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ASYMMETRIC SYNTHESIS OF β-AMINO-γ-HYDROXYSULFOXIDES

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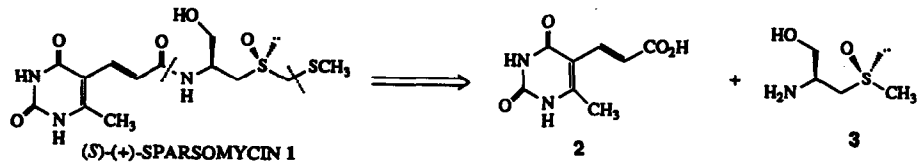
Abstract: Optically pure [4-(3'-oxazoline)]methyl methyl- and p-tolylsulfoxides (5R, 5S, 6R and 6S) were prepared from the enolate of the 3-oxazoline 4 and the corresponding o.p. diacetone-D-glucofuranosyl methanesulfinate and menthyl p-toluenesulfinate. The highly diastereoselective reduction of these substrates was successfully achieved using DIBAL/ZnCl2 at -78°C. In this way, four o.p. N-cyclohexyl β-amino-γ-hydroxysulfoxides, chiral key intermediates in the asymmetric synthesis of various biologically active molecules, were obtained.

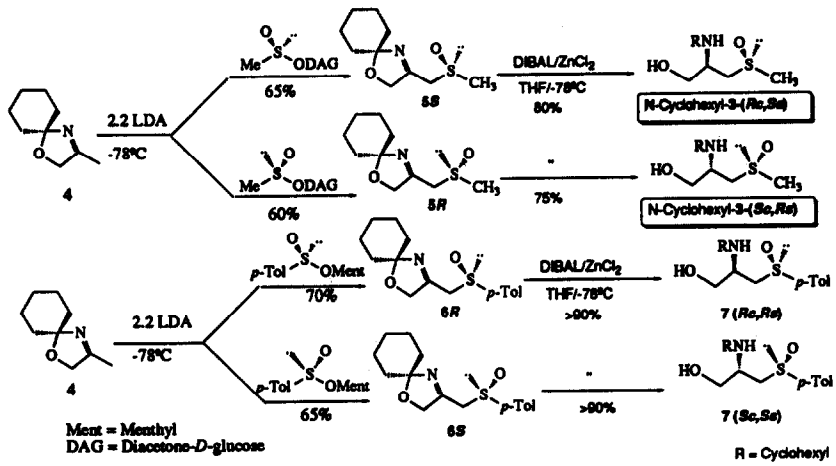
Chiral sulfoxides have proven themselves as chiral auxiliaries in highly asymmetric synthesis.[1] Moreover, biologically active molecules bearing a sulfinyl group are of great biological interest. Among these compounds Sparsomycin has attracted considerable attention because of its biological activity.[2] From a retrosynthetic study, Sparsomycin 1 (Scheme 1) can be viewed as an amide between the acid 2[2] and the β-amino-γ-hydroxysulfoxide 3. The asymmetric synthesis of the highly functionalized compounds type 3 is a challenge because one of the two chiral centers present in the molecule is a methylsulfinyl group, which can not be obtained by the widely used Andersen method.[3]



SCHEME 1

In this communication we present a general method for the asymmetric synthesis of β-amino-γ-hydroxysulfoxides taking advantages of two methodologies we have recently develop ed: (a) The asymmetric synthesis of both o.p. (optically pure) methylsulfoxides, epimers at sulfur, using diacetone-*D*-glucose (DAG) as unique inducer of chirality,[4] (b) The synthesis and reduction of α-sulfinylketimines obtained from 4-methyl-3-oxazolines and a sulfinate ester.[5]

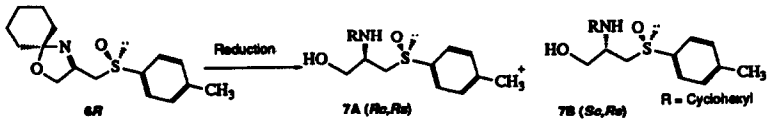
The treat ment of 1 eq. of the 3-oxazoline 4[5] with 2.2 eq. of LDA and (*R*)- or (*S*)-methanesulfinate of DAG gives the o.p. methylsulfoxides **5*R*** and **5*S***,[6a] respectively (Scheme 2). The enantiomerically pure *p*-tolylsulfinyl analogs **6*R*** and **6*S***[6b] were obtained in a similar way from the corresponding menthyl *p*-toluenesulfinates. These last sulfoxides were prepared because derivatives with hydrophobic substituents replacing the CH_2SMe group in the sulfinyl sulfur of Sparsomycin seems to be more potent inhibitors of peptide bond formation than Sparsomycin itself.[7]



SCHEME 2

The asymmetric induction in the reduction of the C=N double bond was studied in detail, using the *p*-tolylsulfoxide **6*R*** as a model. Several reducting systems were used in different solvents and temperatures. The results obtained are summarized in Table 1.

Table 1 : Asymmetric induction in the reduction of **6*R*** with different metal hydrides

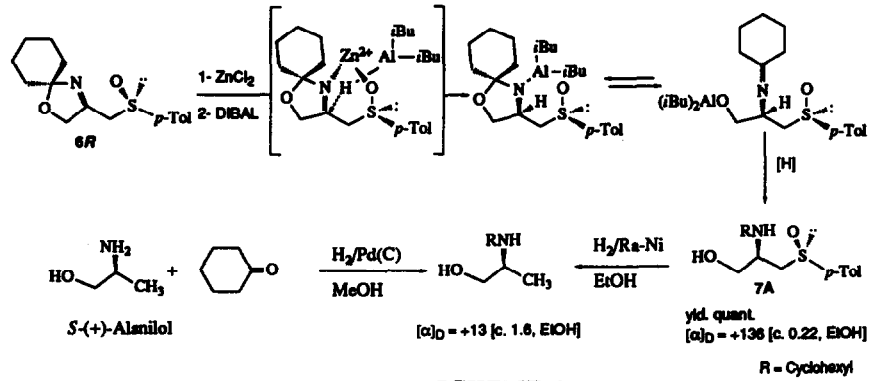


Entry	Reductor	Lewis Acid	Solvent	Temperature	Time	Yield	7A : 7B
1	DIBAL	-	THF	-78°C	-	-	-
2	**DIBAL**	**$ZnCl_2$**	**THF**	**-78°C**	**30 min**	**>90%**	**100 : 0**
3	$NaCNBH_3$	-	MeOH	r.t.	-	-	-
4	$NaCNBH_3$	-	AcOH/TFA	0°C to r.t.	2hrs	83%	43 : 57
5	$NaCNBH_3$	-	AcOH	0°C to r.t.	2 hrs	85%	42 :58
6	$NaBH_4$	-	THF	r.t.	-	-	-
7	$NaBH_4$	$ZnCl_2$	THF	r.t.	30 min	>90%	66 : 34
8	$NaBH_4$	$MgClO_4$	CH_3CN	-78°C to r.t.	overnight	80%	62 : 38
9	LAH	-	Ether	-78°C	-	-	_
10	LAH	$ZnCl_2$	THF	-78°C	30 min	>90%	72 : 28

The diastereomeric ratio of the two N-cyclohexyl β-amino-γ-hydroxysulfoxides **7(R_C, R_S)/7(S_C, R_S)** was easily determined by ^1H NMR analysis of the reaction mixture, based on the different chemical shift of the AB fragment of the ABX system corresponding to the HOC*H*$_2$-CH protons for each isomer. These signals were unequivocally assigned, after chromatographic separation and spectroscopic characterization of both diastereomers.[8]

When DIBAL or LAH were used as reductors the reaction was carried out at -78ºC in order to avoid the formation of the sulfide derivative,[5] but at this temperature only the starting material was recovered in both cases (entries 1 and 9). The presence of an acid ($ZnCl_2$, $MgClO_4$ or AcOH) is necessary for an efficient reduction of the C=N double bond, probably by increasing its electrophilicity, and low temperatures are requared for a good stereoselection. Thus, in the reduction of **6*R*** with DIBAL/$ZnCl_2$ at -78ºC the **7**(R_C, R_S)[8] amine derivative was obtained as a single isomer. Similarly, the corresponding enantiomer **7**(S_C, S_S)[9] was prepared in 90% yield and 100% d.e. when the oxazoline **6*S*** was used as starting material. The replacement of the *p*-tolyl substituent by a methyl group does not change the stereocourse of the reaction. Accordingly, o.p. N-cyclohexyl derivatives **3**(R_C, S_S) and **3**(S_C, R_S)[9] were obtained from **5*S*** and **5*R***, in 80% and 75% yields, respectively.

The configurational assignment of **7A** as (R_C, R_S) was unequivocally made by chemical correlation. The desulfinylation of **7A** by Raney Ni gave o.p. *S*-(+)-N-cyclohexylalanilol with the same specific rotation, $[\alpha]_D$=+13 (c 1.6, EtOH), than that obtained by reductive amination of cyclohexanone with *S*-(+)-alanilol, (Scheme 3). It is worth noting that the same assignment can be deduced from the ^1H NMR analysis of the CH-CH_2SO fragment of the reduced products. Thus, the value of ΔJ (J_{anti}-J_{gauche}) as well as the non-equivalence of the methylenic protons, $\Delta\upsilon$, are higher in the **7**(S_C, R_S) aminosulfoxide than in the **7**(R_C, R_S) isomer,[8] as it was previously reported for several β-amino- and β-hydroxysulfoxides.[10]



SCHEME 3

The high stereoselectivity obtained in the reduction with DIBAL/$ZnCl_2$ can be rationalized, as in the case of β-ketosulfoxides,[11] by an initial chelation of Zn^{2+} to the iminic nitrogen and the sulfinylic oxygen, through a six member ring, followed by addition of the bulky hydride to the carbon of the C=N double bond from the less hindered face. Further hydride transfer to the ring-open tautomer yields the corresponding N-alkylated β-amino-γ-hydroxysulfoxide (Scheme 3).

In conclusion, the reduction of [4–(3'-oxazoline)]methyl *p*-tolyl- and methylsulfoxides, with DIBAL in the presence of $ZnCl_2$ at -78ºC, proceeds with high yield and high diastereoselection. This methodology has permitted the synthesis of four optically pure N-alkylated β-amino-γ-hydroxysulfoxides. The use of these chiral key intermediates in the asymmetric synthesis of o.p. analogs of Sparsomycin, as well as that of o.p. analogs of natural ocurring amino acids sulfoxides, is actually in due course.

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6. (a) **5***S* : $[\alpha]_D$= + 5 (c 1.0, EtOH abs.); **5***R* : $[\alpha]_D$= - 5 (c 0.48, EtOH abs.). Spectroscopic characteristics of both enantiomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.39 (AB system, *J* = 14.8 Hz, Δυ = 20.0 Hz, 2H, OCH_2CN), 3.52 (AB system, *J* = 13.6 Hz, Δυ = 38.9 Hz, 2H, CH_2SO), 2.45 (s, 3H, $SOCH_3$), 1.51-1.22 (m, 10H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.60, 110.38, 75.03, 52.45, 37.74, 36.17,35.82, 24.40, 22.61. (b) **6***R*: $[\alpha]_D$= + 170 (c 0.34, EtOH abs.); **6***S*: $[\alpha]_D$ = - 174 (c 0.26, EtOH abs.). Spectroscopic data of both enantiomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 (A_2B_2 system, *J* = 8.2 Hz, Δυ = 36.7 Hz, 4H, SOC_6H_4-), 4.45 (AB system, *J* = 14.9 Hz, Δυ = 19.3 Hz, 2H, OCH_2C), 3.80 (s, 2H, CH_2SOAr), 2.38 (s, 3H, *p*-Me), 1.70-1.30 (m, 10H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.49, 142.02, 138.50, 129.90, 124.13, 110.61, 75.27, 56.78, 36.24, 24.91, 23.11, 21.33.
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8. **7**(R_C, R_S): ^{1}H NMR (200 MHz, $CDCl_3$+D_2O) δ 7.42 (A_2B_2 system, *J* = 8.1 Hz, Δυ = 39.0 Hz, 4H, SOC_6H_4-), 3.70 (AB fragment of an ABX system, *J* = 13.4, 4.7, 4.1 Hz, Δυ = 27.9 Hz, 2H, OCH_2), 3.37 (m, 1H, C*H*CH_2S), 2.97 (AB fragment of an ABX system, *J* = 13.5, 6.4, 5.0 Hz, Δυ = 17.0 Hz, 2H, CH_2SO), 2.41 (s, 3H, *p*-Me), 1.90-1.50 (m, 5H, cyclohexyl), 1.30-0.98 (m, 6H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.51, 139.95, 129.87, 123.89, 63.03, 60.02, 53.66, 51.86, 33.39, 25.71, 24.79, 24.68, 21.23. **7**(S_C, R_S): ^{1}H NMR (200 MHz, $CDCl_3$+D_2O) δ 7.43 (A_2B_2 system, *J* = 8.2 Hz, Δυ = 36.9 Hz, 4H, SOC_6H_4-), 3.64 (AB fragment of an ABX system, *J* = 11.4, 4.2, 4.1 Hz, Δυ = 36.0 Hz, 2H, OCH_2), 3.41 (m, 1H, C*H*CH_2S), 3.00 (AB fragment of an ABX system, *J* = 13.9, 8.0, 4.5 Hz, Δυ = 34.5 Hz, 2H, CH_2SO), 2.44 (s, 3H, *p*-Me), 1.90-1.60 (m, 5H, cyclohexyl), 1.45-1.10 (m, 6H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.38, 138.28, 130.42, 123.96, 61.58, 59.84, 54.88, 52.05, 32.01, 31.25, 24.45, 21.44.
9. **7**(S_C, S_S): $[\alpha]_D$= -131 (c 0.58, EtOH abs). ^{1}H NMR and ^{13}C NMR spectroscopic data identical to those of **7**(R_C, R_S) described in ref. 8. **3**(R_C, S_S): $[\alpha]_D$= +64 (c 1.0, EtOH abs.). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.71 (AB fragment of an ABX system, *J* = 11.6, 4.5, 3.7 Hz, Δυ = 30.6 Hz, 2H, OCH_2), 3.41 (m, 1H, C*H*CH_2SO), 3.03-2.83 (m, 4H, CH_2SO, NH, OH), 2.66 (s, 3H, $SOCH_3$), 1.95-1.60 (m, 5H, cyclohexyl), 1.29-1.10 (m, 6H, cyclohexyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 62.33, 57.02, 54.23, 52.39, 39.11, 33.23, 32.93, 25.71, 24.79. **3**(S_C, R_S): $[\alpha]_D$ = -65 (c 1.0, EtOH abs.). ^{1}H NMR and ^{13}C NMR similar to those of **3**(R_C, S_S).
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