka*. All reactions were performed under N_2. The reactions described are not optimized in respect of yields. Reactions with diphenyl disulfide should be carried out in a hood, because of the formation of stinking thiophenol. NMR Spectra: *Brucker Avance-400* spectrometer; δ in ppm. MS: *Hewlett-Packard GC-6890* connected to an *Agilent 5973 Mass Selective Detector*.

*Methyl (3*R,*4a*S,*10a*R*)-6-Methoxy-1-methyl-3-(phenylsulfanyl)-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylate* (**4**). To a soln. of $(i\text{-}Pr)_2NH$ (23.6 g, 234 mmol) in 120 ml of THF 1.6M BuLi (98.7 g, 226 mmol) were added at $-20°$ within 2 h. After stirring for another h the mixture was cooled to $-75°$, and a soln. of 45 g (155 mmol) of methyl (3*R*,4a*R*,10a*R*)-6-methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]quinoline-3-carboxylate (**1**) [1] in THF (300 ml) was added within 2 h. The mixture was stirred for another h, and then a soln. of 40.7 g (187 mmol) of diphenyl disulfide in THF (210 ml) was added within 0.5 h. The mixture was stirred at $-75°$ for 0.5 h and then warmed to 0°. Then, 15% aq. NaCl (200 ml) was added, and the phases were separated. The aq. phase was reextracted with toluene, and the combined org. phase was washed with H_2O. The solvent was evaporated under reduced pressure, and the residue was dissolved in a mixture of 300 ml of MeOH and 150 ml of AcOH. By adding 250 g of Et_3N the product was precipitated, filtered, washed with MeOH, and dried *in vacuo* at 50° to give **4** (47 g, 76%). ^{1}H-NMR ((D_6)DMSO): 1.32–1.43 (*m*, H_{ax}–C(4)); 1.45–1.58 (*m*, H–C(4a)); 1.82–1.93 (*m*, H–C(10a)); 2.03–2.15 (*m*, H_{ax}–C(5)); 2.42 (*s*, NMe); 2.28–2.43 (*m*, H_{ax}–C(2), H_{eq}–C(4), H_{ax}–C(10)); 2.69–2.80 (*m*, H_{eq}–C(5)); 3.02–3.12 (*m*, H_{eq}–C(10)); 3.17–3.24 (*m*, H_{eq}–C(2)); 3.54 (*s*, OMe); 3.74 (*s*, OMe); 6.65–6.77 (*m*, H–C(7), H–C(9)); 7.03–7.12 (*m*, H–C(8)); 7.38–7.54 (*m*, H–C(5)). Anal. calc. for $C_{23}H_{27}NO_3S$: C 69.49, H 6.85, N 3.52; found: C 69.52, H 6.86, N 3.61.

*Methyl (3*R,*4a*S,*10a*R*)-6-Methoxy-1-methyl-3-[(*S*)-phenylsulfinyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]-quinoline-3-carboxylate* (**3a**) *and Methyl (3*R,*4a*S,*10a*R*)-6-Methoxy-1-methyl-3-[(*R*)-phenylsulfinyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylate* (**3b**). To a mixture of intermediate **4** (10 g, 25 mmol) in acetone (250 ml), a soln. of 15.46 g (25 mmol) of oxone in H_2O (60 ml) was added within 0.5 h at 5°. After the addition was complete, the mixture was stirred for another h, and then 10% aq. $Na_2S_2O_3$ was added. The acetone was removed *in vacuo*, and the residue was worked up with CH_2Cl_2/H_2O. The CH_2Cl_2 phase was evaporated to dryness, and the diastereoisomers were separated by CC (SiO_2; AcOEt/CH_2Cl_2/25% NH_3 800 : 600 : 6). Yield: **3a**: 1.2 g; **3b**: 4.9 g. Both diastereoisomers are crystalline and X-ray-crystallographic analysis was performed.

Data of **3a**: ^{1}H-NMR ($CDCl_3$): 1.76–2.01 (*m*, 2 H–C(4), H–C(4a), H–C(10a)); 2.25–2.32 (*m*, H_{ax}–C(5)); 2.41 (*s*, NMe); 2.57–2.64 (*m*, H_{ax}–C(10)); 2.77 (*d*, *J* = 11, H_{ax}–C(2)); 2.99–3.02 (*m*, H_{eq}–C(5)); 3.12–3.17 (*m*, H_{eq}–C(10)); 3.58 (*s*, OMe); 3.71 (*d*, *J* = 11, H_{eq}–C(2)); 3.84 (*s*, OMe); 6.67–6.74 (*m*, H–C(7)), H–C(9)); 7.10–7.14 (*m*, H–C(8)); 7.53–7.59 (*m*, 5 H). Anal. calc. for $C_{23}H_{27}NO_4S$: C 66.80, H 6.58, N 3.39; found: C 66.61, H 6.55, N 3.52.

Data of **3b**: ^{1}H-NMR ($CDCl_3$): 1.47–1.53 (*m*, H_{ax}–C(4)); 1.67–1.77 (*m*, H–C(4a)); 1.92–2.04 (*m*, H–C(10a)); 2.17–2.29 (*m*, H_{eq}–C(4), H_{ax}–C(5)); 2.41 (*s*, NMe); 2.57–2.62 (*m*, H_{ax}–C(2), H_{ax}–C(10)); 2.96–3.01 (*m*, H_{eq}–C(5)); 3.09–3.15 (*m*, H_{eq}–C(10)); 3.49 (*s*, OMe); 3.63–3.67 (*m*, H_{eq}–C(2)); 3.81 (*s*, OMe); 6.64–6.70 (*m*, H–C(7), H–C(9)); 7.07–7.11 (*m*, H–C(8)); 7.51–7.58 (*m*, H–C(5)). Anal. calc. for $C_{23}H_{27}NO_4S$: C 66.80, H 6.58, N 3.39; found: C 66.92, H 6.75, N 3.51.

Crystal-Structure Analyses of **3a** *and* **3b**. The intensities of both crystals were collected on an *Enraf-Nonius CAD4* diffractometer using CuK_α radiation ($\lambda = 1.54178$ Å) and $\omega/2\theta$ scan. The structures were solved by direct methods and refined on F^2 (SHELXS86 [11] and SHELX93 [12]). H-atoms were treated as riding[1]).

---

[1]) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-176663 (**3a**) and -176664 (**3b**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Crystals of **3a** were grown from an AcOEt/hexane soln. They were orthorhombic, $C_{23}H_{27}NO_4S$, M_r 413.52 g mol^{-1}, crystal size $0.43 \times 0.32 \times 0.30$ mm, space group $P2_12_12_1$, $a = 11.324(1)$ Å, $b = 13.416(1)$ Å, $c = 14.478(2)$ Å; $V = 2199.5(4)$ Å^3, $Z = 4$, d(calc.) = 1.249 g/cm^3, $\varepsilon = 1.54$ mm^{-1}, $F(000) = 880$, No. of reflection measured = 2542, observed = 2428 ($I > 2\sigma(I)$), No. of reflections in least squares = 2428, intensity decay = 2%, $\theta_{max} = 74.19°$, No. of refined parameters = 262, R factor = 0.060, $wR = 0.136$, $S = 1.151$, diff. density$_{max}$ = 0.327 e/Å^3, diff. density$_{min}$ = −0.494 e/Å^3.

Crystals of **3b** were grown from an AcOEt/hexane soln. They were orthorhombic, $C_{23}H_{27}NO_4S$, M_r 413.52 g mol^{-1}, crystal size $0.67 \times 0.38 \times 0.08$ mm, space group $P2_12_12_1$, $a = 8.255(1)$ Å, $b = 10.779(2)$ Å, $c = 24.042(4)$ Å, $V = 2139.3(6)$ Å^3, $Z = 4$, d(calc.) = 1.284 g/cm^3, $\varepsilon = 1.58$ mm^{-1}, $F(000) = 880$, No. of reflection measured = 4189, observed = 3558 ($I > 2\sigma(I)$), No. of reflections in least squares = 3558, intensity decay = 3%, $\theta_{max} = 74.23°$, No. of refined parameters = 262, R factor = 0.060, $wR = 0.154$, $S = 1.257$, diff. density$_{max}$ = 0.470 e/Å^3, diff. density$_{min}$ = 0.171 e/Å^3.

*Methyl (4a*S*,10a*R*)-6-Methoxy-1-methyl-1,4,4a,5,10,10a-hexahydrobenzo[*g*]quinoline-3-carboxylate* (**2b**). Sulfide **4** (10 g) was oxidized with oxone as described above. The crude product of **3a** and **3b** was purified by the following extractive procedure: It was dissolved in 200 ml of AcOEt and extracted with 1M HCl (5 × 100 ml). The pH of the aq. phase was brought to 9 by adding 30% NaOH to the ice cold acidic aq. phase, and the product was extracted with CH_2Cl_2 (3 × 100 ml). The CH_2Cl_2 phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue (9 g) was dissolved in a mixture of 80 ml of toluene and 80 ml of DBU. This mixture was heated to 80° for 16 h. HPLC control showed a ratio **2a**/**2b** of 1:1.2. Then, it was diluted with 80 ml of toluene and washed with H_2O, followed by 0.3M HCl (to remove DBU and most of **2a**) and finally with H_2O again. The toluene phase was evaporated to dryness and the residue was crystallized from toluene/hexane to give 3.5 g of **2b** (48%, based on **4**). ^{1}H-NMR ($CDCl_3$): 1.87–2.08 (*m*, H_{ax}–C(4), H–C(4a)); 2.24–2.32 (*m*, H_{ax}–C(5)); 2.66–2.78 (*m*, H_{eq}–C(4), H_{ax}–C(10)); 3.03 (*s*, NMe); 3.08–3.16 (*m*, H–C(10a)); 3.21–3.37 (*m*, H_{eq}–C(5), H_{eq}–C(10)); 3.72 (*s*, OMe); 3.86 (*s*, OMe); 6.71–6.78 (*m*, H–C(7), H–C(9)); 7.12–7.18 (*m*, H–C(8)); 7.38 (br. *s*, H–C(2)). Anal. calc. for $C_{17}H_{21}NO_3$: C 71.06, H 7.37, N 4.87; found: C 70.86, H 7.29, N 5.09.

*Methyl (4a*S*,10a*R*)-6-Methoxy-1-methyl-1,2,4a,5,10,10a-hexahydrobenzo[*g*]quinoline-3-carboxylate* (**2a**). Sulfide **4** (10 g) was oxidized with oxone as described above. The mixture **3a**/**3b** was purified by the same extractive procedure as described for the synthesis of **2b**. The residue (9 g) of the two diastereoisomeric sulfoxides **3a** and **3b** was dissolved in 100 ml AcOH and heated to 80° for 15 h. The HPLC control showed a ratio **2a**/**2b** of 15:1. Then, the mixture was cooled to r.t., H_2O (50 ml) and toluene (100 ml) were added, and the phases were separated. The toluene phase was extracted 3 times with 1M HCl (180 ml), and the combined aq. phase was washed once with toluene (50 ml). In the ice bath, the pH was adjusted to 8 by addition of 30% NaOH (250 g). Finally, the pH was brought to >9 by the addition of 15% aq. Na_2CO_3 (30 ml). The aq. phase was extracted 3 times with toluene (200 ml). The combined org. phase was washed twice with H_2O (100 ml) and evaporated to dryness, to yield 6.5 g crude product. Crystallization from toluene/hexane 20:35 gave 3.9 g pure product **2a** (54% based on **4**). ^{1}H-NMR ($CDCl_3$): 2.15–2.36 (*m*, H_{ax}–C(5), H–C(10a)); 2.43–2.58 (*m*, NMe, H_{ax}–C(10)); 2.74–2.82 (*m*, H–C(4a)); 2.97–3.23 (*m*, H_{ax}–C(2), H_{eq}–C(5), H_{eq}–C(10)); 3.68–3.78 (*m*, H_{eq}–C(2)); 3.80 (*s*, OMe); 3.84 (*s*, OMe); 6.64–6.80 (*m*, H–C(7), H–C(9)); 6.97 (br. *s*, H–C(4)); 7.10–7.19 (*m*, H–C(8)).

Ethyl 1-Methyl-3-(phenylsulfanyl)piperidine-3-carboxylate (**6**). A mixture of 51 g (324 mmol) of ethyl piperidine-3-carboxylate (**7**), 52 g of 37% aq. CH_2O (641 mmol), AcOH (74 ml), and 5.5 g of Pd/C (5%) in 520 ml of EtOH was hydrogenated at atmospheric pressure and r.t. until no more hydrogen was consumed. Then, the catalyst was filtered off and washed with 50 ml of EtOH, and the EtOH was evaporated under reduced pressure. The residue was dissolved in toluene/H_2O and the pH was brought to 9 by addition of 20% aq. K_2CO_3. The phases were separated, the aq. phase was extracted again with toluene, and the combined toluene phase was washed with H_2O. The toluene was evaporated to dryness to give 42.09 g of ethyl 1-methyl-piperidine-3-carboxylate, which was used without further purification in the next step. ^{1}H-NMR ($CDCl_3$): 1.23 (*t*, *J* = 7.2, 3 H); 1.33–1.43 (*m*, 1 H); 1.53–1.64 (*m*, 1 H); 1.68–1.75 (*m*, 1 H); 1.91–1.97 (*m*, 2 H); 2.07–2.12 (*m*, 1 H); 2.27 (*s*, NMe); 2.52–2.60 (*m*, 1 H); 2.68–2.72 (*m*, 1 H); 2.92–2.95 (*m*, 1 H); 4.12 (*q*, *J* = 7.2, 2 H).

A mixture of 19.5 g (193 mmol) of (i-Pr)$_2$NH in 110 ml of THF was cooled to −30°, and then 110 ml of 1.6M BuLi (176 mmol; in hexane) were added. The mixture was stirred for 1 h at −30° and then cooled to −70°. To this LDA mixture, a soln. of 27.5 g (161 mmol) of the above ethyl 1-methyl-piperidine-3-carboxylate in 100 ml of THF was added within 45 min. After stirring for another 45 min, a soln. of 36.8 g (169 mmol) of diphenyl disulfide in 138 ml of THF was added within 45 min. The mixture was stirred for another 30 min at −70° and then warmed to 0° within 1 h. Then 138 ml of H_2O and 138 ml of brine were added, the phases were separated,

and the aq. phase was re-extracted with toluene. The combined org. phase was washed with brine and then evaporated to dryness. The residue was purified by dissolution in 300 ml of toluene and extracting the desired product with 1M HCl (4 × 200 ml) aq. into the aq. phase. After washing the aq. phase with toluene, the pH was brought to > 9 by adding 30% NaOH, and the product was extracted twice with 200 ml of toluene. The combined org. phase was washed with H_2O and evaporated to dryness, to yield 31.4 g of **6** (52% based on **7**). ^{1}H-NMR ($CDCl_3$): 1.11 (*t*, *J* = 7.1, 3 H); 1.48–1.65 (*m*, 2 H); 1.76–1.81 (*m*, 1 H); 2.05–2.19 (*m*, 2 H); 2.23 (*s*, 3 H); 2.32–2.39 (*m*, 1 H); 2.42–2.52 (*m*, 1 H); 2.87–2.93 (*m*, 1 H); 4.04 (*q*, *J* = 7.1, 2 H); 7.29–7.36 (*m*, 3 H); 7.42–7.45 (*m*, 2 H).

Ethyl 1-Methyl-3-(phenylsulfinyl)piperidine-3-carboxylate (**5**). To a soln. of 10 g (33.8 mmol) of intermediate **6** in 50 ml of acetone a soln. of 17.6 g (28.7 mmol) of oxone in 67 ml of H_2O was added at 0–5° within 20 min. After stirring for another 30 min, 10 ml of 10% aq. $Na_2S_2O_3$ was added, and the acetone was evaporated under reduced pressure. To the aq. phase, 100 ml of toluene were added, and the product was extracted with 0.1M HCl (3 × 80 ml) into the aq. phase. The pH of the aq. phase was brought to 9 by adding 100 ml of 15% aq. Na_2CO_3, and the product was extracted with TBME (3 × 100 ml). The org. phase was washed with H_2O, and the solvent was removed under reduced pressure at 35° to yield 6.7 g of **5** as a 2:3 diastereoisomeric mixture (63% based on **6**), which was used without further purification in the elimination step.

Ethyl 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**8**). A soln. of 1 g (3.4 mmol) of the above residue of **5** in 10 ml of AcOH was heated to 80° for 22 h. Then, the mixture was checked by GC (ratio of **8**/**9** 98:2) and cooled to r.t. H_2O (20 ml) and toluene (30 ml) were added, the phases were separated, and **8** was extracted from the org. phase with 0.1M HCl (3 × 33 ml). The combined aq. phase was washed with 50 ml of toluene, and then the pH was brought to 9 by adding 80 ml of 15% aq. Na_2CO_3. The product **8** was extracted with toluene (3 × 40 ml). The toluene phase was washed with H_2O, and then the toluene was evaporated under reduced pressure to yield 0.61 g of crude **8**, which was purified by CC (60 g SiO_2; AcOEt/toluene/25% NH_3 80:20:2) to give 370 mg of pure **8** (64%). ^{1}H-NMR ($CDCl_3$): 1.23 (*q*, *J* = 7.1, 3 H); 2.19–2.39 (*m*, 5 H); 2.45 (*t*, *J* = 5.6, 2 H); 3.09–3.12 (*m*, 2 H); 4.14 (*q*, *J* = 7.1, 2 H); 6.92–6.96 (*m*, 1 H). MS: 169 ($M^{\cdot+}$), 140, 124, 106, 96, 81, 53.

Ethyl 1-Methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**9**). A soln. of 2 g (6.8 mmol) of **5** in 5 ml of toluene and 5 ml of DBU was heated to 110° for 1 h. Then, the mixture was cooled to r.t., checked by GC (ratio of **8**/**9** 1:2), diluted with 20 ml of toluene, and washed with 1M HCl (3 × 10 ml), followed by H_2O. The toluene phase was evaporated to dryness, and the residue was purified by CC (85 g of SiO_2; AcOEt) to give 0.4 g of **9** (34% based on **5**). ^{1}H-NMR ($CDCl_3$): 1.27 (*q*, *J* = 7.1, 3 H); 1.82–1.89 (*m*, 2 H); 2.27 (*t*, *J* = 6.1, 2 H); 2.94 (*s*, 3 H); 3.05 (*t*, *J* = 5.7, 2 H); 4.14 (*q*, *J* = 7.1, 2 H); 7.32 (*s*, 1 H). MS: 169 ($M^{\cdot+}$), 154, 140, 124, 106, 96, 81.

The skillfull work of our technical staff (*J. Keusch*, *P. Ritschard*) is gratefully acknowledged. We thank Mr. *L. Oberer* for the interpretation of the NMR spectra and Ms. *G. Rihs* and her crew for performing the single-crystal analyses. We thank also Prof. *D. Seebach* for many helpful discussions.

REFERENCES

[1] R. Nordmann, T. J. Petcher, *J. Med. Chem*. **1985**, *28*, 367.
[2] E. Küsters, C. Spöndlin, S. Redey, A. Widmer, *Chirality* **1993**, *5*, 36.
[3] B. M. Trost, T. N. Salzmann, *J. Am. Chem. Soc.* **1973**, *95*, 6840; D. Seebach, M. Teschner, *Tetrahedron Lett*. **1973**, 5113; B. M. Trost, K. K. Leung, *Tetrahedron Lett*. **1975**, 4197; B. M. Trost, T. N. Salzmann, *J. Org. Chem*. **1975**, *40*, 148; D. Seebach, M. Teschner, *Chem. Ber*. **1976**, *109*, 1601; B. M. Trost, T. N. Salzmann, K. Hiroi, *J. Am. Chem. Soc*. **1976**, *98*, 4887; J. C. Estevez, R. J. Estevez, L. Castedo, *Tetrahedron* **1995**, *51*, 10801; J. C. Estevez, M. C. Villaverde, R. J. Estevez, L. Castedo, *Synth. Commun*. **1993**, *23*, 2489.
[4] B. M. Trost, *Chem. Rev.* **1978**, *78*, 363.
[5] B. M. Trost, D. P. Curran, *Tetrahedron Lett*. **1981**, *22*, 1287; K. S. Webb, *Tetrahedron Lett*. **1994**, *35*, 3457.
[6] G. J. Moriello, L. Yang, A. A. Patchett, U.S. Pat. 5,721,250; *Chem. Abstr.* 128:205144.
[7] D. H. Hua, S. W. Miao, A. A. Bravo, D. J. Takemoto, *Synthesis* **1991**, 970.
[8] C. U. Kim, B. Luh, R. A. Partyka, *Tetrahedron Lett*. **1987**, *28*, 507; S. Roland, J. O. Durand, M. Savignac, J. P. Genêt, F. Jung, *Tetrahedron Lett*. **1995**, *36*, 3007.
[9] N. Grabowsky, *Justus Liebigs Ann. Chem*. **1875**, *175*, 348.
[10] C. Kingsbury, D. J. Cram, *J. Am. Chem. Soc*. **1960**, *82*, 1810; C. Walling, L. Bollyky, *J. Org. Chem.* **1964**, *29*, 2699; I. D. Entwistle, R. A. W. Johnstone, *Chem. Commun.* **1965**, *29*; D. W. Emerson, A. P. Craig, I. W. Potts, *J. Org. Chem*. **1967**, *32*, 102; J. L. Kice, J. D. Campbell, *J. Org. Chem*. **1967**, *32*, 1631.

[11] G. M. Sheldrick, SHELXS86, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1986.
[12] G. M. Sheldrick, SHELX93, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1993.

Received January 8, 2002