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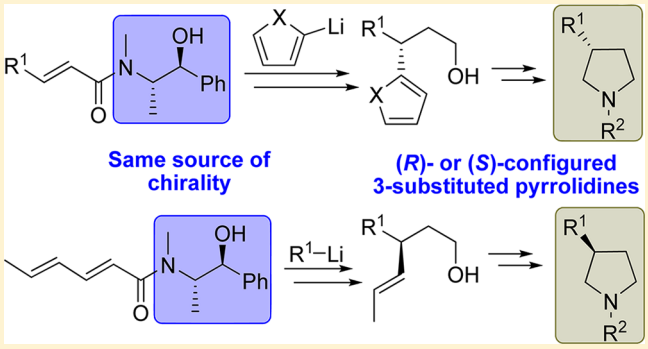
# Using Heteroaryl-lithium Reagents as Hydroxycarbonyl Anion Equivalents in Conjugate Addition Reactions with (*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary; Enantioselective Synthesis of 3-Substituted Pyrrolidines

Beatriz Alonso, Marta Ocejo, Luisa Carrillo,* Jose L. Vicario,* Efraim Reyes, and Uxue Uria

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, P.O. Box 644, E-48080 Bilbao, Spain

Supporting Information

**ABSTRACT:** We have developed an efficient protocol for carrying out the stereocontrolled formal conjugate addition of hydroxycarbonyl anion equivalents to $\alpha,\beta$-unsaturated carboxylic acid derivatives using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary, making use of the synthetic equivalence between the heteroaryl moieties and the carboxylate group. This protocol has been applied as key step in the enantioselective synthesis of 3-substituted pyrrolidines in which, after removing the chiral auxiliary, the heteroaryl moiety is converted into a carboxylate group followed by reduction and double nucleophilic displacement. Alternatively, the access to the same type of heterocyclic scaffold but with opposite absolute configuration has also been accomplished by making use of the regio- and diastereoselective conjugate addition of organolithium reagents to $\alpha,\beta,\gamma,\delta$-unsaturated amides derived from the same chiral auxiliary followed by chiral auxiliary removal, ozonolysis, and reductive amination/intramolecular nucleophilic displacement sequence.




## INTRODUCTION

The pyrrolidine skeleton is a structural motif shared by many different natural products and synthetic bioactive compounds.[1] The ubiquitous occurrence of this heterocyclic moiety either as itself or as a part of a more complex chemical entity has led to active research toward the development of efficient procedures for the stereocontrolled preparation of pyrrolidines incorporating different substitution patterns.[2] In this context, simple 3-alkyl- or 3-aryl-substituted pyrrolidines constitute a particularly interesting subgroup of compounds with interesting pharmacologic activities. Representative examples are depicted in Figure 1 and include several well-known pharmaceuticals such as premafloxacin,[3] an antibiotic for veterinary use that has also shown potential for fighting against several cases of bacterial resistance to commonly used antibiotics; $\beta$-homoproline,[4] which is a conformationally restrained $\gamma$-amino acid that acts as a potent inhibitor of the neuronal and glial uptake mechanism of $\gamma$-aminobutyric acid neurotransmitter; and also the antidepressant rolipram,[5] which is based on a related 3-arylpyrrolidin-2-one structure. In addition, this type of structure can also be found in a few natural products such as, for example, leptothoracine and other simple *N*-alkylated 3-methylpyrrolidines,[6] which have been isolated from the poison gland of ants of the Leptothorax gender (*Myrmicinae* family). In addition, $\beta$-proline and homoproline derivatives have also found recent applicability as organocatalysts in several reactions proceeding *via* enamine formation.[7] However, despite their potential as lead compounds for drug discovery or as promising

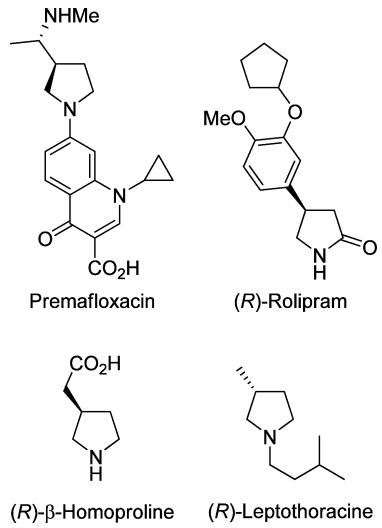



**Figure 1.** Some representative examples of important 3-alkyl and 3-aryl pyrrolidines.

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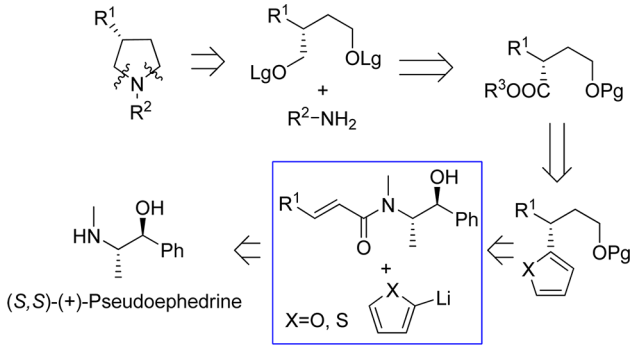
candidates to be used as organocatalysts, the number of reports dealing with the development of procedures for the enantioselective preparation of these simple 3-substituted pyrrolidine scaffolds is significantly smaller,[8−10] especially compared with the huge amount of information appearing in the literature focused on the stereocontrolled preparation of other more elaborated pyrrolidines.

In general, the existing methodologies reported to date for the stereoselective preparation of 3-alkyl or 3-aryl pyrrolidines can be classified into two main different approaches. Most reports focus on the construction of the five-membered heterocyclic moiety by a ring-closure process,[8] typically involving an intramolecular reaction starting from a conveniently functionalized acyclic substrate that incorporates the required functionalities that will interact between each other in the cyclization reaction. Alternatively this ring-closing process can also consist of a [3 + 2] cycloaddition reaction,[9] in which the simultaneous formation of two C−C bonds accounts for the formation of the heterocyclic ring. The second most frequently used approach comprises the functionalization of commercially available pyrrolidines and related derivatives such as proline, pyrrolidin-2-ones, or maleimides among others.[10]

We wish to report herein our efforts directed toward the development of a practical and efficient protocol for the preparation of 3-alkyl or 3-aryl pyrrolidines as highly enantioenriched materials with a focus on their possible applicability as efficient organocatalysts for transformations proceeding *via* either enamine or iminium ion formation.[11] For this reason, we also decided to design a synthetic approach that should be flexible enough to allow the incorporation of substituents of different size and nature at the 3-position of the pyrrolidine ring and that also should allow the enantioselective preparation of both enantiomers, if possible, by using the same chirality source. In this context, we planned the access to these compounds by taking into account the possible application of our previously reported methodology for carrying out the conjugate addition of organometallic reagents to conjugated amides using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary as key reaction with regard to the installation of the stereocenter present at the final compounds (Scheme 1).[12] In this report, we

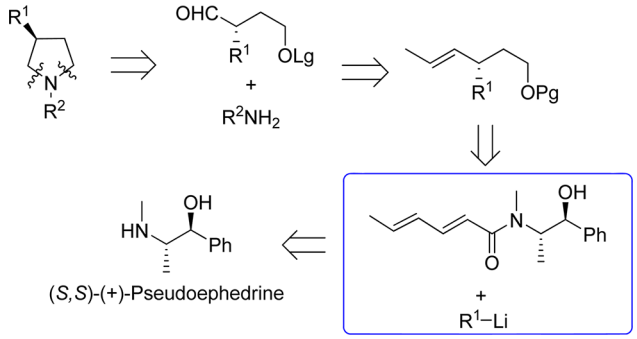
**Scheme 1**




have shown that organolithiums add selectively in a 1,4-fashion to $\alpha,\beta$-unsaturated amides incorporating this chiral aminoalcohol, furnishing the corresponding conjugate addition products in good yields and diastereoselectivities, and therefore we initially designed a first synthetic approach for the preparation of a 3-substituted pyrrolidine derivatives according to the retrosynthetic analysis indicated in Scheme 1. As is shown in this Scheme, simultaneous disconnection of the two C−N bonds shows that the pyrrolidine skeleton can be built up from a conveniently functionalized diol that, in turn, should be accessible from a highly enantioenriched 2-substituted 4-hydroxybutanoate derivative. The enantioselective preparation of this key intermediate was envisaged to be carried out by conjugate addition of an heteroaryl-lithium reagent to $\alpha,\beta$-unsaturated amides that incorporates (*S*,*S*)-(+)-pseudoephedrine as the stereocontrolling element, also having in mind the known feasibility of converting the heteroaryl moiety into a carboxylate by means of an oxidative cleavage process.[13] It has to be pointed out that, in overall, this initial synthetic plan called for the development of a convenient protocol for carrying out the formal conjugate addition of hydroxycarbonyl anion to $\alpha,\beta$-unsaturated acid derivatives making use of the synthetic equivalence between the heteroaryl moiety and the carboxylate group and also by exploiting our background knowledge on the use of pseudoephedrine as chiral auxiliary linked to the Michael acceptor in conjugate addition reactions.[14]

As an alternative approach, we also planned access to the same type of compounds by making use of our recently reported methodology for carrying out the conjugate addition of organolithium reagents to $\alpha,\beta,\gamma,\delta$-unsaturated amides also incorporating the same chiral $\beta$-aminoalcohol (*S*,*S*)-(+)-pseudoephedrine as auxiliary (Scheme 2).[15] In this case, the

**Scheme 2**




simultaneous formation of the two C−N bonds for building up the heterocycle was planned to be carried out by a cascade reductive amination/intramolecular nucleophilic substitution sequence, which in turn refers back to an $\alpha$-substituted 4-hydroxybutanal derivative as suitable precursor. We envisaged that the formyl group at this key substrate could be formed by ozonolysis starting from the corresponding alkene, the later being accessible in a stereocontrolled fashion by applying our aforementioned methodology for carrying out the regio- and diastereoselective 1,4-addition of organolithium reagents to the 2,4-hexadienamide derived from (*S*,*S*)-(+)-pseudoephedrine.

It should be pointed out at this point that, comparing these two approaches depicted in Schemes 1 and 2, in the second one the alkyl/aryl substituent of the final 3-substituted pyrrolidine would be incorporated at the organolithium reagent during the conjugate addition reaction to the dienamide substrate, whereas in the first one this substituent is supposed to be already installed at the initial Michael acceptor, which has to be used as the starting material. As a consequence of this and to the fact that in both cases the same chirality source is intended to be employed as stereocontrolling element in the generation of the stereocenter that ultimately will be present at the 3-substituted


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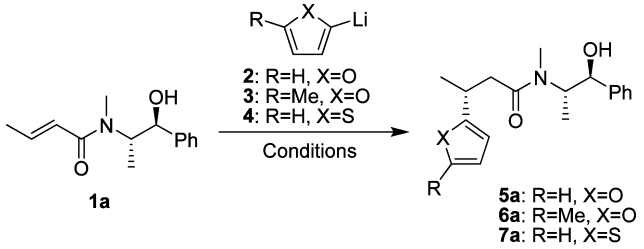
**Table 1. Diastereoselective Conjugate Addition of Heteroaryl-lithium Reagents to Crotonamide 1a Derived from (*S*,*S*)-(+)-Pseudoephedrine**




| entry | HetArLi[a] | product | additive | solvent | *T* (°C) | yield (%)[b] | dr[c] |
|---|---|---|---|---|---|---|---|
| 1 | **2** (2 equiv) | **5a** | LiCl (5 equiv) | THF | −105 | <5 | nd[d] |
| 2 | **2** (4 equiv) | **5a** | LiCl (5 equiv) | THF | −105 | 17 | 96:4 |
| 3 | **2** (4 equiv) | **5a** | LiCl (5 equiv) | THF | −78 | 30 | 96:4 |
| 4 | **2** (4 equiv) | **5a** | None | THF | −78 | 40 | 86:14 |
| 5 | **2** (6 equiv) | **5a** | LiCl (5 equiv) | THF | −78 | 54 | 96:4 |
| 6 | **2** (10 equiv) | **5a** | LiCl (5 equiv) | THF | −78 | 40 | 96:4 |
| 7 | **2** (6 equiv) | **5a** | TMEDA (6 equiv) | THF | −78 | 40 | 77:23 |
| 8 | **2** (6 equiv) | **5a** | LiCl (5 equiv) | Toluene | −78 | 56 | 90:10 |
| 9 | **2** (6 equiv) | **5a** | LiCl (5 equiv) | $Et_2O$ | −78 | 23 | 82:18 |
| 10 | **3** (6 equiv) | **6a** | LiCl (5 equiv) | THF | −78 | 50 | 96:4 |
| 11 | **4** (6 equiv) | **7a** | LiCl (5 equiv) | THF | −78 | 88 | 96:4 |
| 12 | **4** (4 equiv) | **7a** | LiCl (5 equiv) | THF | −78 | 46 | 96:4 |

[a]The heteroaryl-lithium reagents were prepared *in situ* by metalation of the corresponding heteroaryl bromide with *n*-BuLi for 1 h at 0 °C in the required solvent. [b]Yield after flash column chromatography. [c]Determined by HPLC analysis of crude reaction mixture under conditions optimized for a 1:1 mixture of C-4 epimers as standard (see Supporting Information). [d]nd: not determined.

pyrrolidine skeleton, both approaches should result to be enantiodivergent, each one providing the final pyrrolidine compounds with opposite absolute configuration at their stereocenter. This increases the synthetic utility of our methodology.

## RESULTS AND DISCUSSION

We started our work with the implementation of the synthetic approach shown in Scheme 1, in which heteroaryl-lithium reagents were planned to be used as hydroxycarbonyl anion equivalents in conjugate addition reactions to α,β-unsaturated enamides derived from (*S*,*S*)-(+)-pseudoephedrine. For this reason, we started with the optimization of the reaction conditions for this initial transformation using different heteroaryl-lithium reagents as nucleophiles and (*S*,*S*)-(+)-pseudoephedrine crotonamide **1a** as model substrate (Table 1). Initially, we proceeded with the use of 2-furyl-lithium (**2**), which was found to be the most widely used hydroxycarbonyl anion equivalent in the literature.[13] Disappointingly, when we carried out the reaction between **2** and **1a** under the reaction conditions already reported by us[12] for the general conjugate addition of organolithium reagents to the same type of α,β-unsaturated amides (5 equiv of LiCl as additive, in THF at −105 °C, entry 1), no reaction was observed to occur, providing unchanged starting material **1a** after 7 h reaction time. This result contrasts with the parent reaction using phenyl-lithium, which we had observed to proceed in 86% yield after 7 h reaction time (see ref 12). A small amount of the expected conjugate addition product **5a** was obtained when the reaction was carried out using an excess of furyl-lithium reagent (entry 2), and remarkably, in this case the reaction was also found to proceed with an excellent level of diastereoselection. The yield could be slightly improved by increasing the temperature of the reaction with no negative effect on the diastereoselectivity (entry 3), and the key role played by the presence of LiCl as an additive in the dr of the reaction was confirmed with the results shown in entry 4 compared to entry 3 (the dr was increased from 86:14 to 96:4), which is also in good agreement with what we had already found in the same reaction with other organolithium reagents.[12] Better yield of conjugate addition product **5a** was obtained by increasing the amount of furyl-lithium to 6 equiv (entry 5), but no further improvement was observed when a higher amount was employed (entry 6). We also tested the use of TMEDA as additive with the aim to increase the reactivity of the organolithium reagent but with no success (entry 7). Also the use of other solvents such as toluene or diethyl ether was surveyed, but in those cases the diastereoselectivity of the reaction decreased (entries 8 and 9). The use of more nucleophilic furyl-lithium reagent such as **3** was next surveyed (entry 10), and it was observed that, in this case, and under the best reaction conditions found up to this moment (those shown in entry 5), the reaction proceeded with similar yield and diastereoselectivity. Remarkably, changing to the use of 2-thienyl-lithium (**4**) as nucleophile led to an important improvement in the yield of the reaction, maintaining an excellent level of stereocontrol (entry 11). We finally tried to carry out the reaction using lower amounts of the organolithium reagent, but once again, lowering the amount of nucleophile resulted in a drop in the yield of the reaction (entry 12).

After all of these experiments we decided to survey the scope of the reaction with regard to the substitution pattern at the Michael acceptor, with the results shown in Table 2. In all cases we assumed that the best reaction conditions for the transformation were those shown in entries 5, 10, and 11 of Table 1, which involved working in THF at −78 °C and in the presence of LiCl as an additive. As can be seen in Table 2, when


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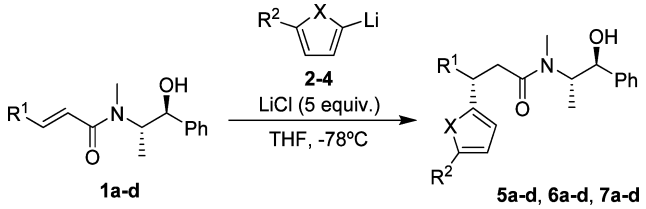
**Table 2. Diastereoselective Conjugate Addition of Heteroaryl-lithium Reagents to α,β-Unsaturated Amides Derived from (*S*,*S*)-(+)-Pseudoephedrine 1a−d**



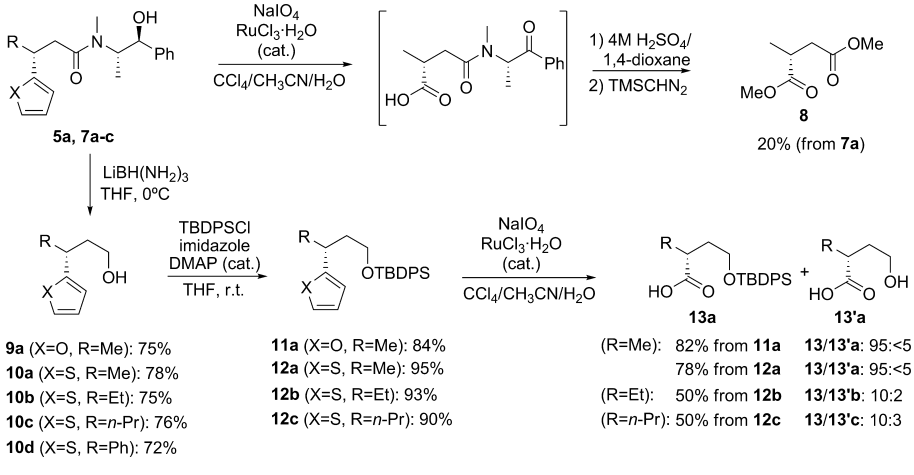

| entry | HetArLi[a] | $R^1$ | $R^2$ | X | product | yield (%)[b] | dr[c] |
|---|---|---|---|---|---|---|---|
| 1 | **2** | Me | H | O | **5a** | 54 | 96:4 |
| 2 | **2** | Et | H | O | **5b** | 41 | 96:4 |
| 3 | **2** | *n*-Pr | H | O | **5c** | 32 | nd[d,e] |
| 4 | **2** | Ph | H | O | **5d** | <5 | nd[d] |
| 5 | **3** | Me | Me | O | **6a** | 50 | 96:4 |
| 6 | **3** | Et | Me | O | **6b** | 44 | 94:4 |
| 7 | **3** | *n*-Pr | Me | O | **6c** | 39 | 96:4 |
| 8 | **3** | Ph | Me | O | **6d** | <5 | nd[d] |
| 9 | **4** | Me | H | S | **7a** | 85 | 96:4 |
| 10 | **4** | Et | H | S | **7b** | 74 | 97:3 |
| 11 | **4** | *n*-Pr | H | S | **7c** | 72 | 97:3 |
| 12 | **4** | Ph | H | S | **7d** | 22 | 97:3 |

[a]The heteroaryl-lithium reagents were prepared *in situ* by metalation of the corresponding heteroaryl bromide with *n*-BuLi for 1 h at 0 °C in THF. [b]Yield after flash column chromatography. [c]Determined by HPLC analysis of crude reaction mixture under conditions optimized for a 1:1 mixture of C-4 epimers as standard (see Supporting Information). [d]nd: not determined. [e]We were not able to find conditions for the separation of two epimers.

furyl-lithium-type organolithium reagents **2** and **3** were employed (entries 1−8), the yields were in all cases found to be moderate at best, and also a dramatic drop in this parameter was observed when progressively increasing the size of the β-substituent at the α,β-unsaturated enamide from $R^1$ = methyl to $R^1$ = ethyl and *n*-propyl (entries 1−3 and 5−7). Nevertheless, with regard to stereocontrol, the reaction performed excellently, furnishing high levels of diastereoselection in all cases. On the other hand, when these organolithiums were tested as nucleophiles in the conjugate addition with cinnamide **1d**, no reaction was observed even after prolonged stirring (entries 4 and 8), which was attributed to the lower reactivity of β-aryl-substituted α,β-unsaturated carbonyl compounds toward conjugate addition. The use of thienyl-lithium **4** led to better results, providing good yields in all cases in which β-alkyl-substituted α,β-unsaturated amides **1a−c** were employed as substrates (entries 9−11). Moreover, in this case, even though the yield was also found to decrease when the size of the β-alkyl substituent was increased, the effect was not as striking as when we used heteroaryl-lithium reagents **2** and **3**. Importantly, the diastereoselectivity was not affected by the substitution pattern at the α,β-unsaturated amide, and it was observed in all cases that the reaction proceeded with excellent levels of stereocontrol. Finally, we could also carry out the reaction in this case using cinnamide **1d** as substrate (entry 12), providing the corresponding conjugate addition product with only a 22% yield but with excellent diastereoselectivity.

We next focused on the conversion of the heteroaryl moiety into the target carboxylic group by the projected oxidative cleavage of the heterocyclic ring (Scheme 3). We started by subjecting furyl- and thienyl-containing adducts **5a** and **7a** to standard conditions reported for converting electron-rich aromatic groups into the carboxylate functionality,[16] which involved the use of $NaIO_4$ as the oxidant in the presence of a catalytic amount of $RuCl_3{\cdot}xH_2O$, observing that a clean reaction proceeded leading to the formation of a cleavage product in which, in addition, the secondary alcohol moiety present at the pseudoephedrine core had also undergone oxidation. We were not able to completely purify this product, and for this reason, we submitted the crude reaction mixture obtained after the oxidative cleavage process to standard hydrolytic conditions, leading to the formation of succinic acid (not isolated), which was further subjected to esterification, forming dimethyl succinate in ca. 20% overall yield for the three-step sequence. We could use this sequence of reactions for the determination of the absolute configuration of the stereogenic center created during the conjugate addition step by chemical correlation. Comparison of the obtained $[\alpha]^{20}_D$ value for **8** ($[\alpha]^{20}_D$ = +4.0 (*c* 0.7, $CH_2Cl_2$)) with the reported in the literature for (*R*)-dimethylsuccinate ($[\alpha]^{20}_D$ = +3.1 (*c* 2.9, $CH_2Cl_2$))[17] allowed us to establish the absolute configuration of **8** as (2*R*), which could be extended by analogy to the rest of the adducts **5a−d**, **6a−d**, and **7a−d** obtained in the asymmetric conjugate addition of heteroaryl-lithium reagents to α,β-unsaturated amides **1a−d** derived from (*S*,*S*)-(+)-pseudoephedrine. This absolute configuration is also in agreement with previous results in our group

**Scheme 3**





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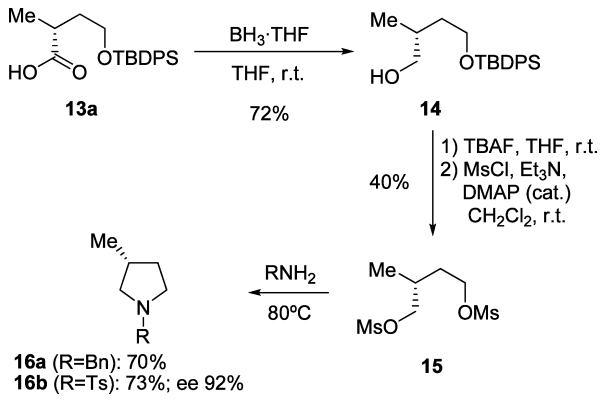
dealing with the conjugate addition of different types of nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds using pseudoephedrine as chiral auxiliary.[12]

Alternatively, we also explored the possibility of carrying out the oxidative cleavage of the heterocyclic moiety after removing the chiral auxiliary in order to avoid the oxidation of the latter (Scheme 3). For this reason, we proceeded first to carry out the reduction of the pseudoephedrine amide moiety by using lithium triamidoborate (LAB) under previously reported conditions,[18] obtaining primary alcohols **9a** and **10a−d** in excellent yields in all cases. Next, these alcohols were protected as the corresponding TBDPS-ethers **11a** and **12a−c**, and these were subsequently subjected to oxidative cleavage conditions, leading to the formation of the corresponding protected $\gamma$-hydroxyacid derivatives **13a−c** in good overall yields, although in some cases the reaction also furnished minor amounts of the corresponding unprotected derivative **13′** together with the target compounds.

Once the protocol for using heteroaryl-lithium reagents as hydroxycarbonyl anion equivalents undergoing stereocontrolled conjugate addition using pseudoephedrine as chiral auxiliary had been implemented, we next focused on the synthesis of our target 3-substituted pyrrolidines by using this methodology as key step with regard to the installation of the stereocenter. Therefore, and according to what was planned based on the retrosynthetic analysis shown in Scheme 1, we took *O*-TBDPS-protected $\gamma$-hydroxy acid **13a** and proceeded to carry out the reduction of the carboxylate in order to obtain the corresponding primary alcohol **14**, which was subsequently deprotected and reacted *in situ* with excess methanesulfonyl chloride, leading to the formation of dimesylate **15** (Scheme 4).

**Scheme 4**




This was finally converted into 3-methylpyrrolidines **16a** and **16b** by double nucleophilic displacement upon heating to 80 °C in the presence of benzylamine and tosylamide, respectively. Optical purity of the final compounds was checked by chiral HPLC on *N*-tosyl derivative **16b** for which conditions could be found for HPLC separation of the corresponding racemic standard on a chiral stationary phase. The high ee obtained for this compound matched that obtained for amides **5a** and **7a** from which this compound was prepared and in which the stereocenter had been installed by means of the diastereoselective conjugate addition of furyl-lithium and thienyl-lithium to amide **1a**. This final result indicates that all of the transformations carried out on the adducts **5** and **7** proceeded with no racemization.

At the same time, we also evaluated the alternative synthetic approach proposed previously to reach the target 3-substituted pyrrolidines, which has been previously outlined in Scheme 2 and which made use of the conjugate addition of organolithium reagents to polyunsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine as the key step with regard to the stereocontrolled installation of the stereocenter. It should be remembered here that this approach would lead to the formation of the final 3-substituted pyrrolidines with configuration opposite to that obtained for **16a** and **16b**.

We therefore started with the preparation of adducts **18a−d**, which were prepared by carrying out the conjugate addition reaction of different alkyl-lithium reagents to $\alpha,\beta,\gamma,\delta$-unsaturated amide **17**, under our previously reported conditions (Scheme 5 and Table 3).[15] The reaction proceeded with good yields and high diastereoselectivity, and as was pointed out in our previous report, we observed only the exclusive formation of the desired 1,4-addition products, and no byproduct arising from the potential competitive 1,2- or 1,6-addition was formed for the organolithium compounds used in this study. In this respect, it should be noted that the reaction could not be carried out using MeLi as the organolithium reagent (which would lead after the complete synthetic route to the corresponding 3-methylpyrrolidine) because in this case the reaction furnished only the undesired 1,2-addition product, as we had already stated previously.[15] Nevertheless, with adducts **18a−d** in hand, we next carried out the removal of the chiral auxiliary by LAB-mediated reduction, isolating the corresponding primary alcohols **19a−d** in excellent yields in all cases. Proceeding with the synthesis, these alcohols **19a−d** were mesylated, and the olefin moiety was converted into a formyl group by the projected ozonolysis reaction, which proceeded smoothly providing mesylated chiral $\alpha$-substituted $\gamma$-hydroxyaldehydes **21a−d** in excellent yields.

**Scheme 5**

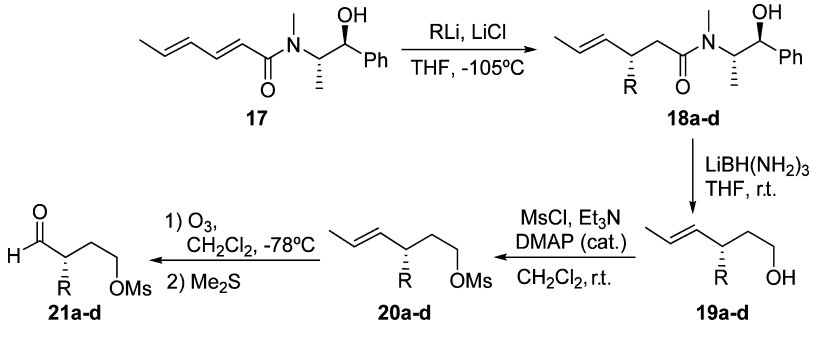




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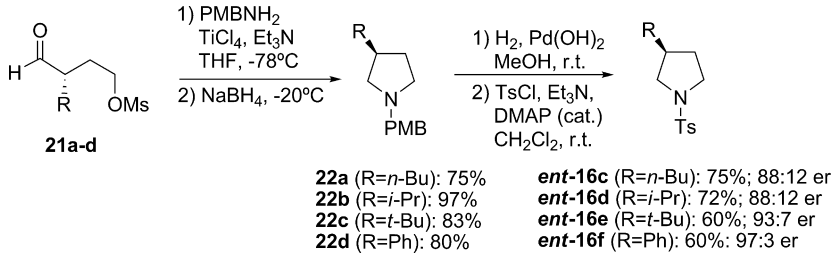
**Table 3. Conjugate Addition of Organolithium Reagents to Enamide 17 and Synthesis of Protected α-Substituted 4-Hydroxyaldehydes 21**

| entry | R | product[a] | yield (%)[b] | dr[c] | product[a] | yield (%)[d] | product | yield (%)[d] | product | yield (%)[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *n*-Bu | **18a** | 60 | 88:12 | **19a** | 91 | **20a** | 90 | **21a** | 80 |
| 2 | *i*-Pr | **18b** | 65 | 88:12 | **19b** | 94 | **20b** | 91 | **21b** | 85 |
| 3 | *t*-Bu | **18c** | 86 | 93:7 | **19c** | 80 | **20c** | 94 | **21c** | 99 |
| 4 | Ph | **18d** | 80 | 97:3 | **19d** | 99 | **20d** | 99 | **21d** | 85 |

[a]Results described in ref 15. [b]Combined yield for both diastereoisomers after column chromatography purification. [c]Determined by HPLC analysis of crude reaction mixture under conditions optimized for a 1:1 mixture of epimers as standard (see Supporting Information). [d]Yield after flash column chromatography.

**Scheme 6**




We next faced the final reductive amination/cyclization step that should lead directly to the formation of the target 3-substituted pyrrolidines (Scheme 6), for which *p*-methoxybenzylamine was selected as the amine component in the reductive amination step because of the known good ability of this group to undergo hydrogenolysis faster than the parent benzyl group. However, this final reductive amination/cyclization step required some optimization because when this transformation was carried out under the typical *in situ* Borch conditions or by generating first the corresponding *p*-methoxybenzylimine followed by $NaBH_4$ reduction in a one-pot procedure at 0 °C, the final products were isolated with a significant decrease in their enantiopurity when compared with the dr of their corresponding precursors. When we tried to perform this imine formation/$NaBH_4$ reduction process at lower temperatures, low conversions were observed even after prolonged reaction times. For this reason and working under the hypothesis that racemization was taking place by the presence of the imine/enamine tautomeric equilibrium, we decided to apply modified reaction conditions for this transformation that involved formation of the imine at very low temperature (−78 °C), which would in principle slow down the aforementioned imine/enamine equilibrium, allowing reduction to take place without racemization of the starting material. Working at such low temperatures during the formation of the imine intermediate required the incorporation of $TiCl_4$ as Lewis acid for the activation of the formyl moiety, which also participates as water-scavenging reagent.[19] After imine formation was complete, $NaBH_4$ was added to the reaction mixture, and reduction of the imine and the subsequent intramolecular nucleophilic displacement took place smoothly, providing directly *N*-*p*-methoxybenzylated pyrrolidines **22a−d** in good yields and maintaining the stereochemical integrity of the stereocenter present at the starting material. The optical purity of the final pyrrolidines was determined after conversion into the corresponding *N*-tosyl derivatives by hydrogenolytic cleavage of the *p*-methoxybenzyl group followed by *in situ* tosylation. This also established a procedure for removing the *N*-alkyl substituent that also ensured our capability to obtain free NH-containing 3-substituted pyrrolidines, which in this particular case could not be isolated for purification and characterization because of their high volatility.

## CONCLUSIONS

In conclusion we have demonstrated that thienyl-lithium and furyl-lithium can be employed as hydroxycarbonyl anion equivalents in stereocontrolled conjugate addition reactions using the aminoalcohol (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary by making use of the chemical equivalency of these heterocyclic moieties with the carboxylate group by means of oxidative cleavage. This methodology has been successfully applied to the synthesis of 3-substituted pyrrolidines by a set of simple transformations, and alternatively, we have also shown that the opposite enantiomers of the same type of chiral heterocycles can also be accessed from the same chirality source by means the regio- and diastereoselective conjugate addition of organolithium reagents to α,β,γ,δ-unsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine under conditions previously developed in our group, followed by chiral auxiliary removal, ozonolysis, and reductive amination/intramolecular nucleophilic displacement sequence.

## EXPERIMENTAL SECTION

**General Procedure for the Conjugate Addition of Heteroaryl-lithiums.** A solution of organolithium (6.0 mmol) was carefully added to a suspension of the corresponding enamide **1a−d** (1.00 mmol) and LiCl (5.0 mmol) in dry THF (15 mL) at −78 °C, and the reaction was stirred at this temperature for 4−7 h (TLC monitoring). The mixture was allowed to warm to rt and quenched with a saturated $NH_4Cl$ solution (15 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo affording the wanted amides after flash column chromatography purification.

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-3-(furan-2-yl)-*N*-methylbutanamide (5a).** Following the general procedure amide **5a** was prepared from enamide **1a** (500 mg, 2.14 mmol), LiCl (460 mg, 10.7 mmol), and 2-furyl-lithium (17.0 mL of a *in situ* prepared 0.74 M solution, 12.8 mmol) using dry THF (15 mL) as solvent and isolated after FC purification (*n*-hexane/AcOEt 1:1) in 54% yield (350 mg, 1.16 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) δ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.95* (d, 3H, *J* = 6.7 Hz), 1.05 (d, 3H, *J* = 6.7 Hz), 1.25−1.29 (m, 2H), 2.42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(dd, 1H, $J$ = 15.1, 7.7 Hz), 2.70 (dd, 1H, $J$ = 15.1, 6.3 Hz), 2.77 (s, 3H), 2.90* (s, 3H), 3.38−3.41 (m, 1H), 3.42−3.60* (m, 1H), 3.95−4.09 (m, 1H), 4.10−4.18 (bs, 1H), 4.49−4.55 (m, 2H), 5.99 (d, 1H, $J$ = 3.1 Hz), 6.00* (d, 1H, $J$ = 3.1 Hz), 6.16−6.26 (m, 1H), 7.21−7.32 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 14.5, 15.4*, 19.0, 30.1, 40.1, 58.4, 58.9, 76.5, 104.0, 110.1, 126.5, 126.9*, 127.6, 128.3*, 128.7, 138.7, 141.7, 142.0, 142.8*, 159.1, 159.5*, 173.0*, 173.7. IR ($cm^{-1}$): 3385 (OH), 1625 (CO). HRMS calcd for $[C_{18}H_{23}NO_3]^+$: 301.1678 ($M^+$), found 301.1683. MS (70 eV) $m/z$ (%): 301 (12, $M^+$), 194 (40), 148 (16), 126 (21), 121 (18), 95 (56), 81 (23), 79 (28), 72 (100), 67 (30), 59 (53). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min; $\tau_{major}$ = 61.98 min, $\tau_{minor}$ = 54.30 min. $[\alpha]^{20}_D$ +71.3 ($c$ 0.92, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-3-(furan-2-yl)-*N*-methylpentanamide (5b).** Following the general procedure amide **5b** was prepared from enamide **1b** (100 mg, 0.40 mmol), LiCl (95 mg, 2.0 mmol), and 2-furyl-lithium (3.3 mL of a *in situ* prepared 0.74 M solution, 2.4 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 41% yield (50 mg, 0.17 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.84 (t, 3H, $J$ = 7.3 Hz), 0.95* (d, 3H, $J$ = 6.7 Hz), 1.00 (d, 3H, $J$ = 6.7 Hz), 1.59−1.68 (m, 2H), 2.51 (dd, 1H, $J$ = 15.1, 6.5), 2.66 (dd, 1H, $J$ = 15.1, 7.7 Hz), 2.72 (s, 3H), 2.88* (s, 3H), 3.18−3.23 (m, 1H), 3.25−3.35* (m, 1H), 3.99−4.11* (m, 1H), 4.12−4.44 (bs, 1H), 4.49−4.57 (m, 2H), 6.00 (d, 1H, $J$ = 2.8 Hz), 6.06* (d, 1H, $J$ = 2.1 Hz), 6.25−6.28 (m, 1H), 7.23−7.39 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 11.8, 14.2, 15.0*, 26.9, 37.5, 37.1, 38.5, 58.4, 76.5, 105.5, 110.1, 126.4, 126.9*, 127.6, 128.3, 128.7*, 140.9, 142.2, 157.3, 173.9. IR $cm^{-1}$: 3381 (OH), 1620 (CO). HRMS calcd for $[C_{19}H_{25}NO_3]^+$: 315.1834 ($M^+$), found 315.1842. MS (70 eV) $m/z$ (%): 315 (13, $M^+$), 206 (21), 147 (60), 121 (64), 109 (50), 91 (25), 83 (100), 77 (22), 65 (16). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min; $\tau_{major}$ = 56.28 min, $\tau_{minor}$ = 43.65 min. $[\alpha]^{20}_D$ +71.4 ($c$ 1.00, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-3-(furan-2-yl)-*N*-methylhexanamide (5c).** Following the general procedure amide **5c** was prepared from enamide **1c** (100 mg, 0.38 mmol), LiCl (90 mg, 1.98 mmol), and 2-furyl-lithium (3.1 mL of a *in situ* prepared 0.74 M solution, 2.4 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 32% yield (40 mg, 0.12 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.88 (t, 3H, $J$ = 7.2 Hz), 0.99 (d, 3H, $J$ = 6.9 Hz), 1.15−1.39 (m, 2H), 1.54−1.84 (m, 2H), 2.34−2.66 (m, 2H), 2.70 (s, 3H), 2.86* (s, 3H), 3.28−3.35 (m, 1H), 3.36−3.50* (m, 1H), 4.02−4.09 (bs, 1H), 4.18−4.30* (m, 1H), 4.41−4.57 (m, 2H), 6.00−6.05 (m, 1H), 6.25−6.28 (m, 1H), 7.25−7.39 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 13.9, 14.3*, 14.4, 15.3*, 20.4, 25.3, 35.5, 35.6*, 35.9*, 36.1, 37.9*, 38.8, 64.3, 75.3*, 76.4, 105.0*, 105.4, 109.9*, 110.0, 126.5, 126.9*, 127.7, 128.4, 128.7*, 140.8, 142.3, 157.4, 159.4*, 172.8*, 173.9. IR $cm^{-1}$: 3379 (OH), 1620 (CO). HRMS calcd for $[C_{20}H_{27}NO_3]^+$: 329.1991 ($M^+$), found 329.1987. MS (70 eV) $m/z$ (%): 329 (16, $M^+$), 268 (99), 222 (31), 148 (30), 121 (67), 85 (96), 83 (100), 81 (37), 71 (20). $[\alpha]^{20}_D$ +72.6 ($c$ 0.92, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(5-methylfuran-2-yl)butanamide (6a).** Following the general procedure amide **6a** was prepared from enamide **1a** (100 mg, 0.34 mmol), LiCl (46 mg, 1.7 mmol), and (5-methylfuran-2-yl)lithium (3.4 mL of a *in situ* prepared 0.60 M solution, 2.06 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 50% yield (53 mg, 0.17 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.94* (d, 3H, $J$ = 6.7 Hz), 1.04 (d, 3H, $J$ = 6.7 Hz), 1.25 (d, 3H, $J$ = 6.9 Hz), 2.23 (s, 3H), 2.38 (dd, 1H, $J$ = 15.0, 7.8 Hz), 2.48* (dd, 1H, $J$ = 15.2, 8.8 Hz), 2.67 (dd, 1H, $J$ = 15.0, 6.8 Hz), 2.77 (s, 3H), 2.89* (s, 3H), 3.28−3.38 (m, 1H), 3.39−3−51* (m, 1H), 4.00−4.05* (m, 1H), 4.17−4.30 (bs, 1H), 4.22−4.52 (m, 1H), 5.83−5.87 (m, 2H), 7.30−7.33 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 13.5, 14.4, 15.3*, 18.9*, 19.0, 26.8, 30.2, 32.5*, 39.3*, 40.1, 57.9*, 58.4, 75.3*, 76.5, 104.3*, 104.5, 105.8, 126.4, 127.0*, 127.6, 128.3, 128.6*, 141.4*, 142.3, 150.3, 157.3, 157.9*, 172.5*, 173.7. IR ($cm^{-1}$): 3385 (OH), 1625 (CO). HRMS calcd for $[C_{19}H_{25}NO_3]^+$: 315.1834 ($M^+$), found 315.1830. MS (70 eV) $m/z$ (%): 315 (8, $M^+$), 282 (100), 208 (38), 149 (30), 135 (82), 109 (89), 83 (42), 77 (20). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min; $\tau_{major}$ = 32.95 min, $\tau_{minor}$ = 23.55 min. $[\alpha]^{20}_D$ +79.5 ($c$ 1.02, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(5-methylfuran-2-yl)pentanamide (6b).** Following the general procedure amide **6b** was prepared from enamide **1b** (100 mg, 0.40 mmol), LiCl (93 mg, 2.0 mmol), and (5-methylfuran-2-yl)lithium (4.0 mL of a *in situ* prepared 0.60 M solution, 2.40 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 44% yield (60 mg, 0.18 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.85 (t, 3H, $J$ = 7.2 Hz), 0.94* (d, 3H, $J$ = 6.7 Hz), 1.01 (d, 3H, $J$ = 6.7 Hz), 1.58−1.69 (m, 2H), 2.23 (s, 3H), 2.48 (dd, 1H, $J$ = 15.0, 6.7 Hz), 2.63 (dd, 1H, $J$ = 15.0, 7.5 Hz), 2.75 (s, 3H), 2.87* (s, 3H), 3.09−3.14 (m, 1H), 3.17−3.30* (m, 1H), 3.95−4.10* (m, 1H), 4.16−4.19 (bs, 1H), 4.42−4.54 (m, 2H), 5.82−5.92 (m, 2H), 7.24−7.34 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 11.7, 13.5, 14.4, 15.3*, 26.7*, 26.8, 37.2*, 37.4, 37.4*, 37.6, 38.6, 58.2*, 58.4, 75.3*, 76.4, 105.8, 106.0, 126.4, 126.9*, 127.3, 128.3, 128.6*, 141.2*, 142.3, 148.5*, 150.3, 156.1*, 156.1, 172.6*, 174.2. IR ($cm^{-1}$): 3377 (OH), 1619 (CO). HRMS calcd for $[C_{20}H_{27}NO_3]^+$: 329.1991 ($M^+$), found 329.1984. MS (70 eV) $m/z$ (%): 329 (17, $M^+$), 282 (100), 222 (23), 148 (21), 135 (76), 123 (41), 84 (18). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min; $\tau_{major}$ = 43.85 min, $\tau_{minor}$ = 38.43 min. $[\alpha]^{20}_D$ +59.6 ($c$ 0.98, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(5-methylfuran-2-yl)hexanamide (6c).** Following the general procedure amide **6c** was prepared from enamide **1c** (100 mg, 0.38 mmol), LiCl (90 mg, 1.9 mmol), and (5-methylfuran-2-yl)lithium (4.0 mL of a *in situ* prepared 0.60 M solution, 2.40 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 39% yield (50 mg, 0.15 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.86 (t, 3H, $J$ = 7.2 Hz), 0.94* (d, 3H, $J$ = 6.7 Hz), 0.98 (d, 3H, $J$ = 6.7 Hz), 1.01−1.39 (m, 2H), 1.54−1.63 (m, 2H), 2.23 (s, 3H), 2.47 (dd, 1H, $J$ = 14.9, 6.7 Hz), 2.64 (dd, 1H, $J$ = 14.9, 7.4 Hz), 2.75 (s, 3H), 2.88* (s, 3H), 3.19−3.24 (m, 1H), 3.26−3.40* (m, 1H), 4.00−4.10* (m, 1H), 4.12−4.19 (bs, 1H), 4.42−4.57 (m, 2H), 5.82−5.91 (m, 2H), 7.23−7.34 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 13.5, 13.9, 14.0*, 14.4, 15.3*, 20.4, 35.3*, 35.6, 35.8, 36.0, 36.3*, 38.9, 58.2*, 58.4, 75.3*, 76.5, 105.6*, 105.8, 105.9, 126.5, 127.0*, 127.6, 128.3, 128.5*, 142.3, 150.2, 157.7, 174.0. IR ($cm^{-1}$): 3374 (OH), 1620 (CO). HRMS calcd for $[C_{21}H_{29}NO_3]^+$: 343.2147 ($M^+$), found 343.2146. MS (70 eV) $m/z$ (%): 343 (15, $M^+$), 282 (100), 234 (29), 147 (79), 137 (51), 135 (89), 107 (38), 95 (90), 71 (32). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min;

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(thien-2-yl)butanamide (7a).** Following the general procedure amide **7a** was prepared from enamide **1a** (100 mg, 0.42 mmol), LiCl (46 mg, 1.7 mmol), and thienyl-lithium (2.6 mL of a 1 M solution, 2.6 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 85% yield (115 mg, 0.36 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.97* (d, 3H, $J$ = 6.7 Hz), 1.03 (d, 3H, $J$ = 6.7 Hz), 1.33−1.41 (m, 3H), 2.51 (dd, 1H, $J$ = 15.1, 7.4 Hz), 2.64 (dd, 1H, $J$ = 15.2, 6.6 Hz), 2.77 (s, 3H), 2.91* (s, 3H), 3.65−3.71 (m, 1H), 3.71−3.83* (m, 1H), 4.00−4.03 (m, 1H), 4.10−


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4−18 (bs, 1H), 4.47−4.59 (m, 2H), 6.83 (d, 1H, $J$ = 3.5 Hz), 6.86* (d, 1H, $J$ = 6.4 Hz), 6.90 (dd, 1H, $J$ = 5.0, 3.5 Hz), 6.92 (dd, 1H, $J$ = 5.0, 0.9 Hz), 7.11−7.36 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 14.5, 15.4*, 22.8, 26.9, 32.1, 32.3*, 43.2*, 43.5, 58.3*, 58.4, 75.2*, 76.4, 122.7, 122.8, 123.0*, 126.5, 126.6, 126.7*, 128.4, 128.7, 141.2*, 142.3, 150.4, 151.0*, 172.5*, 173.5. IR ($cm^{-1}$): 3376 (OH), 1619 (CO). HRMS calcd for $[C_{18}H_{24}NO_2S]^+$: 318.1527 [$(M + H)^+$], found 318.1529. MS (70 eV) $m/z$ (%): 318 [24, $(M + H)^+$], 300 (100), 210 (35), 148 (26). The dr (96:4) was determined by HPLC using Chiralpak IA column, $n$-hexane/$i$-PrOH 97:3, flow rate 1.0 mL/min; $\tau_{major}$ = 33.29 min, $\tau_{minor}$ = 27.25 min. $[\alpha]^{20}_D$ +59.6 ($c$ 0.98, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(thien-2-yl)pentanamide (7b).** Following the general procedure amide **7b** was prepared from enamide **1b** (100 mg, 0.40 mmol), LiCl (70 mg, 2.0 mmol), and thienyl-lithium (2.4 mL of a 1 M solution, 2.4 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 74% yield (99 mg, 0.30 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.86 (t, 3H, $J$ = 7.3 Hz), 0.96 (d, 3H, $J$ = 6.5 Hz), 1.55−1.65 (m, 1H), 1.72−1.79 (m, 1H), 2.57 (d, 1H, $J$ = 7.3 Hz), 2.58 (d, 1H, $J$ = 6.7 Hz), 2.72 (s, 3H), 2.85* (s, 3H), 3.39−3.44 (m, 1H), 3.49−3.57* (m, 1H) 3.99−4.19 (m, 1H), 4.17−4.25 (bs, 1H), 4.45−4.52 (m, 2H), 6.81 (d, 1H, $J$ = 3.4 Hz), 6.89 (dd, 1H, $J$ = 5.0, 3.4 Hz), 7.06 (d, 1H, $J$ = 5.0 Hz), 7.23−7.34 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 12.0, 14.4, 15.4*, 30.1*, 30.3, 39.2, 39.4, 41.3*, 42.0, 58.1*, 58.4, 76.4, 122.9, 122.9*, 124.2, 126.5, 126.6*, 126.9, 127.5, 128.3, 128.6*, 141.2*, 142.4, 148.4, 148.9*, 172.3*, 173.5. IR ($cm^{-1}$): 3419 (OH), 1620 (CO). HRMS calcd for $[C_{19}H_{26}NO_2S]^+$: 332.1684 [$(M + H)^+$], found 332.1678. MS (70 eV) $m/z$ (%): 332 [32, $(M + H)^+$], 315 (19), 314 (100), 225 (8), 224 (37), 148 (20). The dr (97:3) was determined after transformation to the alcohol **10b**. $[\alpha]^{20}_D$ +43.2 ($c$ 0.98, $CH_2Cl_2$).

**(+)-(3*R*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*-methyl-3-(thien-2-yl)hexanamide (7c).** Following the general procedure amide **7c** was prepared from enamide **1c** (100 mg, 0.38 mmol), LiCl (65 mg, 1.90 mmol), and thienyl-lithium (2.3 mL of a 1 M solution, 2.3 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 72% yield (95 mg, 0.27 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.89 (t, 3H, $J$ = 7.3 Hz), 0.99 (d, 3H, $J$ = 6.9 Hz), 1.22−1.34 (m, 2H), 1.55−1.73 (m, 2H), 2.59 (d, 1H, $J$ = 6.5 Hz), 2.60 (d, 1H, $J$ = 7.4 Hz), 2.73 (s, 3H), 2.87* (s, 3H), 3.52−3.57 (m, 1H), 3.58−3.72 (bs, 1H), 3.99−4.05 (m, 1H), 4.42−4.57 (m, 2H), 6.82 (d, 1H, $J$ = 3.3 Hz), 6.86* (d, 1H, $J$ = 3.0 Hz), 6.90 (dd, 1H, $J$ = 4.5, 3.3 Hz), 6.97 (d, 1H, $J$ = 4.5 Hz), 7.22−7.36 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 13.9, 14.4, 15.3*, 20.6, 26.5, 37.3*, 37.5, 39.4*, 39.5, 41.6*, 42.4, 58.4, 76.2, 122.8, 122.9, 124.0*, 124.2, 126.4, 126.6*, 126.9, 127.7, 128.3, 128.7*, 142.3, 148.8, 172.2*, 173.8. IR ($cm^{-1}$): 3382 (OH), 1617 (CO). HRMS calcd for $[C_{20}H_{28}NO_2S]^+$: 346.1763 [$(M + H)^+$], found 346.1741. MS (70 eV) $m/z$ (%): 346 [46, $(M + H)^+$], 329 (28), 328 (100), 225 (8), 238 (33), 148 (10). The dr (97:3) was determined after transformation to the alcohol **10c**. $[\alpha]^{20}_D$ +58.7 ($c$ 1.00, $CH_2Cl_2$).

**(+)-(3*S*,1′*S*,2′*S*)-*N*-(1′-Hydroxy-1′-phenylpropan-2′-yl)-*N*,4,4-trimethyl-3-phenyl-3-(thien-2-yl)propanamide (7d).** Following the general procedure amide **7d** was prepared from enamide **1d** (100 mg, 0.34 mmol), LiCl (60 mg, 1.85 mmol), and thienyl-lithium (2.0 mL of a 1 M solution, 2.0 mmol) using dry THF (15 mL) as solvent and isolated after FC purification ($n$-hexane/AcOEt 1:1) in 22% yield (28 mg, 0.07 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 0.73* (d, 3H, $J$ = 6.7 Hz), 0.98 (d, 3H, $J$ = 6.7 Hz), 2.33−2.41* (bs, 1H), 2.76 (s, 3H), 2.84* (s, 3H), 3.04 (d, 1H, $J$ = 7.3 Hz), 3.07 (d, 1H, $J$ = 8.3 Hz), 3.13* (dd, 1H, $J$ = 7.3, 5.2 Hz), 3.25* (dd, 1H, $J$ = 15.0, 7.3 Hz), 3.70−3.90 (bs, 1H), 3.91−4.05* (m, 1H), 4.35−4.60 (m, 2H), 4.93 (dd, 1H, $J$ = 7.4, 7.3 Hz), 6.82 (d, 1H, $J$ = 3.6 Hz), 6.86* (d, 1H, $J$ = 3.2 Hz), 6.92 (dd, 1H, $J$ = 5.0, 3.6 Hz), 6.94−6.99* (m, 1H), 7.15 (d, 1H, $J$ = 5.0 Hz) 7.26−7.40 (m, 10H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (proportion of rotamers 1:3, *denotes minor rotamer signals): 14.2, 15.2*, 27.1, 41.1*, 41.7, 42.8, 43.1*, 58.1*, 58.4, 75.4*, 76.1, 123.7, 124.3, 126.6, 127.0, 127.7*, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7*, 142.0, 143.7, 144.1*, 148.1, 172.7. IR ($cm^{-1}$): 3395 (OH), 1620 (CO). HRMS calcd for $[C_{23}H_{25}NO_2S]^+$: 379.1606 ($M^+$), found 379.1608. MS (70 eV) $m/z$ (%): 379 (4, $M^+$), 339 (12), 338 (29), 337 (100), 317 (64), 183 (12), 139 (29), 97 (3). The er (97:3) was determined after transformation to the alcohol **10d**. $[\alpha]^{20}_D$ +50.2 ($c$ 0.99, $CH_2Cl_2$).

**Synthesis of (*R*)-Dimethyl 2-Methylsucccinate (8).** To a solution of amide **7a** (0.08 g, 2,5 mmol) in $CCl_4/CH_3CN/H_2O$ 1:1:1.7 at room temperature were added $NaIO_4$ (0.86 g, 37.5 mmol) and $RuCl_3{\cdot}H_2O$, in a catalytic amount. After 1 h of stirring, the layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were dried over $Na_2SO_4$ and filtered through Celite. The solvent was removed in vacuo to yield the corresponding carboxylic acid. This carboxylic acid intermediate was dissolved in 1,4-dioxane (10 mL), the solution was cooled to 0 °C, and $H_2SO_4$ 4 M (10 mL) was slowly added. The mixture was refluxed for 12 h after which it was cooled to rt. Water was added (20 mL), and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were dried over $Na_2SO_4$, and the solvent was removed in vacuo to yield the corresponding diacid compound, which was directly subject to esterification by addition of $TMSCHN_2$ (10 mmol) to a cooled solution (0 °C) of the crude diacid in dry THF (10 mL). After 2 h, MeOH (2 mL) was added at once, and the mixture was stirred for a further 45 min after which it was quenched with water (10 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were dried over $Na_2SO_4$, and the solvent was removed in vacuo to yield succinate **8** after flash column chromatography purification in 20% yield (80 mg, 0.50 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.20 (d, 3H, $J$ = 7.1 Hz), 2.39 (dd, 1H, $J$ = 16.4, 6.1 Hz), 2.73 (dd, 1H, $J$ = 16.4, 8.2 Hz), 2.87−2.94 (m, 1H), 3.66 (s, 1H), 3.68 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 16.9, 35.7, 37.4, 51.7, 51.9, 172.3, 175.7. IR ($cm^{-1}$): 1639, 1675 (CO). HRMS calcd for $[C_7H_{12}O_4]^+$: 160.0736 ($M^+$), found 160.0733. MS (70 eV) $m/z$ (%): 101 (82), 74 (17), 59 (90), 72 (20), $[\alpha]^{20}_D$ +4.0 ($c$ 0.7, $CHCl_3$); lit.[17] $[\alpha]^{20}_D$ +3.1 ($c$ 2.9, $CHCl_3$).

**General Procedure for Reduction of Amides 5 and 7.** $n$-BuLi (4.54 mmol) was added over a solution of diisopropylamine (4.36 mmol) in dry THF (10 mL) at −78 °C, and the mixture was stirred for 15 min. The reaction was warmed to 0 °C, and $BH_3{\cdot}NH_3$ (4.45 mmol) was added at once. The mixture was stirred for 15 min at 0 °C and another 15 min at room temperature, after which a solution of the amide (0.89 mmol) in THF (5 mL) was added via canula at 0 °C and the reaction was stirred for 2 h. Then the reaction was quenched with 1 M HCl (15 mL) and extracted with AcOEt (3 × 15 mL). The organic fractions were collected, washed with satd $NaHCO_3$, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording alcohols as a colorless oil after flash column chromatography purification.

**(−)-(*R*)-3-(Furan-2-yl)butan-1-ol (9a).** Following the general procedure **9a** was prepared starting from enamide **5a** (1.00 g, 3.32 mmol), $n$-BuLi (17.0 mL of a 1 M solution, 17.0 mmol), $i$-$Pr_2NH$ (2.28 mL, 16.2 mmol), and $BH_3{\cdot}NH_3$ (0.504 g, 16.6 mmol) and was isolated after FC purification ($n$-hexane/AcOEt 7:3) in 75% yield (350 mg, 2.50 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.26 (d, 3H, $J$ = 7.0 Hz), 1.70−1.90 (m, 3H), 2.94−2.98 (m, 1H), 3.55−3.68 (m, 2H), 5.98 (d, 1H, $J$ = 2.6 Hz), 6.26−6.28 (dd, 1H, $J$ = 2.6, 1.8 Hz), 7.25−7.30 (bs, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 19.3, 29.8, 38.7, 70.6, 103.7, 109.9, 140.8, 159.9. IR ($cm^{-1}$): 3447 (OH). HRMS calcd for $[C_8H_{13}O_2]^+$: 141.0915 [$(M + H)^+$], found 141.0900. MS (70 eV) $m/z$ (%): 141 [26, $(M + H)^+$], 123 (93), 122 (34), 95 (100). $[\alpha]^{20}_D$ −23.0 ($c$ 0.99, $CH_2Cl_2$).

**(−)-(*R*)-3-(Thien-2-yl)butan-1-ol (10a).** Following the general procedure **10a** was prepared starting from enamide **7a** (1.0 g, 3.32 mmol), $n$-BuLi (17 mL of a 1 M solution, 17.0 mmol), $i$-$Pr_2NH$ (2.28 mL, 16.2 mmol), and $BH_3{\cdot}NH_3$ (500 mg, 16.6 mmol) using dry THF (15 mL) as solvent and was isolated after FC purification ($n$-hexane/AcOEt 7:3) in 78% yield (404 mg, 2.59 mmol). $^1$H NMR (300 MHz,


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$CDCl_3$) $\delta$: 1.36 (d, 3H, $J$ = 6.9 Hz), 1.86 (d, 1H, $J$ = 6.6 Hz), 1.91 (d, 1H, $J$ = 6.7 Hz), 2.23 (bs, 1H), 3.20−3.28 (m, 1H), 3.58−3.69 (m, 2H), 6.82−6.84 (m, 1H), 6.92 (dd, 1H, $J$ = 5.0, 3.4 Hz), 7.07 (dd, 1H, $J$ = 5.0, 1.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 23.3, 31.9, 42.0, 60.7, 122.6, 122.8, 126.5, 151.2. IR ($cm^{-1}$): 3443 (OH). HRMS calcd for $[C_8H_{13}SO]^+$: 157.0687 [(M + H)$^+$], found 157.0694. MS (70 eV) $m/z$ (%): 157 [18, (M + H)$^+$], 156 (14, M$^+$), 139 (100), 138 (12), 97 (56). $[\alpha]^{20}_D$ −18.3 ($c$ 1.01, $CH_2Cl_2$).

**(−)-(*R*)-3-(Thien-2-yl)pentan-1-ol (10b).** Following the general procedure **10b** was prepared starting from enamide **7b** (100 mg, 0.30 mmol), *n*-BuLi (1.54 mL of a 1 M solution, 1.54 mmol), *i*-$Pr_2NH$ (0.21 mL, 1.48 mmol), and $BH_3{\cdot}NH_3$ (0.045 g, 1.51 mmol) using dry THF (15 mL) as solvent and was isolated after FC purification (*n*-hexane/AcOEt 7:3) in 75% yield (38 mg, 0.23 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.86 (t, 3H, $J$ = 7.3 Hz), 1.30 (bs, 1H), 1.53−1.80 (m, 3H), 1.82−2.05 (m, 1H), 3.20−3.30 (m, 1H), 3.49−3.77 (m, 2H), 6.81 (d, 1H, $J$ = 3.1 Hz), 6.93 (dd, 1H, $J$ = 5.1, 3.1 Hz), 7.15 (d, 1H, $J$ = 5.1 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 11.9, 30.9, 39.4, 40.2, 60.9, 122.9, 123.9, 126.5, 149.1. IR ($cm^{-1}$): 3456 (OH). HRMS calcd for $[C_9H_{15}OS]^+$: 171.0843 [(M + H)$^+$], found 171.0851. MS (70 eV) $m/z$ (%): 171 [21, (M + H)$^+$], 170 (37, M$^+$), 153 (62), 141 (28), 126 (14), 125 (92), 111 (58), 97 (100), 85 (7). The er (97:3) was determined by HPLC using Chiralcel OJ column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; $\tau_{major}$ = 8.96 min, $\tau_{minor}$ = 7.71 min. $[\alpha]^{20}_D$ −14.5 ($c$ 1.00, $CH_2Cl_2$).

**(−)-(*R*)-3-(Thien-2-yl)hexan-1-ol (10c).** Following the general procedure **10c** was prepared starting from enamide **7c** (0.49 g, 1.43 mmol), *n*-BuLi (7.20 mL of a 1 M solution, 7.20 mmol), *i*-$Pr_2NH$ (0.98 mL, 6.95 mmol), and $BH_3{\cdot}NH_3$ (0.216 g, 7.10 mmol) using dry THF (50 mL) as solvent and was isolated after FC purification (*n*-hexane/AcOEt 7:3) in 76% yield (0.20 g, 1.08 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.88 (t, 3H, $J$ = 7.3 Hz), 1.25−1.30 (m, 2H), 1,59−1.96 (m, 5H), 3.04−3.08 (m, 1H), 3.51−3.63 (m, 2H), 6.80 (d, 1H, $J$ = 3.3 Hz), 6.91 (dd, 1H, $J$ = 5.0, 3.3 Hz), 7.14 (d, 1H, $J$ = 5.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 13.9, 20.5, 37.5, 40.3, 40.5, 60.8, 122.8, 123.9, 126.4, 149.2. IR ($cm^{-1}$): 3339 (OH). HRMS calcd for $[C_{10}H_{17}OS]^+$: 185.1000 [(M + H)$^+$], found 185.0985. MS (70 eV) $m/z$ (%): 185 [5, (M + H)$^+$], 153 (62), 141 (28), 126 (14), 125 (92), 111 (58), 97 (100), 85 (7). The er (97:3) was determined by HPLC using Chiralcel OJ column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; $\tau_{major}$ = 8.96 min, $\tau_{minor}$ = 7.71 min. $[\alpha]^{20}_D$ −6.5 ($c$ 1.16, $CH_2Cl_2$).

**(−)-(*S*)-3-Phenyl-3-(thien-2-yl)propan-1-ol (10d).** Following the general procedure **10d** was prepared starting from enamide **7d** (100 mg, 0.26 mmol), *n*-BuLi (1.34 mL of a 1 M solution, 1.34 mmol), *i*-$Pr_2NH$ (0.18 mL, 1.29 mmol), and $BH_3{\cdot}NH_3$ (0.040 g, 1.32 mmol) using dry THF (15 mL) as solvent (41 mg, 0.18 mmol) and was isolated after FC purification (*n*-hexane/AcOEt 7:3) in 72% yield (41 mg, 0.18 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.25−2.43 (m, 2H), 3.58−3.64 (m, 2H), 4.40 (t, 1H, $J$ = 7.7 Hz), 6.86−6.88 (m, 1H), 6.91−6.94 (m, 1H), 7.14−7.17 (m, 2H), 7.23−7.32 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 39.9, 42.0, 60.7, 123.7, 123.9, 126.6, 126.7, 126.9, 128.0, 146.1, 148.9. IR ($cm^{-1}$): 3440 (OH). HRMS calcd for $[C_{13}H_{15}OS]^+$: 219.0843 [(M + H)$^+$], found 219.0843. MS (70 eV) $m/z$ (%) 219 [10, (M + H)$^+$], 218 (38, M$^+$), 200 (25), 173 (100), 141 (13), 135 (90), 117 (20), 105 (49), 91 (17). (The er (97:3) was determined by HPLC using Chiralcel OJ column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; $\tau_{major}$ = 49.37 min, $\tau_{minor}$ = 40.76 min.). $[\alpha]^{20}_D$ +6.5 ($c$ 1.00, $CH_2Cl_2$).

**General Procedure for the Synthesis of Silanes 11 and 12.** To a solution of the alcohol **9** or **10** (2.5 mmol) in dry THF were added TBDPSCl (5.0 mmol), imidazole (5.60 mmol), and DMAP (cat.). The reaction was stirred at room temperature for 18 h, and then it was quenched with $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording the silane after flash column chromatography purification.

**(−)-(*R*)-*tert*-Butyldiphenyl-[3-(furan-2-yl)butoxy]silane (11a).** Following the general procedure **11a** was prepared starting from alcohol **9a** (0.330 g, 2.36 mmol), TBDPSiCl (1.35 mL, 5.18 mmol), imidazol (0.40 g, 5.89 mmol), and DMAP (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 9:1) in 84% yield (0.759 g, 2.00 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.15 (s, 9H), 1.35 (d, 3H, $J$ = 7.0 Hz), 1.89−1.92 (m, 1H), 2.10−2.17 (m, 1H), 3.20−3.27 (m, 1H), 3.80−3.85 (m, 2H), 6.03−6.05 (m, 1H), 6.36 (dd, 1H, $J$ = 3.0, 1.9 Hz), 7.46−7.53 (m, 7H), 7.80−7.84 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 19.3, 19.4, 27.0, 29.8, 38.7, 61.8, 103.7, 109.9, 127.7, 127.8, 129.6, 129.7, 134.0, 134.1, 135.5, 135.5, 140.7, 160.3. HRMS calcd for $[C_{24}H_{31}SiO_2]^+$: 379.2093 [(M + H)$^+$], found 379.2084. MS (70 eV) $m/z$ (%): 321 (100), 302 (18), 301 (79), 123 (36). $[\alpha]^{20}_D$ −12.0 ($c$ 1.00, $CH_2Cl_2$).

**(−)-(*R*)-*tert*-Butyldiphenyl-[3-(thien-2-yl)butoxy]silane (12a).** Following the general procedure **12a** was prepared starting from alcohol **10a** (0.350 g, 2.24 mmol), TBDPSiCl (1.35 mL, 4.93 mmol), imidazol (0.380 g, 5.60 mmol), and DMAP (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 8:2) in 95% yield (0.84 g, 2.13 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.19 (s, 9H), 1.42 (d, 3H, $J$ = 6.9 Hz), 1.97−2.00 (m, 2H), 3.42−3.49 (m, 1H), 3.76−3.82 (m, 2H), 6.86−6.89 (m, 1H), 7.00 (dd, 1H, $J$ = 5.1, 3.4 Hz), 7.19 (dd, 1H, $J$ = 5.1, 1.1 Hz,), 7.46−7.80 (m, 6H), 7.74−7.83 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 19.4, 23.4, 27.0, 31.7, 42.0, 61.8, 122.5, 122.8, 126.5, 127.7, 127.8, 129.6, 129.7, 134.0, 134.1, 135.5, 135.5, 151.6. HRMS calcd for $[C_{24}H_{31}OSSi]^+$: 395.1865 [(M + H)$^+$], found 395.1852. MS (70 eV) $m/z$ (%): 395 [5, (M + H)$^+$], 338 (18), 337 (100), 318 (14), 317 (67), 183 (7), 139 (32). $[\alpha]^{20}_D$ −8.1 ($c$ 0.97, $CH_2Cl_2$).

**(−)-(*R*)-*tert*-Butyldiphenyl-[3-(thien-2-yl)pentoxy]silane (12b).** Following the general procedure **12b** was prepared starting from alcohol **10b** (0.250 g, 1.47 mmol), TBDPSiCl (0.95 mL, 3.67 mmol), imidazol (0.300 g, 4.41 mmol), and DMAP (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 9:1) in 93% yield (0.558 g, 1.36 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.92 (t, 3H, $J$ = 7.3 Hz), 1.13 (s, 9H), 1.51−2.05 (m, 3H), 2.05−2.20 (m, 1H), 3.13−3.18 (m, 1H), 3.66−3.77 (m, 2H), 6.78−6.82 (m, 1H), 6.96 (dd, 1H, $J$ = 5.0, 3.4 Hz), 7.17 (dd, 1H, $J$ = 5.0, 0.8 Hz), 7.30−7.51 (m, 6H), 7.60−7.77 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 12.0, 19.3, 26.9, 30.8, 39.2, 42.1, 61.7, 122.7, 123.9, 126.4, 127.6, 127.7, 129.5, 129.7, 134.0, 134.1, 135.6, 135.6, 149.5. HRMS calcd for $[C_{25}H_{33}OSSi]^+$: 409.2021 [(M + H)$^+$], found 409.2039. MS (70 eV) $m/z$ (%): 409 [5, (M + H)$^+$], 353 (15), 351 (100), 331 (78), 199 (10), 183 (14), 153(28). $[\alpha]^{20}_D$ −7.1 ($c$ 1.80, $CH_2Cl_2$).

**(−)-(*R*)-*tert*-Butyldiphenyl-[3-(thien-2-yl)hexoxy]silane (12c).** Following the general procedure **12c** was prepared starting from alcohol **10c** (0.150 g, 0.82 mmol), TBDPSiCl (0.53 mL, 2.03 mmol), imidazol (0.166 g, 2.44 mmol), and DMAP (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 9:1) in 90% yield (0.311 g, 0.738 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.93 (t, 3H, $J$ = 7.3 Hz), 1.13 (s, 9H), 1.31−1.36 (m, 2H), 1.55−1.65 (m, 2H), 1.69−1.74 (m, 1H), 1.85−2.05 (m, 1H), 3.15−3.36 (m, 1H), 3.56−3.81 (m, 2H), 6.78 (d, 1H, $J$ = 3.0 Hz), 6.94 (dd, 1H, $J$ = 4.9, 3.5 Hz), 7.15 (d, 1H, J = 4.9 Hz), 7.33−7.52 (m, 6H), 7.65−7.75 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 14.0, 19.3, 20.5, 26.9, 37.1, 40.2, 40.5, 61.6, 122.6, 123.8, 126.3, 127.6, 127.7, 129.5, 129.6, 134.0, 134.1, 135.6, 135.6, 149.8. HRMS calcd for $[C_{26}H_{35}OSSi]^+$: 423.2178 [(M + H)$^+$], found 423.2198. MS (70 eV) $m/z$ (%): 423 [9, (M + H)$^+$], 365 (100), 345 (95), 265 (20), 199 (20), 183 (30), 165(12). $[\alpha]^{20}_D$ −7.0 ($c$ 1.48, $CH_2Cl_2$).

**General Procedure for the Synthesis of Carboxylic Acids 13.** To a solution of the silane **12** (25 mmol) in $H_2O/CH_3CN/CCl_4$ 1.7:1:1 at room temperature were added $NaIO_4$ (375 mmol) and $RuCl_3{\cdot}H_2O$ (cat.). The reaction was stirred at that temperature for 1 h and then was quenched with $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered through Celite, and the carboxylic acid **13** was isolated after the solvent was removed in vacuo.

**(*R*)-4-(*tert*-Butyldiphenylsililoxy)-2-methylbutyric Acid (13a).**[20] Following the general procedure **13a** was prepared starting from **12a** (0.65 g, 1.72 mmol), $NaIO_4$ (5.51 g, 25.8 mmol), and $RuCl_3{\cdot}H_2O$ (cat.) in 78% yield (0.478 g, 1.34 mmol). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.96 (s, 9H), 1.17 (d, 3H, $J$ = 7.0 Hz), 1.62−1.70 (m, 1H), 2.00−2.09 (m, 1H), 2.72−2.79 (m, 1H), 3.68−3.74 (m, 2H), 7.26−7.44 (m, 6H), 7.62−7.71 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$)


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δ: 16.8, 19.1, 26.8, 35.8, 36.1, 61.5, 127.7, 129.6, 133.6, 133.7, 134.6, 135.6, 182.3. HRMS calcd for $[C_{21}H_{28}O_3Si]^+$: 356.1808 ($M^+$), found 356.1794. MS (70 eV) *m/z* (%): 356 (4, $M^+$), 297 (100), 277 (86), 259 (23), 219 (14), 199 (23).

**(−)-(*R*)-4-(*tert*-Butyldiphenylsililoxy)-2-ethylbutyric Acid (13b).** Following the general procedure **13b** was prepared starting from **12b** (0.130 g, 0.32 mmol), $NaIO_4$ (1.36 g, 6.37 mmol), and $RuCl_3{\cdot}H_2O$ (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 7:3) in 50% yield (59 mg, 0.16 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, 3H, *J* = 7.4 Hz), 1.04 (s, 9H), 1.50−1.76 (m, 3H), 1.90−2.00 (m, 1H), 2.55−2.58 (m, 1H), 3.70 (t, 2H, *J* = 6.1 Hz), 7.26−7.42 (m, 6H), 7.62−7.72 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 11.6, 19.1, 25.1, 26.7, 34.0, 43.5, 61.8, 127.7, 129.6, 133.7, 135.6, 133.6, 182.3. HRMS calcd for $[C_{22}H_{29}O_2Si]^+$: 353.1937 [(M − OH)$^+$], found 353.1954. MS (70 eV) *m/z* (%): 353 [32, (M − OH)$^+$], 313 (22), 235 (70), 215 (27), 199 (100). $[\alpha]^{20}_D$ −6.6 (*c* 1.00, $CH_2Cl_2$).

**(−)-(*R*)-4-(*tert*-Butyldiphenylsililoxy)-2-propylbutyric Acid (13c).** Following the general procedure **13c** was prepared starting from **12c** (0.210 g, 0.50 mmol), $NaIO_4$ (2.12 g, 9.95 mmol), and $RuCl_3{\cdot}H_2O$ (cat.) and was isolated after FC purification (*n*-hexane/AcOEt 7:3) in 50% yield (96 mg, 0.25 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, 3H, *J* = 7.2 Hz), 1.04 (s, 9H), 1.31−1.76 (m, 4H), 1.80−2.00 (m, 2H), 2.61−2.66 (m, 1H), 3.69 (t, 2H, *J* = 6.2 Hz), 7.26−7.91 (m, 10H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 13.9, 19.1, 20.3, 26.8, 34.2, 34.4, 41.7, 61.8, 127.6, 129.6, 133.5, 133.7, 133.6, 135.6, 181.7. HRMS calcd for $[C_{23}H_{31}SiO_2]^+$: 367.2094 [(M − OH)$^+$], found 367.2106. MS (70 eV) *m/z* (%): 367 [51, (M − OH)$^+$], 327 (27), 249 (99), 229 (41), 199 (100), 129 (45). $[\alpha]^{20}_D$ −4.4 (*c* 1.00, $CH_2Cl_2$).

**Synthesis of (+)-(*R*)-(*tert*-Butyldiphenylsililoxy)-2-methylbutan-1-ol (14).** To a solution of the carboxylic acid **13a** (0.5 g, 1.40 mmol) in dry THF (15 mL) at room temperature was added borane (2.1 mL, 4.21 mmol), and the mixture was stirred at this temperature. After 3.5 h the solution was cooled at 0 °C, water was added (10 mL, and the mixture was extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording the alcohol **14** after flash column chromatography purification (hexane/AcOEt 8:2) in 72% yield (0.36 g, 1.05 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, 3H, *J* = 6.8 Hz), 1.09 (s, 9H), 1.51−1.56 (m, 1H), 1.61−1.68 (m, 1H), 1.84−1.90 (m, 1H), 2.60−2.70 (bs, 1H), 3.50−3.52 (m, 2H), 3.73−3.81 (m, 2H), 7.39−7.51 (m, 6H), 7.70−7.75 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 17.1, 19.2, 26.8, 33.8, 36.7, 62.5, 68.2, 127.7, 129.7, 135.6, 133.5. IR ($cm^{-1}$): 3340 (OH). HRMS calcd for $[C_{21}H_{31}O_2Si]^+$: 343.2093 [(M + H)$^+$], found 343.2095. MS (70 eV) *m/z* (%): 343 [8, (M + H)$^+$], 285 (39), 239 (35), 228 (100), 199 (70), 179 (29), 166 (40), 69 (13). $[\alpha]^{20}_D$ +5.0 (*c* 0.94, $CH_2Cl_2$).

**Synthesis of (+)-(*R*)-2-Methylbutane-1,4-diyl Dimethanesulfonate (15).** To a solution of the alcohol **14** (0.3 g, 0.87 mmol) in dry THF (15 mL) was added TBAF (3.50 mL of a 1 M solution in THF, 3.5 mmol), and the mixture was stirred for 18 h. The reaction was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo. To a solution of the crude in dry $CH_2Cl_2$ (10 mL) at 0 °C were added $Et_3N$ (0.54 mL, 3.85 mmol), methanesulfonyl chloride (0.3 mL, 3.85 mmol), and DMAP (cat.). After 14 h of stirring at room temperature the reaction was quenched with 2 M KOH (5 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo. Sulfonate **15** was isolated after flash column chromatography purification FC (hexane/AcOEt 2:8) in 20% yield (0.090 g, 0.35 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.04 (d, 3H, *J* = 6.8 Hz), 1.63−1.70 (m, 1H), 1.87−1.96 (m, 1H), 2.08−2.14 (m, 1H, CH), 3.01 (s, 3H), 3.12 (s, 3H), 4.04−4.15 (m, 2H), 4.26−4.34 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 16.1, 29.8, 32.2, 37.3, 37.4, 67.4, 73.5. HRMS calcd for $[C_7H_{17}O_6S_2]^+$: 261.0466 [(M + H)$^+$], found 261.0466. MS (70 eV) *m/z* (%): 261 [8, (M + H)$^+$], 192 (5), 174 (8), 165 (100), 125 (13), 105 (42). $[\alpha]^{20}_D$ +0,5 (*c* 1.00, $CH_2Cl_2$).

**General Procedure for the Synthesis of Pyrrolidines 16.** A mixture of the dimesilate **15** (0.23 mmol) and the corresponding amine (1.48 mmol) was warmed at 80 °C. After 8 h the reaction was cooled to room temperature and was solved in $CH_2Cl_2$ (5 mL) and satd $NaHCO_3$ (5 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording the pyrrolidines **16** after flash column chromatography purification.

**(−)-(3*R*)-*N*-Benzyl-3-methylpyrrolidine (16a).** Following the general procedure **16a** (0.03 g, 0.16 mmol) was isolated by FC purification (*n*-hexane/AcOEt 2:8) in 70% yield starting from dimesilate **15** (0.060 g, 0.23 mmol) and benzylamine (0.20 mL, 1.84 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.03 (d, 3H, *J* = 6.7 Hz), 1.31−1.36 (m, 1H), 1.99−2.03 (m, 2H), 2.04−2.30 (m, 1H), 2.33−2.50 (m, 1H), 2.61−2.77 (m, 1H), 2.82 (m, 1H, *J* = 8.8, 7.5 Hz), 3.57 (d, 1H, *J* = 12.9 Hz), 3.62 (d, 1H, *J* = 12.9 Hz), 7.20−7.36 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 20.4, 31.8, 32.6, 54.1, 60.8, 62.2, 126.8, 128.1, 128.8, 141.1. HRMS calcd for $[C_{12}H_{18}N]^+$: 176.1439 [(M + H)$^+$], found 176.1434. MS (70 eV) *m/z* (%): 176 [100, (M + H)$^+$], 175 (80, $M^+$), 98 (21), 91 (29), 84 (19). $[\alpha]^{20}_D$ −8.4 (*c* 1.44, EtOH), lit.[21] $[\alpha]^{20}_D$ −8.6 (*c* 1.75, EtOH).

**(−)-(3*R*)-*N*-Tosyl-3-methylpyrrolidine (16b).** Following the general procedure **16b** (0.090 g, 0.36 mmol) was isolated by FC purification (*n*-hexane/AcOEt 2:8) in 73% yield starting from dimesilate **15** (0.13 g, 0.50 mmol) and tosylamine (0.20 mL, 1.84 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, 3H, *J* = 6.7 Hz), 1.27−1.37 (m, 1H), 1.86−1.94 (m, 1H), 2.06−2.14 (m, 1H), 2.42 (s, 3H), 2.70−2.76 (m, 1H), 3.22−3.38 (m, 1H), 3.40−3.43 (m, 2H), 7.30 (d, 2H, *J* = 8.1 Hz), 7.70 (d, 2H, *J* = 8.1 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 17.6, 21.5, 33.2, 33.3, 47.6, 54.7, 127.5, 129.5, 134.1, 143.2. HRMS calcd for $[C_{12}H_{18}NO_2S]^+$: 240.1058 [(M + H)$^+$], found 240.1068. MS (70 eV) *m/z* (%): 240 [100, (M + H)$^+$], 239 (19), 148 (7). $[\alpha]^{20}_D$ +8.1 (*c* 1.05, $CH_2Cl_2$). Mp: 90−92 °C (hexane/AcOEt 8:2). The ee (92% ee) was calculated by HPLC: Chiralpak IA, 0.70 mL/min, hexane/*i*-PrOH 98/02. Mayor isomer: $t_R$ = 35.5 min. Minor isomer: $t_R$ = 36.8 min.

**General Procedure for the Synthesis of Mesilates 20.** To a solution of the corresponding alcohol **19**[15] (1.00 mmol) in dry $CH_2Cl_2$ (20 mL) at 0 °C were added $Et_3N$ (3.00 mmol), methanesulfonyl chloride (3.00 mmol), and DMAP (cat.). After 2 h of stirring at room temperature the reaction was quenched with 2 M KOH (10 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were dried over $Na_2SO_4$ and filtered, and the solvent was removed in vacuo, affording the mesilates **20** after flash column chromatography purification.

**(+)-(*S*,*E*)-3-Butylhex-4-enyl Methanesulfonate (20a).** Following the general procedure **20a** (0.38 g, 1.61 mmol) was obtained in 90% yield starting from alcohol **19a** (0.28 g, 1.79 mmol), $Et_3N$ (0.76 mL, 5.38 mmol), MsCl (0.42 mL, 5.38 mmol), and DMAP (0.02 g, 0.18 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 8:2). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, 3H, *J* = 6.1 Hz), 1.19−1.33 (m, 6H), 1.46−1.58 (m, 1H), 1.63 (d, 3H, *J* = 6.3 Hz), 1.69−1.86 (m, 1H), 1.98−2.05 (m, 1H), 2.95 (s, 3H), 4.09−4.24 (m, 2H), 5.06 (dd, 1H, *J* = 15.0, 9.1 Hz), 5.34−5.46 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 13.9, 17.8, 22.5, 29.1, 34.3, 35.1, 37.1, 39.1, 68.8, 126.4, 133.8. IR ($cm^{-1}$): 2927 (C═C), 1355 ($SO_2$), 1175 ($SO_2$). HRMS calcd for $[C_{11}H_{22}O_3S]^+$: 234.1290, found 234.1283. MS (70 eV) *m/z* (%): 234 (1, $M^+$), 218 (38), 138 (53), 123 (59), 109 (94), 96 (98), 81 (99), 79 (100), 67 (99), 55 (98). $[\alpha]^{20}_D$ +13.4 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*R*,*E*)-3-Isopropylhex-4-enyl Methanesulfonate (20b).** Following the general procedure **20a** (0.39 g, 1.79 mmol) was obtained in 91% yield starting from alcohol **19b** (0.28 g, 1.97 mmol), $Et_3N$ (0.83 mL, 5.37 mmol), MsCl (0.45 mL, 5.37 mmol), and DMAP (0.02 g, 0.18 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 8:2). $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.83 (d, 3H, *J* = 6.7 Hz), 0.87 (d, 3H, *J* = 6.7 Hz), 1.49−1.62 (m, 2H), 1.67 (dd, 3H, *J* = 6.3, 1.4 Hz), 1.82−1.93 (m, 2H), 2.97 (s, 3H), 4.08−4.27 (m, 2H), 5.09−5.17 (m, 1H), 5.36−5.47 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 17.9, 18.8, 20.4, 31.6, 32.0,


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37.2, 45.4, 69.2, 127.6, 131.3. IR ($cm^{-1}$): 2958 (C═C), 1355 ($SO_2$), 1176 ($SO_2$). HRMS calcd for $[C_9H_{17}]^+$: 125.1331 [(M − OMs)$^+$], found 125.1323. MS (70 eV) *m*/*z* (%): 125 [89, (M − OMs)$^+$], 124 (10), 123 (17), 109 (11), 97 (55), 83 (31), 81 (14), 69 (100). $[\alpha]^{20}_D$ +17.8 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*S*,*E*)-3-*tert*-Butylhex-4-enyl Methanesulfonate (20c).** Following the general procedure **20c** (0.32 g, 1.38 mmol was obtained in 94% yield starting from alcohol **19c** (0.23 g, 1.47 mmol), $Et_3N$ (0.62 mL, 4.41 mmol), MsCl (0.34 mL, 4.41 mmol), and DMAP (0.02 g, 0.14 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 8:2). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.84 (s, 9H), 1.38−1.50 (m, 1H), 1.67 (dd, 3H, *J* = 6.3, 1.3 Hz), 1.72−1.80 (m, 1H), 1.92−2.02 (m, 1H), 2.97 (s, 3H, $CH_3S$), 4.04−4.12 (m, 1H), 4.19−4.26 (m, 1H), 5.11−5.19 (m, 1H), 5.34−5.46 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 17.9, 27.6, 28.7, 32.6, 37.2, 49.6, 69.6, 128.0, 130.9. IR ($cm^{-1}$): 2958 (C═C), 1354 ($SO_2$), 1176 ($SO_2$). HRMS calcd for $[C_{10}H_{19}]^+$: 139.1487 [(M − OMs)$^+$], found 139.1481. MS (70 eV) *m*/*z* (%): 139 [70, (M − OMs)$^+$], 123 (11), 111 (51), 83 (100), 82 (21), 69 (25). $[\alpha]^{20}_D$ +19.3 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*S*,*E*)-3-Phenylhex-4-enyl Methanesulfonate (20d).** Following the general procedure **20d** (0.46 g, 1.82 mmol) was obtained in >99% yield starting from alcohol **19d** (0.32 g, 1.82 mmol), $Et_3N$ (0.62 mL, 4.41 mmol), MsCl (0.34 mL, 4.41 mmol), and DMAP (0.02 g, 0.18 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 8:2). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.65 (d, 3H, *J* = 6.2 Hz), 2.09 (d, 1H, *J* = 6.6 Hz), 2.14 (d, 1H, *J* = 6.6 Hz), 2.94 (s, 3H), 3.38−3.44 (m, 1H), 4.09−4.24 (m, 2H, $CH_2O$), 5.52−5.55 (m, 2H), 7.18−7.34 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 17.9, 34.8, 37.0, 44.7, 68.4, 126.0, 126.5, 127.3, 128.6, 133.3, 143.3. IR ($cm^{-1}$): 2936 (C═C), 1354 ($SO_2$), 1173 ($SO_2$). HRMS calcd for $[C_{13}H_{18}O_3S]^+$: 254.0977 (M$^+$), found 254.0959. MS (70 eV) *m*/*z* (%): 158 [33, (M − OMs)$^+$], 143 (100), 131 (76), 129 (78), 128 (74), 115 (73), 103 (20), 91 (79), 79 (70), 77 (40). $[\alpha]^{20}_D$ +25.1 (*c* 1.0, $CH_2Cl_2$).

**General Procedure for the Synthesis of Aldehydes 21.** Ozone was bubbled through a cooled solution at −78 °C of mesilate **20a−d** (1.0 mmol) in dry $CH_2Cl_2$ (20 mL), until the solution turned light blue. Then, dimethyl sulfide (5.00 mmol) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with water (20 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were dried over $Na_2SO_4$ and filtered, and the solvent was removed in vacuo, affording the aldehyde **21a−d** after flash column chromatography purification.

**(−)-(*S*)-3-Formylheptyl Methanesulfonate (21a).** Following the general procedure **21a** (0.15 g, 0.63 mmol) was obtained in 80% yield starting from mesilate **20a** (0.20 g, 0.79 mmol) and $Me_2S$ (0.29 mL, 3.94 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 7:3). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.87 (t, 3H, *J* = 6.1 Hz), 1.26−1.29 (m, 4H), 1.41−1.53 (m, 1H), 1.61−1.73 (m, 1H), 1.75−1.90 (m, 1H), 1.99−2.13 (m, 1H,), 2.41−2.49 (m, 1H), 2.93 (s, 3H), 4.14−4.27 (m, 2H), 9.53 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 13.7, 22.5, 27.7, 28.2, 28.7, 37.1, 47.9, 67.6, 203.6. IR ($cm^{-1}$): 1721 (C═O), 1353 ($SO_2$), 1174 ($SO_2$). HRMS calcd for $[C_9H_{18}O_4S]^+$: 222.0926 (M$^+$), found 222.0926. MS (70 eV) *m*/*z* (%): 222 (1, M$^+$), 126 (5), 99 (7), 86 (25), 83 (39), 79 (100), 70 (11), 55 (90). $[\alpha]^{20}_D$ −6.87 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*R*)-3-Formyl-4-methylpentyl Methanesulfonate (21b).** Following the general procedure **21b** (0.14 g, 0.639 mmol) was obtained in 85% yield starting from mesilate **20b** (0.18 g, 0.81 mmol) and $Me_2S$ (0.30 mL, 4.05 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 7:3). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.94 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 1.73−1.84 (m, 1H), 2.03−2.18 (m, 2H,), 2.34−2.41 (m, 1H), 2.97 (s, 3H), 4.12−4.29 (m, 2H), 9.67 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 19.1, 20.0, 24.7, 28.1, 37.2, 53.8, 68.3, 204.1. IR ($cm^{-1}$): 1723 (C═O), 1352 ($SO_2$), 1174 ($SO_2$). HRMS calcd for $[C_7H_{13}O]^+$: 113.0967 [(M − OMs)$^+$], found 113.0968. MS (70 eV) *m*/*z* (%): 112 [42, (M − OMs)$^+$], 97 (100), 84 (10), 83 (11), 79 (12), 69 (13), 67 (11). $[\alpha]^{20}_D$ +8.0 (*c* 1.0, $CH_2Cl_2$).

**(−)-(*R*)-3-Formyl-4,4-dimethylpentyl Methanesulfonate (21c).** Following the general procedure **21c** (0.19 g, 0.89 mmol) was obtained in a quantitative yield starting from mesilate **20c** (0.21 g, 0.89 mmol) and $Me_2S$ (0.30 mL, 4.05 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 7:3). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.01 (s, 9H), 1.82−1.92 (m, 1H), 2.06−2.18 (m, 1H), 2.23−2.35 (m, 1H), 2.96 (s, 3H), 4.04−4.11 (m,1H), 4.17−4.24 (m, 1H), 9.81 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 24.3, 27.9, 33.6, 37.3, 57.7, 68.5, 204.9. IR ($cm^{-1}$): 1716 (C═O), 1349 ($SO_2$), 1174 ($SO_2$). HRMS calcd for $[C_8H_{15}O]^+$: 127.1123 [(M − OMs)$^+$], found 127.1126. MS (70 eV) *m*/*z* (%): 127 [100, (M − OMs)$^+$], 83 (15), 71 (16), 70 (24). $[\alpha]^{20}_D$ −32.0 (*c* 1.0, $CH_2Cl_2$).

**(−)-(*R*)-3-Formyl-3-phenylpropyl Methanesulfonate (21d).** Following the general procedure **21d** (0.27 g, 1.10 mmol) was obtained in 85% yield starting from mesilate **20d** (0.33 g, 1.29 mmol) and $Me_2S$ (0.48 mL, 6.49 mmol) as a colorless oil after flash column chromatography purification (hexane/AcOEt 7:3). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.08−2.12 (m, 1H), 2.48−2.52 (m, 1H), 2.93 (s, 3H), 3.71−3.80 (m, 2H), 4.06−4.14 (m, 1H), 4.21−4.28 (m, 1H), 7.16−7.41 (m, 5H), 9.66 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 28.2, 36.3, 53.9, 66.3, 127.2, 128.0, 128.4, 133.4, 198.0. IR ($cm^{-1}$): 1720 (C═O), 1351 ($SO_2$), 1172 ($SO_2$). HRMS calcd for $[C_{11}H_{14}O_4S]^+$: 242.0613 (M$^+$), found 242.0615. MS (70 eV) *m*/*z* (%): 242 (2, M$^+$), 222 (18), 192 (17), 191 (99), 147 (100), 117 (57), 95 (20), 91 (14) 75 (28). $[\alpha]^{20}_D$ −69.6 (*c* 1.0, $CH_2Cl_2$).

**General Procedure for the Synthesis of Pyrrolidines 22.** Over a cooled (−78 °C) solution of the aldehyde **21** (1.00 mmol) in THF (10 mL) were added *p*-methoxybenzylamine (1.10 mmol) and $Et_3N$ (3 mmol). Then, a solution of $TiCl_4$ (1.0 mmol) in $CH_2Cl_2$ was carefully added, and the reaction was stirred at this temperature for 5 min at −78 °C and 10 min at −20 °C. A solution of $NaBH_4$ (4.5 mmol) in anhydrous MeOH (10 mL) was slowly added to the reaction mixture (30 min), and the reaction was stirred for 2 h at −20 °C. The reaction was quenched with a satd $Na_2CO_3$ solution (15 mL), and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo affording the wanted pyrrolidines after flash column chromatography purification.

**(+)-(*S*)-3-Butyl-*N*-(*p*-methoxybenzyl)pyrrolidine (22a).** Following the general procedure **22a** (0.20 g, 0.83 mmol) was obtained in 75% yield after FC purification (*n*-hexane/AcOEt/$Et_3N$ 7:2.8:0.2) starting from aldehyde **21a** (0.25 g, 1.13 mmol), *p*-methoxybenzylamine (0.16 mL, 1.24 mmol), $Et_3N$ (1 mL, 3.39 mmol), $TiCl_4$ (1.24 mL of a 1.0 M solution in $CH_2Cl_2$, 1.24 mmol), and $NaBH_4$ (0.19 g, 5.10 mmol) in MeOH. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.88 (t, 3H, *J* = 6.4 Hz), 1.16−1.42 (m, 7H), 1.92−2.04 (m, 2H), 2.07−2.17 (m, 1H), 2.33−2.41 (m, 1H), 2.64−2.72 (m, 1H), 2.77−2.83 (m, 1H), 3.50 (d, 1H, *J* = 12.6 Hz), 3.52 (d, 1H, *J* = 12.6 Hz),, 3.79 (s, 3H), 6.84 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.4 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 14.0, 22.7, 30.5, 30.7, 35.4, 37.5, 53.8, 55.1, 60.1, 60.5, 113.5, 129.9, 131.3, 158.5. IR ($cm^{-1}$): 2922 (C═C), 1245 (C−O). HRMS calcd for $[C_{16}H_{25}NO]^+$: 247.1936 (M$^+$), found 247.1933. MS (70 eV) *m*/*z* (%): 247 (10, M$^+$), 126 (12), 121 (100), 87 (16), 85 (35), 84 (38), 82(11), 71 (19), 69 (10), 57 (22), 55 (13). $[\alpha]^{20}_D$ +3.5 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*R*)-3-Isopropyl-*N*-(*p*-methoxybenzyl)pyrrolidine (22b).** Following the general procedure **22b** (0.24 g, 1.02 mmol) was obtained in 97% yield after FC purification (*n*-hexane/AcOEt/$Et_3N$ 7:2.8:0.2) starting from aldehyde **21b** (0.22 g, 1.06 mmol), *p*-methoxybenzylamine (0.15 mL, 1.15 mmol), $Et_3N$ (0.44 mL, 3.15 mmol), $TiCl_4$ (1.15 mL of a 1.0 M solution in $CH_2Cl_2$, 1.15 mmol), and $NaBH_4$ (0.18 g, 4.72 mmol) in MeOH. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 0.85 (d, 3H, *J* = 6.6 *Hz*), 0.88 (d, 3H, *J* = 6.6 *Hz*), 1.38−1.50 (m, 2H), 1.78−1.98 (m, 2H), 2.01−2.06 (m, 1H), 2.29−2.37 (m, 1H), 2.69−2.83 (m, 2H), 3.50 (d, 1H, *J* = 12.6 Hz), 3.56 (d, 1H, *J* = 12.6 Hz), 3.78 (s, 3H, $OCH_3$), 6.84 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.4 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 21.0, 21.2, 28.9, 32.9, 45.2, 54.0, 55.0, 58.8, 60.2, 113.4, 129.8, 131.5, 158.4. IR ($cm^{-1}$): 2954 (C═C), 1245 (C−O). HRMS calcd for $[C_{15}H_{24}NO]^+$: 234.1858 [(M + H)$^+$], found 234.1852. MS (70 eV) *m*/*z* (%): 234 [100, (M + H)$^+$],


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233 (63, $M^+$), 232 (54), 218 (11), 149 (8), 126 (19), 121 (41), 112 (3). $[\alpha]^{20}_D$ +10.6 (*c* 2.0, $CH_2Cl_2$).

**(+)-(*R*)-3-*tert*-Butyl-*N*-(*p*-Methoxybenzyl)pyrrolidine (22c).** Following the general procedure **22c** (0.22 g, 0.89 mmol) was obtained in 83% yield after FC purification (*n*-hexane/AcOEt/$Et_3N$ 7:2.8:0.2) starting from aldehyde **21c** (0.24 g, 1.08 mmol), *p*-methoxybenzylamine (0.16 mL, 1.19 mmol), $Et_3N$ (0.45 mL, 3.24 mmol), $TiCl_4$ (1.19 mL of a 1.0 M solution in $CH_2Cl_2$, 1.19 mmol), and $NaBH_4$ (0.18 g, 4.72 mmol) in MeOH. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.84 (s, 9H), 1.49−1.60 (m, 1H), 1.72−1.84 (m, 1H), 1.98−2.06 (m, 1H), 2.09−2.17 (m, 1H), 2.27−2.35 (m, 1H), 2.62−2.73 (m, 2H), 3.47 (d, 1H, *J* = 12.6 Hz), 3.57 (d, 1H, *J* = 12.6 Hz), 3.78 (s, 3H), 6.84 (d, 2H, *J* = 8.5 Hz), 7.23 (d, 2H, *J* = 8.5 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 25.9, 27.4, 31.9, 48.3, 54.6, 55.1, 55.7, 60.2, 113.4, 129.7, 131.5, 158.4. IR ($cm^{-1}$): 2955 (C═C), 1245 (C−O). HRMS calcd for $[C_{16}H_{26}NO]^+$: 248.2014 [$(M + H)^+$], found 248.2019. MS (70 eV) *m*/*z* (%): 248 [100, $(M + H)^+$], 247 (69, $M^+$), 246 (60), 232 (22), 140 (20), 121 (33). $[\alpha]^{20}_D$ +5.5 (*c* 1.0, $CH_2Cl_2$).

**(+)-(*R*)-*N*-(*p*-Methoxybenzyl)-3-phenyl Pyrrolidine (22d).** Following the general procedure **22d** (0.17 g, 0.63 mmol) was obtained in 80% yield after FC purification (*n*-hexane/AcOEt/$Et_3N$ 7:2.8:0.2) starting from aldehyde **21d** (0.20 g, 0.78 mmol), *p*-methoxybenzylamine (0.11 mL, 0.85 mmol), $Et_3N$ (0.33 mL, 2.34 mmol), $TiCl_4$ (0.58 mL of a 1.0 M solution in $CH_2Cl_2$, 0.85 mmol), and $NaBH_4$ (0.13 g, 3.51 mmol) in MeOH. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.90−2.01 (m, 1H), 2.34−2.46 (m, 1H,), 2.55 (dd, 1H, *J* = 9.0, 7.9 Hz), 2.69−2.78 (m, 1H), 2.83−2.92 (m, 1H), 3.09 (dd, 1H, *J* = 9.0, 7.9 Hz), 3.37−3.48 (m, 1H), 3.68 (s, 2H), 3.84 (s, 3H), 6.93 (d, 2H, *J* = 8.7 Hz), 7.21−7.28 (m, 1H), 7.33−7.36 (m, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 33.1, 43.2, 54.4, 55.1, 59.8, 62.1, 113.5, 125.9, 127.2, 128.2, 129.8, 131.3, 145.6, 158.5. IR ($cm^{-1}$): 2932 (C═C), 1248 (C−O). HRMS calcd for $[C_{18}H_{22}NO]^+$: 268.1701 [$(M + H)^+$], found 268.1689. MS (70 eV) *m*/*z* (%): 268 [35, $(M + H)^+$], 267 (60, $M^+$), 266 (18), 163 (7), 160 (12), 122 (8), 121 (100), 91 (2). $[\alpha]^{20}_D$ +17.0 (*c* 0.5, $CH_2Cl_2$).

**General Procedure for the Hydrogenolysis and Synthesis of *p*-Toluenesulfonylpyrrolidines *ent*-16.** A catalytic amount of $Pd(OH)_2$ (40 mol %) was added to a solution of the corresponding pyrrolidine **22** (1.00 mmol) in MeOH (10 mL), and the mixture was stirred at rt under 100 psi pressure of $H_2$ (TLC monitoring). Then the mixture was filtered, and the solvent was removed in vacuo. The reaction crude was disolved in $CH_2Cl_2$ (10 mL) at 0 °C, and $Et_3N$ (3.00 mmol) and *p*-toluenesulfonylchloride (3.00 mmol) and a catalytic amount of DMAP (0.10 mmol) were added. The reaction mixture was stirred at rt for 16 h, quenched with 2 M KOH (10 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo. The wanted pyrrolidines *ent*-**16** were obtained after flash column chromatography purification.

**(+)-(*S*)-3-Butyl-*N*-(*p*-toluenesulfonyl)pyrrolidine (*ent*-16c).** Following the general procedure *ent*-**16c** (0.08 g, 0.27 mmol) was obtained in 75% yield after FC purification (*n*-hexane/AcOEt 8:2) starting from pyrrolidine **22a** (0.09 g, 0.36 mmol), $Et_3N$ (0.15 mL, 1.09 mmol), *p*-toluenesulfonylchloride (0.21 g, 1.09 mmol), and a catalytic amount of DMAP (4.45 mg, 0.04 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.84 (t, 3H, *J* = 6.6 Hz), 1.18−1.25 (m, 6H), 1.30−1.40 (m, 1H), 1.85−2.02 (m, 2H), 2.41 (s, 3H), 2.72−2.78 (m, 1H), 3.13−3.22 (m, 1H), 3.28−3.35 (m, 1H), 3.38−3.44 (m, 1H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.69 (d, 2H, *J* = 8.4 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 13.88, 21.5, 22.6, 30.2, 31.5, 32.7, 38.8, 47.5, 53.3, 127.5, 129.5, 133.9, 143.2. IR ($cm^{-1}$): 2925 (C═C), 1344 ($SO_2$), 1161 ($SO_2$). HRMS calcd for $[C_{15}H_{23}NO_2S]^+$: 281.1449 ($M^+$), found 281.1454. MS (70 eV) *m*/*z* (%): 281 (8, $M^+$), 280 (12), 184 (47), 155 (38), 126 (100), 91 (46), 85 (14), 83 (24), 65 (10). $[\alpha]^{20}_D$ +7.9 (*c* 1.0, $CH_2Cl_2$). The er (88:12) was determined by HPLC using Chiralcel OJH column, *n*-hexane/*i*-PrOH 98:2, flow rate 0.85 mL/min; $\tau_{major}$ = 28.95 min, $\tau_{minor}$ = 26.65 min.

**(−)-(*R*)-3-Isopropyl-*N*-(*p*-toluenesulfonyl)pyrrolidine (*ent*-16d).** Following the general procedure *ent*-**16d** (0.07 g, 0.26 mmol) was obtained in 72% yield after FC purification (*n*-hexane/AcOEt 8:2) starting from pyrrolidine **22b** (0.08 g, 0.36 mmol), $Et_3N$ (0.14 mL, 1.03 mmol), *p*-toluenesulfonylchloride (0.19 g, 1.03 mmol), and a catalytic amount of DMAP (4.19 mg, 0.03 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.84 (d, 6H, *J* = 6.6 Hz), 1.29−1.43 (m, 2H), 1.62−1.76 (m, 1H), 1.86−1.95 (m, 1H), 2.43 (s, 3H), 2.78 (t, 1H, *J* = 9.6 Hz), 3.10−3.23 (m, 1H), 3.33−3.47 (m, 2H), 7.31 (d, 2H, *J* = 8.1 Hz), 7.70 (d, 2H, *J* = 8.1 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 20.9, 21.3, 21.5, 30.0, 31.8, 46.4, 48.1, 52.1, 127.5, 129.6, 134.0, 143.2. IR ($cm^{-1}$): 2957 (C═C), 1344 ($SO_2$), 1162 ($SO_2$). HRMS calcd for $[C_{14}H_{22}NO_2S]^+$: 268.1371, found 268.1370. MS (70 eV) *m*/*z* (%): 268 [100, $(M + H)^+$], 267 (10, $M^+$), 176 (3), 112 (15), 91 (1). $[\alpha]^{20}_D$ −23.5 (*c* 0.2, $CHCl_3$). The er (88:12) was determined by HPLC using Chiralcel OJH column, *n*-hexane/*i*-PrOH 98:2, flow rate 1.00 mL/min; $\tau_{major}$ = 27.44 min, $\tau_{minor}$ = 25.36 min.

**(+)-(*R*)-3-*tert*-Butyl-*N*-(*p*-toluenesulfonyl)pyrrolidine (*ent*-16e).** Following the general procedure *ent*-**16e** (0.07 g, 0.26 mmol) was obtained in 50% yield after FC purification (*n*-hexane/AcOEt 8:2) starting from pyrrolidine **22c** (0.11 g, 0.44 mmol), $Et_3N$ (0.19 mL, 1.33 mmol), *p*-toluenesulfonylchloride (0.25 g, 1.33 mmol), and a catalytic amount of DMAP (5.44 g, 0.04 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 0.81 (s, 9H), 1.39−1.61 (m, 1H), 1.70−1.91 (m, 2H), 2.43 (s, 3H), 2.93 (t, 1H, *J* = 9.6 Hz), 3.04−3.13 (m, 1H), 3.25−3.35 (m, 1H), 3.36−3.43 (m, 1H), 7.31 (d, 2H, *J* = 8.2 Hz), 7.71 (d, 2H, *J* = 8.2 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.5, 26.6, 27.3, 31.2, 48.3, 48.9, 49.4, 127.5, 129.6, 133.8, 143.2. IR ($cm^{-1}$): 2923 (C═C), 1346 ($SO_2$), 1164 ($SO_2$). HRMS calcd for $[C_{15}H_{24}NO_2S]^+$: 282.1527 [$(M + H)^+$], found 282.1520. MS (70 eV) *m*/*z* (%): 282 [100, $(M + H)^+$], 261 (10, $M^+$), 190 (7), 126 (15), 91 (1). $[\alpha]^{20}_D$ +7.9 (*c* 1.0, $CH_2Cl_2$). The er (97:3) was determined by HPLC using Chiralcel OJH column, *n*-hexane/*i*-PrOH 98:2, flow rate 0.85 mL/min; $\tau_{major}$ = 20.31 min, $\tau_{minor}$ = 17.57 min.

**(+)-(*R*)-3-Phenyl-*N*-(*p*-toluenesulfonyl)pyrrolidine (*ent*-16f).** Following the general procedure *ent*-**16f** (0.06 g, 0.22 mmol) was obtained in 50% yield after FC purification (*n*-hexane/AcOEt 8:2) starting from pyrrolidine **22d** (0.10 g, 0.37 mmol), $Et_3N$ (0.16 mL, 1.12 mmol), *p*-toluenesulfonylchloride (0.21 g, 1.12 mmol), and a catalytic amount of DMAP (4.57 mg, 0.04 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.79−1.93 (m, 1H), 2.17−2.23 (m, 1H), 2.45 (s, 3H), 3.16−3.25 (m, 2H), 3.31−3.40 (m, 1H), 3.49−3.57 (m, 1H), 3.69−3.79 (m, 1H), 7.12 (m, 2H), 7.18−7.32 (m, 3H), 7.36 (m, 2H), 7.75 (d, 2H, *J* = 8.1 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.5, 32.8, 43.7, 47.8, 54.0, 126.9, 127.5, 128.6, 129.7, 133.9, 140.6, 143.4. IR ($cm^{-1}$): 2968 (C═C), 1342 ($SO_2$), 1160 ($SO_2$). HRMS calcd for $[C_{17}H_{19}NO_2S]^+$: 301.1136 ($M^+$), found 301.1137. MS (70 eV) *m*/*z* (%): 302 [100, $(M + H)^+$], 300 (4), 210 (1), 184 (3), 148 (6), 146 (12). Mp (°C): 89−92 (AcOEt/hexane 1:1) $[\alpha]^{20}_D$ +6.3 (*c* 0.5, EtOH); lit.[22] $[\alpha]^{20}_D$ −6.6, *c* 1.16, EtOH, for *S* isomer. The er (97:3) was determined by HPLC using Chiralpak IA column, *n*-hexane/*i*-PrOH 98:2, flow rate 0.85 mL/min; $\tau_{major}$ = 31.25 min, $\tau_{minor}$ = 29.66 min.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1H$ and $^{13}C$ NMR spectra of all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: marisa.carrillo@ehu.es; joseluis.vicario@ehu.es.


### Notes

The authors declare no competing financial interest.

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