Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2437–2450

TETRAHEDRON:
ASYMMETRY

Synthesis of enantiomerically pure acyclic α-sulfinyl ketimines

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Received 11 May 1998; accepted 25 May 1998

Abstract

Two different methods to obtain enantiomerically pure *N*-alkyl and *N*-aryl α-sulfinyl ketimines are reported. Reaction of enantiomerically pure α-sulfinyl ketones (**1–6**) with benzylamine or *p*-methoxyaniline, in the presence of molecular sieves (3 Å), yields the corresponding of *N*-benzyl and *N*-*p*-methoxyphenyl ketimines (**7A–12A** and **7B–12B**). Better results were achieved by α-sulfinylation of ketimines (**13A–18A** and **13B–18B**) with (−)-menthyl *p*-toluenesulfinate in the presence of lithium (*N*-arylimines) or magnesium (*N*-benzylimines) bases. The different tautomeric behaviour of the obtained *N*-aryl and *N*-alkyl derivatives is reported. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

The sulfinyl group has been used profusely as a chiral auxiliary in asymmetric synthesis.[1] Its influence on the stereochemical course of nucleophilic additions to α-sulfinyl ketones, such as hydride reductions,[2] alkylations,[3] and hydrocyanations,[4] has been widely studied. By contrast, α-sulfinyl imines have been much less studied despite their increasing importance in the synthesis of biologically active molecules,[5] and their usefulness in asymmetric synthesis.[6] This could be due to the fact that efficient synthetic methods to prepare enantiomerically pure α-sulfinyl imines have only just recently been reported and they usually lack general scope. Thus, if the reported methods of synthesising α-sulfinyl imines are classified according to the bond of the fragment N–C–C–S which is created during the synthesis, those involving the N–C bond formation, such as the Michael addition of amines to allenic sulfoxides[7] (the low energetic barrier to racemize allenes precludes obtaining optically active substrates) and condensation reactions of α-sulfinyl ketones with amines catalysed by $TiCl_4$[8] (the yields are lower than 30% presumably due to concomitant reduction of the sulfinyl group by the catalyst), are not very efficient. Better results were obtained by addition of amines to sulfinyl acetylenes[5a,9] and aza-Wittig reactions of triphenyliminophosphoranes with α-sulfinyl ketones,[6] but the first method is limited to

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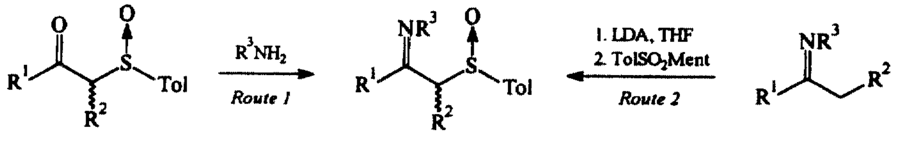
PII: S0957-4166(98)00211-0

the synthesis of sulfinyl enamines derived from aldehydes and the second one can be applied only to α′-fluorinated ketones. Reactions of imidoyl chlorides with lithium enolates of chiral non-racemic methyl *p*-tolyl sulfoxide, involving C(1)–C(2) bond formation, has been successfully used to prepare *N*-substituted γ-fluorinated α-sulfinyl imines,[10] but the authors only describe reactions of substrates lacking an α-hydrogen. The same strategy was used in reactions of metallated sulfoxides with nitriles to give unstable *N*-unsubstituted enamines, which are reduced in situ into equimolecular mixtures of diastereoisomeric aminosulfoxides.[11] This procedure has also been used to prepare racemic α-sulfenyl α-sulfinyl enamines.[12] Reactions involving C(2)–S bond formation were first reported by Annunziata et al. in 1982,[13] who studied the reaction of lithium enamines with menthyl *p*-toluenesulfinate to afford optically active sulfinyl imines. Unfortunately, the yields described starting from ketimines were not satisfactory. Good results in the synthesis of sulfinyl ketimines have only been reported for compounds exhibiting endocyclic[5b,14] and exocyclic[15] C=N bonds.

Hence, we can conclude that efficient methods of preparing enantiomerically pure acyclic α-sulfinyl ketimines have not yet been described. We report herein the complete results obtained in the synthesis of the *N*-benzyl and *N*-*p*-methoxyphenyl imines by two different methods: condensation of α-sulfinyl ketones with amines (C–N bond formation, route 1) and addition of α-metallated enamines to menthyl *p*-toluenesulfinate (C–S bond formation, route 2) (Scheme 1).[16]



1-6 **7-12** **13-18**

Scheme 1.

2. Results and discussion

α-Sulfinyl imines **7–12** were initially synthesised by reaction of the amines with enantiomerically pure α-sulfinyl ketones **1–6**[17] (route 1, Scheme 1) in the presence of molecular sieves (3 Å).[18] The yields and reaction conditions used with *p*-methoxyaniline (**A**) and benzylamine (**B**) are shown in Table 1. The use of $TiCl_4$ as a catalyst in the reactions of compounds **1–6** with benzylamine, under similar conditions to those used by Kagan and Baldenius in similar processes,[8] was not successful because it leads to the reduction of the sulfinyl group to sulfenyl.

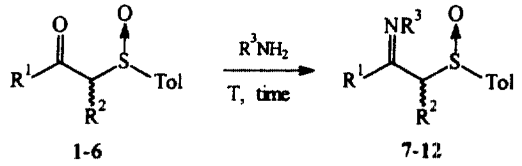
Benzene was the solvent used for the reactions of **1–4** (R^1=alkyl) with benzylamine whereas diethyl ether gave better results with **5** and **6** (R^1=Ph). The reactions of **1** and **2** with *p*-methoxyaniline required higher temperatures and evolved with lower yields than those corresponding to benzylamine, whereas compounds **9A–12A** could not be obtained by this procedure (Table 1).

The second route to obtain sulfinyl imines involved the α-sulfinylation of imines **13–18**, prepared in high yields (75–95%) from the corresponding ketones by condensation with *p*-methoxyaniline (**A**) or benzylamine (**B**), in the presence of molecular sieves (3 Å).

Reaction of benzyl imines **15** and **17** with menthyl *p*-toluenesulfinate, using LDA as a base, yielded the expected α-sulfinyl imines **9A** and **11A**, which were partially racemized (Scheme 2)[20], as could be demonstrated by their hydrolysis into sulfinyl ketones **3** (77% ee) and **5** (11% ee) respectively.[19]

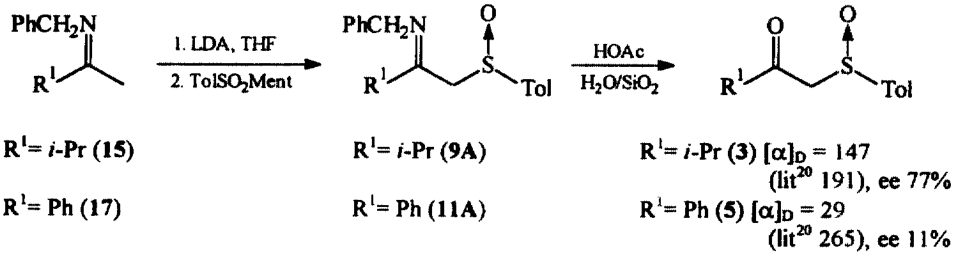
This partial racemization can be explained as the result of the ambident nucleophilic character of the azaenolates,[21] determining the formation of the *C*-sulfinylated and *N*-sulfinylated products, the

Table 1
Results obtained in the reaction of α-sulfinylketones **1–6** with benzylamine (**A**) and *p*-methoxyaniline (**B**)



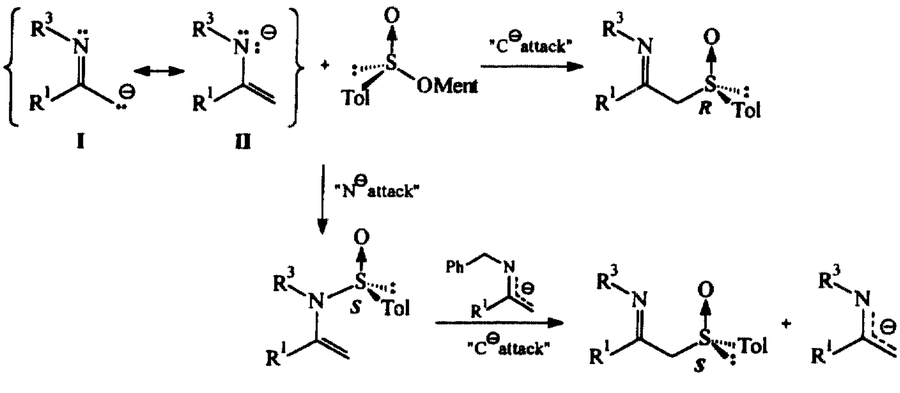
Substrate	R¹	R²	R³	T (° C)	time (h)	Product	Yield(%)
1	Me	H	p-MeOC$_6$H$_4$	40	24	**7A**	65
2	*n*-Pr	H	p-MeOC$_6$H$_4$	60	48	**8A**	60
3	*i*-Pr	H	p-MeOC$_6$H$_4$	65	24	**9A**	0
4	*t*-Bu	H	p-MeOC$_6$H$_4$	80	72	**10A**	0
5	Ph	H	p-MeOC$_6$H$_4$	38	24	**11A**[a]	0
6	Ph	Me	p-MeOC$_6$H$_4$	38	24	**12A**[a]	0
1	Me	H	PhCH$_2$	20	14	**7B**	88
2	*n*-Pr	H	PhCH$_2$	20	12	**8B**	90
3	*i*-Pr	H	PhCH$_2$	20	60	**9B**	54
4	*t*-Bu	H	PhCH$_2$	70	72	**10B**	60
5	Ph	H	PhCH$_2$	38	72	**11B**[b]	50
6	Ph	Me	PhCH$_2$	38	48	**12B**[b]	10

[a] Diethylether or benzene as the solvent. [b] Diethyl ether as the solvent.



Scheme 2.

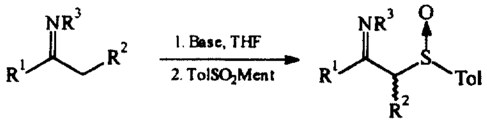
latter being able to act as a sulfinylating agent in a new attack of the azaenolate with inversion of the configuration at sulfur (Scheme 3).[22] Therefore mixtures of sulfinyl imine epimers at sulfur are obtained.



Scheme 3.

To avoid sulfur epimerization, magnesium azaenolates instead of the corresponding lithium ones

Table 2
Results obtained in the reaction of α-metallated imines **13–18** with menthyl *p*-toluenesulfinate



13-18 **7-12, 19**

Substrate	R^1	R^2	R^3	T (° C)	Product	Yield(%)
13A	Me	H	p-MeOC$_6$H$_4$	-48	**7A**	80
14A	n-Pr	H	p-MeOC$_6$H$_4$	-78	**8A**[a]	80
14A	Me	Et	p-MeOC$_6$H$_4$	0	**19A**[a]	80
15A	i-Pr	H	p-MeOC$_6$H$_4$	-48	**9A**	93
16A	t-Bu	H	p-MeOC$_6$H$_4$	20	**10A**	82
17A	Ph	H	p-MeOC$_6$H$_4$	20	**11A**	95
18A	Ph	Me	p-MeOC$_6$H$_4$	30	**12A**	87
13B	Me	H	PhCH$_2$	-48	**7B**	83
14B	n-Pr	H	PhCH$_2$	-48	**8B**	80
15B	i-Pr	H	PhCH$_2$	-48	**9B**	84
16B	t-Bu	H	PhCH$_2$	20	**10B**	35
17B	Ph	H	PhCH$_2$	0	**11B**	92
18B	Ph	Me	PhCH$_2$	0	**12B**	22

[a] Mixture of **8A** and **19A**, see text.

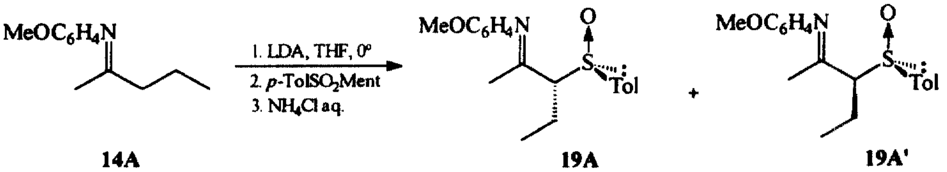
were used. The best results were obtained by reaction of the imine with LDA in THF followed by transmetallation with MgBr$_2$ prior to the addition of the sulfinate (the direct use of magnesium bases is less satisfactory probably due to solubility problems). The yields and reaction conditions used with the different substrates are collected in Table 2. The generation of the azaenolate by slow addition of imine to the base (thus precluding the coexistence of imine/enolate and, therefore, their autocondensation) improved the yield in the case of **11B**. Steric hindrance probably precludes achieving high yields in the synthesis of compounds **10B** and **12B**.

Lithium azaenolates derived from *N*-arylimines **13A–18A** do not produce racemization at sulfur in their reactions with menthyl *p*-toluenesulfinate. Their higher reactivity, as compared with the magnesium ones, and the lower tendency of arylimines to give autocondensation, allowed better yields under milder conditions to be achieved. As we can see in Table 2, the synthesis of compounds **7A–12A** was highly satisfactory in all cases. The lower nucleophilic character of the nitrogen in azaenolates derived from arylimines would explain that '*N*-sulfinylation' does not compete in these reactions with '*C*-sulfinylation', thus avoiding the epimerization at sulfur.

Regioselectivity in the formation of azaenolates is a problem inherent to unsymmetrical imines **14** and **15** (with R^1=n-Pr or i-Pr and R^2=H), but it was only observed in the case of **14A** (in the other cases the azaenolate is formed exclusively on the less substituted methyl carbon). At −78°C sulfinylation of imine **14A** afforded an 80:20 mixture of compounds **8A** and **19A**, whereas at 0°C the ratio of both products in the mixture was inverted. These results are compatible with the known influence of temperature in the kinetic (at low temperatures the less hindered positions are favoured) or thermodynamic (at higher temperatures the most substituted positions are favoured) control of the formation of the enolates, but it contrasts with the reported results indicating that *syn*-azaenolates on the less substituted carbon are the most stable ones[23] (in this sense, the expected behaviour is that of the *N*-benzylimine **14B**, yielding the same azaenolate regardless of the conditions used).

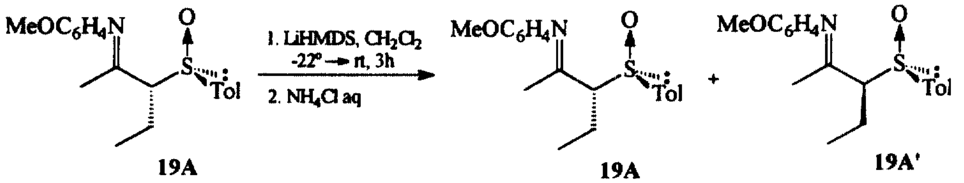
This different behaviour of **14A** and **14B** could be rationalised by considering the relative contribution of the two mesomeric forms describing the structure of their azaenolates (see Scheme 3). Carbanionic form **I** must be the most important one for alkylimines such as **14B**, whereas enamine anionic form **II** would be the most important for arylimines such as **14A**, due to the ability of the R^3 to stabilise (aromatic ring) or destabilise (alkyl group) the negative charge at the nitrogen. Thus, under thermodynamic control conditions, factors governing the relative stability of the C=C double bonds (such as their degree of substitution) will be the main ones responsible for the control of the regioselectivity for substrates exhibiting higher contribution of the form **II** (arylimines), whereas factors accounting for the stability of the carbanions (primary more stable than secondary) must be mainly invoked to predict or explain the regioselectivity for substrates with form **I** as predominant (alkylamines). In any case, the strongly negative influence of the substitution in the reactivity of the carbanions determines that the tertiary ones do not react, the reactions conducted on **15A** and **15B** being completely regioselective.[24]

Sulfinylimine **19A** was obtained as a mixture of epimers at C-α (**19A** and **19A′**) (Scheme 4), their ratio being dependent on the temperature of protonation in the work-up of the reaction mixture.[25] Thus, when the quenching is done at room temperature, mixtures of **19A** and **19A′** (ranging between a 70:30 and an 80:20 ratio) were isolated, whereas if the reaction mixture obtained at 0°C is cooled to −78°C before its hydrolysis, a 95:5 mixture of **19A** and **19A′** was obtained, from which epimer **19A** could be isolated in high yield by easy column chromatography.



Scheme 4.

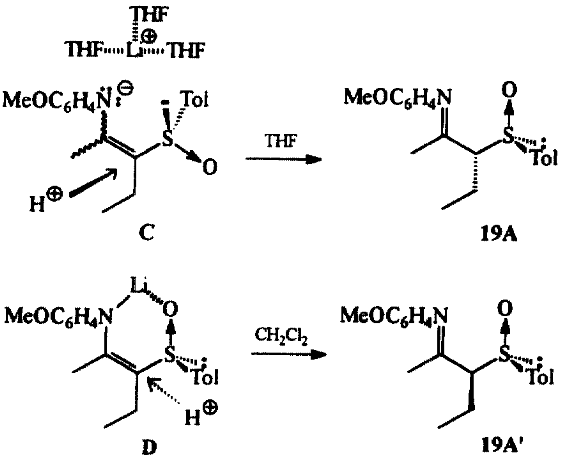
On the other hand, the equilibration of isomer **19A** in an acidic medium (HCl(g):CH_2Cl_2) yielded a 1:1 mixture of epimers. Nevertheless, its treatment with LiHMDS (from −22°C to rt) in CH_2Cl_2 for 3 h followed by protonation at room temperature determines the formation of epimeric mixtures in which compound **19A′** is clearly predominant. The composition of the mixture depends on the concentration, being most favourable when dilution is increased (see Scheme 5).



CH_2Cl_2(mL)/substrate(g)	19A	19A'
40:1	1.0	10
36:1	1.3	10
30:1	1.5	10
25:1	4.3	10

Scheme 5.

Presumably the strong differences observed in the composition of the epimeric mixtures are mainly related to the ability of the solvent to coordinate the metallic cation (Scheme 6). The THF used in the reaction of formation of **19** from imine **14A** is able to do this, and the azaenolate will exhibit conformation **C** as the most stable one in order to minimise the electrostatic repulsion between the negative charge at sulfinylic oxygen and nitrogen. In contrast, the poor coordinating ability of CH_2Cl_2 must determine that the metal remains joined to the azaenolate forming a chelate **D**. By assuming that protonation takes place from the less hindered face of **C** and **D** respectively, we can explain the stereochemistry assigned to epimers **19A** and **19A′**.



Scheme 6.

2.1. Imine–enamine structure

All the prepared α-sulfinyl imines have α-hydrogens and therefore they can exhibit the imine–enamine prototropic equilibrium. In general, the iminic form is the most stable one in the solid state,[26] whereas there have been described several examples of α-sulfinyl imines where the proportion of the enaminic tautomer is significant or the major one in solution.[13,15b,27,28] The interaction of the enaminic double bond with aromatic and/or electron withdrawing groups and the formation of intra- or intermolecular hydrogen bonding, are the main factors responsible for the stabilisation of the enaminic tautomer. However, the relative contribution of both tautomers depends on the solvent, concentration, temperature, as well as the substituents existing in the NCC framework of the studied compound.

Tautomers are easily identified from NMR parameters of the crude reaction mixtures or of the isolated compounds. In Table 3 the significant NMR chemical shifts used for determination of the imine and/or enamine structure of compounds **7–12** and **19** are collected.

The imine structure in compounds without substituents at C-2 (**7–11**) show an AB system at 4.4–3.5 ppm in the ^{1}H-NMR spectrum, corresponding to methylenic protons at this carbon. In the enamine tautomer this system is replaced by a singlet corresponding to a vinylic proton in the 5.4–4.9 ppm range and other signals of the NH group. The identification of both tautomeric forms in the ^{13}C-NMR spectrum is also straightforward. The chemical shift of C-2 ranges from 101 to 98 ppm in the enamine form whereas this signal appears at a higher field (69–56 ppm) in the imine form. The *C*–N signal can also be used for differentiation since it appears up to 10 ppm deshielded in the imine tautomer with respect to that corresponding to the enamine form, even though in some cases the difference can be smaller.

As we can see, *N*-benzyl derivatives adopt an exclusive [R^1=*n*-Pr (**8B**), *i*-Pr (**9B**), Ph (**11B**)] or predominantly [R^1=Me (**7B**)] enaminic form, which can be explained by assuming the formation of an intramolecular hydrogen bond in this form. Only *t*-butyl derivative **10B** is present as an imine, probably due to the steric hindrance between benzyl and *t*-butyl groups present in the intramolecularly associated enaminic tautomer. It is important to emphasise that the imine–enamine equilibrium for compound **7B** (the only *N*-benzylderivative where both tautomers were present) showed a considerable dependence on the concentration of the studied $CDCl_3$ solutions. The imine–enamine ratio changed from 1:2.2 for a

Table 3
Significant ^{1}H- and ^{13}C-NMR chemical shifts of compounds **7–12** and **19** (δ ppm, $CDCl_3$)

Comp.	Structure [a]	R^1	R^2	R^3	R^4	NH	C(1)	C(2)
7A	imine (50)	Me	H (3.91)	p-$MeOC_6H_4$	H (3.80)	-	163.0	68.1
	imine (10)	Me	H (3.73)	p-$MeOC_6H_4$	H (3.53)	-	161.3	67.0
	enamine (40)	Me	H (5.33)	p-$MeOC_6H_4$	-	5.63	155.8	100.1
8A	imine (53)	n-Pr	H (3.94)	p-$MeOC_6H_4$	H (3.78)		164.3	64.9
	imine (38)	n-Pr	H (3.73)	p-$MeOC_6H_4$	H (3.51)		167.2	59.6
	enamine (9) [b]	n-Pr	H (5.38)	p-$MeOC_6H_4$	-	5.37	157.6	99.8
19A	imine	Me	Et	p-$MeOC_6H_4$	H (3.46)	-	166.8	75.2
19A'	imine	Me	Et	p-$MeOC_6H_4$	H (3.50)	-	166.6	77.0
9A [c]	imine (42)	i-Pr	H (4.05)	p-$MeOC_6H_4$	H (3.68)		171.4	61.4
	imine (52)	i-Pr	H (3.83)	p-$MeOC_6H_4$	H (3.57)		168.6	58.8
	enamine (6)	i-Pr	H (5.20)	p-$MeOC_6H_4$	-	5.51	161.7	99.7
10A	imine	t-Bu	H (3.83)	p-$MeOC_6H_4$	H (3.71)	-	171.3	57.8
11A	imine	Ph	H (4.37)	p-$MeOC_6H_4$	H (4.10)	-	158.6	57.4
12A [d]	enamine	Ph	Me	p-$MeOC_6H_4$	-	5.87	155.0	113.7
7B	imine (31)	$C\underline{H}_3$	H (3.82)	$PhCH_2$	H (3.71)	-	162.5	68.5
	enamine (69)	$C\underline{H}_3$	H (5.04)	$PhCH_2$	-	4.95	154.2	99.3
8B	enamine	n-Pr	H (5.04)	$PhCH_2$	-	4.42	158.4	98.6
9B	enamine	i-Pr	H (4.94)	$PhCH_2$	-	4.39	166.4	98.0
10B	imine	t-Bu	H (4.04)	$PhCH_2$	H (3.66)	-	167.7	55.7
11B	enamine	Ph	H (5.34)	$PhCH_2$	-	4.43	157.5	101.0
12B	enamine	Ph	Me	$PhCH_2$	-	4.73	154.3	107.3

[a] Isomers ratio (%) (NMR) in $CDCl_3$ solutions (15-30 mg/mL). [b] Only tautomer in 17% $CDCl_3$ solution.
[c] Uncertain assignment. [d] Only the enamine is described, obtained by crystallisation of a mixture of several compounds.

30 mg/ml solution to 1:8 for a 140 mg/ml solution. On the other hand, we assume that all compounds, including **7B**, adopt a Z-configuration for the enaminic double bond, with an intramolecular associated hydrogen bonding, because of the invariability of ^{1}H-NMR parameters with concentration and according to information given in the literature.[26a,b27,13]

The lower importance of the intramolecular hydrogen bond as the stabilising factor of the enaminic form in N-aryl derivatives must be responsible for the presence of both tautomers **7A–9A** and **12A** and only the iminic form in **10A**, **11A**, **19A** and **19A′**. The NMR spectra of the crude **9A** and **12A** isolated by chromatography showed signals corresponding to several structures including tautomeric and stereoisomeric forms, making their individual assignation and relative ratio determination difficult. Fortunately, compounds **8A** and **12A** crystallise as exclusively enaminic tautomers in concentrated solutions of diethyl ether or methylene chloride, allowing us to characterise them. Enamine **8A** quickly tautomerises to the original tautomer mixture whereas **12A** remains unchanged after several days even in solutions at low concentration.

3. Experimental

3.1. General methods

All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of argon and monitored by TLC. Solvents were dried according to literature procedures.[29] Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 ml). The NMR spectra were recorded in $CDCl_3$ solutions at 200.1 and 50.3 MHz for ^1H- and ^{13}C-NMR respectively; δ chemical shifts refer to TMS (^1H) or deuterated chloroform (^{13}C) signals. The IR spectra were obtained as CH_2Cl_2 solutions. Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyser.

3.2. Synthesis of sulfinyl imines

Method A: In a round bottomed flask containing 5–7 g of molecular sieves (3 Å) were introduced 2.23 mmol (1 equiv.) of the corresponding sulfinyl ketone and 1.1–2.0 equiv. of *p*-methoxyaniline or benzylamine dissolved in 20 ml of benzene. The reaction mixture was gently stirred (in order to avoid the break up of molecular sieves) at the indicated temperature for the corresponding reaction time (Table 1) and filtered over Celite. The solid was washed with CH_2Cl_2, the combined filtrates were concentrated at reduced pressure, and the residue purified by flash chromatography.

Method B: To a solution of 1.54 ml (11.22 mmol, 3.3 equiv.) of diisopropylamine in 10 ml of anhydrous THF cooled at −48°C was added 4.65 ml (10.71 mmol, 3.15 equiv.) of a 2.3 M solution of *n*-butyllithium in hexane. The mixture was stirred for 15 min and then a solution of 2.1–6.0 equiv. of the corresponding imine in 20 ml of THF was slowly added (20–90 min). To *N*-benzylimines (after 15 min) at −48°C, 43 ml (11.9 mmol, 3.5 equiv.) of a freshly prepared 0.28 M solution of $MgBr_2$ in THF was added (this was not necessary for *N*-*p*-methoxyphenylimines). After 20 min, 1 g (3.4 mmol, 1 equiv.) of menthyl (*S*)-*p*-toluenesulfinate dissolved in 10 ml of THF was added. The mixture was then allowed to reach room temperature which decomposed after 1 h with 20 ml of a saturated aqueous NH_4Cl solution. The organic layer was washed with 20 ml of CH_2Cl_2, dried and concentrated, and the residue purified by chromatography or crystallisation.

3.3. (R)-N-(p-Methoxyphenyl)-1-methyl-2-(p-tolylsulfinyl)ethylidenamine 7A

Compound **7A** was prepared as an oil from sulfinyl ketone **1** and 1.5 equiv. of *p*-methoxyaniline [method A; the crude product was purified by chromatography, hexane:acetone (35:10) containing 10% triethylamine as the eluent; yield 65%] or from *N*-(*p*-methoxyphenyl)-1-methylethylidenamine (**13A**) (2.1 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 45 min; the crude product was purified by chromatography, AcOEt:hexane (20:25) containing 10% triethylamine as the eluent; yield 80%]. The product was present as a mixture of two imines and one enamine (50:10:40, NMR); $[\alpha]_D$ +109 (c 0.6, CH_2Cl_2); δ_H imine (50): 7.60 and 7.36 (AA′BB′ system, 4H), 6.83 and 6.52 (AA′BB′ system, 4H), 3.91 and 3.80 (AB system, 2H, J 12.9 Hz), 3.78 (s, 3H), 2.43 (s, 3H), 1.89 (s, 3H); imine (10): 7.60 and 7.36 (AA′BB′ system, 4H), 6.82 and 6.54 (AA′BB′ system, 4H), 3.78 (s, 3H), 3.73 and 3.53 (AB system, 2H, J 12.4 Hz), 2.41 (s, 3H), 2.33 (s, 3H); enamine (40): 7.45 and 7.22 (AA′BB′ system, 4H), 7.04 and 6.83 (AA′BB′ system, 4H), 5.63 (bs, 1H), 5.33 (s, 1H), 3.75 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H); δ_C 163.0, 161.3, 156.4, 155.8, 153.3, 152.0, 143.3, 142.5, 142.2, 141.7, 141.4, 139.8, 139.5, 139.1, 131.5, 129.7, 129.5, 129.0, 125.6, 124.0, 123.6, 123.4, 120.4, 120.3, 115.9, 114.2, 113.8, 113.7, 100.1, 68.1, 67.0, 59.9, 55.2, 54.9, 31.4, 27.3, 21.0, 20.8, 17.6; IR 3410, 2970, 1645, 1595, 1507, 1440, 1240, 1185, 1090, 1030, 840 cm^{-1}.

3.4. *(*R*)-*N*-Benzyl-1-methyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***7B***[30]

Compound **7B** was obtained as a white solid from sulfinyl ketone **1** and 1.5 equiv. of benzylamine [method A; purification of the crude product was carried out by grinding it with a mixture of diethyl ether:hexane (3:1); yield 88%] or from *N*-benzyl-1-methylethylidenamine (**13B**) (2.5 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 45 min; the crude product was purified by chromatography, AcOEt:hexane (2:1) containing 10% triethylamine as the eluent; yield 83%]. The product was present as a mixture of one imine and one enamine (31:69, NMR); mp 102–104°C; $[\alpha]_D$ −8 (c 1.0, CH_2Cl_2); δ_H imine: 7.53–7.16 (m, 9H), 4.50 (s, 2H), 3.82 and 3.71 (AB system, 2H, J 10 Hz), 2.41 (s, 3H), 2.02 (s, 3H); enamine: 7.45–7.16 (m, 9H), 5.04 (s, 1H), 4.95 (m, 1H), 4.22–4.01 (m, 2H), 2.38 (s, 3H), 2.31 (s, 3H); δ_C imine: 162.5, 129.8, 128.3, 126.6, 68.5, 55.5, 21.3, 19.6; enamine: 154.2, 143.9, 139.5, 137.0, 129.3, 128.7, 127.7, 124.4, 124.2, 99.3, 47.4, 21.1, 18.0.

3.5. *(*R*)-*N*-(*p*-Methoxyphenyl)-1-*n*-propyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***8A***

Compound **8A** was obtained as an oil from sulfinyl ketone **2** and 1.1 equiv. of *p*-methoxyaniline [method A; the crude product was purified by chromatography, AcOEt:hexane (4:3) containing 10% triethylamine as the eluent; yield 60%] or from *N*-(*p*-methoxyphenyl)-1-methylbutylidenamine (**14A**) (2.1 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 20 min; the crude was stirred in hexane for 1 h at room temperature and at −20°C for 3 h. Work-up of the mixture afforded an oil which was chromatographed using AcOEt:hexane (20:30) containing 5% triethylamine as the eluent; yield 80%]. The product was obtained as an imine–enamine mixture (dependent on the concentration) which solidified into a white solid on standing. NMR data refer to a 17% $CDCl_3$ solution where the enamine is the only tautomer present; mp 83–84°C; $[\alpha]_D$ +153 (c 1.0, CH_2Cl_2); δ_H 7.55 and 7.31 (AA′BB′ system, 4H), 7.12 and 6.86 (AA′BB′ system, 4H), 5.38 (s, 1H), 5.37 (bs, 1H), 3.82 (s, 3H), 2.82 (m, 2H), 2.46 (s, 3H), 1.93 (m, 2H), 1.19 (t, 3H, J 7.4 Hz); δ_C 157.6, 156.7, 143.5, 139.3, 132.8, 129.2, 125.9, 124.2, 114.1, 99.8, 55.1, 33.7, 23.0, 21.0, 13.6. IR 3230, 3200, 2800, 1650, 1580, 1510, 1470, 1420, 1295, 1240, 1180, 1090, 1040, 840, 810 cm^{-1}; anal. calcd for $C_{19}H_{23}NO_2S$: C 69.27, H 7.04, N 4.25. Found: C 69.34, H 7.21, N 4.34.

3.6. *[2*R*,(*S*)*R*]-*N*-(*p*-Methoxyphenyl)-1-methyl-2-(*p*-tolylsulfinyl)butylidenamine* ***19A***

Compound **19A** was obtained as a white solid in the reaction of *N*-(*p*-methoxyphenyl)-1-methylbutylidenamine (**14A**) (2.1 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 20 min. The reaction mixture was quenched at −78°C and the resulting mixture was allowed to reach room temperature. The purification of the crude product was carried out as for compound **8A** using AcOEt:hexane (18:30) containing 5% triethylamine as the eluent; yield 80%]. The product is present as the imine tautomer; mp 96–97°C; $[\alpha]_D$ +115 (c 1.0, CH_2Cl_2); δ_H 7.51 and 7.34 (AA′BB′ system, 4H), 6.77 and 6.26 (AA′BB′ system, 4H), 3.75 (s, 3H), 3.46 (m, 1H), 2.43 (s, 3H), 2.04 (m, 2H), 1.83 (s, 3H), 1.11 (t, 3H, J 7.4 Hz); δ_C 166.8, 155.9, 143.0, 141.4, 138.1, 129.5, 124.7, 120.2, 113.9, 75.2, 55.3, 21.3, 20.2, 19.7, 11.6; IR 2940, 1610, 1509, 1470, 1370, 1295, 1250, 1100, 1090, 1060, 1040 cm^{-1}; anal. calcd for $C_{19}H_{23}NO_2S$: C 69.27, H 7.04, N 4.25. Found: C 69.63, H 6.98, N 4.24.

*3.7. [2S,(S)R]-N-(p-Methoxyphenyl)-1-methyl-2-(p-tolylsulfinyl)butylidenamine **19A′***

To a solution of 1 g (3 mmol, 1 equiv.) of **19A** in 40 ml of anhydrous CH_2Cl_2 was added at −22°C, 3.3 ml of a 1 M solution of LiHMDS in hexane (3.3 mmol, 1.1 equiv.). The reaction mixture was allowed to reach room temperature and then stirred for 3 h and hydrolysed with a saturated aqueous NH_4Cl solution. The organic layer was dried (Na_2SO_4) and concentrated. The resulting oil was purified by chromatography using AcOEt:hexane (18:30) containing 5% triethylamine as the eluent; yield 80% (white solid). The product was present as the imine tautomer; mp 115–116°C; $[\alpha]_D$ −151 (c 1.0, CH_2Cl_2); δ_H 7.60 and 7.32 (AA′BB′ system, 4H), 6.83 and 6.46 (AA′BB′ system, 4H), 3.74 (s, 3H), 3.50 (t, 1H, J 7.2 Hz), 2.40 (s, 3H), 2.25 (m, 2H), 1.56 (s, 3H), 1.09 (t, 3H, J 7.3 Hz); δ_C 166.6, 155.7, 142.6, 141.6, 139.0, 129.2, 125.0, 119.9, 113.7, 77.0, 54.8, 20.9, 20.7, 10.8; IR 2990, 1655, 1500, 1470, 1380, 1300, 1250, 1190, 1110, 1090, 1060, 1050, 840, 810 cm^{-1}; anal. calcd for $C_{19}H_{23}NO_2S$: C 69.27, H 7.04, N 4.25. Found: C 69.05, H 6.94, N 4.16.

*3.8. (R)-N-Benzyl-1-n-propyl-2-(p-tolylsulfinyl)ethylidenamine **8B***

Compound **8B** was obtained as a white solid from sulfinyl ketone **2** and 1.1 equiv. of benzylamine [method A; the crude product was crystallised from acetone:hexane; yield 90%] or from *N*-benzyl-1-methylbutylidenamine (**14B**) (2.3 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 30 min; the crude product was purified by chromatography, hexane:acetone:triethylamine (4:3:1) as the eluent; yield 80%]. The product was present as the enamine tautomer; mp 112–113°C; $[\alpha]_D$ −50 (c 1.0, CH_2Cl_2); δ_H 7.47–7.21 (m, 9H), 5.04 (s, 1H), 4.42 (m, 1H), 4.21–4.02 (m, 2H), 2.83–2.37 (m, 2H), 2.38 (s, 3H), 1.84–1.54 (m, 2H), 1.03 (t, 3H, J 7.3 Hz); δ_C 158.4, 144.0, 139.3, 137.2, 129.2, 128.5, 127.5, 127.4, 124.5, 98.6, 47.2, 33.9, 23.1, 21.1, 13.7; IR ($CHCl_3$ solution): 3420, 3040, 1580, 1500, 1460, 1030, 810 cm^{-1}; anal. calcd for $C_{19}H_{23}NOS$: C 72.80, H 7.40, N 4.47. Found: C 72.65, H 7.65, N 4.30.

*3.9. (R)-N-(p-Methoxyphenyl)-1-isopropyl-2-(p-tolylsulfinyl)ethylidenamine **9A***

Compound **9A** was obtained as an oil from *N*-(*p*-methoxyphenyl)-1,2-dimethylpropylidenamine (**15A**) (2.3 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 45 min; the treatment of the crude product was carried out as compound **8A** using AcOEt:hexane (13:30) containing 5% triethylamine as the eluent; yield 93%]. The product was present as a mixture of two imines and one enamine [estimated ratio 52:42:6 (NMR)]; $[\alpha]_D$ +71.34 (c 0.8, CH_2Cl_2); δ_H, assigned signals: imine (52): 3.83 and 3.57 (AB system, 2H, J 12.4 Hz), 3.79 (s, 3H), 2.80 (septuplet, 1H, J 6.9 Hz), 2.43 (s, 3H), 1.24 (d, 3H, J 6.9 Hz), 1.22 (d, 3H, J 6.9 Hz); imine (42): 4.05 and 3.68 (AB system, 2H, J 14.6 Hz), 3.80 (s, 3H), 2.79 (septuplet, 1H, J 6.9 Hz), 2.38 (s, 3H), 1.02 (d, 3H, J 6.9 Hz), 0.72 (d, 3H, J 6.9 Hz); enamine (6): 5.51 (bs, 1H), 5.20 (s, 1H), 3.74 (s, 3H), 2.40 (s, 3H), 1.35 (d, 3H, J 7.0 Hz), 1.39 (d, 3H, J 7.0 Hz); δ_C 171.4, 168.8, 161.7, 156.9, 155.8, 143.6, 142.9, 141.8, 141.6, 141.0, 139.3, 129.8, 129.5, 129.2, 126.4, 124.7, 124.1, 123.6, 120.3, 119.7 116.1, 115.5, 114.5, 114.0, 99.7, 77.6, 61.4, 58.8, 55.4, 55.1, 37.2, 30.9, 29.1, 27.3, 21.4, 21.2, 21.0, 20.7, 19.7, 19.0, 18.8, 14.0; IR 3080, 3000, 2410, 1515, 1430, 1270, 1050, 910 cm^{-1}.

*3.10. (*R*)-*N*-Benzyl-1-isopropyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***9B***

Compound **9B** was obtained as a white solid from sulfinyl ketone **3** and 1.1 equiv. of benzylamine [method A; the crude product was purified by chromatography, AcOEt:hexane (2:1) containing 5% triethylamine as the eluent; yield 54%] or from *N*-benzyl-1,2-dimethylpropylidenamine (**15B**) (2.3 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 30 min; the crude product was purified by chromatography, AcOEt:hexane (2:1) containing 5% triethylamine as the eluent; yield 84%]. The product was present as the enamine tautomer; mp 136–138°C; $[\alpha]_D$ −66.1 (c 1.0, CH_2Cl_2); δ_H 7.60–7.19 (m, 9H), 4.94 (s, 1H), 4.39 (m, 1H), 4.22–3.97 (m, 2H), 3.75 (septuplet, 1H, J 7.0 Hz), 2.40 (s, 3H), 1.26 (t, 6H, J 7.0 Hz); δ_C 166.4, 144.1, 139.3, 137.2, 129.2, 128.6, 127.5, 127.4, 124.3, 98.0, 47.0, 29.1, 21.7, 21.1, 20.8; IR 3485, 3000, 2415, 1590, 1510, 1215, 1020 cm^{-1}; anal. calcd for $C_{19}H_{23}NOS$: C 72.80, H 7.40, N 4.47. Found: C 72.90, H 7.39, N 4.33.

*3.11. (*R*)-*N*-(*p*-Methoxyphenyl)-1-*t*-butyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***10A***

Compound **10A** was obtained as a white solid from *N*-*p*-methoxyphenyl)-1,2,2-trimethylpropylidenamine (**16A**) (2.5 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 90 min; the crude product was purified by chromatography, AcOEt:hexane (1:4) containing 5% triethylamine as the eluent. The obtained oil was treated with AcOEt:hexane (1:4) until solidification occurred; 82% yield]. The product was present as the imine tautomer; mp 96–98°C; $[\alpha]_D$ −88.3 (c 0.8, CH_2Cl_2); δ_H 7.22 and 7.12 (AA′BB′ system, 4H), 6.89 and 6.67 (AA′BB′ system, 4H), 3.82 (s, 3H), 3.83 and 3.71 (AB system, 2H, J 9.2 Hz), 2.38 (s, 3H), 1.31 (s, 9H); δ_C 171.3, 156.0, 143.6, 141.5, 129.8, 123.4, 120.2, 114.2, 57.8, 55.4, 40.3, 28.0, 21.3; IR 3060, 3000, 2310, 1430, 1270, 1160, 1050 cm^{-1}; anal. calcd for $C_{20}H_{25}NO_2S$: C 69.93, H 7.33, N 4.08. Found: C 69.99, H 7.06, N 4.35.

*3.12. (*R*)-*N*-Benzyl-1-*t*-butyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***10B***

Compound **10B** was obtained as a white solid from sulfinyl ketone **4** and 2.0 equiv. of benzylamine [method A; the crude product was purified by chromatography, AcOEt:hexane (1:5) containing 10% triethylamine as the eluent; yield 60%]. The product was present as the imine tautomer; mp 71–72°C; $[\alpha]_D$ +145.2 (c 1.0, CH_2Cl_2); δ_H 7.57 and 7.33 (AA′BB′ system, 4H), 7.31–7.26 (m, 5H), 4.71 and 4.52 (AB system, 2H, J 16.5 Hz), 4.04 and 3.66 (AB system, 2H, J 12.8 Hz), 2.42 (s, 3H), 1.21 (s, 9H); δ_C 167.7, 142.1, 141.2, 140.1, 130.1, 128.1, 127.1, 126.3, 123.7, 55.7, 55.3, 40.9, 28.4, 21.3; IR 3400, 2950, 1575, 1430, 1130, 1050 cm^{-1}; anal. calcd for $C_{20}H_{25}NOS$: C 73.60, H 7.65, N 4.05. Found: C 73.35, H 7.70, N 4.27.

*3.13. (*R*)-*N*-(*p*-Methoxyphenyl)-1-phenyl-2-(*p*-tolylsulfinyl)ethylidenamine* ***11A***

Compound **11A** was obtained as a yellow solid from *N*-(*p*-methoxyphenyl)-1-methylbenzylidenamine (**17A**) (2.8 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 60 min; the crude product was purified by chromatography, hexane:acetone (3:1) containing 7% triethylamine as the eluent; 95% yield]. The product was present as the imine tautomer; mp 73–74°C; $[\alpha]_D$ −144.6 (c 1.0, CH_2Cl_2); δ_H 7.98–7.21 (m, 9H), 6.84 and 6.54 (AA′BB′ system, 4H), 4.37 and 4.10 (AB system, 2H, J 12.7 Hz), 3.82 (s, 3H), 2.39 (s, 3H); δ_C 158.6, 156.1, 142.8, 141.8, 139.7, 137.4, 130.7, 129.6, 128.3, 127.7, 123.8, 120.4, 113.9, 57.4, 55.2, 21.1; IR 3200, 2625, 1725, 1690, 1610, 1405, 1330, 1150, 1040 cm^{-1}; anal. calcd for $C_{22}H_{21}NO_2S$: C 72.70, H 5.82, N 3.85. Found: C 72.19, H 5.74, N 3.86.

3.14. (R)-N-Benzyl-1-phenyl-2-(p-tolylsulfinyl)ethylidenamine 11B

Compound **11B** was obtained as a white solid from sulfinyl ketone **5** and 1.3 equiv. of benzylamine using diethyl ether as the solvent [method A; the crude product was purified by chromatography, AcOEt:hexane (2:1) containing 10% triethylamine as the eluent; yield 50%] or from *N*-benzyl-1-methylbenzylidenamine (**17B**) (4.0 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 90 min; the crude product was purified by chromatography, acetone:hexane:triethylamine (3:4:1) as the eluent. The obtained oil was stirred in hexane until solidification occurred (12 h); yield 92%]. The product was present as the enamine tautomer; mp 97–98°C; $[\alpha]_D$ −121 (c 1.0, CH_2Cl_2); δ_H 7.63–7.20 (m, 14H), 5.34 (s, 1H), 4.43 (m, 1H), 4.35–4.15 (m, 2H), 2.38 (s, 3H); δ_C 157.5, 144.0, 139.2, 136.8, 135.3, 129.6, 129.1, 128.8, 128.5, 128.2, 127.4, 127.0, 124.3, 101.0, 47.6, 21.0; IR ($CHCl_3$ solution) 3440, 2980, 1580, 1500, 1430, 1020, 810 cm^{-1}; anal. calcd for $C_{22}H_{21}NOS$: C 76.05, H 6.09, N 4.03. Found: C 75.94, H 6.15, N 3.94.

3.15. (R)-N-(p-Methoxyphenyl)-1-phenyl-2-(p-tolylsulfinyl)propylidenamine 12A

Compound **12A** was obtained from *N*-(*p*-methoxyphenyl)-1-ethylbenzylidenamine (**18A**) (3.3 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 60 min; the crude product was purified by chromatography, hexane:acetone (3:1) containing 7% triethylamine as the eluent]. The analysis of the obtained product showed the presence of a mixture of different isomers, from which the major tautomer enamine could be isolated by precipitation from acetone (white solid; 87% yield); mp 163–165°C; $[\alpha]_D$ −157 (c 1.0, CH_2Cl_2); δ_H 7.55–7.22 (m, 9H), 6.61 (s, 4H), 5.87 (bs, 1H), 3.68 (s, 3H), 2.39 (s, 3H), 1.69 (s, 3H); δ_C 155.0, 149.8, 141.0, 139.5, 134.0, 130.4, 129.3, 129.0, 128.0, 124.6, 122.8, 113.7, 113.3, 55.1, 21.1, 8.43; IR 3440, 3000, 1610, 1520, 1450, 1350, 1310, 1240, 1170, 1040, 1020, 940 cm^{-1}; anal. calcd for $C_{23}H_{23}NO_2S$: C 73.17, H 6.14, N 3.71. Found: C 72.72, H 6.25, N 3.80.

3.16. (R)-N-Benzyl-1-phenyl-2-(p-tolylsulfinyl)propylidenamine 12B

Compound **12B** was obtained as a white solid from sulfinyl ketone **6** and 3.0 equiv. of benzylamine using diethyl ether as the solvent [method A; the crude product was purified by chromatography, AcOEt:hexane (1:1) containing 5% triethylamine as the eluent; yield 10%] or from *N*-benzyl-1-ethylbenzylidenamine (**18B**) (6.0 equiv.) and menthyl (*S*)-*p*-toluenesulfinate [method B; addition time of the imine was 90 min; the crude product was purified by chromatography, acetone:hexane (2:4) containing 10% triethylamine as the eluent; yield 22%]. The product was present as the enamine tautomer; mp 99–101°C; $[\alpha]_D$ −179 (c 1.1, CH_2Cl_2); δ_H 7.42–7.05 (m, 14H), 4.73 (m, 1H), 4.02–3.98 (m, 2H), 2.34 (s, 3H), 1.64 (s, 3H); δ_C 154.3, 141.3, 139.5, 139.1, 133.3, 129.6, 129.1, 128.8, 128.3, 128.1, 127.0, 126.8, 124.6, 107.3, 48.0, 21.0, 7.4.

Acknowledgements

We thank Dirección General de Investigación Científica y Tecnica (DGICYT, Grant PB95-210) for financial support.

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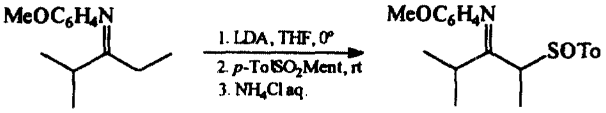
24. To check this assumption, we prepared imine **20A** and studied its reaction with menthyl *p*-toluenesulfinate at room temperature. The reaction is completely regioselective, yielding only imino sulfoxide **21A**.



20A **21A**

25. Configurational assignment of compounds **19A** and **19A′** could be unequivocally established from the results obtained in the stereoselective reductions of these substrates and mainly from the stereochemistry of rigid cyclic substrates (aziridines and sulfonium salts derived from 1,4 oxathian) obtained from them through stereoselective processes. All these results will be published in due course.
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