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A new approach to vinyl glycine derivatives from (+)-(R_S)-3-[(*p*-toluenesulfinyl)methyl]-1-oxa-4-azaspiro[4,5]decen-3-ene

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Dedicated to the memory of Juan Carlos del Amo-Aguado

Abstract—The diastereoselective reduction of α-benzyl-α-sulfinylketimine **1a** with DIBAL–H/$ZnCl_2$, $LiEt_3BH$, and $NaCNBH_3$/AcOH–TFA has been studied. Under the first conditions, the reaction was completely stereoselective and the sulfinyl group involving the formation of a chelated complex with the metallic ion became the sole chiral controller, regardless of the presence of the α-stereocentre. The title compound **6-I** was derivatized as cyclic carbamate **2** and the base induced desulfinylation of this compound allowed the synthesis of the enantiomerically pure *N*,*O*-protected *N*-cyclohexyl-1,2-amino alcohol **3** with total regio- and stereocontrol.

1. Introduction

β,γ-Unsaturated α-amino acid derivatives have received special attention since they are important enzyme inhibitors. For example, it is known that α-vinyl amino acids are inhibitors of pyridoxal phosphate-dependent enzymes and, in particular, of amino acid decarboxylases.[1] They are also potential precursors to new α-branched α-amino acids as building blocks for the novo peptide design.[2] Their unique conformational properties have also been a matter of particular interest.[3] The majority of the synthetic efforts towards β,γ-unsaturated amino acids have been specifically directed towards vinyl glycine,[4] with few reports describing routes towards other β,γ-unsaturated amino acids.[4b] However, some general strategies have been reported including olefination of serine derivatives,[5] reduction of alkynyl glycine derivatives,[6] Heck coupling approaches,[7] and the Mannich reaction involving its three components, the organoboronic acid or boronate, the amine and a α-keto acid.[8]

Herein we report our progress in the evaluation of the ability of the sulfinyl group to control stereoselectivity[9,10] in the reduction of sulfinylketimine **1a** (Chart 1). Previous studies have shown that analogue **1b** (Chart 1) is reduced with DIBAL–H/$ZnCl_2$ with total stereocontrol.[11] Bearing this in mind, the first question to address was whether the α-benzyl derivative **1a** displays a similar behaviour in spite of the new stereocentre at the α-position.

Moreover, the elimination of the sulfinyl group under basic conditions has been proved possible in the synthesis of γ,δ-unsaturated β-amino alcohols in a regio- and stereoselective manner. This methodology could be applied to the synthesis of β,γ-unsaturated α-amino acids.

Herein we prove the capability of the sulfinyl group to solely determine the stereoselective outcome of the

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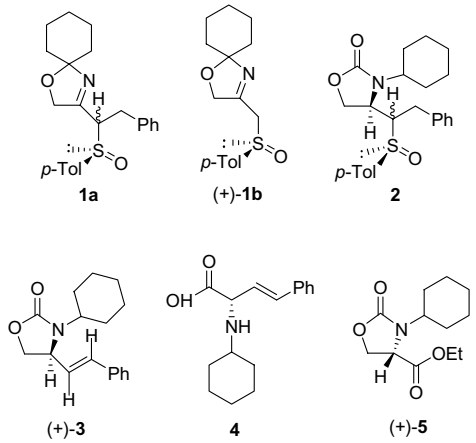


Chart 1.

reduction regardless of the presence of a second stereocentre next to the reaction site.

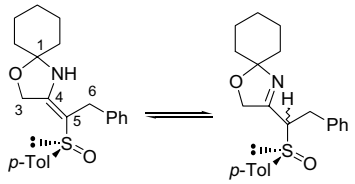
In addition, the sulfinyl grouping derivative **2** was removed under basic conditions with entire regio- and stereoselectivity to yield compound **3**, an immediate precursor of (*E*)-*N*-cyclohexylstyryl glycine **4**.[12] The absolute configuration was determined by chemical correlation between the ethyl ester derivative of L-serine (+)-**5** and its enantiomeric counterpair obtained from (+)-**3** through $RuCl_3/NaIO_4$ oxidation (Chart 1).

2. Results

Compound **1a** was prepared by benzylation of the α-sulfinylketimine **1b**, which was obtained from 3-methyl-1-oxa-4-azaspiro[4,5]dec-3-ene and methyl (S_S)-(−)-*p*-toluenesulfinate as previously reported by Khiar et al. and ourselves.[10,11] The α-sulfinylketimine **1a** was isolated by column chromatography using silica gel (Hex/EtOAc: 2/1, 1/1, 1/2) in 72% yield. The analysis of the spectrum between 4.5 ppm (CH_2O), 3.2–3.8 ppm (H_5, H_6, $H_{6'}$) and 2.2–2.5 ppm (CH_3–Ar) showed the presence of three isomers (**A**:**B**:**C** = 56:34:10) (Table 1). Isomer **A** was identified as a single enamine form, as shown by the multiplicity of the methylene protons H_6 and $H_{6'}$ (AB system). Isomers **B** and **C** must be two imine epimers in C_5 since protons H_3 and $H_{3'}$ appear as an apparent singlet while protons H_6 and $H_{6'}$ are split as a doublet of doublets being appreciable its vicinal coupling with proton H_5, as shown in Table 1.

Compound **1a** was reduced with different agents in the conditions shown in Table 2. ^1H NMR (200 or 500 MHz) spectra allowed the analysis of the reaction crudes. The assignment of the signals to protons of each isomer was made possible by comparison with the spectra of the pure isomers or concentrated fractions of them. As shown by entries 1–3 and 4, respectively, the reactions with DIBAL–H/$ZnCl_2$ and $LiEt_3BH$ in THF are fully diastereoselective in (2*R*)-amino alcohol **6-I** showing no dependence of the configuration of the adjacent stereocentre C_3. This was determined by chemical correlation between this compound and the ethyl ester derivative of L-serine (+)-**5**, following the sequence described in Scheme 1. Thus, **6-I** was converted into 2-oxazolidinone **2**, which underwent elimination of *p*-toluenesulfenic acid in the presence of DBU to afford (+)-**3**. A small amount of **3** was oxidized with $RuCl_3/NaIO_4$, and the resulting acid derivatized to ethyl (−)-(4*R*)-3-cyclohexyl-2-oxo-1,3-oxazolidine-4-carboxylate (−)-**5** using conventional methods. The specific rotation, $[\alpha]_D^{25} = -108.5$ (*c* 8.6, $CHCl_3$), was compared to that of the derivative obtained from L-serine (OEt) as can be seen in Scheme 1. According to the opposite sign of the specific rotation in both compounds, (−)-**5** has an (*R*)-configuration and so does **6-I** as a result. The reaction of **1a** with $NaCNBH_3$ in AcOH/TFA was less stereoselective (Table 2, entry 5). Before purification, the

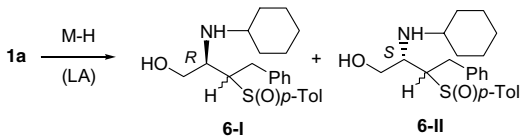
Table 1. ^1H NMR (200 MHz) spectroscopic data[a] of compound **1a** in $CDCl_3$[b]



Isomer **A**	Isomer **B**	Isomer **C**
4.417	4.505	4.865
(AB system, 1H, ^2J = 15.0, H_3)	(s, 2H, H_3, $H_{3'}$)	(s, 2H, H_3, $H_{3'}$)
4.378	3.907	3.739
(AB system, 1H, ^2J = 15.0, H3′)	(dd, 1H, ^3J = 6.6, 9.8, H_5)	(dd, 1H, ^3J = 4.0, 11.95, H_5)
3.796	3.412	3.537
(AB system, 1H, ^2J = 14.6, H6)	(dd, 1H, ^2J = 14.0, ^3J = 9.8, $H_{6'}$)	(dd, 1H, ^2J = 13.1, ^3J = 11.95, H_6)
3.697	3.217	3.305
(AB system, 1H, ^2J = 14.6, $H_{6'}$)	(dd, 1H, ^2J = 14.0, ^3J = 9.8, $H_{6'}$)	(dd, 1H, ^2J = 13.1, ^3J = 11.95, $H_{6'}$)
2.392	2.408	2.408
(s, 3H, Me–Ar)	(s, 3H, Me–Ar)	(s, 3H, Me–Ar)

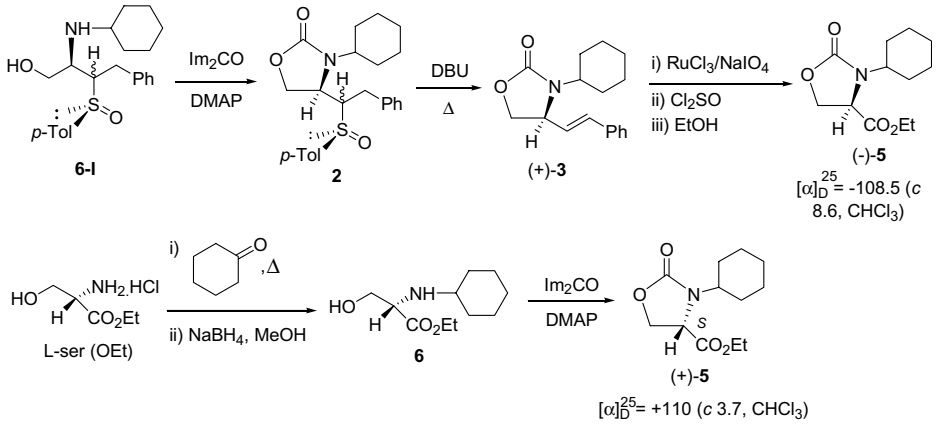
[a] Chemical shifts are given in ppm, and coupling constants in Hz.
[b] Spectroscopic data showing no difference are not included: 7.60–7.15 (m, 9H, Ar) and 1.71–1.30 (m, 10H, cyclohexyl).

Table 2. Reduction of **1a** with different reducing agents (M–H)



Entry	M–H (equiv)	LA (equiv)	Solvent	*T* (°C)	Time (h)	Yield (%)	**6-I/6-II**[a] (3*R*/3*S*)
1	DIBAL (2)	$ZnCl_2$ (1.5)	THF	−78 to 23	16	35	56/43:<2
2	DIBAL (5)	$ZnCl_2$ (2.0)	THF	−78 to 23	16	98	44/56:<2
3	DIBAL (5)	$ZnCl_2$ (2.0)	DCM	−78 to 23	16	98	44/56:<2
4	$LiEt_3BH$	—	THF	0 to 23	12	19	0/92:<8
5	$NaCNBH_3$	—	AcOH/TFA	0 to 23	12	92	47/18.5:23.5/11[b]

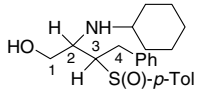
[a] Diastereoselectivity was determined by ^1H NMR (500 or 200 MHz) analysis of the reaction crudes, using the chemical shifts of the AB part of the ABX system corresponding to the HO–CH_2–CH rest of each isomer. The assignment 3*R*/3*S* can be changed.
[b] A: 47%; B: 18.5%; C: 23.5%; D: 11%.



Scheme 1.

analysis of the spectral zones between 3.2–4.0 ppm (ABX system, HO–CH_2) and 2.4–2.5 ppm (*Me*–Ar) of the ^1H NMR spectra (200 MHz) of the crude showed the presence of four isomers: **A** (47%), **B** (18.5%), **C** (23.5%) and **D** (11%). The crude was then purified by column chromatography in silica gel (DCM/acetone: 1/1). The ^1H NMR (500 MHz) spectra of the fractions allowed the characterization of the different isomers, and also their distribution in each fraction [fraction 1: **A** (59%), **D** (41%); fraction 2: **A** (63%), **B** (37%); fraction 3: **C** (100%)]. The spectroscopic data are summarized in Table 3.

Table 3. ^1H NMR (500 MHz) spectroscopic data for the configurational isomers **6-I** (2*R*,3*R*/3*S*) and **6-II** (2*S*,3*R*/3*S*)[a]



Signal	**6-I** (2*R*,3*R*/3*S*)		**6-II** (2*S*,3*R*/3*S*)	
	A	**B**	**C**	**D**
H_1	3.914 (*AB*X); ^2J = 12.1, ^3J = 3.7	3.710 (*AB*X) ^2J = 11.6, ^3J = 6.6	3.720 (*AB*X); ^2J = 10.6, ^3J = 5.2	3.800 (m)
$H_{1'}$	3.700 (*AB*X); ^2J = 12.1, ^3J = 5.4	3.450 (*AB*X) ^2J = 11.6, ^3J = 3.7	3.659 (*AB*X); ^2J = 10.6, ^3J = 6.2	3.680 (m)
H_2	3.07–3.03 (m)	3.07–3.03 (m)	3.150 (ddd); ^3J = 6.2, ^3J = 5.2, ^3J = 2.5	3.40–3.25 (m)
H_3	2.963 (td); ^3J = ^3J = 4.2, ^3J = 14.6	3.00–2.93 (m)	3.168 (ddd); ^3J = 7.7, ^3J = 6.5 ^3J = 2.5	3.40–3.25 (m)
H_4	2.840 (dd); ^2J = 14.7, ^3J = 4.6	3.00–2.93 (m)	2.870 (dd); ^2J = 14.3, ^3J = 7.7	2.898 (dd); ^2J = 13.6, ^3J = 6.8
$H_{4'}$	2.762 (dd); ^2J = 14.7, ^3J = 3.9	2.817 (dd); ^2J = 13.0, ^3J = 5.7	2.774 (dd); ^2J = 14.3, ^3J = 6.5	2.898 (dd); ^2J = 13.6, ^3J = 6.8
Me–Ar	2.432 (s)	2.422 (s)	2.419 (s)	2.410 (s)

[a] Chemical shifts are in ppm, and coupling constants in Hz. All spectra were recorded in $CDCl_3$ as solvent, using TMS as internal reference.

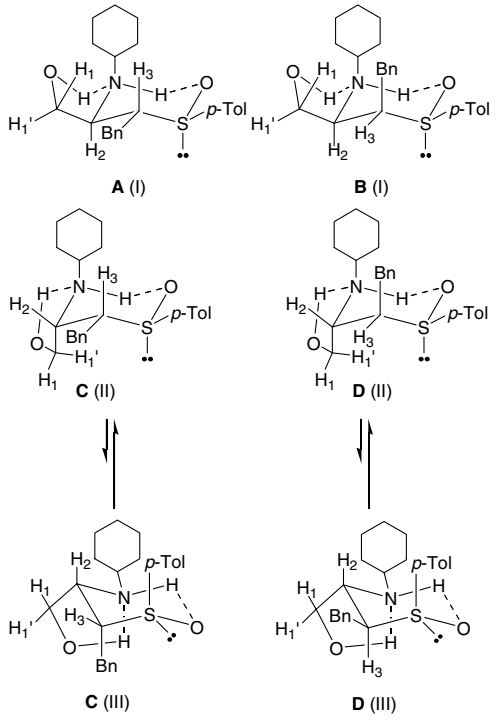


Figure 1. Tentative structures for **A**, **B**, **C** and **D** isomers proposed on the basis of spectroscopic data (^{1}H NMR).

The spectrum of fraction 2 is identical to that of the crude obtained in the reaction with DIBAL–H/$ZnCl_2$. This allows the identification of **A** and **B** as epimers at C_3, with an (*R*)-configuration for C_2. In the same way, isomers **C** and **D** must be epimers (2*S*,3*R*/3*S*) in this carbon. Both pairs of stereoisomers show very different spectroscopic behaviour for the chemical shifts of protons H_1 and $H_{1'}$ ($\Delta\delta\mathbf{A} = 107$ Hz, $\Delta\delta\mathbf{B} = 133$ Hz; $\Delta\delta\mathbf{C} = 30.5$ Hz; $\Delta\delta\mathbf{D} = 24$ Hz). On the other hand, the value of $^2J_{H2/H3}$ could only be measured in the spectra of fractions 2 and 3, for isomers **A** and **C**, respectively, $\{[^3J_{H2/H3}]^{\mathbf{A}} = 14.6$ Hz; $[^3J_{H2/H3}]^{\mathbf{C}} = 2.5$ Hz$\}$.

From a first evaluation, the extreme values of $^3J_{H2/H3}$ for **A** and **C** allows us to presume that in the conformation adopted by these isomers, H_2 and H_3 are in an antiperiplanar and synclinal stereoposition, respectively. A possible explanation for this behaviour lies in the presence of hydrogen bonding involving the basic centres in the molecule, giving rise to the corresponding pseudo-bicyclic structures for **A** and **C**, as shown in Figure 1.

As depicted, a *trans*-like configuration between the two cycles in **A** could account for the high value of $^3J_{H2,H3}$ as suggested by the restricted conformation **A**(I), and an (*R*)-configuration for C_3. This seems to be supported by the significant difference in the chemical shifts of H_1 and $H_{1'}$, indicative of a different steric shield. Since isomer **B** shows similar behaviour, an analogous *trans*-like configuration can be tentatively proposed, again compatible with an (*S*)-configuration for C_3 [**B**(I) in Figure 1].

On the other hand, a *cis*-like configuration of the pseudo-bicyclic structure can be considered to explain the opposite behaviour of isomer **C**. In this case, an equilibrium between conformations **C**(II) and **C**(III) would account for the low value of $^3J_{H2,H3}$; it is worthy of note that the relative stereoposition between the H_2 and H_3 nuclei is synclinal in both conformations. Also, the proposed equilibrium would explain the similarly averaged value for the chemical shifts of H_1 and $H_{1'}$. Thus, an (*R*)-configuration for C_3 is coherent with these data, and since **C** and **D** are epimers in C_3, an opposite (*S*)-configuration can be assumed for **D** according to the same model [**D**(II) and **D**(III); Figure 1].

Finally, transformation of compound **6-I** (fraction 2) to the cyclic carbamate **2** (Chart 1) allowed the regioselective elimination of *p*-toluenesulfenic acid induced by DBU. The *E* configuration of compound **3** was determined from the experimental value of the vicinal coupling constant ($^3J_{trans} = 15.6$ Hz).

3. Stereochemical outcomes of the 1a reduction

At this stage, it becomes necessary to comment on the key step of the synthesis of **3**, that is, the diastereoselective reduction of compound **1a**. Regarding data in Table 2, it is obvious that the different systems used as reduction reagents yielded different stereochemical outcomes. On the one hand, treatment of **1a** with the DIBAL–H/$ZnCl_2$ (entries 1–3) system yields **6-I** as a mixture of the two epimers in C_3 [(2*R*,3*R*/3*S*) and (2*R*,3*S*/3*R*)]. Two parallel reaction pathways $\mathbf{A}^{\ddagger}$ and $\mathbf{B}^{\ddagger}$ (Figure 2) would account for the observed stereochemical results. The attack directed to the *si* face of the imine is preferred, the reason being the sulfinyl group (*anti* attack vs *p*-Tol group) in the Zn-quelate complex, regardless of the configuration of the C_3 carbon.

On the other hand, the observed stereoselectivity with $LiEt_3BH$ is quite different. The major product in this case is stereoisomer **6-I** (2*R*,3*S*,R_S). It seems that a reagent both nucleophilic and basic, as the superhydride, could make the kinetic substrate similar to an aza-enolate.

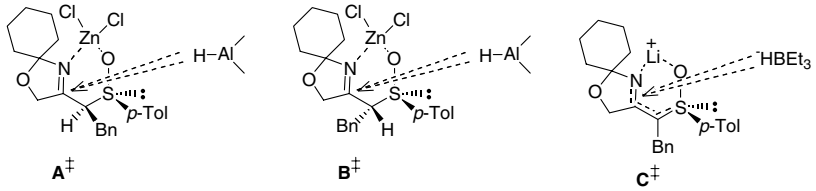


Figure 2. Proposed transition states in the diastereoselective reduction of **1a** with DIBAl–H/$ZnCl_2$ ($\mathbf{A}^{\ddagger}$ and $\mathbf{B}^{\ddagger}$) and $LiEt_3BH$ ($\mathbf{C}^{\gamma}$).

Thus, the *si* attack would be preferred owing to a chelating effect of Li^+ similar to that of zinc (vide infra), so that the (2*R*)-configuration in the product would be favoured (**C**‡; Fig. 2). Protonation of this product would then be doubly induced by the two stereocentres C_2^* and S* (Fig. 3), the attack of the electrophile (H^+) to the *re* face of the enolate yielding the diastereomer (2*R*,3*S*,R_S) as major product (e.d. 84%).

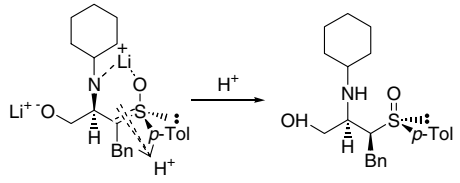


Figure 3. Diastereoselective control in the protonation of the product formed in the reduction of **1a** with $LiEt_3BH$.

Finally, the reduction of **1a** with $NaCNBH_3$ in AcOH/TFA shows little diastereoselectivity. This is probably due to protonation of the acetalic oxygen, which would prevent the formation of a cyclic transition state. A wider number of acyclic transition states would then be formed because the non-restricted rotation of the C_2–C_3 and C_3–S bonds, resulting in an averaged distribution of stereoisomers (Fig. 4).

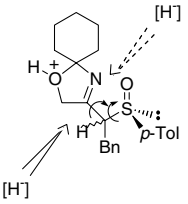


Figure 4. Open chain TS^{γ} in the stereochemical pathway of the reduction **1a** with $NaCNBH_3$ in AcOH/TFA.

4. Conclusion

The synthesis of **3** has been achieved with complete regio- and stereoselectivity in four steps with a 46% yield. This sequence could be of general use for the synthesis of other γ,δ-unsaturated amino alcohols. Taking into account that the synthesis of the starting product **1b** can be scaled-up to multigram amounts, this can lead to a useful strategy for the rapid generation of structurally related β,γ-unsaturated amino acid libraries in a controlled manner.

5. Experimental

5.1. General

The ^1H and ^{13}C NMR spectra were recorded at 200 or 500 MHz and 50 or 125 MHz, in a Bruker AC-200 or Bruker AM-500 spectrometer, respectively, using $CDCl_3$ for the chemical shifts, (δ) refers to TMS (^1H) or deuterated chloroform (^{13}C) signals. Coupling constants (*J*) are reported in hertz. Multiplicities in proton spectra are indicated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Elemental analyses were performed with a Perkin–Elmer 2400 C, H, N analyzer.

All reactions in non-aqueous media were carried out in flame-dried glassware under an argon atmosphere. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran (THF) was distilled from sodium and benzophenone, and dichloromethane from P_2O_5. In all other cases, commercially available reagent-grade solvents were employed without purification. Analytical TLC was routinely used to monitor reactions. Plates precoated with Merck silica gel 60 F_{254} of 0.25 mm thickness were used, and visualized with UV light or vainillin (acid solution in ethanol) or phosphomolibdic acid solution (PMA, 10% in ethanol). Flash column chromatography was carried out using Merck silica gel (grade 60, 230–240 mesh). Deactivated silica gel was performed by eluting with 2% aqueous solution of $NaHCO_3$/MeOH (5/95, v/v) until pH of the eluent was basic, and then passing through it dry acetone. Chemicals for the reactions were used as purchased from the Aldrich Chemical Co. The synthesis for starting compound (+)-**1b** has previously been described.

5.2. Benzylation of (+)-(R_S)-3-{[4-methyl(phenyl)sulfinyl]-methyl}-1-oxa-4-azaspiro[4.5]dec-3-ene, 1b

To a solution of 2 g of (+)-**1b** (6.86 mmol) in THF (9 mL) was added 5.57 mL of a 1.6 M solution of *n*-BuLi in hexane (8.92 mmol) at −50 °C. After stirring for 40 min, a solution of 2.35 g of benzyl bromide (13.72 mmol) in THF (4 mL) was added. The temperature was slowly raised to 22 °C and the reaction mixture left stirring for 12 h. Next, a saturated solution of NaCl (10 mL) and EtOAc (10 mL) were added and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue (3.5 g) was purified by flash chromatography on silica gel using hexane/EtOAc (2/1, 1/1, 1/2) as eluent. The unique fraction of **1a** (yield: 72%) was a mixture of enamine **A** and two diastereomeric imines **B** and **C** (**A**:**B**:**C** = 56:34:10).

5.2.1. (R_S)-3-{[4-methyl(phenyl)sulfinyl]-2-phenylethyl}-1-oxa-4-azaspiro[4.5]dec-3-ene, 1a. **A** Isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.30–1.71 (m, 10H, cyclohexyl), 2.392 (s, 3H, Me–Ar), 3.637, 3.796 (AB system, 2H, ^2J = 14.6 Hz, CH_2-S*), 4.378, 4.417 (AB system, 2H, ^2J = 15.0 Hz, CH_2O), 7.15–7.60 (m, 9H, Ar).

B Isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.30–1.71 (m, 10H, cyclohexyl), 2.408 (s, 3H, Me–Ar), 3.217 (dd, 1H, ^2J = 14.0 Hz, ^3J = 9.8 Hz, CH_2Ph), 3.412 (dd, 1H, ^2J = 14.0 Hz, ^3J = 6.6 Hz, CH_2Ph), 3.907 (dd, 1H, ^3J = 9.8, 6.6 Hz, H–C(SO)), 4.505 (s, 2H, CH_2O), 7.15–7.60 (m, 9H, Ar).

C Isomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.30–1.71 (m, 10H, cyclohexyl), 2.408 (s, 3H, Me–Ar), 3.305 (dd, 1H,

^{2}J = 13.1 Hz, ^{3J} = 11.95 Hz, CH_2Ph), 3.537 (dd, 1H, ^{2}J = 13.1 Hz, ^{3}J = 4.0 Hz, CH_2Ph), 3.739 (dd, 1H, ^{3}J = 11.95, 4.0 Hz, H–C(SO)), 4.865 (s, 2H, CH_2O), 7.15–7.60 (m, 9H, Ar).

^{13}C NMR (50.32 MHz, $CDCl_3$) δ 21.35, 21.50, 23.15, 23.20, 24.99, 25.02, 32.96, 34.15, 36.04, 36.11, 36.41, 36.50, 66.61 (B), 68.13 (A), 74.33 (A), 75.50 (B), 109.80 (B), 111.43 (A), 124.25, 125.32, 127.00, 127.10, 128.66, 128.71, 129.08, 129.10, 129.79, 129.93, 136.40, 136.81, 137.35, 138.49, 141.70 (A), 142.71 (B), 164.37 (A), 165.35 (B).

5.3. General procedure for DIBAL–H/$ZnCl_2$ reduction reactions

To a solution of **1a** (1 mmol) in THF (4 mL), a solution of $ZnCl_2$ (1.5 or 2 mmol) in THF (8 mL) at 0 °C was added under argon. After stirring for 1 h at 0 °C, the temperature was lowered to −78 °C and a 1.5 M solution of DIBAL–H in toluene (2 or 5 mmol) added dropwise. The reaction mixture was stirred for 0.5 h at −78 °C and then 15 h at rt. Then, 2 mL of MeOH were added and the mixture concentrated under reduced pressure. The residue was treated with NH_4Cl (saturated solution) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL) and the combined extracts washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR (500 MHz) and characterized as (R_S,2*R*,3*R*/3*S*)-2-(cyclohexylamine)-3-[(4-methylphenyl)sulfinyl]-4-phenylbutan-1-ol (mixture of epimers **A** and **B** in C_3; Tables 2 and 3).

5.4. $LiEt_3BH$ reduction

To a solution of 1 g of **1a** (2.622 mmol) in THF (4 mL) at 0 °C, a 1 M solution of $LiEt_3BH$ in THF (3.1 mL) was added under argon. The temperature was kept at 22 °C and after stirring for 2 h, a saturated aqueous solution of $NaHCO_3$ (6 mL) and 0.5 mL of H_2O_2 (30% vol) added. The reaction mixture was stirred for 15 min and then 10 mL of H_2O and 10 mL of EtOAc added. The aqueous phase was extracted with EtOAc (5 × 10 mL) and the combined extracts dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was analyzed by ^{1}H NMR (200 MHz) and characterized as (R_S,2*R*,3*R*/3*S*)-2-(cyclohexylamine)-3-[(4-methylphenyl)sulfinyl]-4-phenylbutan-1-ol (mixture of epimers) (conversion: 19%). The results are summarized in Tables 2 and 3.

5.5. $NaCNBH_3$–AcOH–TFA reduction

To a solution of 1 g of **1a** (2.622 mmol) in AcOH (4 mL) at 0 °C, 4 μL of TFA and 576.3 mg of $NaCNBH_3$ (9.26 mmol) were added under argon. After stirring for 12 h at 0 °C, a 3 M solution of NaOH was added dropwise until neutral pH. The reaction mixture was then extracted with DCM (3 × 10 mL) and the combined extracts washed with brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. The residue (929 mg) was analyzed by ^{1}H NMR and identified as a mixture of four stereoisomers **A**:**B**:**C**:**D** = 47:18.5:23.5:11. The crude product was purified by flash chromatography on silica gel using DCM/acetone: 1/1 as eluent (92% yield). Three fractions were obtained: fraction 1 (D: 41% and A: 59%), fraction 2 (A: 63% and B: 37%), and fraction 3 (C: 100%). The key spectroscopic data (^{1}H NMR, 500 MHz) are included in Table 3.

5.5.1. (R_S)-2-(Cyclohexylamine)-3-[(4-methylphenyl)sulfinyl]-4-phenylbutan-1-ol, 6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10–1.30 (m, 5H, cyclohexyl), 1.50–1.65 (m, 5H, cyclohexyl), 2.10–2.44 (m, 1H, C*H*-cyclohexyl), 2.30–2.40 (br s, 1H, NH), 2.41–2.43 (s, 3H, Me–Ar), 2.76–2.90 (part AB of a six spins system, 1H, CH_2Ph), 2.84–3.00 (part AB of a six spins system, 1H, CH_2Ph), 3.25–3.40 (ddd, 1H, H_2), 3.25–3.40 (ddd, 1H, H_3), 3.45–3.70 (part AB of a six spins system, 1H, H_1), 3.71–3.91 (part AB of a six spins system, 1H, $H_{1'}$), 6.86–7.05 (AA'XX' system, 2H, H_{ortho}–Me, Tol), 7.05–7.37 (m, 5H, Ph), 7.50–7.55 (AA'XX' system, 2H, H_{ortho}–SO, Tol). ^{13}C NMR (125 MHz, $CDCl_3$) 21.31–21.43 (Me), 24.68–33.71 (*C*H_2Ph, *C*H_2 cyclohexyl), 53.63–54.72 (C_3, *C*H cyclohexyl), 59.76–62.35 (*C*H_2O), 67.40–72.11 (C_2), 124.43–125.47 (C_{ortho}–SO, Tol), 126.37–126.79 (C_{para}, Ph), 128.55–129.94 (C_{ortho} and C_{meta}–Ph and C_{meta}–Tol), 137.82–142.07 (C_{ipso}).

5.6. *N*,*O*-protection of 6-I

To a solution of 202 mg of **6-I** [epimeric mixture at C_3, (A + B)] (0.525 mmol) in DCM (4 mL) at rt, 298 mg (0.772 mmol) of *N*,*N*-carbonyldiimidazol were added. The reaction mixture was stirred for 16 h and then concentrated under reduced pressure. The residue (214 mg) was purified by flash chromatography on silica gel using DCM/EtOAc = 8/1 as eluent, yielding 200 mg (0.486 mmol) of **2** (mixture of two epimeric compounds at C3) (92% yield) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98–1.82 (m, 10H, cyclohexyl), 2.42 (**A** isomer), 2.45 (**B** isomer) (s, 3H, Me–Ar), 2.83–3.43 (m, 3H, H_4, $H_{4'}$, C*H*-cyclohexyl), 3.43 (**A** isomer, dd, 1H, ^{2}J = 9.8 Hz, ^{3}J = 2.9 Hz, H_1), 3.793 (**B** isomer, dd, 1H, ^{2}J = 9.8 Hz, ^{3}J = 8.8 Hz, H_1), 4.014 (ddd, 1H, ^{3}J = 9.0, 3.4, 2.1 Hz, H_3), 4.272 (**A** isomer, dd, 1H, ^{2}J = 10.0 Hz, ^{3}J = 9.0 Hz, H1′), 4.559 (ddd, 1H, ^{3}J = 8.9, 3.0, 2.1 Hz, H_2), 4.636 (**B** isomer, dd, 1H, ^{2}J = 10.0 Hz, ^{3}J = 3.4 Hz, $H_{1'}$), 7.06–7.51 (m, 9H, Ar). ^{13}C NMR/DEPT (50 MHz, $CDCl_3$) δ **A** isomer: 21.28, 25.14, 25.53, 25.71, 29.31, 29.31, 29.93, 32.21, 51.34, 54.31, 64.24, 67.40, 123.85, 127.16, 128.98, 129.25, 130.04, 137.26, 138.52, 141.73, 157.91. **B** isomer: 21.40, 25.04, 25.74, 25.80, 27.68, 29.31, 31.31, 52.16, 54.99, 63.29, 66.44, 124.44, 126.88, 128.60, 128.81, 130.31, 136.14, 137.07, 142.53, 157.36. Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.04; H, 7.10; N, 3.40. Found: C, 70.12; H, 7.22; N, 3.01.

5.7. Base induced desulfinylation of 2

To a solution of 200 mg (0.486 mmol) of **2** in toluene (7 mL) were added 615 mg (4.04 mmol) of DBU. The reaction mixture was stirred at 70 °C during 4 days.

Next, a 20% solution of NH_4Cl (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted with DCM (3 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue (107 mg) was purified by flash chromatography on silica gel (hexane/EtOAc = 1/1). The product (93 mg, 70.5% yield) was isolated as a colourless oil and identified as **3**.

5.7.1. (+)-(4*S*)-3-Cyclohexyl-4-[(*E*)-2-phenylvinyl]-1,3-oxazolidin-2-one, 3. $[\alpha]_D^{25} = +110.6$ (*c* 2.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–1.51 (m, 10H, cyclohexyl), 3.570 (tt, 1H, $^3J_{ax,ax} = {}^3J_{ax,ax} = 11.7$ Hz, $^3J_{ax,ec} = 3.9$ Hz, C*H*-cyclohexyl), 3.976 (ddd, 1H, $^3J = 13.2$, 8.5, 6.3 Hz, C*H*–N), 4.434 (dd, 1H, $^2J = 8.3$ Hz, $^3J = 13.2$ Hz, CH_2O), 4.523 (dd, 1H, $^2J = 8.3$ Hz, $^3J = 6.3$ Hz, CH_2O), 6.100 (dd, 1H, $^3J_{trans} = 15.6$ Hz, $^3J = 8.5$ Hz, C*H*=CHPh), 6.601 (d, 1H. $^3J_{trans} = 15.6$ Hz, CH=C*H*Ph), 7.30–7.42 (m, 5H, Ph). ^{13}C NMR/DEPT (50 MHz, $CDCl_3$) δ 25.27, 25.76, 25.84, 30.06, 31.80, 54.13, 57.85, 67.36, 126.64, 127.99, 128.52, 128.80, 133.70, 135.51, 157,56. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.01; H, 7.95; N, 5.27.

5.8. Chemical sequence to establish the configuration of 3

5.8.1. $NaIO_4/RuCl_3$ oxidation of 3. To 90 mg (0.332 mmol) of **3**, CH_3CN (1.2 mL), CCl_4 (1.2 mL) and H_2O (1.9 mL) were added at rt. Next, 332 mg (1.36 mmol) of $NaIO_4$ and 1.5 mg (0.0007 mmol) of $RuCl_3 \cdot H_2O$ were added and the reaction mixture stirred at rt during 12 h. The mixture was then extracted with DCM (3 × 5 mL) and the combined extracts dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), and passed through a short pad of Celite. The solvent was concentrated and the crude product transformed without further purification in the ethyl ester.

To a solution of 70 mg of crude carboxylic acid in EtOH (3 mL) at 0 °C, 72 mg (0.6 mmol) of Cl_2SO was added dropwise. The reaction mixture was stirred for 12 h at room temperature. The solution was then concentrated under reduced pressure and the residue purified by flash chromatography on silica gel using DCM/EtOAc = 8/1 as eluent, obtaining 79 mg (0.329 mmol) of compound (−)-**5** (99% yield) as a colourless oil.

5.8.1.1. Ethyl (−)-(4*R*)-3-cyclohexyl-2-oxo-1,3-oxazolidin-4-carboxylate, (−)-5. $[\alpha]_D^{25} = -108.5$ (*c* 8.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.321 (t, 3H, $^3J = 7.1$ Hz, CH_3CH$_2$), 1.04–1.95 (m, 10H, cyclohexyl), 3.60–3.75 (m, 1H, H_9), 4.249 (dd, 1H, $^3J = 7.1$, 3.0 Hz, H_4), 4.260 (q, 2H, $^3J = 7.1$ Hz, CH_2CH$_3$), 4.336 (dd, 1H, $^2J = 8.65$ Hz, $^3J = 3.0$ Hz, H_5), 4.434 (dd, 1H, $^2J = 8.65$ Hz, $^3J = 7.1$ Hz, $H_{5'}$). ^{13}C NMR/DEPT (50 MHz, $CDCl_3$) δ 13.89 (Me ester), 25.11, 25.39, 25.47, 30.09, 30.58 (CH_2, cyclohexyl), 54.21, 55.68 (*C*H–N, *C*H-cyclohexyl), 61.95 (*C*H_2O ester), 65.02 (*C*H_2O), 157.13 (C_2), 171.05 (C_6). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.80; H, 7.87; N, 5.71.

5.8.2. Synthesis of ethyl (+)-(4*S*)-3-cyclohexyl-2-oxo-1,3-oxazolidine-4-carboxylate from ethyl L-serinate, (+)-5. To a solution of 300 mg (1.77 mmol) of L-serine. HCl in anhydrous MeOH (4 mL) at 0 °C were added 179.1 mg (1.77 mmol) of Et_3N and the mixture stirred at 0 °C for 10 min. The temperature was then raised to 22 °C and 0.183 mL (1.77 mmol) of cyclohexanone added. After stirring the reaction mixture for 2 h, the temperature was kept at 0 °C and 134 mg (3.54 mmol) of $NaBH_4$ added over 30 min. The temperature was raised to 22 °C and the reaction mixture stirred for 12 h. Next, 15 mL of a 20% solution of HCl and 15 mL of Et_2O were added and the aqueous phase extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue (273 mg) was identified as ethyl L-*N*-cyclohexylserinate, which was transformed without previous purification in the compound (+)-**5**.

5.8.2.1. Ethyl (4*S*)-3-cyclohexyl-2-oxo-1,3-oxazolidin-4-carboxylate, (+)-5. $[\alpha]_D^{25} = +110$ (*c* 3.7, $CHCl_3$). 157 mg were obtained (70% yield) from 198 mg of crude amino alcohol and carbonyldiimidazol under the conditions described in Section 5.6. Spectroscopic data were identical to those of compound (−)-**5** arising from **3**.

The enantiomeric excesses of the samples were confirmed from LIS experiment with (+)-Eu(hfc)$_3$.

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