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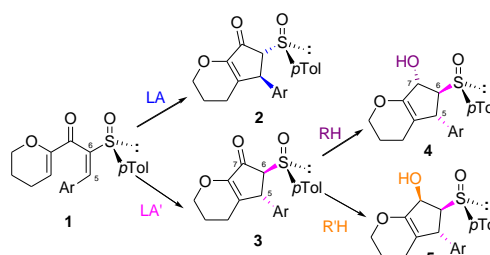
Doubly Switchable Diastereodivergent Strategy Mediated by a Chiral Sulfoxide to Access Disubstituted Tetrahydrocyclopentapyranone and Hexahydrocyclopentapyranol Scaffolds via a Nazarov Cyclization

Erwann Grenet^a
Arie van der Lee^b
Xavier J. Salom-Roig^{*a}

^a Institut des Biomolécules Max Mousseron
Université de Montpellier, CNRS, ENSCM,
1019, route de Mende, 34293 Montpellier, France

^b IEM, Université de Montpellier, CNRS, ENSCM,
Place Eugène Bataillon,
34095 Montpellier, France

*Corresponding author: Xavier.Salom-Roig@umontpellier.fr



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Abstract Activated dienones bearing a chiral sulfoxide were transformed diastereodivergently into the corresponding disubstituted 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2H)-ones. The torquoselectivity of the reaction could be switched by changing the Lewis acid used as promoter. From the four possible stereoisomers, only the two *trans* were observed. In a second switchable diastereodivergent step, both corresponding diastereomeric 2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-7-ols were obtained via the diastereoselective reduction of the ketone by changing the reducing agent. The Lewis acids as well as the reducing agents employed in both diastereodivergent steps were achiral, the diastereoselectivities being dictated by the sulfinyl auxiliary.

Key words asymmetric synthesis, chiral auxiliaries, cyclization, diastereoselectivity, stereoselective synthesis

Introduction

Accessing the different stereoisomers of bioactive compounds remains a challenging problem in the field of drug discovery. Indeed, the aforesaid stereoisomers can exhibit different pharmacological, toxicologic, pharmacokinetic and metabolic properties. For this reason, their effects must be precisely evaluated during the drug discovery process. These considerations mandate the improvement of strategies to quickly obtain all stereoisomers of a chiral molecule to be tested.¹

In this context, the development of switchable stereodivergent strategies, enabling the access to stereoisomeric compounds from a common precursor *via* a stereoselective reaction by employing different reactants, brings an effective solution in terms of atom and synthetic steps economy.

Importantly, in switchable reactions of substrates bearing a homochiral auxiliary, the diastereodivergence can be tuned by parameters that don't involve necessarily chiral chemicals. This is a major advantage compared to enantioselective approaches, where the diastereodivergence usually requires the antipode of the catalyst or chiral reagent.²

A few years ago, we described the Nazarov cyclization of polarized dienones bearing a dihydropyran (DHP) as electron donating group (EDG) and a chiral sulfoxide playing the double role of electron withdrawing group (EWG) and chiral auxiliary (Figure 1).^{3a} We observed a torquoselectivity switch in the cyclization by changing the Lewis acid used as promoter owing the obtention of both *trans* stereoisomers 2 and 3 of the corresponding disubstituted 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2H)-one. More recently, we reported a DFT study to explain how the nature of the Lewis acid can provide a switch in the torquoselectivity of this cyclization.^{3b}

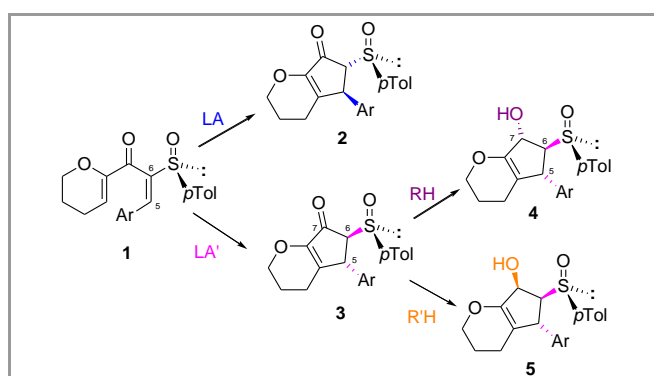


Figure 1 Our doubly switchable stereodivergent strategy.

This methodology provides access to the 3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one scaffold (**6**, Figure 2), which is embedded in the chemical structure of natural products of interest like Sterhirsutins A-D. These are bioactive heterodimeric sesquiterpenes isolated from a strain of *Stereum hirsutum* (L515), a fungus collected in the region of Tibet Plateau. Sterhirsutins A, B and C show cytotoxicity against K562 and HCT116 cell lines.⁴ Scaffold **6** is also found in the structure of the strigolactone analogue PLO65 endowed with a remarkable activity as germination stimulant for seeds of the parasitic weeds *Orobanchae aegyptiaca*.⁵

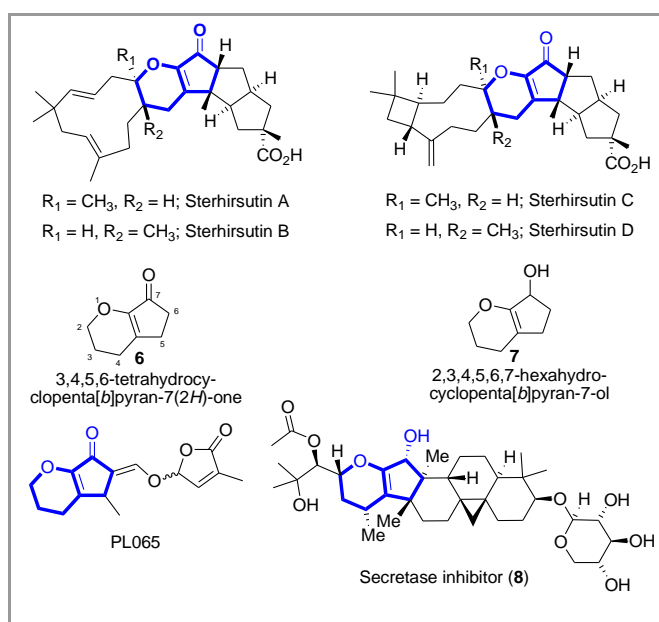


Figure 2 Bioactive compounds bearing scaffolds **6** and **7**.

Furthermore, a 2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-7-ol moiety (**7**, Figure 2) is embedded in the skeleton of the triterpene monoglycoside **8**, isolated from the black cohosh plant (*Actaea racemosa*). This natural product is a γ -secretase inhibitor, which selectively lowers levels of amyloid-beta peptide A β 42 and has been used as a lead for the development of potential treatments for Alzheimer's disease.⁶ Very recently, a semisynthetic molecule derived from compound **8** has shown a promising potential to alleviate chronic inflammatory skin diseases.⁷

The interest for these targets warranted further study and extension of our previously reported diastereodivergent synthetic methodology. Thus, in this full paper, we first describe the synthesis of the activated dienones used as substrates for the Nazarov cyclization and the corresponding NMR studies employed to determine their geometrical configuration, which was confirmed by the single crystal X-ray diffraction analysis of two compounds. Then, we detail the optimisation study involving a series of Lewis acids that provided the best conditions to access the Nazarov cyclized products and the NMR studies that led us to determine the absolute configuration of the two new generated stereocenters. Next, we report the studies leading to the diastereodivergent reduction of the

carbonyl in our Nazarov cyclized products. Indeed, by the diastereoselective reduction of the carbonyl group in cyclopentenone **3** (Figure 1) both 2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-7-ols **4** and **5** can be obtained. Overall, this is a doubly switchable diastereodivergent strategy in which both the Lewis acids used to switch the torquoselectivity of the cyclization and the reducing agents used to reduce diastereoselectively the carbonyl are achiral. Indeed, no introduction or exchange of any chiral parameter has been done, as the chiral sulfoxide group is particularly effectively dictating two stereoselective transformations leading to the generation of stereocenters at C-5, C-6 and C-7 positions. Finally, we address the cyclization of activated dienones bearing a cycloalkene as EDG and particularly we describe a halogen-interrupted Nazarov reaction giving rise to a tetra-substituted cyclopentanone in which four stereocenters have been generated in a single step.

Results and discussion

Chiral sulfoxides have been demonstrated to be highly efficient in controlling diastereoselective transformations.⁸ In particular, the use of Lewis acids to form chelated species, taking advantage of the sulfinyl oxygen Lewis basicity, has been evidenced in many 1,2- and 1,3-asymmetric induction processes.⁹ We were inspired by the fact that chiral vinylic sulfoxides have proven to be effective to create a sp³ β -carbon atom due to the intramolecular chirality transferred by 1,3-asymmetric induction.¹⁰ Based on this, we expected that a chiral sulfoxide installed in the C-6 of a divinyl ketone bearing a nucleophilic dihydrofuran moiety would impart torquoselectivity in the corresponding Nazarov cyclization and that it would be possible to modulate this torquoselectivity with the nature of the Lewis acid (LA) associated to the sulfoxide group.

Our initial efforts focused on the two-steps synthesis of polarized divinyl keto-4-sulfoxides bearing a DHP moiety (compounds **1a-g**), a cyclohexene (**13a-b**) or a cyclopentene (**14a-b**) as a vinyl nucleophile and an aromatic group as substituent at C-5 (Table 1). Thus, esters **9a-c** were added to the lithiated anion of (*S*)-methyl-*p*-tolylsulfoxide at -78 °C leading to the corresponding β -ketosulfoxides **10-12** in 94, 78 and 95% yield, respectively. A Knoevenagel-type condensation between compounds **10-12** and the corresponding aromatic aldehydes led to the desired divinyl keto-4-sulfoxides **1a-g**, **13a-b** and **14a-b**.

Table 1 Synthesis of divinyl keto-4-sulfoxides **1a-g**, **13a-b** and **14a-b**.

		$n = 1, X = O; \mathbf{10}, 94\%$ $n = 1, X = CH_2; \mathbf{11}, 78\%$ $n = 0, X = CH_2; \mathbf{12}, 95\%$		$n = 1, X = O; \mathbf{1}$ $n = 1, X = CH_2; \mathbf{13}$ $n = 0, X = CH_2; \mathbf{14}$
		$n = 1, X = O; \mathbf{9a}$ $n = 1, X = CH_2; \mathbf{9b}$ $n = 0, X = CH_2; \mathbf{9c}$		
Entry	Ar	Procedure ^a	Yield ^b (%)	³ J _{C=O/Hβ} (Hz) H _{cis} H _{trans}

1	Ph (1a)	A	64	4.2	10.0
2	4-NO ₂ Ph (1b)	A	62	4.6	10.0
3	4-MeOPh (1c)	A	46	4.6	10.1
4	4-ClPh (1d)	A	45	4.3	9.8
5	3,4,5-TMPH (1e)	A	44	3.8	10.2
6	2-NO ₂ Ph (1f)	A	49	4.0	9.6
7	2-furfuryl (1g)	A	62	4.5	9.6
8	2,4,6-TMPH (13a)	B	35	2.8	9.8
9	Ph (13b)	B	38	2.5	9.0
10	2,4,6-TMPH (14a)	B	53	7.8	9.8
11	Ph (14b)	B	51	7.9	9.1

^a Procedure A: ArCHO (1 equiv), piperidine (1.1 equiv), MeCN, rt then MeI (3 equiv), DCM, rt. Procedure B: ArCHO (1 equiv), piperidine (1.1 equiv), MeCN, rt.
^b Diastereoselectivity (*E:Z*) was in all cases 99:1 and was determined by ¹H NMR (400 MHz, CDCl₃).

The assignment of the *E* configuration in divinyl keto-4-sulfoxides **1a-g**, **13a-b** and **14a-b** was made by analysis of ³J_{C,H} coupling constants between the carbon atom of the carbonyl group and the *cis* and *trans* protons (see Figure 3 and Table 1).¹¹ Indeed, the coupling constant involving the H_{*cis*} proton was lower than that observed for the H_{*trans*}, indicating an *E* configuration. Moreover, this configuration was confirmed by X-ray analysis of compounds **1b** and **13a**.

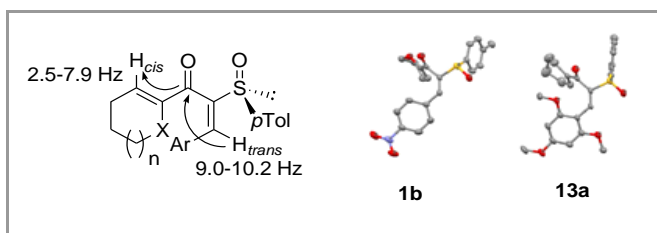


Figure 3 Coupling constants between the carbonyl C-atom and the H_{*cis*} and H_{*trans*} atoms on divinyl keto-4-sulfoxides and ORTEP plot of the structures **1b** and **13a**.

With divinyl keto-4-sulfoxides **1a-g**, **13a-b** and **14a-b** in hand, we conducted our initial experiments on the polarized alkoxy divinyl β-ketosulfoxide **1a** bearing a dihydropyran electron-donating group, an electron-withdrawing chiral sulfoxide group at C-6 and a phenyl group as substituent at C-5, with the aim of finding a general approach to efficiently promote the torquoselective Nazarov cyclization (Table 2). Our investigation began by identifying a Lewis acid able to give the expected cyclopentenones. The direction and extent of the asymmetric induction was found to be dependent on the nature of the Lewis acid.

Thus, when the reaction was performed in the presence of 1.1 equivalents of ZrCl₄ or MgCl₂ at room temperature using 1,2-DCE as a solvent, no reaction took place (entries 1 and 2). With FeCl₃, a 50:50 mixture of disubstituted *trans* cyclopentenones **2a** and **3a** was obtained after 30 minutes (entry 3). This was also the case of Sc(OTf)₃ but with a much longer reaction time (48 hours), which caused the concomitant formation of non-identified side-products (entry 4). With InCl₃ and Cu(OTf)₂, stereoisomer **2a** was obtained preferentially (entries 5 and 6). ZnCl₂ and ZnI₂, which had never been employed as promoters in a Nazarov cyclization, showed the best results, giving **2a** as the major stereoisomer with 75:25 and 83:17 ratios, respectively (entries 7 and 8). Interestingly, the use of the strong Lewis acids

AlCl₃ and TiCl₄ (entries 9 and 10) resulted in reversal of torquoselectivity, providing stereoisomer **3a** as the major product after only 20 minutes and 2 hours with 34:66 and 10:90 ratios, respectively.

It is worthy to note that in all the cases the reaction was highly diastereoselective since only two of the four possible stereoisomers (**2a** and **3a**) were ever observed. Indeed, the C-5/C-6 substituents were shown to adopt a *trans* relationship. Moreover, the reaction occurred with complete regioselectivity; the final unsaturation is located on the side of the alkoxy substituent.

Table 2 Effect of Lewis acids on the torquoselective Nazarov cyclization.

Entry	Lewis acid ^a	t(h)	Ratio 2a:3a ^b
1	ZrCl ₄	No reaction	-
2	MgCl ₂	No reaction	-
3	FeCl ₃	0.5	50:50 ^c
4	Sc(OTf) ₃	48	50:50 ^c
5	InCl ₃	6	55:45
6	Cu(OTf) ₂	24	66:34 ^c
7	ZnCl ₂	24	75:25 ^d
8	ZnI ₂	24	83:17 ^{e,e}
9	AlCl ₃	0.3	34:66 ^e
10	TiCl ₄	2	10:90 ^f

^a Reaction conditions: Substrate **1a**, 1.1 equivalents of the promoter in 1,2-DCE (0.06 M) at rt.

^b *d.r.* (*trans:syn* ratios) were 99:1 in all cases. *d.r.* and **2a:3a** ratios were determined by HPLC analysis or from the crude ¹H-NMR spectra.

^c The reaction crude showed, by HPLC and ¹H-NMR, the presence of unidentified side-products.

^d **2a** and **3a** were isolated in 59 and 21% yield.

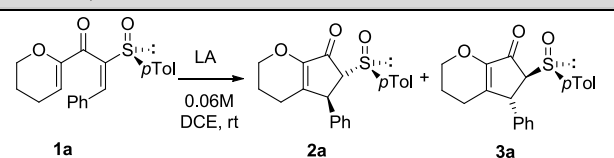
^e Yields for this reaction are shown in table 3.

^f This reaction was performed at 0 °C and the major diastereoisomer **3a** could be isolated in 71% yield.

With these results in hand, we focused on the optimization of the reaction conditions with the Lewis acids that gave the best torquoselectivities. Although promising, TiCl₄ proved to be problematic. Indeed, the reaction promoted by TiCl₄ afforded cyclopentenone **3a** in 71% yield (entry 10, Table 2). This yield was reduced by side-reactions, as evidenced by the presence of unidentified side-products in the reaction mixture. Shorter reaction times, lower temperature reactions and the use of sub-stoichiometric amounts of TiCl₄ didn't allow the total conversion of substrate **1a**. Consequently, we elected to optimize the reaction conditions with AlCl₃¹² and ZnI₂ (Table 3). By performing the reaction with a sub-stoichiometric quantity of AlCl₃ (0.5 equiv), the diastereomeric ratio was notably improved (13:87, entry 2). The use of 0.5 equivalent of AlCl₃ at 0 °C further improved the torquoselectivity (7:93, entry 3), providing 88% yield of stereoisomer **3a**. With 0.25 equivalent similar trends were observed (entries 4 and 5). The optimal conditions involve 0.25 equivalent of AlCl₃ at 0 °C during 3 hours of reaction, giving a 7:93 ratio of both *trans* adducts and 90% yield of the major stereoisomer **3a**. The reaction provides a very good yield of **3a** with high stereocontrol in both the relative and absolute sense,

as only one of the four possible stereoisomers was obtained (*trans*-**3a**). When carrying out the reaction with sub-stoichiometric quantities of ZnI_2 we could not achieve complete conversion of **1a**. Further experimentation showed that the optimum procedure involved the use of 1.1 equivalents of ZnI_2 , which produced a 83:17 ratio mixture of the *trans* stereoisomers with 68% yield of the major stereoisomer **3a**. The use of 3 equivalents of ZnI_2 gave similar results (compare entries 6 and 7).

Table 3 Optimization of the reaction parameters for the torquoselective Nazarov cyclization.



Entry	Lewis Acid (LA)	Eq. LA	T (°C)/t (h)	d.r. (2a:3a)	Yield 2a (%)	Yield 3a (%)
1	AlCl_3	1.1	25 °C/0.3 h	34:66	17	57
2	AlCl_3	0.5	25 °C/1 h	13:87	3	80
3	AlCl_3	0.5	0 °C/2 h	7:93	-	88
4	AlCl_3	0.25	25 °C/2.5 h	9:91	2	82
5	AlCl_3	0.25	0 °C/3 h	7:93	-	90
6	ZnI_2	1.1	25 °C/24 h	83:17	68	12
7	ZnI_2	3	25 °C/24 h	84:16	65	-

The *trans* relative configuration within cyclopentenones **2a** and **3a** is consistent with the low coupling constant between vicinal protons at C-5 and C-6 ($J_{5,6} = 0\text{--}2$ Hz), which are higher for the *cis*-stereoisomers.¹³ 2D NOESY analyses also support a relative 5,6-*trans*-configuration within compounds **2a** and **3a**. Thus, for compound **2a** (Figure 4, a) hydrogens H_5 and H_6 showed a NOE interaction with the *ortho* proton of the *p*-tolyl group (H_o) and the *ortho* proton of the phenyl group at C-5 (H_o'), respectively. On the other hand, as depicted in Figure 4, b, the opposite NOE interactions are observed for compound **3a** (H_5 interacts with H_o' and H_6 with H_o). These observations are consistent with an *anti* stereochemical relationship. Moreover, in the case of compound **2a** (Figure 4, c), H_5 couples with the axial proton of the dihydropyranic ring (H_{4a}), while for **3a** (Figure 4, d) H_5 couples with the equatorial proton of the same ring (H_{4e}), confirming that the absolute configuration at C-5 and C-6 between both stereoisomers is reversed. Finally, the absolute configuration for the stereogenic centers at C-5 and C-6 in cyclopentenone **3a** was determined as $5S,6S$ by single crystal X-ray diffraction analysis.^{3a}

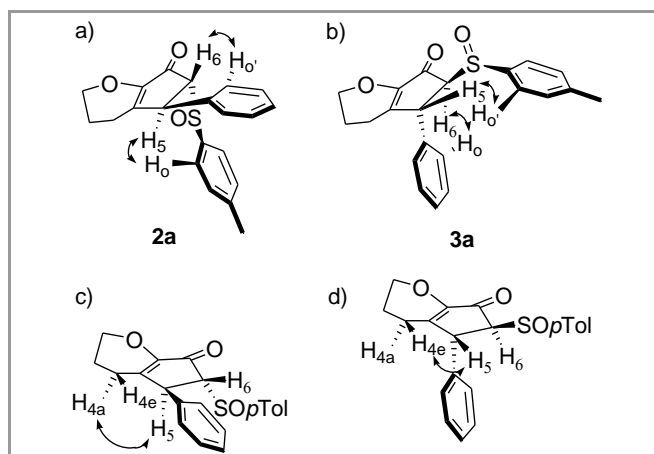
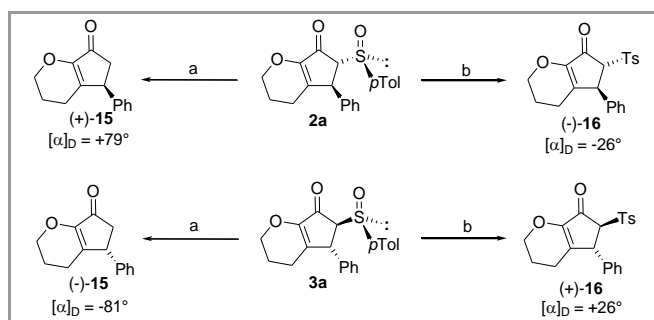


Figure 4 NOE correlations for compounds **2a** and **3a**.

For the determination of the absolute stereochemistry of stereoisomer **2a**, we proceeded to the removal of the sulfoxide auxiliary from **2a** and **3a**. By using zinc and ammonium chloride,¹⁴ we obtained in very good yields the desired enantiomeric C-5 aryl-substituted cyclopentenones (+)-**15** and (-)-**15** respectively (Scheme 1). Consequently, the absolute configuration of the stereogenic centers for the stereoisomer **2a** could be established as $5R,5R,6R$. This stereochemical assignment was supported by the conversion of the sulfinyl group in cyclopentenones **2a** and **3a** into their corresponding sulfones by reaction with *m*-CPBA in CH_2Cl_2 at 0 °C. The enantiomers (-)-**16** and (+)-**16** were obtained in excellent yields. Both samples exhibited entirely the same magnitude of specific rotation.



Scheme 1 C-S bond cleavage and sulfinyl oxidation of **2a** and **3a**. a) Zn , NH_4Cl , $\text{THF}/\text{H}_2\text{O}$, rt, 30 min, 88% for (+)-**15** and 100% for (-)-**15**; b) *m*-CPBA (1.1 equiv), DCM , 0 °C, 3 h, 93% for (-)-**16** and 100% for (+)-**16**.

Density functional theory investigations shed light on the reaction mechanism.^{3b} The Lewis acid ZnI_2 leads to a transition state in which it is chelated by the carbonyl and the sulfinyl oxygen atoms and consequently the orientation of the sulfoxide is considerably constrained, favoring compound **2a** (Figure 5). However, the Lewis acid AlCl_3 is not prone to chelation, leading to a transition state in which it is bound only to the carbonyl, the sulfoxide group is free to rotate and thus can orient itself as to minimize the total molecular dipole, favoring compound **3a**.^{3b}

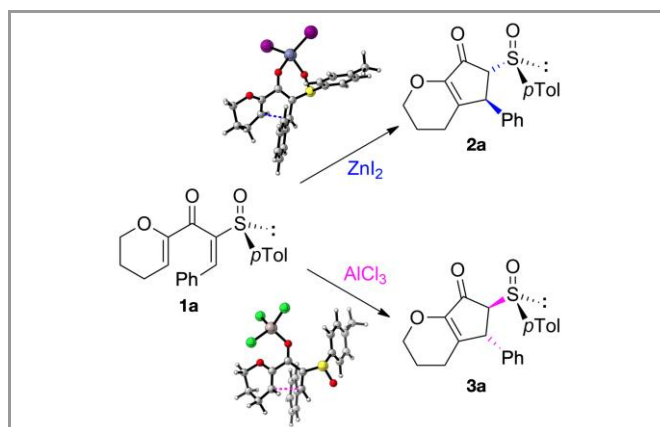


Figure 5 Transitions states leading to compounds **2a** and **3a** from **1a**.

The substrate scope was then evaluated on diversely substituted dihydropyran substrates (**1b-g**) at C-5. We initially focused our study on the use of 0.25 equivalents of AlCl_3 as catalyst in 1,2-DCE at 0 °C. The reaction proceeded with a complete conversion into the corresponding *trans* cyclopentenones **3b-g** and was compatible with both electron-donating and electron-withdrawing aryl substituents, as summarized in Table 4. Thus, it was found that substrates with a *p*-chloro (**1b**, entry 2) and *p*-methoxy (**1c**, entry 3) substituents afforded as major stereoisomers **3b** and **3c** with similar torquoselectivities and yields than the observed for the parent compound **1a** (entry 1). The strong electron-withdrawing *p*-nitro group (**1d**, entry 4) slightly diminished the torquoselectivity but the yield was maintained. An *o*- NO_2 substituent (**1e**, entry 5) required a higher temperature and a longer reaction time that did not significantly affect either the d.r. nor the yield. In contrast, 3,4,5-trimethoxyphenyl (**1f**) and 2-furfuryl (**1g**) groups led to a slight drop in selectivity and yield (entries 6 and 7). As expected, the use of 1.1 equivalents of ZnI_2 at room temperature resulted in a reversal of torquoselectivity, with stereoisomers **2b-g** being obtained preferentially. *p*-ClPh and 2-furfuryl substituents were well tolerated and no loss either in the yield nor in the d.r. was observed (entries 9 and 14) respect to compound **1a** (entry 8). With a *p*-nitro substituent, the d.r. declined (entry 11). *o*-Nitro (entry 12) and 3,4,5-TMP (entry 13) substituents lowered the torquoselectivity and **1c** led to a 51:49 mixture of diastereomers (entry 10). Major stereoisomers (**2b**, **2d-e** and **2g**) were obtained in 65-70% yield. The absolute configurations of the newly formed stereogenic centers within disubstituted cyclopentenones **2b-2g** and **3b-3g** were attributed unambiguously on the basis of comparable ^1H and ^{13}C NMR data between these compounds and those obtained for the parent ones **2a** and **3a**.

Table 4 Scope of the Nazarov cyclization of dihydropyran substrates **1a-g**.

Entry	R_5	Lewis acid	t(h)	d.r.(2:3) ^f	Yield 2 (%)	Yield 3 (%)
1	Ph (1a)	AlCl_3^a	3	7:93	-	90
2	<i>p</i> -ClPh	AlCl_3^a	3	7:93	-	88

3	<i>p</i> -MeOPh (1c)	AlCl_3^a	3	7:93	-	90
4	<i>p</i> - NO_2 Ph (1d)	AlCl_3^a	3	10:90	-	90
5	<i>o</i> - NO_2 Ph (1e)	AlCl_3^b	24	8:92	-	90
6	3,4,5-TMPH (1f)	AlCl_3^b	3	12:88	-	87
7	2-furfuryl (1g)	AlCl_3^a	3	15:85	12	80
8	Ph (1a)	ZnI_2^c	24	83:17	68	-
9	<i>p</i> -ClPh (1b)	ZnI_2^c	24	85:15	69	14
10	<i>p</i> -MeOPh (1c)	ZnI_2^c	24	51:49	19	19
11	<i>p</i> - NO_2 Ph (1d)	ZnI_2^c	24	77:23	70	18
12	<i>o</i> - NO_2 Ph (1e)	ZnI_2^d	24	70:30	65	-
13	3,4,5-TMPH (1f)	ZnI_2^c	24	60:40	24	24
14	2-furfuryl (1g)	ZnI_2^c	24	81:19	67	13

^a Reaction conditions: 0.25 equivalent of AlCl_3 in 1,2-DCE (0.06M) at 0 °C.

^b The reaction was performed at rt.

^c 1.1 equivalents of ZnI_2 in 1,2-DCE (0.06M) at 0 °C.

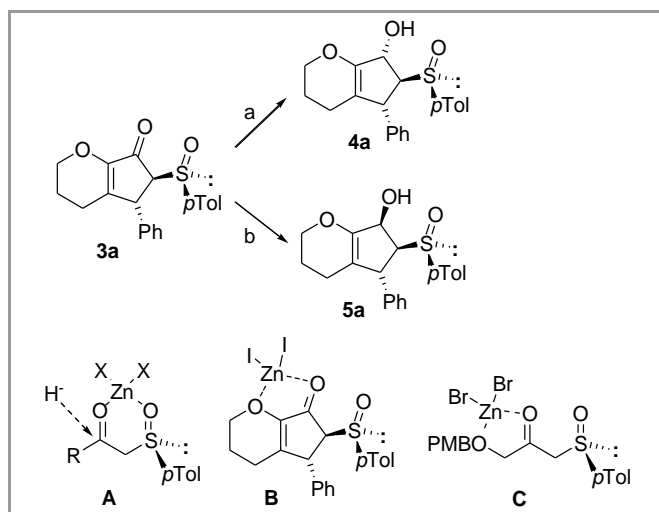
^d The reaction was performed at 50 °C.

^e Diastereoisomeric ratio were determined by HPLC analysis or from the crude ^1H -NMR spectra.

We then decided to increase the molecular complexity of the cyclopentenones obtained to further extend our diastereodivergent strategy (Figure 1). Thus, we wondered whether the sulfoxide group auxiliary, which dictates the torquoselectivity of the Nazarov cyclization, could also guide the diastereoselective reduction of the carbonyl group in compound **3a**, providing access to cyclopentenols **4a** and **5a**, which bear three contiguous stereocenters.

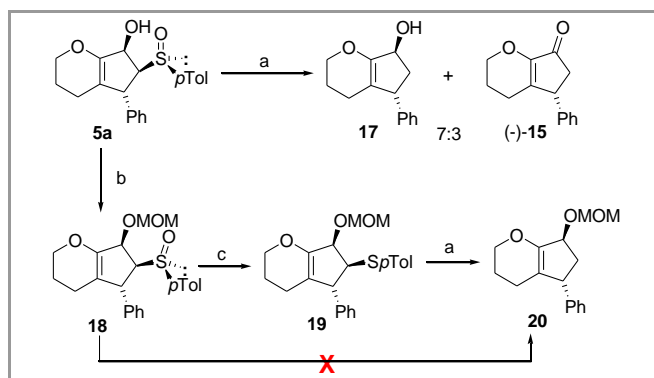
Thus, cyclopentenone **3a** was treated with DIBAL-H in THF at -78 °C, providing **4a** in 86% yield as sole diastereoisomer (Scheme 2). This stereochemical outcome can be explained in terms of a chelated conformer involving the aluminium and the sulfinyl oxygen, followed by an intramolecular hydride transfer.¹⁵ Cyclopentenol **5a**, epimer of **4a** having a *R* configuration at C-7, could be accessed by reacting cyclopentenone **3a** with NaBH_4 in THF at -15 °C with a good diastereoselectivity (93:7) and in 92% isolated yield of the major stereoisomer. The absolute configuration of the newly formed stereocenter was confirmed by X-ray crystal-structure diffraction analysis.^{3a} The hydride addition occurred from the diastereotopic face opposite to the bulky sulfinyl group. When the reaction was carried out with the more sterically congested L-Selectride no conversion was observed. Interestingly, the reaction of **3a** with DIBAL-H in the presence of ZnI_2 at -78 °C, using THF as a solvent,¹⁶ displayed a low degree of control, providing a 70:30 mixture of epimers **5a** and **4a**, respectively from which **5a** could be isolated in 62% yield. The diastereoselective reduction of a β -ketosulfoxide with the system DIBAL-H/ ZnX_2 involves the initial complexation of Zn with the sulfinyl and carbonyl oxygens and subsequent attack of a hydride from DIBAL-H on the less hindered side of the

chelated species (**A**, Scheme 2).¹⁶ In our case, the lack of diastereoselectivity could be ascribed to the presence of the dihydropyran oxygen atom, which could compete with the sulfinyl oxygen in the chelation with Zn (**B**, Scheme 2). Indeed, complexation of ZnBr₂ with an oxygenated function next to the carbonyl of a β-ketosulfoxide and its competition with the sulfinyl oxygen in the chelation with Zn has been invoked in the literature¹⁷ to explain the lack of stereoselectivity when the system DIBAL-H/ZnBr₂ is used to reduce the carbonyl in β-ketosulfoxides (**C**, Scheme 2).



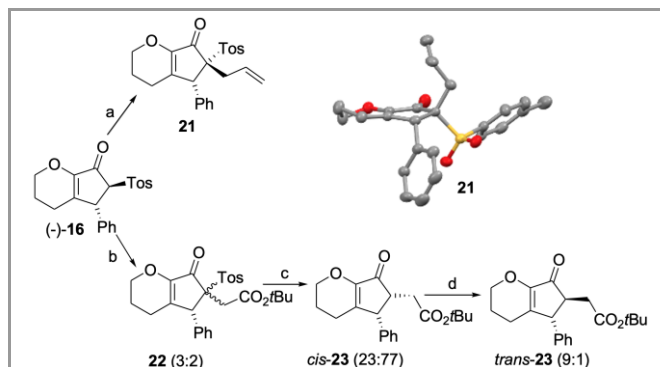
Scheme 2 Second switchable diastereodivergent step. a) DIBAL-H, THF, -78 °C, 86%; b) NaBH₄, THF, -15 °C, 92%.

To highlight the synthetic potential of this methodology, we explored the further elaboration of cyclopentanol **5a**. Thus, attempts to cleave the C-S bond by reaction with Raney nickel returned a 7:3 mixture of cyclopentanol **17** and cyclopentenone (-)-**15** (Scheme 3). The formation of (-)-**15** could be attributed to competing oxidative processes.¹⁸ In order to suppress this unwanted side reaction, we decided to protect the free alcohol. Attempts to generate the corresponding *tert*-butyldimethylsilyl ether only afforded the starting material despite extensive experimentation. Finally, the hydroxy group could be masked as its methoxymethyl ether affording **18** in 96% yield. Disappointingly, hydrogenolysis of the C-S bond by exposure of **18** to Raney nickel led to massive decomposition of the starting material. We addressed this issue by first reducing the sulfoxide group into the corresponding sulfide **19** by reaction with TFAA and NaI in acetone at -40 °C with an excellent yield. Gratifyingly, the C-S bond could then be cleaved by hydrogenolysis with Raney nickel, providing the desired protected-cyclopentanol **20** in 86% yield.



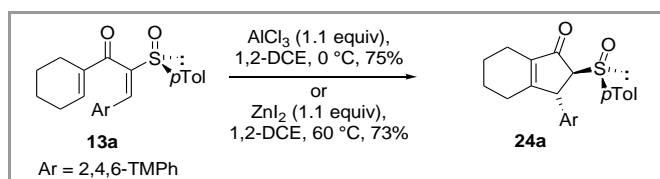
Scheme 3 Synthesis of protected-cyclopentanol **20**. a) Ra-Ni, MeOH, 88% for **17**/(-)-**15** and 86% for **20**; b) MOMCl, Et₃N, 96%; c) TFAA (5 equiv), NaI (3 equiv), acetone, -40 °C, 5 min, 98% yield.

As a second application, and to increase the molecular complexity of our Nazarov products, we focused on the introduction of functionalized side chains in the cyclopentenyl core of cyclopentenone (+)-**16** (Scheme 4). Indeed, the sulfinyl group can be used not only as an effective temporary chiral auxiliary but also, if it is initially oxidized to sulfone, as an excellent means of allowing alkylations at the α-position using mild conditions (weak bases and room temperature). Thus, treatment of sulfone (+)-**16** with 3 equivalents of K₂CO₃ in acetonitrile at room temperature, followed by the addition of allyl bromide, delivered quantitatively the alkylated cyclopentenone **21** as a single stereoisomer. The stereochemistry of the new stereocenter was unambiguously assigned through use of its X-ray crystal structure (Scheme 4). This analysis reveals that the alkylation at C-6 occurred *trans* to the C-5 aromatic substituent. Encouraged by this result, (+)-**16** was treated with *tert*-butyl bromoacetate, using the experimental conditions described above. After 48 hours of reaction at room temperature, we obtained **22** as an inseparable mixture of two diastereoisomers (60:40 d.r.) in 91% yield. By heating **22** at 50 °C, the reaction time could be reduced to 15 hours, but the yield decreased to 81% and no impact was observed in the diastereoselectivity. It is noteworthy that reductive removal of the sulfone group by exposure of **22** to Al-Hg primary afforded a 23:77 mixture of two C-6 alkylated cyclopentenones, in which the less thermodynamically stable *cis*-**23** was the major diastereoisomer. At this point, this epimeric mixture was treated with basic Al₂O₃ in CH₂Cl₂ at room temperature for 24 hours.¹⁹ Subsequently, a 90:10 inseparable mixture, in which the more stable diastereoisomer *trans*-**23** was the major product, was obtained in 80% yield from **22**.



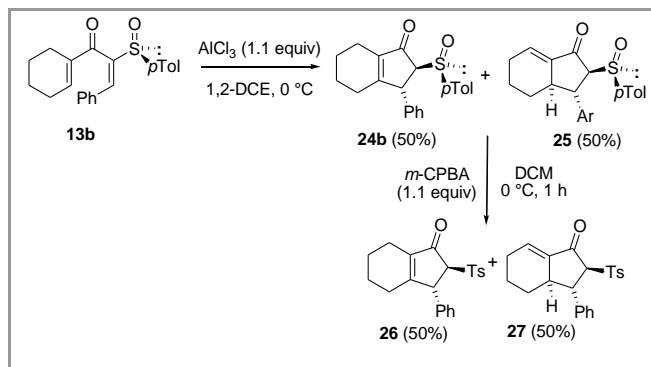
Scheme 4 Synthesis of cyclopentenones **21** and *trans*-**23**. a) K_2CO_3 (3 equiv), MeCN, allyl bromide (3 equiv), rt, 100%; b) K_2CO_3 (3 equiv), MeCN, $BrCH_2CO_2tBu$ (3 equiv), rt, 91%; c) Al-Hg, THF/H₂O 9:1, rt, 1 h; d) Al_2O_3 , DCM, rt, 24 h, 80% yield (from **22**).

Next, we turned our attention to substrates **13a** and **13b** bearing a cyclohexene as EDG. As expected, these compounds were less reactive than their DHP analogues. Thus, reaction of **13a**, bearing a 2,4,6-trimethoxy phenyl group as substituent at C-5, with $AlCl_3$ required a stoichiometric amount of the promoter at 0°C for its total conversion and provided cyclopentenone **24a** in 75% yield (Scheme 5). Interestingly, by using ZnI_2 as the promoter the same stereoselectivity was observed and **24a** was obtained in 60% yield. Indeed, in the reaction with ZnI_2 DFT calculations show that, due to the absence of the donating oxygen, *E-Z* isomerization of the double bond takes place before the cyclization step.^{3b}



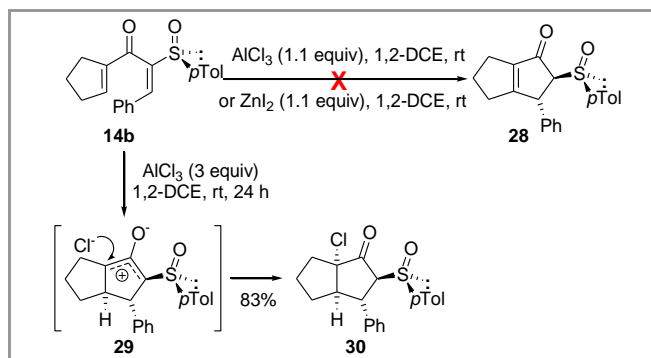
Scheme 5 Nazarov cyclization of substrate **13a** bearing a cyclohexene as EDG.

On the other hand, substrate **13b**, bearing a phenyl group as substituent at C-5, by reaction with $AlCl_3$, provided an inseparable 50/50 mixture of cyclopentenone **24b** and its regioisomer **25**, bearing three contiguous new stereocenters, in 80% yield (Scheme 6). These compounds were quantitatively transformed into their corresponding sulfones **26** and **27** that could be separated. By reaction with ZnI_2 now conversion of **13b** was observed after 15 hours at 60°C. The absolute configuration of the three new stereocenters of **27** were determined by X-ray diffraction analysis.^{3b}



Scheme 6 Nazarov cyclization of substrate **13b** and oxidation of **24b** and **25**.

Finally, we explored the Nazarov cyclization of divinylketones **14a,b**, bearing a cyclopentene as electron-rich moiety, targeting the cyclopentenone **28** (Scheme 7). Thus, by using a stoichiometric amount of $AlCl_3$ or ZnI_2 no conversion could be observed in neither case. The lower reactivity of cyclopentene substrates was already observed by Alison Frontier and co-workers.²⁰ However, upon treatment with an excess of $AlCl_3$, substrate **14b** delivered the α -chloroketone **30**, bearing four new stereocenters that were created in a single step, in 83% yield. This product resulted from an interrupted Nazarov cyclization, in which the cationic intermediate **29** was highly regioselectively intercepted by a nucleophilic chloride anion in preference to deprotonation, and which preserves the three new stereocenters generating an additional one.²¹



Scheme 7 Interrupted Nazarov cyclization of substrate **14b**.

Conclusion

Starting from activated dienones bearing a DHP and a chiral sulfoxide, we have developed a doubly switchable diastereodivergent strategy, which in a first operation provides selective access, *via* a torquoselective Nazarov cyclization, to two *trans* disubstituted aryl cyclopentenones with a complete diastereoselectivity and good torquoselectivity. In a second diastereodivergent step, these cyclopentenones can lead, *via* the high diastereoselective reduction of the carbonyl group, to two cyclopentenols with three adjacent stereocenters. It is important to point out that, in both diastereoselective steps, the asymmetric induction was dictated by the chiral sulfoxide auxiliary and could be switched according to the nature of the Lewis acid or the reducing agent that was employed without

introducing a new chiral parameter. Furthermore, synthetic elaborations of the resulting cyclopentenones and cyclopentenols lead to highly functionalized heterobicyclic compounds as potentially useful building blocks, highlighting the synthetic utility of this methodology. Particularly, we reported a halogen-interrupted Nazarov reaction giving rise to a tetra-substituted cyclopentanone in which four stereocenters were generated in a single step.

All reagents and solvents were purchased from commercial sources. THF was distilled on sodium/benzophenone; diisopropylamine was distilled from KOH. Solvents for chromatography were of technical grade and distilled prior to use. Reactions were performed in flame-dried glassware under an argon atmosphere. ^1H NMR spectra were recorded at 300 or 400 MHz in CDCl_3 ; ^{13}C NMR spectra were recorded at 75 or 101 MHz in CDCl_3 . Chemical shifts are given in ppm and are reported relative to the residual solvent peak (CDCl_3 : $\delta = 7.26$ ppm (^1H), $\delta = 77.16$ ppm (^{13}C)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Analytical TLC was performed on silica gel 60 F254 plates. Column chromatography was performed on silica gel 60 (63–200 μm). Melting points were recorded on a Büchi apparatus and are uncorrected. Optical rotations were measured by using a Perkin-Elmer apparatus at 20°C, 589 nm (sodium ray); concentrations are reported in g/100 mL. IR spectra were recorded on a Thermo Nicolet Avatar 320 FTIR spectrometer by using an ATR device. HRMS was recording by using electrospray ionization (ESI) and Q-ToF detection.

(R)-2-(p-tolylsulfinyl)-1-(5,6-dihydro-4H-pyran-2-yl)ethanone (10)

A solution of diisopropylamine (1.18 mL, 8.46 mmol) in dry THF (10 mL) under argon atmosphere was cooled to -40 °C and treated with *n*-butyllithium (1.6 M in hexanes, 6.0 mL, 8.46 mmol). The reaction mixture was stirred at -40 °C for 30 min and a solution of 1.24 g (8.06 mmol) of (*R*)-methyl-*p*-tolylsulfinyl in dry THF (6 mL) was introduced via cannula. The resulting suspension was stirred at -40 °C for 2 h, and a solution of 5,6-dihydro-4H-pyran-2-carboxylate (0.561 g, 3.94 mmol) in dry THF (4 mL) was added. The mixture was stirred at 0 °C for 12 h, and then quenched with saturated aqueous NH_4Cl (50 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 3:2 v/v) affording 0.976 g of **10**.

Yield: 94%; white solid; $R_f = 0.37$ (cyclohexanes/EtOAc 1:3 v/v); mp 54–56 °C; $[\alpha]_{\text{D}}^{20} +139$ (*c* 1.0, CHCl_3).

IR (neat): 2927, 2874, 1674, 1622, 1265, 1083, 1045, 1003, 914, 807, 505 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): $\delta = 7.55$ (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 6.00 (t, $J = 4.3$ Hz, 1H), 4.22 (d, $J = 13.6$ Hz, 1H), 4.02 (t, $J = 5.1$ Hz, 2H), 3.93 (d, $J = 13.6$ Hz, 1H), 2.40 (s, 3H), 2.21–2.16 (m, 2H), 1.84–1.76 (m, 2H).

^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 187.5$, 150.9, 142.2, 140.4, 130.1, 124.5, 112.9, 66.6, 65.2, 21.6, 21.4, 20.9.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3\text{S}$: 265.0898; found: 265.0901.

(R)-1-(cyclohex-1-en-1-yl)-2-(p-tolylsulfinyl)ethan-1-one (11)

Diisopropylamine (4.15 mL, 29.3 mmol) was dissolved in dry THF (35 mL) under argon atmosphere and the resulting solution was cooled to -

40 °C and treated with *n*-butyllithium (1.4 M in hexanes, 21.0 mL, 29.4 mmol). The system was stirred at -40 °C for 30 min and a solution of (*R*)-methyl-*p*-tolylsulfinyl (4.41 g, 28.6 mmol) in dry THF (20 mL) was introduced via cannula. After stirring at -40 °C for 1.5 h, methyl cyclopent-1-ene-1-carboxylate (2.00 g, 14.3 mmol) in dry THF (15 mL) was added at -78 °C. The reaction mixture was stirred at 0 °C for 12 h and then quenched with saturated aqueous NH_4Cl (50 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 3:2 v/v) providing 2.93 g of **11**.

Yield: 78%; white solid; $R_f = 0.37$ (cyclohexanes/EtOAc 1:1 v/v); mp 80–82 °C; $[\alpha]_{\text{D}}^{20} +188$ (*c* 1.0, CHCl_3).

IR (neat): 2934, 2861, 1649, 1629, 1275, 1250, 1041, 814 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): $\delta = 7.54$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 6.87–6.84 (m, 1H), 4.09 (AB system, $\Delta\nu = 102.1$ Hz, $J = 13.6$, 2H), 2.40 (s, 3H), 2.27–2.19 (m, 2H), 2.18–2.11 (m, 2H), 1.61–1.51 (m, 2H).

^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 191.8$, 145.0, 142.1, 140.4, 139.9, 130.1, 124.4, 65.0, 26.5, 22.9, 21.6, 21.4.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2\text{S}$: 263.1106; found: 263.1107.

(R)-1-(cyclopent-1-en-1-yl)-2-(p-tolylsulfinyl)ethan-1-one (12)

Diisopropylamine (1.43 mL, 10.1 mmol) was dissolved in dry THF (12 mL) under argon atmosphere and the resulting solution was cooled at -40 °C. *n*-butyllithium (1.4 M in hexanes, 7.20 mL, 10.1 mmol) was then added dropwise, at -40 °C. The system was stirred at -40 °C for 30 min and a solution of (*R*)-methyl-*p*-tolylsulfinyl (1.24 g, 8.04 mmol) in dry THF (8 mL) was introduced via cannula. After stirring 1.5 h at -40 °C, methyl cyclopent-1-ene-1-carboxylate (614 mg, 4.87 mmol) in dry THF (5 mL) was added at -78 °C. The reaction mixture was stirred at 0 °C for 12 additional hours and then quenched with saturated aqueous NH_4Cl (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 3:2 v/v) affording 1.15 g of **12**.

Yield: 95%; colorless oil; $R_f = 0.34$ (cyclohexanes/EtOAc 1:1 v/v); $[\alpha]_{\text{D}}^{20} +180$ (*c* 1.0, CHCl_3).

IR (neat): 2927, 2874, 1674, 1622, 1265, 1083, 1045, 1003, 914, 807, 505 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): $\delta = 7.53$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 6.75–6.72 (m, 1H), 4.07 (AB system, $\Delta\nu = 91.7$ Hz, $J = 13.3$ Hz, 2H), 2.54–2.47 (m, 2H), 2.39 (s, 3H), 1.93–1.83 (m, 2H).

^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 189.0$, 148.6, 146.1, 142.2, 140.2, 130.1, 124.3, 66.4, 34.5, 30.5, 22.8, 21.6.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_2\text{S}$: 249.0949; found: 249.0954.

General Procedure for the syntheses of divinyl- β -ketosulfoxides 1a-g

To a solution of γ,δ -unsaturated- β -ketosulfoxide (1 equiv) in dry CH_2Cl_2 [0.1 M] under argon atmosphere the corresponding aryl aldehyde (1.2 equiv) and piperidine (1.2 equiv) were added at room temperature. After 4 days stirring, the reaction mixture was concentrated under reduced

pressure and solubilized in CH₂Cl₂ [0.1 M]. Iodomethane (3 equiv) was added at rt. The reaction mixture was stirred overnight, and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc see *ratio* thereafter) to afford pure divinyl-β-ketosulfoxide **1a-g**.

Assignment of olefin geometry for divinyl-β-ketosulfoxides **1a-g**

The “*in*” configuration of substrates **1a-g**, **13a-b** and **14a-b** was assumed by analogy to **1b** and **13a**, which geometry was determined by single-crystal X-ray diffraction analysis (see the text and the **1b** and **13a** single-crystal X-ray diffraction analysis given below). Another argument to assign the geometries was based on carbon–hydrogen coupling constants obtained for the ketone with the cyclic proton (H₁) or the vinylic one (H₅). The last values for H₅ are always higher than the ones concerning H₁.¹¹

(*R*)-(2*E*)-2-(*p*-tolylsulfinyl)-1-(5,6-dihydro-4*H*-pyran-2-yl)-3-phenylprop-2-en-1-one (**1a**)

Prepared following the General Procedure, and purified by column chromatography (CH₂Cl₂/EtOAc 95:5 v/v).

Yield: 64%; yellow oil; *R*_f = 0.56 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ +184 (c 1.0, CHCl₃).

IR (neat): 2924, 1647, 1620, 1084, 1055, 809, 693 cm⁻¹.

¹H NMR (CDCl₃, 600 MHz): δ = 7.47 (d, *J* = 8.2 Hz, 2H), 7.43 (s, 1H), 7.29–7.23 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.51 (t, *J* = 4.3 Hz, 1H), 3.82–3.63 (m, 2H), 2.31 (s, 3H), 1.85–1.69 (m, 2H), 1.58–1.42 (m, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ = 188.1, 151.0, 143.9, 142.4, 138.8, 134.5, 133.6, 130.0, 129.8, 129.7, 128.8, 125.6, 118.3, 66.4, 21.6, 21.1.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₁O₃S: 353.1211; found: 353.1208. *E*-stereochemistry: ³*J*_{C-H} = 10.0 Hz for C_{ketone-H}, ³*J*_{C-H} = 4.2 Hz for C_{ketone-H_{cycle}}

(*R*)-(2*E*)-2-(*p*-tolylsulfinyl)-1-(5,6-dihydro-4*H*-pyran-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one (**1b**)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 95:5 v/v).

Yield: 62%; yellow solid; *R*_f = 0.53 (cyclohexanes/EtOAc 1:1 v/v); mp 139–141 °C; [α]_D²⁰ +211 (c 1.0, CHCl₃).

IR (neat): 2957, 1638, 1616, 1594, 1521, 1344, 1088, 1060, 508 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 8.17 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.48 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.3 Hz), 5.58 (t, *J* = 4.3 Hz, 1H), 3.84–3.72 (m, 2H), 2.38 (s, 3H), 1.95–1.79 (m, 2H), 1.64–1.50 (m, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ = 187.2, 150.8, 148.8, 148.0, 143.0, 139.9, 137.9, 130.7, 130.2, 130.2, 125.7, 124.0, 118.5, 66.5, 21.6, 21.6, 21.1.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₀NO₅S: 398.1062; found: 398.1060.

E-stereochemistry: ³*J*_{C-H} = 10.0 Hz for C_{ketone-H}, ³*J*_{C-H} = 4.6 Hz for C_{ketone-H_{cycle}}

(*R*)-(2*E*)-2-(*p*-tolylsulfinyl)-1-(5,6-dihydro-4*H*-pyran-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1c**)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 95:5 v/v).

Yield: 46%; yellow oil; *R*_f = 0.43 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ +123 (c 1.0, CHCl₃).

IR (neat): 2025, 1647, 1622, 1601, 1511, 1255, 1176, 1084, 1055, 752, 503 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.51 (d, *J* = 8.2 Hz, 2H), 7.39 (s, 1H), 7.27 (d, *J* = 9.9 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.66 (t, *J* = 4.3 Hz, 1H), 3.86 (t, *J* = 4.9 Hz, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 1.93–1.86 (m, 2H), 1.66–1.59 (m, 2H).

¹³C NMR (CDCl₃, 75 MHz): δ = 188.3, 160.9, 151.2, 142.2, 140.9, 139.0, 134.6, 131.8, 130.0, 126.0, 125.6, 118.5, 114.2, 66.5, 55.5, 21.6, 21.2.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₂H₂₃O₄S: 383.1317; found: 383.1317. *E*-stereochemistry: ³*J*_{C-H} = 10.1 Hz for C_{ketone-H}, ³*J*_{C-H} = 4.6 Hz for C_{ketone-H_{cycle}}

(*R*)-(2*E*)-2-(*p*-tolylsulfinyl)-1-(5,6-dihydro-4*H*-pyran-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one (**1d**)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 96:4 v/v).

Yield: 45%; beige solid; *R*_f = 0.72 (cyclohexanes/EtOAc 1:1 v/v); mp 93–95 °C; [α]_D²⁰ +164 (c 1.0, CHCl₃).

IR (neat): 2989, 2923, 1643, 1620, 1489, 1085, 1066, 1051, 923, 808.

¹H NMR (400 MHz, CDCl₃): δ = 7.46 (d, *J* = 8.2 Hz, 2H), 7.35 (s, 1H), 7.25–7.20 (m, 3H), 5.54 (t, *J* = 4.3 Hz, 1H), 3.81–3.72 (m, 2H), 2.32 (s, 3H), 1.90–1.74 (m, 2H), 1.61–1.47 (m, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 187.6, 150.8, 144.6, 142.4, 138.3, 135.6, 132.5, 131.8, 130.8, 129.9, 128.9, 125.4, 118.4, 66.3, 21.5, 21.0, 20.9.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₀O₃SCl: 387.0822; found: 387.0820.

E-stereochemistry: ³*J*_{C-H} = 9.8 Hz for C_{ketone-H}, ³*J*_{C-H} = 4.3 Hz for C_{ketone-H_{cycle}}

(*R*)-(2*E*)-2-(*p*-tolylsulfinyl)-1-(5,6-dihydro-4*H*-pyran-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**1e**)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 93:7 v/v).

Yield: 44%; yellow solid; *R*_f = 0.36 (cyclohexanes/EtOAc 1:1 v/v); mp 41–43 °C; [α]_D²⁰ +125 (c 1.0, CHCl₃).

IR (neat): 2934, 2838, 1650, 1621, 1579, 1505, 1328, 1240, 1123, 1084, 1055, 810, 503 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.50 (d, *J* = 8.0 Hz, 2H), 7.36 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.54 (s, 2H), 5.57 (t, *J* = 4.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 2.35 (s, 3H), 1.91–1.83 (m, 2H), 1.65–1.51 (m, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 188.2, 153.1, 151.3, 143.0, 142.4, 139.4, 138.8, 134.4, 130.0, 128.9, 125.5, 117.7, 107.0, 66.4, 61.0, 56.1, 21.6, 21.2, 21.1.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₂₇O₆S: 443.1528; found: 443.1530. *E*-stereochemistry: ³*J*_{C-H} = 9.9 Hz for C_{ketone-H}, ³*J*_{C-H} = 4.2 Hz for C_{ketone-H_{cycle}}

(R)-(2E)-2-(p-tolylsulfinyl)-1-(5,6-dihydro-4H-pyran-2-yl)-3-(2-nitrophenyl)prop-2-en-1-one (1f)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 95:5).

Yield: 56%; yellow solid; *R*_f = 0.42 (cyclohexanes/EtOAc 1:1 v/v); mp 108-110 °C; [α]_D²⁰ +219 (c 1.0, CHCl₃).

IR (neat) 3072, 2983, 2935, 2870, 1647, 1616, 1526, 1342, 1085, 1061, 494 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.95 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.56 (td, *J* = 7.5, 1.0 Hz, 1H), 7.49 (td, *J* = 7.6, 1.0 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.37 (t, *J* = 4.3 Hz, 1H), 3.61-3.51 (m, 2H), 1.67-1.62 (m, 2H), 1.38-1.32 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ = 186.7, 150.9, 146.8, 146.6, 142.7, 138.6, 134.1, 132.3, 131.4, 131.4, 130.2, 129.7, 125.7, 125.1, 117.1, 66.2, 21.6, 20.8, 20.8.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₀N₂O₅S: 398.1062; found: 398.1060.

E-stereochemistry: ³*J*_{C-H} = 9.6 Hz for C_{ketone}-H, ³*J*_{C-H} = 4.0 Hz for C_{ketone}-H_{cycle}

(R)-(2E)-2-(p-tolylsulfinyl)-1-(5,6-dihydro-4H-pyran-2-yl)-3-(furan-2-yl)prop-2-en-1-one (1g)

Prepared following the General Procedure and purified by column chromatography (CH₂Cl₂/EtOAc 9:1 v/v).

Yield: 62%; yellow oil; *R*_f = 0.36 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ +38 (c 1.0, CHCl₃).

IR (neat): 2926, 1651, 1621, 1084, 1054, 1015, 919, 809, 504 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.45 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.17 (s, 1H), 6.58 (d, *J* = 3.4 Hz, 1H), 6.38 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.63 (t, *J* = 4.3 Hz, 1H), 3.91 (t, *J* = 5.2 Hz, 2H), 2.33 (s, 3H), 2.06-1.86 (m, 2H), 1.74-1.58 (m, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 186.9, 151.6, 149.1, 145.3, 142.4, 140.2, 138.7, 129.9, 125.4, 120.5, 117.7, 115.7, 112.2, 66.4, 21.5, 21.2, 21.0.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₉H₁₉O₄S: 343.1004; found: 343.1005. *E*-stereochemistry: ³*J*_{C-H} = 9.6 Hz for C_{ketone}-H, ³*J*_{C-H} = 4.5 Hz for C_{ketone}-H_{cycle}

(S)-(2E)-1-(cyclohex-1-en-1-yl)-2-(p-tolylsulfinyl)-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (13a)

Prepared following the General Procedure and purified by column chromatography (cyclohexanes/EtOAc 2:1 v/v).

Yield: 34%; pale yellow solid; *R*_f = 0.35 (cyclohexanes/EtOAc 1:1 v/v); mp 158-160 °C; [α]_D²⁰ +232 (c 1.0, CHCl₃).

IR (neat): 2939, 1601, 1576, 1204, 1130, 1038, 820, 514 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.61 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.25-6.17 (m, 1H), 6.03 (s, 2H), 3.81 (s, 3H), 3.72 (s, 6H), 2.34 (s, 3H), 2.08-1.85 (m, 2H), 1.80-1.65 (m, 2H), 1.42-1.20 (m, 4H).

¹³C NMR (75 MHz, CDCl₃): δ = 193.3, 162.7, 159.1, 143.1, 141.4, 140.6, 137.7, 129.6, 126.0, 125.9, 105.7, 100.1, 90.4, 55.5, 55.5, 26.0, 22.7, 21.9, 21.7, 21.6.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₅H₂₉O₅S: 441.1736; found: 441.1738. *E*-stereochemistry: ³*J*_{C-H} = 9.8 Hz for C_{ketone}-H, ³*J*_{C-H} = 7.8 Hz for C_{ketone}-H_{cycle}

(S)-(2E)-1-(cyclohex-1-en-1-yl)-3-phenyl-2-(p-tolylsulfinyl)prop-2-en-1-one (13b)

Prepared following the General Procedure and purified by column chromatography (cyclohexanes/EtOAc 9:1 v/v).

Yield: 51%; yellow oil; *R*_f = 0.53 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ +200 (c 1.0, CHCl₃).

IR (neat): 2930, 1625, 1201, 1083, 1056, 809, 693 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.47 (d, *J* = 8.2 Hz, 2H), 7.42 (s, 1H), 7.30-7.22 (m, 7H), 6.41-6.38 (m, 1H), 2.36 (s, 3H), 2.16-1.91 (m, 2H), 1.87-1.78 (m, 2H), 1.46-1.22 (m, 4H).

¹³C NMR (75 MHz, CDCl₃): δ = 194.1, 147.4, 144.9, 142.3, 138.8, 138.7, 133.6, 132.8, 129.9, 129.6, 129.5, 128.7, 125.4, 26.3, 22.6, 21.6, 21.5, 21.3.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₂H₂₂O₂S: 351.1419; found: 351.1418. *E*-stereochemistry: ³*J*_{C-H} = 9.1 Hz for C_{ketone}-H, ³*J*_{C-H} = 7.9 Hz for C_{ketone}-H_{cycle}

(S)-(2E)-1-(cyclopent-1-en-1-yl)-3-phenyl-2-(p-tolylsulfinyl)prop-2-en-1-one (14a)

Prepared following the General Procedure and purified by column chromatography (cyclohexanes/EtOAc 3:7 v/v).

Yield: 35%; yellow solid; *R*_f = 0.37 (cyclohexanes/EtOAc 1:1 v/v); mp 168-170 °C; [α]_D²⁰ +255 (c 1.0, CHCl₃).

IR (neat): 2924, 1647, 1620, 1084, 1055, 809, 693 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.60 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.07-6.03 (m, 3H), 3.81 (s, 3H), 3.72 (s, 6H), 2.34 (s, 3H), 2.31-2.24 (m, 2H), 2.14-2.06 (m, 2H), 1.71-1.56 (m, 3H).

¹³C NMR (CDCl₃, 75MHz): δ = 190.0, 162.8, 159.1, 145.7, 144.2, 141.6, 141.5, 140.7, 129.6, 125.9, 125.5, 105.7, 90.4, 55.5, 55.4, 33.8, 30.2, 23.1, 21.6.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₂₇O₅S: 427.1579; found: 427.1573. *E*-stereochemistry: ³*J*_{C-H} = 9.8 Hz for C_{ketone}-H, ³*J*_{C-H} = 2.8 Hz for C_{ketone}-H_{cycle}

(S)-(2E)-1-(cyclopent-1-en-1-yl)-3-phenyl-2-(p-tolylsulfinyl)prop-2-en-1-one (14b)

Prepared following the General Procedure and purified by column chromatography (cyclohexanes/EtOAc 9:1 v/v).

Yield: 38%; yellow oil; *R*_f = 0.48 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ +184 (c 1.0, CHCl₃).

IR (neat): 2924, 1647, 1620, 1084, 1055, 809, 693 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (s, 1H), 7.26 (s, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.19 -6.16 (m, 1H), 2.36-2.28 (m, 5H), 2.17-2.07 (m, 2H), 1.67 (quin, *J* = 7.6 Hz, 4H).

¹³C NMR (CDCl₃, 75MHz): δ = 190.8, 150.4, 145.6, 144.8, 142.2, 138.8, 133.5, 132.4, 129.8, 129.6, 129.5, 128.6, 125.3, 34.0, 30.0, 22.8, 21.5.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₁H₂₁O₂S: 353.1211; found: 353.1208. *E*-stereochemistry: ³*J*_{C-H} = 9.0 Hz for C_{ketone}-H, ³*J*_{C-H} = 2.5 Hz for C_{ketone}-H_{cycle}

General Procedure A for zinc iodide-promoted Nazarov cyclization

To a solution of zinc iodide (1.1 equiv) in 1,2-DCE [0.12 M] under argon atmosphere was added a solution of the corresponding divinyl- β -ketosulfoxide **1a-g** (1 equiv) in 1,2-DCE [0.12 M]. After 24 h stirring at rt, the reaction mixture was quenched with brine (20 mL). The two layers were separated and aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc; see *ratio* thereafter) to afford **2a-g**.

General Procedure B for aluminium chloride-promoted Nazarov cyclization

To a solution of aluminium chloride (0.25 equiv) in 1,2-DCE [0.12 M] under argon atmosphere was added a solution of the corresponding divinyl- β -ketosulfoxide **1a-g** (1 equiv) in 1,2-DCE [0.12 M]. After 3 h stirring at 0 °C, the reaction mixture was quenched with brine (20 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluent (cyclohexane/EtOAc; see *ratio* thereafter) to afford **3a-g**.

(5S,6R,S(R))-6-(p-tolylsulfinyl)-3,4,5,6-tetrahydro-5-phenylcyclopenta[b]pyran-7(2H)-one (2a)

Prepared following the General Procedure A and purified by column chromatography (cyclohexane/EtOAc 7:3).

Yield: 68%; colourless oil; R_f = 0.53 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{20} +178$ (c 1.0, CHCl₃).

IR (neat): 3004, 2928, 1701, 1642, 1596, 1492, 1453, 1402, 1302, 1269, 1215, 1164, 1112, 1079, 1048, 953, 906, 811, 746, 699, 665, 645, 510 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.48 (d, J = 8.2 Hz, 2H), 7.34-7.18 (m, 5H), 7.18-7.07 (m, 2H), 4.10 (s, 1H), 4.01-3.88 (m, 2H), 3.82-3.66 (m, 1H), 2.39 (s, 3H), 2.07-1.89 (m, 1H), 1.89-1.61 (m, 2H), 1.61-1.41 (m, 1H).

¹³C NMR (CDCl₃, 75MHz): δ = 191.7, 151.7, 147.9, 142.3, 139.3, 135.6, 129.5, 129.2, 127.7, 127.6, 124.8, 72.3, 66.9, 42.6, 22.3, 21.5, 21.0.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₁O₃S: 353.1211; found: 353.1212.

(5S,6R,S(R))-6-(p-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-chlorophenyl)cyclopenta[b]pyran-7(2H)-one (2b)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 69%; yellow solid; R_f = 0.48 (cyclohexanes/EtOAc 1:1 v/v); mp 143-145 °C; $[\alpha]_D^{20} +234$ (c 1.0, CHCl₃).

IR (neat) 2922, 1703, 1638, 1116, 1047, 806, 518 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.47 (d, J = 8.1 Hz, 2H), 7.27 (t, J = 8.7 Hz, 4H), 7.07 (d, J = 8.3 Hz, 2H), 4.07 (s, 1H), 3.98-3.91 (m, 2H), 3.77-3.71 (m, 1H), 2.40 (s, 3H), 1.96 (dt, J = 13.8, 6.6 Hz, 1H), 1.83-1.69 (m, 2H), 1.52-1.43 (m, 1H).

¹³C NMR (CDCl₃, 75MHz): δ = 191.0, 152.4, 147.4, 147.1, 145.9, 142.8, 135.1, 129.8, 128.9, 124.9, 124.5, 72.0, 67.1, 42.0, 22.4, 21.5, 20.9.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₀O₃SCl: 387.0822; found: 387.0821.

(5S,6R,S(R))-6-(p-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-methoxyphenyl)cyclopenta[b]pyran-7(2H)-one (2c)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 19%; yellow solid; R_f = 0.47 (cyclohexanes/EtOAc 1:1 v/v); mp 132-134 °C; $[\alpha]_D^{20} +243$ (c 1.0, CHCl₃).

IR (neat): 2924, 1711, 1700, 1643, 1511, 1246, 1041, 811, 516 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.50 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.08 (s, 1H), 3.99-3.91 (m, 2H), 3.78-3.73 (m, 4H), 2.41 (s, 3H), 2.00 (dt, J = 13.7, 6.6 Hz, 1H), 1.85-1.65 (m, 2H), 1.58-1.48 (m, 1H).

¹³C NMR (CDCl₃, 75MHz): δ = 192.0, 159.1, 151.7, 148.1, 142.3, 135.9, 131.3, 129.6, 128.9, 125.0, 114.7, 72.5, 67.1, 55.5, 42.0, 22.4, 21.6, 21.1.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₂H₂₂O₄S: 383.1317; found: 383.1316.

(5S,6R,S(R))-6-(p-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-nitrophenyl)cyclopenta[b]pyran-7(2H)-one (2d)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 70%; yellow solid; R_f = 0.39 (cyclohexanes/EtOAc 1:1 v/v); mp 54-56 °C; $[\alpha]_D^{20} +250$ (c 1.0, CHCl₃).

IR (neat): 2924, 1703, 1642, 1596, 1517, 1492, 1345, 1301, 1270, 1111, 1074, 1047, 1014, 811, 748, 510 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 8.17 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 4.22 (s, 1H), 4.02-3.95 (m, 1H), 3.98 (s, 1H), 3.80-3.70 (m, 1H), 2.42 (s, 3H), 2.03-1.92 (m, 1H), 1.85-1.69 (m, 2H), 1.58-1.44 (m, 1H).

¹³C NMR (CDCl₃, 75MHz): δ = 191.0, 152.5, 147.5, 147.1, 145.9, 142.8, 135.2, 129.8, 129.0, 124.9, 124.5, 72.03, 67.2, 42.0, 22.4, 21.5, 20.9.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₀NO₅S: 398.1062; found: 398.1060.

(5S,6R,S(R))-6-(p-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(2-nitrophenyl)cyclopenta[b]pyran-7(2H)-one (2e)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 3:2 v/v).

Yield: 65%; white solid; R_f = 0.30 (cyclohexanes/EtOAc 1:1 v/v); mp 66-68 °C; $[\alpha]_D^{20} +59$ (c 1.0, CHCl₃).

IR (neat): 2923, 1706, 1643, 1524, 1351, 1113, 1048, 513 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.82 (dd, J = 8.1, 1.1 Hz, 1H), 7.55 (dd, J = 7.6, 1.2 Hz, 1H), 7.47-7.38 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 4.82 (s, 1H), 4.01-3.94 (m, 2H), 3.85-3.78 (m, 1H), 2.40 (s, 3H), 2.05 (dt, J = 15.7, 9.6 Hz, 1H), 1.90 (dt, J = 15.8, 9.7 Hz, 1H), 1.74-1.68 (m, 1H), 1.63-1.57 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3): δ =191.4, 152.3, 150.5, 147.1, 142.5, 135.5, 134.0, 133.4, 129.8, 129.1, 128.7, 125.0, 124.9, 72.7, 67.1, 38.0, 22.2, 21.5, 21.0.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_5\text{S}$: 398.1062; found: 398.1061.

(5S,6R,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(3,4,5-trimethoxyphenyl)cyclopenta[b]pyran-7(2H)-one (2f)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 1:1 v/v).

Yield: 24%; yellow oil; R_f = 0.22 (cyclohexanes/EtOAc 1:1 v/v); $[\alpha]_{\text{D}}^{20}$ +170 (c 0.2, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ =7.51 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.32 (s, 2H), 4.05 (s, 1H), 4.02-3.97 (m, 2H), 3.81 (s, 9H), 3.78-3.69 (m, 1H), 2.42 (s, 3H), 2.05 (dt, J = 18.3, 5.8 Hz, 1H), 1.89-1.56 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ = 191.9, 153.9, 151.9, 147.7, 142.5, 137.5, 135.8, 135.1, 129.7, 125.0, 104.6, 72.2, 67.1, 61.0, 56.4, 42.9, 22.5, 21.6, 21.2.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{27}\text{O}_6\text{S}$: 443.1528; found: 443.1531.

(5S,6R,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(furan-2-yl)cyclopenta[b]pyran-7(2H)-one (2g)

Prepared following the General Procedure A and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 67%; yellow oil; R_f = 0.43 (cyclohexane/EtOAc 1:1 v/v); $[\alpha]_{\text{D}}^{20}$ +228 (c 1.0, CHCl_3).

IR (neat) 2925, 1703, 1644, 1591, 1505, 1458, 1422, 1237, 1122, 1049, 810, 508 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 7.46 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.8 Hz, 3H), 6.28 (s, 1H), 6.13 (s, 1H), 4.20 (s, 1H), 4.12 (s, 1H), 3.95-3.90 (m, 1H), 3.78-3.73 (m, 1H), 2.39 (s, 3H), 2.07 (dt, J = 9.2, 6.3 Hz, 1H), 1.86 (dt, J = 19.2, 5.5 Hz, 1H), 1.76-1.66 (m, 1H), 1.58-1.42 (m, 1H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 191.1, 151.6, 151.5, 145.3, 142.6, 142.4, 135.5, 129.7, 124.9, 110.7, 107.5, 69.2, 67.0, 36.5, 22.4, 21.5, 21.0.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_4\text{S}$: 343.1004; found: 343.1006.

[5R,6S,S(R)]-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-phenylcyclopenta[b]pyran-7(2H)-one (3a)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 90%; white solid; R_f = 0.40 (cyclohexanes/EtOAc 1:1 v/v); mp 185-187 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20}$ +228 (c 1.0, CHCl_3).

IR (neat): 3036, 2900, 2871, 1711, 1648, 1492, 1118, 1042, 699 cm^{-1} .

^1H NMR (CDCl_3 , 600 MHz): δ = 7.42 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.10-7.03 (m, 3H), 6.54-6.52 (m, 2H), 4.19-4.11 (m, 2H), 4.09 (d, J = 1.2 Hz, 1H), 3.37 (d, J = 1.7 Hz, 1H), 2.37 (s, 3H), 2.21 (dt, J = 13.6, 6.4 Hz, 1H), 2.02-1.93 (m, 2H), 1.89-1.83 (m, 1H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 192.7, 151.7, 149.7, 141.7, 139.2, 138.1, 129.9, 128.8, 127.3, 127.2, 124.2, 74.7, 67.2, 40.9, 22.4, 21.4, 21.3.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{21}\text{O}_3\text{S}$: 353.1211; found: 353.1212.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-chlorophenyl)cyclopenta[b]pyran-7(2H)-one (3b)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 6:4 v/v).

Yield: 88%; white solid; R_f = 0.38 (cyclohexanes/EtOAc 1:1 v/v); mp 162-164 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20}$ +120 (c 1.0, CHCl_3).

IR (neat): 3030, 2923, 1708, 1646, 1320, 1304, 1138, 751, 675, 573, 519 cm^{-1} .

^1H NMR (CDCl_3 , 600 MHz): δ = 7.41 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 6.9 Hz, 2H), 6.44 (d, J = 8.1 Hz, 2H), 4.19-4.14 (m, 2H), 4.06 (s, 1H), 3.33 (s, 1H), 2.38 (s, 3H), 2.25-2.16 (m, 1H), 2.01-1.83 (m, 3H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 192.3, 149.0, 141.8, 137.9, 137.8, 133.1, 130.0, 128.9, 128.6, 124.1, 74.5, 67.2, 40.2, 22.3, 21.4, 21.2.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{20}\text{O}_3\text{SCl}$: 387.0822; found: 387.0822.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-methoxyphenyl)cyclopenta[b]pyran-7(2H)-one (3c)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 3:2 v/v).

Yield: 90%; white solid; R_f = 0.35 (cyclohexanes/EtOAc 1:1 v/v); mp 116-118 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20}$ +77 (c 1.0, CHCl_3).

IR (neat): 2913, 1708, 1643, 1612, 1510, 1460, 1299, 1245, 1175, 1117, 1083, 1068, 1037, 815, 749 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 7.41 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 8.7 Hz, 2H), 4.19-4.11 (m, 2H), 4.07 (s, 1H), 3.69 (s, 3H), 3.32 (d, J = 1.7 Hz, 1H), 2.38 (s, 3H), 2.24-2.13 (m, 1H), 2.04-1.78 (m, 3H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 192.8, 158.7, 151.5, 149.9, 141.6, 138.1, 131.1, 129.9, 128.2, 124.2, 114.1, 74.6, 67.2, 55.3, 40.2, 22.4, 21.4, 21.3.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{O}_4\text{S}$: 383.1317; found: 383.1318.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(4-nitrophenyl)cyclopenta[b]pyran-7(2H)-one (3d)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 3:2 v/v).

Yield: 90%; white solid; R_f = 0.34 (cyclohexanes/EtOAc 1:1 v/v); mp 68-70 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20}$ +63 (c 1.0, CHCl_3).

IR (neat): 2925, 1708, 1642, 1597, 1515, 1493, 1343, 1301, 1268, 1118, 1069, 1045, 1014, 816, 749 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 7.92 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.1 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 4.25-4.12 (m, 2H), 4.22 (s, 1H), 3.37 (d, J = 1.9 Hz, 2H), 2.40 (s, 3H), 2.30-2.18 (m, 1H), 2.06-1.85 (m, 3H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 191.8, 152.3, 147.8, 147.1, 147.0, 142.2, 138.0, 130.1, 128.3, 124.1, 124.0, 74.4, 67.3, 40.6, 22.4, 21.5, 21.2.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_5S$: 398.1062; found: 398.1060.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(2-nitrophenyl)cyclopenta[b]pyran-7(2H)-one (3e)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 3:2 v/v).

Yield: 90%; white solid; R_f = 0.29 (cyclohexanes/EtOAc 1:1 v/v); mp 164-166 °C; $[\alpha]_D^{20}$ +287 (c 1.0, $CHCl_3$).

IR (neat): 2950, 2923, 1711, 1645, 1523, 1360, 1123, 1037, 516 cm^{-1} .

1H NMR (400 MHz, DMSO, 353K): δ = 7.67 (dd, J = 8.1, 1.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.40-7.32 (m, 3H), 7.15 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 4.65 (s, 1H), 4.23 (d, J = 2.4 Hz, 1H), 4.10-4.03 (m, 2H), 2.39-2.32 (m, 1H), 2.27 (s, 3H), 1.89-1.69 (m, 3H).

^{13}C NMR (101 MHz, DMSO, 353K): δ = 190.8, 150.5, 148.8, 148.0, 140.4, 137.1, 132.9, 129.8, 129.1, 127.9, 123.7, 123.1, 72.7, 66.3, 35.3, 21.4, 20.4, 20.2.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_5S$: 398.1062; found: 398.1066.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(3,4,5-trimethoxyphenyl)cyclopenta[b]pyran-7(2H)-one (3f)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 2:3 v/v).

Yield: 87%; white solid; R_f = 0.10 (cyclohexanes/EtOAc 1:1 v/v); mp 68-70 °C; $[\alpha]_D^{20}$ +131 (c 1.0, $CHCl_3$).

IR (neat): 2928, 1706, 1643, 1591, 1421, 1121, 1071, 1048, 514 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.2 Hz, 2H), 7.24 (m, 2H), 5.72 (s, 2H), 4.13 (dd, J = 12.6, 8.0 Hz, 2H), 3.99 (s, 1H), 3.71 (s, 3H), 3.60 (s, 6H), 3.40 (d, J = 1.6 Hz, 1H), 2.34 (s, 3H), 2.23 (dt, J = 13.0, 6.1 Hz, 1H), 2.09-1.80 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7, 153.4, 151.7, 149.5, 141.5, 138.2, 137.0, 134.8, 129.9, 124.3, 103.9, 74.2, 67.2, 60.8, 55.9, 41.1, 22.4, 21.3, 21.3.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{27}O_6S$: 443.1528; found: 443.1530.

(5R,6S,S(R))-6-(*p*-tolylsulfinyl)-3,4,5,6-tetrahydro-5-(furan-2-yl)cyclopenta[b]pyran-7(2H)-one (3g)

Prepared following the General Procedure B and purified by column chromatography (cyclohexanes/EtOAc 7:3 v/v).

Yield: 80%; white solid; R_f = 0.38 (cyclohexanes/EtOAc 1:1 v/v); mp 190-192 °C; $[\alpha]_D^{20}$ +95 (c 1.0, $CHCl_3$).

IR (neat): 2978, 2920, 2876, 1712, 1651, 1120, 1039, 1009, 810, 741, 501 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.09 (s, 1H), 6.04 (dd, J = 2.9, 1.8 Hz, 1H), 5.43 (d, J = 3.0 Hz, 1H), 4.31 (s, 1H), 4.21-4.06 (m, 2H), 3.54 (d, J = 1.8 Hz, 1H), 2.38 (s, 3H), 2.27 (dt, J = 19.1, 5.5 Hz, 1H), 2.09 (dt, J = 19.1, 6.0 Hz, 1H), 2.01-1.85 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 151.3, 151.1, 146.9, 142.2, 141.7, 137.9, 129.9, 124.0, 110.3, 107.2, 71.2, 67.2, 34.1, 22.5, 21.5, 21.3.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{19}O_4S$: 343.1004; found: 343.1007.

(S)-5-phényl-3,4,5,6-tetrahydrocyclopenta[b]pyran-7(2H)-one ((+)-15)

To a rapidly stirred solution of **2a** (75 mg; 1equiv) in 3 mL THF at rt, 417 mg (30 equiv) of activated zinc dust was added, followed by 3 mL of saturated aqueous NH_4Cl solution. After stirring for 1 h at rt, the solids were filtered through celite and washed with EtOAc. The two layers were separated and the aqueous phase was extracted with three 25 mL portions of ethyl acetate. The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by chromatography on silica gel (cyclohexanes/EtOAc 4:1 v/v) furnished 40 mg of (+)-**15**.

Yield: 88%; beige solide; R_f = 0.60 (cyclohexanes/EtOAc, 1:1); mp 68-70 °C; $[\alpha]_D^{20}$ +79 (c 1.0, $CHCl_3$).

IR (neat): 2925, 1700, 1643, 1115, 1702, 701 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 3H), 7.14-7.10 (m, 2H), 4.19-4.07 (m, 2H), 3.84 (dd, J = 6.6, 1.6 Hz, 1H), 2.88 (dd, J = 19.0, 6.6 Hz, 1H), 2.31 (d, J = 19.0 Hz, 1H), 2.21-1.98 (m, 2H), 2.00-1.80 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 151.5, 147.5, 141.7, 129.8, 129.0, 127.2, 127.1, 66.9, 43.7, 42.9, 22.2, 21.5.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}O_2$: 215.1072; found: 215.1072.

(R)-5-phenyl-3,4,5,6-tetrahydrocyclopenta[b]pyran-7(2H)-one ((-)-15)

By the above procedure 88,1 mg of **3a** were reacted with 490 mg of activated zinc dust yielding 53.5 mg of (-)-**15**.

Yield: 100%; beige solide; R_f 0.60 (cyclohexanes/EtOAc 1:1 v/v); mp 68-70 °C; $[\alpha]_D^{20}$ -81 (c 1.0, $CHCl_3$).

IR (neat): 2926, 1699, 1642, 1114, 1071, 701 cm^{-1} .

1H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 3H, H_{arom}), 7.14-7.10 (m, 2H, H_{arom}), 4.19-4.07 (m, 2H, H_6), 3.84 (dd, J = 6.6, 1.6 Hz, 1H, H_5), 2.88 (dd, J = 19.0, 6.6 Hz, 1H, H_1), 2.31 (d, J = 19.0 Hz, 1H, H_1), 2.21-1.98 (m, 2H, H_8), 2.00-1.80 (m, 2H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 151.5, 147.5, 141.7, 129.8, 129.0, 127.2, 127.1, 66.9, 43.7, 42.9, 22.2, 21.5.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}O_2$: 215.1072; found: 215.1062.

(5S,6R)-6-(*p*-tolylsulfonyl)-3,4,5,6-tetrahydro-5-phenylcyclopenta[b]pyran-7(2H)-one ((-)-16)

To a solution of **2a** (1 equiv) in dichloromethane [0.1 M] at 0 °C under argon atmosphere, was added *m*-CPBA (1.1 equiv). After 4 h stirring at 0 °C, the mixture was hydrolysed with a 10% aqueous Na_2SO_3 solution. The two phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 7:3 v/v) to afford (-)-**16**.

Yield: 93%; white solid; R_f = 0.43 (cyclohexanes/EtOAc 1:1 v/v); mp 168-170 °C; $[\alpha]_D^{20}$ -26 (c 1.0, $CHCl_3$).

IR (neat): 2965, 2925, 1716, 1653, 1314, 1147, 1122, 1070, 1057, 764, 700, 588 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.73 (d, J = 8.2 Hz, 2H), 7.34–7.28 (m, 5H), 7.14 (d, J = 6.7 Hz, 2H), 4.49 (s, 1H), 4.19–4.11 (m, 2H), 3.76 (d, J = 1.4 Hz, 1H), 2.45 (s, 3H), 2.26 (dt, J = 12.2, 5.9 Hz, 1H), 2.12 (dt, J = 19.3, 6.0 Hz, 1H), 2.02–1.84 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ = 188.7, 151.4, 147.3, 145.5, 138.9, 134.7, 129.8, 129.5, 129.4, 128.1, 127.6, 73.4, 67.3, 45.4, 22.5, 21.9, 21.2.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{21}\text{O}_4\text{S}$: 369.1161; found: 369.1160.

[5R,6S]-6-(*p*-tolylsulfonyl)-3,4,5,6-tetrahydro-5-phenylcyclopenta[b]pyran-7(2H)-one ((+)-16)

Prepared following the same procedure as (-)-16 using **3a** as starting material.

Yield 100%; white solid; R_f = 0.66 (cyclohexanes/EtOAc 1:1 v/v); mp 168–170 °C; $[\alpha]_{\text{D}}^{20}$ -26 (c 1.0, CHCl_3).

IR (neat): 2966, 2925, 1716, 1653, 1314, 1147, 1122, 1070, 1057, 764, 700, 588 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.73 (d, J = 8.3 Hz, 2H), 7.34–7.27 (m, 5H), 7.14 (d, J = 6.7 Hz, 2H), 4.48 (d, J = 1.4 Hz, 1H), 4.19–4.10 (m, 2H), 3.76 (d, J = 1.8 Hz, 1H), 2.44 (s, 3H), 2.25 (dt, J = 19.3, 5.8 Hz, 1H), 2.12 (dt, J = 19.3, 6.0 Hz, 1H), 2.01–1.84 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ = 188.6, 151.4, 147.3, 145.5, 138.9, 134.7, 129.8, 129.5, 129.4, 128.1, 127.5, 73.4, 67.3, 45.4, 22.4, 21.8, 21.2.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{21}\text{O}_4\text{S}$: 369.1161; found: 369.1161.

(5R,6S,7S,8R)-6-(*p*-tolylsulfinyl)-2,3,4,5,6,7-hexahydro-5-phenylcyclopenta[b]pyran-7-ol (4a)

In a dried two-necked round-bottom flask under argon atmosphere, compound **3a** (91.6 mg, 1 equiv) was solubilised in 2.6 mL of anhydrous THF under argon, and the resulting solution was cooled at -78 °C. DIBAL-H (0.38 mL; 1.7 M in toluene, 2.5 equiv) was added dropwise via syringe. Stirring was continued for 1 h at -78 °C, and then the reaction was quenched with 0.5 ml MeOH. 10 mL of a saturated potassium sodium *L*-tartrate tetrahydrate solution was then added and the reaction mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and evaporated in vacuo. The crude was purified by column chromatography on silica gel (cyclohexanes/EtOAc 1:1 v/v) obtaining 79 mg of **4a**.

Yield: 86%; white solid; R_f = 0.20 (cyclohexanes/EtOAc 1:1 v/v); mp 152–154 °C; $[\alpha]_{\text{D}}^{20}$ +26 (c 1.0, CHCl_3).

IR (neat): 3363, 3050, 2970, 2918, 2849, 1695, 1280, 1035, 1015, 955, 807, 767, 718, 701, 522, 503, 451.

^1H NMR (CDCl_3 , 300 MHz): δ = 7.39 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.06–7.03 (m, 3H), 6.80–6.75 (m, 2H), 5.13–5.08 (m, 1H), 4.09–3.98 (m, 2H), 3.82 (d, J = 4.0 Hz, 1H), 3.17 (t, J = 3.9 Hz, 1H), 2.34 (s, 3H), 2.73 (s, large, 1H), 1.81–1.69 (m, 3H), 1.64–1.52 (m, 1H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 150.7, 142.5, 141.4, 137.7, 129.7, 128.3, 127.8, 126.4, 124.7, 114.3, 74.9, 73.8, 67.4, 45.8, 22.1, 21.4, 20.1.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{O}_3\text{S}$: 355.1368; found: 355.1367.

(5R,6S,7R,8R)-6-(*p*-tolylsulfinyl)-2,3,4,5,6,7-hexahydro-5-phenylcyclopenta[b]pyran-7-ol (5a)

To a solution of NaBH_4 (24.6 mg; 2.5 equiv) in 0.8 mL of anhydrous THF in a dried two-necked round-bottom flask under argon atmosphere, was added dropwise **3a** (91.6 mg, 1 equiv) in 1.8 mL of anhydrous THF at -78 °C. After 4 h at -15 °C, the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 2:3 v/v) to afford **5a**. Yield: 92%; white solid; R_f = 0.10 (cyclohexanes/EtOAc 1:1 v/v); mp 152–154 °C (decomposition); $[\alpha]_{\text{D}}^{20}$ +13 (c 1.0, CHCl_3).

IR (neat): 3205, 3053, 3025, 2974, 2922, 2878, 2844, 1684, 1489, 1452, 1299, 1199, 1129, 1061, 1037, 1014, 1000, 755, 707.

^1H NMR (CDCl_3 , 300 MHz): δ = 7.37 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.02–6.96 (m, 3H), 6.48–6.46 (m, 2H), 5.22–5.20 (m, 1H), 4.17–4.15 (m, 1H), 4.14–4.05 (m, 2H), 3.30 (dd, J = 8.1, 3.9 Hz, 1H), 2.35 (s, 3H), 1.94–1.83 (m, 2H), 1.80–1.70 (m, 1H), 1.59–1.52 (m, 1H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 151.5, 142.7, 141.0, 137.9, 129.7, 128.3, 127.3, 126.3, 124.7, 115.3, 74.5, 70.8, 67.5, 45.8, 22.2, 21.4, 19.9.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{O}_3\text{S}$: 355.1368; found: 355.1368.

(5R,6S,7R)-7-(methoxymethoxy)-5-phenyl-6-((*R*)-*p*-tolylsulfinyl)-2,3,4,5,6,7 hexahydrocyclopenta[b]pyran (18)

To a solution of **5a** (116 mg; 1equiv) in 4 mL in dichloromethane under argon atmosphere, was added diisopropylethylamine (170 μL ; 3 equiv) and chloromethoxymethane (75 μL ; 3 equiv) at 0 °C. After 24 h at room temperature, the mixture was quenched with a saturated NH_4Cl aqueous solution. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 7:3) yielding **18**.

Yield: 96%; white solid; R_f = 0.31 (cyclohexanes/EtOAc 1:1); mp 99–101 °C; $[\alpha]_{\text{D}}^{20}$ -25 (c 1.0, CHCl_3).

IR (neat): 3030, 2932, 2888, 1695, 1150, 1093, 1028, 914, 512 cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 7.42 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.03–7.01 (m, 3H), 6.58 (dd, J = 6.4, 2.9 Hz, 2H), 5.13 (d, J = 7.9 Hz, 1H), 4.91 (d, J = 6.8 Hz, 1H), 4.74 (d, J = 6.8 Hz, 1H), 4.25 (s, 1H), 4.10–4.07 (m, 2H), 3.46 (s, 3H), 3.29 (dd, J = 7.9, 3.1 Hz, 1H), 2.34 (s, 3H), 2.01–1.84 (m, 2H), 1.81–1.58 (m, 2H).

^{13}C NMR (CDCl_3 , 75MHz): δ = 150.7, 142.7, 140.8, 139.9, 129.6, 128.4, 127.4, 126.4, 125.0, 114.3, 96.9, 77.2, 71.4, 67.3, 56.2, 45.5, 22.2, 21.4, 20.0.

HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{O}_4\text{S}$: 399.1630; found: 399.1628.

(5R,6S,7R)-7-(methoxymethoxy)-5-phenyl-6-(*p*-tolylthio)-2,3,4,5,6,7hexahydrocyclopenta[b]pyran (19)

To a solution of the protected alcohol (95.6 mg; 1 equiv) and NaI (108 mg; 3 equiv) in 3 mL of acetone at -40 °C, was added trifluoroacetic anhydride (165 μL ; 5 equiv) under argon atmosphere. After 15 min the mixture was quenched with a 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The two

phases were separated and the aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 9:1 v/v) to afford the expected sulfide.

Yield: 98%; colourless oil; *R_f* = 0.56 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ -10 (c 1.0, CHCl₃).

IR (neat): 3026, 2925, 2884, 1686, 1492, 1149, 1094, 1040, 1019, 701, 491 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.28-7.24 (m, 1H), 7.23-7.16 (m, 2H), 7.08-7.01 (m, 4H), 6.94 (d, *J* = 7.0 Hz, 2H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.75-4.69 (m, 2H), 4.15-4.03 (m, 2H), 3.80 (d, *J* = 5.4 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 1H), 3.41 (s, 3H), 2.25 (s, 3H), 1.94-1.71 (m, 4H).

¹³C NMR (CDCl₃, 75 MHz): δ = 151.9, 142.0, 136.3, 132.7, 130.8, 129.6, 128.6, 128.0, 126.8, 114.5, 96.4, 67.3, 58.1, 56.9, 55.7, 22.4, 21.1, 20.2.

IR (neat) 3026, 2925, 2884, 1686, 1492, 1149, 1094, 1040, 1019, 701, 491.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₃H₂₇O₃S: 383.1681; found: 383.1683.

(5*R*,7*R*)-7-(methoxymethoxy)-5-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[b]pyran (20)

To a solution of the precedent sulphide (41 mg; 0.107 mmol) in methanol (1 mL), was added Raney nickel previously amply washed with water and methanol. After 5 h, the mixture was filtered through Celite and washed with ethyl acetate (3x20 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 9:1 v/v) to afford **20**.

Yield: 86%; colourless oil; *R_f* = 0.57 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ -64 (c 1.0, CHCl₃).

IR (neat): 3025, 2929, 2880, 1690, 1147, 1095, 1041, 1023, 700 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.31-7.28 (m, 2H), 7.22-7.16 (m, 1H), 7.12-7.09 (m, 2H), 4.82-4.72 (m, 3H), 4.12-4.07 (m, 2H), 3.87-3.82 (m, 1H), 3.40 (s, 3H), 2.32 (ddd, *J* = 14.0, 8.2, 3.3 Hz, 1H), 2.07 (ddd, *J* = 14.0, 7.4, 4.3 Hz, 1H), 1.94-1.69 (m, 4H).

¹³C NMR (75 MHz, CDCl₃): δ = 152.2, 145.3, 128.6, 127.4, 126.4, 115.8, 96.0, 78.9, 67.2, 55.5, 48.7, 39.7, 22.3, 20.4.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₁₄H₁₅O: 199.1123 [M-OMOM]; found: 119.1124.

(5*R*,6*S*)-6-allyl-5-phenyl-6-tosyl-3,4,5,6-tetrahydrocyclopenta[b]pyran-7(2*H*)-one (21)

To a solution of (-)-**16** (55.3 mg; 1 equiv) in 1.9 mL of acetonitrile at room temperature and under argon atmosphere, was added K₂CO₃ (62.2 mg; 3 equiv) and allylbromide (39 μ L; 3 equiv). After stirring overnight, the mixture was quenched with water. The two phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 8:2 v/v) to afford **21**.

Yield: 100%; white solid; mp 49-51 °C; *R_f* = 0.60 (cyclohexanes/EtOAc 1:1 v/v). [α]_D²⁰ -63 (c 1.0, CHCl₃).

IR (neat): 3028, 2925, 1708, 1645, 1320, 1304, 1137, 1081, 1047, 750, 675, 572, 520 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.53 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.36-7.33 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 5.56-5.49 (m, 1H), 5.32 (d, *J* = 16.6 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.31-4.28 (m, 1H), 4.27 (s, 1H), 4.25-4.21 (m, 1H), 2.89 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.74 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.58-2.54 (m, 1H), 2.41 (s, 3H), 2.09-2.04 (m, 2H), 1.95-1.89 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ = 191.8, 151.8, 146.0, 145.1, 134.4, 133.5, 131.8, 131.2, 131.1, 129.1, 128.1, 128.1, 121.4, 76.3, 67.3, 51.2, 37.5, 22.9, 21.8, 21.5.

HRMS (ESI): *m/z* [M+H]⁺ calcd for C₂₄H₂₅O₄S: 409.1474; found: 409.1478.

tert-butyl 2-((5*R*,6*S*)-7-oxo-5-phenyl-3,4,5,6-tetrahydrocyclopenta[b]pyran-6-yl)acetate (*trans*-23)

Aluminium amalgam was freshly prepared by immersing aluminium foil in a 2% aqueous mercuric chloride solution for 10-15 sec, followed rinsing the amalgamated foil quickly with ethanol and ethyl ether. Aluminium amalgam was immediately added to a solution of **22** (114 mg; 1 equiv) in 4 mL of THF/H₂O 9:1. After 24 h stirring, the mixture was filtered through celite and washed with ethyl acetate (3x20 mL). The filtrate was concentrated under reduced pressure. The obtained oil was solubilized in 2 mL of CH₂Cl₂. After 24 h stirring with basic alumina, the mixture was filtered and washed with EtOAc (3x20 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/Et₂O 3:2 v/v) to afford *trans*-**23**.

Yield: 80%; white solid; mp 64-66 °C; *R_f* = 0.71 (cyclohexanes/EtOAc 1:1 v/v); [α]_D²⁰ -67 (c 1.0, CHCl₃).

IR (neat): 2977, 2926, 1710, 1648, 1162, 1129, 1065, 702 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.35-7.22 (m, 3H), 7.14-7.11 (m, 2H), 4.22-4.08 (m, 2H), 3.58 (d, *J* = 1.5 Hz, 1H), 2.76-2.64 (m, 1H), 2.59-2.49 (m, 2H), 2.16-2.02 (m, 2H), 1.96-1.88 (m, 2H), 1.31 (s, 9H), 1.29 (s, 1H, *t*Bu *cis*-**23**).

¹³C NMR (151 MHz, CDCl₃): δ = 200.1 (*trans*-**23**), 171.4 (*cis*-**23**), 170.6 (*trans*-**23**), 151.4 (*cis*-**23**), 150.8 (*trans*-**23**), 145.8 (*trans*-**23**), 145.6 (*cis*-**23**), 140.8 (*trans*-**23**), 138.0 (*cis*-**23**), 129.0 (*trans*-**23**), 128.7 (*cis*-**23**), 127.6 (*trans*-**23**), 127.4 (*cis*-**23**), 127.3 (*trans*-**23**), 81.0 (*trans*-**23**), 80.4 (*cis*-**23**), 67.2 (*cis*-**23**), 67.0 (*trans*-**23**), 50.8 (*trans*-**23**), 50.7 (*trans*-**23**), 48.1 (*cis*-**23**), 45.6 (*cis*-**23**), 35.7 (*trans*-**23**), 32.5 (*cis*-**23**), 29.7 (*cis*-**23**), 27.9 (*trans*-**23**), 22.5 (*cis*-**23**), 22.0 (*trans*-**23**), 21.7 (*cis*-**23**), 21.6 (*trans*-**23**).

HRMS (ESI): *m/z* [M+Na]⁺ calcd for C₂₀H₂₅O₄: 351.1572 ; found: 351.1575.

(2*S*,3*S*)-2-((*R*)-*p*-tolylsulfinyl)-3-(2,4,6-trimethoxyphenyl)-2,3,4,5,6,7-hexahydro-1*H*-inden-1-one (24a)

To a solution of AlCl₃ (13.4 mg; 0.100 mmol) in freshly distilled 1,2-DCE (0.5 mL) under argon atmosphere, was added a solution of **13a** (40.3 mg; 91.5 μ mol) in freshly distilled 1,2-DCE (1 mL). After 12 h stirring at 0 °C, the reaction mixture was quenched with saturated aqueous NaCl. The two phases were separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced

pressure. The crude product was purified column chromatography (cyclohexanes/EtOAc 7:3) to afford 30.0 mg of the title product **24a**.

Yield: 75%; white solid; R_f = 0.45 (cyclohexanes/EtOAc 1:1); mp 153-155 °C; $[\alpha]_D^{20}$ -20 (c 1.0, CHCl₃).

IR (neat): 2943, 1688, 1642, 1458, 1198, 1145, 1112, 1045, 818 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.35 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 5.85 (dd, J = 8.0, 2.1 Hz, 2H), 4.83 (bs, 1H), 3.93 (d, J = 2.6 Hz, 1H), 3.72 (s, 3H), 3.56 (d, J = 4.8 Hz, 6H), 2.27 (s, 3H), 2.22-2.17 (m, 2H), 2.09 (dt, J = 11.6, 5.5 Hz, 1H), 1.80 (dt, J = 11.6, 5.5 Hz, 1H), 1.66-1.59 (m, 2H), 1.57-1.47 (m, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 201.1, 177.9, 160.4, 159.6, 158.6, 140.3, 138.7, 137.4, 129.0, 124.3, 106.4, 90.6, 89.9, 74.1, 55.5, 55.4, 55.4, 34.3, 26.3, 22.1, 21.7, 21.4, 20.3.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₅H₂₉O₅S: 441.1737; found: 441.1736.

(2S,3R)-3-phenyl-2-tosyl-2,3,4,5,6,7-hexahydro-1H-inden-1-one (26) and (2S,3S)-3-phenyl-2-tosyl-2,3,3a,4,5,6-hexahydro-1H-inden-1-one (27)

To a solution of AlCl₃ (40.0 mg; 0.300 mmol) in freshly distilled 1,2-DCE (1.6 mL) at 0 °C and under argon atmosphere, was added a solution of **13b** (95.0 mg; 0.271 mmol) in freshly distilled 1,2-DCE (3 mL). After 16 hours stirring at 0 °C, the reaction mixture was quenched with saturated aqueous NaCl. The organic part was separated, and the aqueous part was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified column chromatography (cyclohexanes/EtOAc 4:1) to afford **24b** and **25** as a 1:1 mixture. To a solution of this mixture (57.0 mg; 0.162 mmol) in dry dichloromethane (1.6 mL) at 0 °C and under argon atmosphere, was added *m*-CPBA (41.0 mg; 0.238 mmol). After 2 h at 0 °C, the mixture was hydrolysed with a 10% aqueous Na₂SO₃ solution. The two phases were separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexanes/EtOAc 6:1 v/v) providing 30.0 mg of **26**.

Yield: 50%; white solid; mp 118-120 °C; R_f = 0.69 (cyclohexanes/EtOAc 1:1 v/v); $[\alpha]_D^{20}$ -15 (c 1.0, CHCl₃).

IR (neat): 3059, 2928, 2863, 1700, 1646, 1315, 1145, 1086, 700, 652, 590, 572.

¹H NMR (300 MHz, CDCl₃): δ = 7.73 (d, J = 8.3 Hz, 2H), 7.34-7.28 (m, 5H), 7.08- 7.05 (m, 2H), 4.48 (s, 1H), 3.83 (d, J = 2.3 Hz, 1H), 2.44 (s, 3H), 2.28-2.10 (m, 4H), 1.76-1.55 (m, 4H).

¹³C NMR (75 MHz, CDCl₃): δ = 196.1, 174.8, 145.3, 139.9, 139.0, 135.1, 129.7, 129.3, 129.3, 127.9, 127.6, 75.4, 49.8, 26.7, 21.9, 21.8, 21.3, 20.4.

HRMS (ESI): m/z calcd for C₂₂H₂₃O₃S: 367.1368 [M+H]⁺; found: 367.1366.

And 30.0 mg of **27**.

Yield: 50%; off-white solid; mp 163-165 °C; R_f = 0.62 (cyclohexanes/EtOAc 1:1 v/v); $[\alpha]_D^{20}$ +69 (c 1.0, CHCl₃)

IR (neat): 3032, 2922, 2854, 1709, 1643, 1316, 1142, 1084, 574, 524 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.64 (d, J = 8.3 Hz, 2H), 7.28-7.24 (m, 1H), 7.24-7.18 (m, 3H), 7.16 (s, 1H), 7.15-7.12 (m, 2H), 6.87 (dd, J = 6.7, 3.3 Hz, 1H), 4.25 (d, J = 11.0 Hz, 1H), 3.30 (t, J = 10.7 Hz, 1H), 2.57-2.45 (m, 1H), 2.36 (s, 3H), 2.33-2.13 (m, 2H), 1.96-1.78 (m, 2H), 1.48-1.32 (m, 1H), 1.25-1.09 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): δ = 193.4, 144.9, 140.3, 139.5, 137.0, 135.8, 129.5, 129.2, 128.8, 127.4, 127.2, 75.0, 50.2, 44.7, 26.9, 25.8, 21.7, 21.5.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₂H₂₃O₃S: 367.1368; found: 367.1370.

(2S,3S,3aR,6aS)-6a-chloro-3-phenyl-2-((R)-p-tolylsulfinyl)hexahydropentalen-1(2H)-one (30)

In a 5 mL sealed tube, AlCl₃ (53.6 mg; 0.400 mmol) was suspended in freshly distilled 1,2-DCE (0.8 mL) under argon atmosphere. **14b** (45.0 mg; 0.134 mmol) was solubilized in freshly distilled 1,2-DCE (1.4 mL) and added to the suspension at room temperature. After 24 h stirring at rt, the reaction mixture was quenched with brine (20 mL). The two phases were separated and the aqueous layer was extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by washing with Et₂O to give 41.5 mg of **30**.

Yield: 83%; white solid; R_f = 0.63 (cyclohexanes/EtOAc 4:1 v/v); mp 118-120 °C; $[\alpha]_D^{20}$ -153 (c 1.0, CHCl₃).

IR (neat): 3068, 2903, 1755, 1084, 1064, 1038, 805, 749, 702, 508, 454 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 7.13 (d, J = 8.2 Hz, 2H), 6.99-6.94 (m, 3H), 6.88 (d, J = 8.0 Hz, 2H), 6.76-6.73 (m, 2H), 3.94 (d, J = 10.2 Hz, 1H), 3.22 (t, J = 9.9 Hz, 1H), 2.77-2.72 (m, 1H), 2.66-2.58 (m, 1H), 2.18 (s, 3H), 2.11-1.93 (m, 4H), 1.83-1.69 (m, 1H).

¹³C NMR (CDCl₃, 101MHz): δ = 204.3, 141.3, 140.8, 135.9, 129.5, 128.4, 127.5, 126.4, 123.9, 78.3, 75.6, 61.2, 40.9, 35.4, 28.9, 23.7, 21.2.

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₁O₂SCl: 373.1029; found: 373.1031.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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Dr. Erwann Grenet graduated at the ENSICAEN (University of Caen, France) and obtained a Ph.D. degree from University of Montpellier in 2016 on torquoselective Nazarov reactions guided by a chiral sulfoxide under the supervision of Dr. Xavier J. Salom-Roig. In 2017, he joined the group of Pr. Jérôme Waser at the Institute of Chemical Sciences and Engineering (Ecole Polytechnique Fédérale de Lausanne, Switzerland) where he worked with hypervalent iodine reagents. He currently works as Research Scientist in Evotec (Toulouse, France).



Dr. Arie van der Lee graduated at the University of Groningen in the Netherlands in experimental physics followed by a doctoral thesis in 1992 on the crystallography of superionic materials. A postdoctoral study at the Institut des Matériaux de Nantes in France focused on the structure determination of commensurately and incommensurately modulated inorganic compounds. In 1995 he was appointed by the French Agency of Scientific Research, CNRS, at the Institut Européen des Membranes in Montpellier to work in the field of thin film reflectometry and structure determination of inorganic and organic compounds by single-crystal and powder diffraction. He has had over the years a strong commitment within different national and international learned societies such as the *International Union of Crystallography* and the *Association Française de Cristallographie*. He is the current Vice-President of the *European Crystallographic Association* (2021-2024).



Dr. Xavier J. Salom-Roig studied chemistry at the Universities of València (Spain) and Strasbourg (France). He obtained a Ph.D. degree from University of Strasbourg in 1999 under the supervision of Prof. Guy Solladié by working on the enantioselective total synthesis of Pamamycin-607 using a sulfoxide as chiral auxiliary. In 2000, he joined the group of Prof. Jean-Pierre Sauvage at the University of Strasbourg, where he worked in the field of photoinduced charge separation. In November 2001, he joined Prof. P. Renaud's team and worked on the synthesis of frondosin C. He currently works as Associated Professor at University of Montpellier (France) and his research interests include the development of new asymmetric reactions mediated by a chiral sulfoxide and the total synthesis of natural products.