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An Improvement of the Synthesis of (1*R*,2*S*,5*R*)-(-)-Menthyl (*S*)-*p*-Toluenesulfinate

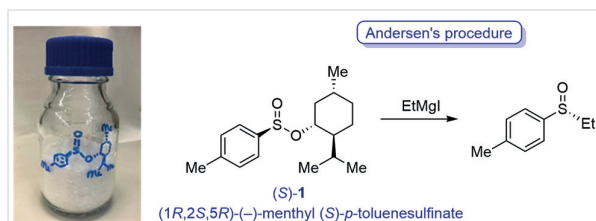
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The chiral sulfoxide is one of the privileged motifs in asymmetric synthesis. Its efficiency was initially proved in diastereoselective transformations as a chiral auxiliary.¹ Subsequently, application of sulfoxides as a ligand in asymmetric catalysis² and also as a directing group for diastereoselective reactions, including C–H activation, have emerged.³

To access enantiopure sulfoxides on a large scale, one of the most established and still standard approaches is the Andersen procedure.⁴ At the beginning of the 1960s, Andersen reported the synthesis of enantiopure sulfoxides by addition of Grignard reagents to (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (*S*)-**1** (Scheme 1), liberating (-)-menthol. To date, it is still the most widely used¹ and convenient way to obtain chiral sulfoxides.²



Scheme 1 (1*R*,2*S*,5*R*)-(-)-Menthyl (*S*)-*p*-toluenesulfinate and Andersen's procedure



Gaspard Hedouin received his engineering degree from the Ecole Nationale Supérieure de Chimie de Rennes and a master's degree in chemistry from the University of Rennes in 2017. Then, he started a PhD at the University of Strasbourg, under the supervision of Pr. Françoise Colobert and Dr. Joanna Wencel-Delord, which he will defend in early 2021. He is currently working on the development of new di-phosphine ligands and their application in asymmetric catalysis.

Quentin Dherbassy received his PhD from the University of Strasbourg (France) in the group of Pr. Françoise Colobert (2017, University of Strasbourg/CNRS, France). His doctoral studies focused on the control of axial chirality by sulfoxide-directed C–H activation. He then joined the Procter group (University of Manchester, UK) as a PDRA in 2018, studying borylative copper-catalyzed asymmetric multicomponent reactions. He is currently a postdoctoral fellow in the Moran Group (Isis, University of Strasbourg) working on the prebiotic origins and functions of biological cofactors.

The preparation of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (*S*)-**1** has been known for decades and was described for the first time in 1925 by Phillips (Table 1, **A**).⁵ *p*-Toluenesulfinic acid, initially activated with thionyl chloride, is esterified with a solution of (-)-menthol in pyridine to allow the formation of **1** as a diastereomeric mixture. Then, both diastereomers can be separated by crystallization to afford pure (*S*)-**1** with a yield lower than 50%. This major drawback was later overcome by the group of Solladié.⁶ Applying observations made by Herbrandson⁷ and Mislow⁸ concerning the racemization of sulfinic esters and sulfoxides in the presence of hydrogen chloride, (*S*)-**1** could be isolated on large scale in 80% yield thanks to iterative crystallization/epimerization cycles (Table 1, **B**).

Table 1 Different Methodologies to Access the (1*R*,2*S*,5*R*)-(-)-Menthyl (*S*)-*p*-Toluenesulfinate; Price: 5.92 €/mmol on Sigma-Aldrich

(A) Philipps, 1925 : first synthesis of (<i>S</i>)- 1 price of production: 0.34 €/mmol	<p>1 equiv. $\xrightarrow[2) (-)\text{-menthol (1 equiv.), pyridine}]{1) \text{SOCl}_2 (1.1 \text{ equiv.}), \text{Et}_2\text{O}}$ (<i>S</i>)-1 24% yield 7 g scale</p>
(B) Solladié, 1987 : modified procedure affording (<i>S</i>)- 1 with yields higher than 50% thanks to successive crystallizations/epimerizations price of production: 0.18 €/mmol + high yield + large scale - excess of thionyl chloride - benzene as solvent - pyridine as base	<p>1 equiv. $\xrightarrow[3) \text{HCl (4-5 drops), recrystallization in acetone}]{1) \text{SOCl}_2 (5 \text{ equiv.}), \text{benzene}, 0^\circ\text{C}$ $2) (-)\text{-menthol (1.1 equiv.), pyridine, Et}_2\text{O}, 0^\circ\text{C}, 1 \text{ h}}$ (<i>S</i>)-1 80% yield 60 g scale</p>
(C) Trost, 2013 : use of <i>p</i> -toluenesulfonylchloride as starting material price of production: 0.74 €/mmol + cheap starting material + short time reaction + simple reaction protocol - purification via chromatography and crystallization - 1 equivalent of triphenylphosphine oxide as waste - low yield - small scale	<p>1 equiv. $\xrightarrow[\text{NEt}_3, 0^\circ\text{C to rt, 4 h}]{(-)\text{-menthol (1 equiv.)}, \text{PPh}_3 (1 \text{ equiv.})}$ (<i>S</i>)-1 15% yield 300 mg scale</p>
(D) Hajipour, 2006 : neat synthesis of 1 by grinding price of production: 0.10 €/mmol for the diastereomeric mixture + very rapid reaction time + absence of solvent + yield - purification via chromatography - DCC toxicity as reagent and by-product - products isolated as a mixture of diastereomers - small scale	<p>1 equiv. $\xrightarrow[\text{grinding, 8 min}]{(-)\text{-menthol (1 equiv.)}, \text{DCC (1 equiv.)}}$ (<i>S</i>)-1 + (<i>R</i>)-1 95% yield 300 mg scale</p>
(E) Wencel-Delord & Colobert, 2019 : recent enhancement of the Solladié procedure price of production: 0.14 €/mmol + decreased amount of thionyl chloride + solvent-free reaction (only used for azeotropic distillation of SOCl ₂) + pyridine replaced by triethylamine + large scale	<p>1 equiv. $\xrightarrow[4) \text{HCl (4-5 drops), recrystallization in acetone}]{1) \text{SOCl}_2 (1.5 \text{ equiv.}), 0^\circ\text{C}, 5-20 \text{ min}$ $2) \text{DMF (1 mol\%), } 80^\circ\text{C}, 1 \text{ h}$ $3) (-)\text{-menthol (1 equiv.), Et}_3\text{N}, 0^\circ\text{C to rt, 3 h}}$ (<i>S</i>)-1 72% yield 60 g scale</p>

In addition to this efficient strategy, several other procedures have been described. In 1987, Sharpless developed the synthesis of menthyl sulfinate esters, starting from the cheaper starting material, *p*-toluenesulfonyl chloride (TsCl).⁹ The sulfinyl chloride can be obtained *in situ* by reduction of the *p*-toluenesulfonyl chloride with trimethylphosphite, followed by the addition of (-)-menthol to afford **1**. More recently, the group of Trost has also applied this strategy, using triphenylphosphine to reduce the toluenesulfonyl chloride into the desired sulfinyl chloride, which can subsequently react with (-)-menthol to afford (*S*)-**1** after iterative recrystallizations, albeit with a low yield (Table 1, C).¹⁰

Another major contribution has been reported by Hajipour who developed several methodologies for the synthesis of **1** under solvent-free conditions. To avoid the use of the unstable and moisture-sensitive sulfinyl chloride, he described various preparations of **1** from sulfinic acids, in solid phase using silica.¹¹ His final report demonstrated the efficiency of this general strategy by accomplishing the esterification of *p*-toluenesulfinic acid with *N,N'*-dicyclohexylcarbodiimide as the coupling reagent. Grinding the reaction mixture for a brief period allowed the formation of

the desired sulfinate ester in an excellent yield, but as a mixture of the two diastereomers (Table 1, D).¹² Likewise, the group of Hitchcock also developed the synthesis of sulfinate esters by activation of the *p*-toluenesulfinic acid with EDC-HCl.¹³

Among these diverse methodologies, the procedure of Solladié remains the most convenient and efficient to access menthyl *p*-toluenesulfinate (*S*)-**1** on large scale. Slight modifications have been made since, for example, the use of hydrated sodium sulfinate as starting material presented by Blakemore.¹⁴ Moreover, our group has been actively involved in the chemistry of chiral sulfoxides and recently a number of fundamental modifications of the reaction conditions have been discovered to improve the Solladié procedure.

Following our developed methodology,¹⁵ the reaction proceeds under solvent-free conditions instead of using benzene as solvent. Additionally, to reduce the amount of thionyl chloride used for the formation of the sulfinic chloride from the sulfinic acid, addition of a catalytic amount of DMF allowed a significant decrease to 1.5 equivalents of SOCl₂ (compared to the standard 5 equivalents).

This modification renders the procedure more suitable scale-up, having the advantage of consuming less solvent during the azeotropic distillation of the excess thionyl chloride. Moreover, greater efficiency is observed upon replacing pyridine with triethylamine. Thus, a tens-of-gram synthesis of (*S*)-**1**, without significant byproduct formation, can be achieved in one day with an excellent yield of 72% and a d.r. > 98:2 (Table 1, E). Furthermore, to compare the different procedures, the price of production¹⁶ has been approximately evaluated. This clearly showed that all the published procedures are significantly less costly than the commercial product (currently 5.92 €/mmol as purchased from Sigma-Aldrich), but the protocol optimized in our laboratory is the most cost-efficient (0.14 €/mmol) to afford diastereopure (*S*)-**1**.

As sulfoxides continue to be valuable moieties for stereoselective reactions, this refinement should prove to be very helpful for the large-scale synthesis of this key precursor, (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate [(*S*)-**1**].¹⁷

Conflict of Interest

The authors declare no conflict of interest.

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- (16) The costings were evaluated for the synthesis of 1 mmol of product according to the yields reported based on the price of starting materials and reagents available from Sigma-Aldrich (12/2020).
- (17) In a 250 mL flask, equipped with either a large stirrer bar or mechanical stirring, neat SOCl₂ (1.47 equiv., 49.2 g, 30 mL, 0.414 mol) was added and then cooled to 0 °C. Dried solid sodium 4-methylbenzene-1-sulfinate (1 equiv., 50 g, 0.281 mol) was then added portionwise as quickly as possible to avoid blow back of the powder by the evolving sulfur dioxide (addition generally takes around 5–10 min and should not be longer than 20 min). **NOTE:** After about two-thirds of the addition, depending on the speed of the addition, a solid paste can form that will impede the stirrer bar. If this happens, the addition should be continued nonetheless, and the mixture should recover its initial appearance after a few minutes. After addition was complete, DMF (1 mol%, 0.21 g, 0.222 mL, 0.00287 mol) was then added, the cold bath removed, and the solution stirred for 1 h at 80 °C with a drying tube fitted containing a desiccant such as Na₂SO₄. At this point toluene (100 mL) was added and the flask fitted for reduced pressure distillation to remove the excess SOCl₂ as a toluene azeotrope. In so doing, the pressure was slowly reduced so that the thick solution would not bump. At the end of the distillation the reaction mixture was bright straw yellow, with very little residual toluene. The SOCl₂-free solution was then cooled to 0 °C in an ice-water bath and the flask fitted with an addition funnel charged with a solution of (-)-menthol (0.958 equiv., 42 g, 47.2 mL, 0.269 mol) in triethylamine (44 mL). The menthol solution was slowly added dropwise at 0 °C. After addition was complete, the resulting mixture was stirred at 0 °C for 1 h and at rt for 2 h. It was then poured into a mixture of brine (50 mL) and aqueous HCl (1 M, 50 mL) along with Et₂O (50 mL) to reach pH ca. 1–2. Then the minimum of Et₂O was added to achieve a homogeneous biphasic mixture. The phases were separated, and the organic phase washed with 1 M HCl (2 × 50 mL) followed by saturated NaHCO₃ (2 × 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure. The residue was dissolved in acetone (100 mL) to which was added 3–5 drops of 37% HCl and the whole mixture put into a freezer. The resultant crystals were filtered and washed once with cold acetone (-18 °C); the mother liquor was then concentrated to half its volume, 1–2 drops of concentrated HCl were added, and the process repeated as long as appreciable amounts of crystals could be recovered (6–8 iterations). The combined batches were recrystallized from acetone (reflux to rt to -18 °C), affording large rectangular colorless crystals of (-)-menthyl (*S*)-*p*-toluenesulfinate (57.3 g, 0.194 mol, 72.4%).