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Synthesis of C3-substituted enantiopure 2-(*p*-tolylsulfinyl)-furans: the sulfoxide group as a chiral inductor for furan dienes as precursors of a wide variety of chiral intermediates

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ABSTRACT

(−)-(1*R*,2*S*,5*R*)-Menthyl (S_S)-*p*-toluenesulfinate and its enantiomer are a common source for a chiral sulfoxide group in organic synthesis, by means of nucleophilic substitution. The replacement of the menthyloxy group, with complete inversion of configuration at the sulfur center of the chiral sulfoxide, allows the inclusion of this organic function into numerous substrates, with defined stereochemistry and high enantiomeric purity. Nine C3-substituted, enantiomerically pure, 2-sulfinylfurans were prepared by this synthetic methodology with moderate to high yields. These enantiopure C3-substituted 2-sulfinylfurans can be used as chiral dienes for [4+3] cycloaddition reactions and in other chemical transformations, in which π-facial selectivity should be induced in order to obtain enantioselective reactions.

1. Introduction

The configurationally stable asymmetric sulfoxide group has been widely used as a chiral inductor in many chemical processes.[1] Thus it has been used for the induction of enantioselectivity in nucleophilic additions,[2,3] in the reduction of carbonyls (with the sulfinyl group at the α position)[4] as well as in Diels–Alder cycloadditions,[5,6] amongst other chemical transformations.[7,8] In Scheme 1 some of these enantioselective processes are illustrated.

Since the resolution of (−)-menthyl (S_S)-*p*-tolylsulfinate and its enantiomer in 1925, these two compounds have been the most common source for a chiral sulfoxide group in organic synthesis.[9] The replacement of the methoxy group with complete inversion or total retention of the configuration at the sulfur center of chiral sulfoxide, allows for the inclusion of this organic function in numerous substrates, with a defined stereochemistry and with high enantiomeric purity. For this reason the *p*-tolylsulfinyl group has been chosen for our studies.

In order to understand the role and efficiency of this chiral auxiliary, it is necessary to take into account that the stereogenic center is located at the sulfur atom and the three ligands linked to it are different: an oxygen atom with high electron density, a non-shared electron pair, and a bulky and flat tolyl group. These big differences between these three ligands both on steric and electronic levels, allow the induction of asymmetry.

In addition, the presence in the diene substrate of the oxygen atom of the sulfoxide, together with the oxygen atom of the furan ring, favors the formation of bidentated chelating structures in such a way that the conformation of the chiral auxiliary group could be fixed in the reaction intermediate or in the transition state, thus increasing the effectiveness of the asymmetric induction by coordination, when there is a metallic ion or a Lewis acid involved in the reaction process. It should be noted that all of the examples shown in Scheme 1 have a carbonyl group located at a suitable distance to coordinate in a bidentate manner to the Lewis acid used as a catalyst in the coupling reaction (see also Fig. 1). A clear case of this effect is highlighted in example (b) of Scheme 1 (reaction conditions *b* and *b′*), in which coordination with a Lewis acid changes the sense of the asymmetric induction of the carbonyl group reduction reaction, since this reaction occurs via the less stable conformation in the absence of a Lewis acid.

Our objective was to use the configurationally stable *p*-tolylsulfinyl group as a chiral inductor in stereoselective [4+3] cycloaddition reactions in order to obtain enantiomerically pure polyfunctionalized oxabicyclic systems (Scheme 2), strategically functionalized at C1 in order to allow the opening of the oxygen bridge, and also to perform further derivatizations and/or

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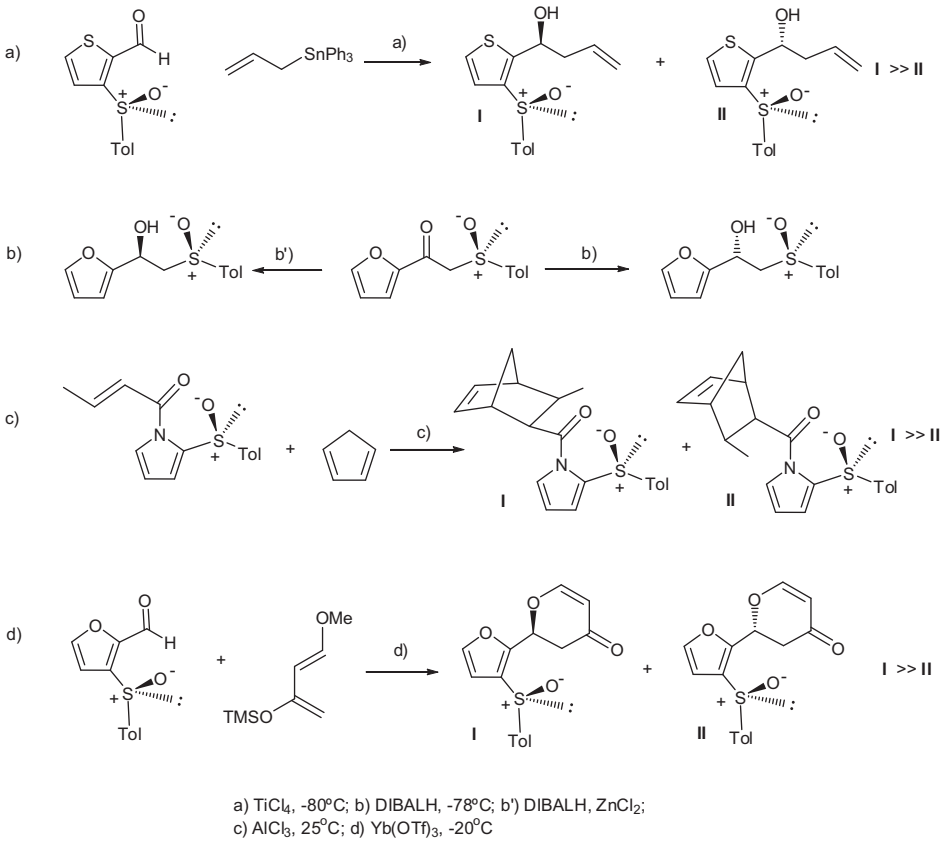


Scheme 1. Examples of the application of chiral sulfoxides to asymmetric versions of different organic reactions.

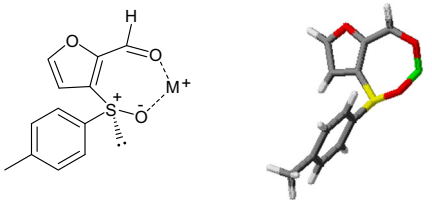
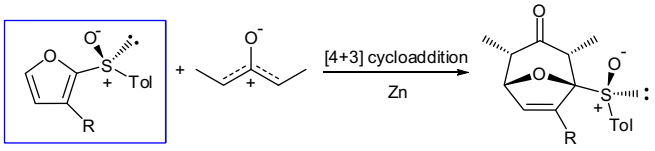


Figure 1. Bidentate coordination of a sulfoxide group and a carbonyl group to a Lewis acid or a metallic ion.



Scheme 2. C3 substituted 2-sulfinylfurans as substrates in [4+3] cycloaddition reactions.

functionalizations. These cycloadducts were intended to be prepared in a stereoselective manner, by starting from C2, C3, and/or C5 functionalized furans as dienes and 2,4-dihalo-3-pentanones as precursors of oxyallyl cations.[10] The substitution at C3 of furans as dienes is thought to decrease the conformational freedom of the *p*-tolylsulfinyl group attached to C2, which in turn would determine a preferential stereochemical approach between the diene and dienophile in the cycloaddition process, due to a different accessibility of both faces of the furan diene. Herein we report the synthesis of C3 substituted 2-sulfinylfurans, which will be used as substrates for enantioselective [4+3] cycloaddition reactions.[11]

We consider that the synthesis and physical and spectroscopic characterization of these chiral furans could be of interest to synthetic chemists who may use these substrates for a wide variety of stereoselective reactions.

The use of cycloheptane synthons as precursors of natural and unnatural products with biological activity has been an objective of many chemists. We have also made contributions to this field over the past few years.[12,13] When five-membered cyclic dienes are used as starting materials, it is possible to further functionalize the cycloadducts, in a regio- and stereoselective manner, due to the lack of conformational freedom, in the resultant bicyclic system because of the presence of a carbocyclic or heterocyclic bridge.[14,15]

Herein our main aim was to synthesize C3-substituted 2-*p*-tolylsulfinylfuran derivatives in order to evaluate the effects of steric hindrance, and the inductive and coordination capabilities of those substituents attached to C3 of the furan ring, which have been shown to be important with regard to the stereochemical outcome of cycloaddition reactions.[16] For this purpose nine chiral, enantiomerically pure, sulfinylfurans (Fig. 2) were prepared so that they could be evaluated under the [4+3] cycloaddition reaction conditions.[11] However, these enantiopure furan derivatives may also be used as substrates for other types of reactions.[1–8]

An added value of this methodology is the commercial availability of both enantiomeric forms of the precursor menthyl *p*-toluenesulfinate, making the obtention of both enantiomers of 2-(*p*-toluenesulfinyl)furan derivatives possible.[17]

Nine furan derivatives, all of them functionalized at the C2 position by the (*S*)-*p*-tolylsulfinyl group (see Fig. 2) and substituted at the C3 position by a chelating function, were prepared. The brominated derivative **2** was synthesized in order to analyze the effect of steric hindrance on the conformational freedom and also the influence of its inductive effect. The other dienes, all of them

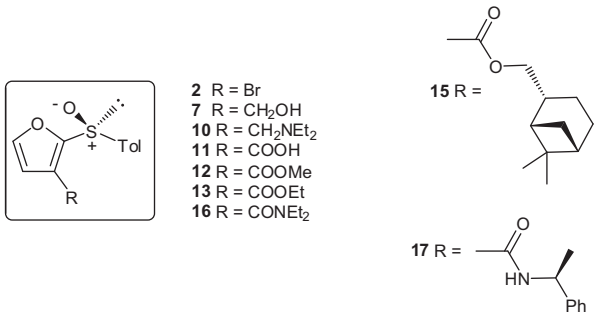


Figure 2. Derivatives of (*S*)-2-(*p*-tolylsulfinyl)furan, resulting from substitution at the C3 position.

substituted at the C3 position by groups containing chelating heteroatoms, were designed in order to analyze the potential effects of bidentate coordination to metal ions or a Lewis acid, present in the reaction medium (see Figs. 1 and 3), or hydrogen bonding effects (as in the case of sulfinylfuran **7**) (Fig. 3).

2. Results and discussion

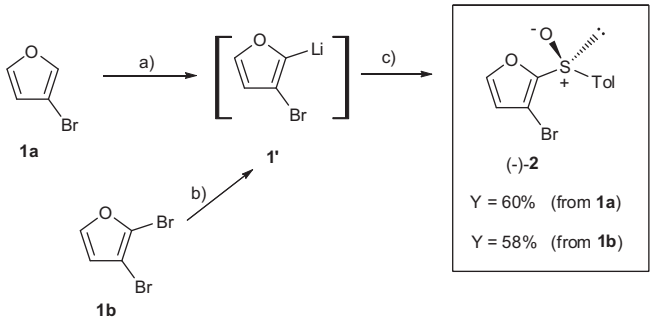
2.1. Introduction of the (*S*)-2-*p*-tolylsulfinyl group at the C2 position of the furan ring

The replacement of the menthyloxy group, from (−)-(1*R*,2*S*,5*R*)-menthyl (S_S)-*p*-toluenesulfinate, by means of nucleophilic substitution with complete inversion of the configuration at the sulfur center of chiral sulfoxide, allowed the insertion of this chiral auxiliary into numerous substrates, with a defined stereochemistry and with high enantiomeric purity.

In the literature, there are examples concerning the use of nucleophiles with a furan structure or similar, in this type of reaction.[18] They all confirm that the S_N2 reaction is carried out with total inversion of configuration at the sulfur asymmetric center when the nucleophile used is the corresponding Grignard reagent or the lithium derivative generated from the furyl substrate and LDA (Scheme 3).

2.2. Synthesis of (*S*)-3-bromo-2-(*p*-tolylsulfinyl)furan

Bromosulfinylfuran **2** was prepared for a comparative study in order to evaluate the possible stereoelectronic effects exerted by the bromine atom, especially steric, inductive, and coordinating effects. The synthesis of (−)-**2** was carried out by starting from 3-bromofuran **1a** via intermediate **1′**, followed by a nucleophilic substitution of (−)-menthyl (S_S)-*p*-tolylsulfinate. Compound **2** was also prepared from dibromoderivative **1b** via a bromine-lithium exchange (Scheme 4).



a) LDA, THF, -78 °C; b) MeLi, Et_2O, -44°C;
c) menthyl (-)-(*S*)-*p*-toluenesulfinate, THF, -78 to 20°C

Scheme 4. Synthesis of (*S*)-3-bromo-2-(*p*-tolylsulfinyl)furan **2**.

The synthesis of compound **2** was carried out by starting from commercially available 3-bromofuran **1a** and using LDA as a base in THF at −78 °C,[19] to give a 60% yield with complete enantiomeric purity as checked by GC on a chiral stationary phase. An alternative synthesis of **2** was accomplished by starting from commercially available 2,3-dibromofuran and using MeLi in diethyl ether at −44 °C to generate intermediate **1′**, by bromine–lithium exchange,[20,21] followed by reaction with (−)-menthyl (S_S)-*p*-tolyl-

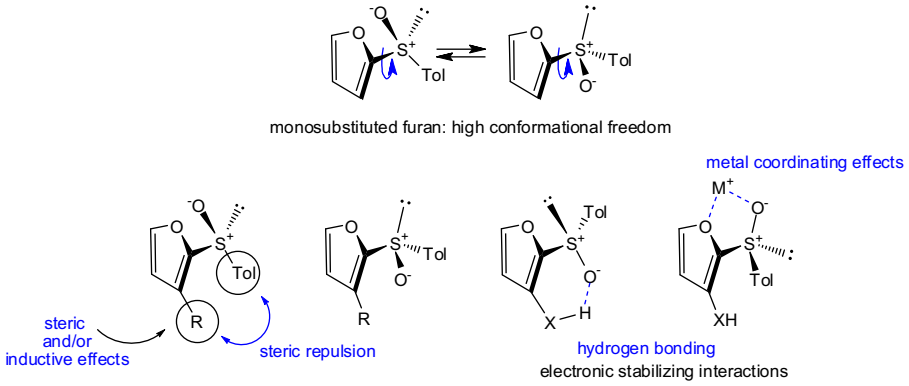
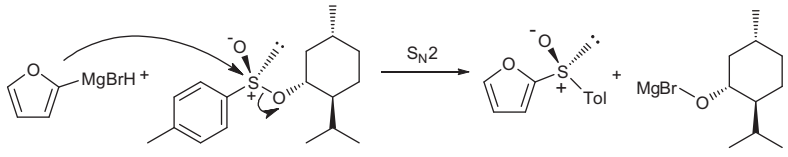


Figure 3. Modification of the conformational freedom of the 2-(*p*-toluenesulfinyl)furan by insertion of a functional group at the C3 position.



Scheme 3. Synthesis of (*S*)-2-(*p*-tolylsulfinyl)furan from (−)-(1*R*,2*S*,5*R*)-menthyl (S_S)-*p*-toluenesulfinate.

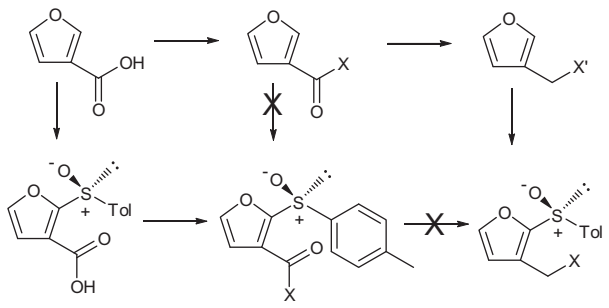


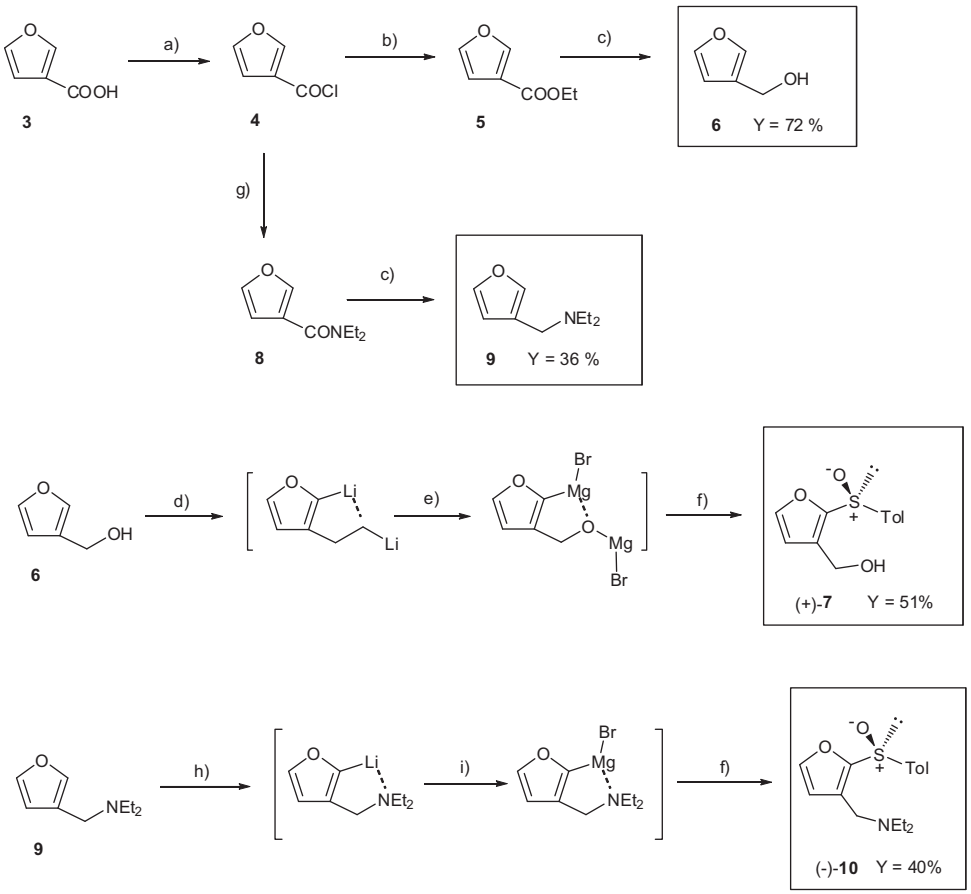
Figure 4. Strategies for the synthesis of 2-(*p*-tolylsulfinyl)furan derivatives substituted at the C3 position.

sulfinate, which afforded compound **2** with a similar yield (58%) and enantiomeric purity to that of the previous method. In this last method, no reaction of the bromine atom at C3 was observed when using equimolar ratios of reagents. The temperature was seen to be an important factor with regard to the conversion and chemoselectivity; the use of MeLi at −78 °C produced a low conversion (30%). Increasing the reaction temperature to −44 °C improved the conversion to 68% and afforded a 58% yield (the remaining 32% of starting material was isolated and identified spectroscopically). In an attempt to improve the conversion, *n*-BuLi was tested, but in ether at rt; however, these reaction conditions afforded a complex reaction mixture.

This chemical behavior led us to believe that in the case of substituted furans with C3-coordinating groups, the use of Grignard reagents as intermediates in the S_N2 reaction is not essential in order to achieve complete enantioselectivity, due to the stabilizing coordinating effects of these C3-groups in the lithium intermediate. A confirmation of this hypothesis could also be found in the preparation of **15** and/or **17**.

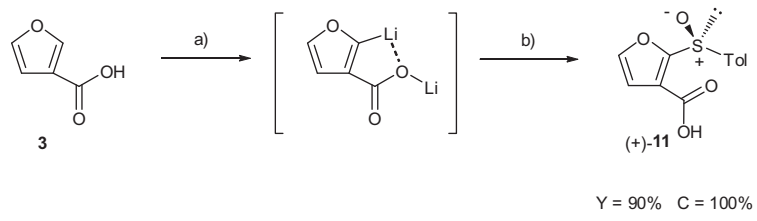
2.3. Synthesis of C3-substituted (*S*)-2-(*p*-tolylsulfinyl)furan derivatives from 3-furoic acid

The other sulfinylfuran derivatives mentioned in Figure 2 were synthesized from available starting materials such as 3-furoic acid, already functionalized at the C3 position. Bearing in mind that the introduction of the sulfoxide group is expected to be performed via an S_N2 reaction in which an organometallic compound is involved, the synthesis of derivatives with an ester or an amide function (compounds **11**–**17**) was conducted by derivatization of the carboxylic acid after the sulfoxide group had been introduced into the molecule (Fig. 4). The hydroxymethyl and *N*,*N*-diethylaminomethyl groups were generated by reduction with $LiAlH_4$ of the corresponding carboxylic derivatives (ester and amide, respectively). This derivatization was performed before the introduction of the sulfoxide group (otherwise the reduction conditions used would



a) $SOCl_2$ (excess), reflux; b) abs. EtOH, reflux; c) $LiAlH_4$, anh. ether, r.t.; d) 2 eq. *n*-BuLi, Et_2O, 0°C to 34°C; e) 2 eq. $MgBr_2$, Et_2O, 0°C to 20°C; f) Menthyl (-)-(*S*)-*p*-toluenesulfinate, Et_2O, -78°C to 20°C; g) $NHEt_2$, 0°C; h) 1 eq. *n*-BuLi, Et_2O, 0°C to 34°C; i) 1 eq. $MgBr_2$, Et_2O, 0°C to 20°C

Scheme 5. Synthesis of sulfoxides **7** and **10**.



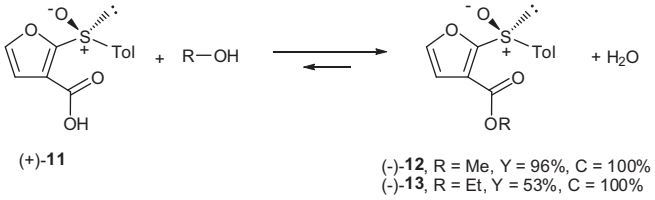
Scheme 6. Synthesis of acid **11**.

evolve toward the formation of the corresponding *p*-tolylsulfenyl derivatives, thus losing the chirality of the initial sulfinyl group).

Alcohol **6** and amine **9** were used as key intermediates for the synthesis of sulfinylfurans **14** and **17** respectively, (Scheme 5). In the first case, using two equivalents of *n*-BuLi as the base, the hydroxyl group was converted into the corresponding alkoxide, while a second deprotonation at the more acidic neighboring position, in this case the C2 position, afforded the lithium 2-furyllithium-3-alkoxide intermediate.[22] This dilithium intermediate was transmetallated into the corresponding Grignard reagent with $MgBr_2$ and in this way a single product **7** was obtained in a regioselective manner. In the case of *N*,*N*-diethylaminomethyl derivative **10**, using a single equivalent of base, the anion in the neighboring C2 position was obtained selectively by chelation effects, although the steric hindrance exerted by the Et_2N-group should be also taken in consideration (Scheme 5) to explain the lower yield.

The same principle of directed deprotonation used for the synthesis of **10** was applied to the synthesis of carboxylic acid **11**, a precursor of the esters and amides. The use of two equivalents of base, in this case LDA, regioselectively generated the anion at the C2 position of the furan ring (Scheme 6). Taking into account precedents in which nucleophilic substitution occurs with total inversion of the configuration at the asymmetric sulfur atom of the menthyl (−)-(*S*)-*p*-toluenesulfinate, by using similar nucleophiles, generated with LDA, the Li–Mg exchange was not considered essential in this strategy.[18] Unlike all other previous cases, the reaction was conducted in THF as a solvent due to the insolubility of the dilithium derivative intermediate in diethyl ether.

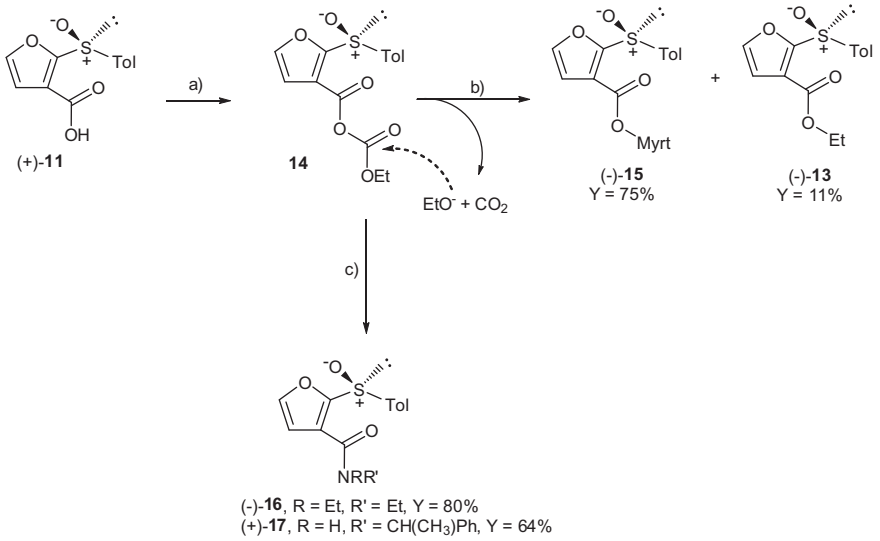
The synthesis of esters and amides derived from acid **11** was carried out in various methods. The synthesis of esters of volatile alcohols (methyl and ethyl esters **12** and **13**, respectively) was conducted by esterification under acidic catalysis (Fischer conditions). Total conversions were obtained by this procedure while the performance in the first case (Y = 96%) was higher than in the second (Y = 53%) (see Scheme 7).



Scheme 7. Synthesis of methyl and ethyl esters, **12** and **13**, respectively.

The synthesis of esters from bulkier and chiral alcohols, such as (−)-(1*S*,2*R*,5*S*)-myrtanol was addressed by esterification under acidic catalysis in an inert solvent and shifting the esterification equilibrium by distilling off the water formed (by azeotropic distillation), or by activation of the carboxylic acid as an acid chloride or as a mixed carbonic-carboxylic acid anhydride (compound **14**).

The application of the Fischer esterification, under stoichiometric conditions, resulted in the decomposition of the starting acid **11**, without obtaining the desired product. Likewise, the activation



Scheme 8. Formation of esters by reaction of alcohols with the mixed anhydride **14**.

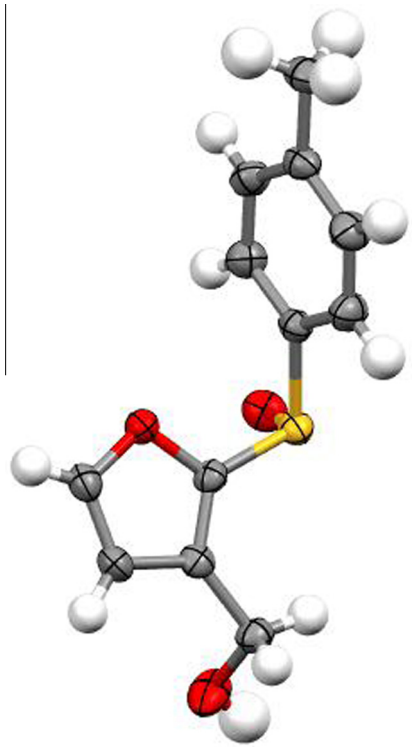


Figure 5. X-ray structure of **7**. Ellipsoid diagram at 50% probability level for **7**.

Table 1
Crystal data and structure refinement for **7**

Chemical formula	$C_{12}H_{12}O_3S$
Formula Mass	236.28
Crystal system, Space group	Monoclinic, P $2_1/a$
a/Å	8.6744(5)
b/Å	10.8606(7)
c/Å	12.1615(8)
α/°	90
β/°	100.777(4)
γ/°	90
Unit cell volume/Å^3	1125.52(12)
Temperature/K	150(2)
Space group	$P21/a$
No. of formula units per unit cell, Z	4
Density (Calcd) g cm^{-3}	1.394
Radiation type	MoKα
Absorption coefficient, μ/mm^{-1}	0.275
No. of reflections measured	19236
No. of independent reflections	1987
R_{int}	0.1249
Final R_1 values ($I > 2\sigma(I)$)	0.0464
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1011
Final R_1 values (all data)	0.0870
Final $wR(F^2)$ values (all data)	0.1165
Goodness of fit on F^2	1.034

of the carboxylic acid in the form of an acid chloride was useless for the synthesis of esters, since acid **11** in the presence of thionyl chloride, underwent multiple side reactions: chlorination of the acid group, chlorination of the C5 position of the furan ring and concomitant reduction of the sulfoxide group to a thioether group.

Finally, activation of acid **11** in the form of a mixed anhydride with ethoxycarbonic acid, by using ethyl chloroformate, and subsequent in situ reaction with (−)-(1*S*,2*R*,5*S*)-myrtanol gave the desired ester in 75% yield. In this process, one equivalent of ethoxide anion was formed, as a byproduct of the esterification reaction. This anion, although in a low extent, came into competition with (−)-(1*S*,2*R*,5*S*)-myrtanol, generating ethyl ester **13** in 11% yield (Scheme 8). Alternative mixed anhydrides to obviate this side reaction could be considered.[23]

Taking into account the previous synthesis of the esters of acid **11**, the preparation of amides **16** and **17** of this acid was addressed through activation of the acid in the form of mixed anhydride **14**. Chiral amine (−)-(*S*)-1-methylbenzylamine was used for this purpose and also diethylamine as an achiral amine (see Scheme 8). The reaction was conducted under conditions analogous to those of the synthesis of the myrtanyl ester **15**, obtaining the corresponding amides in moderate to good yields.

A possible alternative to this reaction, based on the replacement of the methoxy group from the methyl ester **12** by these amines, via an addition–elimination mechanism, did not give the expected results for either of the two evaluated amines. On the other hand, it is worth noting that the chiral amine (1-methylbenzylamine) and the chiral alcohol (mirtanol) used were enantiomerically pure and that by this amidation/esterification process a second chiral subunit was inserted into compounds **17** and **15**, respectively. Since these compounds were obtained as pure diastereoisomers (confirmed by GC and ^{1}H NMR), it was possible to confirm that the synthesis of acid **11**, by using LDA instead of the organomagnesium intermediate, occurred with total inversion of configuration at the stereogenic sulfur atom, without racemization of the sulfoxide group.[24] Thus, as mentioned in the Introduction, commercially available (−)-(1*R*,2*S*,5*R*)-menthyl (S_S)-*p*-toluenesulfinate precursor was used to prepare enantiomerically pure sulfinylfurans with an (S_S)-configuration, via an S_N2 reaction, with complete inversion of configuration (see Scheme 3). Due to the availability of the other enantiomer of the precursor, (+)-(1*S*,2*R*,5*S*)-menthyl (R_S)-*p*-toluenesulfinate, the enantiomers of the sulfinylfurans prepared here could also be obtained by applying the same chemistry described herein.

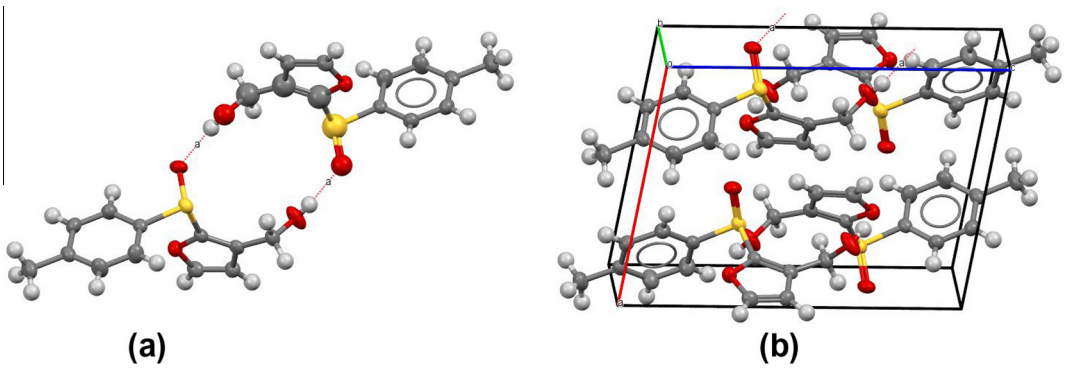


Figure 6. (a) Hydrogen bonds between the hydroxyl group and the oxygen atom of the sulfoxide group of a neighbor molecule. (b) Crystal cell packing of **7**.

Table 2
Modification of the reaction condition in the preparation of **11**

Entry	3-Furoic acid (mmol)	LDA (mmol)	Reaction conditions (1st step)	$MgBr_2$[a] (mmol)	Reaction conditions[a] (2nd step)	Menthyl sulfinate (mmol)	Reaction condition (3rd step)	Conversion (%)	Yield (%)
1	2	4.2	2 h, 20 °C[b]	4.2	2 h, 20 °C[b]	2	2 h, −78 °C; then 16 h, 20 °C[b]	0	0
2	2	4.2	2 h, 20 °C[b]	—	—	2	2 h, −78 °C; then 16 h, 20 °C[b]	0	0
3	0.9	1.8	1 h, 20 °C[c]	—	—	0.9	16 h, 20 °C[c]	48	25
4	0.9	1.8	45 min, −78 °C[c]	—	—	0.9	1 h, −78 °C; then 1 h, 20 °C[b]	32	28
5	0.9	3	45 min, −78 °C[c]	—	—	0.9	1 h, −78 °C; then 1 h, 20 °C[b]	50	22
6	1.8	3.7	45 min, −78 °C[c]	—	—	0.9	1 h, −78 °C[c]	100	90
7	1.8	3.7	45 min, −78 °C[c]	3.7	2 h, −78 °C[c]	0.9	1 h, −78 °C[c]	0	0
8	8.9	17.8	45 min, −78 °C[c]	—	—	4.5	1 h, −78 °C[c]	100	77

[a] Transmetallation process according to the procedure described for the preparation of compound **2**.
[b] Diethyl ether as the solvent.
[c] THF as a solvent.

The structure of **7** was confirmed by X-ray diffraction analysis on a single crystal (Fig. 5). All of the bond lengths and angles are within the normal ranges. In the crystal packing, the molecules are arranged parallel to each other along the *c* axis as shown in Figure 6. Hydrogen bonding between the hydroxyl group and the oxygen of sulfoxide is also observed in the crystal cell. Crystal data and structure refinement for enantiopure furan **7** are quoted in Table 1. The molecular illustrations (Figs. 5 and 6) were made by using MERCURY software.[25]

3. Conclusion

Nine C3-substituted, enantiomerically pure, 2-sulfinylfurans were prepared from (−)-(1*R*,2*S*,5*R*)-menthyl (S_S)-*p*-toluenesulfinate as the precursor via an S_N2 reaction that took place with total inversion of the configuration at the sulfur asymmetric center. According to the literature, in a non-substituted furan or in C4 or C5-substituted furans, a nucleophilic shift via an S_N2 of the menthyloxy group could be obtained with complete inversion of the configuration at the sulfur center of the chiral sulfoxide, when the generated intermediate is the corresponding 2-furyl Grignard reagent, or a 2-furyllithium intermediate, in turn generated from the corresponding furan derivative and LDA. When the 2-furyllithium nucleophile is generated by the reaction of furan and *n*-BuLi or MeLi, the product obtained was a quasi-racemic mixture. However, as deduced from the present work, in the case of substituted furans with C3-coordinating groups, the use of Grignard reagents or LDA is not essential to obtain complete enantioselectivity, due to the stabilizing coordinating effects of these C3-groups in the lithium intermediate.

Herein we have reported on the synthesis of several C3-substituted 2-sulfinylfurans, which will be used as substrates for enantioselective [4+3] cycloaddition reactions and other types of reactions, whose results, will be published in due course. We anticipate that the synthesis and physical and spectroscopic characterization of these chiral furans could be of interest to synthetic chemists as substrates for a wide variety of reactions intended to be stereoselective via π-facial stereodifferentiation. This stereodifferentiation may be induced by the sulfinyl chiral auxiliary and favored by the C3-substituent, due to its stereoelectronic effects such as coordination, steric hindrance, hydrogen bonding, and decrease of the conformational freedom of the sulfinyl subunit.

Our results could also be applied to the enantiomer of the precursor (+)-(1*S*,2*R*,5*S*)-menthyl (R_S)-*p*-toluenesulfinate, which is also commercially available, in such a way that all of the enantiomers of the furan derivatives described herein may be obtained.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were conducted under an atmosphere of dry nitrogen or argon in oven-dried glassware. Raw materials were obtained from commercial suppliers and used as received. All solvents were purified using standard techniques before use: ether, tetrahydrofuran, hexane, and pentane were distilled under nitrogen from sodium/benzophenone. Acetonitrile was distilled under nitrogen from CaH_2. Infrared spectra were recorded on a FT-IR NICOLET 510 spectrophotometer as thin films over NaCl plates. NMR spectra were obtained in $CDCl_3$ on VARIAN spectrometers at 200 MHz (GEMINI 200), 300 MHz (INOVA-300), and/or 400 MHz (MERCURY-400) for ^1H NMR and at 50 and/or 100 MHz for ^{13}C NMR. For ^1H NMR tetramethylsilane was used as internal standard. ^{13}C NMR spectra were referenced to the 77.0 ppm resonance of chloroform. When necessary, assignments were established by DEPT, ^1H–^1H–COSY, and HMBC or gHMQC ^{13}C–^1H correlation experiments. Mass spectra were measured on a HEWLETT-PACKARD 5890 mass spectrometer using the chemical ionization technique and ammonia as ionizing gas. GC analyses were performed on HP-8790 gas chromatograph equipped with a HEWLETT-PACKARD-crosslinked MePhe-silicone capillary column (L = 25 m, Φ_{ID} = 0.2 mm, δ_{film} = 2.5 μm) using helium as the gas carrier and an FID detector (T = 250 °C, P_{H2} = 4.2 psi, P_{air} = 2.1 psi). The chiral GC analyses of furan derivatives and cycloadducts were carried out by using an ALLTECH Chirasil-Val® capillary column (L = 25 m, Φ_{ID} = 0.25 mm, δ_{film} = 0.16 μm) in the range of 40–220 °C. The working conditions are specified for each compound. The elemental analyses were obtained in a FISONS elemental analyzer, Model Na-1500. The samples were previously pyrolized at 1000 °C under an oxygen atmosphere and the content of carbon, hydrogen, sulfur, and nitrogen was determined by evaluation of the combustion gases by gas chromatography using an FID detector. Melting points were determined in a GALLENKAMP apparatus Mod 5A 6797.

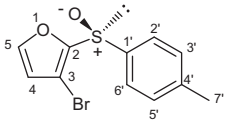
4.2. X-ray crystal structure analysis of 7

3-Hydroxymethyl-2-*p*-tolylsulfinylfuran **7** was dissolved in the minimum amount of ethyl acetate, at room temperature. A few drops of hexane were then added and the saturated solution was kept in a refrigerator at 4 °C. Suitable crystals for X-ray diffraction studies grew over a period of two weeks.

Intensity data were collected at 150 K on a Nonius KappaCCD diffractometer equipped with an Oxford Cryosystem, using graphite monochromated MoKα radiation (λ = 0.71073 Å). Data were processed using the Nonius Software.[26] A symmetry-related (multi-scan) absorption correction was applied. The structures were solved by direct methods (SIR-97)[27] and refined with full-matrix least-squares techniques against F^2 (SHELXL-2013)[28] using the program platform SHELXle.[29] Non-hydrogen atoms were anisotropically refined. Heteroatom and hydrogen atoms were located in the difference Fourier map and were isotropically refined and all others were placed onto calculated positions.

Details of crystal data and summary of the intensity data collection for **7** are summarized in Table 1. Crystallographic data (excluding structure factors) for these structures have been deposited at the Cambridge Crystallographic Data Centre (Cambridge, UK) as a CIF file with reference no. CCDC-959635. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.3. Synthesis of (*S*)-3-bromo-2-(*p*-tolylsulfinyl)furan, 2



4.3.1. Use of 3-bromofuran as the starting material

In an oven-dried 50 mL round bottomed flask, fitted with a magnetic stirrer and septum, commercially available 3-bromofuran **1a** (0.68 g, 4.62 mmol) and dry diethyl ether (10 mL) were placed and the system purged with argon. The system was cooled down to −78 °C and a solution of 2.0 M LDA in THF (2.34 mL, 4.68 mmol) was added portionwise by a syringe. The reaction mixture turned reddish and was maintained under these conditions for 2 h. This solution of 3-bromo-2-furyllithium was then transferred via cannula to another flask containing (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluenesulfinate (1.36 g, 4.62 mmol) dissolved in dry THF (10 mL), and cooled to −78 °C. The resulting reaction mixture was maintained under these conditions for 2 h, and then left at room temperature for 16 h. The ether reaction mixture was washed with saturated aqueous solution of NH_4Cl (30 mL), dried over anhydrous $MgSO_4$, filtered, and percolated through a short pad of activated neutral alumina. The ether solution was concentrated to dryness in vacuo after which the resulting crude product was submitted to flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. With hexane/ethyl acetate 50:50, pure product was eluted and isolated as an orange solid (756 mg, yield = 60%). Mp = 97–98.5 °C (hexane/ethyl acetate). IR (film): $\overline{\nu}$ = 3148, 3116, 2921, 1559, 1539, 1491, 1466, 1360, 1192, 1122, 1082, 1057 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.41 (3H, s, H7′), 6.52 (1H, d, *J* = 1.8 Hz, H4), 7.33 (2H, d, *J* = 8.2 Hz, H5′ and H3′), 7.44 (1H, d, *J* = 1.8 Hz, H5), 7.59 (2H, d, *J* = 8.2 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 21.5 (C7′), 106.9 (C3), 115.24 (C4), 124.5 (C2′ and C6′), 129.9 (C3′ and C5′), 137.6 (C4′), 141.7 (C1′), 147.0 (C5), 149.9 (C2) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: *m*/*z* (%) = 304 (100, M+NH_3+2, isotopic distribution), 302 (97, M+NH_3), 287 (19, M+2, isotopic distribution), 285 (19, M^+). Anal. Calcd for $C_{11}H_9BrO_2S$: C, 46.33; H, 3.18. Found: C, 46.12; H, 3.02. $[\alpha]_D^{21} = -71.0$ (*c* 1.5, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 19.5 min. Ee = 100. CCF (SiO_2, hexane: ethyl acetate, 9:1, two elutions): R_f = 0.21 (developed as a blue spot with anisaldehyde and sulfuric acid).

4.3.2. Use of 2,3-dibromofuran as the starting material

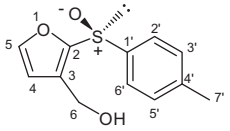
In an oven-dried 50 mL round bottomed flask, fitted with a magnetic stirrer and septum, commercially available 2,3-dibromofuran **1b** (1 g, 4.46 mmol) and dry diethyl ether (10 mL) were placed and the system purged with argon. The system was cooled down to −44 °C and a solution of 1.0 M MeLi in cumene (4.50 mL, 4.50 mmol) was added portionwise by a syringe. The reaction mixture turned reddish and was maintained under these conditions for 2 h. This solution of 3-bromo-2-furyllithium was then cooled to −78 °C and transferred via cannula to another flask containing (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluenesulfinate (1.31 g, 4.46 mmol) dissolved in dry THF (10 mL), and also cooled to −78 °C. The resulting reaction mixture was maintained under these conditions for 2 h, and then at room temperature for 16 h. Work-up was similar to the previous method, and compound **2** was isolated in 58% yield. Also, a 32% of unchanged starting material **1b** was isolated in the nonpolar fractions of the column.

4.4. Synthesis of (*S*)-[2-(*p*-tolylsulfinyl)-3-furyl]methanol 7

4.4.1. Synthesis of ethyl 3-furoate 5 and 3-furylmethanol 6

While 3-furylmethanol is commercially available, we synthesized it from 3-furoic acid to illustrate how this synthetic route could be used to prepare a wide variety of structurally related derivatives (see Scheme 5).

4.4.2. Synthesis of (*S*)-[2-(*p*-tolylsulfinyl)-3-furyl]methanol 7

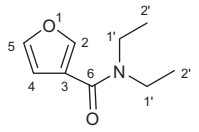


In an oven-dried 50 mL round-bottomed flask fitted with a magnetic stirrer and a reflux condenser and purged with argon, 3-furylmethanol **6** (425 mg, 4.42 mmol), dissolved in dry diethyl ether (10 mL) was placed. The system was cooled down to 0 °C and BuLi, 1.6 M in hexane (6.64 mL, 10.62 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and then for an additional hour at reflux, observing the formation of lithium (furan-2-yl-lithium-3-yl)methoxide as a yellowish solid. Simultaneously in another reaction flask (25 mL), activated magnesium turnings (594 mg, 10.62 mmol)[30] were placed in dry diethyl ether (10 mL) at room temperature and 1,2-dibromoethane (0.46 mL, 5.30 mmol) was added dropwise. This reaction mixture was refluxed for 1 h to give $MgBr_2$. The ether solution of magnesium dibromide was filtered out via cannula to remove the excess magnesium turnings. The resulting clear solution of $MgBr_2$ was added portionwise via cannula at 0 °C to the solution of the dilithium intermediate, already prepared in the first reactor. The new reaction mixture was stirred for 2 h at room temperature to give the corresponding Grignard intermediate. Over this solution, cooled down to −78 °C, (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluenesulfinate (1.49 g, 5.06 mmol), dissolved in dry diethyl ether (15 mL) was added at once. The reaction was maintained under stirring at −78 °C for 2 h and then 16 additional hours at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of NH_4Cl (50 mL). Afterward, the aqueous phase was washed with ethyl acetate (4 × 30 mL). All organic phases were combined, dried over anhydrous $MgSO_4$, and concentrated to dryness in vacuo. The resulting crude oil was submitted to flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The elution with hexane/ethyl acetate 30:70 afforded pure product as a white solid [533 mg, yield = 51% (with respect

to 3-furylmethanol), conversion = 49%]. Mp = 98–99 °C (ethyl acetate/hexane). IR (film): $\overline{\nu}$ = 3382 (H–O, st), 3059, 2925, 2875, 1647, 1595, 1485, 1389, 1157, 1128, 1043, 889 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 2.41 (3H, s, H7′), 3.47 (1H, br s, O–H), 4.67 (1H, d, J = 3 Hz, H6), 4.70 (1H, d, J = 3 Hz, H6), 6.47 (1H, d, J = 1.8 Hz, H4), 7.32 (2H, d, J = 7.4 Hz, H3′ and H5′), 7.43 (1H, d, J = 1.8 Hz, H5), 7.59 (2H, d, J = 7.4 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 21.3 (C7′), 55.7 (C6), 112.3 (C4), 125.0 (C3′ and C5′), 130.0 (C2′ and C6′), 132.3 (C3), 138.0 (C4′), 141.9 (C1′), 145.9 (C5), 147.7 (C2) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 256 (7), 254 (100, M+NH_4), 237 (90, M+1). Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12. Found: C, 61.20; H, 5.06. $[\alpha]_D^{21} = +12.1$ (c 0.66, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 19.03 min. Ee = 100%. TLC (SiO_2, ethyl acetate): R_f = 0.66 (developed as a white spot that turns black with anisaldehyde/sulfuric acid).

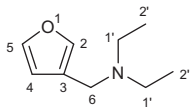
4.5. Synthesis of (*S*)-*N*-ethyl-*N*-[(2-(*p*-tolylsulfinyl)furan-3-yl)-methyl]ethanamine 10

4.5.1. Synthesis of *N*,*N*-diethyl-3-furamide[31] 8



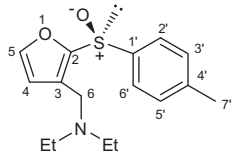
In a three-necked oven-dried 100 mL round-bottomed flask fitted with a condenser, an argon atmosphere, and efficient magnetic stirrer, furoic acid **3** (5 g, 44.3 mmol) was placed. Thionyl chloride (12.9 mL, 177 mmol) was then slowly added though the condenser tip and a $CaCl_2$ tube was fitted to this end. The reaction mixture was refluxed for 3 h, observing the release of HCl gas. The excess $SOCl_2$ was removed under atmospheric distillation using a Vigreux column. In another flask, fitted with an addition funnel, magnetic stirrer, and an argon atmosphere, a solution of diethylamine (13.88 mL, 133 mmol) in dry THF (10 mL) was prepared. The furoyl chloride **11** obtained was diluted with dry THF (20 mL) and placed in the addition funnel. This solution was added dropwise to the amine solution at 0 °C and with vigorous stirring. The reaction mixture was stirred at room temperature overnight, which led to the formation of a white solid (diethyl ammonium chloride). The crude product was concentrated to dryness in vacuo at room temperature and the resulting residue diluted with ethyl acetate (100 mL) and washed with water (2 × 25 mL). The aqueous phase was acidified with concentrated HCl up to pH = 3 and the resulting solution was extracted with ethyl acetate (3 × 25 mL). All organic phases were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness in vacuo, to give a pure product (5.86 g, Y = 72%), as a colorless oil. IR (film): $\overline{\nu}$ = 3060, 2990, 2970, 1630 (amide I st.), 1510 (amide II, st.), 1420, 1390, 1370, 1320, 1300, 1220, 1160, 1120, 1070, 1020 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (6H, t, J = 7.0 Hz, H2′), 3.47 (4H, q, J = 7.0 Hz, H1′), 6.58 (1H, dd, J_1 = 1.8 Hz, J_2 = 0.8 Hz, H4), 7.40 (1H, t, J = 1.8 Hz, H5), 7.69 (1H, dd, J_1 = 1.8 Hz, J_2 = 0.8 Hz, H2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (C2′), 41.7 (C1′), 90.2 (C3), 110.2 (C4), 142.6 (C5), 142.7 (C2), 164.1 (C6) ppm. MS [GC–MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 185 (100, M+NH_4), 168 (79 (M+H^+). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.70; H, 7.90; N, 8.35. GC (50 °C, 1 min, 10 °C/min, 250 °C, 15 min): t_R = 13.84 min. TLC (SiO_2, hexane/ethyl acetate, 50/50): R_f = 0.46 (developed as a white spot on a pink background, with anisaldehyde/sulfuric acid).

4.5.2. Synthesis of *N*,*N*-diethyl-3-furylmethylamine 9



In an oven-dried 100 mL round-bottomed flask fitted with a condenser, an argon atmosphere, and efficient magnetic stirrer, a suspension of $LiAlH_4$ (796 mg, 21 mmol) in dry ether (10 mL) was placed. A solution of *N*,*N*-diethyl-3-furamide **8** (4 g, 21 mmol) in dry ether (10 mL) was then added slowly, at room temperature, though the condenser tip and a $CaCl_2$ tube were fitted to this end. An immediate release of H_2 gas from the reaction medium was observed. The reaction mixture was stirred at reflux overnight. The excess of hydride was quenched with ethyl acetate (50 mL). The aluminum hydroxide was filtered off by a Büchner filter and the solid washed with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (2 × 25 mL). All of the organic phases were combined together, dried over anhydrous $MgSO_4$, filtered, and concentrated by simple distillation at atmospheric pressure using a Vigreux column to give a pure product (1.78 g, Y = 50%, C = 100%), as a colorless oil. IR (film): $\overline{\nu}$ = 3040, 2990, 2980, 2800, 1510, 1450, 1400, 1200, 1150, 1030, 880 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.06 (6H, t, J = 7.0 Hz, H2′), 2.51 (4H, q, J = 7.0 Hz, H1′), 3.49 (2H, s, H6), 6.37 (H1, br d, J = 0.8 Hz, H4), 7.32 (1H, dd, J_1 = 1.8 Hz, J_2 = 0.8 Hz, H2), 7.37 (1H, t, J = 1.8 Hz, H5) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.8 (C2′), 46.5 (C1′), 46.9 (C6), 111.4 (C4), 121.8 (C3), 140.5 (C2), 142.6 (C5) ppm. MS [GC-MS (CI), NH_3, 70 eV, 150 °C]: m/z (%) = 154 (100, M+H^+). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.61; H, 9.83; N, 9.02.

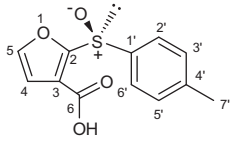
4.5.3. Synthesis of (*S*)-*N*-Ethyl-*N*-[(2-(*p*-tolylsulfinyl)furan-3-yl)methyl]ethanamine 10



In an oven-dried 50 mL round-bottomed flask fitted with a magnetic stirrer, a reflux condenser, and purged with argon, *n*-BuLi, 1.6 M in hexane (3.75 mL, 6 mmol) and dry diethyl ether (5 mL) were placed. The system was cooled down to −24 °C and *N*,*N*-diethyl-3-furylmethylamine **9** (850 mg, 5 mmol) dissolved in dry diethyl ether (5 mL) was added dropwise. The cooling bath was changed and the reaction mixture was stirred at 0 °C for 2 h and for an additional hour at reflux, not observing the formation of any precipitate (different from what was observed in previous cases). Simultaneously in another reaction flask (25 mL), activated magnesium turnings (727 mg, 13 mmol) were placed in dry diethyl ether (10 mL) at room temperature and 1,2-dibromoethane (0.57 mL, 6.5 mmol) was added dropwise. This reaction mixture was refluxed for 1 h with the formation of $MgBr_2$. The ether solution of magnesium dibromide was filtered out *via* cannula to remove the excess magnesium turnings. The resulting clear solution of $MgBr_2$ was added portionwise via cannula at 0 °C to the solution of lithium intermediate, already prepared in the first reactor. The new reaction mixture was stirred for 2 h at room temperature to give the corresponding Grignard intermediate. To this solution cooled down to −78 °C, (−)-(1*R*,2*S*,5*R*)-menthyl

(S_S)-*p*-toluenesulfinate (1.47 g, 5 mmol) dissolved in dry diethyl ether (15 mL) was added at once. The reaction was stirred at −78 °C for 2 h and then 16 additional hours at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous HCl 3% (w/w) (4 × 25 mL) to give the product as an ammonium salt. The organic phase was washed with water (50 mL). The resulting aqueous phase was combined with the previous acidic phases. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness in vacuo to recover the unchanged menthyl sulfinate. Aqueous NaOH 5% (w/v) was added to the acidic aqueous phase up until pH = 10 and then extracted with ethyl acetate (4 × 25 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness, to give a pure product as a viscous oil (583 mg, yield = 40%, conversion = 40%). IR (film): $\overline{\nu}$ = 2969, 2934, 2811, 1597, 1493, 1385, 1182, 1085, 1047, 1016, 810, 764, 621 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.05 (6H, t, J = 7.4 Hz, $NCH_2\underline{CH_3}$), 2.40 (3H, s, H7′), 2.55 (4H, dq, J_1 = 7.4 Hz, J_2 = 1.4 Hz, $N\underline{CH_2}CH_3$), 3.70 (2H, d, J = 7 Hz, H6), 6.48 (1H, d, J = 1.8 Hz, H4), 7.30 (2H, d, J = 7.4 Hz, H3′ and H5′), 7.43 (1H, d, J = 1.8 Hz, H5), 7.56 (2H, d, J = 7.4 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.7 ($NCH_2\underline{CH_3}$), 21.4 (C7′), 46.5 ($N\underline{CH_2}CH_3$), 46.8 (C6), 112.9 (C4), 124.7 (C3′ and C5′), 129.7 (C2′ and C6′), 131.5 (C3), 138.2 (C4′), 141.1 (C1′), 146.4 (C5), 148.8 (C2) ppm. MS [GC–MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 299 (100, M+1), 274 (3, M-17). Anal. Calcd for: C, 65.95; H, 7.26. Found: C, 66.03; H, 7.10. $[\alpha]_D^{21} = -20.9$ (c 1.0, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 25.71 min. Ee = 100%. TLC (SiO_2, ethyl acetate): R_f = 0.15 (two elutions and developed as a brown spot with anisaldehyde/sulfuric acid).

4.6. Synthesis of (*S*)-2-(*p*-tolylsulfinyl)-3-furoic acid 11

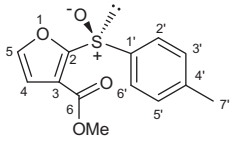


In a 100 mL oven-dried round-bottomed flask, fitted with a magnetic stirrer and under an argon atmosphere, a solution of 2.0 M LDA in THF (1.86 mL, 3.72 mmol) and dry tetrahydrofuran (5 mL) were placed. The solution was cooled down to −78 °C and 3-furoic acid **3** (200 mg, 1.78 mmol) dissolved in dry THF (9 mL) was added dropwise. The reaction mixture was maintained at −78 °C for 45 min and the formation of the dilithium intermediate took place without precipitation. This solution was maintained at −78 °C and (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluenesulfinate (275 mg, 0.93 mmol), dissolved in dry THF (10 mL) was added dropwise after which the reaction mixture was stirred for 1 h, at −78 °C. Next, the quenching was carried out by the addition of aqueous 3% (w/w) HCl (10 mL). The reaction mixture was then extracted with ethyl acetate (3 × 50 mL). The aqueous acidic phase (pH <1) was discarded and the organic phase extracted with aqueous 10% (w/v) NaOH (3 × 30 mL) in order to recover the product as a sodium carboxylate. The aqueous basic extracts were combined together and washed with ethyl acetate (3 × 25 mL). The organic phases contain mainly menthol and unreacted sulfinate as by-products. Finally, the basic aqueous phase (pH >10), containing the product as a sodium carboxylate, was acidified by the dropwise addition of concentrated HCl (until pH = 1) and extracted with ethyl acetate (3 × 50 mL). The resulting organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness in vacuo, to give a solid residue containing the desired product and unreacted 3-furoic acid. This crude mixture was subjected to a flash column chromatography on silica gel (eluting with mixture of hexane and ethyl acetate of increasing polarity). The product was isolated by elution with hexane/ethyl acetate 60:40 as a yellowish solid (209.5 mg, yield = 90%, respect to menthyl *p*-toluenesulfinate, conversion = 100%). Mp = 94–95 °C (ethyl/acetate hexane). IR (film): $\overline{\nu}$ = 3200–2000 (br, H–O, st), 2927, 1723 (C=O, st), 1489, 1173, 1024, 1007, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.41 (3H, s, H7′), 6.88 (1H, d, J = 1.8 Hz, H4), 7.34 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.53 (1H, d, J = 1.8 Hz, H5), 7.70 (2H, d, J = 8.0 Hz, H2′ and H6′), 9.90 (1H, br s, O-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (C7′), 112.9 (C4), 121.5 (C3), 125.0 (C3′ and C5′), 130.2 (C2′ y C6′), 137.3 (C4′), 142.8 (C1′), 146.0 (C5), 154.8 (C2), 163.8 (C6) ppm. MS [GC–MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 268 (100, M+NH_4), 251 (37, M+1). Anal. Calcd for: C, 57.59; H, 4.03. Found: C, 57.40; H, 4.12. $[\alpha]_D^{21} = +27.4$ (c 0.5, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 19.10 min. Ee = 100%. TLC (SiO_2, ethyl acetate): R_f = 0.12.

4.6.1. Modifications and optimizations of the experimental procedure

The reaction conditions evaluated in order to optimize this reaction process are quoted in Table 2. When diethyl ether was used as the solvent, the reaction did not take place (due to the low solubility of the dilithium intermediate) (entries 1 and 2). When an excess of dilithium intermediate versus menthyl sulfinate was used, a great increase in yield was observed (from moderate to quantitative yield) (entry 6). On the other hand, a large excess of LDA led to a decrease in the yield due to the reaction of this strong base with menthyl sulfinate (entry 5). Finally, it is worth noting that a transmetallation process with $MgBr_2$ afforded a null yield of the desired product (entries 1 and 7), probably due to the low reactivity of the intermediate Grignard reagent.

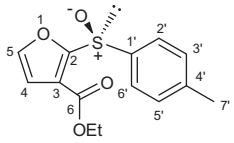
4.7. Synthesis of methyl (*S*)-2-(*p*-tolylsulfinyl)-3-furoate 12



In a 100 mL round-bottomed flask, fitted with a magnetic stirrer and a simple distillation setup, (*S*)-2-(*p*-tolylsulfinyl)-3-furoic acid **11** (250 mg, 1 mmol) was placed, and dissolved in dry methanol (40 mL). Four drops of 96% (w/w) H_2SO_4 were added as a catalyst, for the Fisher esterification to take place, and the mixture was slowly heated up to reflux temperature. Methanol was slowly distilled (35 mL collected) to give a residue of 5 mL. It is important not to concentrate to dryness because the yield considerably decreases. An additional volume of dry methanol (35 mL) was added to the reaction flask and the process was repeated. This process was carried out for third time until the control by TLC showed complete conversion (esterification). The concentrated residue was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) in order to remove sulfuric acid. The aqueous phase was extracted with ethyl acetate (2 × 25 mL) and all of the organic phases were combined together, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under vacuum, to give a pure product as a white solid (254 mg, 96% yield). Mp = 130.5–131.5 °C (ethyl acetate). IR (film): $\overline{\nu}$ = 3158, 2952, 1711 (C=O, st), 1485, 1306, 1180, 1163, 1115, 1083, 1059, 1045, 1024 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.40 (3H, s, H7′), 3.93

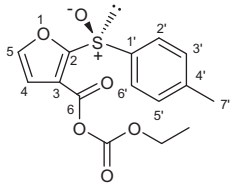
(1H, s, OCH_3), 6.76 (1H, d, J = 1.8 Hz, H4), 7.32 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.50 (1H, d, J = 1.8 Hz, H5), 7.69 (2H, d, J = 8.0 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (C7′), 52.34 (O-CH_3), 111.7 (C4), 120.7 (C3), 124.8 (C3′ and C5′), 129.9 (C2′ and C6′), 138.5 (C4′), 142.0 (C1′), 146.0 (C5), 154.8 (C2), 162.0 (C6) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 283 (16, MH+NH_4), 282 (100, M+NH_4), 265 (35, MH^+). Anal. Calcd for: C, 59.08; H, 4.58. Found: C, 59.19; H, 4.67. $[\alpha]_D^{21} = -86.7$ (c 0.66, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 25.80 min. Ee = 100%. TLC (SiO_2, hexane/ethyl acetate): R_f = 0.33 (7:3), 0.63 (1:1), 0.9 (0:1).

4.8. Synthesis of ethyl (*S*)-2-(*p*-tolylsulfinyl)-3-furoate 13



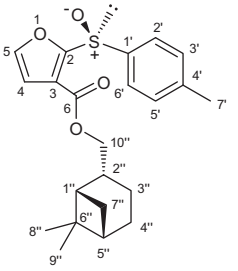
An esterification reaction, under conditions similar to the ones previously described, was carried out with ethanol to obtain the ethyl ester, but the yield was lower under all tried reaction conditions. The best results obtained correspond to a 100% conversion and a 53% yield. White solid. Mp = 93–94.5 °C (ethyl acetate). IR (film): $\overline{\nu}$ = 3129, 2983, 2925, 1792 (C=O, st), 1734 (C=O, st), 1636, 1559, 1489, 1456, 1302, 1259, 1177, 1086, 1028, 810 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.40 (3H, s, H7′), 4.40 (2H, q, J = 7.0 Hz, OCH_2CH_3), 6.76 (1H, d, J = 1.8 Hz, H4), 7.32 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.49 (1H, d, J = 1.8 Hz, H5), 7.69 (2H, d, J = 8.0 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 21.5 (C7′), 61.6 (OCH_2CH_3), 111.8 (C4), 120.7 (C3), 124.9 (C3′ and C5′′), 130.0 (C2′ and C6′), 138.5 (C4′), 140.1 (C1′), 146.0 (C5), 154.8 (C2), 161.1 (C6) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 296 (100, M+NH_4), 279 (37, M+1). Anal. Calcd for: C, 60.42; H, 5.07; S, 11.52. Found: C, 60.45; H, 5.02; S, 11.60. $[\alpha]_D^{25} = -159.1$ (c 0.11, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 26.98 min. Ee = 100%. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f = 0.75.

4.9. Synthesis of the mixed anhydride from (*S*)-2-(*p*-tolylsulfinyl)-3-furoic acid and ethyl hydrogencarbonate 14



In a 5 mL oven-dried round-bottomed flask, fitted with a magnetic stirrer and in an argon atmosphere (*S*)-2-(*p*-tolylsulfinyl)-3-furoic acid was placed (80 mg, 0.32 mmol) and dissolved in dry THF (2 mL). To this solution and at 0 °C, triethylamine (44 μL, 0.32 mmol) and ethyl chloroformate (30 μL, 0.32 mmol) were added sequentially dropwise. The reaction mixture was stirred at 0 °C for 1 h, observing the formation of a solid (triethylammonium chloride), which was removed by filtration via cannula at 0 °C. The mixed anhydride, dissolved in THF, was directly used for the derivatization reactions of the carboxylic group. This solution is stable in the freezer for at least one week. A sample of this product was isolated for its physical and spectroscopic characterization. IR (film): $\overline{\nu}$ = 3120, 2984, 1807, 1728, 1489, 1302, 1227, 1088, 1041, 989, 754 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 2.41 (3H, s, H7′), 4.33–4.47 (2H, m, $OC\underline{H}_2CH_3$), 6.96 (1H, d, J = 1.8 Hz, H4), 7.31 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.59 (1H, d, J = 1.8 Hz, H5), 7.69 (2H, d, J = 8.0 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 ($OCH_2\underline{C}H_3$), 21.5 (C7′), 61.5 ($O\underline{C}H_2CH_3$), 111.8 (C4), 118.9 (C3), 124.9 (C3′ and C5′), 129.9 (C2′ and C6′), 138.7 (C4′), 142.0 (C1′), 146.5 (C5), 154.6 (C2), 159.0 (OCO_2), 161.0 (C6) ppm. Anal. Calcd for $C_{15}H_{14}O_6S$: C, 55.89; H, 4.38; S, 9.95. Found: C, 55.92; H, 4.43; S, 10.01. MS [DIP-EI, 70 eV, 150 °C]: m/z (%) = 332 (20, M), 233 (100, M−OCOOEt), 231 (45, M−C_6H_4Me), 205 (20, M−$C_4H_5O_4$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 28.4 min. Ee = 100%. TLC (SiO_2, ethyl acetate): R_f = 0.45.

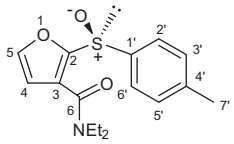
4.10. Synthesis of (1*S*,2*R*,5*S*)-myrtanyl (*S*)-2-(*p*-tolylsulfinyl)-3-furoate 15 and the concomitant formation of by-product 13



In an oven-dried round-bottomed 25 mL flask, fitted with a magnetic stirrer and under an argon atmosphere, mixed anhydride **14** (148.3 mg, 0.46 mmol) was placed and dissolved in dry THF (6 mL). The system was cooled down to 0 °C and triethylamine (0.28 mL, 1.84 mmol) was added, followed by the dropwise addition of a solution of (−)-(1*S*,2*R*,5*S*)-myrtanol (283 mg, 1.84 mmol) in dry THF (3 mL). The reaction mixture was stirred at room temperature for 4 h. Afterward, the solvent was removed under vacuum and the resulting residue was subjected to flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The product was isolated by elution with hexane/ethyl acetate 95:5 as a thick oil (133.5 mg, yield = 75%). IR (film): $\overline{\nu}$ = 3118, 2917, 2869, 1723 (C=O, st), 1541, 1489, 1300, 1240, 1169, 1086, 1059, 1043, 1118, 889 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (3H, s, H8″), 1.22 (3H, s, H9″), 1.26-2.30 (9H, m, H1″, H2″, H3″, H4″, H5″, H7″), 2.40 (3H, s, H7′), 4.14 (2H, q, J = 7.4 Hz, H10″), 6.76 (1H, d, J = 1.8 Hz, H4), 7.31 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.50 (1H, d, J = 1.8 Hz, H5), 7.67 (2H, d, J = 8.0 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.2 (C9″), 18.2 (C8″), 19.5 (C4″), 21.4 (C7′), 21.9 (C3″), 24.6 (C7″), 32.3 (C2″), 37.2 (C6″), 38.7 (C5″), 40.3 (C1″), 109.8 (C4), 119.4 (C3), 122.7 (C3′ and C5′), 127.9 (C2′ and C6′), 136.3 (C4′), 139.9 (C1′), 143.9 (C5), 154.8 (C2), 159.8 (C6) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 404 (100, M+NH_4), 387 (16, M+1), 386 (4, M^+). Anal. Calcd for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78; S, 8.29. Found: C, 68.41; H, 6.75; S, 8.24. $[\alpha]_D^{25} = -158.8$ (c 0.072, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 30.29 min. Ee = 100%. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f = 0.85.

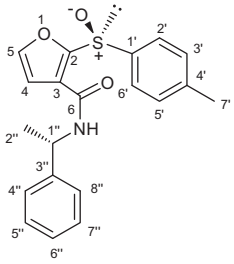
In this reaction ethyl (*S*)-2-(*p*-tolylsulfinyl)-3-furoate **13** was formed as a by-product. It was isolated in the same column chromatography purification by elution with hexane/ethyl acetate 80:20 to give a pure white solid (14 mg, yield = 11%).

4.11. Synthesis of (*S*)-*N*,*N*-diethyl-2-(*p*-tolylsulfinyl)-3-furamide 16



In an oven-dried round-bottomed 10 mL flask, fitted with a magnetic stirrer and under an argon atmosphere, mixed anhydride **14** (128.9 mg, 0.40 mmol) was placed and dissolved in dry THF (5 mL). The system was cooled down to 0 °C and diethylamine (0.17 mL, 1.6 mmol) was added at once and the mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum and the resulting residue was subjected to flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The product was isolated by elution with hexane/ethyl acetate 1:1, as a viscous oil (97.7 mg, yield = 80%, conversion = 100%). IR (film): $\bar{\nu}$ = 2977, 1636, 1576, 1559, 1541, 1506, 1489, 1456, 1437, 1126, 1084, 1049, 891, 812, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (6H, q, J = 7.0 Hz, $NCH_2\underline{CH_3}$), 2.39 (3H, s, H7′), 3.33-3.53 (4H, m, $NC\underline{H_2}CH_3$), 6.48 (1H, d, J = 1.8 Hz, H4), 7.31 (2H, d, J = 8.0 Hz, H3′ and H5′), 7.70 (1H, d, J = 1.8 Hz, H5), 7.71 (2H, d, J = 8.0 Hz, H2′ and H6′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8 and 14.5 ($NCH_2\underline{C}H_3$), 21.4 (C7′), 39.7 and 43.4 ($N\underline{C}H_2CH_3$), 110.2 (C4), 124.7 (C3′ and C5′), 126.4 (C3), 129.8 (C2′ and C6′), 137.7 (C4′), 141.5 (C1′), 146.0 (C5), 151.2 (C2), 162.9 (C6) ppm. MS [GC–MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 323 (19, M+NH_4), 307 (19, M+2), 306 (100, MH^+). $[\alpha]_D^{25} = -82.3$ (c 0.13, $CHCl_3$). Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 37.5 min. Ee = 100%. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.98; H, 6.25; N, 4.62; S, 10.48. TLC (SiO_2, ethyl acetate): R_f = 0.52 (developed as a brown spot with anisaldehyde/sulfuric acid).

4.12. Synthesis of (*S*$_S$,*S*)-*N*-(1-phenylethyl)-2-(*p*-tolylsulfinyl)-3-furamide 17



In an oven-dried round-bottomed 25 mL flask, fitted with a magnetic stirrer and under an argon atmosphere, mixed anhydride **14** (257.8 mg, 0.80 mmol) was placed and dissolved in dry THF (10 mL). The system was cooled down to 0 °C and (*S*)-(−)-1-methylbenzylamine (414 μL, 3.2 mmol) was added at once and the mixture was stirred at room temperature for 20 h. The solvent was removed under vacuum and the resulting residue was submitted to a flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The product was isolated by elution with hexane/ethyl acetate 1:1, as a colorless oil (182 mg, yield = 64%, conversion = 100%). IR (film): $\bar{\nu}$ = 3309 (N–H, st), 3114, 3031, 2977, 2929, 1653, 1576, 1526, 1493, 1451, 1375, 1213, 1126, 1082, 1038, 891, 810 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (3H, d, J = 7.0 Hz, H2″), 2.30 (3H, s, H7′), 5.18 (1H, q, J = 7.0 Hz, H1″), 6.80 (1H, t, J = 1.8 Hz, H4), 7.09-7.31 (7H, m, H3′, H5′, H4″, H5″, H6″, H7″, H8″), 7.34 (1H, t, J = 1.8 Hz, H5), 7.50 (2H, d, J = 8.0 Hz, H2′ and H6′), 8.87 (1H, br d, J = 7 Hz, N–H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (C7′), 22.5 (C2″), 49.6 (C1″), 114.4 (C4), 124.7 (C3′ and C5′), 126.0 (C4″ and C8″) 126.5 (C3), 127.1 (C6″), 128.5 (C5″ and C7″), 130.2 (C2′ and C6′), 138.1 (C4′), 142.6 (C1′), 143.4 (C3″), 144.5 (C5), 151.0 (C2), 159.1 (C6) ppm. MS [GC-MS(CI), NH_3, 70 eV, 150 °C]: m/z (%) = 355 (24, M+1), 354 (100, M^+). $[\alpha]_D^{25} = +77.5$ (c 0.18, $CHCl_3$). Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42. Found: C, 68.05; H, 5.34. Chiral GC (100 °C, 1 min, 5 °C/min, 220 °C, 20 min): t_R = 29.94 min. TLC (SiO_2, ethyl acetate): R_f = 0.60 (developed as a brown spot with anisaldehyde/sulfuric acid).

Acknowledgments

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References

1. (a) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559–5601; (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z. H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93–104; (c) Hanquet, G.; Colobert, F.; Lanners, S.; Solladie, G. *Arkivoc* **2003**, *7*, 328–401; (d) De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755–6794; (e) Andersen, K. K.; Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley and Sons, Ltd: Chichester, England, 1988. Chapter 3, pp. 55–94; Chapter 16, pp. 823–849; (f) Fernández, I.; Khiar, N. Asymmetric Catalysis Using Sulfoxides as Ligands. In *Organosulfur Chemistry in Asymmetric Synthesis*, Toru, T.; Bolm, C., Eds.; 2008, pp 265–290 Wiley-VCH, Weinheim.
2. Girodier, L.; Maignan, C.; Rouessac, F. *Tetrahedron: Asymmetry* **1992**, *3*, 857–858.
3. Arai, Y.; Suzuki, A.; Masuda, T.; Masaki, Y.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2913–2917.
4. Llera, J. M.; Trujillo, M.; Blanco, M. E.; Alcudia, F. *Tetrahedron: Asymmetry* **1994**, *5*, 709–716.
5. (a) Benjamin, N. M.; Martin, S. F. *Org. Lett.* **2011**, *13*, 450–453; (b) Fernández de la Pradilla, R.; Tortosa, M.; Castellanos, E.; Viso, A.; Baile, R. *J. Org. Chem.* **2010**, *75*, 1517–1533; (c) Rivero, M.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2004**, *10*, 5443–5459; (d) Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P. *Synthesis* **2003**, *14*, 2241–2248; (e) Maruoka, K., In: *Catalytic Asymmetric Synthesis*, 2nd ed., Ojima, I. Ed., 2000, 467–491 John Wiley, New York.; (f) Arai, Y.; Masuda, T.; Masaki, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1078–1083; (g) Bravo, P.; Bruche, L.; Merli, A.; Fronza, G. *Gazz. Chim. Ital.* **1994**, *124*, 275–277; (h) Arce, E.; Carreño, M. C.; Cid, M. B.; García-Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421–3426; (i) Carreño, M. C.; García-Ruano, J. L.; Urbano, A. *J. Org. Chem.* **1992**, *57*, 6870–6876.
6. (a) Arai, Y.; Masuda, T.; Masaki, Y. *Chem. Lett.* **1997**, 145–146; (b) Arai, Y.; Masuda, T.; Masaki, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1199–1204; (c) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509–5512.
7. Arai, Y.; Masuda, T.; Masaki, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *7*, 1199–1204.
8. Arroyo, Y.; Carreño, M. C.; García-Ruano, J. L.; Rodríguez-Amo, J. F.; Santos, M.; Sanz-Tejedor, M. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1183–1191.
9. Philips, H. *J. Chem. Soc.* **1925**, *127*, 2552–2587.
10. (a) Montaña, A. M.; Ribes, S.; Grima, P. M.; García, F. *Acta Chem. Scand.* **1998**, *52*, 453–460; (b) Montaña, A. M.; García, F.; Grima, P. M. *Tetrahedron Lett.* **1999**, *40*, 1375–1378; (c) Montaña, A. M.; García, F.; Grima, P. M. *Tetrahedron* **1999**, *55*, 5483–5504.
11. Montaña, A. M.; Grima, P. M.; Batalla, C.; Sanz, F.; Kociok-Köhn, G. *Eur. J. Org. Chem.* **2014**, in press. doi: http://dx.doi.org/10.1002/ejoc.201301814.
12. (a) Montaña, A. M.; Fernández, D. *Tetrahedron Lett.* **1999**, *40*, 6499–6502; (b) Montaña, A. M.; Grima, P. M.; Mesas, J. M.; Alegre, M. T. *Microsc. Anal.* **2000**, *1*, 9–11; (c) Montaña, A. M.; Fernández, D.; Pagès, R.; Filippou, A. C.; Kociok-Köhn, G. *Tetrahedron* **2000**, *56*, 425–439; (d) Montaña, A. M.; Grima, P. M. *J. Chem. Educ.* **2000**, *77*, 754–757; (e) Montaña, A. M.; Grima, P. M. *Tetrahedron Lett.* **2001**, *42*, 7809–7813; (f) Montaña, A. M.; Grima, P. M. *Synth. Commun.* **2003**, *32*, 265–279; (g) Montaña, A. M.; García, F.; Batalla, C. *Tetrahedron Lett.* **2004**, *45*, 8549–8552; (h) Montaña, A. M.; Barcia, J. A. *Tetrahedron Lett.* **2005**, *46*, 8475–8478; (i) Montaña, A. M.; Ponzano, S. *Tetrahedron Lett.* **2006**, *47*, 8299–8304; (j) Montaña, A. M.; Ponzano, S.; Kociok-Köhn, G.; Font-Bardia, M.; Solans, X. *Eur. J. Org. Chem.* **2007**, *26*, 4383–4401; (k) Montaña, A. M.; Grima, P. M.; Batalla, C. *Targets in Heterocyclic Systems: Chemistry and Properties* **2009**, *13*, 231–251; (l) Montaña, A. M.; Ponzano, S.; Batalla, C.; Font-Bardia, M. *Tetrahedron* **2012**, *68*, 8276–8285.

13. (a) Montaña, A. M.; Barcia, J.; Kociok-Köhn, G.; Font-Bardia, M.; Solans, X. *Helv. Chim. Acta* **2008**, *91*, 187–208; (b) Montaña, A. M.; Batalla, C.; Barcia, J. *Curr. Org. Chem.* **2009**, *13*, 919–938; (c) Montaña, A. M.; Barcia, J. A.; Kociok-Köhn, G.; Font-Bardía, M. *Tetrahedron* **2009**, *65*, 5308–5321.
14. (a) Montaña, A. M.; García, F.; Batalla, C. *Lett. Org. Chem.* **2005**, *2*, 480–484; (b) Montaña, A. M.; García, F.; Batalla, C. *Lett. Org. Chem.* **2005**, *2*, 475–479.
15. (a) Montaña, A. M.; Grima, P. M. *Tetrahedron Lett.* **2002**, *43*, 2017–2021; (b) Montaña, A. M.; Grima, P. M. *Tetrahedron* **2002**, *58*, 4769–4786.
16. Montaña, A. M.; Grima, P. M.; Castellví, M.; Batalla, C. *Tetrahedron* **2012**, *68*, 9982–9998.
17. Herein (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluenesulfinate has been used. It is worth noting that the enantiomer (1*S*,2*R*,5*S*)-(+)-menthyl (R_S)-*p*-toluenesulfinate is also commercially available.
18. Girodier, L. D.; Rouessac, F. *Tetrahedron: Asymmetry* **1994**, *4*, 1203–1206.
19. Ly, N. D.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 2085–2088.
20. Girodier, L. D.; Maignan, F.; Rouessac, F. P. *Tetrahedron: Asymmetry* **1995**, *6*, 2045–2052.
21. Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry*; Springer-Verlag: Stutgart, 1987. p 158.
22. (a) Knight, D. W. *Tetrahedron Lett.* **1979**, *5*, 469–472; (b) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835–5838; (c) Katsumure, S.; Fujiware, S.; Sachihiko, I. *Tetrahedron Lett.* **1985**, *26*, 5827–5830.
23. (a) Morales-Serna, J. A.; Sánchez, E.; Velázquez, R.; Bernal, J.; García-Ríos, E.; Gaviño, R.; Negrón-Silva, G.; Cárdenas, J. *Org. Biomol. Chem.* **2010**, *8*, 4940–4948; (b) Chan, L. C.; Cox, B. G. *J. Org. Chem.* **2007**, *72*, 8863–8869; (c) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron Lett.* **2005**, *61*, 10827–10852; (d) López-Alonso, J. P.; Díez-García, F.; Font, J.; Ribó, M.; Scholtz, M.; González, C.; Vottariello, F.; Gotte, G.; Libonati, M.; Laurents, D. V. *Bioconjugate Chem.* **2009**, *20*, 1459–1473.
24. As can be observed, both the precursory menthyl sulfinate and the sulfinylfuran have the same stereochemical notation (*S*) for the stereogenic sulfur atom, even though a complete inversion of configuration took place in the S_N2 reaction. This is a nomenclature issue due to the change of priorities of atoms connected to the stereogenic sulfur in both compounds according to the Cahn-Ingold-Prelog rules.
25. (a) *Mercury 3.1 Software for Crystal Structure Visualization, Exploration and Analysis*. The Cambridge Crystallographic Data Centre (CCDC): Cambridge, UK, 2013.; (b) Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M. K.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. *Acta Crystallogr. B* **2002**, *58*, 389–397.
26. Otwinowski, Z.; Minor, W. Denzo and Scalepack Programs for Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods in Enzymology*; Carter, C. W., Jr., Sweet, R. M., Eds.; Macromolecular Crystallography, Part A; Academic Press: New York, 1997; Vol. 276, pp 307–326.
27. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
28. Hübschle, C. B.; Sheldrick, G. M.; Dittrich, B. *J. Appl. Crystallogr.* **2011**, *44*, 1281–1284.
29. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *A64*, 112–122.
30. Magnesium turnings were activated by washing them successively with 0.1 M HCl, distilled water and acetone and then dried under vacuum.
31. Cope, A. C.; Ciganek, E. *Org. Synth. Coll.* **1963**, *IV*, 339–342.