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Diastereoselective synthesis of 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones. A new approach to methyl L-(2*S*,4*S*)-4-methyl-6-oxopipecolate

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Abstract—The sulfoxide-mediated diastereoselective Michael reaction of homochiral α-sulfinylketimines **1a–d** and β-substituted ene esters **2a–d** (Hua's reaction) was explored. Straightforward cyclization of the open-chain adducts take place under the reaction conditions to provide the 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones **3** and **7–12**, whose stereochemistry is formed in the prior step. Furthermore, the role of the metal ion of the aza-enolate reagents and the steric demands of the *O*-alkyl ester group have been examined. It seems that the *anti*-diastereoselectivity depends on metal chelation by the oxygen of the ester as well as the oxygen of the sulfinyl group and the nitrogen in the aza-enolate ((*Z*)-configuration). In addition, the synthesis of methyl L-(2*S*,4*S*)-4-methyl-6-oxopipecolate has been achieved from the suitably functionalized 2-sulfinylketimine **1a** (five steps; overall yield: 53–65%).

1. Introduction

Chiral piperidines are found in many naturally occurring and biologically important compounds, and methods for their asymmetric synthesis have been recently reviewed.[1,2] In particular, pipecolic acid ((*S*)-2-piperidincarboxylic acid), the next high homolog of proline, has attracted considerable attention. Substitution of the six-membered ring by any side chain moiety found in natural amino acids yields a constrained chimeric amino acid. By holding the side chains and the backbone in a limited number of conformations, analogs of biologically active peptides containing this unusual amino acid can provide valuable insights into the conformational requirements of ligand binding.[3] Thus, the incorporation of carefully designed pipecolic acid analogs as building blocks in peptides at appropriate positions can trigger the formation of turns while retaining the side chain functionality for important molecular recognition.

Recently, procedures for easy transformations of 6-oxopipecolic acid through the lactam enolate and further ring functionalization have been described.[4,5] This compound has been previously obtained in enantiopure form from α-aminoadipic acid[6] but the expense of this starting material precludes this route. More recently, several alternative methods for the preparation of 6-oxopipecolic acid derivatives have been reported.[7–16]

In a preliminary communication, we noticed the application of the Hua methodology[17] for the synthesis of chiral non- racemic 4-substituted 5,6-dehydropiperidin-2-one **3**, which is easily converted into interesting 6-oxopipecolic acid and piperidine derivatives.[18] This methodology provides the required lactam **3** in good yield and high diastereoselectivity through Michael addition of the azaenolate arising from **1a** at the ene ester **2a** followed by a transenolization of the adduct and subsequent cyclization (Scheme 1).

In order to form the 6-oxopipecolic acid derivative **5α**, the lactam **3α** (major diastereomer) was transformed into **4α** by reduction of the vinyl sulfoxide moiety with Raney Nickel W-2 in refluxing ethanol. In this way, the removal of the sulfinyl group and the generation of the new stereogenic center at C(8a) (indolizine numeration) in **4α** was achieved (Scheme 2). Finally, deprotection of

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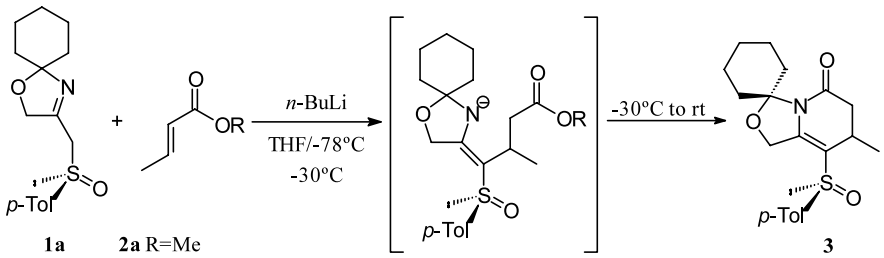
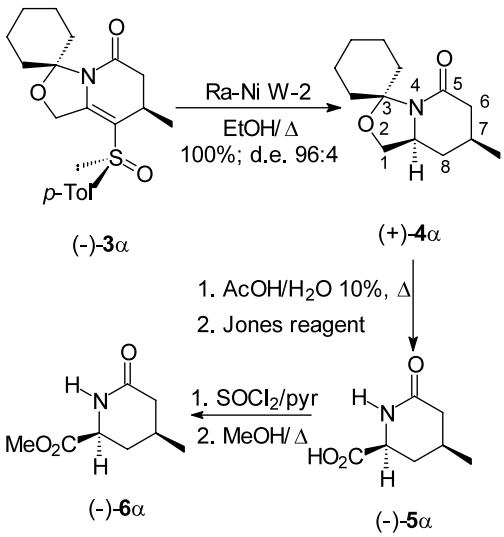


Scheme 1.



Scheme 2.

the cyclohexylidene acetal of the diastereomerically pure derivative (+)-**4α** and subsequent oxidation of hydroxymethyl group afforded L-(2*S*,4*S*)-4-methyl-6-oxopipecolic acid (−)-**5α** in four steps, the overall yield of the synthesis (22%) being limited by the last two steps.

We have now improved the overall yield for the synthesis of (−)-**5α** and these results together with the derivatization of (−)-**5α** to (−)-**6α** are reported herein. Furthermore, the synthesis of six new diastereomerically pure 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones **7**–**12** (Table 1) is described in order to establish the scope and limitations of this methodology.

2. Results and discussion

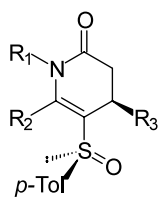
2.1. Preparation of α-sulfinylketimines 1a–d

The methods used for the synthesis of enantiomerically pure α-sulfinylketimines **1a**–**d** as well as the experimental results are shown in Table 2. Because there is not a general method for the preparation of α-sulfinylketimines,[19] it was necessary to use two different synthetic approaches. The first (method A) involves the reaction of the azaenolate derived from a ketimine with (−)-menthyl (S_S)-*p*-toluenesulfinate.[17a,20] Although this method allows an easy access to α-sulfinylketimines, partial epimerization of the sulfinyl group has been observed in some cases.[20a]

Method B requires the previous preparation of a β-ketosulfoxide (by reaction of methyl (+)-*p*-tolylsulfoxide with esters or other acid derivatives) and subsequent reaction of this with an amine.[21] Thus, the configuration of the initial β-ketosulfoxide is entirely preserved in the derived α-sulfinylketimine.

Compound **1a** has been prepared previously[22] from 2,2-pentamethylene-4-methyl-2,5-dihydrooxazol and (−)-menthyl (S_S)-*p*-toluenesulfinate (method A); the product was obtained in similar yield and had identical specific rotation to that reported. In the same way, compound **1b** was prepared from (1-phenylethylidene) *p*-methoxyphenyl azane and (−)-menthyl (S_S)-*p*-toluenesulfinate. Quantitative inversion of the configuration at the sulfinyl group was experimentally established from the observed optical rotation for a sample of the

Table 1. Diastereomerically pure 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones **3α** and **7α**–**12α**



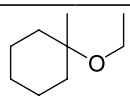
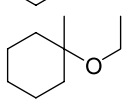
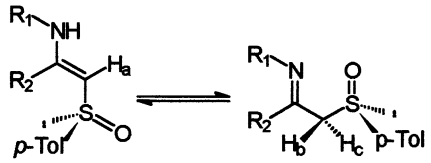
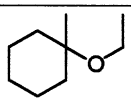
Compound	R_1	R_2	R_3
3α			Me
7α			Ph
8α	PMP	Ph	Me
9α	PMP	Ph	Ph
10α	$PhCH_2$	H	Me
11α	$PhCH_2$	*n*-Pr	Me
12α	$PhCH_2$	*n*-Pr	Ph

Table 2. Enantioselective synthesis and predominant tautomeric form of α-sulfinylketimines **1a–d**



enamine **1a-d** imine

Compound	R_1	R_2	Method	Yield (%)[a]	$[\alpha]^{23}_D$	Tautomeric form	δ_{Ha}	δ_{Hb}	δ_{Hc}
1a			A	84	+172[b]	imine	--	3.80[c]	3.80[c]
1b	PMP	Ph	A	87	-161.8[d]	imine	--	4.10	4.40
1c	$PhCH_2$	H	B	73[e]	--	enamine	4.83	--	--
1d	$PhCH_2$	*n*-Pr	B	90	-50[f]	enamine	4.94	--	--

[a]Overall yield in isolated product. [b](c 0.34, EtOH). [c]Observed as an A_2 system. [d](c 1.0, $CHCl_3$). [e]Estimated value from the ^1H NMR spectrum of the reaction mixture. [f](c 1.0, CH_2Cl_2).

β-ketosulfoxide derived by hydrolysis of **1b** (HCl/H_2O). The observed value was concordant with that reported for the same compound obtained by an independent process.[23]

Compound **1c** was obtained by reaction of the benzylamine and the mesyl derivative of (*R*)-α-sulfinylacetaldehyde, which was prepared following the reported procedure for the (*S*)-enantiomer.[24] Because compound **1c** was found to be unstable in solution, it was quickly used without purification.

Compound **1d** was prepared from (*R*)-1-*p*-tolylsulfinyl-2-pentanone and benzylamine (method B) following the procedure described in the literature.[21a]

The ^1H NMR spectra (in $CDCl_3$) of the compounds **1a–d** pointed out that they are present in solution as a single tautomeric form (imine or enamine; Table 2), although slow equilibration between compounds **1a** and **1d** was observed.

2.2. Synthesis of 4-methyl-6-oxopipecolic acid, 5α and its methyl ester 6α

The synthesis of **5α** was accomplished from **3α** as outlined in Scheme 2. Compound **3** was successfully prepared as a mixture of α and β epimers at carbon C(4) from the reaction of α-sulfinylketimine **1a** and (*E*)-methyl crotonate (Scheme 1). The best result was obtained by addition of *n*-BuLi (1.5 equiv.) to **1a** at −78°C, and then allowing the temperature to raise to −30°C before the unsaturated ester was added. Next, the reaction mixture was allowed to reach room temperature and stirred for 12–16 h in an attempt to drive cyclization to the lactam **3** to completion. The diastereoselectivity was moderate (**3α**:**3β** = 66:34) but the lactams formed in good yields (92%). The diastereomeric lactams **3α** and **3β** were easily separated by flash chromatography on silica gel (hexanes/ethyl acetate: 1/1, v/v) and then reduced with freshly prepared Raney Nickel W-2 (5 equiv.) in refluxing ethanol over 30 min to give **4α** and **4β**, respectively, in quantitative yield. The ^1H NMR spectra (300 MHz) of **4α** and **4β** were identical, although the determination of their optical rotation revealed the enantiomeric relationship of these isomers (a lanthanide induced shift study with (+)-$Eu(hfc)_3$ showed the diastereomeric purity of them). It occurs because the chiral sulfinyl group is removed prior to reduction of the ene function and so, the actual precursors of lactams **4α** and **4β** must also be enantiomers. Thus, the C(7) stereogenic center is the inductive center, its chirality being transferred from the sulfinyl group in **3** (vide infra). Desulfinylated derivatives could be detected by using not freshly prepared Ra–Ni or by decreasing of the number of equivalents of this metal reagent.

A unique reaction path for the hydrogenation of the carbon–carbon double bond (*anti* with regard to the methyl group of C(7) could be established from the relative configuration of carbons C(7) and C(8a). It was suitably tested by differential NOESY experiments through irradiations of hydrogens C(7)H and C(8a)H in **4α** (Fig. 1), which was evaluated as 5% to account for the 1,3-diaxial arrangement. The absolute configuration of **4α** and **4β** could be established from that of their precursors **3α** and **3β**, respectively, which are closely related with the compounds **13α** and **13β** whose absolute configuration was unequivocally established from their diffractometric X-ray data (Fig. 2).[17b] In fact, the ^1H NMR spectra of the isomers **13α** and **13β** show remarkable differences in the chemical shifts of the methyl group attached to the carbon C(4) that are identical to those observed for the isomers **3α** and **3β** (Fig. 2). So, the absolute configurations of **4α** and **4β** are (7*S*,8a*S*) and (7*R*,8a*R*), respectively.[25]

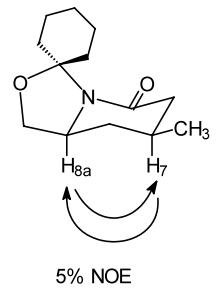
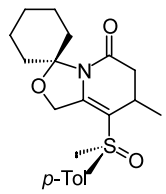
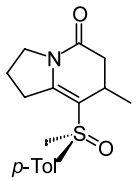


Figure 1. Differential observed NOEs on the compound (+)-**4α**.



3

(S_S,7R) **3**α: δ_{Me}=0.36 ppm
(S_S,7S) **3**β: δ_{Me}=1.21 ppm



13

(S_S,7R) **13**α: δ_{Me}=0.35 ppm
(S_S,7S) **13**β: δ_{Me}=1.21 ppm

Figure 2. Significant ^{1}H NMR data for compounds **3** and **13**.

Next, we attempted the hydrolysis of the *N*,*O*-acetal moiety in **4α** but it was not a trivial process because all usual methods[26] (AcOH/TFA/rt; AlI_3 and H_2SO_4/CH_3CN) were unsuccessful. Finally, use of AcOH/H_2O mixture (10/90: v/v) at reflux over 12 h afforded the alcohol in high yield (98%). The reaction mixture was directly treated with the Jones reagent to give the carboxylic acid, which was used without purification for the subsequent transformation. Methyl ester **6α** was performed from the acid chloride ($SOCl_2$) and methanol in 87% yield from **4α**, and its optical rotation ($[\alpha]_D^{23}$ −20.7 (*c* 4.5, $CHCl_3$) was determined on an analytical sample obtained by flash chromatography (ethyl acetate). ^{1}H NMR chiral shift experiments with (+)-Eu(hfc)$_3$ confirmed that no racemization occurs during the synthesis (e.e. ≥97%).

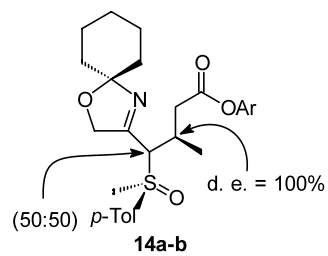
2.3. Synthesis of 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones

Our previous results on the reactivity of the α-sulfinylketimine **1a** with several Michael acceptors[18] prompted us to apply this method for synthesizing chiral non-racemic 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydro-piperidin-2-ones. The stereochemistry of this process can depend on either kinetic or thermodynamic control of the Michael addition, or the kinetic resolution of the open chain adducts in the cyclization step.

In order to answer this preliminary question, 4-methoxy-2,6-di-*tert*-butylphenyl crotonate (Seebach ester)[27] was prepared and reacted with the α-sulfinylketimine **1a** under the standard conditions. It was thought that because of the greater bulk of the ester, a decrease in the rate of cyclization would occur and the retro-Michael reaction could then become a competitive process. The reaction was monitored by TLC between 0 and 23°C to notice an increase in the conversion and none evolution of the former products (two spots). In fact, ^{1}H NMR analysis (300 MHz) of the different reaction mixtures proved the progressive disappearance of **1a** (up to 57%) and its evolution to two open chain adducts **14a** and **14b**, which were found to be epimeric at the carbon attached to the sulfinyl group (50:50) (Fig. 3). This is in accordance with kinetic control in the formation of the C(7) stereogenic center (d.e. 100%), the stability of the intermediates aza-enolate being the driving force for this process. Both epimers were isolated by flash chromatography and treatment of each one with NaMeO/MeOH at 25°C gave rise to mixtures with identical composition (50:50) to the original one. This showed the enolizable nature of the adducts and their stability, as the products remained unchanged after 6 days under the indicated reaction conditions.

In order to accomplish the synthesis of 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones with complete or high diastereoselectivity and good yields, in a one-pot procedure, isopropyl and methyl crotonates and cinnamates were selected. Presumably, similar stereochemical results to that observed for the Seebach ester would be obtained with *iso*-propyl esters and, furthermore, easier cyclization should be expected in soft conditions, which are compatible with the kinetic control of the reaction.

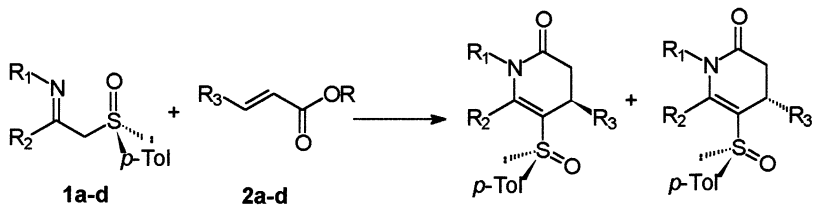
The α-sulfinylketimines **1b**–**d** were also put into reaction with the aim of evaluate the generalization of the process. The obtained results are summarized in Table 3.

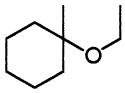
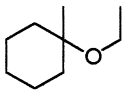
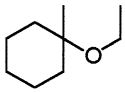
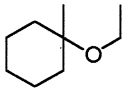


14a-b

Figure 3. Adducts **14a**–**b** obtained in the reaction of **1a** and 4-methoxy-2,6-di-*tert*-butylphenyl crotonate.

Table 3. Reaction of α-sulfinylketimines **1a–d** with (*E*)-ene esters **2a–d**[a]



Entry	1	2	R_1	R_2	R_3	R	Product	Yield[b] (conv.)	Diastereoselectivity α:β
1	**1a**	**2a**			Me	Me	**3**	92 (95)[c]	66:34
2	**1a**	**2b**			Me	*i*-Pr	**3**	70 (75)[c]	100:-
3	**1a**	**2c**			Ph	Me	**7**	58 (64)[c]	86:14
4	**1a**	**2d**			Ph	*i*-Pr	**7**	33 (77)[d,e]	100:-
5	**1b**	**2a**	PMP	Ph	Me	Me	**8**	58 (60)[c]	80:20
6	**1b**	**2b**	PMP	Ph	Me	*i*-Pr	**8**	46 (50)[c]	100:-
7	**1b**	**2d**	PMP	Ph	Ph	*i*-Pr	**9**	68 (84)[d,e]	100:-
8	**1c**	**2a**	CH_2Ph	H	Me	Me	**10**	40 (46)[c]	86:14
9	**1c**	**2b**	CH_2Ph	H	Me	*i*-Pr	**10**	69 (75)[c]	100:-
10	**1d**	**2b**	CH_2Ph	*n*-Pr	Me	Me	**11**	62 (68)[c]	88:12
11	**1d**	**2b**	CH_2Ph	*n*-Pr	Me	*i*-Pr	**11**	50 (52)[c]	100:-
12	**1d**	**2d**	CH_2Ph	*n*-Pr	Ph	*i*-Pr	**12**	36 (54)[d,e]	100:-

[a]The best results were obtained by lithiation (*n*-BuLi, 1.2 equiv.) of **1** in THF at –78°C followed by addition of the ene ester (2 equiv.) at –30°C and then allowing the reaction mixture to reach the rt. and standing with stirring for 12 to 16 h. [b]Isolated products. [c]No traces of open chain adducts could be observed within the detection limits of ^{1}H NMR (200 MHz). [d]The open chain adducts (diastereomeric excess 100% in the carbon bearing R^3) were detected from ^{1}H NMR analysis of the reaction mixture. [e]The yield was increased between 7-15% (isolated product) by allowing the reaction mixture to remain at rt for 24 h.

Some considerations can be made from the data included in Table 3. Firstly, the diastereoselectivity is entirely dependent on the nature of the *O*-alkyl group in the ester (d.e. = 100%, R = *i*-Pr; entries 2, 4, 6, 7, 9, 11 and 12) just as was hoped from the results concerning to the reaction of **1a** and the Seebach ester. Secondly, the cyclization is incomplete for R^3 = Ph and R = *i*-Pr (Table 3; entries 4, 7 and 12) although the yield in lactam was improved by increasing the reaction time at rt (between 16 and 24 h), the stereoselectivity going to be unchanged, cf. the degree that the yield was modified. These results indicate that the open chain adducts, detected by ^{1}H NMR analysis of the reaction mixtures, also have the α-configuration at the carbon bearing the group R^3.

In all cases, the α-configuration of the major lactam was established on the basis of the identical stereochemical behavior of the α-sulfinylketimines with regard to the preparation of lactams **3α** and **3β** (vide supra).

2.4. Stereochemical pathway of the Michael reaction

The present reactions proceed through the nucleophilic addition of the aza-enolates derived from the α-sulfinylketimines to (*E*)-ene esters. It can be supposed that the α-sulfinylketimines form predominantly lithium (*Z*)-enolates by treatment with *n*-BuLi or LDA.[28] On this basis, and assuming an *s-cis*-conformation for the C(1)–C(2) bond of the ester, two approaches can be taken into account, both supported in a chelated model involving the three coordinative centers in the activated complex (Fig. 4). In this way, the *anti*- and *syn*-adducts are, respectively, formed from an *re-re* (transition state $A^‡$) and an *re-si* attack (transition state $B^‡$), the *re* facial selectivity of the (*Z*)-enolate being mediated by the sulfinyl group (*trans* to the *p*-tolyl group). Thus, it

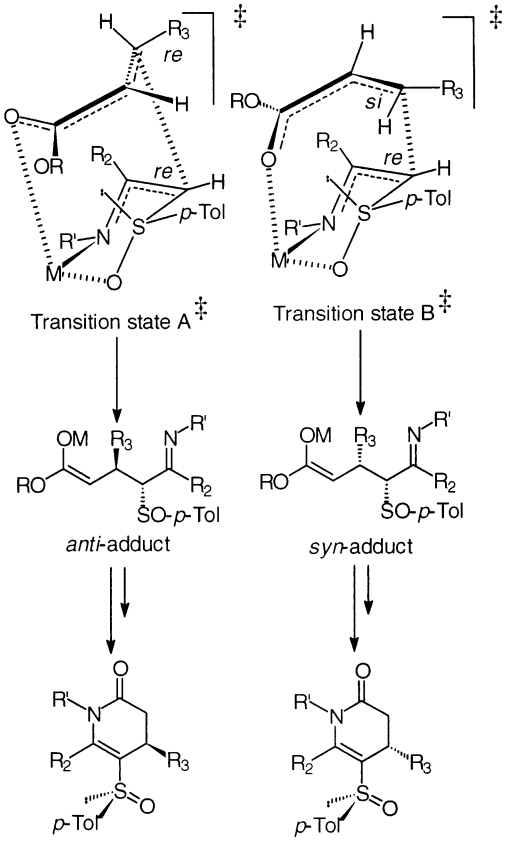


Figure 4. Proposed transition states for the reaction of α-sulfinylketimines **1a**–**d** with (*E*)-ene esters **2a**–**d**.

seems that the TS A‡ would be sterically more favored than the TS B‡ regardless of the nature of groups R^1 and R^2, since the interactions of these groups with the OR moiety of the ester are more strongly developed in the TS B‡ than TS A‡. Consequently, *anti*-selectivity becomes favorable and the sole formation of the lactam from the *anti*-adduct occurs for the bulkiest R group (*i*-Pr>Me).

Since the sulfoxide-based diastereoselectivity depends on the *Z*-configuration of the aza-enolates, it being mediated through the chelation of metal by the nitrogen and oxygen atoms, we think that a modification in the metal counter-ion nature could enhance the *anti*-selectivity if the covalent character of the coordinative bonds is increased. On the contrary, the *syn*-selectivity could be favored either by increasing of the ionic character of these coordinative bonds or by improving a saturated coordinative species in the metal.

Thus, the aza-enolates derived from **1a** with *iso*-propyl magnesium chloride and potassium *tert*-butoxide, and the Ti(IV) ate-complex arising from the lithium aza-enolate and Ti(i-PrO)$_4$[29] were reacted under standard conditions with methyl crotonate. The obtained results have been summarized in Table 4.

As can be seen, the stereochemical results are in accordance with our previous hypotheses. Thus, a meaningful increase in the *anti*-selectivity is observed (Table 4, entry 2) for the most covalent magnesium enolate,[28] whereas a decrease occurs for the most ionic potassium derivative (Table 4, entry 3). Furthermore, the *syn*-selectivity became the most important reaction pathway for the Ti(IV) ate-complex species[29] owing to its saturated coordinative character which precludes chelation with the nitrogen atom (Table 4, entry 4).

3. Conclusions

The base-mediated reaction of the enantiomerically pure α-sulfinylketimines with (*E*)-ene esters is a useful method for the diastereoselective synthesis of enantiomerically pure 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones. The observed *anti*-selectivity depends on the chirality of the sulfoxide, the nature of the metal counter-ion and the steric demand of the *O*-alkyl group of the ene ester. The use of *iso*-propyl ene esters and lithium aza-enolates allowed to obtain a sole diastereomer. In addition, chirality transfer from the sulfinyl group at the 4- and 2-position of the ring was observed in the synthesis of methyl L-(2*S*,4*S*)-4-methyl-6-oxopipecolate.

4. Experimental

4.1. Methods and materials

Melting points were determined in a Gallemkamp apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Perkin–Elmer 781 IR Spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 200 or 300, and 50 or 75 MHz, in a Bruker AC-200 or Bruker AM-300 spectrometer, respectively, using $CDCl_3$, and the chemical shifts (δ) refer to TMS (^{1}H) 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), m (multiplet) and bs (broad singlet). Elemental analyses were performed with a Perkin–Elmer 2400 C,H,N analyzer.

Table 4. Reaction of the aza-enolate derived from **1a** and (*E*)-methyl crotonate[a,b]

Entry	Base	Diastereoselectivity α:β	Yield (%)
1	*n*-BuLi	2:1	92
2	*i*-PrMgCl	15:1	43
3	*t*-BuOK	1:1	66
4	*n*-BuLi/Ti(*i*-PrO)$_4$	1:4	20

[a] The result obtained with the lithium aza-enolate (entry 1) is also included for comparison.

[b] Formation of the aza-enolate was carried out between −78 and −40°C over 15 min. Next, the ester addition was accomplished at −78°C, the temperature was then allowed to increase slowly to 20°C and the reaction mixture was stirred at this temperature for 12 h.

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, dimethylformamide (DMF) from calcium hydride and dichloromethane (DCM) 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, with UV light, either anisaldehyde:sulfuric acid:ethanol (2:1:100) or 7% ethanolic phosphomolybdic acid-heat as developing agents. Merck silica gel 60 (230–400 ASTM mesh) was employed for column chromatography. Deactivated silica gel was performed by eluting with 2% aqueous solution of $NaHCO_3$/MeOH (5/95, v/v) until the pH of the eluent was basic, and then passing through it dry acetone. Chemicals for reactions were used as purchased from the Aldrich Chemical Co. 4-Methyl-2,2-pentamethylene-2,5-dihydrooxazol,[22] (4-methoxyphenyl) 1-phenylethyliden azane,[30] (*R*)-(*E*)-2-(*p*-tolylsulfinyl)vinyl methanesulfonate[24] and (+)-(*R*)-(1-p-tolylsulfinyl)-2-pentanone[21a,30] were accomplished following the reported procedures, their spectroscopic and analytical data being in accordance with those described in the literature. (−)-Menthyl *p*-toluenesulfinate was prepared using Posner's procedure.[28a,31] 4-Methoxy-2,6-di-*tert*-butylphenyl crotonate was obtained following the Seebach procedure.[27,32]

4.2. Synthesis of α-sulfinyl ketimines 1a and 1b. Typical procedure

n-Buthyl lithium (12.72 mL, 1.6 M in hexane, 20.4 mmol) was added dropwise at −40°C to a stirred solution of diisopropylamine (2.85 mL, 20.4 mmol) in dry THF (40 mL). The mixture was stirred at −10°C for 30 min, cooled at −40°C, and the imine (13.0 mmol) in THF (20 mL) was added dropwise over ca. 45 min. The mixture was stirred at −10°C for 60 min, cooled at −78°C and a solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (3.04 g, 10.3 mmol) in THF (25 mL) was slowly added. After stirring at −78°C for 2 h, the reaction mixture was quenched with a few drops of methanol. The mixture was brought to rt and the solvents evaporated off under reduced pressure at rt. The residue was dissolved in DCM, the organic phase was washed with brine, separated off and dried over dry $MgSO_4$. The solvent was removed at reduced pressure and the residue was purified by flash chromatography.

4.2.1. (*R*)-2,2-Pentamethylene-4-(*p*-tolylsulfinyl)methyl-2,5-dihydrooxazol 1a.[22] From 4-methyl-2,2-pentamethylene-2,5-dihydrooxazol: R_f 0.2 (hexane/ethyl acetate: 2/1, v/v). 86% yield. Yellow oil. $[\alpha]_D^{23}$ +170 (*c* 0.34, EtOH). IR ($CHCl_3$) 1720, 1090 cm^{-1}. ^1H NMR (200 MHz) δ 1.30–1.70 (m, 10H, cyclohexyl), 2.417 (s, 3H, Me), 3.837 (s, 2H, CH_2-S*), 4.456, 4.521 (AB, 2H, $^2J=14.9$, CH_2O), 7.343 (d, 2H, $^3J=8.1$, H_{ortho}), 7.523 (d, 2H, $^3J=8.1$, H_{ortho}). ^{13}C NMR (50 MHz) δ 21.41, 23.21, 25.03, 36.35, 36.43, 57.02, 75.38, 97.40, 110.75, 124.24, 130.01, 139.05, 142.14, 161.62. Anal. calcd for $C_{16}H_{21}NO_2S$%: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.68; H, 7.12; N, 4.75.

4.2.2. (*R*)-[1-Phenyl-2-*p*-tolylsulfinyl](4-methoxyphenyl) ethylidene azane 1b. From (4-methoxyphenyl) 1-phenylethylidene azane: R_f 0.6 (hexane/ethyl acetate: 3/1, v/v). 87% yield. White solid: Mp 77°C (hexane). $[\alpha]_D^{23}$ −161.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 1360, 1050 cm^{-1}. ^1H NMR (200 MHz) δ 2.390 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.40, 4.10 (AB, 2H, $^2J=12.6$, CH_2-S*), 6.55 (dd, 2H, $J=8.8$, 1.5, H-PMP), 6.84 (dd, 2H, $J=7.2$, 1.5, H-PMP), 7.23 (m, 4H, H-Tol), 7.48 (m, 3H, Ph), 7.95 (dd, 2H, $J=7.9$, 1.7 Ph). Anal. calcd for $C_{22}H_{21}NO_2S$%: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.61; H, 5.72; N, 3.95.

4.3. Synthesis of (*R*)-(*E*)-*N*-benzyl-[2-(*p*-tolylsulfinyl) vinyl]amine 1c

To (*R*)-(*E*)-2-(*p*-tolylsulfinyl)vinyl methanesulfonate[24] (2.15 g, 8.8 mmol) in dry DMF (40 mL) was added benzylamine (3.5 mL, 30.6 mmol) and the mixture was stirred at rt for 12 h. Water (20 mL) was added and the aqueous phase was extracted with EtAcO (4×20 mL). The combined organic layers were washed with HCl soln (2%) (4×5 mL), dried over $MgSO_4$ and concentrated at reduced pressure. The residue (1.7 g) was unstable and had to be used directly, without purification. Best yield: 73%. IR (film) 1090, 1650 cm^{-1}. ^1H NMR (200 MHz) δ 2.430 (s, 3H, Me), 4.272, 4.301 (AB, 2H, $^2J=14.0$, CH_2Ph), 5.101 (d, 1H, $J=12.1$, =CHS), 7.15–7.45 (m, 8H, Ar, =CH(N)), 7.50 (d, 2H, $J=8.6$, H_{ortho}).

4.4. Synthesis of (*R*)-(*E*)-*N*-benzyl-(1-*p*-tolylsulfinyl)-2-pentenylamine 1d

To a solution of (+)-(*R*)-(1-*p*-tolylsulfinyl)-2-pentanone[21a,30] (1.0 g, 4.4 mmol) in dry benzene (20 mL) were added 3 Å molecular sieves (1.5 g) and benzylamine (0.73 mL, 6.6 mmol). The mixture reaction was stirred at rt for 48 h then filtered through a thigh pad of Celite and the filtrate was concentrated at reduced pressure at rt. The residue was purified by flash chromatography on silica gel (hexane/EtOAc: 4/1, v/v). The isolated product (1.2 g, 3.8 mmol) was obtained as a white solid. 86% yield. Mp 112–113°C (hexane–acetone). $[\alpha]_D$ −50.3 (*c* 1.0, CH_2Cl_2). $[\alpha]_D^{23}$ −50 (*c* 1.0, CH_2Cl_2).[21a,33] ^1H NMR (200 MHz) δ 0.967 (t, 3H, $^3J=7.0$, Me), 1.440–1.810 (m, 2H, CH_2-CH_3), 2.317 (s, 3H, Me-Ar), 2.472 (ddd, 1H, $^3J=9.0$, 6.1, $^2J=14.0$, CH_2-Et), 2.692 (ddd, 1H, $^2J=14.0$, $^3J=8.9$, 7.0, CH_2-Et), 3.982 (dd, 1H, $^2J=13.5$, $^3J=4.6$, CH_2Ph), 4.097 (dd, 1H, $^2J=13.5$, $^3J=4.6$, CH_2Ph), 4.253 (t, 1H, $^3J=$

4.6, NH), 4.940 (s, 1H, H-C=), 7.1–7.5 (m, 9H, Ar). Anal. calcd for $C_{19}H_{23}NOS$%: C, 72.80; H, 7.40; N, 4.47. Found: C, 72.76; H, 7.28; N, 4.43.

4.5. Synthesis of 4,6-disubstituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones, 3 and 7–12. General procedure

To a cold (−78°C) solution of sulfinyl ketimine (0.9 mmol) in dry THF (20 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.67 mL, 1.07 mmol). The solution was stirred at −78°C for 0.5 h, the temperature was raised to −30°C and the ene ester (2 mmol, 0.15 M solution in THF) was added. The reaction mixture was kept to rt and was stirred for 12 h. The mixture was diluted with H_2O (1 mL) and saturated aqueous NH_4Cl solution (10 mL) and extracted with EtAcO (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated at reduced pressure and chromatographed. Diastereomeric ratio and conversion were determined from analysis (^{1}H NMR) of the reaction mixtures prior isolation. Yields are quoted as isolated products (Table 2).

4.5.1. (S_S,7*R*)-7-Methyl-3,3-pentamethylene-8-(*p*-tolylsulfinyl)-1,2,3,5,6,7-hexahydro-2-oxa-5-indolizinone 3α. R_f=0.26 (hexane/EtAcO: 1/1, v/v). Yellow solid. Mp 126–7°C. $[\alpha]_D^{23}$ −98.3 (*c* 0.54, $CHCl_3$). IR ($CHCl_3$) 1697, 1074 cm^{-1}. ^{1}H NMR (300 MHz) δ 0.418 (d, 3H, ^3J=7.1, CH_3-C7), 1.8–2.0 (m, 10H, cyclohexyl), 2.415 (s, 3H, Me-Ar), 2.289 (dd, 1H, ^2J=16.0, ^3J=2.3, H6), 2.676 (dd, 1H, ^2J=16.0 ^3J=6.6, H6′), 2.891 (dq, ^3J=2.6, 6.8, H7), 4.991 (s, 2H, CH_2O), 7.314 (d, 2H, ^3J=7.3, H_{ortho}-Tol), 7.513 (d, 2H, ^3J=7.3, H_{ortho}-Tol). ^{13}C NMR (75 MHz) δ 18.7, 21.4, 22.4, 22.9, 23.6, 24.3, 31.0, 33.9, 41.5, 64.9, 99.25, 115.2, 124.4, 127.9, 129.9, 138.7, 141.5, 142.6, 166.4. MS[34] (70 eV) 359 813), 342 (87), 311 (100), 296 (5), 268 (32), 91 (9), 77 (17), 65 (17). Anal. calcd for $C_{20}H_{25}NO_3S$%: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.73; H, 7.05; N, 3.97%.

4.5.2. (S_S,7*S*)-7-Methyl-3,3-pentamethylene-8-(*p*-tolylsulfinyl)-1,2,3,5,6,7-hexahydro-2-oxa-5-indolizinone 3β. R_f=0.47 (hexane/EtAcO: 1/1, v/v). Yellow solid. Mp 182–3°C. $[\alpha]_D^{23}$ +43.3 (*c* 0.21, $CHCl_3$). IR ($CHCl_3$) 1690, 1085 cm^{-1}. ^{1}H NMR (300 MHz) δ 1.21 (d, 3H, ^3J=7.1, Me-C7), 1.4–1.8 (m, 8H, cyclohexyl), 2.2–2.4 (m, 3H, cyclohexyl and H6), 2.42 (s, 3H, Me-Ar), 2.49 (m, 1H, H6′), 4.99 (s, 2H, CH_2O), 7.30 (d, 2H, ^3J=7.9, H_{ortho}-Tol), 7.43 (d, 2H, ^3J=8.2, H_{ortho}-Tol), ^{13}C NMR (75 MHz) δ 20.9, 21.0, 21.3, 22.7, 22.8, 24.2, 26.4, 31.3, 33.6, 41.2, 64.8, 99.2, 114.5, 124.1, 129.9, 137.2, 139.7, 140.9, 142.8, 165.9. MS[34] (70 eV) 421 (10), 404 (100), 373 (85), 330 (23), 91 (13), 77 (7), 65 (5). Anal. calcd for $C_{20}H_{25}NO_3S$%: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.85; H, 6.98; N, 3.93.

4.5.3. (S_S,7*S*)-3,3-Pentamethylene-7-phenyl-8-(*p*-tolylsulfinyl)-1,2,3,5,6,7-hexahydro-2-oxa-5-indolizinone 7α. R_f=0.13 (hexane/EtAcO on desactivated silica gel: 2/1, v/v). Isolated as a colourless oil. $[\alpha]_D^{23}$ +28.6 (*c* 0.35, $CHCl_3$). IR ($CHCl_3$) 1670, 1080 cm^{-1}. ^{1}H NMR (200 MHz) δ 1.55–1.83 (m, 8H, cyclohexyl), 2.181 (s, 3H, Me-Ar), 2.374 (ddd, 2H, ^3J=13.1, 5.0, cyclohexyl), 2.533 (dd, 1H ^2J=16.1, ^3J=1.7, H6), 3.006 (dd, 1H, ^2J=16.1, ^3J=8.2, H6′), 3.922 (dd, 1H, ^3J=8.1, 1.7, H7), 5.132 (dd, 1H, ^2J=13.9, ^5J=0.9, CH_2O), 5.180 (dd, 1H, ^2J=13.9, ^5J=0.9, CH_2O), 6.61–6.65 (m, 2H, Ar), 6.83–6.99 (m, 5H, Ar), 7.165 (d, 2H, 3J=8.1, H_{ortho}-Tol). ^{13}C NMR (50 MHz) δ 21.10, 22.77, 22.88, 24.30, 31.28, 33.82, 34.31, 42.16, 65.15, 99.57, 113.18, 124.41, 126.28, 126.34, 128.32, 129.12, 136.81, 140.99, 141.06, 144.66, 165.78. MS[34] (70 eV) 421 (10), 404 (100), 373 (85), 330 (23), 91 (13), 77 (7), 65 (5). Anal. calcd for $C_{25}H_{27}NO_3S$%: C, 71.23; H, 6.46; N, 3.32. Found: C, 71.37; H, 6.39; N, 3.30.

4.5.4. (S_S,7*R*)-3,3-Pentamethylene-7-phenyl-8-(*p*-tolylsulfinyl)-1,2,3,5,6,7-hexahydro-2-oxa-5-indolizinone 7β. R_f=0.18 (hexane/EtOAc: 2/1 on desactivated silica gel). ^{1}H NMR (200 MHz) δ 1.58–1.84 (m, 8H, cyclohexyl), 2.182 (s, 3H, Me-Ar), 2.38 (m, 2H, cyclohexyl), 2.44 (m, 1H, H6), 3.044 (dd, 1H, ^2J=15.0, ^3J=8.4, H6′), 3.92 (m, 1H, H7), 5.184, 5.140 (AB, 2H, ^2J=13.3, CH_2O), 6.63–6.68 (m, 2H, Ar), 6.85–7.02 (m, 5H, Ar), 7.168 (dd, 2H, $^3J_{ortho}$=8.0, H_{ortho}-Tol).

4.5.5. (S_S,4*R*)-1-(*p*-Methoxyphenyl)-4-methyl-6-phenyl-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-one 8α. R_f=0.2 (hexane/EtAcO: 1/3, v/v). Isolated as brown oil. $[\alpha]_D^{23}$ −161.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 1697, 1034 cm^{-1}. ^{1}H NMR (200 MHz) δ 0.605 (d, 3H, ^3J=7.1, Me-C4), 2.445 (s, 3H, Me-Ar), 2.619 (dd, 1H, ^2J=15.6, ^3J=1.8, H3), 3.074 (dd, 1H, ^2J=15.6, ^3J=5.9, H3′), 3.219 (ddq, 1H, ^3J=7.1, 5.9, 1.8, H4), 3.691 (s, 3H, OMe), 6.682 (d, 2H, ^3J=9.0, H_{ortho}-PMP), 6.862 (d, 2H, ^3J=9.0, H_{ortho}-PMP), 7.190 (m, 5H, Ph), 7.359 (d, 2H, ^3J=8.0, Ar), 7.628 (d, 2H, ^3J=8.0, Ar). ^{13}C NMR (50 MHz) δ 18.39, 21.38, 21.67, 40.75, 55.25, 113.94, 124.83, 127.94, 129.19, 129.72, 129.82, 130.32, 132.20, 138.57, 141.10, 147.79, 158.44, 170.02. MS[34] (70 eV) 431 (6), 414 (68), 383 (100), 368 (41), 340 (28), 210 (47), 77 (28). Anal. calcd for $C_{26}H_{25}NO_3S$%: C, 72.36; H, 5.84; N, 3.25. Found: C, 72.71; H, 5.99; N, 3.21.

4.5.6. (S_S,4*S*)-1-(*p*-Methoxyphenyl)-4-methyl-6-phenyl-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-one 8β. R_f=0.25 (hexane/EtAcO: 1/3, v/v). Non isolated. ^{1}H NMR (200 MHz) δ 1.444 (d, 3H, ^3J=7.1, Me-C4), 2.396 (s, 3H, Me-Ar), 2.475 (d, 2H, ^3J=4.0, H3), 2.788 (ddq, 1H, ^3J=7.1, 4.3, 3.5, H4), 3.688 (s, 3H, OMe), 6.53–6.87 (m, 2H, PMP), 6.82–6.91 (m, 2H, PMP), 7.23–7.49 (m, 9H, Ar).

4.5.7. (S_S,4*S*)-1-(*p*-Methoxyphenyl)-4,6-diphenyl-5-(p-tolyl-sulfinyl)-5,6-dehydropiperidin-2-one 9α. R_f=0.06 (hexane/EtAcO: 1/1, v/v). Isolated as white solid. Mp 185–7°C. $[\alpha]_D^{23}$ −470.6 (*c* 0.16, $CHCl_3$). IR ($CHCl_3$) 1706, 1082 cm^{-1}. ^{1}H NMR (200 MHz) δ 2.171 (s, 3H, Me-Ar), 2.917 (dd, 1H, ^2J=15.8, ^3J=1.7, H3), 3.388 (dd, 1H, ^2J=15.8, ^3J=7.4, H3′), 3.693 (s, 3H, OMe), 4.370 (dd, 1H, ^3J=1.7, 7.4, H4), 6.67–6.72 (m, 2H, Ar), 6.85–7.02 (m, 8H, Ar), 7.25–7.30 (m, 8H, Ar). ^{13}C NMR (50 MHz) δ 21.08, 31.98, 41.46, 55.28, 114.00, 124.81, 126.02, 126.32, 126.49, 128.26, 128.98, 129.30, 129.97, 130.17, 132.20, 137.19, 140.27, 140.66, 149.81, 150.24, 158.52. MS[34] (70 eV) 493 (3), 476 (100), 445 (17), 210 (19), 77

(9). Anal. calcd for $C_{31}H_{27}NO_3S$%: C, 75.43; H, 5.51; N, 2.84. Found: C, 75.03; H, 5.61; N, 2.93.

4.5.8. (S_S,4*R*)-1-Benzyl-4-methyl-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-one 10α. R_f=0.47 (EtAcO). Isolated as yellow oil. $[\alpha]_D^{23}$ −47.0 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 1687, 1029 cm^{-1}. ^1H NMR (200 MHz) δ 0.596 (d, 3H, ^3J=6.8, Me-C4), 2.401 (s, 3H, Me-Ar), 2.417 (dd, 1H, ^2J=18.1, ^3J=5.2, H3), 2.667 (dd, 1H, ^2J=18.1, ^3J=2.3, H3′), 2.59–2.74 (m, 1H, H4), 4.883, 4.705 (AB, 2H, ^2J=14.9, CH_2Ph), 6.898 (s, 1H, H6), 7.25–7.37 (m, 7H, Ar), 7.456 (d, 2H, ^3J=8.3, H_{ortho}-Tol). ^{13}C NMR (50 MHz) δ 18.42, 21.37, 24.11, 39.54, 49.36, 124.99, 127.72, 127.81, 127.93, 128.86, 129.90, 132.97, 136.34, 139.12, 141.79, 168.66. MS[34] (70 eV) 339 (1), 322 (1), 291 (47), 276 (18), 91 (100), 65 (12). Anal. calcd for $C_{20}H_{21}NO_2S$%: C, 70.77; H, 6.24; N, 4.13. Found: C, 71.05; H, 5.98; N, 4.08.

4.5.9. (S_S,4*R*)-1-Benzyl-4-methyl-6-propyl-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-one 11α. R_f=0.28 (hexane/EtAcO: 1/1, v/v). Isolated as a colourless oil. $[\alpha]_D^{23}$ −142.7 (*c* 0.22, $CHCl_3$). IR (CCl_4) 1624, 1078 cm^{-1}. ^1H NMR (200 MHz) δ 0.268 (d, 3H, ^3J=7.1, Me-C4), 1.037 (t, 3H, ^3J=7.3, CH_2CH_3), 1.641 (sext., 2H, ^3J=7.6, $CH_2CH_2CH_3$), 2.396 (s, 3H, Me-Ar), 2.448 (dd, 1H, ^2J=15.4, ^3J=1.96, H3), 2.511 (dt, 1H, ^2J=14.5, ^3J=7.6, $CH_2CH_2CH_3$), 2.699 (dd, 1H, ^2J=15.4, ^3J=6.2, H3′), 3.032 (qdd, 1H, ^3J=7.1, 6.2, 1.96, H4), 3.066 (dt, 1H, ^2J=14.5, ^3J=8.4, $CH_2CH_2CH_3$), 4.456, 5.496 (AB, 2H, ^2J=16.1, CH_2Ph), 7.18–7.39 (m, 9H, Ar). ^{13}C NMR (50 MHz) δ 13.59, 17.70, 20.53, 21.30, 22.63, 30.65, 40.03, 44.78, 124.05, 124.33, 126.94, 127.45, 128.67, 129.65, 137.55, 138.95, 140.80, 146.18, 170.58. MS[34] (70 eV) 381 (6), 364 (20), 333 (40), 318 (13), 290 (6), 91 (100), 65 (11). Anal. calcd for $C_{23}H_{27}NO_2S$%: C, 72.41; H, 7.13; N, 3.67. Found: C, 72.01; H, 7.20; N, 3.75.

4.5.10. (S_S,4*S*)-1-Benzyl-4-phenyl-6-propyl-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-one 12α. R_f=0.14 (hexane/EtAcO: 1/1, v/v). Isolated as white solid. Mp 167°C. $[\alpha]_D^{23}$ −266 (*c* 0.08, $CHCl_3$). IR (KBr) 1630, 1082 cm^{-1}. ^1H NMR (200 MHz) δ 0.872 (t, 3H, ^3J=7.3, CH_3CH_2), 1.562 (sext., 2H, ^3J=7.3, $CH_2CH_2CH_3$), 2.417 (s, 3H, Me-Ar), 2.730 (dd, 1H, ^2J=15.6, ^3J=1.7, H3), 2.824 (ddd, 1H, ^2J=14.8, ^3J=5.5, 9.0, $CH_2CH_2CH_3$), 3.014 (dd, 1H, ^2J=15.6, ^3J=7.3, H3′), 3.215 (ddd, 1H, ^2J=14.8, ^3J=7.1, 9.5, $CH_2CH_2CH_3$), 4.109 (dd, 1H, ^3J=1.7, 7.3, H4), 4.637, 5.312 (AB, 2H, ^2J=15.6, CH_2Ph), 6.396 (d, 2H, 3*J*=7.8, H_{ortho}-Tol), 6.71–6.79 (m, 4H, Ar), 7.113 (d, 2H, ^3J=7.8, H_{ortho}-Tol), 7.21–7.35 (m, 6H, Ar). ^{13}C NMR (50 MHz) δ 13.77, 20.95, 23.20, 29.65, 31.33, 40.85, 46.85, 124.04, 124.39, 125.91, 126.71, 127.78, 127.97, 128.61, 128.83, 130.08, 131.26, 136.92, 137.03, 139.55, 140.52, 148.90, 169.91. MS[34] (70 eV) 443 (6), 426 (36), 395 (15), 352 (5), 91 (100), 65 (10). Anal. calcd for $C_{28}H_{29}NO_2S$%: C, 75.81; H, 6.59; N, 3.16. Found: C, 75.64; H, 6.53; N, 3.15.

4.6. Reaction of the lithium azaenolate derivated from 1a and 4-methoxy-2,6-di-*tert*-butylphenyl crotonate (Seebach ester)

The general procedure was followed starting from **1a** (1.25 g, 4.3 mmol) and 4-methoxy-2,6-di-*tert*-butylphenyl crotonate (2.5 g, 8.6 mmol)[27,32] The reaction was monitored taking aliquotes at 12, 16, 24 and 48 h which were analyzed by ^1H NMR (300 MHz) testing an increase of conversion (25–57%) in compound **14** [mixture of two diastereomers (50:50)] which were isolated by flash chromatography on silica gel using hexane/EtAcO 4:1 as eluent.

4.6.1. 4-Methoxy-2,6-di-*tert*-butylphenyl (3*R*,S_S)-4-(2,2-pentamethylene-3-oxazolin-4-yl)-4-(*p*-tolylsulfinyl)-3-methyl butanoate 14a. R_f=0.3 (hexane/EtAcO: 2/1, v/v). Yellow oil. IR (film) 1750, 1182 cm^{-1}. ^1H NMR (300 MHz) δ 1.17 (d, 3H, ^3J=6.9, Me), 1.19–1.39 (m, 10H, cyclohexyl), 1.28 (s, 18H, 2×*t*-Bu), 2.31 (s, 3H, Me-Ar), 2.74 (m, 1H, -C*H*-CH_3), 3.18 (m, 2H, CH_2-CO_2Ar), 3.73 (s, 3H, OMe), 3.96 (d, 1H, *J*=10.9, -CH-S), 4.10, 4.40 (AB, 2H, ^2J=14.9, CH_2O), 6.81 (s, 2H, Ar), 7.22 (d, 2H, ^3J=8.2, H_{ortho}-Tol), 7.31 (d, 2H, ^3J=8.2, H_{ortho}-Tol).

4.6.2. 4-Methoxy-2,6-di-*tert*-butylphenyl (3*R*,S_S)-4(2,2-penta-methylene-3-oxazolin-4-yl)-4-(*p*-tolylsulfinyl)-3-methyl butanoate 14b. R_f=0.2 (hexane/EtAcO: 2/1, v/v). Yellow oil. IR (film) 1749, 1176 cm^{-1}. ^1H NMR (300 MHz) δ 1.24 (s, 9H, *t*-Bu), 1.31 (s, 9H, *t*-Bu), 1.41 (d, 3H, ^3J=6.9, Me), 1.37–1.61 (m, 10H, cyclohexyl), 2.33 (s, 3H, Me-Ar), 2.69–2.80 (m, 2H, -C*H*-CH_3 and 1× CH_2CO_2Ar), 3.45 (dd, 1H, ^2J=17.2, ^3J=4.1, CH_2CO_2Ar), 3.59 (AB, 1H, ^2J=14.6, CH_2O), 3.72 (s, 3H, OMe), 3.77 (d, 1H, *J*=3.6, CH-S), 4.26 (AB, 1H, ^2J=14.6, CH_2O), 6.78–6.80 (m, H_{ortho}-Ar), 7.20 (d, 2H, ^3J=8.1, H_{ortho}-Tol), 7.48 (d, 2H, ^3J=8.1, H_{ortho}-Tol). Anal. calcd for $C_{35}H_{49}NO_5S$%: C, 70.59; H, 8.23; N, 2.35. Found: C, 70.48; H, 8.22; N, 2.38.

4.7. Reactions of aza-enolates formed from 1a and different metalated species, and methyl crotonate 2a

Magnesium aza-enolate was formed from **1a** (50 mg, 0.17 mmol) in THF (0.5 mL) and 0.170 mL (0.34 mmol) of *i*-PrMgCl (2 M in Et_2O) between −78 and −40°C. The reaction mixture was stirred at −40°C for 15 min, next cooled at −78°C, and then the ene ester (45 μL, 0.45 mmol) were added. The temperature was slowly raised until 22°C and the reaction mixture was stirred for 12 h. Work up was made as it described in the general procedure. Yield and diastereomeric ratio are collected in Table 4.

Potassium aza-enolate was preformed from **1a** (75 mg, 0.26 mmol) in THF (0.5 mL) and *t*-BuOK (35 mg, 0.31 mmol) at −40°C. Next, the ene ester (54 μL, 0.51 mmol) was added following the procedure described before. Yield and diastereomeric ratio are collected in Table 4.

Titanium aza-derivative was formed from the lithium enolate (*n*-BuLi, 0.13 μL, 0.21 mmol of a 1.6 M solution in hexane) of **1a** (60 mg; 0.21 mmol) by addition of Ti(*i*-PrO)$_4$ (0.140 mL, 0.23 mmol) at −40°C. The reaction mixture was stirred at −40°C for 1 h, cooled at −78°C and the ene ester (44 μL, 0.41 mmol) was added following the procedure described before. Yield and diastereoselectivity are collected in Table 4.

4.8. Synthesis of (+)-(7*S*,8a*S*)-7-methyl-3,3-pentamethylene-1,2,3,5,6,7,8,8a-octahydro-2-oxa-5-indolizinone (4α), and (−)-(7*R*,8a*R*)-7-methyl-3,3-pentamethylene-1,2,3,5,6,7,8,8a-octahydro-2-oxa-5-indolizinone (4β)

To a stirred solution of **3α** or **3β** (111 mg, 0.31 mmol) in absolute EtOH (15 mL) was added Raney Nickel W-2[35] (5 equiv.) and the reaction mixture was refluxed for 1.5 h. Then, it was cooled until rt, filtered on a thigh pad of Celite, and the metallic salts were washed with ether. The combined organic layer was evaporated at reduced pressure to give a white solid that was purified by flash chromatography (hexane/EtAcO: 2/1, v/v).

4.8.1. (+) - (7*S*,8a*S*) - 7 - Methyl - 3,3 - pentamethylene-1,2,3,5,6,7,8,8a-octahydro-2-oxa-5-indolizinone 4α. Yield from **3α**: 100%. R_f = 0.25 (hexane/EtAcO: 2/1). Mp 101.7–102.8°C. $[\alpha]_D^{23}$ +24.0 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$) 1650 cm^{-1}. ^1H NMR (300 MHz) δ 1.08 (d, 3H, ^3J = 7.0, CH_3), 1.18–1.35 (m, 1H, H6), 1.35–1.70 (m, 8H, cyclohexyl), 1.94 (m, 3H, H6′, H7, H8), 2.50 (m, 3H, 2H of cyclohexyl and H8), 3.41 (dd, 1H, ^3J = 10.3, 8.3, H1), 3.66 (dddd, 1H, ^3J = 11.2, 10.3, 5.4, 3.0, H8a), 4.06 (dd, 1H, J = 8.3, 5.4, H1). ^{13}C NMR (75 MHz) δ 21.5, 23.0, 23.1, 24.5, 28.4, 31.0, 34.0, 34.2, 41.1, 57.4, 69.1, 95.9, 166.8. Anal. calcd for $C_{13}H_{21}NO_2$%: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.30; N, 6.16.

4.8.2. (−) - (7*R*,8a*R*) - 7 - Methyl - 3,3 - pentamethylene-1,2,3,5,6,7,8,8a-octahydro-2-oxa-5-indolizinone 4β. Yield from **3β**: 100%. R_f = 0.25 (hexane/EtAcO: 2/1). Mp 102°C. $[\alpha]_D^{23}$ −25.8 (*c* 0.95, $CHCl_3$). Spectroscopic parameters are identical of enantiomer **4α**.

4.9. Synthesis of (−)-(2*S*,4S)-4-methyl-6-oxopipecolic acid, 5α and its methyl ester (−)-6α

A stirred solution of **4α** (0.768 g, 3.44 mmol) in AcOH (10% v/v in H_2O, 27.30 mL) was heated under reflux for 12 h. The reaction mixture was left to cool to rt and was then cooled to 0°C. Saturated aqueous $NaHCO_3$ was added until the pH of the mixture was 7 and the neutral solution was partitioned in $CHCl_3$/*i*-PrOH (80/20). The aqueous layer was extracted with a $CHCl_3$/*i*-PrOH mixture (80/20, 4×30 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and the filtrate concentrated at reduced pressure. The aqueous solution was further extracted (continued extraction) with $CHCl_3$ to give a brown oil that was chromatographied on silica gel (EtAcO/EtOH: 8/1) to afford a white solid (482 mg), mp 89.6–92.0°C, which was identified as the lactam (4*S*,6*S*)-6-hydroxymethyl-4-methylpiperidin-2-one (yield: 98%). $[\alpha]_D^{23}$ −0.1 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$) 3388, 1651 cm^{-1}. ^1H NMR (200 MHz) δ 1.023 (d, 3H, ^3J = 6.1, CH_3), 0.95–1.06 (m, 1H, H4), 1.70–2.04 (m, 2H, H5, H5′), 1.866 (t, 1H, ^3J = 12.6, H3), 2.444 (dd, 1H, ^2J = 12.6, ^3J = 2,2, H3′), 3.403 dd, 1H, ^2J = 10.3, ^3J = 8.1, H7), 3.573 (dddd, 1H, ^3J = 2.7, 3.7, 8.1, 15.0, H6), 3.697 (dd, 1H, ^2J = 10.3, ^3J = 2.7, H7), 3.778 (bs, 1H, OH), 7.383 (bs, 1H, NH). ^{13}C NMR (50 MHz) δ 21.4, 27.09, 27.10, 32.83, 54.82, 66.08, 182.58. Anal. calcd for $C_7H_{13}NO_2$%: C, 58.72; H, 9.15; N, 9.78. Found: C, 59.11; H, 9.24; N, 10.3.

The deprotected lactam (134 mg, 0.94 mmol) was oxidized in dry acetone with Jones reagent (1.5 equiv.) at 0°C over 3 h and at 25°C for 3 h. Next, *i*-PrOH (0.17 mL) was added and the mixture was stirred at rt for 30 min. Subsequently, water was added and the mixture was extracted with EtAcO (3×10 mL). The combined organic layer was dried on $MgSO_4$, filtered on Celite and concentrated under reduced pressure at rt. The crude product **5α** was directly transformed in the acid derivative.

A solution of **5α** (87 mg, 0.55 mmol) in dry MeOH (3 mL) was cooled at 0°C and $SOCl_2$ (0.77 mmol) was slowly added. Next, the temperature was raised to rt and the mixture was stirred overnight at rt. Then, saturated aqueous $NaHCO_3$ was added and the reaction mixture was extracted with EtAcO (3×5 mL). The organic layer was dried on Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by chromatography (EtAcO) to give 94 mg of a colourless oil that was identified as (2*S*,4*S*)-methyl 4-methyl-6-oxopipecolate (−)-**6α**. Yield: 89% from deprotected lactam. $[\alpha]_D^{23}$ −20.7 (*c* 4.5, $CHCl_3$). IR ($CHCl_3$) 1746, 1666 cm^{-1}. ^1H NMR (200 MHz) δ 0.992 (d, 3H ^3J = 6.3, Me), 1.139 (ddd, 1H, ^2J = 11.7, ^3J = 4.6, H5′), 1.316 (dt, 1H, ^2J = ^3J = 11,7, ^3J = 12.9, H5), 2.08–1.86 (m, 1H, H4), 2.312 (dd, 1H, ^2J = 12.4, ^3J = 6.8, H3′), 2.409 (dd, 1H, ^2J = 12.4, ^3J = 1.96, H3), 3.717 (s, 3H, OMe), 4.047 (dd, 1H, ^3J = 11.7, 4.6, H6), 6.459 (bs, 1H, NH). ^{13}C NMR (50 MHz) δ 174.20, 171.15, 54.46, 52.60, 39.23, 33.56, 27.58, 21.19. Anal. calcd for $C_8H_{13}NO_3$%: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.01; H, 7.74; N, 7.99.

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