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Grau de Química

Treball Final de Grau

Towards the total synthesis of (−)-Curcumene and (−)-Curcuquinone.
Cap a la síntesi total del (−)-Curcumè i la (−)-Curcuquinona.

Carlos Riego Mejías

June 2022

Universitat de Barcelona

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Non si può mai attraversare l'oceano se non si ha il coraggio di perdere di vista la riva.

Cristoforo Colombo

Primerament, vull agrair al Prof. Antoni Riera per haver-me donat l'oportunitat i la confiança de poder treballar al seu grup, per tots els consells i per guiar-me a través d'aquest projecte. Moltes gràcies al Prof. Xavier Verdaguer pel seu suport durant tots aquests mesos.

A la Marina, per ser la meva referent. Per tots els cafès, reflexions i moments que hem viscut i per ensenyar-me a gaudir i estimar la química, gràcies de tot cor.

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Als meus pares, per ensenyar-me a no rendir-me mai i per haver-me transmès el valor i la confiança que necessitava durant aquests anys.

REPORT

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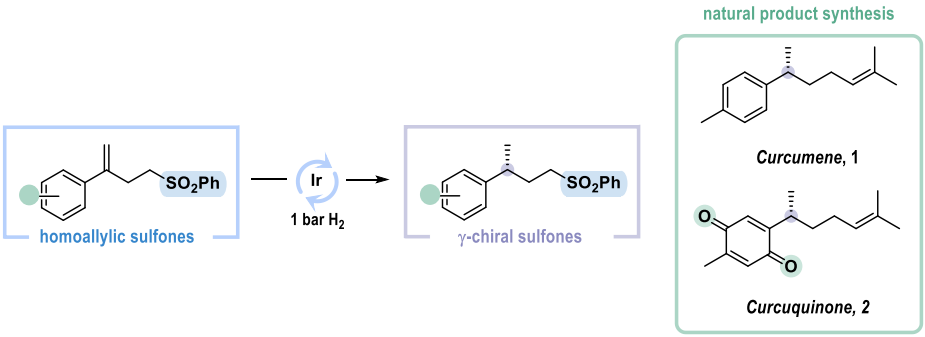
1. SUMMARY

The synthesis of chiral natural products has long been the focal point in the field of asymmetric catalysis since both stereoisomers usually have different bioactivity. Within all the catalytic asymmetric methodologies, homogeneous transition-metal catalyzed hydrogenation plays a pivotal role.

Our group has been working in the Ir-catalyzed asymmetric hydrogenation reactions of several substrates such as sulfones, which are versatile building blocks in synthetic chemistry. In this respect, the group recently developed a methodology to synthesize homoallylic sulfones through a highly selective process which has set the stage for the synthesis of different natural products.

The previously mentioned methodologies have established the framework for the synthesis and the Ir-catalyzed asymmetric hydrogenation of homoallylic sulfones. In the present work, the applicability of these methodologies has been demonstrated through the synthesis of (+)-α-curcumene **1** and an advanced intermediate of (−)-curcuquinone **2**.



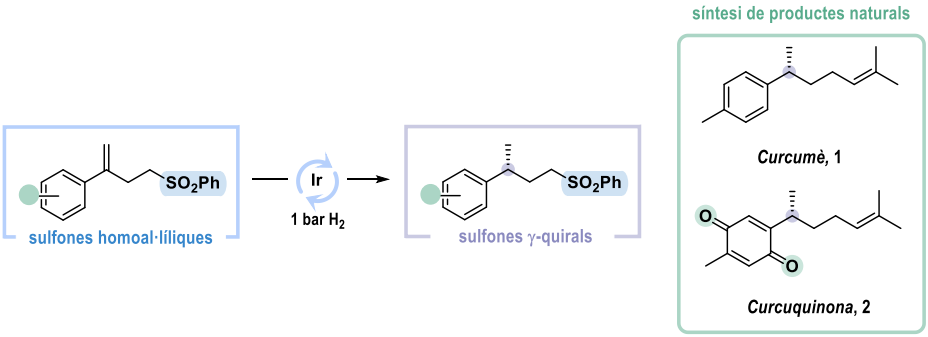
Keywords: Ir-catalyzed asymmetric hydrogenation, homoallylic sulfones, γ-chiral sulfones, natural product synthesis.

2. RESUM

La síntesi de productes naturals quirals ha estat durant molt de temps l'objectiu en el camp de la catàlisi asimètrica, ja que ambdós estereoisòmers solen tenir bioactivitats diferents. Entre totes les metodologies asimètriques catalítiques, la hidrogenació homogènia catalitzada per metalls de transició és de gran importància.

El nostre grup ha estat treballant en les reaccions d'hidrogenació asimètriques catalitzades per complexos d'iridi de diversos substrats, com ara les sulfones, que son intermedis versàtils en la química sintètica. En aquest sentit, el grup ha desenvolupat recentment una metodologia per sintetitzar sulfones homoal·líliques mitjançant un procés altament selectiu que ha posat les bases per a la síntesi de diferents productes naturals.

Les metodologies esmentades anteriorment han establert les bases per a la síntesi i la hidrogenació asimètrica catalitzada de sulfones homoal·líliques. En el present treball, s'ha demostrat l'aplicabilitat d'aquestes metodologies mitjançant la síntesi de l'(−)-α-curcumè **1** i un intermedi avançat de la (−)-curcuquinona **2**.



Paraules clau: Hidrogenació asimètrica catalítica, sulfones homoal·líliques, sulfones γ-quirals, síntesi de productes naturals.

3. INTRODUCTION

3.1. TOTAL SYNTHESIS OF NATURAL PRODUCTS

Gorgorian octocorals are found throughout the world's oceans and are crucial for coral reef communities, representing a countless source of structurally complex and biologically active compounds.[1] More particularly, soft corals of the genus *Pseudopterogorgia* are responsible of producing significant bioactive metabolites. For instance, those belonging to the bisabolene family of sesquiterpenes depicted in Figure 1.

This group of compounds display a wide range of biological activity and have been used in traditional medicine.[2] In fact, both enantiomers of some compounds have been isolated and have different but important biological activities. For instance, (−)-curcuphenol shows antibiotic activity whereas (+)-curcuphenol exhibits cytotoxicity against human tumours and inhibits HK-ATPase.[3]

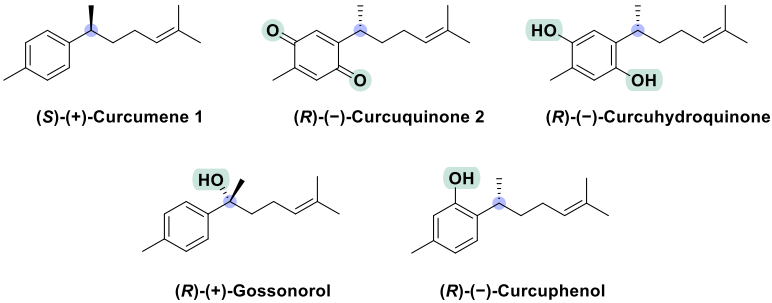


Figure 1. Bisabolene family of sesquiterpenes from *Pseudopterogorgia rigida*.

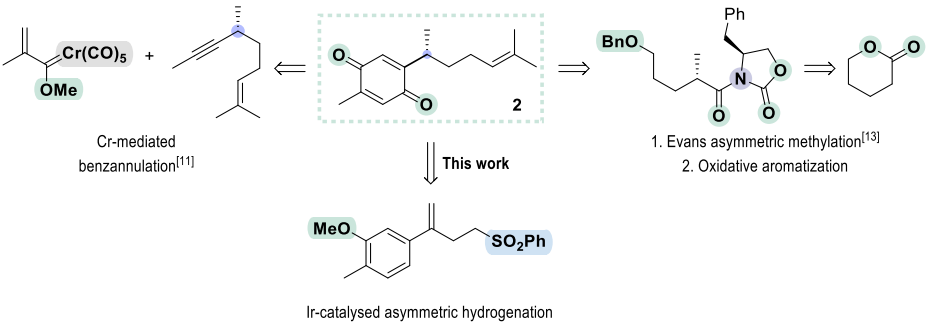
Despite the significant value of these terpenoids due to their biological profile, there are not many efficient synthetic reports of the optically active forms, since introducing defined absolute stereochemistry at the nonfunctionalized benzylic position remains a challenge. For that purpose, the development and optimization of a synthetic pathway towards the total synthesis of both enantiomers are of interest. Herein, we focused on the total synthesis of curcumene and curcuquinone using catalytic asymmetric methodologies.

3.1.1. Curcumene and curcuquinone

According to the World Health Organization, antimicrobial resistance endangers the identification and treatment of a growing range of infections caused, for example, by bacteria and fungi. Thus, the discovery of new antimicrobial compounds is crucial. More information about bacterial antibiotic resistance can be found in the work of the Nobel laureate Ada E. Yonath.[4]

Compounds isolated from plants have been used since ancient times. Despite this, there are few reports of those obtained from marine flora such as (+)-α-curcumene 1 or (−)-curcuquinone 2. These molecules are aromatic terpenoids isolated from the Caribean gorgorian sea plume, *Pseudopterogorgia rigida*,[5] and are responsible for its antibiotic and antifungal properties. Moreover, it has been proved that α-curcumene, besides its antimicrobial activity,[6] has antitumoral activity against Sarcoma 180.[7] In addition, they have proven to be functional chiral building blocks for constructing biologically important natural products such as heliannuols A and B.[8]

α-Curcumene has been isolated from different natural sources in both enantiomeric forms. To date, the most common methodology to synthesize curcumene included enzymatic resolution. Non-enzymatic methods involve chirality transfer via diastereoselective synthesis, starting from different quiral auxiliaries such as oxazolines or sulfoximines. More effective catalytic procedures to install the stereocenter have used Itsuno-Corey ketone reduction,[9] Sharpless asymmetric epoxidation,[10] and Ni-catalyzed cross-coupling of benzyl Grignard reagents.[8] Furthermore, curcuquinone has been synthetized via regioselective Cr-mediated benzannulation,[11] ring-closing metathesis,[12] lithiation-borylation reaction,[2] and Evans asymmetric methylation followed by an oxidative aromatization.[13]



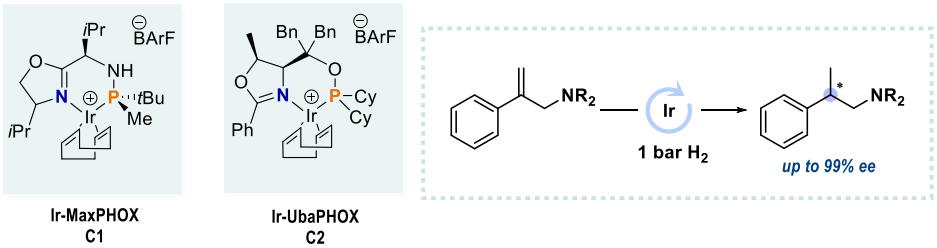
Scheme 1. Some synthetic strategies and our approach towards the total synthesis of curcuquinone

In this work we will focus on the introduction of the chirality by asymmetric hydrogenation. Asymmetric synthesis is a growing topic in the field of chemistry,[14] and it has become an essential tool for the enantioselective synthesis of drugs and biologically active compounds. One of the best advantages is that both enantiomers can be synthesized starting from the same prochiral substrate. Since biological activities of both enantiomers differ significantly, we envisioned a practical synthesis able to afford both enantiomers independently in high stereochemical purity starting from the same achiral starting material.

4. PREVIOUS WORK

During the last decade our group has been focusing in the Ir-catalyzed asymmetric hydrogenation reaction developing several *P*-stereogenic chiral ligands that have proven to be excellent precursors of chiral catalysts.[15–18]

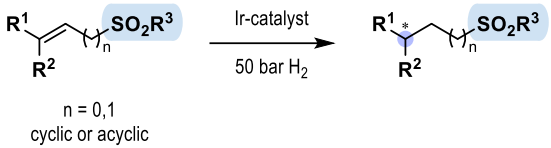
Our Iridium-*P,N* MaxPHOX (**C1**) family of catalyst have been successfully applied to the asymmetric hydrogenation of functionalized olefins, including 2-aryl *N*-allyl phthalimides.[19] However, in the case of protected *N*-tosyl-2-aryl allyl amines, it was found that the commercially available [((4*S*,5*S*)-Cy$_2$-Ubaphox)Ir(COD)]BArF$_4$ **(Ir-Ubaphox, C2)** catalyst gave the best results (Scheme 2).[20,21]



Ir-MaxPHOX C1 Ir-UbaPHOX C2

Scheme 2. Previous work on Ir-catalysed asymmetric hydrogenation

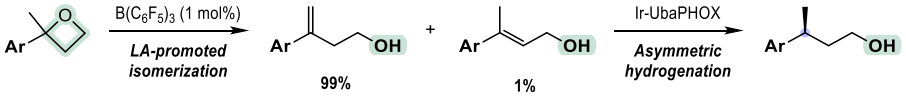
To date, the asymmetric hydrogenation of many different functionalized *E*/*Z*-olefins has been widely reported.[22] As for example, both the Andersson's and the Pfaltz's groups independently demonstrated the utility of the sulfonyl group in the Ir-catalyzed asymmetric hydrogenation of cyclic and acyclic sulfones with outstanding enantioselectivities (Scheme 3).[23–25] Nevertheless, these trisubstituted olefins often encounter *E*/*Z*-selectivity issues and their hydrogenation needs high pressure conditions.



Scheme 3. Andersson's and Pfaltz's asymmetric hydrogenation of trisubstituted olefins bearing a sulfonyl group.

In this context, our group has been focusing in the Ir-catalyzed asymmetric hydrogenation reaction of several 1,1-disubstituted functionalized olefins, since they do not suffer from *E*/*Z*-selectivity issues, such as allylic phthalimides or allylic tosyl amines (Scheme 2).

With the aim to expand the substrate scope to other terminal olefins, the group developed a new methodology to synthesize homoallylic alcohols through a highly selective Lewis acid catalyzed isomerization of 2,2-oxetanes (Scheme 4).[26]

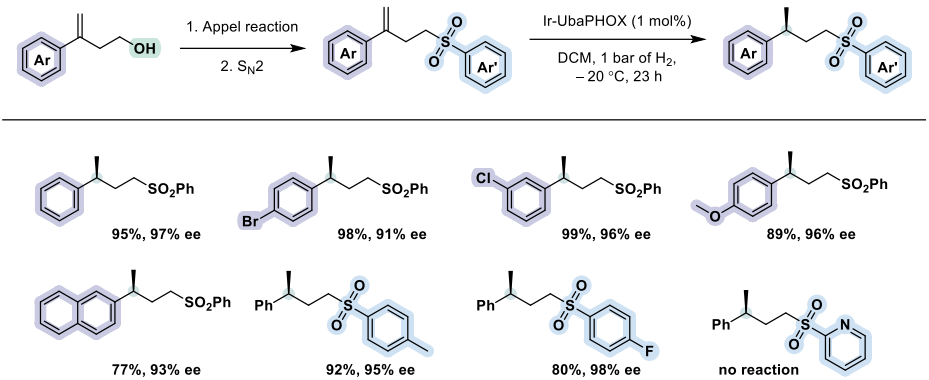


Scheme 4. 2,2-Oxetane isomerization and asymmetric hydrogenation of homoallylic alcohols.

Although the reaction was highly diastereoselective, some homoallylic alcohols were difficult to purify from their corresponding *E*/*Z*-allylic isomer, which decreased the enantioselectivities upon hydrogenation. To overcome this issue, our group envisioned a new strategy based on the replacement of the alcohol for a sulfonyl group, as it might ease the separation of the regioisomers.

The corresponding sulfones were obtained via an Appel reaction followed by nucleophilic substitution with sodium benzenesulfinate in a highly efficient process. Following this methodology, the obtained homoallylic sulfones exhibited easy column separation and were more versatile than their alcohol analogues. This strategy allowed the substrate scope in the catalyzed hydrogenation of several homoallylic sulfones in low pressure and temperature conditions (Scheme 5).

Even though these γ-chiral sulfones had already been synthetized by the Andersson's group by means of hydrogenation of the (*E*)-allylic sulfone, their absolute configuration was not determined, and they only reported the optical rotation.



Scheme 5. Substrate scope in the catalysed hydrogenation of functionalized sulfones.

To solve this problem, our group performed an X-ray analysis of a hydrogenated analogue **3** with heavy atoms to facilitate the anomalous scattering technique. The X-ray confirmed the absolute configuration being the (*S*)-enantiomer our major product when using (*S*,*S*)-Ir-UbaPHOX as the catalyst (Figure 2).

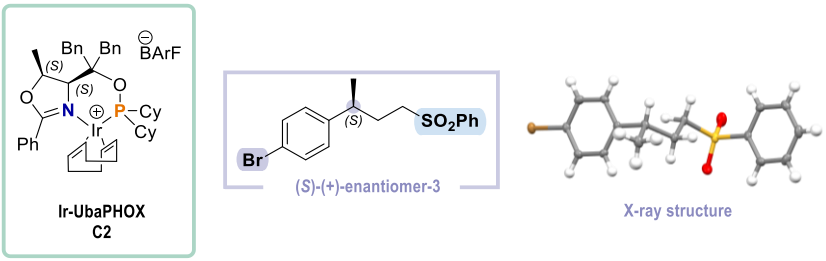
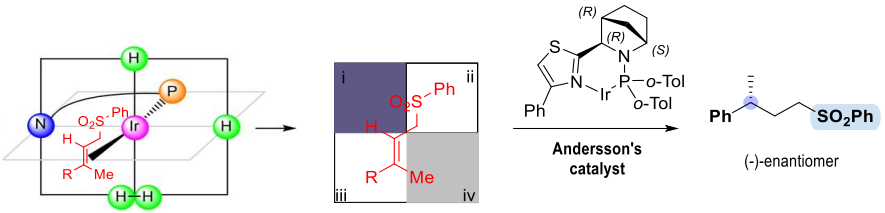


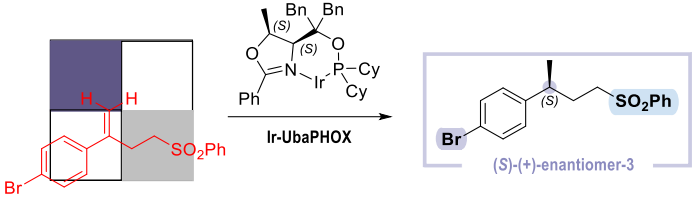
Figure 2. Iridium catalyst, hydrogenated product, and its X-ray structure.

The stereochemical course of the hydrogenation reaction could be predicted following the Andersson's quadrant model (Scheme 6).[27,28] Taking into consideration the chirality of the catalyst by means of its X-ray structure, the plane where the olefin will coordinate can be divided in four different quadrants that can be more hindered (purple), slightly hindered (grey) and open (white). To minimize the steric interactions, the hydrogen substituents of the olefin must be placed in the more hindered quadrant whereas the bulkier groups in the open quadrants. Therefore, one of the enantiotopic faces of the prochiral substrate is preferred depending on the chirality of the ligand. As a result, when using their allylic sulfone and their type of catalyst, they obtained the levorotatory enantiomer (Scheme 6).



Scheme 6. Quadrant diagram model for the Andersson's catalyst and type of substrate.

Nevertheless, as the enantioenriched product **3** that we obtained in our hydrogenation was the (*S*)-enantiomer and the optical rotation was the opposite to the Andersson's one, we could also propose a theoretical quadrant model based on our catalyst-substrate system. When deciding the preferred enantiotopic face, the less hindered groups should be placed in the purple quadrant. In order to match the stereochemical outcome observed by means of X-ray and optical rotation, we consider the aromatic ring bulkier than the alkyl chain, placing them in the white and grey quadrants, respectively, as shown in Scheme 7.

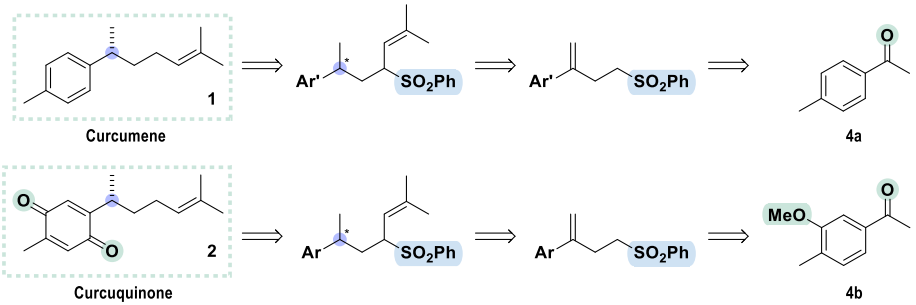


Scheme 7. Quadrant diagram model for our catalyst/substrate system.

The recently developed methodology allows the synthesis of γ-chiral sulfones, which are of special interest due to their presence in natural products. Several drugs containing sulfonyl groups are used for the treatment of leprosy, dermatitis herpetiformis, tuberculosis and have shown antifungal, antimalarial, and anticancer activity.[29] In addition, sulfones are versatile intermediates for the construction of several building blocks,[30] and had been studied due to their importance to produce a wide variety of biologically active compounds. Homoallylic, allylic and benzylic sulfones have been used to extend carbon-chain length as intermediates in C-C bond formation, due to the α-proton acidity. We envisioned that the γ-chiral sulfones prepared following our methodology could be used in the synthesis of natural products, such as (+)-α-curcumene or (−)-curcuquinone.

5. OBJECTIVES

The aim of this work is to explore both the racemic and the enantioselective total synthesis of (−)-curcuquinone and (−)-α-curcumene. The syntheses of both natural products of biological interest in cancer science would demonstrate the applicability of the recently reported methodology by our group.[26] The proposed pathway focuses on catalytic processes and tries to achieve the greenest and most efficient reactions as possible, using sulfones as building blocks.



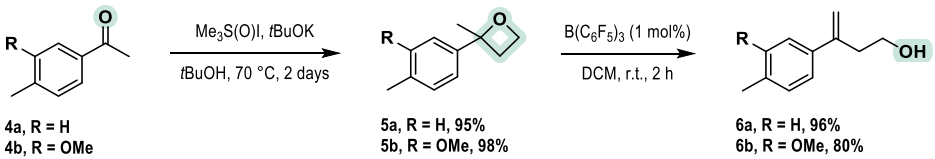
Scheme 8. Proposed synthesis of curcumene and curcuquinone.

6. RESULTS AND DISCUSSION

6.1. FORMATION OF THE HOMOALLYLIC ALCOHOL

Starting from the initial ketones, the first step of the proposed pathway was the synthesis of the 2,2-disubstituted oxetane. Following the literature,[31] the transformation of both acetophenones into their corresponding oxetane was straightforward by a double Corey-Chaykovsky reaction.

The reaction goes through a nucleophile attack toward the initial ketone's carbonyl from an initial equivalent of ylide, affording the corresponding epoxide, which reacts with a second equivalent of trimethylsulfoxonium iodide to furnish the corresponding 4-membered oxetane (Scheme 9). Even though the reaction was planned to last 3 days, we envisioned the possibility to lower the reaction time to 2 days, as both ketones were very electron rich. That way, we achieved the same results and a faster and more efficient procedure. The products were obtained with good yields without the need of further purification.



Scheme 9. Homoallylic alcohol synthesis.

With the 2,2-disubstituted oxetanes in hand, the next step consisted in a ring-opening to afford the homoallylic alcohols. The strategy proposed went through a catalytic regioselective isomerization, employing the organic and bulky tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) catalyst, following the methodology reported by the group.[26] We had to increase the catalyst loading from 0.5 mol% to 1 mol% as we were working on a bigger scale than the referenced procedure. In this way, we made sure to obtain the desired product, as this step could have generated three isomers

(Figure 3). The results showed that employing such a bulky catalyst made the oxetanes to evolute to their corresponding homoallylic/allylic alcohols in a 99:1 ratio.

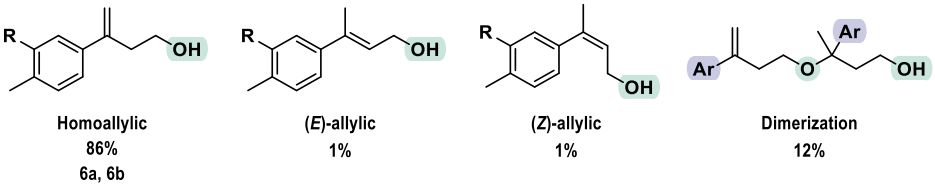


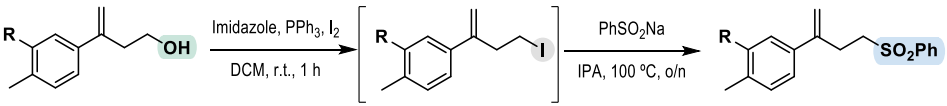
Figure 3. Possible regioisomers and dimer obtained from the oxetane ring opening.

However, despite the excellent selectivity toward the homoallylic isomer, ^{1}H NMR showed the formation of the dimer as a by-product (Figure 3). This might be due to the electron-richness of the substrates. As a result, we obtained a mixture of the corresponding homoallylic alcohol and dimer in an 88:12 ratio in both cases, checked by proton NMR at 5.02 ppm. Nevertheless, both syntheses were continued without further purification.

6.2. TRANSFORMATION OF THE ALCOHOL INTO A SULFONE

The next step was the substitution of the alcohol into a sulfone. The strategy proposed went through a transformation of the alcohol into a suitable leaving group via an Appel reaction at room temperature for an hour. The reaction afforded an apolar intermediate that was not isolated, but it was purified by filtration in hexanes to remove the remaining triphenylphosphine oxide.

The yellow oils were redissolved in anhydrous isopropanol and heated in a pressure tube affording sulfones **8a** and **8b** through a nucleophilic substitution reaction with sodium phenyl sulfinate (Scheme 10). The homoallylic sulfones were purified by column chromatography and the corresponding by-products were easily separated as expected.



Scheme 10. Transformation of the homoallylic alcohols into sulfones in two steps.

6.3. HYDROGENATION OF HOMOALLYLIC SULFONES

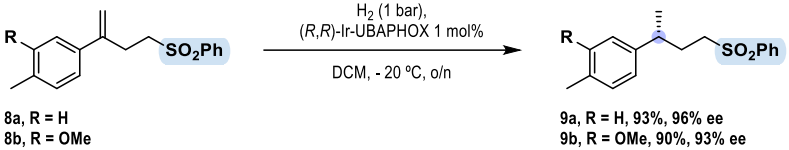
6.3.1. Racemic Pd-catalyzed hydrogenation

With the aim to explore the possibilities of the proposed pathway, we performed a hydrogenation using palladium on carbon as heterogeneous catalyst. This way, we obtained the corresponding racemic sulfones to work in parallel with their enantioenriched analogues (Scheme 11).

Scheme 11. Pd-catalyzed racemic hydrogenation of our homoallylic sulfones.

6.3.2. Ir-catalyzed asymmetric hydrogenation

Having attested the potential and applications of the Ir-Ubaphox catalyst in Marina Bellido's PhD Thesis, we conducted the Ir-catalyzed asymmetric hydrogenation of our homoallylic sulfones at 1 mol% of catalyst loading (Scheme 12).



Scheme 12. Ir-catalyzed asymmetric hydrogenation of our homoallylic sulfones.

The samples were placed into a pressure vessel, charged with 1 barG of H_2 and stirred at −20 °C overnight. Both reactions gave good yields after column chromatography and excellent enantioselectivities. The enantiopurity results were obtained using chiral High-Performance Liquid Chromatography (HPLC) techniques, as shown in Figure 4 for both racemic and enantiopure **9a**.

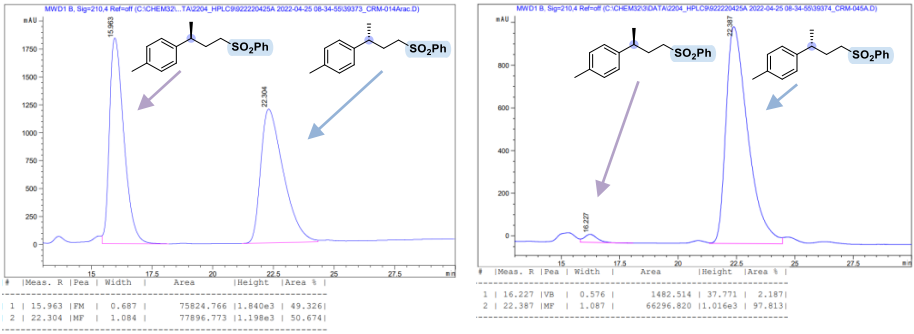
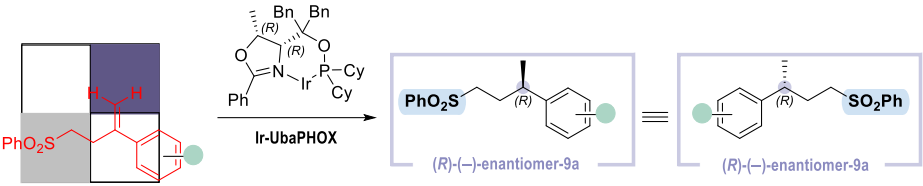


Figure 4. HPLC spectra of **9a** racemic and enantiopure forms, respectively.

6.3.3. Application of the quadrant diagrams model to predict the stereochemical outcome

Based on the previously described theoretical quadrant model, we could also predict the stereochemical outcome of enantioenriched products **9a** and **9b**. Considering that we changed the chirality of the catalyst to the (*R*,*R*)-enantiomer to obtain the desired product **9a**, the new quadrant model is the opposite (Scheme 13).



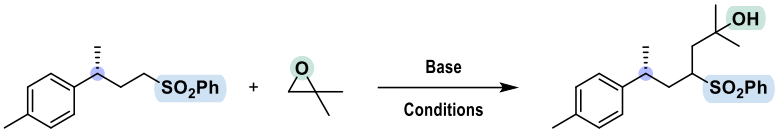
Scheme 13. Quadrant diagram model for our catalyst/substrate system.

This model was confirmed by the rotation of the plane of light in the polarimeter obtained which was levorotary (−).

6.4. EPOXIDE RING OPENING

With the installed stereocenter, we proceeded by introducing an alkyl group at the α-position of the sulfone by means of α-deprotonation and treatment with an epoxide as the electrophile. A small screening was performed to obtain the optimal conditions summarized in Table 1.

Table 1. Optimization study of the alkylation reaction.

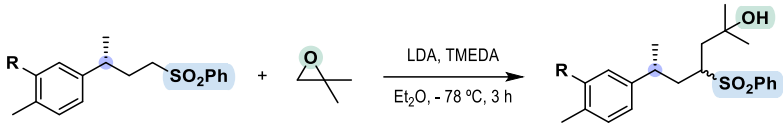


9a 10a

Entry	Base	Solvent	Conditions	Yield [%]
1	*n*-BuLi (1.1 eq)	THF	−78 ºC to r.t., overnight	0
2	**LDA (4 eq)**	THF	TMEDA, −50 ºC to 0 ºC, overnight	10
3	LDA (4 eq)	**Et_2O**	**TMEDA, −78 ºC to 0 ºC, 3 h**	58

The acidity of the α-carbon of the sulfone allows its deprotonation with a base to convert it into a nucleophile. If the deprotonation is successful, this carbanion can attack several electrophiles. In our specific case, we expected the reaction to go through nucleophilic epoxide ring opening by attack in the less substituted carbon of the 2,2-dimethyloxirane.[32]

When using *n*-butyllithium as base in anhydrous tetrahydrofuran, a complex reaction mixture was observed in the crude. As a result, we changed the reaction conditions to a milder base such as LDA stabilized with TMEDA in diethyl ether (Scheme 14), allowing the full deprotonation and the alkylation to occur with satisfactory yields after column chromatography.

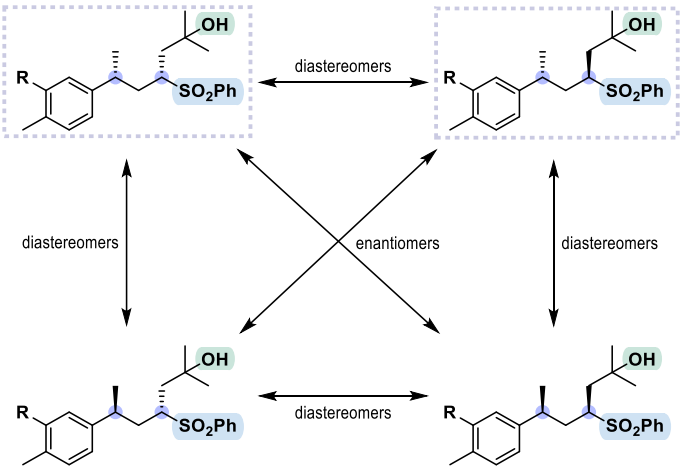


9a, R = H
9b, R = OMe

10a, R = H, 58%, dr 65:35
10b, R = OMe, 86%, dr 66:33

Scheme 14. Alkylation reaction of the sulfones.

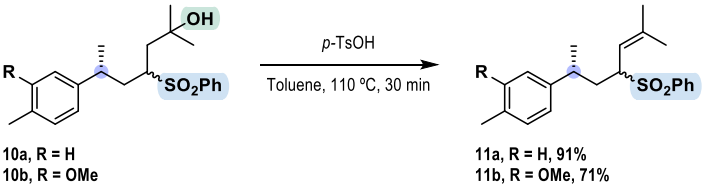
Consequently, we generated a new stereocenter which would disappear in future steps. As a result, we obtained a mixture of both diastereomers (Scheme 15) in a 66:33 ratio, checked by ^1H NMR analysis of **10a** and **10b**.



Scheme 15. Mixture of stereoisomers obtained and their corresponding enantiomers.

6.5. ALCOHOL DEHYDRATION

With the alkylated compound in hand, the next step consisted in the treatment of the alcohol with a strong acid such as *para*-toluenesulfonic acid to give the corresponding alkene (Scheme 16). The dehydration of the alcohol proceeds through a carbocation formation followed by an E1 reaction.



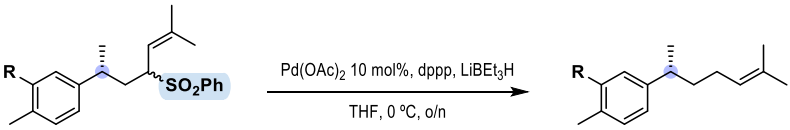
Scheme 16. Dehydration of the alcohol to give the corresponding olefin.

Although the tosylate anion is a very poor nucleophile and tends to form the elimination product, the reaction was carried out at high temperatures and reflux conditions to increase the elimination reaction relative to the substitution.

6.6. Pd-catalyzed desulfonylation

Without doubt, the most employed strategy for the desulfonylation of all types of sulfones is the reduction with metal amalgams, especially sodium amalgam. Nonetheless, the conditions of this methodology involve hazardous chemicals such as sodium or mercury.

With the purpose of achieving a greener synthetic route, we considered the possibility of introducing another catalytic step, in which the corresponding allylic sulfone would be desulfonylated with a Pd(0) catalyst in the presence of a hydride reagent (Scheme 17).[33] As a result, the selective alkyl–SO_2 bond cleavage was accomplished in moderate to good yields.



11a, R = H
11b, R = OMe

1, R = H (Curcumene), 87%
12b, R = OMe, 53%

Scheme 17. Pd-catalyzed desulfonylation.

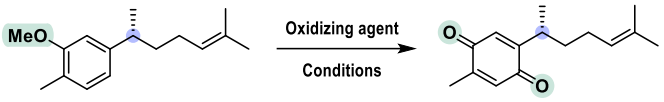
Thus, we finally synthesized and isolated α-curcumene **1** both in racemic and enantioenriched manner, affording our first objective. The low yield obtained in the synthesis of **12b** could be due to the presence of unwanted by-products which could have deactivated the Pd catalyst, since product **11b** was not purified.

6.7. Deprotection and oxidation

The last step consisted in the synthesis of the benzoquinone. With that purpose, we tried the oxidation of the intermediate **12b** with different oxidizing agents, as shown in Table 2.

Firstly, we tried a direct oxidative workup of the reaction mixture with ceric ammonium nitrate (CAN) in acetonitrile at 0 °C, to afford the corresponding quinone. Unfortunately, only the starting material was observed in the crude mixture by ^{1}H NMR studies. Next, we tried an environmentally friendly procedure based on the use of hydrogen peroxide (H_2O_2) as oxygen atom donor, but it did not work either because it oxidized the ring in different positions, giving a complex mixture. An ultimate attempt to directly oxidize the methoxy group was performed, using the commercially available Oxone® reagent as oxidizing agent, and a hypervalent iodine oxidant **(2-IB)** as a mediator. However, it did not work either.

Table 2. Oxidation of product **12b**.

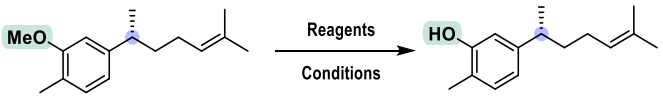


12b 2

Entry	Oxidizing agent	Conditions	Yield [%]
1	CAN	ACN, 0 ºC, 2 h	0
2	H_2O_2	HCOOH, r.t., overnight	0
3	Oxone®, 2-IB, H_2O_2	ACN / H2O, r.t., 3 h	0

In view of this situation, we thought that the problem could be the presence of the methoxy group in the benzene ring. Alternatively, we turned our attention into hydrolyzing it to obtain the corresponding phenol which is also an important natural product for cancer science, named Xanthorrhizol **13** (Table 3).

Table 3. Hydrolysis of the benzenic methoxy group.



12b 13

Entry	Reagents	Conditions	Yield [%]
1	1-Dodecanethiol, NaH	DMF, 160 ºC, 1 h	0
2	BBr_3	DCM, 0 ºC to r.t., overnight	0

The first attempt was performed in a pressure tube with dodecanethiol in presence of base until bubbling was observed. Then, product **12b** was added to the mixture. Disappointingly, no conversion was observed by ^{1}H NMR analysis. Next, we proceeded by trying with boron tribromide, a well-known strategy for methoxy deprotection. However, we had very low quantities of the desired product to work with, which resulted in an inaccessible purification. Further efforts will be invested in the improvement of this reaction to finally synthetize Curcuquinone **2**.

7. EXPERIMENTAL SECTION

7.1. MATERIALS AND METHODS

Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and used without further purification. All reactions that required anhydrous conditions were performed in oven-dried glassware under positive pressure of nitrogen. Dichloromethane and THF were degassed and anhydrised with a solvent purification system (SPS PS-MD-3). Solvents were removed under reduced pressure using rotary evaporators. Silica gel chromatography was performed using an automated chromatography system (PuriFlash® 430, Interchim).

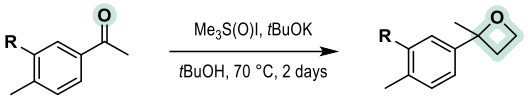
NMR spectroscopy: 1H and 13C were recorded on the NMR spectrometers of the Centres Científics i Tecnològics de la Universitat de Barcelona. The employed spectrometers were a Bruker 400 MHz and Bruker 500 MHz. Chemical shifts (δ) were referenced to internal solvent resonances and reported relative to TMS (tetramethylsilane). The coupling constants (*J*) are reported in Hertz (Hz).

High Resolution Mass Spectrometry: High resolution ESI-MS spectra were recorded in an LC/MSD-TOF G1969A (Agilent Technologies) of the Centres Científics i Tecnològics de la Universitat de Barcelona.

IR spectroscopy: IR spectra were measured in a Thermo Nicolet 6700 FT-IR spectrometer using an ATR system, of the Department of Organic Chemistry in the Universitat de Barcelona.

Optical rotations ($[\alpha]_D$) were measured at room temperature (28°C) using a Jasco P-2000 iRM- 800 polarimeter. Concentration is expressed in g/100 mL. The cell size is 10 cm long and has 1 mL of capacity, measuring λ was 589 nm, which corresponds to a sodium lamp.

7.2. General procedure 1: Preparation of 3,3-disubstituted oxetanes

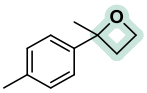


4a, R = H
4b, R = OMe

5a, R = H, 95%
5b, R = OMe, 98%

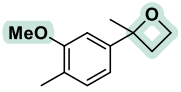
To a solution of trimethylsulfoxonium iodide (41.6 mmol, 5.0 equiv.) in *tert*-butanol (7.9mL/mmol of ketone), was added potassium *tert*-butoxide (41.6 mmol, 5.0 equiv.) in 4 portions. The reaction mixture was then heated to 50 °C and stirred for 30 minutes. A solution of the corresponding ketone (8.32 mmol, 1.0 equiv.) in *tert*-butanol (2.0 mL/ mmol of ketone) was added dropwise to the initial solution. Afterwards, the reaction mixture was heated to 70 ºC and stirred for 2 days. Water was added and the resulting layers were separated. The aqueous phase was extracted with hexane (x3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was redissolved in hexane and filtered for further purification. The analytical data for these compounds were in excellent agreement with the reported data.[26]

7.2.1. 2-methyl-2-(*p*-tolyl)oxetane, 5a



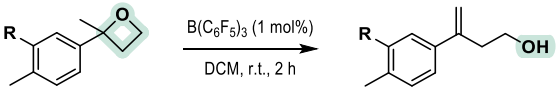
Following GP1, **5a** was obtained as a yellow oil (2.29 g, 14.2 mmol, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (ddt, 2H), 7.19 (ddt, 2H), 4.62 (ddd, J = 8.6, 6.6, 5.9 Hz, 1H), 4.52 (ddd, J = 8.7, 6.9, 5.9 Hz, 1H), 2.84 – 2.68 (m, 2H), 2.36 (s, 3H), 1.72 (s, 3H).

7.2.2. 2-(3-methoxy-4-methylphenyl)-2-methyloxetane, 5b



Following GP1, **5b** was obtained as an orange oil (1.14 g, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (dq, J = 7.6, 0.8 Hz, 1H), 6.96 (d, J = 1.7 Hz, 1H), 6.81 (dd, J = 7.6, 1.7 Hz, 1H), 4.63 (ddd, J = 8.5, 6.6, 5.9 Hz, 1H), 4.53 (ddd, J = 8.7, 7.0, 5.9 Hz, 1H), 3.87 (s, 3H), 2.85 – 2.69 (m, 2H), 2.22 (d, J = 0.8 Hz, 3H), 1.73 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 147.3, 130.3, 124.8, 115.2, 105.5, 86.7, 64.5, 55.3, 35.6, 30.8, 15.9. **HRMS (ESI)** calculated for $C_{12}H_{16}O_2$ 193.1223, found 193.1215 $[M+H]^+$. **IR (ATR-FTIR)** ν_{max} = 3448, 2964, 2923, 2879, 1612, 1581, 1368, 1200, 1092, 720, 631 cm^{-1}.

7.3. GENERAL PROCEDURE 2: PREPARATION OF HOMOALLYLIC ALCOHOLS

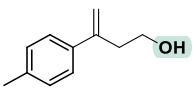


5a, R = H
5b, R = OMe

6a, R = H
6b, R = OMe

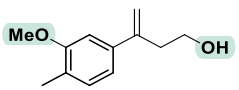
An oven dried round bottom flask with a stirring beam was taken into the GloveBox and $B(C_6F_5)_3$ (0.04 mmol, 0.005 equiv.) was weighted. The flask was taken out of the GloveBox and the corresponding oxetane (8 mmol, 1.0 equiv.) was dissolved in anhydrous dichloromethane (10mL/mmol). The reaction mixture was stirred for 2 hours at room temperature. Afterwards, water was added, and the two resulting layers were separated. The aqueous layer was extracted with DCM (x2) and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was further purified by flash column chromatography. The analytical data for these compounds were in excellent agreement with the reported data.[26]

7.3.1. 3-(p-tolyl)but-3-en-1-ol, 6a



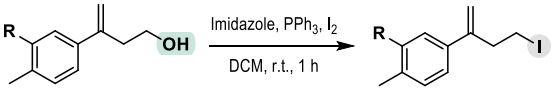
Following GP2, **6a** was obtained as a yellow oil (1.006 g, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.39 (d, J = 1.5 Hz, 1H), 5.34 (s, 0H), 5.12 (q, J = 1.3 Hz, 1H), 5.09 (s, 0H), 3.73 (t, J = 6.3 Hz, 2H), 2.78 (td, J = 6.4, 1.2 Hz, 2H), 2.35 (s, 4H).

7.3.2. 3-(3-methoxy-4-methylphenyl)but-3-en-1-ol, 6b



Following GP2, **6b** was obtained as a transparent oil (0.73 g, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.11 – 7.05 (m, 2H), 5.57 (d, *J* = 1.4 Hz, 1H), 5.30 (q, *J* = 1.3 Hz, 1H), 4.03 (s, 3H), 3.96 – 3.86 (m, 2H), 2.96 (td, *J* = 6.4, 1.1 Hz, 2H), 2.40 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 145.0, 139.3, 130.4, 126.3, 118.0, 113.8, 107.9, 61.0, 55.2, 38.7, 15.9. **HRMS (ESI)** calculated for $C_{12}H_{16}O_2$ 193.1223, found 193.1223 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3357, 2938, 1608, 1572, 1204, 1173, 816, 766 cm^{-1}.

7.4. GENERAL PROCEDURE 3: IODINATION OF ALCOHOLS

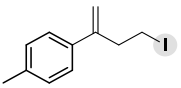


6a, R = H
6b, R = OMe

7a, R = H
7b, R = OMe

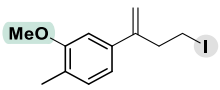
The corresponding alcohol (12.6 mmol, 1.0 equiv.), imidazole (17.7 mmol, 1.4 equiv.) and triphenylphosphine (15.1 mmol, 1.2 equiv.) were added to a 250 mL Schlenk flask and purged under N_2 atmosphere. The reactants were then dissolved in anhydrous dichloromethane (60 mL). Iodine (12.6 mmol, 1 equiv.) was added carefully to the mixture stopping the addition once the solution turns yellow. The reaction mixture was stirred at room temperature for 1 hour. Afterwards, water was added, and the two resulting layers separated. The aqueous phase was extracted with DCM (x3), the resulting organic layers were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was then redissolved in hexane and filtered to remove the remaining triphenylphosphine oxide. The desired products were used for the following step without further purification.

7.4.1 1-(4-iodobut-1-en-2-yl)-4-methylbenzene, 7a



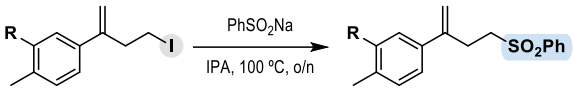
Following GP3, **7a** was obtained as a yellow oil (3.48 g**). ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.16 – 7.13 (m, 2H), 5.35 (d, J = 1.2 Hz, 1H), 5.07 (q, J = 1.2 Hz, 1H), 3.24 – 3.17 (m, 2H), 3.07 – 3.00 (m, 2H), 2.34 (s, 3H).

7.4.2. 4-(4-iodobut-1-en-2-yl)-2-methoxy-1-methylbenzene, 7b



Following GP3, **7b** was obtained as a yellow oil (4.70 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.78 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 5.28 (d, *J* = 1.1 Hz, 1H), 5.02 (q, *J* = 1.2 Hz, 1H), 3.78 (s, 3H), 3.15 (ddd, *J* = 7.9, 7.3, 0.8 Hz, 2H), 2.98 (ddt, *J* = 8.3, 7.5, 0.9 Hz, 2H), 2.14 (s, 3H).

7.5. General procedure 4: Formation of Homoallylic Sulfones

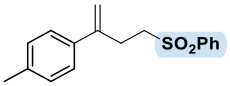


7a, R = H
7b, R = OMe

8a, R = H
8b, R = OMe

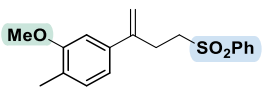
The corresponding iodine (12.1 mmol, 1 equiv.) and sodium phenyl sulfinate (36.4 mmol, 3 equiv.) were added to a 100 mL round bottom flask and dissolved in isopropyl alcohol (3mL/mmol of iodine). Afterwards, the flask was sealed, and the solution was heated to 100 ºC and stirred overnight. The reaction mixture was filtered through a filter funnel. The solvent was removed under reduced pressure and the resulting oil was purified by flash column chromatography.

7.5.1 1-methyl-4-(4-(phenylsulfonyl)but-1-en-2-yl)benzene, 8a



Following GP4, **8a** was obtained as a yellow oil (0.40 g, 29% yield).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.71 – 7.65 (m, 1H), 7.62 – 7.51 (m, 2H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 2H), 5.28 (d, J = 0.9 Hz, 1H), 5.03 (q, J = 1.2 Hz, 1H), 3.34 – 3.15 (m, 2H), 3.01 – 2.87 (m, 2H), 2.33 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9, 139.0, 137.9, 136.1, 133.7, 129.3, 129.3, 128.1, 125.7, 113.5, 55.0, 28.4, 21.1. **HRMS (ESI)** calculated for $C_{17}H_{18}O_2S$ 309.092, found 309.0919 $[M+Na]^+$. **IR** (ATR-FTIR) ν_{max} = 2956, 2919, 1624, 1583, 1511, 1446, 1295, 1155, 1132, 1083, 907, 828^{-1}.

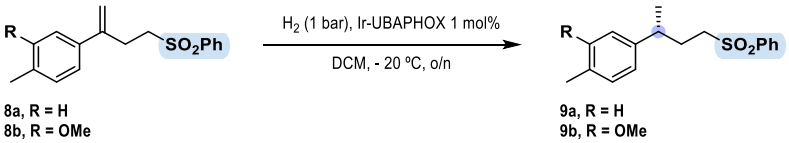
7.5.2. 2-methoxy-1-methyl-4-(4-(phenylsulfonyl)but-1-en-2-yl)benzene, 8b



Following GP4, **8b** was obtained as yellow oil (0.55 g, 40% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.64 – 7.56 (m, 1H), 7.56 – 7.45 (m, 2H), 6.97 (dd, J = 8.1, 0.8 Hz, 1H), 6.67 (d, J = 1.7 Hz, 1H), 6.66 (q, J = 1.8 Hz, 2H), 5.22 (d, J = 0.9 Hz, 1H), 4.97 (q, J = 1.2 Hz, 1H), 3.72 (s, 3H), 3.17 – 3.08 (m, 2H), 2.90 – 2.81 (m, 2H), 2.12 (d, J = 0.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8, 144.3, 139.0, 137.9, 133.7, 130.6, 129.3, 128.1, 126.7, 117.8, 113.6, 107.6, 60.4, 55.2, 55.0, 28.5, 15.9. **HRMS (ESI)** calculated for $C_{18}H_{20}O_3S$ 317.1206, found 317.1207 $[M+H]^+$.

IR (ATR-FTIR) ν_{max} = 2920, 1608, 1572, 1506, 1463, 1406, 1304, 1236, 1147, 1131, 1084, 1035, 893 cm^{-1}.

7.6. General procedure 5: Hydrogenation of homoallylic sulfones

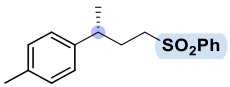


8a, R = H
8b, R = OMe

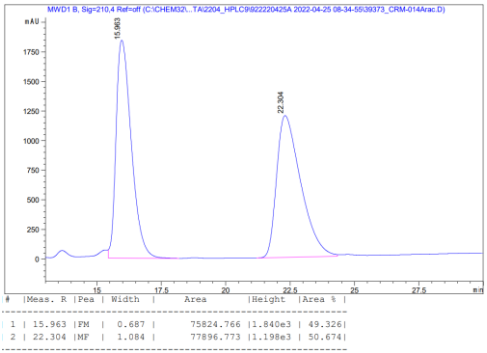
9a, R = H
9b, R = OMe

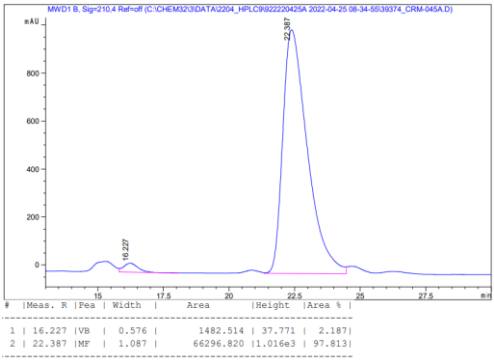
In a low-pressure reactor filled with sand, into a vial equipped with PTFE-coated stir-bar, the corresponding sulfone (0.21 mmol, 1.0 equiv.) and catalyst (0.002 mmol, 0.01 equiv.) were added and dissolved in anhydrous dichloromethane (0.1 M). Once sealed, the reactor was purged and charged with 1 bar of H_2. The reaction was left stirring at – 20 ºC for 23 h. The conversion was measured by ^{1}H-NMR spectroscopy and the enantiomeric excess using chiral HPLC chromatography.

7.6.1. 1-methyl-4-(4-(phenylsulfonyl)-2-butan-2-yl)benzene, 9a

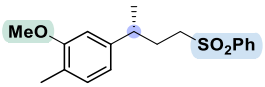


Following GP5, **9a** was obtained as a white solid (0.19 g, 93% yield, 96% ee). **Mp =** 89.0 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.68 – 7.61 (m, 1H), 7.58 – 7.50 (m, 2H), 7.10 – 7.04 (m, 1H), 6.98 – 6.93 (m, 2H), 2.97 (ddd, J = 14.0, 11.2, 5.3 Hz, 1H), 2.88 (ddd, J = 14.0, 11.1, 4.9 Hz, 1H), 2.30 (s, 3H), 2.02 (ddt, J = 13.6, 10.9, 5.4 Hz, 1H), 1.93 (dddd, J = 13.5, 11.1, 9.5, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 139.3, 136.3, 133.7, 129.5, 129.4, 128.1, 126.8, 54.8, 38.6, 30.6, 22.6, 21.1. **HRMS (ESI)** calculated for $C_{17}H_{20}O_2S$ 289.1257, found 289.1263 [M+H]+. **IR** (ATR-FTIR) ν_{max} = 3057, 2949, 2925, 2865, 1584, 1151, 1443, 1308, 1284, 1152, 1134, 953 cm^{-1}. **HPLC:** Chiralcel OJ. Aprox: 3.0 mg/mL. Heptane / iPrOH 60:40, 0.5 mL/min, λ = 210 nm. $t_{min}(+)$ = 16.3 min, $t_{min}(-)$ = 22.4 min. The analytical data for this compound were in excellent agreement with the reported data.[25] **[α]$_D$**: −12.5 (c 0.12, $CHCl_3$).

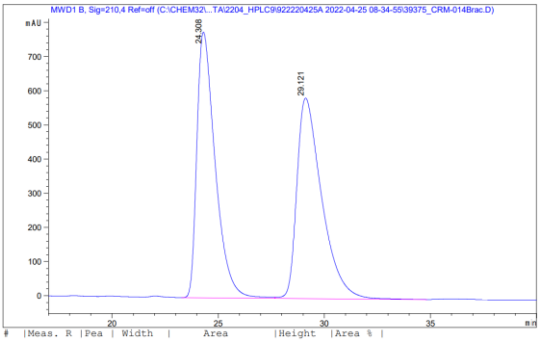




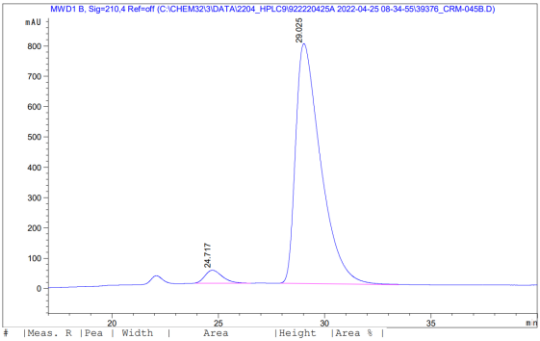
7.6.2. 2-methoxy-1-methyl-4-(4-(phenylsulfonyl)-2-butan-2-yl)benzene, 9b



Following GP5, **9b** was obtained as a yellow oil (0.15 g, 90% yield, 93% ee). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.79 (m, 2H), 7.69 – 7.60 (m, 1H), 7.59 – 7.50 (m, 2H), 7.01 (dd, J = 7.5, 0.9 Hz, 1H), 6.59 – 6.51 (m, 2H), 3.78 (s, 3H), 3.05 – 2.84 (m, 2H), 2.78 – 2.65 (m, 1H), 2.17 (s, 3H), 2.10 – 1.86 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 143.6, 139.2, 133.6, 130.7, 129.2, 128.0, 124.9, 118.4, 108.4, 55.2, 54.6, 38.9, 30.5, 22.5, 15.8. **HRMS (ESI)** calculated for $C_{18}H_{22}O_3S$ 341.1182, found 341.1182 $[M+Na]^+$. **IR** (ATR-FTIR) ν_{max} = 2957, 1610, 1581, 1503, 1446, 1413, 1304, 1254, 1139, 1085, 1037 cm^{-1}. **HPLC:** Chiralcel OJ. Aprox: 3.0 mg/mL. Heptane / iPrOH 80:20, 0.5 mL/min, λ = 210 nm. $t_{min}(+)$ = 24.7 min, $t_{maj}(-)$ = 29.0 min. **[α]$_D$**: −12.1 (c 0.2, $CHCl_3$).

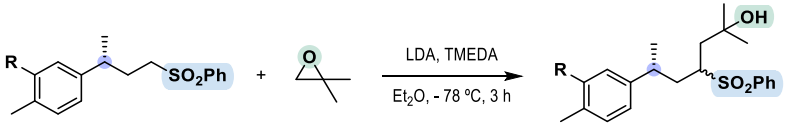


#	Meas. R	Pea	Width	Area	Height	Area %
1	24.308	BV	0.887	46619.809	777.715	49.399
2	29.121	VB	1.163	47754.629	586.804	50.601



#	Meas. R	Pea	Width	Area	Height	Area %
1	24.717	MM	0.940	2403.526	42.631	3.577
2	29.025	MM	1.366	64798.102	790.633	96.423

7.7. GENERAL PROCEDURE 6: NUCLEOPHILE EPOXIDE OPENING



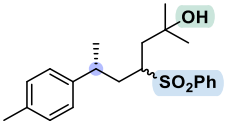
9a, R = H
9b, R = OMe

10a, R = H, 58%, dr 65:35
10b, R = OMe, 86%, dr 66:33

The corresponding sulfone was added to a 10 mL round bottom flask and dissolved in diethyl ether (3 mL), under a static N_2 atmosphere, at -78 ºC. Afterwards, LDA and TMEDA were added dropwise. Immediately after, 2,2-dimethyloxirane was added and the solution was allowed to slowly reach 0 ºC with stirring for 4 hours. The reaction was quenched by the

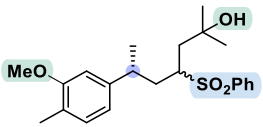
addition of water, and the aqueous phase was extracted with ethyl acetate. The organic layers were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting oil was purified by flash column chromatography.

7.7.1. 2-methyl-4-(phenylsulfonyl)-6-(p-tolyl)-6-heptan-2-ol, 10a



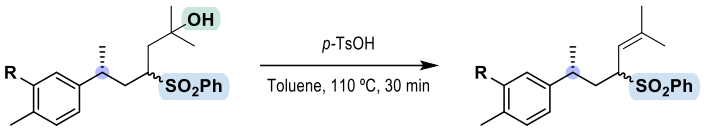
Following GP6, **10a** was obtained as a colorless oil (72 mg, 58% yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.74 – 7.66 (m, 1H), 7.60 – 7.52 (m, 2H), 6.87 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 3.32 (s, 1H), 3.04 (ddt, J = 10.0, 7.5, 2.3 Hz, 1H), 2.72 (dqd, J = 10.8, 6.9, 3.9 Hz, 1H), 2.43 (dd, J = 16.1, 7.5 Hz, 1H), 2.26 (s, 3H), 2.02 (ddd, J = 13.9, 11.4, 2.4 Hz, 1H), 1.74 (dd, J = 16.1, 2.2 Hz, 1H), 1.66 (ddd, J = 14.2, 10.3, 3.9 Hz, 1H), 1.28 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.0, 137.1, 135.9, 133.7, 129.3, 129.1, 129.1, 129.0, 126.5, 68.8, 58.9, 41.0, 38.0, 36.2, 31.5, 28.6, 24.5, 20.9. **HRMS (ESI)** calculated for $C_{21}H_{28}KO_3S$ 399.1391, found 399.1392 $[M+K]^+$. **IR (ATR-FTIR)** ν_{max} = 3508, 2964, 2924, 2869, 1282, 1139, 1083, 816 cm^{-1}.

7.7.2. 6-(3-methoxy-4-methylphenyl)-2-methyl-4-(phenylsulfonyl)-6-heptan-2-ol, 10b



Following GP6, **10b** was obtained as a yellow oil (0.21 g, 86% yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 2H), 7.71 – 7.64 (m, 1H), 7.56 – 7.50 (m, 2H), 6.81 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.14 (dd, *J* = 7.5, 1.7 Hz, 1H), 3.81 (s, 1H), 3.65 (s, 3H), 3.29 (s, 1H), 3.11 (ddt, *J* = 10.0, 7.5, 2.3 Hz, 1H), 2.79 – 2.67 (m, 1H), 2.42 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.13 (d, *J* = 0.8 Hz, 3H), 1.75 (dd, *J* = 16.0, 2.3 Hz, 1H), 1.66 (ddd, *J* = 14.1, 10.3, 3.9 Hz, 1H), 1.55 (s, 3H), 1.29 (s, 3H), 1.13 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.8, 143.0, 137.1, 133.6, 130.7, 129.2, 129.1, 129.0, 124.8, 118.1, 108.7, 68.8, 58.9, 55.1, 41.2, 40.1, 38.4, 36.8, 31.5, 28.8, 24.3, 15.8. **HRMS (ESI)** calculated for $C_{22}H_{31}O_4S$ 391.1938, found 391.1943 $[M+H]^+$.

7.8. GENERAL PROCEDURE 7: DEHYDRATION

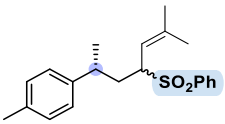


10a, R = H
10b, R = OMe

11a, R = H
11b, R = OMe

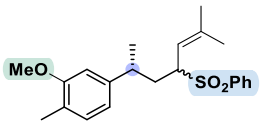
To a solution of the corresponding sulfone in dry toluene (50 ml) were added a few crystals of *p*-toluenesulfonic acid. The solution was refluxed for 30 min and allowed to cool down to room temperature. Water was added and the reaction mixture was extracted with diethyl ether. The extracts were dried over $MgSO_4$, and the ether was removed under reduced pressure. **8a** and **8b** were obtained as yellow oils.

7.8.1. 1-methyl-4-(6-methyl-4-(phenylsulfonyl)-2-hept-5-en-2-yl)benzene, 11a



Following GP7, **11a** was obtained as yellow oil (0.22 g, 91% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H), 7.52 – 7.48 (m, 1H), 7.41 – 7.36 (m, 2H), 7.00 – 6.95 (m, 3H), 6.86 – 6.80 (m, 2H), 4.87 (dp, *J* = 10.4, 1.5 Hz, 1H), 3.28 (ddd, *J* = 11.7, 10.3, 2.8 Hz, 1H), 2.57 (ddt, *J* = 13.8, 6.9, 3.6 Hz, 1H), 2.35 – 2.28 (m, 1H), 2.23 (s, 3H), 1.85 (ddd, *J* = 13.2, 11.7, 3.6 Hz, 1H), 1.61 (d, *J* = 1.4 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 141.5, 137.9, 135.9, 133.1, 129.2, 129.1, 128.6, 127.0, 126.7, 117.5, 116.9, 63.6, 63.3, 36.7, 35.0, 25.8, 23.9, 21.0, 21.0, 17.9. **HRMS (ESI)** calculated for $C_{21}H_{26}NaO_2S$ 365.1546, found 365.1553 $[M+Na]^+$.

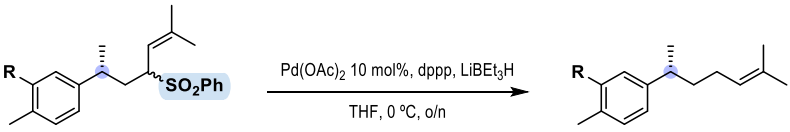
7.8.2. 2-methoxy-1-methyl-4-(6-methyl-4-(phenylsulfonyl)-2-hept-5-en-2-yl)benzene, 11b



Following GP7, **11b** was obtained as yellow oil (31 mg, 71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 2H), 7.60 – 7.54 (m, 1H), 7.48 – 7.43 (m, 2H), 6.98 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.52 (d, *J* = 1.6 Hz, 1H), 6.50 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.95 (dp, *J* = 10.4, 1.4 Hz, 1H), 3.78 (s, 3H), 3.39 (ddd, *J* = 11.7, 10.3, 2.7 Hz, 1H), 2.64 (ddq, *J* = 13.9, 6.9, 3.5 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.17 (s, 3H), 1.96 – 1.89 (m, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.28 – 1.23 (m, 3H), 0.83 (d, *J* = 1.4 Hz, 3H).

HRMS (ESI) calculated for $C_{22}H_{28}NaO_3S$ 395.1651, found 395.1657 $[M+Na]^+$.

7.9. General procedure 8: Palladium catalysed desulfonylation

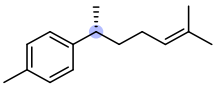


11a, R = H
11b, R = OMe

12a, R = H (Curcumene)
12b, R = OMe

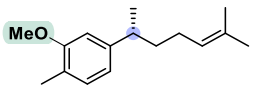
To a solution of the corresponding allyl sulfone, palladium (II) acetate (2.20 mg, 4.89 µmol) and 1,3-bis(diphenylphosphano)propane complex (dppp) (4.00 mg, 4.89 µmol) in dry THF (3 mL), was added a solution of lithium triethylhydroborate ($LiBEt_3H$) (1.0 M in THF, 29.0 mL, 29.0 mmol) at 0 °C under a static N_2 atmosphere. The mixture was stirred at 4 °C overnight, then was diluted with a saturated NH_4Cl solution and extracted with ethyl acetate. The extracts and the organic layer were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (80 g, 40:1 hexane/ethyl acetate) to give the product as a yellow oil.

7.9.1. 1-methyl-4-(6-methyl-2-hept-5-en-2-yl)benzene, 12a



Following GP8, **12a** was obtained as a yellow oil (17 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.8 Hz, 4H), 5.09 (tdq, *J* = 7.1, 2.8, 1.4 Hz, 1H), 2.74 – 2.58 (m, 1H), 2.31 (s, 3H), 1.94 – 1.81 (m, 2H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.63 – 1.54 (m, 2H), 1.52 (d, *J* = 1.3 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H). The analytical data for this compound were in excellent agreement with the reported data.

7.9.2. 2-methoxy-1-methyl-4-(6-methyl-2-hept-5-en-2-yl)benzene, 9b

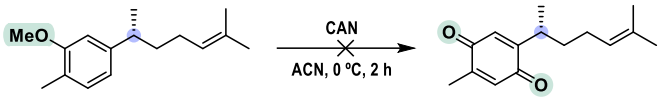


Following GP8, **12b** was obtained as a colorless oil (27 mg, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.62 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 5.03 (ddq, *J* = 8.6, 5.7, 1.5 Hz, 1H), 3.75 (s, 3H), 2.66 – 2.50 (m, 1H), 2.11 (s, 3H), 1.87 – 1.76 (m, 2H), 1.60 (q, *J* = 1.3 Hz, 3H), 1.57 – 1.49 (m, 2H), 1.46 (d, *J* = 1.3 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** ($CDCl_3$) δ

157.6, 146.7, 131.4, 130.3, 124.6, 123.8, 118.7, 108.9, 55.2, 39.5, 38.4, 26.2, 25.8, 25.7, 22.5, 17.7, 15.8. **HRMS (ESI)** calculated for $C_{16}H_{25}O$ 233.1900, found 233.1905 $[M+H]^+$.

7.10. GENERAL PROCEDURE 9: OXIDATION ATTEMPTS

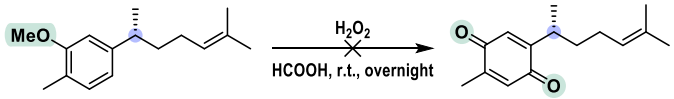
7.10.1. Ceric ammonium nitrate



12b 2

To a round bottom flask containing **9b** (0.095 mmol, 22 mg) was added cerium ammonium nitrate (0.13 mmol, 96 mg). Then, the mixture was dissolved in ACN (1 mL) under N_2 atmosphere. The reaction mixture was left stirring for 2 h in the fridge. Then, the organic phase was separated, and the filtrate was extracted with diethyl ether and then concentrated in vacuo. The product was analyzed by ^{1}H NMR studies.

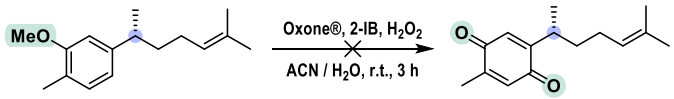
7.10.2. Hydrogen peroxide



12b 2

To a suspension of **9b** (0.095 mmol, 22 mg) in formic acid (5 mL) was added aqueous hydrogen peroxide (1 mL). The reaction mixture was stirred overnight at room temperature under N_2 atmosphere. The solution was poured into water and the products were extracted with DCM. The organic layer was washed with water, and dried over $MgSO_4$. The product was analyzed by ^{1}H NMR studies.

7.10.3. Oxone®

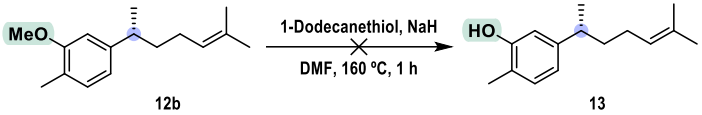


12b 2

To a suspension of **9b** (0.026 mmol, 6 mg), organoiodine catalyst **2-IB** (1.0 equiv., 6.4 mg) and Oxone® (10 equiv., 0.13 mmol, 80 mg) was added water (0.7 mL) and ACN (0.7 mL). Then, 10M H_2O_2 (5.0 equiv., 0.12 mol, 12 µL) was added to the mixture. After the mixture was stirred for 3 h at room temperature, the crude was analyzed by ^{1}H NMR studies.

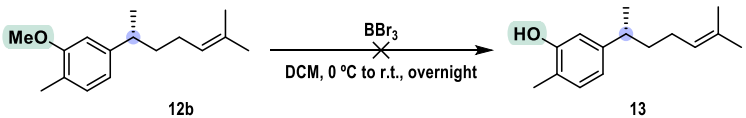
7.11. General procedure 10: Deprotection attempts

7.11.1. Dodecanethiol



To a suspension of 1-dodecanethiol (5 equiv., 0.19 mmol, 39 mg) dissolved in dimethylformamide (1 mL), in a pressure tube, was added sodium hydride (5 equiv., 0.038 mmol, 8 mg). The reaction mixture was stirred for 1 min, until bubbling was observed. Then, **9b** (0.039 mmol, 9 mg) was added to the reaction mixture with 2 mL DMF. Then, the tube was sealed, and the reaction mixture was left stirring for 1 h at 160 ºC. The solution was poured into water and the products were extracted with dioxane. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The product was analyzed by ^{1}H NMR studies.

7.11.2. Boron tribromide



To a dry 25 mL round bottom flask equipped with a stir bar and septum was added **9b** (0.039 mmol, 9 mg) followed by the addition of dry dichloromethane (1 mL). The solution was cooled down to 0 ºC. Then, BBr_3 (80 µL, 1M) was added slowly through the septum with stirring, under a N_2 atmosphere. The reaction was left to stir overnight at room temperature. The solvent was removed under reduced pressure and the resulting product was purified by flash column chromatography.

8. CONCLUSIONS

The main aim of this work was to demonstrate the applicability of our group's recently developed methodologies by synthetizing two natural products, curcumene and curcuquinone.

Thus, we have expanded the scope of the synthesis and the isomerization reaction to obtain homoallylic alcohols to other substrates with more electron-rich substituents, obtaining great results.

Those alcohols have been successfully converted into homoallylic sulfones and have overcome the impurities problems due to their easier purification.

The Ir-catalyzed asymmetric hydrogenation of the homoallylic sulfones has worked excellently, providing full conversion and enantiomeric excess of 96% and 93%, respectively.

Finally, the total synthesis of Curcumene **1** both racemic and enantioselective has worked perfectly, being the first reported synthesis to include an Ir-catalyzed asymmetric hydrogenation reaction for this type of substrate. The synthetic route proposed has proven to be very versatile and opens up new possibilities through the use of sulfones as building blocks.

On the other hand, several different conditions have been tested for the last step of the synthesis of curcuquinone. Unfortunately, it could not be synthetized. Further efforts will be invested in the improvement of this reaction to finally synthetize Curcuquinone **2**.

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10. ACRONYMS

ACN	Acetonitrile
CAN	Cerium (IV) ammonium nitrate
Conv.	Conversion
δ	Chemical shift
DCM	Dichloromethane
DMF	Dimethylformamide
dppp	1,3-Bis(diphenylphosphino)propane
E	Electrophile
ee	Enantiomeric excess
Equiv.	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
GP	General procedure
IPA	2-Propanol
iPr	Isopropyl
HRMS	High resolution mass spectrometry
2-IB	2-iodobenzoic acid
IR	Infrared spectroscopy
LG	Leaving group
LDA	Lithium diisopropylamide
m/z	Mass-to-charge ratio
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ppm	Part per million
r.t.	Room temperature
S_N2	Secondary nucleophilic substitution
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
*t*Bu	*Tert*-butyl