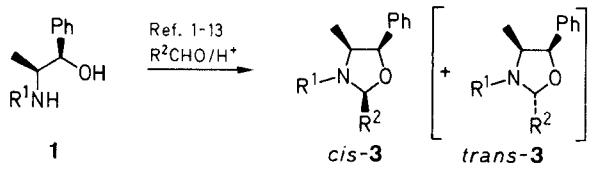
# Diastereoselective Synthesis of Enantiomerically Pure 3-Organosulfonyl-2-(2-oxocycloalkyl)-1,3-oxazolidines from 2-Formylcycloalkanones and β-Aminoalkanols[1]

Inga Hoppe, Holger Hoffmann, Ingeborg Gärtner, Thomas Krettek, Dieter Hoppe*
Institut für Organische Chemie der Universität Kiel, Olshausenstr. 40, D-2300 Kiel, Germany

*Dedicated to Professor H.J. Bestmann in recognition of his contribution as Executive Editor of Synthesis*

The title compounds (3-arylsulfonyl- or 3-mesyl-2-(2-oxocycloalkyl)-1,3-oxazolidines) belonging to two different diastereomeric series, are prepared selectively by variation of the condensation conditions. By this, the chiral information of the 2-amino-1-alkanol is extended to the cycloalkanone ring. Opposite configuration can be set up at the stereogenic center adjacent to the carbonyl group by using the same chiral auxiliary.




1 *cis*-3 *trans*-3

| 1, 3 | $R^1$ | 1, 3 | $R^1$ |
|---|---|---|---|
| a | alkyl | d | RCH=CHCO |
| b | $BnO_2C$ | e | $ArSO_2$ |
| c | aroyl | | |

Scheme 1

As reported by several research groups,[2] 2-(alkylamino)-1-alkanols, such as (1*R*,2*S*)-ephedrine (**1a**, $R^1 = CH_3$) condense with aldehydes **2** to form predominantly the diastereomers *cis*-**3a** (Scheme **1**). Agami and Rizk[3] demonstrated that a rapid epimerization takes place between *cis*- and *trans*-**3a** via an open-chain iminium ion, giving rise to the thermodynamically favored 2,4-*cis*-isomer. Enantiomerically pure 2-(1-alkenyl) derivatives of type **3a** have been used for asymmetric functionalization reactions of the double bond;[4] however, the hydrolytic instability hampered upgrading of the product by diastereomer separation and broader synthetic applications. The stability of the oxazolidines **3** is enhanced by the introduction of electron-withdrawing groups to the nitrogen atom. Meyers and co-workers[5] applied bicyclic 3-acyl-1,3-oxazolidines, derived from enantiomercially pure 2-aminoalkanols and 4-oxoalkanoic acids successfully in several asymmetric syntheses. 3-Benzyloxycarbonyl derivatives *cis*-**3b** were used by Scolastico and co-workers.[6,7] In our own independent studies[8] of oxazolidines of type **3b** in 1985, we were unable to assign its relative configuration free of doubt since we expected that the planar nitrogen atom, being involved in amide resonance, should decrease the energy difference between *cis*- and *trans*-diastereomers.

In 3-aroyl- or 3-alkenoyl-1,3-oxazolidines[9,10] of types **3c** or **3d**, derived from phenylglycinol and valinol, of which several X-ray crystal structure analyses could be obtained,[11] we encountered indeed variable amounts of the *trans*-isomers. Furthermore, poorly resolved NMR-spectra, caused by the slowly rotating amide group, made their synthetic applications less attractive.

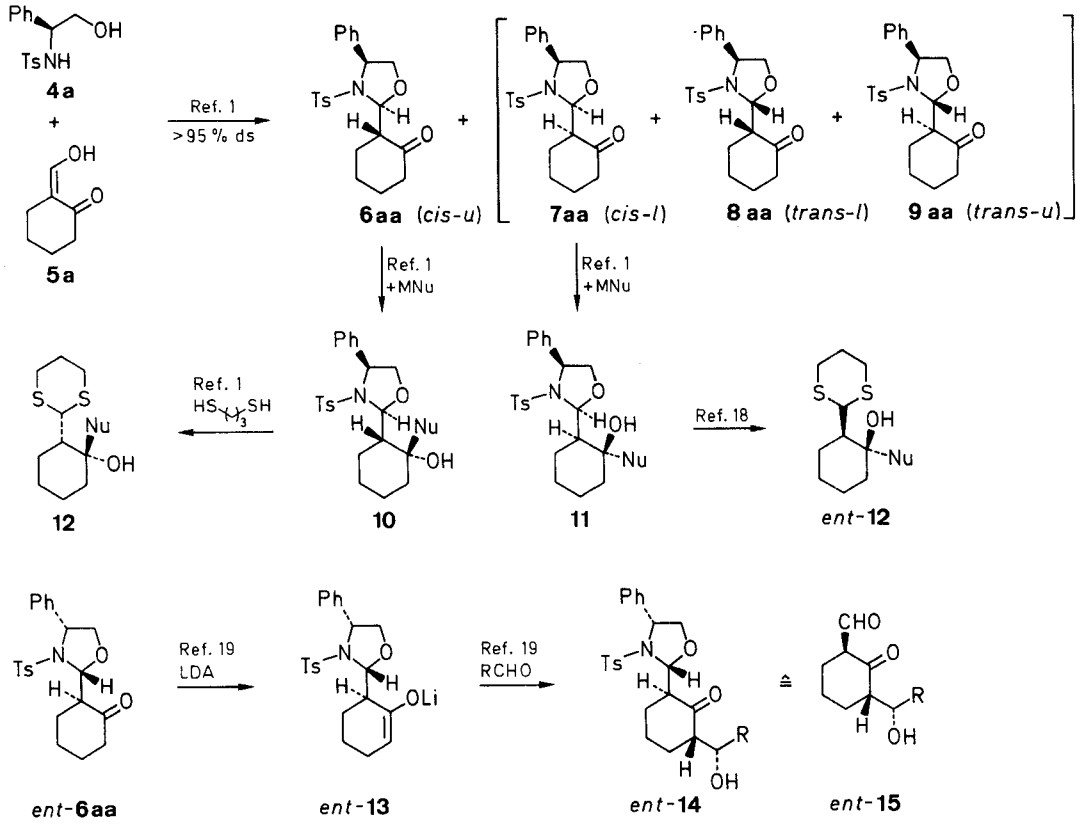
These problems were eliminated by the introduction of the strongly electron-withdrawing *p*-toluenesulfonyl group to the 3-position, which was published independently by us[1] and Scolastico and co-workers.[7,12] Since no partial double bond is developed in the sulfonamide moiety and thus, the nitrogen atom has pyramidal configuration,[13] a reliable thermodynamic preference for the *cis*-diastereomers **3e** is retained.

In a preliminary communication[1] we reported that the acid-catalyzed condensation of (*S*)-*N*-tosyl-2-phenylglycinol [(*S*)-2-phenyl-2-(tosylamino)ethanol, **4a**] and 2-(hydroxymethylene)cyclohexanone (**5a**) under kinetically controlled reaction conditions furnishes the diastereomer **6aa** (type *cis*-*u*[14,15]) with > 95% ds; out of the three other ones, **7aa**–**9aa**, only **7aa** (type *cis*-*l*[14,15]) is found in traces (Scheme **2**). The appropriate *trans*-oxazolidines **8** (type *trans*-*l*[14,15]) are obtained by asymmetric formylation of silylenol ethers[16,17] or enamines[17] from cycloalkanones by 2-methoxyoxazolidines.

The diastereotopic faces of the carbonyl group in **6aa** are efficiently differentiated by the adjacent, newly created stereogenic center. Carbon nucleophiles $Nu^-$ thus approach exclusively the *Si*-face in **6aa** to form the homochiral addition products **10**, which give the dithioacetals **12** after removal of the chiral auxiliary.[1] Similarly, from **7aa** via the diastereomers **11** the enantiomers *ent*-**12** are accessible,[18] since the opposite face of the carbonyl group is shielded. We also found, that the lithium enolate *ent*-**13** serves as a chiral, highly stereoselective equivalent of the 6-formyl-1-cyclohexenolate in asymmetric aldol addition reactions for the construction of 2,6-disubstituted cyclohexanones of types *ent*-**14** and *ent*-**15**.[19] As demonstrated in the lower part of Scheme **2**, the enantiomeric series is obtained via *ent*-**6aa**, readily prepared from (*R*)-*N*-tosyl-2-phenylglycinol (*ent*-**4a**).

The access to both enantiomers of a target molecule, using the same chiral auxiliary, is appealing, because by far the cheapest of the commercially available homochiral β-aminoalkanols is 2-amino-1-butanol[20] (*ent*-**16c**), which has the *R*-configuration. The *cis*-*l*[14]-diastereomer **7aa**, together with the *trans*-*l*[14]-isomer **8aa** in a 1:1 ratio, could be prepared by the Lewis acid mediated reaction of 1-trimethylsiloxycyclohexene with a 2-methoxy-3-tosyl-1,3-oxazolidine[16] and was shown by epimerization experiments to be slightly lower in energy than the *cis*-*u*-diastereomer **6aa** and to differ by 1.5 to 2 kcal/mol from **8aa** (*trans*-*l*).

In this work, methods were developed for the selective synthesis of chirally modified cyclohexanones and cyclopentanones of type **6** and type **7**. Several homochiral 2-amino-1-alcohols **16** (or *ent*-**16**) were tested as precursors




Scheme 2

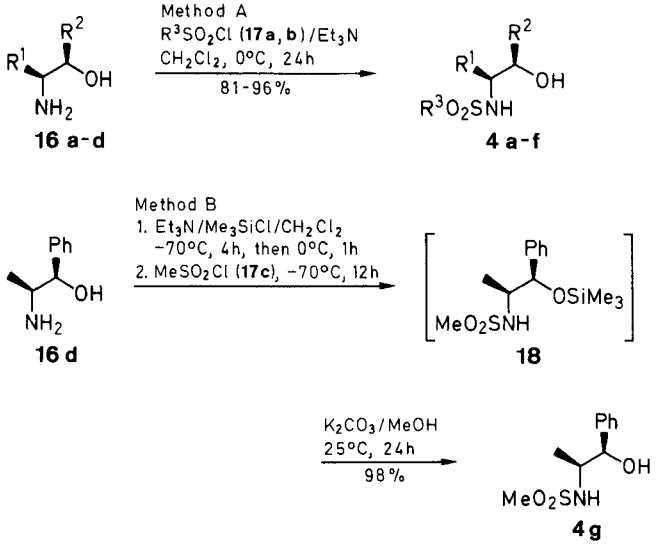
and, in addition, the size of the organosulfonyl group was varied in order to find optimal systems. Further, in a NMR study some indications on the origin of stereoselectivity are presented.

### *N*-(2-Hydroxyalkyl)sulfonamides 4

The homochiral sulfonamides **4a–f** or its enantiomers *ent*-**4** were prepared from enantiomerically pure 2-amino-1-alkanols **16a** (*S*), *ent*-**16a**(*R*), **16b**, *ent*-**16c**, or **16d** by the usual method (Scheme **3**, Table 1). When applying methanesulfonyl chloride **(17c)**/triethylamine under these conditions, mainly the formation of aziridines was observed, which occurs by 1,3-cycloelimination of the *N*,*O*-bis-(methylsulfonyl) derivative. Thus sulfonamide **4g** was prepared by in situ *O*-silylation of **16d** prior to the reaction with **17c** and subsequent methanolysis of the silylether **18** after *N*-sulfonation.

### 3-Arylsulfonyl- or 3-Mesyl-1,3-oxazolidines 6 and 7

The condensation of 2-(hydroxymethylene)cyclohexanone **(5a)** or -cyclopentanone **(5b)** with sulfonamides **4** under the influence of methanesulfonic acid and molecular sieve (4 Å, Method C) yields the *cis-u*-diastereomers **6**, usually with > 90% diastereoselectivity (Scheme **4**). Small amounts of minor diastereomers were separated by LC or by crystallization (Table 2). In Method D we used dichlorodimethylsilane as a cheap dehydrating agent, coupled with the expectation that an equilibration via silylenol ethers might occur, leading predominantly to the most stable *cis-l*-diastereomers **7**.




| 16 | $R^1$ | $R^2$ | 17 | $R^3$ | 4 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|---|---|
| a | Ph | H | a | 4-$MeC_6H_4$ | a | Ph | H | 4-$MeC_6H_4$ |
| b | *i*-Pr | H | b | 2,4,6-$Me_3C_6H_2$ | b | *i*-Pr | H | 4-$MeC_6H_4$ |
| c | Et | H | c | Me | c | Et | H | 4-$MeC_6H_4$ |
| d | Me | Ph | | | d | Me | Ph | 4-$MeC_6H_4$ |
| | | | | | e | Ph | H | 2,4,6-$Me_3C_6H_2$ |
| | | | | | f | *i*-Pr | H | 2,4,6-$Me_3C_6H_2$ |
| | | | | | g | Me | Ph | Me |

Scheme 3

It turned out that, when the conditions given in the experimental part are followed carefully, compounds **7** dominate over **6** in ratios from 70:30 to 90:10.

**Table 1.** Sulfonamides **4** Prepared

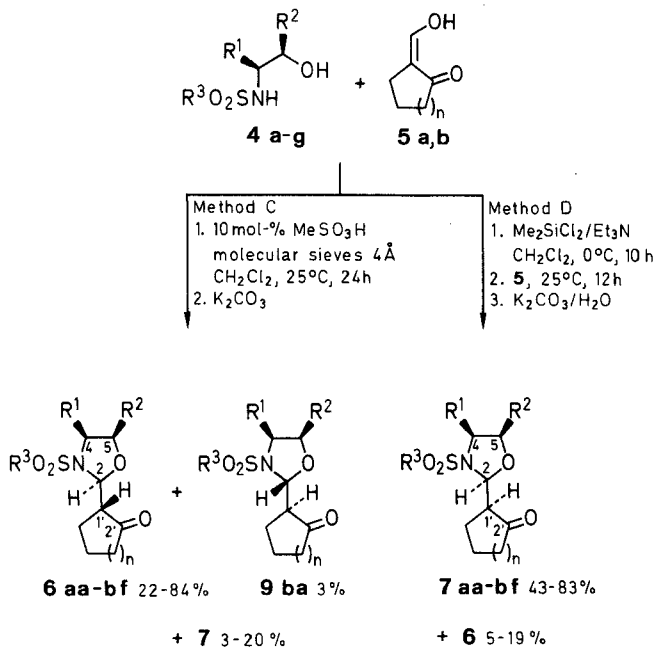
| Product | Educts | Yield (%)[a] | $[\alpha]_D^{20}$ [b,c] | mp (°C) (solvent) | Molecular Formula[d] | IR (KBr) $\nu$ ($cm^{-1}$) | $^1$H-NMR (solvent/TMS)[e] $\delta$, $J$ (Hz) |
|---|---|---|---|---|---|---|---|
| **4a** | **16a** + **17a** | 93 | +81.5[b] | 106 (EtOAc/hexane) | $C_{15}H_{17}NO_3S$ (291.4) | 3485, 3310, 1320, 1170 | acetone-$d_6$: 3.64 (d, 2H, 2-H), 4.43 (dd, $J$ = 6.7, 1-H), 2.95 (s, OH), 6.11 (d, NH) |
| **4b** | **16b** + **17a** | 96 | −27.4[b] | 86 ($Et_2O$) | $C_{12}H_{19}NO_3S$ (257.3) | 3460, 3195, 1320, 1170 | $CDCl_3$: 1.77 (dq, 2-H), 2.88 (t, OH), 3.03 (ddt, $J$ = 6.7, 1-H), 5.58 (d, NH) |
| *ent*-**4c** | *ent*-**16c** + **17a** | 81 | +26.0[c] | 58 ($Et_2O$) | $C_{11}H_{17}NO_3S$ (243.3) | 3500, 3180, 1320, 1165 | $CDCl_3$: 3.13 (ddddd, $J_{1,2a}$ = 5.1, $J_{1,2b}$ = 4.9, 1-H), 3.47 (dd, 2-H), 3.54 (dd, 2-H), 5.50 (d, NH) |
| **4d** | **16d** + **17a** | 82 | −14.2[b] | 86–88 (EtOAc) | 86–88[12] | – | – |
| **4e** | **16a** + **17b** | 82 | +77.6[b] | 131 (EtOAc/hexane) | $C_{17}H_{21}NO_3S$ (319.5) | 3420, 3210, 1320, 1170 | acetone-$d_6$: 3.63 (d, 2H, 2-H), 4.06 (s, OH), 4.32 (dd, $J$ = 6.5, 1-H), 6.57 (NH) |
| **4f** | **16b** + **17b** | 88 | −33.8[b] | 62 (EtOAc/pentane) | $C_{17}H_{23}NO_3S$ (285.4) | 3520, 3280, 1320, 1180 | acetone-$d_6$: 1.96 (ddq, 2-H), 2.10 (dddd, $J$ = 5.6, 1-H), 3.74 (OH), 6.08 (NH) |
| **4g** | **16d** + **17c** | 81 | −30.9[c] | 108 ($Et_2O$) | $C_{10}H_{15}NO_3S$ (229.3) | 3500, 3340, 1338, 1148 | $CDCl_3$: 3.27 (d, OH), 3.72 (qdd, $J$ = 3.7, 1-H), 4.84 (t, 2-H), 5.04 (d, NH) |

[a] After crystallization
[b] $CHCl_3$, $c$ = 1
[c] $CH_2Cl_2$, $c$ = 1.
[d] Satisfactory microanalysis obtained: C ±0.21, H ±0.16.
[e] 300 MHz $^1$H-NMR.

**Table 2.** Oxazolidines **6**, **7**, **8** and **9** Prepared

| Product | Configuration | Educts (Method) | Minor Diastereomer (ratio or yield) | Yield (purification)[a] | $[\alpha]_D^{20}$ ($c$, solvent) | mp (°C) (solvent) | Molecular Formula[b] | IR (KBr) $\nu$ ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| **6aa** | 2*S*,2(1*R*),4*S* | **5a** + **4a** (C) | **7aa**, >95 : 5 | 71, LC | +136.0 (1, $CH_2Cl_2$) | 144 ($Et_2O$/pentane) | $C_{22}H_{25}NO_4S$ (399.5) | 1660, 1355, 1165 |
| *ent*-**6aa** | 2*R*,2(1*S*),4*R* | **5a** + *ent*-**4a** (C) | *ent*-**7aa**, >95 : 5 | 71, LC | −136.1 (1, $CH_2Cl_2$) | 144 ($Et_2O$/pentane) | $C_{22}H_{25}NO_4S$ (399.5) | 1660, 1355, 1165 |
| **6ab** | 2*S*,2(1*R*),4*S* | **5a** + **4b** (C) | **7ab**, 20% | 61, LC ($Et_2O$/pentane) | +20.3 (1, $CH_2Cl_2$) | 138 ($Et_2O$/pentane) | $C_{19}H_{27}NO_4S$ (365.5) | 1705, 1340, 1160 |
| *ent*-**6ac** | 2*R*,2(1*S*),4*R* | **5a** + *ent*-**4c** (C) | *ent*-**7ac**, >95 : 5 | 52, LC ($Et_2O$/pentane); 41, Cr($Et_2O$) | −19.9 (1, $CH_2Cl_2$) | 134 ($Et_2O$/pentane) | $C_{18}H_{25}NO_4S$ (337.5) | 1710, 1345, 1170 |
| *ent*-**7ac** | 2*R*,2(1*R*),4*R* | **5a** + *ent*-**4c** (D) | *ent*-**6ac**, 19% | 43, LC ($Et_2O$/pentane) | +42.1 (1, $CH_2Cl_2$) | 138 ($Et_2O$/pentane) | $C_{18}H_{25}NO_4S$ (337.5) | 1710, 1345, 1160 |
| **6ad** | 2*S*,2(1*R*),4*S*,5*R* | **5a** + **4d** (C) | **7ad**, >90 : 10 | 57, LC ($Et_2O$/pentane); 35, Cr(cyclohexane/EtOAc) | +33.6 (1, $CH_2Cl_2$) | 122 ($Et_2O$/pentane) | $C_{23}H_{27}NO_4S$ (413.5) | 1708, 1355, 1170 |
| **6ag** | 2*S*,2(1*R*),4*S*,5*R* | **5a** + **4g** (C) | **7ag**, >95 : 5 | 22, LC ($Et_2O$/pentane) | −36.3 (1, $CH_2Cl_2$) | 46 ($Et_2O$/pentane) | $C_{17}H_{23}NO_4S$ (337.4) | 1710, 1335, 1165 |
| **6ba** | 2*S*,2(1*R*),4*S* | **5b** + **4a** (C) | **9ba**, 3% | 61, LC (EtOAc/pentane) | +184.3 (1, $CHCl_3$) | 109 ($Et_2O$) | $C_{21}H_{23}NO_4S$ (385.5) | 1760, 1355, 1150 |
| **9ba** | 2*R*,2(1*R*),4*S* | | | | −19.4 (1, $CHCl_3$) | 134 ($Et_2O$) | $C_{21}H_{23}NO_4S$ (385.5) | 1760, 1355, 1155 |
| **7ba** | 2*S*,2(1*S*),4*S* | **5b** + **4a** (D) | **6ba**, 5–7% | 83, Cr(EtOAc/pentane) | +21.9 (1, $CHCl_3$) | 98 (EtOAc) | $C_{21}H_{23}NO_4S$ (385.5) | 1735, 1355, 1155 |
| **6bb** | 2*S*,2(1*R*),4*S* | **5b** + **4b** (C) | **7bb**, 71 : 29 | 84[c] | [d] | [d] | $C_{18}H_{25}NO_4S$ (351.5) | 1740, 1360, 1155 |
| **7bb** | 2*S*,2(1*S*),4*S* | **5b** + **4b** (D) | **6bb**, 86 : 14 | 77, Cr($Et_2O$) | −78.4 (1, $CHCl_3$) | 103 ($Et_2O$) | $C_{18}H_{25}NO_4S$ (351.5) | 1740, 1360, 1155 |
| **7be** | 2*S*,2(1*S*),4*S* | **5b** + **4e** (C) | **6be**, >98 : 2 | 27, Cr($Et_2O$) | +56.6 (1, $CHCl_3$) | 109 ($Et_2O$) | $C_{23}H_{27}NO_4S$ (413.5) | 1730, 1355, 1155 |
| **6bf** | 2*S*,2(1*R*),4*S* | **5b** + **4f** (C) | **7bf**, 3% | 28, Cr, LC | +124.6 (1, $CHCl_3$) | 148 ($Et_2O$) | $C_{20}H_{29}NO_4S$ (379.5) | 1735, 1350, 1160 |
| **7bf** | 2*S*,2(1*S*),4*S* | | | | [d] | [d] | $C_{20}H_{29}NO_4S$ (379.5) | 1735, 1350, 1160 |
| *ent*-**6bc** | 2*R*,2(1*S*),4*R* | **5b** + *ent*-**4c** (C) | *ent*-**7bc**, >90 : 10 | 45, LC ($Et_2O$/pentane); 26, Cr($Et_2O$) | −15.1 (1, $CH_2Cl_2$) | 79 ($Et_2O$) | $C_{17}H_{23}NO_4S$ (337.4) | 1738, 1347, 1158 |

[a] LC: liquid chromatography on silica gel; Cr: crystallization
[b] All compounds gave satisfactory elemental analysis: C ±0.26, H ±0.17.
[c] The diastereomers were not separated, total yield is given.
[d] Not determined.




| 6–9 | n | $R^1$ | $R^2$ | $R^3$ | 6–9 | n | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|---|---|---|
| **aa** | 2 | Ph | H | 4-$MeC_6H_4$ | **ba** | 1 | Ph | H | 4-$MeC_6H_4$ |
| **ab** | 2 | *i*-Pr | H | 4-$MeC_6H_4$ | **bb** | 1 | *i*-Pr | H | 4-$MeC_6H_4$ |
| **ac** | 2 | Et | H | 4-$MeC_6H_4$ | **bc** | 1 | Et | H | 4-$MeC_6H_4$ |
| **ad** | 2 | Me | Ph | 4-$MeC_6H_4$ | **be** | 1 | Ph | H | 2,4,6-$Me_3C_6H_2$ |
| **ag** | 2 | Me | Ph | Me | **bf** | 1 | *i*-Pr | H | 2,4,6-$Me_3C_6H_2$ |

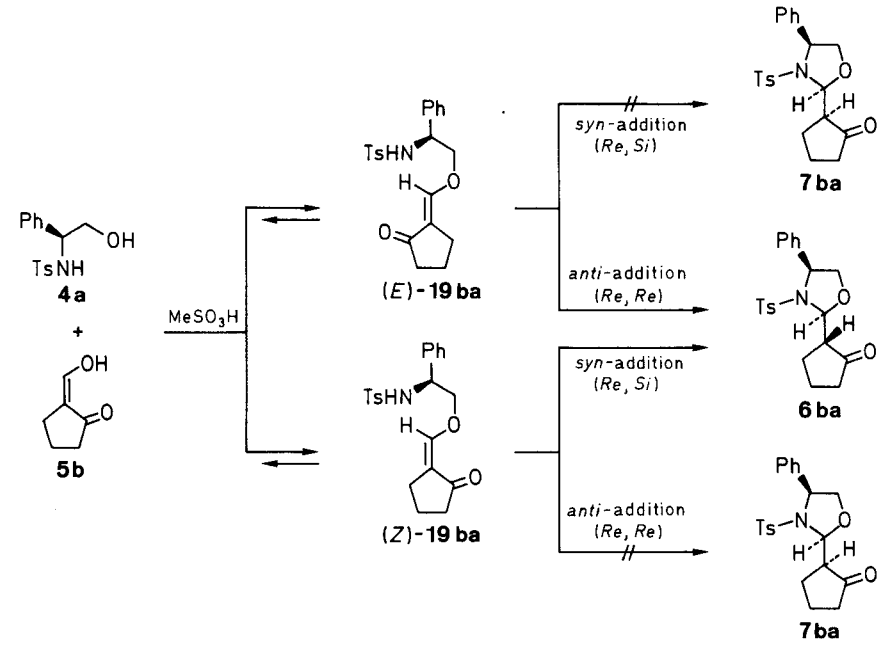
Scheme 4

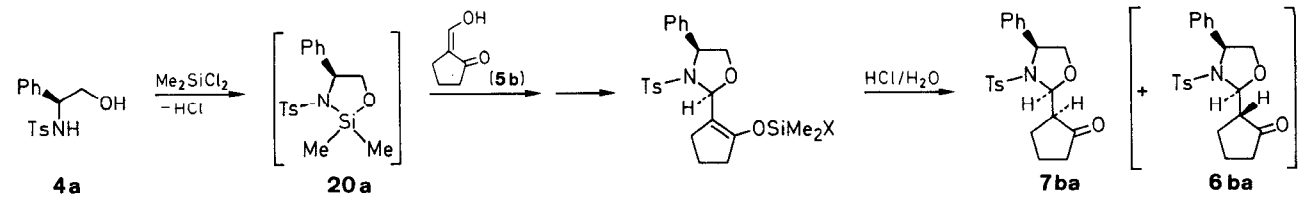
### Assignment of the Stereochemistry

From the Grignard adducts *ent*-**10** (Nu = $CH_3$), derived from *ent*-**6aa**, and also from the phenyl addition product of **6ba**[21,22] X-ray crystal structure analysis could be obtained. These establish the relative and absolute configurations of the precursors **6**. On the other hand the epimerization sequence,[16] in which under catalysis by trimethylsilyl triflate **8aa** (*trans-l*) forms rapidly **6aa** (*cis-u*) and slowly **7aa** (*cis-l*), enables a reliable correlation of the different diastereomers. In addition, in several cases, the correct assignment of the cycloalkanone configuration in **6** or **7** was controlled by conversion into the Grignard addition products of type **12** or *ent*-**12**, respectively.[18] The similarities in the optical rotation values and in the NMR data within the different diastereomeric series further support the assignments, see Tables 2–4.

### Origins of Diastereoselectivity

The reasons for the observed high diastereoselectivities are not clear in detail. In an $^1$H-NMR-study, the condensation of **5b** and **4a** in the presence of methanesulfonic acid in deuterochloroform was monitored.[21] Within few minutes a mixture of the enol ethers (*E*)-**19ba** and (*Z*)-**19ba** appeared, whose ratios 2:1 remained constant during the experiment (Scheme **5**). The concentration of **6ba** (*cis-u*) increased constantly, whereas the relative amounts of the two thermodynamically less stable diastereomers **8ba** (*trans-l*) and **9ba** (*trans-u*) remained under 5% and decreased after 14 hours to approximately 3%. The most stable isomer, **7ba** (*cis-l*) was not detected.




Scheme 5

**Table 3.** Selected $^1$H-NMR Data of Oxazolidines **6, 7, 8** and **9**[a]

| Compound | 2-H | 1′-H ($J_{2,1'}$) | 4-H ($J_{4,5a}$) | 5-H$_a$ ($J_{4,5b}$) | 5-H$_b$ or R$^2$ | R$^1$ |
|---|---|---|---|---|---|---|
| **6aa** | 5.73 (d) | 2.48 (8.5) | 4.75 (dd) (7.3) | 3.82 (5.8) | 3.90 | 7.3–7.4 (m) |
| **7aa** | 5.54 (d) | 3.22 (2.1) | 4.63 (dd) (6.7) | 3.64 (3.3) | 4.09 | 7.3–7.5 (m) |
| **8aa** | 5.82 (d) | 3.50 (ddd) (1.8) | 4.98 (dd) (6.0) | 3.96 (1.7) | 4.31 | 7.1–7.2 (m) |
| **6ab** | 5.53 (d) | 2.48 (m) (8.6) | 3.36 (ddd) (6.6) | 3.17 (dd) (3.9) | 3.62 (dd) | 0.91 (d), 1.09 d 1.78 (m) |
| *ent*-**6ac** | 5.57 (d) | 2.55 (dddd) (8.1) | 3.59 (dddd) (4.5) | 3.55 (m) (8.4) | 3.40 (ddd) | 0.96 (t)[b] |
| *ent*-**7ac** | 5.32 (d) | 3.12 (ddd) (2.0) | 3.47 (dtd) (1.4) | 3.14 (ddd) (8.5) | 3.61 (dd) | 0.95 (t) 1.53 (qdd)[b] |
| **6ad** | 5.62 (d) | 2.74 (dddd) (5.8) | 4.02 (qd) (5.7) | 4.18 (dd) – | 7.0–7.5 (m) | 0.84 (d) |
| **6ag** | 5.65 (d) | 2.80 (dddd) (5.0) | 4.17 (dq) (5.9) | 5.09 (td) – | 7.2–7.4 (m) | 0.86 (d) |
| **7ad** | 5.54 (d) | 3.24 (dddd) (1.7) | 3.90 (dq) (5.85) | 4.29 (dt) – | 7.05 (m) 7.21 (m) | 0.85 (d) |
| **6ba** | 5.31 (d) | 2.0–2.2 (3.3) | 4.67 (dd) (3.65) | 4.00 (dd) (6.9) | 3.65 | 7.36 (m) 7.5–7.8 (m) |
| **9ba** | 5.72 (d) | 2.4–2.5 (0.8) | 4.98 (dd) (5.9) | 4.31 (dd) (1.3) | 3.92 | 7.0–7.1 (m) 7.28 (m) |
| **7ba** | 5.32 (d) | 3.09 (dddd) (2.7) | 4.68 (dd) (2.7) | 4.07 (6.6) | 3.57 | 7.2–7.5 (m) |
| **6bb** | 5.09 (d) | [d] (2.9) | 3.34 (ddd) (6.2) | 3.03 (dd) (1.8) | 3.75 (dd) | 0.92 (d)[c] 1.10 (d) |
| **7bb** | 5.13 (d) | 3.00 (ddd) (2.7) | 3.26 (dd) (5.8) | 2.94 (dd) (1.8) | 3.72 (ddd) | 0.92 (d)[c] 1.10 (d) |
| **7be** | 5.61 (d) | 2.97 (dddd) (3.4) | 4.64 (7.2) | 2.94 (dd) (1.8) | 4.24 | 7.06 (m) 7.16 (m) |
| **6bf** | 5.53 (d) | 2.49 (2.6) | 3.46 (ddd) (1.3) | 3.94 (7.1) | 3.93 (dd) | 0.58 (d) 0.83 (d) 1.67 (dqq) |
| **7bf** | 5.38 (d) | 2.61 (2.5) | 3.27 (ddd) (2.2) | 3.79 (dd) (5.9) | 3.93 (ddd) | 0.55 (d) 0.77 (d) 1.52 (dqq) |
| *ent*-**6bc** | 5.11 (d) | 2.49 (dddd) (2.4) | 3.58 (dddd) (2.1) | 3.63 (ddd) (6.0) | 3.16 (ddd) | 0.97 (t) 1.59 (qdd) |

[a] 300 MHz, $CDCl_3$
[b] Only one of the diastereotopic $CH_2$ protons was recognized.
[c] Diastereotopic $CH_3$ groups only.
[d] Not determined.

**Table 4.** Selected $^{13}$C-NMR Data of Oxazolidines **6, 7, 8 and 9**[a]

| Compound | C-2 | C-4 | C-5 | C-1′ | C-2′ |
|---|---|---|---|---|---|
| **6aa** | 91.5 | 62.1 | 71.1 | 54.6 | 209.9 |
| *ent*-**7aa** | 90.47 | 61.52 | 72.25 | 54.46 | 209.85 |
| *ent*-**8aa** | 88.56 | 63.36 | 74.18 | 55.57 | 210.18 |
| **6ab** | 90.81 | 65.66 | 67.80 | 55.78 | 210.08 |
| *ent*-**6ac** | 90.71 | 60.91 | 69.61 | 55.32 | 209.69 |
| *ent*-**7ac** | 89.94 | 60.54 | 69.93 | 54.09 | 209.87 |
| **6ad** | 89.55 | 58.52 | 80.86 | 56.39 | 209.11 |
| **7ad** | 88.75 | 57.97 | 81.16 | 54.18 | 209.66 |
| **6ag** | 89.84 | 58.66 | 81.79 | 55.19 | 209.12 |
| **6ba** | 91.70 | 62.29 | 71.92 | 52.91 | 216.53 |
| **9ba** | 89.50 | 63.73 | 73.58 | 55.74 | 216.78 |
| **7ba** | 91.51 | 61.48 | 72.53 | 53.29 | 216.88 |
| **6bb** | 91.26 | 65.63 | 69.52 | 53.20 | 216.63 |
| **7bb** | 90.91 | 67.07 | 68.26 | 53.33 | 216.87 |
| **7be** | 91.94 | 71.15 | 68.04 | 51.90 | 216.59 |
| **6bf** | 90.31 | 64.08 | 68.75 | 52.16 | 216.49 |
| **7bf** | 91.74 | 65.02 | 69.06 | 51.35 | 216.08 |
| *ent*-**6bc** | 91.10 | 61.30 | 69.26 | 53.04 | 216.57 |

[a] 75 MHz, $CDCl_3$.

It must be concluded from these observations, that the formation of both stereogenic centers at C-2 and C-1′ is coupled by a stereospecific reaction. Further, the ring closure to form **8ba** and **9ba** under the reaction conditions is reversible, but the most stable diastereomer **7ba** (*cis-l*) is formed very slowly. The main product can either arise in an intramolecular stereospecific *anti-* or *syn*-addition of either (*E*)-**19ba** or (*Z*)-**19ba**, respectively. We are unable to understand, why the barrier for the formation of **7ba** is comparatively high under the conditions of Method C.

However, **7ba** arises predominantly under the influence of dichlorodimethylsilane (Method D). We assume that in the condensation of **5b** with the intermediate 1-oxa-2-sila-3-azacyclopentane **20a** (and its oligomers) the *cis*-oxazolidine substituted enol ether is the thermodynamically controlled major intermediate. As it was demonstrated in a control experiment for the appropriate trimethylsilyl enolether, hydrolysis furnishes preferentially the diastereomer **7ba**.

Enantiomerically pure 2-amino-1-alkanols **16** were either purchased, **16c,d**, and used without further purification or prepared by $LiAlH_4$ reduction of the corresponding amino acids, **16a,b** and *ent*-**16a**[23]. 2-(Hydroxymethylene)cycloalkanones **5a,b**[24,25] were freshly prepared or distilled prior use. $^1H$- and $^{13}C$-NMR spectra were recorded on Varian XL-200, FT 80A, and Bruker AM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 298 or 283b spectrophotometer. Optical rotations were recorded on Perkin-Elmer polarimeter 241.

**N-(2-Hydroxyalkyl)sulfonamides 4 or *ent*-4; General Procedures:**

Method A: for Arenesulfonamides **4a–f**: A solution of 2-amino-1-alkanol **16** or *ent*-**16** (10 mmol), $Et_3N$ (1.53 mL, 11 mmol), and arenesulfonyl chloride **17a,b** (10 mmol) in $CH_2Cl_2$ is stirred for 24 h at 0 °C. The mixture is diluted with $CH_2Cl_2$ (20 mL), washed with 2N aq $H_2SO_4$ (10 mL each) and the $CH_2Cl_2$ solution is dried ($Na_2SO_4$) and evaporated. The residue is recrystallized from $Et_2O$. Yields and physical data see Table 1.

Method B: for (1*S*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-methanesulfonamide (**4g**): To a solution of L-norephedrine (**16d**; 1.51 g, 10 mmol) and $Et_3N$ (2.78 mL, 20 mmol) in $CH_2Cl_2$ (40 mL) at − 70 °C $Me_3ClSi$ (1.08 g, 10 mmol) is added dropwise. After 4 h stirring the temperature is allowed to raise to 0 °C (1 h) and the mixture is again chilled to − 70 °C. Methanesulfonyl chloride (**17c**; 1.14 g, 10 mmol) is added, stirring is continued for 12 h and then the temperature raised to 0 °C. The solution is washed with $H_2O$ (2 × 10 mL), dried ($Na_2SO_4$) and the solvent evaporated. The crude product (5.3 g) is dissolved in MeOH (50 mL) and is stirred with powdered $K_2CO_3$ (3.4 g) for 24 h at 25 °C. The solid is filtered off, the solution evaporated, the residue dissolved in $CH_2Cl_2$ (50 mL), washed with $H_2O$ (2 × 15 mL), dried ($Na_2SO_4$) and the solvent evaporated. Recrystallization of the residue from $Et_2O$ affords 3.7 g (81%) **4g** (see Table 1).

**(*cis-u*)-3-Arylsulfonyl- or -3-Mesyl-2-(2-oxocycloalkyl)-1,3-oxazolidines 6 or *ent*-6; General Procedure:**

Method C: A mixture of sulfonamide **4** or *ent*-**4** (10 mmol) and freshly prepared 2-(hydroxymethylene)cycloalkanone[24,25] **5** (10 mmol) in $CH_2Cl_2$ (50 mL) is stirred with $MeSO_3H$ (0.15 g) and molecular sieve 4 Å (10 g) at 25 °C for 24 h. Solid $K_2CO_3$ (0.5 g) is added and after stirring for 5 min the solids are filtered off, and the solvent is evaporated. The product is crystallized from the appropriate solvent (Table 2), the residue separated by LC on silica gel (120 g, solvent: EtOAc/hexane, 1:2).

**(*cis-l*)-3-Arylsulfonyl- or -3-Mesyl-2-(2-oxocycloalkyl)-1,3-oxazolidines 7 or *ent*-7; General Procedure:**

Method D: To a solution of sulfonamide **4** or *ent*-**4** (30 mmol) in $CH_2Cl_2$ (100 mL) $Me_2SiCl_2$ (3.9 g, 30 mmol) is added at 0 °C and stirring continued at this temperature for 10 h with exclusion of moisture. The solvent and HCl are evaporated in vacuum (4 h, 16 Torr, bath temperature 20 °C). The residue is dissolved in $CH_2Cl_2$ (100 mL), 2-(hydroxymethylene)cycloalkanone **5** (30 mmol) is added. After 12 h stirring at 25 °C, $K_2CO_3$ 81.5 g) is added, the mixture washed with $H_2O$ (2 × 30 mL) and the solution dried ($Na_2SO_4$). Work-up is accomplished as described above.

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