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Use of Lithiated Chiral *ortho*-Sulfinyl Benzyl Carbanions for the *One-pot* Building of Linear Fragments Containing up to Four Connected Stereocenters.

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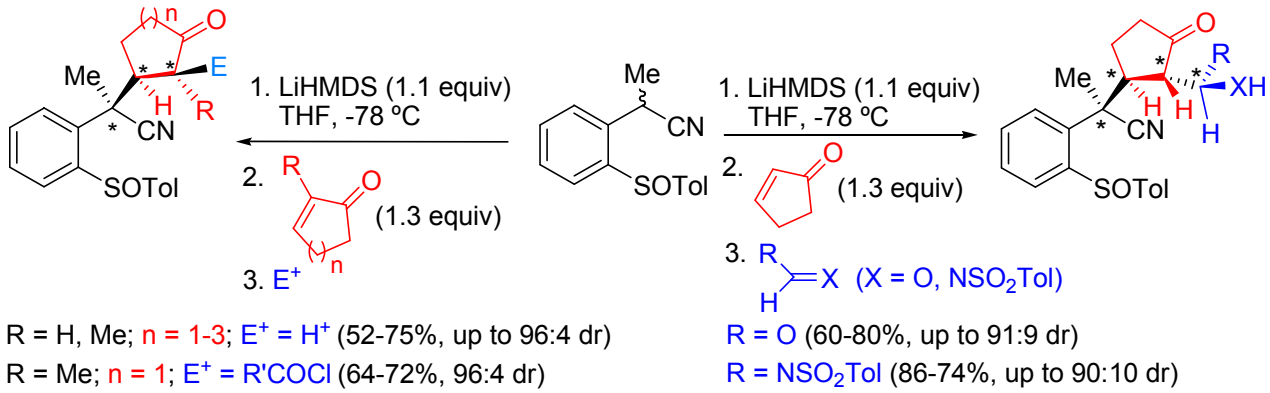
Dedicated to the memory of Dr. Christian G. Claessens

SYNOPSIS TOC (TABLE OF CONTENTS GRAPHIC)



ABSTRACT.

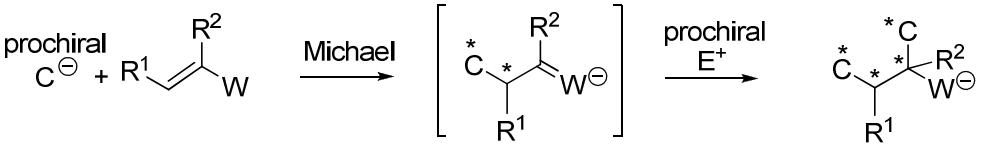
The reaction of *ortho*-sulfinyl benzyl carbanions with prochiral Michael acceptors, such as differently sized cycloalkenones, proceeded with high levels of stereoselectivity, generating molecules containing up to three asymmetric carbon centers in just one synthetic step. All these reactions involved the use of either a proton or an acylating reagent as the final electrophile. Furthermore, the trapping of the enolate resulting from Michael addition with prochiral electrophiles, such as aldehydes or *N*-sulfonyl imines, allowed the highly stereoselective synthesis of densely functionalized compounds containing four chiral centers in just a one-pot sequence, the stereochemical outcome of the sequence being controlled by the sulfinyl auxiliary.

KEYWORDS: asymmetric synthesis, quaternary carbons, benzyl carbanions, Michael addition, sulfoxides, remote stereocontrol.

Introduction

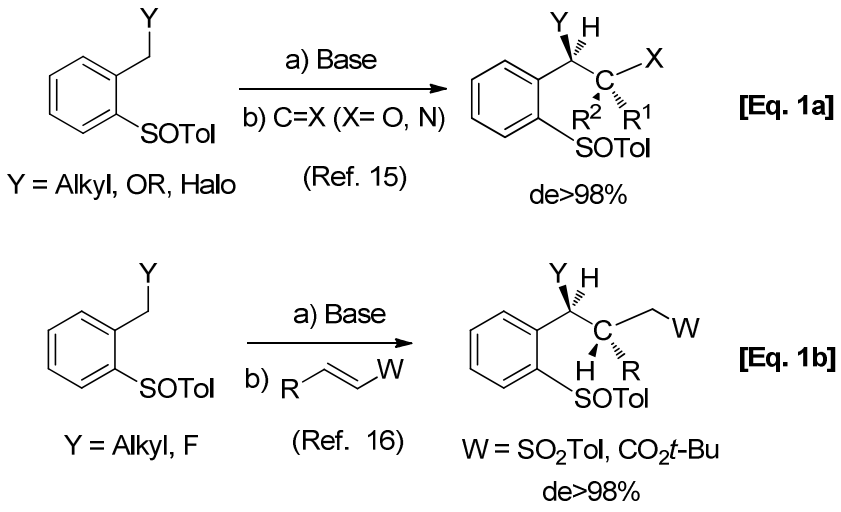
Molecular fragments containing several connected stereogenic carbon atoms are present in many natural products. Asymmetric cycloadditions provide the most efficient method for the simultaneous creation of up to four asymmetric centers in only one synthetic step and have been widely used in the synthesis of cyclic substrates.[1-14] By contrast, the preparation of linear fragments containing more than two connected asymmetric centers in only one synthetic step, usually requires the concatenation of two (or more) reactions susceptible to be applied in one-pot sequence. A very simple strategy for achieving

these processes would involve the trapping of the intervening enolates resulting from the Michael reactions with suitable electrophiles (Scheme 1). Hence, the Michael reactions of prochiral carbanions with activated olefins would provide enolates containing two stereocenters, and the trapping of such enolates with prochiral electrophiles would provide acyclic compounds with up to four connected asymmetric carbon atoms.



Scheme1. Strategy for obtaining linear fragments containing up to four connected stereocenters.

Despite the apparent simplicity of this strategy, to our knowledge, there are no reported papers illustrating it. Two main problems limit the application of this strategy to the synthesis of acyclic compounds. One of them is the difficulty of finding proper prochiral nucleophiles capable of reacting stereoselectively in Michael additions. The second one derives from the required stereocontrol of the second step, which imposes the regioselective formation of the enolate and the facial discrimination of the favored regioisomer. We have recently reported that the *ortho*-sulfinyl group is an efficient stereoselectivity controller of the configuration of benzyl carbanions in their reactions with different electrophiles (Equation **1a**, Scheme 2).[15] Amongst them, 2-*p*-tolylsulfinyl derivatives of ethylbenzene and benzyl fluoride have been satisfactorily used as precursors of the nucleophiles used in Michael-type processes with sulfonylethylenes and unsaturated *t*-butyl esters (Equation **1b**, Scheme 2).[16] However, all the attempts starting from unsaturated carbonyl compounds proved to be unsuccessful and afforded complex mixtures as the result of a competence between the 1,2- and 1,4-addition processes (ethyl esters also gave similarly complex mixtures).

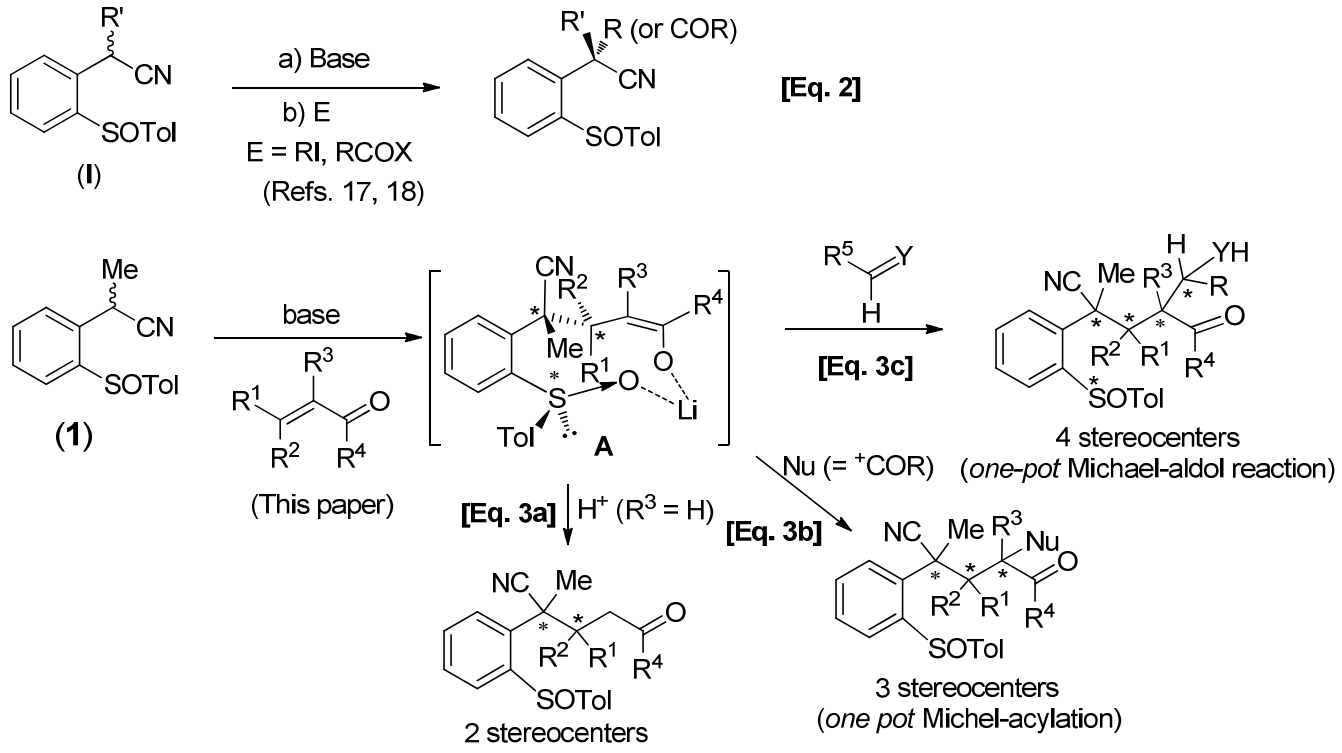


Scheme 2. Reported strategies for the asymmetric construction of two vicinal stereocenters based on the use of a sulfinyl group as remote chiral inductor.

On the other hand, we have also reported the high efficiency of the *ortho*-sulfinyl group for the configurational stabilization of the benzyl carbanions derived from α-alkyl phenylacetonitriles (**I**) (Equation **2**, Scheme 3), allowing the construction of quaternary stereocenters in their reactions with alkylating[17] and acylating[18] reagents. Taking into account that these tertiary carbanions are softer than the previously commented secondary ones (Equation **1b**, Scheme 2), and, therefore, presumably more efficient in Michael-type processes, we decided to use compounds **1** as precursors of the nucleophiles depicted in Scheme 1. This would determine the formation of linear fragments with up to four stereogenic centers, the first one being quaternary, in a one-pot process (Equations **3**, Scheme 3), which would be an even more relevant synthetic challenge.[19, 20] Moreover, the stability of the enolates resulting from these Michael reactions could be substantially stabilized by chelation (**A** in Equation **3**, Scheme 3), thus preventing or minimizing the retro-Michael processes, and fixing one conformation of the enolate with their two faces sterically very well differenciated and, therefore, susceptible to evolve stereoselectively in the presence of appropriate electrophiles.

We report herein the results obtained in the Michael reactions of cyclic and acyclic enones with the anion derived from 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1**) affording ketones with two

connected asymmetric centers, one of them quaternary (Equation **3a**, Scheme 3). Additionally, the *in situ* trapping of the enolates formed in these reactions with acylating reagents (*one-pot* Michael-acylation processes, Equation **3b**, Scheme 3) as well as with aldehydes or aldimines (*one-pot* Michael-aldol processes, Equation **3c**, Scheme 3), allowing the simultaneous creation highly functionalized linear fragments containing three or four connected asymmetric centers in only one synthetic step, will also be presented.



Scheme 3. Proposed strategies for the asymmetric synthesis of fragments containing two, three or four connected stereocenters, the first one being quaternary.

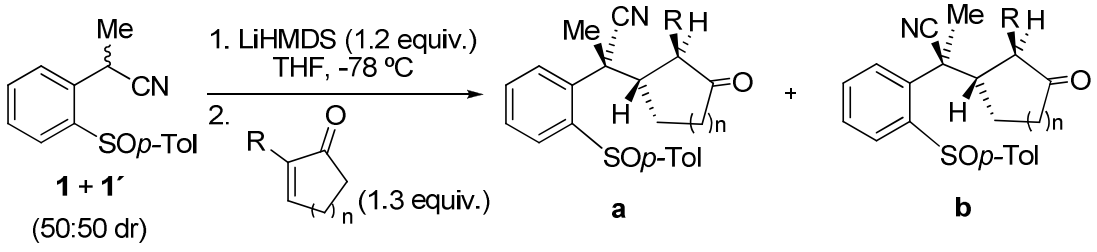
Results and Discussion

Initially we studied the reaction of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile,[17] as an epimeric 50:50 mixture at the benzylic carbon atom (**1** + **1'**), with cyclopent-2-enone under different experimental conditions (Table 1, entries 1-4). The use of THF as the solvent afforded the best conversions into diastereomerically enriched mixtures of isomers **2a** and **2b** (Table 1, entries 1-3), **2a**

being the major product under all the assayed conditions. The highest yield (75%) and diastereoselectivity (dr 95:5) were obtained with LiHMDS (Table 1, entry 3). A substantial erosion of both reactivity (40% conversion) and stereoselectivity (dr 80:20) was observed in the presence of 12-crown-4 ether, which suggests that a relevant role should be played by the cation Li^+ in the course of the process (Table 1, entry 4). These reactions conducted under NaHMDS (dr 80:20, Table 1, entry 2) or KHMDS (dr 85:15, Table 1, entry 1) gave lower stereoselectivities.

When the size of the cycloalkenone ring became larger, the stereoselectivity decreased. Thus, the reactions of **1** + **1'** with cyclohex-2-enone (Table 1, entry 5) and cyclohept-2-enone (Table 1, entry 6), both under LiHMDS, also afforded mixtures of two diastereoisomers, with 85:15 and 82:18 dr, respectively. The use of 2-methyl-2-cyclopentenone as the electrophile afforded a mixture of only two isomers, **5a** and **5b**, despite an additional stereocenter was created in the reaction (Table 1, entry 7). The stereoselectivity was similar (96:4 dr) to that observed in the reaction with cyclopentenone (compare entries 3 and 7, Table 1), which suggests that the resulting isomers in both reactions should be epimers at the same carbon. Unfortunately, the reaction of **1** + **1'** with 3-methylcyclopent-2-enone, which would provide adducts containing two adjacent quaternary stereocentres, proved to be unsuccessful and the unaltered starting materials were recovered after long reaction times.

Table 1. Reactions of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1** + **1'**) with different cycloalkenones.



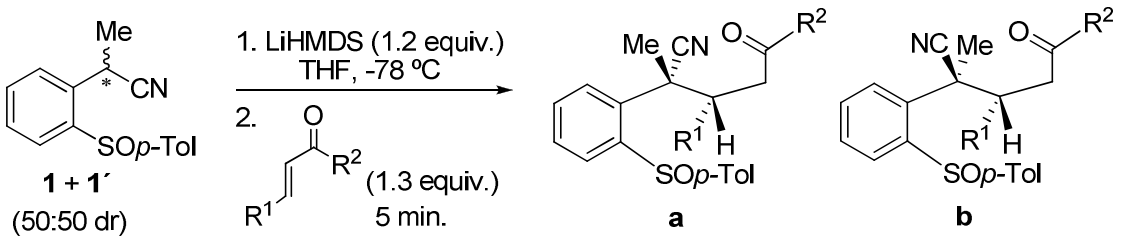
entry	base (additive)	time (min)	product	n	R	Yield (%)[a]	d.r. (**a**:**b**)
1	KHMDS	5	**2a** + **2b**	1	H	68	85:15
2	NaHMDS	5	**2a** + **2b**	1	H	65	80:20

3	LiHMDS	5	**2a** + **2b**	1	H	91	95:5
4	LiHMDS (12-crown-4 ether)	15	**2a** + **2b**	1	H	n.d.[b]	80:20
5	LiHMDS	5	**3a** + **3b**	2	H	70	85:15
6	LiHMDS	5	**4a** + **4b**	3	H	52	82:18
7	LiHMDS	5	**5a** + **5b**	1	Me	67	96:4

[a]Isolated yield for diastereoisomeric **a** + **b** mixtures. [b]40% Conversion.

The behavior of the benzylic carbanion derived from **1** + **1'** in the presence of acyclic Michael acceptors, such as α,β-unsaturated methyl ketones and esters, was investigated next. These reactions also gave mixtures of only two diastereoisomers under mild experimental conditions (-78 ºC), in good yields (Table 2). The reaction with methyl vinyl ketone afforded a 85:15 mixture of **6a** and **6b** (Table 2, entry 1), which should be obviously epimeric at the benzylic carbon, since this is the only stereocenter formed in the reaction. The dr value was identical to that obtained in the reaction with cyclohexanone (Table 1, entry 6). The reaction with ethyl acrylate was even more stereoselective, and yielded a mixture of epimers **8a** and **8b** (Table 2, entry 3) with identical dr value (95:5) to that obtained from cyclopentenone (Table 1, entry 3). The reactions of **1** + **1'** with both β-substituted enonic and acrylic systems also afforded mixtures of two diastereoisomers, despite two asymmetric carbon atoms were simultaneously created in the reaction. Mixtures of **7a** + **7b** (80:20 dr) and **9a** + **9b** (85:15 dr) were obtained from (*E*)-pent-3-en-2-one and ethyl crotonate, respectively (Table 2, entries 2 and 4). The similar dr values obtained in the reactions of Tables 1 and 2 suggest that the obtained diastereoisomers differ in all the cases in the configuration of the quaternary carbon atom. This suggestion is supported by the fact that similar dr's had been obtained in reactions of **1** + **1'** with alkylating[17] and acylating[18] reagents.

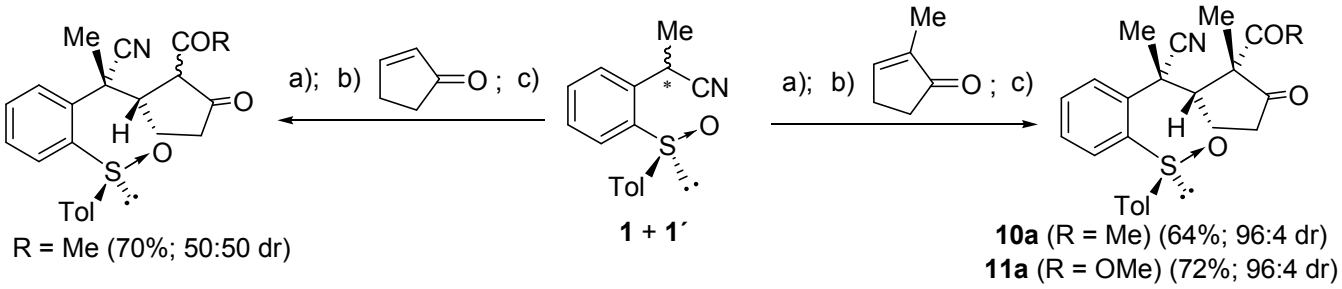
Table 2. Reactions of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1** + **1'**) with acyclic Michael acceptors.



entry	product	R^1	R^2	Yield (%)[a]	d.r. (**a**:**b**)
1	**6a** + **6b**	H	Me	78	85:15
2	**7a** + **7b**	Me	Me	65	80:20 [b]
3	**8a** + **8b**	H	OEt	76	95:5
4	**9a** + **9b**	Me	OEt	80	85:15 [b]

[a]Isolated yield for diastereoisomeric **a** + **b** mixtures. [b]The configuration of C-β relative to carbonyl group was not determined.

We next investigated tandem processes involving the trapping of some of the enolate intermediates generated in the Michel addition reactions collected in Table 1, with a variety of electrophiles different from proton. The reaction of **1** + **1'** with cyclopent-2-enone and further addition of MeI was unsuccessful. Fortunately, the addition of acetyl chloride produced the expected products. A diastereoisomeric 1:1 mixture was obtained in the reaction of the intermediate enolate generated from cyclopentenone, whereas the enolate derived from 2-methylcyclopent-2-enone evolved in a highly stereoselective manner (96:4 dr) when it was trapped by acetyl chloride or methyl chloroformate, affording **10a** and **11a**, respectively (Scheme 4). The similarity between the stereochemical results of this reaction with those observed when proton was used as the electrophile (Table 1, entry 7) suggests that the stereochemical outcome is not dependent on the nature of the electrophile used in the second step and, therefore, the resulting adducts do not differ in the configuration of the α-carbonyl quaternary stereocenter. So, the formation of fragments containing three connected stereogenic carbons, two of them quaternary, is possible from these reactions.



Conditions: a) LiHMDS (1.2 equiv), THF, -78 ºC; b) enone (1.3 equiv); c) RCOCl (2.5 equiv)

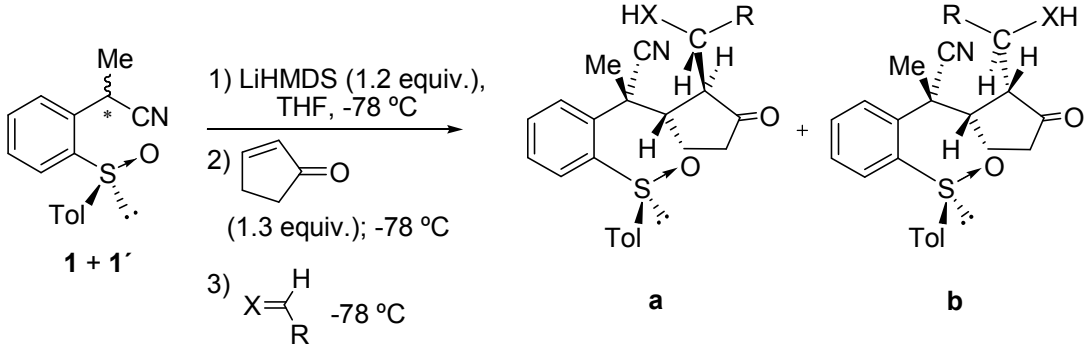
Scheme 4. Tandem Michael addition/acylation sequences resulting from reactions of **1** + **1'** with cyclopent-2-enone or 2-methylcyclopent-2-enone, and then with R'COCl.

Finally, the intermediate enolates of the conjugate addition were treated with prochiral electrophiles (aldehydes and aldimines),[21] so that chiral compounds with four contiguous stereocenters could be formed in only one synthetic step (*one-pot* Michael addition/aldol reaction sequence), the stereoselectivity of which would be controlled by the sulfinyl group present in the initially formed carbanion. Thus, the enolate resulting from the reaction of **1** + **1'** with cyclopent-2-enone reacted with an excess amount of a variety of both aliphatic and aromatic aldehydes yielding mixtures of only two isomers, **a** and **b**, one of them being clearly predominant in all the cases (Table 3). The reactivity with aliphatic aldehydes was seemingly dependent on the steric size of the aldehyde, *i*-Pr-CHO being the less reactive (Table 3, entry 3), whereas the stereoselectivity was similar for compounds **12-15** and the dr values ranged between 87:13 and 91:9 (Table 3, entries 1-4). The reactivity of the aryl aldehydes (Table 3, entries 5-7) was dependent on the electronic density at the aromatic ring. As expected, it was lower when electron-donating groups were present in the aromatic ring (Table 3, entry 6). The presence of an electron-withdrawing NO_2 substituent also slowed down the reaction although to lower extent (Table 3, entry 7); this result was probably due to the fact that in this aldehyde the carbonyl group is no longer conjugated with the aromatic ring and other effects rather than the electrostatic ones are playing a role. The stereoselectivity was also lower (dr's ranged between 86:14 and 80:20) than that observed for the aliphatic aldehydes. Taking into account that a substantially higher dr had been obtained in the reaction of **1** + **1'** with cyclopent-2-enone (95:5, Table 1, entry 3), the factors determining the composition of the

diastereomeric mixtures must be different in both sets of reactions.

Our next goal was to apply the methodology described above to the development of the tandem Michael addition / aldol reaction sequence to trapping the intervening enolates with *N*-sulfonyl imines (Table 3, entries 8-10). When the enolate formed in the reaction of **1** + **1'** with cyclopent-2-enone was treated with both aliphatic (Table 3, entries 8-9) and aromatic (Table 3, entry 10) *N*-sulfonyl aldimines, mixtures of only two diastereoisomers were obtained with very good stereoselectivities (dr's ranged between 87:13 and 90:10) and a similar reactivity to that of the aliphatic aldehydes. The attempts to perform the reactions of the intermediate enolate resulting from the reaction of **1** + **1'** with 2-methylcyclopent-2-enone with aldehydes and *N*-sulfonyl imines failed.

Table 3. *One-pot* Michael addition/aldol reaction of **1** + **1'** with cyclopent-2-enone and then with aldehydes and *N*-sulfonyl imines.



entry	electrophile R; X (equiv.)	time (min.)[a]	product	d.r. (**a** : **b**)[b]	Yield (%)[c]
1	Me; O (2.5)	5	**12a** + **12b**	87:13	79
2	Et; O (2.5)	5	**13a** + **13b**	90:10	80
3	*i*-Pr; O (2.5)	180	**14a** + **14b**	87:13	65
4	*i*-Bu; O (2.5)	5	**15a** + **15b**	91:9	72
5	Ph; O (5.0)	5	**16a** + **16b**	86:14	77
6	*p*-$MeOC_6H_4$; O (5.0)	180	**17a** + **17b**	85:15	60
7	*p*-$NO_2C_6H_4$; O (2.5)	30	**18a** + **18b**	80:20	75
8	*n*-Pent; NSO_2Tol (1.5)	60	**19a** + **19b**	90:10	68
9	*i*-Pr; NSO_2Tol (1.5)	60	**20a** + **20b**	87:13	72

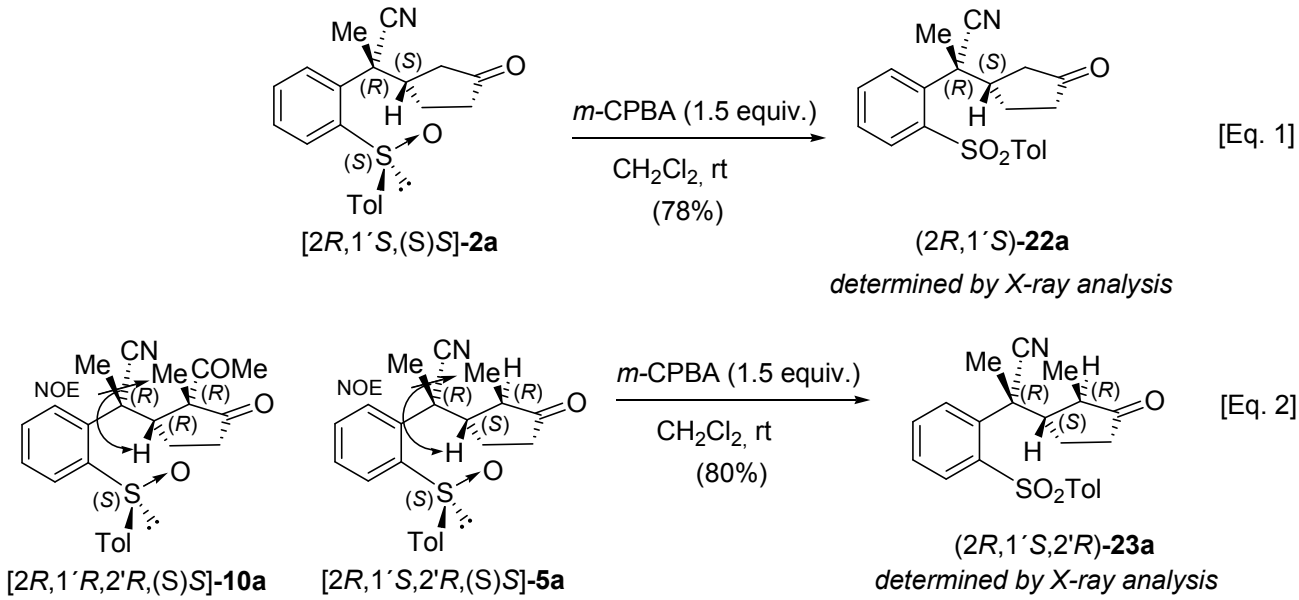
10	Ph; NSO_2Tol (1.5)	5	**21a + 21b**	89:11	74

[a]Reaction time in the presence of the electrophile (aldehyde or *N*-sulfonyl imine). [b]Diastereomeric ratio determined by integration of well-separated signals of the ^{1}H NMR spectra and by HPLC analysis of the crude reaction. [c]Yield of the diastereomeric mixture.

Chromatographic separation of the mixtures obtained in reactions of Tables 1-3 allowed us to obtain the major **a** isomers in their diastereomerically pure form. However, usually the minor **b** isomers could not be obtained as pure isomers (see S.I. for some exception) and their characterization was performed from the spectroscopic data obtained from diastereomeric mixtures containing them.

Configurational assignments

The impossibility of obtaining good crystals from the major diastereoisomers **2a** and **5a** prevented us from assigning their absolute configurations by X-ray analysis. Fortunately, sulfones **22a** and **23a**, prepared by oxidation of **2a** and **5a**, respectively, afforded suitable crystals, which allowed us to unequivocally establish their absolute configurations as 2*R*,1´*S* and 2*R*,1'*S*,2'*R*, respectively, by X-ray diffraction studies. As the sulfur configuration of sulfoxides **2a** and **5a** was previously known, its absolute configurations were, therefore, unequivocally established as 2*R*,1'*S*,(S)*S* and 2*R*,1'*S*,2'*R*,(S)*S*, respectively (Scheme 5).[22] Since the stereochemical pathway of the conjugate addition should be similar for all the assayed cycloalkenones, the absolute configuration 2*R*,1'*S*,(S)*S* was assigned to the major isomers **3a** and **4a** (Table 1). The similar NOE effects between the Me and the H indicated in Scheme 5 (Eq. 2) observed for compounds **5a** and **10a**, indicative of a *syn* spatial arrangement of both groups in the cyclopentenone fragment, suggest that both compounds have the same relative arrangement of the substituents, although the stereochemical notation is different [2*R*,1'*R*,2'*R*,(S)*S* for **10a**, see Scheme 5]. Since a similar stereochemical evolution must be predicted for reactions affording **10a** and **11a**, the absolute configuration of **11a** should be the same as that assigned to **10a**.



Scheme 5. Configurational assignment of the adducts from Michael additions and tandem Michael addition/acylation sequences.

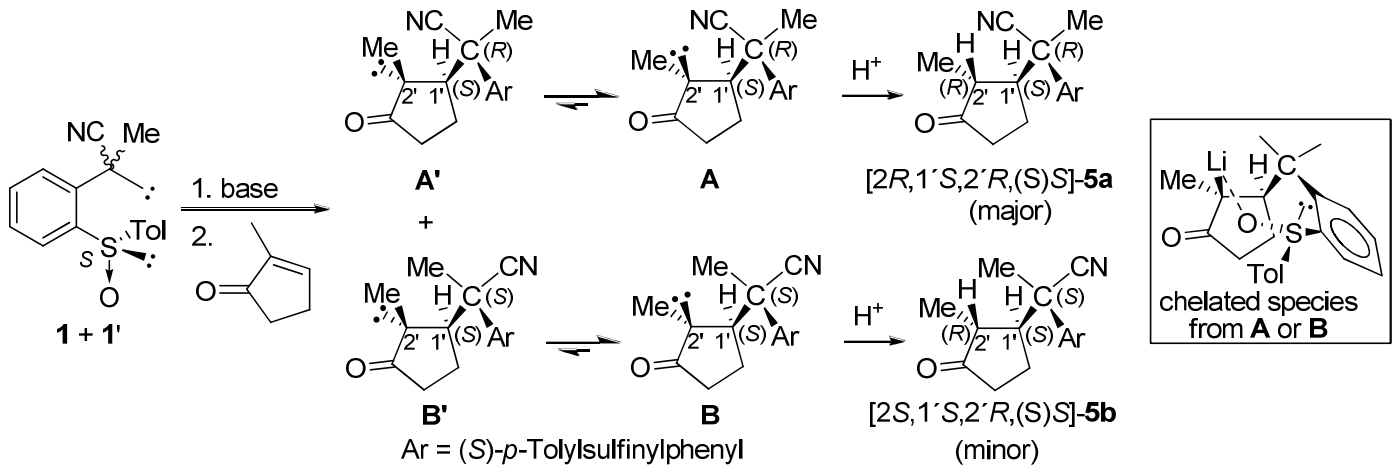
The absolute configurations of **14a** [2*R*,1'*S*,2'*S*,1"*R*,(S)*S*] and **21a** [2*R*,1'*S*,2'*S*,1"*S*,(S)*S*] were unequivocally established by X-Ray diffraction analysis.[22] Therefore, all the major diastereoisomers **12a-18a** (Table 3) should exhibit the same absolute configuration as **14a** (although the *R/S* notation for the C-1" stereocenter will be dependent on the nature of the R substituent of the corresponding aldehyde). Analogously, the configurations of **19a** and **20a** should be identical to that of **21a**.

Finally, from the assumption of a similar stereochemical evolution for all the reactions of Tables 1 and 2, we assigned the same configuration of the benzylic carbon atom to all the major isomers **a** collected in both Tables. Thus, the absolute configurations of **6a** and **8a** were established as 2*R*,(S)*S*, whereas those for **7a** and **9a** must be 2*R*,1'*R*,(S)*S*, with the configuration at C-1' different to that of adducts **2a-4a**, because of the different stereochemistry of the double bonds of the respective starting materials (*Z* in cycloalkenones and *E* in pent-3-en-2-one and ethyl crotonate).

The configuration of the isomers **b** at Table 1 was tentatively assigned as 2*S*,1'*S*,(S)*S* by NMR (see S. I.), differing from that for the epimers **a** in the configuration of the benzylic quaternary carbon atom. This assignment was mainly supported by the fact that the stereoselectivity observed in reactions

of **1** + **1'** with cycloalkenones (Table 1) was similar to that obtained with methyl vinyl ketone and methyl acrylate (Table 2, entries 1 and 3, respectively), where only one stereocenter was formed.

From the above configurational assignments, it can be concluded that the reactions affording **2**, **5**, **10** and **11**, always produce epimeric mixtures at the benzylic C-2 carbon atom. This suggests a completely stereoselective reaction of the intermediate enolate with the electrophile (proton or acyl derivative) in those processes using 2-methylcyclopent-2-enone (synthesis of **5**, **10** and **11**, respectively), which can be understood by assuming the thermodynamic equilibration of the carbanions obtained in the conjugate addition step (Scheme 6). The carbanion exhibiting a *cis* arrangement between the lone electron pair and the quaternary carbon atom, regardless of the configuration of the latter, must be clearly favored in the equilibrium in order to avoid unstabilizing Me/quaternary carbon interactions. Furthermore, species **A** and **B** could be additionally stabilized (with respect to **A'** and **B'**) by formation of chelated species with the sulfinyl oxygen, such as depicted in Scheme 6. Therefore, the electrophile (H^+ in Scheme 6) should approach the face exhibiting the electron pair in the anions derived both from the major (anion **A**) and the minor (anion **B**) isomers. Consequently, the isomers **a** and **b** of compounds **2**, **5**, **10**, and **11** will differ only in the configuration at the benzylic carbon C-2.



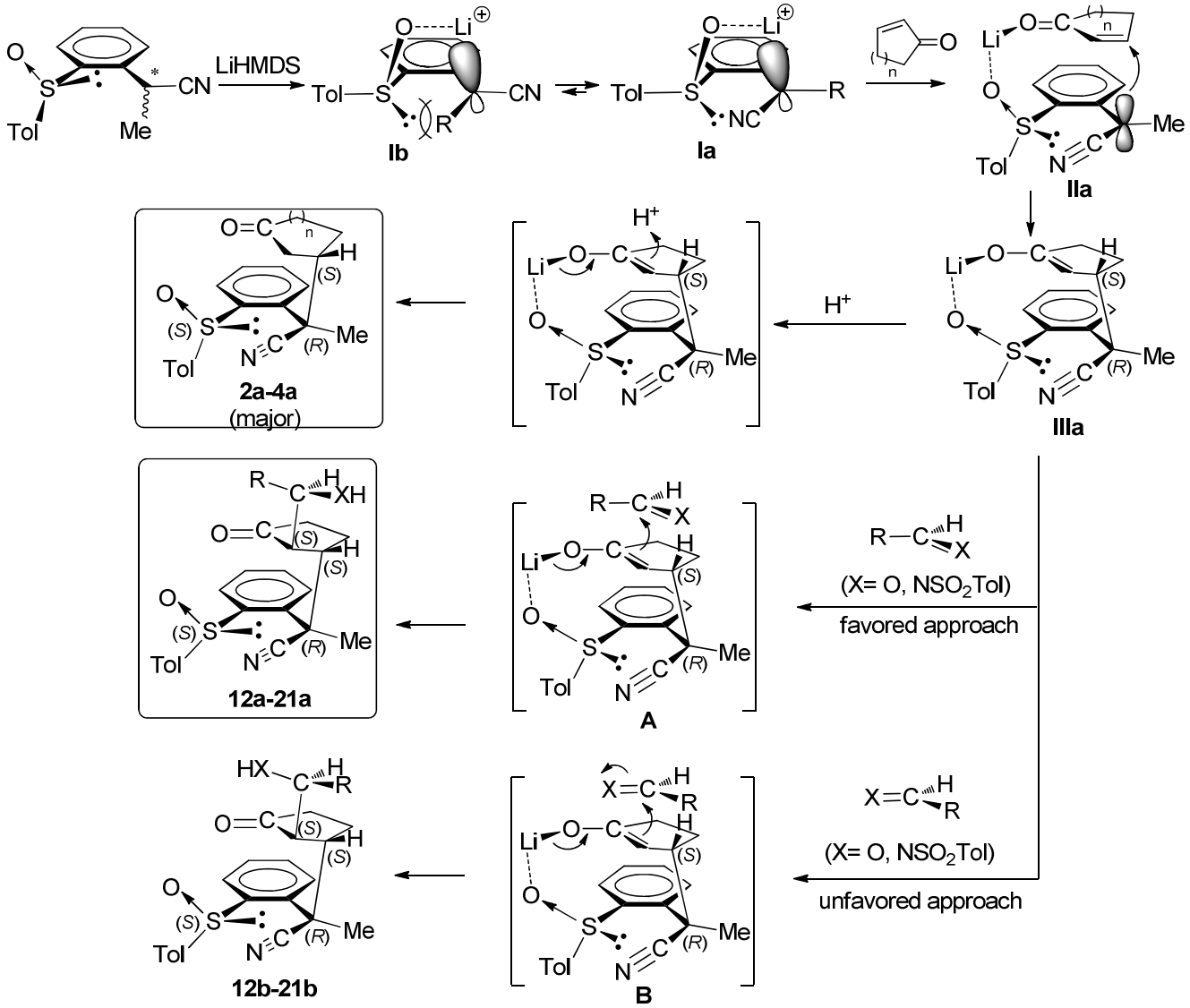
Scheme 6. Proposed thermodynamic intermediate equilibrium accounting for the stereoselectivity of the reactions of **1** + **1'** and 2-methylcyclopent-2-enone.

The results collected in Table 3 are indicative of a lower diastereoselectivity for the *one-pot* Michael addition/aldol reaction sequences (< 90:10 dr) than that observed for the conjugate addition to cyclopent-2-enone (95:5 dr, Table 1, entry 3), which is the first step common to all these sequences. This different stereochemical outcome suggests that the isomers **a** and **b** obtained in the reactions of Table 3 would differ in the configuration of one of the two stereocenters created in the reaction of the intermediate enolate with the prochiral electrophile (aldehyde or imine), and both (**a** and **b**) should exhibit the same configuration at the quaternary benzylic carbon atom (the compounds with the opposite configuration at this center should be present in too low proportion as to be detected).

Mechanistic proposal.

The stereochemical results obtained in the above described reactions can be explained as follows. The reaction of **1** + **1'** with LiHMDS initially generates the boat-like chelated sp^3 carbanionic species **Ia** (more stable than **Ib** from a steric and electrostatic viewpoint, Scheme 7) predominantly,[17] with the metal associated to both the sulfinyl oxygen and the benzylic carbon atom. Such as it had been postulated for the acylation processes of these carbanions,[18] the carbonyl oxygen atom of cycloalkenones may coordinate with the cation Li^+, thus breaking the initial boat-like chelate **Ia** and generating a new intermediate species **IIa**. Intramolecular addition from **IIa** would afford **IIIa** with the *R* configuration at the benzylic stereocenter, coincident with that observed for the major diastereoisomers **a**. Simultaneously, the *S* configuration of the C-β atom at the cycloalkenone ring can also be predicted from this approach (Scheme 7). The formation of the chelated species **IIIa**, with the lithium doubly stabilized, can be considered as crucial for the chemical success of these reactions, because it is responsible for the shifting of the equilibrium involved in the Michael addition toward the final product (otherwise, the steric demand of the quaternary center would favor the retro-Michael process). Additionally, it is also determinant of the stereochemical control of the electrophilic approach, which will take place to the less hindered face of the intermediate, generating the major

diastereoisomers **a** in all the cases. Thus, when the electrophile is a proton, compounds **2a-4a** are formed (Scheme 5). With prochiral electrophiles (aldehydes or imines) two new stereocenters will be formed. The configuration at C-α of the cyclopentenone ring will be *S*, such as can be predicted from the stereochemical model proposed for the process, in complete agreement with the unequivocal configurational assignment for **12a-21a** (see above) and **12b-21b** (Scheme 7). The configuration of C-X in these epimers will depend on the face of the C=X bond favoured for the approach of **IIIa**.



Scheme 7. Mechanistic proposal accounting for the stereochemical outcome of Michael-type additions of carbanion derived from **1** + **1'** to cycloalkenones, and subsequent reaction with a proton or a prochiral electrophile (aldehyde or imine).

The **A** and **B** approaches of the electrophile (Scheme 7), both arranging the C-H bond inward the cyclopentanone ring in order to minimize the steric interactions, are plausible. The smaller dipolar repulsion in the approach **A** would make easier the formation of epimers **a**, thus justifying their formation as the major products in reactions with acyclic enones (Table 2) and with 2-methylcyclopent-2-enone.[23, 24]

From all the above results we can conclude that the *ortho*-sulfinyl group has proved to be highly efficient as a stabilizer of the configuration of tertiary benzylic carbanions in their reactions with Michael acceptors affording compounds bearing quaternary centers connected to other asymmetric carbons. Additionally, the capture of the resulting enolates with acyl chlorides (*one pot* Michael addition/acylation process) and aldehydes or *N*-sulfonylimines (*one pot* Michael addition/aldolic reaction) has allowed us the preparation of structural fragments respectively containing three connected stereocenters (two quaternary carbons joined to the same tertiary carbon) and four consecutive stereocentres (quaternary-tertiary-tertiary-tertiary) in high enantiomeric purities. We are now extending the scope of this methodology to the reactions to *ortho*-sulfinylated benzylcyanohydrins and benzylamino nitriles and using this methodology for the preparation of natural product fragments.

EXPERIMENTAL SECTION

GENERAL PROCEDURES

NMR spectra were registered (300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively) in $CDCl_3$ solutions. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Melting points were measured in open capillary tubes. Mass spectra (MS) were determined by EI, FAB and ESI, as indicated in each case. High resolution mass spectra (HRMS) were performed by using a magnetic-sector mass analyzer (for FAB ionization mode) or time-of-flight (TOF) mass analyzer (for EI and ESI ionization modes), as indicated for each compound. All reactions were carried out in anhydrous solvents under argon atmosphere. Commercially available anhydrous tetrahydrofuran (THF) and ethyl ether (Et_2O)

were dried over 4Å molecular sieves. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates and visualized by ultraviolet irradiation or $KMnO_4$ stain. Purification of reaction products was carried out by flash column chromatography using silica gel (230-400 mesh) or by *Combiflash* system using normal phase column (ISCO). The diastereomeric excess (*de*) of products was determined by chiral stationary phase HPLC. Commercially available Michael acceptors and aldehydes were used without further purification.

General procedure for Michael addition reaction of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile. To a solution of diastereoisomerc 50:50 mixture of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1** + **1'**, 40.0 mg, 0.15 mmol) in anhydrous THF (1.5 mL) at -78 °C under argon was added LiHMDS (1M in THF) (162 μL, 0.18 mmol). The mixture was stirred at -78 °C for 5 min. and then 0.19 mmol of the corresponding Michael acceptor was added dropwise. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed using the method indicated in each case. The mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4) and the solvent was evaporated. The diastereoisomeric mixture was purified by flash column chromatography or by *Combiflash* system using a normal phase column (ISCO), the used eluent was indicated in each case.

[2*R*,1′*S*,(S)*S*] and [2*S*,1′*S*,(S)*S*]-2-(3′-Oxocyclopentyl)-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (2a + 2b). Cyclopent-2-enone was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. following by hydrolysis with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 95:5 mixture of **2a** + **2b**, from which **2a** was separated and purified by flash column chromatography using a *Combiflash* system (EtOAc-hexane gradient 10:90 to 100:0). Yield 91%, 47.9 mg (mixture **2a** + **2b**). Diastereoisomer [2*R*,1′*S*,(S)*S*]-**2a**: colorless oil; $[\alpha]^{20}_D$ -146.9 (*c* 1.2, $CHCl_3$); IR (film): 3468, 2253, 1746, 1216, 1046, 729 cm^{-1}; ^1H NMR: δ 8.01-7.98 (m, 1H), 7.75-7.59 (m, 1H), 7.57-7.53 (m, 2H), 7.45 and 7.28 (AA′BB′ system, 4H), 2.99-2.89 (m, 1H), 2.47-2.21 (m, 2H), 2.38 (s, 3H), 2.05 (s, 3H), 1.91-1.73 (m, 2H), 1.64-1.59 (m, 2H) ppm; ^{13}C NMR: δ 214.5, 143.7, 141.9, 140.9, 137.6, 132.2, 130.2 (2C), 129.7, 127.7, 126.0 (2C), 121.5, 77.2, 47.3, 46.9, 40.9, 38.2, 26.2, 25.3, 21.3 ppm; MS (FAB+) *m/z* 352 $[M+H]^+$ (100), 259 (15); HRMS (ESI+) calcd. for $C_{21}H_{22}NO_2S$: 352.1371; found: 352.13800. Diastereoisomer [2*S*,1′*S*,(S)*S*]-**2b** (significant chemical shifts obtained from an epimeric 86:14 mixture **2a** + **2b**): ^1H NMR: δ 7.95-7.91 (m, 1H), 7.89-7.85 (m, 1H), 3.43 (m, 1H), 2.65 (m, 1H), 1.65-1.59 (m, 1H), 2.10 (s, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^1H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD

[hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]; major diastereoisomer **2a**: t_R = 26.8 min. (95%) and minor diastereoisomer **2b**: t_R = 30.6 min. (5%).

[2*R*,1´*S*,(S)*S*] and [2*S*,1´*S*,(S)*S*]-2-(3´-Oxocyclohexyl)-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (3a + 3b). Cyclohex-2-enone was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 86:14 mixture **3a** + **3b**, which was purified by flash column chromatography using a *Combiflash* system (EtOAc-hexane gradient 10:90 to 100:0). Yield 70%, 38.3 mg (mixture **3a** + **3b**, colorless oil). Diastereoisomer [2*R*,1´*S*,(S)*S*]-**3a**: IR (film): 3356, 2401, 1714, 756 cm^{-1}; ^1H NMR (86:14 mixture **3a** + **3b**): δ 7.95 (dd, *J* 3.2 and 5.9 Hz, 1H), 7.78-7.69 (m, 1H), 7.55-7.45 (m, 2H), 7.36 and 7.25 (AA´BB´ system, 4H), 2.76-2.64 (m, 1H), 2.52-2.10 (m, 4H), 2.37 (s, 3H), 2.03 (s, 3H), 1.96-1.86 (m, 1H), 1.64-1.55 (m, 2H), 1.12-0.95 (m, 1H) ppm; ^{13}C NMR (86:14 mixture **3a** + **3b**): δ 208.4, 143.6, 141.8, 141.0, 138.1, 132.1, 130.2 (2C), 129.9, 128.2, 125.9 (2C), 125.4, 121.6, 77.2, 44.4, 40.6, 27.5, 26.7, 24.1, 23.8, 21.3 ppm; MS (FAB+) *m/z* 366 $[M+H]^+$ (100), 225 (14); HRMS (ESI+) calcd. for $C_{22}H_{24}NO_2S$: 366.1527; found: 366.1528. Diastereoisomer [2*S*,1´*S*,(S)*S*]-**3b** (significant chemical shifts obtained from an epimeric 86:14 mixture **3a** + **3b**): ^1H NMR: δ 7.89-7.86 (m, 1H), 7.78-7.69 (m, 1H), 7.55-7.45 (m, 2H), 7.38 and 7.26 (AA´BB´ system, 4H), 2.86 (tt, *J* 4.2 and 11.6 Hz, 1H), 2.38 (s, 3H), 2.00 (s, 3H), 1.81-1.67 (m, 2H), 0.91-0.82 (m, 1H) ppm; ^{13}C NMR: δ 208.1, 143.7, 141.7, 140.4, 137.9, 130.7, 130.3, 130.1 (2C), 130.0, 128.1, 126.1 (2C), 121.4, 46.1, 43.1, 40.7, 26.6, 24.5, 23.6, 21.3 ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^1H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]; major diastereoisomer **3a**: t_R = 27.6 min. (86%) and minor diastereoisomer **3b**: 30.0 min. (14%).

[2*R*,1´*S*,(S)*S*] and [2*R*,1´*S*,(S)*S*]-2-(3´-Oxocycloheptyl)-2-[2-(*p*-tolylsulfinyl)phenil]propanenitrile (4a + 4b). Cyclohept-2-enone was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 82:18 mixture **4a** + **4b**, from which **4a** was separated and purified by flash column chromatography using a *Combiflash* system (EtOAc-hexane gradient 10:90 to 100:0). Yield 52%, 29.6 mg (mixture **4a** + **4b**). Diastereoisomer [2*R*,1´*S*,(S)*S*]-**4a**: colorless oil; $[\alpha]^{20}_D$ -106.6 (*c* 0.8, $CHCl_3$); IR (film): 3322, 2360, 1703, 1214, 754 cm^{-1}; ^1H NMR: δ 7.77-7.74 (m, 1H), 7.54 and 7.29 (AA´BB´ system, 4H), 7.52-7.40 (m, 3H), 3.11-2.95 (m, 1H), 2.62-2.54 (m, 1H), 2.47-2.31 (m, 2H), 2.39 (s, 3H), 2.24-2.03 (m, 1H), 2.01-1.90 (m, 2H), 1.92 (s, 3H), 1.57-1.33 (m, 3H), 0.94-0.91 (m, 1H) ppm; ^{13}C NMR: δ 211.4, 145.0, 141.5, 140.3, 138.2, 132.0, 130.5, 130.0 (2C), 127.2, 125.8 (2C), 125.6, 123.2, 77.2, 44.4, 43.9, 43.2, 33.0, 29.7, 28.7, 24.7, 21.3 ppm; MS (FAB+) *m/z* 380 $[M+H]^+$ (100), 362 (15), 259 (17); HMRS

(FAB+) calcd. for $C_{23}H_{26}NO_2S$: 380.1684; found: 380.1678. Diastereoisomer [2*S*,1´*S*,(S)*S*]-**4b** (significant chemical shifts obtained from an epimeric 82:18 mixture **4a** + **4b**): ^{1}H NMR: δ 7.70-7.65 (m, 1H), 3.11-2.95 (m, 1H), 1.95 (s, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **4a**: t_R = 28.3 min. (82%) and minor diastereoisomer **4b**: t_R = 32.6 min. (18%).

[2*R*,1´*S*,2´*R*,(S)*S*] and [2*S*,1´*S*,2´*R*,(S)*S*]-2-(2´-Methyl-3´-oxocyclopentyl)-2-[2-(*p*-tolylsulfinyl) phenyl]propanenitrile (5a + 5b). 2-Methylcyclopent-2-enone was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 96:4 mixture **5a** + **5b**, from which **5a** was separated and purified by flash column chromatography using a *Combiflash* system (EtOAc-hexane gradient 10:90 to 100:0). Yield 67%, 36.7 mg (mixture **5a** + **5b**). Diastereoisomer [2*R*,1´*S*,2´*R*,(S)*S*]-**5a**: colorless oil; $[\alpha]^{20}_D$ -177.7 (*c* 1.0, $CHCl_3$); IR (film): 3324, 2234, 1742, 1461, 811 cm^{-1}; ^{1}H NMR: δ 7.93-7.90 (m, 1H), 7.68-7.65 (m, 1H), 7.55-7.49 (m, 2H), 7.48 and 7.27 (AA´BB´ system, 4H), 2.76 (m, 1H), 2.38 (s, 3H), 2.34-2.31 (m, 1H), 2.20-2.14 (m, 1H), 2.10 (s, 3H), 2.03-1.84 (m, 1H), 1.80-1.71 (m, 2H), 0.98 (d, *J* 6.9 Hz, 3H) ppm; ^{13}C NMR: δ 217.4, 144.2, 141.8, 140.7, 138.3, 132.1, 130.1 (3C), 130.0, 127.2, 125.9 (2C), 122.3, 77.2, 53.1, 46.1, 36.5, 24.7, 24.0, 21.3, 15.7 ppm; MS (FAB+) *m/z* 366 $[M+H]^+$ (100), 348 (17), 259 (12), 225 (20); HMRS (FAB+) calcd. for $C_{22}H_{24}NO_2S$: 366.1537; found: 366.1541. Diastereoisomer [2*R*,1´*S*,2´*R*,(S)*S*]-**5b** (significant chemical shifts obtained from an epimeric 82:18 mixture **5a** + **5b**): ^{1}H NMR: δ 7.75-7.70 (m, 1H), 3.01 (m, 1H), 0.48 (d, *J* 7.0 Hz, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **5a**: t_R = 20.7 min. (96%) and minor diastereoisomer **5b**: t_R = 35.2 min. (4%).

[2*R*,(S)*S*] and [2*S*,(S)*S*]-2-Methyl-5-oxo-2-[2-(*p*-tolylsulfinyl)phenyl]hexanenitrile (6a + 6b). Methyl vinyl ketone was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 92:8 mixture **6a** + **6b**, from which **6a** was separated and purified by flash column chromatography using EtOAc-hexane (1:1) as the eluent. Yield 78%, 39.7 mg (mixture **6a** + **6b**). Diastereoisomer [2*R*,1´*S*,2´*R*,(S)*S*]-**6a**: white solid; m.p. 94-96 °C (EtOAc-hexane); $[\alpha]^{20}_D$ –111.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 7.89-7.86 (m, 1H), 7.61-7.58 (m, 1H), 7.56 and 7.27 (AA´BB´ system, 4H), 7.59-7.48 (m, 2H), 2.70-2.58 (m, 1H), 2.55-2.43 (m, 2H), 2.43-2.30 (m, 1H), 2.37 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR: δ 205.8, 144.9, 141.5, 140.8, 138.0, 132.1, 130.1 (2C), 130.0, 129.8, 126.9, 125.9 (2C),

123.3, 41.6, 39.4, 36.2, 29.8, 26.9, 21.3 ppm; MS (FAB+) *m/z* 340 $[M+H]^+$ (100), 322 (12); HMRS (FAB+) calcd. for $C_{20}H_{22}NO_2S$: 340.1371; found: 340.1373. Diastereoisomer [2*S*,(S)*S*]-**6b** (significant chemical shifts obtained from an epimeric 92:8 mixture **6a** + **6b**): ^{1}H NMR: δ 2.14 (s, 3H), 1.95 (s, 3H) ppm.

[2*R*,3*S*,(S)*S*] and [2*S*,3*S*,(S)*S*]-2,3-Dimethyl-5-oxo-2-[2-(*p*-tolylsulfinyl)phenyl]hexanenitrile (7a + 7b). (*E*)-Pent-3-en-2-one was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 92:8 mixture **7a** + **7b**, which was purified by flash column chromatography using EtOAc-hexane (1:1) as the eluent. Yield 65%, 34.4 mg (mixture **7a** + **7b**, colorless oil). Diastereoisomer [2*R*,3*S*,(S)*S*]-**7a**: ^{1}H NMR (from a 92:8 mixture **7a** + **7b**): δ 7.76-7.65 (m, 2H), 7.53 and 7.27 (AA´BB´ system, 4H), 7.52-7.40 (m, 2H), 3.16 (dqd, *J* 2.5, 6.4 and 12.9 Hz, 1H), 2.59 (dd, *J* 10.7 and 16.9 Hz), 2.40-2.34 (m, 1H), 2.38 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.15 (d, *J* 6.4 Hz, 3H) ppm; ^{13}C NMR (from a 92:8 mixture **7a** + **7b**): δ 206.0, 145.0, 141.3, 140.7, 138.8, 131.8, 130.7, 130.1 (2C), 129.3, 127.9, 125.6 (2C), 122.1, 46.9, 39.1, 30.6, 30.1, 24.7, 21.3, 15.3 ppm; MS (FAB+) *m/z* 354 $[M+H]^+$ (100), 336 (10); HMRS (FAB+) calcd. for $C_{21}H_{24}NO_2S$: 354.1528; found: 354.1536. Diastereoisomer [2*S*,3*S*,(S)*S*]-**7b** (significant chemical shifts obtained from an epimeric 92:8 mixture **7a** + **7b**): ^{1}H NMR: δ 8.01-7.88 (m, 1H), 2.65 (dd, *J* 10.5 and 17.1 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 1.10 (d, *J* 6.6 Hz, 3H) ppm.

[4*R*,(S)*S*] and [4*S*,(S)*S*] Ethyl 4-Cyano-4-[2-(*p*-tolylsulfinyl)phenyl]pentanoate (8a + 8b). Ethyl acrylate was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 83:17 mixture **8a** + **8b**, which was purified by flash column chromatography using EtOAc-hexane (1:2) as the eluent. Yield 76%, 42.1 mg (mixture **8a** + **8b**, colorless oil). Diastereoisomer [2*R*,3*S*,(S)*S*]-**8a**: ^{1}H NMR (from an 83:17 mixture **8a** + **8b**): δ 7.84-7.81 (m, 1H), 7.59-7.51 (m, 1H), 7.50-7.46 (m, 2H), 7.49 and 7.26 (AA´BB´ system, 4H), 4.15-4.04 (m, 2H), 2.68-2.62 (m, 1H), 2.56-2.47 (m, 2H), 2.37 (s, 3H), 2.28-2.21 (m, 1H), 2.03 (s, 3H), 1.22 (t, 3H, *J* 7.1 Hz) ppm; ^{13}C NMR (from an 83:17 mixture **8a** + **8b**): δ 171.5, 144.9, 141.4, 140.8, 137.9, 132.1, 130.1, 129.9 (2C), 127.0, 125.9, 125.7 (2C), 123.1, 60.8, 41.7, 37.4, 30.5, 26.7, 21.3, 14.1 ppm; MS (FAB+) *m/z* 370 $[M+H]^+$ (100), 352 (14); HMRS (FAB+) calcd. for $C_{21}H_{24}NO_3S$: 370.1477; found: 370.1460. Diastereoisomer [2*S*,(S)*S*]-**8b** (significant chemical shifts obtained from an epimeric 83:17 mixture **8a** + **8b**): ^{1}H NMR: δ 1.95 (s, 3H), 1.24 (t, 3H, *J* 7.2 Hz) ppm.

[3*S*,4*R*,(S)*S*] and [3*S*,4*S*,(S)*S*] Ethyl 4-Cyano-3-methyl-4-[2-(*p*-tolylsulfinyl)phenyl]pentanoate (9a + 9b). Ethyl (*E*)-but-2-enoate was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric

82:18 mixture **9a + 9b**, which was purified by flash column chromatography using EtOAc-hexane (1:2) as the eluent. Yield 80%, 46.0 mg (mixture **9a + 9b**, colorless oil). Diastereoisomer [2*R*,3*S*,(S)*S*]-**9a**: ^{1}H NMR (from an 82:18 mixture **9a + 9b**): δ 7.91-7.84 (m, 1H), 7.74-7.66 (m, 1H), 7.57 and 7.27 (AA´BB´ system, 4H), 7.50-7.42 (m, 2H), 4.18-4.04 (m, 2H), 3.18-3.09 (m, 1H), 2.46-2.26 (m, 2H), 2.38 (s, 3H, s, 3H), 1.90 (s, 3H), 1.28-1.18 (m, 3H), 0.94 (d, 3H, *J* 6.7 Hz) ppm; ^{13}C NMR (from an 82:18 mixture **9a + 9b**): δ 171.2, 144.9, 141.6, 141.0, 138.8, 132.0, 131.0, 130.1, 129.9, 129.8 (2C), 127.7, 125.8 (2C), 121.6, 60.7, 47.8, 40.4, 38.3, 27.1, 21.3, 14.1 ppm; MS (FAB+) *m/z* 384 $[M+H]^+$ (100), 366 (10); HMRS (FAB+) calcd. for $C_{22}H_{26}NO_3S$: 384.1633; found: 384.1625. Diastereoisomer [3*S*,4*S*,(S)*S*]-**9b** (significant chemical shifts obtained from an epimeric 82:18 mixture **9a + 9b**):^{1}H NMR: δ 7.54 and 7.28 (AA´BB´ system, 4H), 4.18-4.04 (m, 2H), 3.31-3.18 (m, 1H), 2.65 (dd, *J* 4.1 and 15.6 Hz, 1H), 2.46-2.26 (m, 2H), 2.04 (s, 3H), 1.02 (d, 3H, *J* 6.7 Hz) ppm; ^{13}C NMR: δ 171.3, 144.7, 141.4, 140.5, 138.4, 131.9, 130.0 (2C), 128.0, 125.5 (2C), 121.9, 60.8, 48.6, 39.7, 37.2, 24.8, 21.3, 14.1 ppm.

General procedure for tandem Michael addition/acylation sequences of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile. To a solution of a diastereoisomeric 50:50 mixture of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1 + 1'**, 40.0 mg, 0.15 mmol) in anhydrous THF (1.5 mL) at -78 °C under argon was added LiHMDS (1M in THF) (162 μL, 0.18 mmol). The mixture was stirred at -78 °C for 5 min. and then 2-methylcyclopent-2-enone (18.2 mg, 0.19 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 5 min. and then the corresponding electrophile was added. The reaction was monitored by TLC. Upon transformation of the substrate (5 min.), the reaction was hydrolyzed with saturated aqueous NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4) and the solvent was evaporated under vacuum. The diastereoisomeric mixture was purified by flash column chromatography using the eluent indicated in each case.

[2*R*,1´*R*,2´*R*,(S)*S*] and [2*S*,1´*R*,2´*R*,(S)*S*]-2-(2´-Acetyl-2´-methyl-3´-oxocyclopentyl)-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (10a + 10b). Acetyl chloride (0.18 mmol), was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. to give a diastereoisomeric 96:4 mixture **10a + 10b**, from which **10a** was separated and purified by flash column chromatography using EtOAc-hexane (1:2) as the eluent. Yield 64%, 39.1 mg (mixture **10a + 10b**). Diastereoisomer [2*R*,1´*R*,2´*R*,(S)*S*]-**10a**: colorless oil; $[\alpha]^{20}_D$ -107.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR: δ 7.66-7.65 (m, 1H), 7.62 and 7.33 (AA´BB´ system, 4H), 7.44-7.40 (m, 3H), 3.97 (m, 1H), 2.76-2.60 (m, 1H), 3.44-2.34 (m, 2H), 2.38 (s, 3H), 2.33-2.14 (m, 1H), 2.12 (s, 3H), 1.90 (s, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR: δ 215.8, 168.1, 149.1, 146.6, 141.0, 140.9, 138.8, 131.6, 130.4, 129.8 (2C), 126.9, 125.3 (2C), 121.0, 77.2, 55.3, 44.2,

30.2, 25.7, 21.3, 20.6, 20.2, 11.9 ppm; MS (FAB+) *m/z* 408 $[M+H]^+$ (100), 366 (20); HMRS (FAB+) calcd. for $C_{24}H_{26}NO_3S$: 408.1633; found: 408.1624. Diastereoisomer [2*S*,1′*R*,2′*R*,(S)*S*]-**10b** (significant chemical shifts obtained from an epimeric 96:4 mixture **10a + 10b**): ^{1}H NMR: δ 7.89-7.85 (m, 1H), 7.65-7.63 (m, 1H), 2.02 (s, 3H), 1.88 (s, 3H), 0.81 (s, 3H) ppm.

[1*S*,5*R*,1′*R*,(S)*S*] and [1*S*,5*R*,1′*S*,(S)*S*] Methyl 5-{1′-Cyano-1′-[2-(*p*-tolylsulfinyl)phenylethyl]}-1-methyl-2-oxocyclopentanecarboxylate (11a + 11b). Methyl chloroformate (0.18 mmol), was used as electrophile. The reaction mixture was stirred at -78 °C for 5 min. to give a diastereoisomeric 96:4 mixture **11a + 11b**, from which **11a** was separated and purified by flash column chromatography using EtOAc-hexane (1:2) as the eluent. Yield 72%, 45.7 mg (mixture **11a + 11b**). Diastereoisomer [1*S*,5*R*,1′*R*,(S)*S*]-**11a**: white solid; m.p. 103-105 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ -141.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 7.69-7.67 (m, 1H), 7.62 and 7.27 (AA′BB′ system, 4H), 7.44-7.41 (m, 3H), 4.06 (m, 1H), 3.82 (s, 3H), 2.73-2.67 (m, 1H), 2.49-2.36 (m, 2H), 2.38 (s, 3H), 2.28-2.20 (m, 1H), 1.96 (s, 3H), 0.96 (s, 3H) ppm; ^{13}C NMR: δ 220.1, 152.8 , 148.9, 146.6, 141.0, 140.8, 138.7, 131.6, 130.5, 129.8 (2C), 126.8, 125.3 (2C), 121.3, 77.2, 55.2, 55.0, 44.2, 29.7, 25.6, 21.3, 20.1, 11.8 ppm; MS (FAB+) *m/z* 424 $[M+H]^+$ (100), 406 (15), 225 (11); HMRS (FAB+) calcd. for $C_{24}H_{26}NO_4S$: 424.1583; found: 424.1569. Diastereoisomer [1*S*,5*S*,1′*R*,(S)*S*]-**11b** (significant chemical shifts obtained from an epimeric 96:4 mixture **11a + 11b**): ^{1}H NMR: δ 3.80 (s, 3H) ppm.

General procedure for tandem Michael addition/aldol reaction of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile with aldehydes and *N*-sulfonyl imines. To a solution of a diastereoisomerc 50:50 mixture of 2-methyl-[2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1** + **1'**, 40.0 mg, 0.15 mmol) in anhydrous THF (1.5 mL) at -78 °C under argon was added LiHMDS (1M in THF) (162 μL, 0.18 mmol). The mixture was stirred at -78 °C for 5 min. and then 2-methylcyclopent-2-enone (18.2 mg, 0.19 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 5 min. and then the corresponding electrophile was added. The reaction was monitored by TLC. Upon transformation of the substrate, the reaction was hydrolyzed with a methanolic HCl solution (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4) and the solvent was evaporated under vacuum. The diastereoisomeric mixture was purified by flash column chromatography using the eluent indicated in each case.

[2*R*,1′*S*,2′*S*,1′′*R*,(S)*S*] and [2*R*,1′*S*,2′*R*,1′′*R*,(S)*S*]-2-[(1′′-Hydroxyethyl)-3′-oxocyclopentyl]-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (12a + 12b). A 1.78 M solution of acetaldehyde (0.37 mmol) in anhydrous THF was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 83:17 mixture **12a +**

12b, from which **12a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (2:1) as the eluent. Yield 79%**,** 46.8 mg (mixture **12a** + **12b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**12a:** colorless oil; $[\alpha]^{20}_{D}$ -116.3 (*c* 1.6, $CHCl_3$); IR (film): 3416, 2972, 2233, 1741, 755 cm^{-1}; ^1H NMR: δ 7.63 and 7.33 (AA´BB´ system, 4H), 7.56-7.43 (m, 4H), 3.76-3.69 (m, 1H), 3.46-3.38 (broad s, 1H), 3.03-2.96 (m, 1H), 2.41 (s, 3H), 2.41-2.33 (m, 4H), 1.93 (s, 3H), 1.94-1.92 (m, 1H), 1.10 (d, *J* 6.5 Hz, 3H) ppm; ^{13}C NMR: δ 216.3, 145.4, 141.8, 138.5, 138.3, 132.5, 132.3, 130.8, 130.2 (2C), 126.1, 125.5 (2C), 123.6, 77.2, 67.4, 54.6, 46.8, 39.6, 24.4, 21.4 (2C), 20.4 ppm; MS (ESI+) *m/z* 396 $[M+H]^+$ (100), 378 (76), 352 (26), 225 (30); HMRS (ESI+) calcd. for $C_{23}H_{26}NO_3S$: 396.1627; found: 396.1647. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-**12b** (significant chemical shifts obtained from an epimeric 87:13 mixture **12a** + **12b**): ^1H NMR: δ 7.79-7.75 (m, 1H), 7.64-7.62 (m, 1H), 2.37 (s, 3H), 2.06 (s, 3H), 1.12 (d, *J* 6.5 Hz, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^1H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min.]. Major diastereoisomer **12a**: t_R = 15.0 min. (87%) and minor diastereoisomer **12b**: t_R = 16.6 min. (13%).

[2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-2-[2´-(1´´-Hydroxypropyl)-3´-oxocyclopentyl]-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (13a + 13b). Propionaldehyde (0.37 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 90:10 mixture **13a** + **13b**, from which **13a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 80%**,** 49.1 mg (mixture **13a** + **13b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**13a:** colorless oil; $[\alpha]^{20}_{D}$ -118.4 (*c* 1.2, $CHCl_3$); IR (film): 3523, 3280, 2236, 1739, 759 cm^{-1}; ^1H NMR: δ 7.63 and 7.33 (AA´BB´ system, 4H), 7.65- 7.52 (m, 1H), 7.54-7.43 (m, 3H), 3.81-3.74 (m, 1H), 3.44 (broad s, 1H), 2.61-2.45 (m, 1H), 2.43-2.27 (m, 3H), 2.41 (s, 3H), 2.00-1.88 (m, 2H), 1.95 (s, 3H), 1.61-1.40 (m, 2H), 0.65 (t, *J* 7.3 Hz, 1H) ppm; ^{13}C NMR: 215.9, 145.9, 141.8, 138.7, 138.5, 132.4, 130.7, 130.6, 130.1 (2C), 126.2, 125.5 (2C), 123.5, 77.2, 73.3, 52.7, 46.9, 39.9, 26.9, 24.4, 21.3 (2C), 10.7 ppm; MS (FAB+) *m/z* 410 $[M+H]^+$ (100), 392 (96), 352 (15), 225 (44); HMRS (FAB+) calcd. for $C_{24}H_{28}NO_3S$: 410.1789; found: 410.1790. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-**13b** (significant chemical shifts obtained from an epimeric 90:10 mixture **13a** + **13b**): ^1H NMR: δ 7.79-7.75 (m, 1H), 3.98-3.92 (m, 1H), 0.47 (t, *J* 7.3 Hz, 1H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^1H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **13a**: t_R = 13.5 min. (90%) and minor diastereoisomer **13b**: t_R = 25.7 min. (10%).

[2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-2-[2´-(1´´-Hydroxyisopropyl)-3´-oxocyclopentyl]-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (14a + 14b). Isobutiraldehyde (0.37 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 180 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 83:17 mixture **14a + 14b**, from which **14a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 65%, 41.2 mg (mixture **14a + 14b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**14a**: white solid; m.p. 113-115 °C (hexane-*i*PrOH); $[\alpha]^{20}_D$ -134.5 (*c* 0.9, $CHCl_3$); IR (KBr): 2962, 2218, 1739, 810 cm^{-1}; ^{1}H NMR: δ 7.68-7.61 (m, 1H), 7.66 and 7.32 (AA´BB´ system, 4H), 7.55-7.52 (m, 3H), 3.90-3.77 (m, 1H), 3.71 (broad s, 1H), 2.43-2.27 (m, 3H), 2.40 (s, 3H), 2.16-1.74 (m, 4H), 1.96 (s, 3H), 0.64 (d, *J* 6.3 Hz, 3H), 0.58 (d, *J* 6.3 Hz, 3H) ppm; ^{13}C NMR: δ 215.6, 145.6, 141.7, 138.7, 138.6, 132.9, 130.6, 130.1 (3C), 125.4, 125.0 (2C), 123.6, 77.6, 77.2, 50.0, 47.1, 40.3, 30.0, 24.4, 21.4, 19.8, 19.5 ppm.; MS (FAB+) *m/z* 424 $[M+H]^+$ (60), 406 (64); HMRS (FAB+) calcd. for $C_{25}H_{30}NO_3S$: 424.1940; found: 424.1949. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-**14b** (significant chemical shifts obtained from an epimeric 87:13 mixture **14a + 14b**): ^{1}H NMR: δ 7.79-7.75 (m, 1H), 1.65 (m, 1H), 0.56 (d, *J* 6.4 Hz, 3H), 0.47 (d, *J* 6.4 Hz, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **14a**: t_R = 10.6 min. (87%) and minor diastereoisomer **14b**: t_R = 20.7 min. (13%).

[2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-2-[2´-(1´´-Hydroxy-3´´-methylbutyl)-3´-oxocyclopentyl]-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (15a + 15b). 2-Methylbutiraldehyde (0.37 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 91:9 mixture **15a + 15b**, from which **15a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 72%, 47.2 mg (mixture **15a + 15b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**15a**: colorless oil; $[\alpha]^{20}_D$ -106.4 (*c* 1.2, $CHCl_3$); IR (film): 2975, 2223, 1760, 775 cm^{-1}; ^{1}H NMR: δ 8.01-7.98 (m, 1H), 7.74-7.70 (m, 1H), 7.57-7.43 (m, 2H), 7.44 and 7.27 (AA´BB´ system, 4H), 2.99-2.90 (m, 1H), 2.47-2.39 (m, 1H), 2.40 (s, 3H), 2.33-2.21 (m, 2H), 2.16-2.02 (m, 2H), 2.05 (s, 3H), 1.97-1.71 (m, 2H), 1.68-1.60 (m, 2H), 0.97 (d, *J* 6.2 Hz, 3H), 0.96 (d, *J* 6.2 Hz, 3H) ppm; ^{13}C NMR: δ 214.6, 143.6, 142.0, 140.8, 137.7, 132.2, 130.2 (2C), 130.0, 129.9, 127.7, 126.0 (2C), 121.6, 77.2, 47.2, 46.9, 40.9, 38.2, 26.2, 26.0, 25.4, 25.2, 22.3, 21.3 ppm; MS (FAB+) *m/z* 424 $[M+H]^+$ (60), 406 (64); HMRS (FAB+) calcd. for $C_{25}H_{30}NO_3S$: 424.1940; found: 424.1949. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-**15b** (significant chemical shifts obtained from an epimeric 91:9 mixture **15a + 15b**): ^{1}H NMR: δ 7.97-7.95 (m, 1H), 7.79-7.75 (m, 1H), 3.46 (m, 1H), 0.98 (d, *J* 6.4 Hz, 3H) ppm. The

diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **15a**: t_R = 26.5 min. (91%) and minor diastereoisomer **15b**: t_R = 30.0 min. (9%).

[2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-2-{2´-[1´´-Hydroxy(phenyl)methyl]-3´-oxocyclopentyl}-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (16a + 16b). Benzaldehyde (0.37 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 86:14 mixture of **16a + 16b**, from which **16a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 77%, 52.8 mg (mixture **16a + 16b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*]-**16a**: colorless oil; $[\alpha]^{20}_D$ -104.1 (*c* 1.8, $CHCl_3$); IR (film): 3062, 2877, 2237, 1793, 809 cm^{-1}; ^{1}H NMR: δ 8.09-8.06 (m, 1H), 7.87-7.84 (m, 1H), 7.72-7.70 (m, 1H), 7.50-7.45 (m, 2H), 7.42 and 7.28 (AA´BB´ system, 4H), 7.55-7.31 (m, 4H), 5.30 (m, 1H), 3.28-3.23 (m, 1H), 2.74 (m, 1H), 2.52 (m, 1H), 2.40 (s, 3H), 2.15-2.03 (m, 1H), 1.68-1.60 (m, 2H), 1.41 (s, 3H) ppm; ^{13}C NMR: δ 219.0, 141.7, 141.5, 140.7, 138.3, 132.1, 130.1 (3C), 129.9, 128.8 (2C), 128.3, 128.2 (2C), 125.8 (2C), 125.7 (2C), 122.3, 77.2, 74.7, 58.5, 45.7, 37.8, 24.9, 21.3 (2C) ppm; MS (FAB+) *m/z* 458 $[M+H]^+$ (47), 440 [M-OH] (100); HMRS (FAB+) calcd. for $C_{28}H_{26}NO_2S$ [M-OH]: 440.1684; found: 440.1672. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*R*,(S)*S*]-**16b** (significant chemical shifts obtained from an epimeric 86:14 mixture **16a + 16b**): ^{1}H NMR: δ 7.93-7.90 (m, 1H), 5.35 (m, 1H), 3.33-3.29 (m, 1H), 2.38 (s, 3H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **16a**: t_R = 20.8 min. (86%) and minor diastereoisomer **16b**: t_R = 27.2 min. (14%).

[2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-2-{2´-[1´´-Hydroxy(*p*-methoxyphenyl)methyl]-3´-oxocyclopentyl}-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (17a + 17b). *p*-Methoxybenzaldehyde (0.74 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 180 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 85:15 mixture **17a + 17b**, which was purified by flash column chromatography using a mixture EtOAc-hexane (2:1) as the eluent. Yield 60%, 43.7 mg (mixture **17a + 17b**, colorless oil). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*]-**17a**: ^{1}H NMR (from an 85:15 mixture **17a + 17b**): δ 7.91-7.82 (m, 1H), 7.56-7.46 (m, 3H), 7.45 and 7.28 (AA´BB´ system, 4H), 7.25 and 6.86 (AA´BB´ system, 4H), 5.22 (broad s, 1H), 3.76 (s, 3H), 3.30-3.20 (m, 1H) 2.90 (d, *J* 5.6 Hz), 2.75-2.71 (m, 1H), 2.57-2.42 (m, 2H), 2.39 (s, 3H), 2.34-2.28 (m, 1H), 2.05 (s, 3H) ppm; ^{13}C NMR (from an 85:15 mixture **17a + 17b**): δ 217.2, 160.1, 141.8, 140.2, 138.4,

137.7, 134.1, 132.2, 130.5, 130.1 (2C), 128.2, 126.7 (2C), 126.4, 113.5 (2C), 113.1 (2C), 120.8, 77.1, 73.8, 56.1, 55.8, 51.9, 45.6, 37.7, 28.9, 21.4, 21.3 ppm; MS (FAB+) *m/z* 470 [M+H-OH] (100), 352 (65); HMRS (FAB+) calcd. for $C_{29}H_{28}NO_3S$: 470.1789; found: 470.1773. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-**17b** (significant chemical shifts obtained from an epimeric 85:15 mixture **17a** + **17b**): ^{1}H NMR: δ 8.01-7.98 (m, 1H), 7.45 and 7.28 (AA´BB´ system, 4H), 7.25 and 6.75 (AA´BB´ system, 4H), 3.74 (s, 3H), 3.30-3.20 (m, 1H), 2.38 (s, 3H), 2.04 (s, 3H), 2.11-1.99 (m, 1H) ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **17a**: t_R = 27.8 min. (85%) and minor diastereoisomer **17b**: t_R = 30.1 min. (15%).

[2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*] and [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-2-{2´-[1´´-Hydroxy(*p*-nitrophenyl)methyl]-3´-oxocyclopentyl}-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (18a + 18b). *p*-Nitrobenzaldehyde (0.23 mmol) was used as the electrophile. The reaction mixture was stirred at -78 °C for 30 min. and then it was hydrolyzed with a methanolic HCl solution to give a diastereoisomeric 80:20 mixture of **18a** + **18b**, which was purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 75%, 56.5 mg (mixture **18a** + **18b**, colorless oil). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*]-**18a**: ^{1}H NMR (from an 80:20 mixture **18a** + **18b**): δ 8.10 and 7.23 (AA´BB´ system, 4H), 7.77-7.71 (m, 1H), 7.68-7.65 (m, 1H), 7.59-7.57 (m, 1H), 7.45 and 7.28 (AA´BB´ system, 4H), 7.43-7.40 (m, 1H), 5.22 (broad s, 1H), 4.83 (m, 1H), 3.44-3.40 (m, 1H), 2.75-2.71 (m, 1H), 2.60-2.52 (m, 2H), 2.41 (s, 3H), 2.33-2.31 (m, 1H), 2.29-2.18 (m, 1H), 1.55 (s, 3H) ppm; ^{13}C NMR (from an 80:20 mixture **18a** + **18b**): δ 218.2, 141.8, 140.2, 138.4, 137.7, 134.1, 132.2, 130.5, 130.1 (2C), 128.2, 126.7 (2C), 126.4, 125.6 (2C), 123.9 (2C), 123.7, 120.8, 77.2, 73.9, 51.9, 45.6, 37.7, 28.9, 21.4, 21.3 ppm; MS (FAB+) *m/z* 503 $[M+H]^+$ (100), 485 (48); HMRS (FAB+) calcd. for $C_{28}H_{27}N_2O_5S$: 503.1640; found: 503.1631. Diastereoisomer [2*R*,1´*S*,2´*R*,1´´*S*,(S)*S*]-**18b** (significant chemical shifts obtained from an epimeric 80:20 mixture of **18a** + **18b**): ^{1}H NMR: δ 8.22 and 7.17 (AA´BB´ system, 4H), 7.57-7.55 (m, 1H), 7.44 and 7.28 (AA´BB´ system, 4H), 7.43-7.40 (m, 1H), 5.50 (m, 1H), 4.85 (m, 1H), 3.32-3.27 (m, 1H), 2.69-2.65 (m, 1H), 2.60-2.52 (m, 2H), 2.52-2.45 (m, 1H), 2.29-2.18 (m, 1H), 2.39 (s, 3H), 1.57 (s, 3H) ppm. ^{13}C NMR: δ 218.3, 133.7, 130.3, 129.0, 127.7, 125.3 (2C), 123.8, 70.8, 50.4, 32.2, 29.4 ppm. The diastereoisomeric excess was determined by HPLC and by integration of well-defined ^{1}H NMR signals of the crude reaction. HPLC analysis: Chiralpack AD [hexane-*i*PrOH (80:20) eluent; flow = 1 mL/min]. Major diastereoisomer **18a**: t_R = 33.6 min. (80%) and minor diastereoisomer **18b**: t_R = 29.7 min. (20%).

[1*R*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [1*R*,1´*R*,2´*S*,1´´*R*,(S)*S*]-*N*-[1-(2´-{1´´-Cyano-1´´-[2-(*p*-tolyl sulfinyl)phenyl]ethyl}-5´-oxocyclopentyl)-1-hexyl]-*p*-toluenesulfonamide (19a + 19b). (*Z*)-*N*-

hexylidene-*p*-toluenesulfonamide (0.23 mmol dissolved in 0.5 mL of anhydrous THF) was used as the electrophile. The reaction mixture was stirred at -78 °C for 60 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 90:10 mixture of **19a** + **19b**, from which **19a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (2:1) as the eluent. Yield 68%, 61.6 mg (mixture **19a** + **19b**). Diastereoisomer [1*R*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**19a**: colorless oil; $[\alpha]^{20}_D$ -82.4 (*c* 1.7, $CHCl_3$); IR (film): 3024, 2236, 1740, 1080, 750 cm^{-1}; ^1H NMR: δ 7.84-7.82 (m, 1H), 7.67 and 7.33 (AA´BB´ system, 4H), 7.64 and 7.25 (AA´BB´ system, 4H), 7.56-7.51 (m, 3H), 5.22 (broad s, 1H), 3.62 (m, 1H), 3.43-3.39 (m, 1H), 2.52 (m, 1H), 2.41-2.30 (m, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 2.18-2.03 (m, 1H), 2.03-1.94 (m, 1H), 1.96 (s, 3H), 1.67 (m, 1H), 1.33-1.20 (m, 4H), 0.99-0.82 (m, 4H), 0.67 (t, *J* 7.0 Hz, 3H) ppm; ^{13}C NMR: δ 217.6, 144.1, 143.2, 141.6, 139.6, 137.6, 137.5, 132.4, 130.7, 130.0 (3C), 129.5 (2C), 127.2 (3C), 125.9 (2C), 123.5, 77.2, 55.2, 54.9, 46.4, 38.3, 30.9 (2C), 25.6, 24.9, 22.2, 21.3 (3C), 13.6 ppm; MS (FAB+) *m/z* 605 $[M+H]^+$ (100), 434 (20), 352 (28); HMRS (FAB+) calcd. for $C_{34}H_{41}N_2O_4S_2$: 605.2508; found: 605.2517. Diastereoisomer [1*R*,1´*R*,2´*S*,1´´*R*,(S)*S*]-**19b** (significant chemical shifts obtained from an epimeric 90:10 mixture **19a** + **19b**): ^1H NMR: 7.75-7.70 (m, 1H), 1.63 (m, 1H), 0.68 (t, *J* 7.0 Hz, 3H) ppm.

[1*R*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [1*R*,1´*R*,2´*S*,1´´*R*,(S)*S*] *N*-[1-(2´-{1´´-Cyano-1´´-[2-(*p*-tolyl sulfinyl)phenyl]ethyl}-5´-oxocyclopentyl)-2-methylpropyl]-*p*-toluenesulfonamide (20a + 20b). (*Z*)-(*E*)-*N*-(2-Methylpropylidene)-*p*-methylphenyltoluenesulfonamide (0.23 mmol dissolved in 0.5 mL of anhydrous THF) was used as the electrophile. The reaction mixture was stirred at -78 °C for 60 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL), to give a diastereoisomeric 87:13 mixture of **20a** + **20b**, from which **20a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (2:1) as the eluent. Yield 72%, 62.2 mg (mixture **20a** + **20b**). Diastereoisomer [2*R*,1´*S*,2´*S*,1´´*S*,(S)*S*]-**20a**: colorless oil; $[\alpha]^{20}_D$ -82.4 (*c* 1.7, $CHCl_3$); ^1H NMR: δ 7.98-7.95 (m, 1H), 7.72-7.68 (m, 1H), 7.67 and 7.29 (AA´BB´ system, 4H), 7.63 and 7.26 (AA´BB´ system, 4H), 7.54-7.50 (m, 2H), 4.82 (m, 1H), 3.59 (c, *J* 8.2 Hz, 1H), 3.36 (dd, *J* 7.9 and 9.5 Hz, 1H), 2.69-2.66 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.35-2.32 (m, 1H), 2.16-1.85 (m, 2H), 2.06 (s, 3H), 1.72-1.67 (m, 1H), 0.77 (d, *J* 6.6 Hz, 3H), 0.46 (d, *J* 6.8 Hz, 3H) ppm; ^{13}C NMR: δ 217.3, 144.6, 143.5, 141.6, 140.8, 138.0, 137.7, 132.1, 130.7, 130.1 (3C), 129.5 (2C), 129.4, 127.1 (2C), 126.1 (2C), 122.3, 77.2, 61.1, 54.8, 48.2, 38.4, 31.8, 25.0, 21.4 (2C), 21.3, 20.7, 18.7 ppm; MS (FAB+) *m/z* 577 $[M+H]^+$ (100), 352 (31), 226 (23); HMRS (FAB+) calcd. for $C_{32}H_{37}N_2O_4S_2$: 577.2195; found: 577.2222. Diastereoisomer [1*R*,1´*R*,2´*S*,1´´*R*,(S)*S*]-**20b** (significant chemical shifts obtained from an epimeric 83:17 mixture of **20a** + **20b**): ^1H NMR: 7.80-7.75 (m, 1H), 7.46-7.41 (m, 1H), 1.60 (m, 1H), 0.81 (d, *J* 6.7 Hz, 3H), 0.38 (d, *J*

6.8 Hz, 3H) ppm.

[1*S*,1´*S*,2´*S*,1´´*R*,(S)*S*] and [1*S*,1´*R*,2´*S*,1´´*R*,(S)*S*] *N*-[1-(2´-{1´´-Cyano-1´´-[2-(*p*-tolyl sulfinyl)phenyl]ethyl}-5´-oxocyclopentyl)-1-(phenyl)methyl-*p*-toluenesulfonamide (21a + 21b). (*E*)-*N*-Benzylidene-*p*-toluenesulfonamide (0.23 mmol dissolved in 0.5 mL of anhydrous THF) was used as the electrophile. The reaction mixture was stirred at -78 °C for 5 min. and then it was hydrolyzed with saturated aqueous NH_4Cl (1 mL) to give a diastereoisomeric 89:11 mixture of **21a + 21b**, from which **21a** was separated and purified by flash column chromatography using a mixture EtOAc-hexane (1:1) as the eluent. Yield 74%, 67.7 mg (mixture **21a + 21b**). Diastereoisomer [1*S*,1´*S*,2´*S*,1´´*R*,(S)*S*]-**21a**: white solid; m.p. 131-133 °C (hexane-*i*PrOH); $[\alpha]^{20}_D$ -69.6 (*c* 0.3, $CHCl_3$); IR (KBr): 3050, 2230, 1728, 1027, 756 cm^{-1}; ^1H NMR: δ 7.92-7.89 (m, 1H), 7.71-7.68 (m, 1H), 7.54-7.42 (m, 5H), 7.14-7.04 (m, 8H), 6.93-6.90 (m, 2H), 6.82 (d, *J* 9.2 Hz, 1H), 4.53 (m, 1H), 2.96-2.89 (m, 1H), 2.82-2.78 (m, 1H), 2.37-2.21 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.08 (s, 3H), 1.58-1.48 (m, 2H) ppm; ^{13}C NMR: δ 219.4, 143.1, 141.7, 140.3, 137.5, 136.7, 132.4, 130.3, 130.0, 129.9 (2C), 129.3 (2C), 128.8 (2C), 128.1, 127.9 (2C), 126.8 (3C), 125.7 (3C), 121.8, 77.2, 58.9, 55.1, 47.2, 39.0, 24.5 , 21.3 (2C), 21.2 ppm; MS (FAB+) *m/z* 611 $[M+H]^+$ (100), 440 (70); HMRS (FAB+) calcd. for $C_{35}H_{35}N_2O_4S_2$: 611.2038; found: 611.2023. Diastereoisomer [1*S*,1´*R*,2´*S*,1´´*R*,(S)*S*]-**21b** (significant chemical shifts obtained from an epimeric 89:11 mixture of **21a + 21b**): ^1H NMR: δ 7.98-7.95 (m, 1H), 4.61 (m, 1H), 2.72-2.65 (m, 1H) ppm.

General procedure for oxidation of sulfoxides to sulfones (22a and 23a).

To a solution of the corresponding sulfinyl nitrile (**2a** or **5a**) (0.11 mmol) in 1.0 mL of anhydrous dichloromethane, cooled at 0 ºC, was slowly added *m*-CPBA (0.16 mmol, 1.5 equiv.). The reaction mixture was stirred initially at 0 ºC and then warmed to room temperature. The reaction was monitored by TLC. Upon transformation of starting material, it was quenched with a $NaHSO_3$ solution (40% w/v, 5 mL). The organic layer was washed with saturated $NaHCO_3$ (3 mL) and the aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography using a mixture of EtOAc-hexane (2:1) as the eluent.

(2*R*,1´*S*)-2-(3´-Oxocyclopentyl)-2-[2-(*p*-tolylsulfonyl)phenyl]propanenitrile (22a). [2*R*,1´*S*,(S)*S*]-2-(3´-Oxocyclopentyl)-2-[2-(*p*-tolylsulfinyl)-phenyl]propanenitrile (**2a**) was used as the starting material. Yield 78%, 31.5 mg; white solid; m.p. 82-84 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ -41.6 (*c* 0.8, $CHCl_3$); ^1H NMR: δ 8.05-8.02 (m, 1H), 7.80-7.73 (m, 1H), 7.74 and 7.36 (AA´BB´ system, 4H), 7.61 (dt, *J* 1.5 and 7.7 Hz), 7.40 (dt, *J* 1.1 and 8.2 Hz, 1H), 4.41-4.32 (td, *J* 4.6 and 10.2 Hz), 4.15 (td, *J* 3.6 and 11.1 Hz, 1H), 3.79 (m, 1H), 2.89 (dd, *J* 5.5 and 10.1 Hz, 1H), 2.59 (dd, *J* 6.4 and 11.1 Hz, 1H), 2.45 (s, 3H), 2.02

(s, 3H), 1.80-1.74 (m, 1H), 1.73-1.60 (m, 1H) ppm; ^{13}C NMR: δ 169.7, 145.1, 140.1, 138.2, 137.2, 133.4, 133.3, 131.4, 130.1 (2C), 129.1, 127.8 (2C), 121.4, 77.2, 67.8, 37.5, 32.8, 26.1, 23.6, 21.6 ppm; MS (ESI+) *m/z* 368 $[M+H]^+$ (100), 286 (75), 259 (35); HMRS (ESI+) calcd. for $C_{21}H_{22}NO_3S$: 368.1314; found: 368.1298.

(2*R*,1´*S*,2´*R*)-2-(2´-Methyl-3´-oxocyclopentyl)-2-[2-(*p*-tolylsulfonyl)phenyl]propanenitrile (23a). [2*R*,1´*S*,(S)*S*]-2-(2´-Methyl-3´-oxocyclopentyl)-2-[2-(*p*-tolylsulfinyl)phenyl]propanenitrile (**5a**) was used as the starting material. Yield 80%, 33.5 mg; white solid; m.p. 149-151 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ -27.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 8.09-8.06 (m, 1H), 7.95-7.92 (m, 1H), 7.74 and 7.34 (AA´BB´ system, 4H), 7.61 (dt, *J* 1.5 and 7.6 Hz, 1H), 7.46 (dt, *J* 1.1 and 7.8 Hz, 1H), 3.57 (m, 1H) 2.44 (s, 3H), 2.37-2.27 (m, 2H), 2.17 (s, 3H), 2.21-1.92 (m, 1H), 1.65-1.52 (m, 2H), 1.28 (d, *J* 6.8 Hz, 3H) ppm.

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SUPPORTING INFORMATION PARAGRAPH

^{1}H and ^{13}C-NMR for sulfinyl derivatives **2a, 3a + 3b, 4a-6a, 7a + 7b, 8a, 9a + 9b, 10a, 11a-21a**, sulfonyl derivatives **22a** and **23a**, bidimensional ^{1}H NMR experiment for compound **11a** and crystallographic data for compounds **14a, 21a, 22a** and **23a** are described in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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21. The sequence empoying ketones and ketimines in the final trapping step proved unsuccessful.

22. Crystallographic data (excluding structure factors) for compounds **14a, 21a, 22a** and **23a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 888726-888729. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0)-1223-366033 or e-mail: deposit@ccdc.cam.ac.uk]

23. The presence of an α–methyl group in the 2-cyclopentenone ring would produce strong steric repulsions with the quaternary carbons in the *O*-enolate intermediate **IIIA** (Scheme 7), thus determining the evolution through the more stable *C*-enolate intermediate indicated at Scheme 6.

24. See S.I. for other possible explanation of the formation of **5a**, **10a** and **11a** as the major isomers obtained in these reactions.