Light-driven molecular motors and switches
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Chapter 4
Enantioselective Synthesis of Second-Generation Light-Driven Molecular Motors

This chapter focuses on the development of a stereoselective synthesis route of second-generation light-driven molecular motors. Two new methods for the preparation of the upper-half ketone precursors are presented. Also, a modified procedure for the Barton-Kellogg coupling reaction, which normally leads to a fully racemized coupling product when the standard conditions are applied, was developed. This synthetic methodology provided the coupling product with only a slight degree of racemization, allowing the desired molecular motors to be obtained enantiomerically pure by crystallization.*

* Parts of this chapter will be submitted for publication: T. C. Pijper, D. Pijper, M. M. Pollard, F. Dumur, S. G. Davey, A. Meetsma, B. L. Feringa, manuscript in preparation.
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4.1 Introduction

As discussed in the previous chapters, the second-generation light-driven rotary molecular motors developed in our group have been the topic of extensive research. An important part of this work was their successful application in several macromolecular and supramolecular systems, e.g. by grafting them on a surface where they produce an absolute molecular rotary movement, adding them as switchable chiral dopants in liquid crystals, or using them as switchable chiral initiators in helical polymers (see Chapters 6 and 7). For all of these applications, the molecular motors are required in their enantiopure form, and in multi-milligram quantities. However, despite the vast amount of research performed on these systems, no good methods for the enantioselective synthesis of second-generation motor molecules have been developed. Therefore, so far all of the research on these motor systems has relied on the separation of the enantiomers, obtained after a racemic synthesis, by chiral HPLC on a preparative scale. In practice, this means performing a large number of sequential HPLC runs on an analytical scale, collecting the resolved compound after each run. This methodology, however, suffers from the fact that often only small amounts of material can be resolved. This is caused by the fact that the molecules are generally not very well soluble in the eluent (with the chiral HPLC columns used in our laboratory only n-heptane:iso-propanol combinations are allowed) and that, due to their apolar nature, the enantiomers often are barely separable on the HPLC columns. As a result, normally large numbers of very long runs are required to collect a reasonable amount of enantiopure compound, making this a very tedious time- and eluent-consuming technique. Moreover, after this tedious resolving process, generally only a few milligrams of enantiopure material are obtained. Toward the applications mentioned at the beginning of this introduction, where the resolved material is subjected to additional synthetic steps or applied as a switchable chiral dopant in LC studies, a larger quantity of the material is required. Therefore, a stereoselective pathway to synthesize these motor molecules would be highly desirable.

In this chapter, first an overview is given of all attempts performed previously to synthesize these molecules in their enantiopure form. Emphasis will be on the enantioselective synthesis of the ketone precursors, which were already successfully coupled giving several enantiomerically pure first-generation motors. Two new and intuitively generally applicable synthesis routes to enantiomerically pure upper-half ketones are presented next. The bottleneck in the synthesis of second-generation motors is the so-called Barton-Kellogg coupling that requires steps under which complete racemization usually takes place. A modified
procedure to this coupling reaction, featuring the conversion of the enantiopure upper-half ketone to the corresponding \textit{tert}-butyldimethylsilylhydrazone for which the racemization was found to be strongly suppressed, is subsequently investigated. In the final part of this chapter, the new methodology is employed in the enantioselective synthesis of two second-generation light-driven molecular motors.

4.2 Overview of Early Attempts to Enantioselectively Synthesize Light-Driven Molecular Motors Based on Sterically Overcrowded Alkenes

In order to circumvent the inefficient method of preparative chiral HPLC to resolve the enantiomers of the light-driven motors after their synthesis, which has often proven to be a huge bottleneck in research where these systems are to be applied in their enantiopure form, several attempts have been made towards enantioselective synthesis routes, of which an overview is presented in this section. As was already shown in the previous chapters, synthesis of these overcrowded alkenes first requires the corresponding ketone precursor, which notably already contains the stereocenter, and a subsequent coupling reaction to form the sterically demanding central double bond. Stereoselective synthetic pathways to these molecules therefore can be dissected in two major parts: the enantioselective synthesis of the ketone, followed by a coupling reaction in which the chirality at the stereocenter is preserved.

4.2.1 Enantioselective Synthesis of Ketone Precursors

The first reported enantioselective synthesis of a ketone precursor of such an overcrowded alkene was published in 1997 by Harada, Feringa and co-workers and described the stereoselective synthesis of (\textit{R}-5 (Figure 4.1a).\textsuperscript{3} This method first requires the racemic synthesis of 1, which subsequently is reduced with NaBH\textsubscript{4} to give racemic \textit{cis}-alcohol 2 as the major product and the corresponding \textit{trans}-alcohol as a minor one. Racemic \textit{cis}-alcohol (\textpm)-2 was then esterified with acid 3 bearing a camphor-based chiral auxiliary, yielding a diastereomeric mixture of esters (1\textit{R},2\textit{R})-(\textpm)-4 and (1\textit{S},2\textit{S})-(\textpm)-4, separable by HPLC on silica gel. Subsequent removal of the chiral auxiliary via reduction with LiAlH\textsubscript{4} to yield the optically pure \textit{cis}-alcohol, followed by oxidation with pyridinium chlorochromate (PCC) yielded the desired methyl ketone (\textit{R}-5 in enantiomerically pure form. Via the same synthetic strategy, later also the enantioselective synthesis of five-membered ketone (\textit{S}-6 (Figure 4.1b) was described.\textsuperscript{4}
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Figure 4.1 a) Preparation of enantiomerically pure methyl ketone \((R)-5\) via the resolution of the corresponding cis-alcohol via esterification with a camphor-based chiral auxiliary, and b) 5-membered ring analogue \((S)-6\) for which this synthetic pathway involving resolution was also successfully applied.

A different stereoselective synthetic pathway towards these ketones has been developed in our group by Ter Wiel (Scheme 4.1a). This synthesis is based on an alkylation protocol developed by Evans, in which oxazolidinone \((S)-8\) is used as an auxiliary to accomplish a diastereoselective methylation.5 The first successfully synthesized enantiopure ketone in this way was \((S)-11.6\) First carboxylic acid chloride precursor \(7\) and chiral oxazolidinone auxiliary \((S)-8\) were prepared,
followed by their coupling to yield (S)-9. Subsequent alkylation with MeI then took place in a diastereoselective fashion, after which the acid was liberated from the auxiliary using hydrogen peroxide. Finally, after conversion of the carboxylic acid to the acid chloride using thionyl chloride, ring closure via a Friedel-Crafts reaction using aluminum trichloride yielded enantiomerically pure ketone (S)-11.

\[
\text{Scheme 4.1} \quad \text{Asymmetric synthesis routes, employing stereoselective alkylation methodology via the Evans oxazolidinone protocol, toward enantiomerically pure ketones a) (S)-11 and b) (R)-6.}
\]
This approach was also successfully used for the preparation of \((R)-6\) (Scheme 4.1b).\(^7\) In this asymmetric synthesis, \((S)-12\) is first acylated to yield \((S)-13\), which is then subjected to an alkylation with 2-(bromomethyl)naphthalene, affording \((R,S)-14\) with a diastereomeric excess of over 99%. Removal of the auxiliary followed by cyclization using the same conditions described above provided enantiomerically pure ketone \((R)-6\).

A different approach to the enantioselective synthesis of ketone 6 was taken by Dr. J. Vicario and Dr. R. Hoen in our group.\(^8\) The key step in their synthesis is an asymmetric rhodium-catalyzed hydrogenation reaction (Scheme 4.2), in which the active catalyst is a rhodium metal complexed by chiral phosphoramidite ligands. For this route, first the synthesis of acid 15 is required. Hydrogenation of 15 under meticulously optimized conditions\(^9\) using a mixed ligand system of tri(orthotoluene)phosphine and the phosphoramidite yielded carboxylic acid \((S)-16\) in 98% \(ee\), which was obtained enantiomerically pure after a single crystallization. Subsequent cyclization, via the formation of the acid chloride and a subsequent Friedel-Crafts reaction, afforded enantiomerically pure ketone \((S)-6\).

\[
\begin{align*}
15 & \quad \text{R}h(\text{COD})\text{BF}_4 \\
& \quad \text{P(ortho-Tol)}_3 \\
\rightarrow & \quad \text{25 bar H}_2 \\
& \quad \text{i-PrOH + H}_2\text{O} \\
& \quad 30^\circ\text{C} \\
& \quad \text{(S)-16} \\
& \quad 98\% \text{ ee} \\
& \quad (>99\% \text{ ee after cryst.}) \\
1 & \quad \text{SOCl}_2 \\
2 & \quad \text{AlCl}_3 \\
\rightarrow & \quad \text{(S)-6} \\
& \quad >99\% \text{ ee}
\end{align*}
\]

**Scheme 4.2** Stereoselective synthesis of ketone \((S)-6\) via an asymmetric rhodium-catalyzed hydrogenation step.

### 4.2.2 Non-Racemizing Coupling Conditions

In the synthesis of the first-generation light-driven molecular motors, whose structures feature two identical halves connected by a central carbon-carbon double bond, the coupling of two ketone precursors is required. This is achieved
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via a McMurry reaction (Scheme 4.3), in which first high-valent titanium is reduced in situ to form metallic Ti(0) particles, on whose surface the reduction and dimerization takes place.\textsuperscript{10} As a general method, a combination of TiCl\(_3\) as the high-valent titanium source and Zn powder as the reducing agent is used for this reaction. These reaction conditions were successfully employed to dimerize both six-membered ring based ketone (R)-5 and (S)-11 to provide the corresponding first-generation light-driven motors in enantiomerically pure form.\textsuperscript{3,6} In the case of five-membered ring based ketone (R)-6, these conditions however led to a fully racemized product, rendering the elegant routes to the enantiomerically pure ketone precursor completely useless.\textsuperscript{7} Later a modified procedure for the McMurry reaction was employed, in which not Zn but LiAlH\(_4\) is used as the reducing agent.\textsuperscript{4} Under these reaction conditions the configuration at the stereogenic centre bearing the methyl group is fully preserved.

Scheme 4.3 General synthesis of first-generation light-driven molecular motors via the McMurry reaction as shown for trans-17.

For the synthesis of second-generation light-driven molecular motors the McMurry approach is not very suitable, as the use of two different ketones in this reaction yields a complex mixture of different coupling products, which usually contains the desired cross-coupled product only in low amounts. A much more efficient method for their synthesis, as described in the previous chapters, is the coupling of a diazo compound and a thioketone in a so-called Barton-Kellogg reaction. This requires the conversion of the upper-half ketone to the corresponding hydrazone, which can subsequently be oxidized to the desired diazo compound, via treatment with hydrazine in refluxing EtOH. These reaction conditions, however, have been shown to lead to rapid racemization, owing to the basicity of hydrazine which causes enolization of the ketone. Also, an attempt to retain the stereochemical integrity via a Barton-Kellogg procedure with inverted functionalities, by conversion of the upper-half ketone to the corresponding thioketone which is subsequently reacted with a lower-half diazo compound, proved unsuccessful as the motor molecules appeared to be fully racemized after their isolation.

In pioneering studies to circumvent this problem, Dr. S. G. Davey in our group found that conversion of the ketone to the corresponding \textit{tert}-butyldimethylsilyl
(TBS) hydrazone by the use of 1,2-bis(TBS)hydrazine leads to a much lower extent of racemization. This work was based on an extensive study by Myers and co-worker who demonstrated the conversion of a series of ketones and aldehydes to the corresponding TBS hydrazones under relatively mild conditions.\textsuperscript{31} Deprotonation by hydrazine at the α-position, leading to the formation of the planar enolate, followed by non-stereoselective reprotonation is most probably the cause of the racemization under these conditions. Owing to the bulky TBS groups, 1,2-bis(TBS)hydrazine is much more sterically hindered as a base, which is probably the origin of the reduced amount of racemization. The bulky TBS groups also hamper its nucleophilicity, however both the presence of a Lewis acid catalyst and the fact that a Si-O bond is formed during the reaction result in its high reactivity towards the formation of the TBS-hydrazone. In an initial attempt, enantiopure ketone \((S)-6\) was converted to the corresponding TBS-hydrazone, which was then immediately treated with [bis(acetoxy)iodo]benzene, leading to oxidation to the diazo compound, and subsequently thioxanthone \textsuperscript{19} was added (Scheme 4.4).\textsuperscript{8} During work-up the reaction mixture was poured in water, upon which a large amount of crystals formed, which were analyzed and shown to consist of enantiomerically pure episulfide \((S)-20\). The small amount of episulfide that had not crystallized during work-up was then isolated and shown to be completely racemic. Apparently, racemization had taken place only to a minor extent.

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.4} Key steps in the synthesis of second-generation light-driven molecular motors via a modified version of the Barton-Kellogg reaction, in which first a TBS-hydrazone is formed, leading to a strong reduction in the extent to which racemization takes place.

Encouraged by this initial result, the TBS-hydrazone approach was further explored in order to investigate whether or not it could serve as a general non-racemizing method for the enantioselective synthesis of second-generation light-driven molecular motors. The conversion of a number of enantiopure ketone upper-halves to their corresponding TBS-hyrazones and their subsequent coupling to yield the overcrowded alkenes will be discussed in Section 4.4.
4.3 More Efficient Enantioselective Synthesis of Upper-Half Ketones

The three synthetic routes described in Section 4.2.1 are all suitable for the preparation of the desired enantiomerically pure ketones. In practice each of these syntheses has its drawbacks however, particularly towards large-scale synthesis. The use of a large and complex chiral auxiliary, which first needs to be synthesized, has to be coupled to and removed from the substrate in two separate synthetic steps. In fact, to separate the diastereoisomers this method requires the use of HPLC. The major goal in searching for a practical asymmetric synthesis of these molecules was actually avoiding HPLC, as it frequently can only be used for the separation of small quantities of material. Applying asymmetric alkylation is more suitable towards large-scale synthesis of the enantiopure ketones. Still, quite a number of synthetic steps are required, as also the chiral oxazolidinone first has to be prepared in two steps, and the conditions under which the asymmetric alkylation takes place need to be carefully controlled. Also the asymmetric hydrogenation pathway has its drawbacks: it requires an expensive rhodium precursor, synthesis of the phosphoramidite ligand, and the stereoselective outcome of reaction is also highly sensitive for the specific substrate used, meaning that the ligand combinations and reaction conditions applied have to be optimized for every new upper-half ketone to be synthesized with high enantioselectivity via this route.

It was envisioned that a more suitable way to synthesize enantiomerically pure ketone upper-halves would be to just use a commercially available enantiopure starting material, of which a successful example is given in this section. Another promising methodology, which employs an enzymatic kinetic resolution as the key step, will also be discussed.

4.3.1 Synthetic Strategy 1: Starting from Enantiomerically Pure Roche Ester

The first pathway that was investigated is based on an enantiomerically pure starting material: the commercially available “Roche ester” (R)-21 (Scheme 4.5). After the tosylation of the alcohol group, this moiety can be subjected to nucleophilic attack, for instance by thiophenols, or maybe even by naphthols. Subsequently, the hydrolysis of the ester has to proceed without racemization at the neighbouring stereogenic center, after which cyclization can be achieved as described before via Friedel-Crafts chemistry to afford the methyl ketone enantiomerically pure. In this way, the synthesis of a large number of enantiomerically pure six-membered ring upper-half ketones with varying heteroatoms at position X should be possible in a few simple steps.
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Scheme 4.5 Retrosynthetic analysis for the preparation of enantiomerically pure six-membered ring upper-half ketones starting from the commercially available Roche ester (R)-21.

Scheme 4.6 Synthesis of enantiomerically pure ketone (S)-25 starting from Roche ester (R)-21.

The first enantiomerically pure ketone that we attempted to synthesize via this route, (R)-25, was based on thionaphthol and (R)-21 (Scheme 4.6). First, the alcohol functionality present in the Roche ester was tosylated by treatment with tosyl chloride, triethylamine and dimethylaminopyridine, yielding tosylated Roche ester (R)-22 in 77%. In the next step, first cesium carbonate was added to thionaphthol dissolved in DMF, leading to a color change of the reaction mixture to orange, due to the formation of the thiolate anion. The addition of the tosylate led to a rapid disappearance of this yellow color, in accordance with the formation of (S)-23. After work-up of this reaction, the excess thionaphthol used for this reaction was the only impurity present, as shown by 1H NMR. This compound is also formed as
a side-product in the next step, therefore the crude methyl ester was used in the next step without further purification. Hydrolysis of the methyl ester was achieved by treatment with lithium hydroxide in aqueous THF, giving (R)-24 in 84% yield over two steps. Conversion of the carboxylic acid to the acid chloride was accomplished using oxalyl chloride and a catalytic amount of DMF, after which ring-closure to the desired ketone was achieved via a Friedel-Crafts reaction using aluminum trichloride, providing (R)-25 in 92% yield and 97% ee as determined with chiral HPLC.

As was already discussed in the previous chapter, the naphthalene group in the upper-half of the second-generation motor can be replaced by a xylyl moiety without significantly changing the isomerization behavior of the molecule, and this re-designed upper half provides an extra handle by which its rotary speed can be tuned. Furthermore, the introduction of substituents selectively at a certain position is much easier with the xylyl than with the naphthalene group. Therefore, also the synthesis of a xylyl-based ketone was pursued via the Roche ester pathway (Scheme 4.7). This synthesis started with the nucleophilic attack of 2,5-dimethylthiophenol on tosylated Roche ester (R)-22, followed by the same sequence of steps as described in Scheme 4.6. In this reaction sequence, (S)-27 was obtained after the hydrolysis step in 60% yield over the first two steps. Subsequent ring-closure gave (S)-28 in 84% yield and >99% ee as determined with chiral HPLC.

Scheme 4.7 Synthesis of enantiomerically pure xylyl-based ketone (S)-28 starting from tosylated Roche ester (R)-22.
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This Roche ester based pathway was also pursued for the synthesis of oxygen-containing six-membered upper-half ketones. The first step in this synthesis requires a nucleophilic attack of napthol onto the tosylated Roche ester (Scheme 4.8a). Owing to the much lower nucleophilicity of napthol compared to thionapthol, this step requires much harsher conditions. A number of attempts were performed to get this reaction to work, among others by increasing the temperature up to reflux conditions, however in none of these attempts any conversion of napthol was observed by TLC and 1H NMR. A possible explanation might be the degradation of (R)-22 under the harsh reaction conditions applied, most probably via elimination of the tosylate giving methyl methacrylate. The enantioselective synthesis of an oxygen-containing six-membered upper-half ketone via this route was not pursued further. However, if the Roche ester (R)-21 could easily be converted to the mono-tosylated diol (S)-30 (Scheme 4.8b), this substitution reaction should work, as this reaction has already been successfully applied using racemic 30 (see Chapter 7).

Scheme 4.8 a) Attempted synthesis of enantiopure upper-half ketone precursor (S)-29 by nucleophilic substitution on tosylated Roche ester (R)-22 using 2-naphthol, and b) the suggested mono-tosylated diol (R)-30, to which the Roche ester should be converted, onto which the substitution reaction would probably be successful.

4.3.2 Synthetic Strategy II: An Enzymatic Kinetic Resolution as Key Step

Recently, an elegant and potentially universally applicable synthetic methodology towards enantiomerically pure upper-half ketones was developed. This pathway, which was pioneered by Dr. F. Dumur and Dr. M. M. Pollard in our group, involves the conversion of an unsubstituted upper half ketone, usually easily obtained in a small number of steps, to an enantiomerically pure α-methoxy substituted ketone in only a few steps. A retrosynthetic analysis of this route for a five-membered ring based ketone is shown in Scheme 4.9a. After synthesis of the unsubstituted ketone 33, first α-hydroxylation is required to obtain α-hydroxy...
ketone 32 as a racemic mixture. In the following key step, this compound is subjected to an enzymatic kinetic resolution in which selectively only for one enantiomer of 32 the hydroxyl group is acetylated (Scheme 4.9b). The remaining enantiomer (S)-32 is then easily separated from the acetylated enantiomer by normal chromatography over silica. Finally, the hydroxyl functionality is methylated, as the hydroxyl group is not compatible with the following steps in the synthesis of the molecular motor. Dr. F. Dumur also completed the racemic synthesis of a second-generation molecular motor containing a methoxy substituent at the stereocenter. Investigating its isomerization behavior using various spectroscopic techniques, the proper functioning of this compound as a molecular motor was strongly indicated.

This enantioselective strategy suffers from one drawback which is inherent to a kinetic resolution pathway: the resolution step is always limited to a maximum yield of 50% - in fact, Dr. F. Dumur reported a yield of 43% for this step. Its potential applicability for a broad range of upper-half ketones is, however, a major advantage of this pathway. In the remainder of this section, the enantioselective synthesis of (S)-31, which was further optimized, will be discussed. To investigate the general applicability of this strategy, an attempt to synthesize a second α-
methoxy ketone, in which again the naphthalene moiety is replaced by a xylyl group, will also be discussed.

Scheme 4.10 Synthesis of methoxy ketone \((S)\)-31 via the enzymatic kinetic resolution of \(\alpha\)-hydroxy ketone \((S)\)-32.

For the enantioselective synthesis of \((S)\)-31 via this pathway (Scheme 4.10), first the synthesis of unsubstituted ketone 33 is required. A Friedel-Crafts acylation of 3-chloropropionyl chloride onto naphthalene 35 gave ketone 36 in 51% yield. Subsequent ring-closure via a Nazarov cyclization was achieved by heating of 36 to 90°C in concentrated sulphuric acid, giving unsubstituted ketone 33 in 59%. The introduction of the hydroxyl substituent at the \(\alpha\)-position was achieved via treatment of 33 with potassium hydroxide and the oxidizing agent \([\text{bis(acetoxy)iodo}]\)benzene in methanol, giving \(\alpha\)-hydroxy acetal 37 as an intermediate, which was converted to the desired \(\alpha\)-hydroxy ketone upon treatment with aqueous hydrochloric acid, yielding 32 in 62% over these two steps. The enzymatic kinetic resolution was performed by selective trans-esterification of the \(R\)-enantiomer with isopropenyl acetate using the enzyme Amano Lipase PS, in a polar organic solvent at room temperature overnight, following a procedure described for the enzymatic kinetic resolution of structurally
related compounds by Adam and coworkers.\textsuperscript{14} After its separation from the acetylated compound, ($S$)-32 was obtained in 47\% yield (a slight improvement to the 43\% yield reported by Dr. F. Dumur\textsuperscript{12}) and >99\% ee as determined by chiral HPLC.

The absolute configuration of $\alpha$-hydroxy ketone ($S$)-32 was assigned by analogy with the enzymatic resolution of ($\pm$)-2-hydroxy-2,3-dihydro-1H-inden-1-one.\textsuperscript{14} The final methylation step is somewhat challenging, as under the basic conditions that are usually applied for this transformation racemization of the stereogenic centre positioned $\alpha$ to the ketone moiety can be expected. Indeed, Dr. F. Dumur found that after the methylation step, performed with methyl iodide in the presence of silver oxide and the mild base calcium sulphate, the ee had dropped to 92\%.\textsuperscript{12} Reproducing this reaction, it was found that the extent of racemization could be minimized by strictly following the conditions described in the literature,\textsuperscript{15} and $\alpha$-methoxy ketone ($S$)-31 was isolated in 67\% yield with 98\% ee.

The second $\alpha$-methoxy upper-half ketone whose enantioselective synthesis was attempted via this enzymatic-resolution-based methodology, to demonstrate its general applicability, was xylil-based five-membered-ring ketone ($S$)-42 (Scheme 11). First, the unsubstituted ketone 40 was obtained via a Friedel-Crafts acylation of 3-chloropropionyl chloride with $p$-xylene 38, yielding 39 in 89\%, which was followed by a Nazarov cyclization under acidic conditions giving ketone 40 in 75\% yield. The subsequent $\alpha$-hydroxylation was performed by treatment of 40 with potassium hydroxide and 1 equivalent of [bis(acetoxy)iodo]benzene, followed by conversion of the acetal to the ketone under acidic conditions, giving 41 in a disappointing 28\% yield with a large amount of unsubstituted ketone 40 recovered. The yield of this reaction can probably be improved by increasing the amount of [bis(acetoxy)iodo]benzene. However, due to the disappointing outcome of the next step, the enzymatic kinetic resolution, this was not pursued. Whereas the enzyme displayed a high selectivity with the resolution of 41, in the case of xylil-based $\alpha$-hydroxy ketone 41 a slow conversion, in combination with a rather poor selectivity, was found following the reaction with chiral HPLC (Table 1). After one night, only 14\% of conversion was found. Addition of an extra batch of enzyme did lead to an enhanced conversion, and after another 24 h almost half of the starting material was acetylated. At this stage, theoretically the ee of the remaining $\alpha$-hydroxy ketone could have already been over 90\%, however a rather disappointing 20\% ee was determined. The addition of a third batch of enzyme was required to get the conversion up to 64\% after three days, when an ee of 34\% of the remaining $\alpha$-hydroxy ketone was determined. Prolonged reaction times did only lead to a slight further conversion, and also the ee of the remaining $\alpha$-hydroxy ketone dropped again, demonstrating the sensitivity to racemization of this compound under the reaction conditions. It therefore has to be concluded that the
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enzyme displays a much too slow conversion of the xylyl-based hydroxyl ketone, which slowly racemizes during the long reaction times required. This enzymatic pathway therefore appears to be less generally suitable than was hoped for initially, however could still be generally applicable for naphthalene-based ketones.

![Scheme 4.11 Attempted synthesis of α-methoxy ketone (S)-42 via the enzymatic kinetic resolution of α-hydroxy ketone (S)-41.](image)

**Table 4.1** Enzymatic kinetic resolution of α-hydroxy ketone 41.

<table>
<thead>
<tr>
<th>reaction time (h)</th>
<th>16*</th>
<th>40*</th>
<th>64</th>
<th>88</th>
<th>112</th>
</tr>
</thead>
<tbody>
<tr>
<td>conversion (%)</td>
<td>14</td>
<td>47</td>
<td>64</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>ee (%)</td>
<td>4</td>
<td>20</td>
<td>34</td>
<td>32</td>
<td>27</td>
</tr>
</tbody>
</table>

*: An additional batch of enzyme was added.

### 4.4 Non-Racemizing Coupling Conditions for the Synthesis of Second-Generation Light-Driven Motors

The standard methodology for the coupling of the two halves of the molecule forming the central overcrowded olefinic bond during the synthesis of second-generation light-driven molecular motors is the Barton-Kellogg reaction, which involves the coupling reaction between a diazo compound and a thioketone. This requires the conversion of the upper-half ketones to the corresponding hydrazones, generally accomplished by treatment with hydrazine at elevated temperatures, whose oxidation subsequently gives the desired diazo compound.
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needed for the coupling with a lower-half thiolactone. As discussed in Section 4.2.2, this pathway leads to fully racemized product, due to the basic nature of hydrazine. This base can deprotonate at the $\alpha$-position next to the carbonyl leading to enolization, and non-stereoselective re-protonation leads to rapid racemization of the ketone. As was also discussed in this section, a potential way to suppress this racemization process could be the use of 1,2-bis(TBS)hydrazine. The presence of the bulky TBS-groups makes this hydrazine analogue a very sterically hindered base. However, under certain optimized conditions conversion of the ketone to the TBS-hydrazone still takes place rapidly. In the following section, for a series of enantiomerically pure ketones (Figure 2), first the conversion to the corresponding TBS-hydrazones is analyzed, to see whether or not this step indeed in general takes place with strongly suppressed racemization at the $\alpha$-position. Thereafter, also the subsequent steps in the coupling - the oxidation to the diazo compound, the subsequent Barton-Kellogg reaction yielding the episulfide and the reduction of this compound to give the desired overcrowded alkene - are investigated in order to see if the synthesis of completely enantiomerically pure second-generation light-driven molecular motors is indeed viable via this route. But first, a more convenient method to synthesize the required 1,2-bis(TBS)hydrazine will be described.

![Figure 4.2](image)

**Figure 4.2** The four enantiomerically pure upper-half ketones to be converted to the corresponding TBS-hydrazones.

### 4.4.1 Synthesis of 1,2-Bis(TBS)hydrazine

The method for the preparation of 1,2-bis(TBS)hydrazine as reported by Myers and co-worker involves the use of anhydrous hydrazine as a reagent (Scheme 4.12a). Unfortunately, however, the sale of pure anhydrous hydrazine in Europe is prohibited as this reagent is highly explosive, and as a consequence we were unable to obtain it from any commercial supplier. The in-house preparation of anhydrous hydrazine via distillation is obviously also highly dangerous, and it can only be performed on a very small scale. In order to obtain the desired 1,2-bis(TBS)hydrazine in large quantities, needed because the TBS-hydrazone formations are performed “neat” in approximately a mL of this reagent, an alternative method for its preparation was used. This synthesis starts of with hydrazine monohydrochloride, which in the presence of two equivalents of TBS-
chloride was heated to 110°C in triethylamine (Scheme 4.12b). This reaction is of course hampered by the large amounts of triethylammonium chloride formed, which rapidly causes the reaction mixture to turn into a solid lump, requiring the reaction to be mechanically stirred vigorously and to add extra amounts of triethylamine a number of times during the reaction. The reaction can easily be followed by 1H NMR, by which it appeared difficult to get the conversion higher than 50%, and at a certain stage also the formation of TBS-alcohol was observed. At this point, it was therefore decided to work up the reaction, performed by an extraction with n-pentane to remove all the salts, after which the crude 1,2-bis(TBS)hydrazine was distilled under reduced pressure three times after which it proved to be completely pure. After only two distillations, the compound appeared to be completely pure by 1H NMR, however racemization in the following TBS-hydrazone formation step (vide infra) was suppressed to a much larger extent after a third distillation. A fourth distillation did not lead to a further suppression of racemization in this step. The incomplete conversion of the reaction and the number of distillation steps needed to purify the compound resulted in a rather poor yield of 27%. This save method can, however, be performed on much larger scale, still providing multiple milliliters of pure 1,2-bis(TBS)hydrazine.

Scheme 4.12 Synthesis of 1,2-bis(TBS)hydrazine via a) the original procedure of Myers et al. requiring explosive anhydrous hydrazine, and b) the more save alternative procedure which is based on hydrazine monohydrochloride as the starting material.

4.4.2 Conversion of the Ketones to the Corresponding TBS-Hydrazones

The conversion of ketones (S)-31, (S)-6, (S)-25 and (S)-28 to the corresponding TBS-hydrazones was performed next, monitoring the conversion by 1H NMR and the ee of both the ketone and the TBS-hydrazone by chiral HPLC. However, conditions for the separation of the enantiomers of the TBS-hydrzones by analytical chiral HPLC were very difficult to find. In fact, a good baseline separation was established only for TBS-hydrazone (S)-43, for (S)-44 only a slight, but far from baseline, separation was found. It was found, however, that for the corresponding hydrazones, obtained by a quick removal of the TBS-group using tetra-butylammonium fluoride (TBAF), in each case a very good separation on chiral
HPLC was established. Importantly, no racemization took place during this step, as proven for the conversion of both (S)-43 and (S)-44 to the corresponding hydrazones. Therefore, in each of the following reactions, the ee of the formed TBS-hydrazone was determined by HPLC analysis of the corresponding hydrazone after removal of the TBS-group using TBAF.

The first enantiomerically pure ketone whose conversion to the corresponding TBS-hydrazone was investigated, was (S)-31 (Scheme 4.13). The initial conditions used comprise of stirring a mixture of (S)-31 in 2 equivalents of 1,2-bis(TBS)hydrazine in the presence of 2 mol% of scandium triflate, a Lewis acid needed to catalyse the reaction, at 70°C. By 1H NMR it was shown that full conversion under these conditions was obtained after 45 min. HPLC analysis of the hydrazone showed that the product (S)-43 was obtained in 84% ee: a small but significant drop compared to the initial 98% ee of the ketone starting material. This result is in agreement with the original results from Dr. S. G. Davey, who found a large portion of enantiomerically pure product crystallizing from the mixture during work-up, and small amount of racemic product remaining in solution. In order to investigate the cause of this small degree of racemization, the ee of both ketone (S)-31 and of TBS-hydrazone (S)-43 was monitored during the conversion (Table 4.2).

<table>
<thead>
<tr>
<th>conversion (%)</th>
<th>0</th>
<th>20</th>
<th>50</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>ee ketone 31 (%)</td>
<td>98</td>
<td>91</td>
<td>84</td>
<td>47</td>
</tr>
<tr>
<td>ee TBS-hydrazone 43 (%)</td>
<td>93</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It was found that the ee of the initially formed TBS-hydrazone (S)-43, after 20% of conversion, was 93%, which is only slightly lower than the ee of the ketone starting material. During the conversion, the ee of ketone (S)-31, however, was found to gradually decrease: after 50% conversion, the ee of the ketone had dropped to 84%. As the reaction progressed, the ee of the formed TBS-hydrazone (S)-43 also
decreased, ending up at 84% ee when full conversion was reached. No further drop in ee of the TBS-hydrazone was observed after the conversion was complete, indicating that the small amount of racemization found is caused solely by gradual racemization of ketone (S)-31, not of hydrazone (S)-43, under these reaction conditions.

Two additional experiments were conducted to determine the cause of the decrease in ee. First, a mixture (S)-31 and 1,2-bis(TBS)hydrazine was stirred overnight at elevated temperature, in absence of scandium triflate. Both at 70°C and 100°C this resulted in only a marginal drop in ee of ketone (S)-31: 97% and 94% ee after overnight stirring at 70°C and 100°C, respectively. This effect is far too small to account for the observed loss in ee after the conversion to the TBS-hydrazone, since this conversion was completed in 45 min. In the second experiment, ketone (S)-31 and a catalytic amount of scandium triflate were dissolved in dichloroethane and stirred at 70°C. In this case, a rapid loss of enantiopurity of (S)-31 was observed: after 3 h the ee had dropped to 50%. These findings suggest that the scandium triflate is the major cause of racemization of (S)-31 during the formation of the TBS-hydrazone, most likely via reversible enolization of the ketone by this Lewis acid.

A number of attempts to further reduce the extent of racemization during this conversion are summarized in Table 4.3.

<table>
<thead>
<tr>
<th>entry</th>
<th>1,2-bis(TBS)hydrazine (eq)</th>
<th>Sc(OTf)3 (mol%)</th>
<th>temperature (°C)</th>
<th>ee 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>60</td>
<td>84</td>
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<td>3</td>
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<td>2</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>2</td>
<td>70</td>
<td>83</td>
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<td>6</td>
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<td>40</td>
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<tr>
<td>7*</td>
<td>8</td>
<td>0.4</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td>8*</td>
<td>2</td>
<td>0.1</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

*: Conversion was completed after 16 h, instead of 45 min.

Lowering the reaction temperature (entries 1-3), increasing the amount of 1,2-bis(TBS)hydrazine only (entry 4), or increasing the amount of both 1,2-bis(TBS)hydrazine and scandium triflate (entry 5) did not lead to an increase in ee of the product, however also not to a significant decrease. A larger amount of scandium triflate, however, did lead to a substantial decrease in ee of the product.
(entry 6). The Lewis acid again appeared to be the major cause of racemization, therefore the amount of scandium triflate was decreased. This however resulted in a much longer reaction time needed to achieve full conversion, causing a small decrease in $ee$ of the product (entry 7-8). Disappointingly, it has to be concluded that the small amount of racemization during the formation of the TBS-hydrazone observed initially has not been successfully suppressed by small alterations of the applied reaction conditions in the case of ketone (S)-31. Full suppression of racemization might be obtainable via a more thorough screening of conditions, including a wider range of Lewis acids. Such an extended screening study lies outside the scope of this work, however. Towards the main goal of this research, obtaining the second-generation light-driven molecular motor enantiomerically pure in a fast way and in rather large quantities, the 84% $ee$ in which the TBS-hydrazone is obtained can also be regarded sufficient. Via a quick recrystallization of the overcrowded alkene, the $ee$ can be increased to get the product enantiomerically pure, as was already demonstrated by Dr. S. G. Davey in his initial experiment.

**Scheme 4.14** Reaction conditions applied for the conversion of ketones (S)-6 (a), (S)-25 (b) and (S)-28 (c) to the corresponding TBS-hydrazones and the $ee$ values of these TBS-hydrazone.
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The results of the conversion of enantiomerically pure ketones (S)-6, (S)-25 and (S)-28 are summarized in Scheme 4.14. Ketone (S)-6, which had been stored about one year at room temperature, was found to have racemized to some extent: an ee of 78% was determined. It was decided, however, to use this partially racemized ketone and evaluate the ee of the formed TBS-hydrazone with respect to the 78% ee of the starting material. Compared to the formation of TBS-hydrazone (S)-43, the formation of (S)-44 required a higher reaction temperature (100°C), due to the higher steric hindrance caused by the methyl substituent compared to that of the methoxy group (Scheme 4.14a). Using the same amounts of 1,2-bis(TBS)hydrazine and scandium triflate as in the case of the formation of (S)-43, conversion again was found to be complete after 45 min and (S)-44 was obtained in 64% ee. As in this case a starting material with only 78% ee was used, the drop in ee over the course of this TBS-hydrazone formation is very similar to what was found in the case of the formation of (S)-43. Monitoring the ee of ketone 6 and TBS-hydrazone 44 over the course of the reaction using HPLC, it was again found that this small drop in ee was due to the gradual racemization of the ketone starting material.

The conversion of ketone (S)-25 to the corresponding TBS-hydrazone appeared to be much more difficult and required harsher reaction conditions (Scheme 4.14b). Full conversion was only achieved by stirring a mixture of (S)-25, 4 equivalents of 1,2-bis(TBS)hydrazine and 5 mol% of scandium triflate at 100°C for 3 h. Applying these reaction conditions, TBS-hydrazone (S)-45 was obtained in only 47% ee. Also the formation of TBS-hydrazone (S)-46 required more drastic reaction conditions: treatment with 3 equivalents of 1,2-bis(TBS)hydrazine and no less than 10 mol% of scandium triflate at 100°C were necessary to drive the conversion of (S)-28 to (S)-46 to completion in 3 h (Scheme 4.14c). TBS-hydrazone (S)-46 was obtained in only 30% ee. The fact that in the case of the six-membered ring based ketones (S)-45 and (S)-46 both a larger amount of Lewis acid and a longer reaction time is needed, by which the enantiopure ketone is subjected to stronger racemizing conditions for a longer period of time, results in the large drop in ee over the course of these reactions. This methodology has to be strongly improved in terms of reaction conditions in the case of these six-membered ring based ketones to be useful towards the enantioselective synthesis of second-generation molecular motors, as now the drop in ee is too large to be “repaired” by one or two crystallizations of the final overcrowded alkene. In the final part of this chapter, where the final steps in the synthesis of enantiomerically pure second-generation molecular motors via the Barton-Kellogg coupling are discussed, therefore only the five-membered ring based upper-half bearing a methoxy substituent will be used. The results obtained in this part are based on TBS-hydrazone (S)-43, which was obtained in 84% ee.
4.4.3 The Barton-Kellogg Coupling Reaction

After the conversion of enantiomerically pure ketone (S)-31 to the TBS-hydrazone with only a slight degree of racemization had been accomplished, it was expected that the ee would not be affected in the remaining steps in the synthesis of a second-generation light-driven molecular motor. Moreover, the ee of the products of the Barton-Kellogg coupling was anticipated to be amenable to improvement via recrystallization. The first motor molecule that was synthesized to test this was (S)-49. The thioketone lower-half that was required for this coupling is 47, which was available in our laboratories in large quantities. The coupling reaction was performed by concentrating a freshly synthesized sample of (S)-43 in vacuo to remove the excess of 1,2-bis(TBS)hydrazine, which was used without further purification in the coupling steps. To a solution containing (S)-43 and thioketone 47 in a 1:1 mixture of DMF and dichloromethane stirred at -50°C, PhI(OAc)$_2$ was added, after which the mixture was allowed to warm up to room temperature in the course of 2 h, affording episulfide (S)-48 in 33% yield from ketone (S)-31 (Scheme 4.15).

![Scheme 4.15 Synthesis of enantiomerically pure second-generation light-driven molecular motor (S)-49.](image-url)

Chiral HPLC analysis showed that the episulfide was obtained in 84% ee, which is identical to the ee of the TBS-hydrazone starting material. Moreover, the ee of the
Episulfide was successfully increased to >99% by recrystallizing the compound twice from ethyl acetate. This did obviously decrease the isolated yield: enantiomerically pure (S)-48 was obtained in 41% after the double recrystallization with respect to the crude product. Treatment of this mixture with triphenylphosphine in refluxing p-xylene smoothly converted the episulfide to the desired alkene (S)-49 without any racemization taking place, as determined by chiral HPLC.

The second molecular motor that was synthesized from TBS-hydrazone (S)-43 was (S)-52, bearing two “legs” with ester functionalities on its lower-half which allows grafting of this molecule to a surface via two points of attachment. Appropriately functionalized thioketone precursor 50 was kindly provided by Dr. M. M. Pollard, and using conditions identical to those described for the synthesis of (S)-49 the Barton-Kellogg coupling was accomplished (Scheme 4.16).

*Scheme 4.16 Synthesis of enantiomerically pure second-generation light-driven molecular motor (S)-52 bearing ester functionalities on its lower half allowing its “double-legged” attachment to a surface.*
The purification of episulfide (S)-51 proved to be challenging, as no conditions were found to separate it by column chromatography from the corresponding ketone of lower-half thioketone 50, formed during the reaction. Therefore, the crude mixture was treated with hydrazine, converting the ketone rapidly to the corresponding hydrazone which was easily separable from the episulfide, affording episulfide (S)-51 in 56% yield from ketone (S)-31. Chiral HPLC analysis showed that the episulfide was obtained in 84% ee, identical to the ee of the TBS-hydrazone, so it can be concluded that the configuration of the episulfide was not affected by the treatment with hydrazine. Again it was demonstrated that the ee of the episulfide can be increased up to enantiopurity via recrystallization: after two recrystallizations from iso-propanol, the ee of (S)-51 had been increased to >99% as determined by chiral HPLC. Enantiomerically pure (S)-51 was isolated in 52% yield after the double recrystallization with respect to the crude product. Subsequent desulphurization with triphenylphosphine finally yielded second-generation light-driven molecular motor (S)-52 containing a functionalized lower-half in 52% yield and >99% ee.

4.5 Conclusions

With the aim to develop a practical and broadly applicable enantioselective synthesis route toward second-generation light-driven molecular motors, in this chapter a number of new strategies have been presented. For the first step, the synthesis of enantiomerically pure ketone upper-halves, methodology employing the enantiopure “Roche ester” as a starting material proved useful for the synthesis of ketones based on a six-membered ring with a sulfur-atom incorporated. Unfortunately, the synthesis of a similar ketone with an incorporated oxygen atom in the ring via this route failed, due to the lower nucleophilicity of naphthol compared to thionaphthol in the key addition step. Alternatively, the enzymatic kinetic resolution of α-hydroxy ketones was used to generate, after a methylation step, an α-methoxy ketone enantiomerically pure. Also, the resolution of a xylyl-based α-hydroxy ketone was attempted via this enzymatic kinetic resolution, in this case unfortunately the enzymatic conversion proceeded slow and unselective, however. It therefore has to be concluded that both of these strategies to synthesize enantiopure upper-half ketones are less generally applicable than was initially hoped for.

Whereas the subsequent conversion of enantiomerically pure upper-half ketones to the corresponding hydrazones proceeds with rapid racemization, conversion to the corresponding TBS-hydrazones in a reaction with 1,2-bis(TBS)hydrazine resulted in suppression of racemization, depending on the substrate used. First a new and saver method for the preparation of 1,2-bis(TBS)hydrazine was developed. It was
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found that the conversion of five-membered ring ketones 31 and 6 to the corresponding TBS-hydrazones was readily achieved with strongly suppressed degrees of racemization, making this a viable route towards second-generation motors containing a five-membered ring in the upper-half. In the case of the six-membered ring based ketones 25 and 28 unfortunately a much higher degree of racemization over the course of the reaction was found, caused by the harsher conditions needed to achieve conversion. To make this synthetic route valuable for the enantioselective synthesis of second-generation motors containing six-membered ring in the upper-half, a more extensive study of reaction conditions, probably focused on different Lewis acid catalysts, would be required.

Finally TBS-hydrazone 43, which was obtained in 84% ee, was employed in the synthesis of two second-generation molecular motors. It was found that by recrystallization of the episulfides obtained after the coupling to the lower-halves, the small drop in ee suffered during the formation of the TBS-hydrazone could be “repaired”, and in both cases the desired overcrowded alkenes were obtained enantiomerically pure. In this way, relatively large amounts of enantiopure molecular motor compound can be accessed via an elegant synthetic route, circumventing tedious and time-consuming preparative chiral HPLC.

4.6 Acknowledgement

Most of the experiments described in this chapter were performed by Thomas C. Pijper during his undergraduate research project (MSc), who is gratefully acknowledged for his contributions.

4.7 Experimental Section

General remarks

For general remarks, see Section 2.6.

(R)-Methyl 2-methyl-3-(tosyloxy)propanoate (22)

To a solution of (R)-methyl 3-hydroxy-2-methylpropanoate (3.5 g, 30 mmol) in CH2Cl2 (50 mL), stirred at 0°C, triethylamine (5.0 mL, 3.6 g, 36 mmol), dimethylaminopyridine (0.73 g, 6 mmol) and tosyl chloride (6.8 g, 36 mmol) were added, and the mixture was stirred overnight during which it was allowed to
warm up to room temperature. The mixture was poured on water (100 mL), the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL), after which the combined organic layers were washed with a saturated solution of sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over sodium sulphate, concentrated \textit{in vacuo}, and purified by column chromatography (SiO₂, CH₂Cl₂ + 5% MeOH, Rᵣ = 0.5), affording the tosylate as a colourless oil (6.3 g, 23.2 mmol, 77%); ¹H NMR (400 MHz, CDCl₃) δ 1.13 (d, J = 6.6 Hz, 3H), 1.40 (s, 3H), 2.78 (m, 1H), 3.59 (s, 3H), 4.02 (dd, J = 15.4, 6.6 Hz, 1H), 4.14 (dd, J = 14.8, 6.0 Hz, 1H), 7.33 (d, J = 7.0 Hz, 2H), 7.73 (d, J = 6.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 12.1 (q), 20.1 (q), 37.7 (d), 50.5 (q), 69.2 (t), 126.4 (2xd), 128.3 (2xd), 131.6 (s), 143.4 (s), 171.8 (s); m/z (EI⁺, %) = 272 (M⁺, 20), 91 (100); HRMS (EI⁺): calcd for C₁₂H₁₆O₅S 272.0718, found 272.0712.

(S)-2-Methyl-3-(naphthalen-2-ylthio)propanoic acid (24)

Cesium carbonate (3.8 g, 11.6 mmol) was added to a solution of thionaphthol (3.5 g, 21.5 mmol) in DMF (150 mL). The mixture was stirred for 15 min, after which \((R)-22\) (4.5 g, 16.5 mmol) was added and the mixture was stirred for another h. The majority of the solvent was removed under reduced pressure, and subsequently the mixture was taken up in EtOAc (200 mL) and the organic solution was washed with an aqueous solution of HCl (0.1 M, 2 x 50 mL) and brine (50 mL). The organic layer was dried over sodium sulphate, concentrated \textit{in vacuo}, affording the crude methyl ester (S)-23 which was used without further purification in the hydrolysis step. ¹H NMR (400 MHz, CDCl₃) δ 1.26 (d, J = 6.6 Hz, 3H), 2.72 (m, 1H), 3.00 (dd, J = 14.4, 5.0 Hz, 1H), 3.36 (dd, J = 15.3, 5.4 Hz, 1H), 3.61 (s, 3H), 7.38-7.44 (m, 3H), 7.69-7.78 (m, 4H). To a solution of (S)-23 (4.3 g, 16.5 mmol) in THF (100 mL), stirred at room temperature, a solution of lithium hydroxide (1.2 g, 50 mmol) in water (75 mL) was added, and the mixture was stirred vigorously overnight. The mixture was poured onto an aqueous solution of HCl (10%, 100 mL) after which it was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulphate and concentrated \textit{in vacuo}, and purified by column chromatography (SiO₂, gradient n-pentane:EtOAc = 4:1, Rᵣ = 0.2, to pure EtOAc) affording acid (S)-24 as an off-white solid (3.4 g, 13.8 mmol, 84%); mp 99-101°C; ¹H NMR (400 MHz, CDCl₃) δ 1.31 (d, J = 6.8 Hz, 3H), 3.76 (m, 1H), 2.96 (dd, J = 15.2, 4.8 Hz, 1H), 3.38 (dd, J = 14.6, 5.8 Hz, 1H), 7.38-7.45 (m, 3H), 7.73-7.82 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 17.0 (q), 36.7 (t), 39.9 (d), 121.5 (d), 126.4 (d), 126.6 (d), 127.5 (d), 127.7 (s), 128.0 (d), 129.0 (d), 129.5 (d), 131.5 (s), 132.5 (s), 181.5 (s); m/z (EI⁺, %) = 246 (M⁺, 100), 173 (83); HRMS (EI⁺): calcd for C₁₄H₁₄O₂S: 246.0715, found: 225.0724.
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(S)-2-Methyl-2,3-dihydro-1H-benzo[f]thiochromen-1-one (25)

To a solution of (S)-24 (3.4 g, 13.8 mmol) in CH$_2$Cl$_2$ (150 mL), stirred at 0°C, oxalyl chloride (13.0 mL, 17.5 g, 138 mmol) was added, followed by a few drops of DMF, after which the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo and the residue dissolved in CH$_2$Cl$_2$ (100 mL). To the solution, stirred at 0°C, aluminum trichloride (5.5 g, 41.5 mmol) was added and the mixture was stirred for 1 h. The mixture was poured on a saturated aqueous solution of sodium bicarbonate (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulphate and concentrated in vacuo, affording ketone (S)-25 as a slightly yellow oil (12.7 g, 92%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.38 (d, $J$ = 6.4 Hz, 3H), 3.03-3.25 (m, 3H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.40 (t, $J$ = 8.8 Hz, 1H), 7.53 (t, $J$ = 8.6 Hz, 1H), 7.68-7.74 (m, 2H), 9.02 (d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 15.3 (q), 32.8 (t), 42.9 (d), 124.9 (d), 125.1 (d), 125.4 (d), 125.6 (s), 128.4 (d), 128.6 (s), 131.5 (d), 132.2 (d), 133.1 (s), 143.8 (s), 199.1 (s); m/z (EI+, %) = 228 (M+, 38), 186 (100); HRMS (EI+): calcd for C$_{14}$H$_{12}$OS: 228.0609, found: 228.0616. The ee was determined by HPLC analysis: Chiralpak AD, n-heptane:i-PrOH = 99.5:0.5, flow rate = 1.0 mL/min, Rt = 17.2 min (R), Rt = 18.6 min (S) (separation conditions found using racemic 25, synthesized before via a different route$^{18}$); ee: 97%.

(S)-3-(2,5-Dimethylphenylthio)-2-methylpropanoic acid (27)

Cesium fluoride (530 mg, 3.5 mmol) was added to a solution of 2,5-dimethylthiophenol (620 mg, 4.5 mmol) in DMF (20 mL), after which the mixture was stirred for 20 min at rt. (R)-22 (950 mg, 3.5 mmol) was added and the mixture was stirred for another h. The majority of the solvent was removed under reduced pressure, the mixture was taken up in EtOAc (100 mL) and the organic solution was washed with an aqueous solution of HCl (0.1 M, 2 x 50 mL) and brine (50 mL). The organic layer was dried over sodium sulphate and concentrated in vacuo affording the crude methyl ester (S)-26 which was used without further purification in the hydrolysis step. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.29 (d, $J$ = 7.0 Hz, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 2.70 (m, $J$ = 7.1 Hz, 1H), 2.88 (dd, $J$ = 13.2, 7.0 Hz, 1H), 3.23 (dd, $J$ = 12.8, 7.0 Hz, 1H), 3.67 (s, 3H), 6.92 (d, $J$ = 7.3 Hz, 1H), 7.05 (d, $J$ = 7.7 Hz, 1H).
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Hz, 1H), 7.19 (s, 1H). To a solution of (S)-26 (830 mg, 3.5 mmol) in THF (15 mL), stirred at room temperature, a solution of lithium hydroxide (240 mg, 10 mmol) in water (10 mL) was added, and the mixture was stirred vigorously overnight. The mixture was poured onto an aqueous solution of HCl (10%, 25 mL) after which it was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulphate and concentrated in vacuo, and purified by column chromatography (SiO2 gradient n-pentane:EtOAc = 4:1, Rf = 0.24, to pure EtOAc) affording acid (S)-27 as a slightly yellow oil (470 mg, 2.1 mmol, 60%). 1H NMR (400 MHz, CDCl3) δ 1.33 (d, J = 7.0 Hz, 3H), 2.31 (s, 3H), 2.35 (s, 3H), 2.73 (m, J = 7.0 Hz, 1H), 2.88 (dd, J = 13.0, 7.2 Hz, 1H), 3.26 (dd, J = 13.0, 6.8 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 7.15 (s, 1H); 13C NMR (100 MHz, CDCl3) δ 16.8 (q), 20.1 (q), 21.1 (q), 36.5 (t), 39.7 (d), 127.4 (d), 130.3 (2xq), 134.3 (s), 135.5 (s), 136.1 (s), 181.7 (s); m/z (EI+, %) = 224 (M+, 82), 151 (100); HRMS (EI+): calcd for C12H16O2S: 224.0871, found: 224.0867.

(S)-3,5,8-Trimethylthiochroman-4-one 28

To a solution of (S)-27 (300 mg, 1.45 mmol) in CH2Cl2 (15 mL), stirred at 0°C, oxalyl chloride (1.4 mL, 1.85 mg, 14.5 mmol) was added, followed by a few drops of DMF, after which the mixture was stirred at rt for 1 h. The mixture was concentrated in vacuo and the residue dissolved in CH2Cl2 (15 mL). To the solution, stirred at 0°C, aluminum trichloride (580 mg, 4.4 mmol) was added and the mixture was stirred for 1 h. The mixture was poured on a saturated solution of sodium bicarbonate (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulphate and concentrated in vacuo, affording ketone (S)-28 as a slightly yellow solid (233 mg, 84%). mp 45-47°C; 1H NMR (300 MHz, CDCl3) δ 1.30 (d, J = 6.2 Hz, 3H), 2.27 (s, 3H), 2.53 (s, 3H), 2.92-3.17 (m, 3H), 6.88 (d, J = 7.7 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 15.1 (q), 19.9 (q), 23.4 (q), 32.1 (t), 42.7 (d), 127.9 (d), 130.1 (s), 132.8 (d), 139.6 (s), 141.4 (s), 199.6 (s); m/z (EI+, %) = 206 (M+, 40), 164 (100); HRMS (EI+): calcd for C12H14O2S: 206.0765, found: 206.0755. The ee was determined by HPLC analysis: Chiralcel AD, n-heptane:i-PrOH = 99:1, flow rate = 1.0 mL/min, Rt = 5.9 min (R), Rt = 6.9 min (S) (separation conditions found using racemic 28, obtained by treatment of (S)-28 with KOH); ee: >99%.
Chapter 4

3-Chloro-1-(naphthalen-1-yl)propan-1-one (36)

Aluminum trichloride (34.2 g, 257 mmol) was suspended in dichloromethane (300 mL). 3-Chloropropionyl chloride (25.7 g, 202 mmol) was added and the mixture was cooled to 0°C. Naphthalene (25.7 g, 201 mmol) was added in portions over 15 min, after which the mixture was stirred overnight at room temperature and poured over ice (400 g). The layers were separated and the aqueous layer was extracted with dichloromethane (400 mL). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate (300 mL), dried over sodium sulphate and concentrated in vacuo. Purification by column chromatography (SiO₂, n-pentane:CH₂Cl₂:Et₂O = 75:20:5) yielded 36 as a grey oil (22.6 g, 51%). ¹H NMR (400 MHz, CDCl₃) δ 3.55 (t, J = 6.6 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 7.50-7.62 (m, 3H), 7.88-7.91 (m, 2H), 8.02 (d, J = 8.1 Hz, 1H), 8.66 (d, J = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 39.2 (t), 44.3 (t), 124.4 (d), 125.8 (d), 126.7 (d), 128.1 (d), 128.3 (d), 128.5 (d), 130.1 (s), 133.3 (d), 134.0 (s), 134.9 (s), 200.5 (s); m/z (EI⁺, %) = 218 (M⁺, 12), 155 (100); HRMS (EI⁺): calcd for C₁₃H₁₁ClO: 218.0498, found: 218.0484.

2,3-Dihydro-1H-cyclopenta[a]naphthalen-1-one (33)

Ketone 36 (22.6 g, 103 mmol) was added dropwise to concentrated sulphuric acid (100 mL) over 25 min. The mixture was heated at 90°C for 80 min, then poured on ice (400 g) after which it was extracted with dichloromethane (5 x 300 mL). The combined organic layers were washed with water (2 x 800 mL), dried over sodium sulphate and concentrated in vacuo. Purification by column chromatography (SiO₂, CH₂Cl₂) afforded ketone 33 as an orange solid (11.1 g, 59%). This compound was synthesized before via a different route, all spectroscopic data were according to those reported.
**2-Hydroxy-2,3-dihydro-1\textsubscript{H}-cyclopenta[a]naphthalen-1-one (32)**

Ketone 33 (5.0 g, 27.4 mmol) was dissolved in methanol (180 mL) and added dropwise to a solution of potassium hydroxide (4.60 g, 82.0 mmol) in methanol (75 mL) over a period of 15 min at 5°C. The mixture was stirred for 10 min, after which [bis(acetoxy)iodo]benzene (9.6 g, 29.8 mmol) was added in small portions over a period of 10 min. The mixture was stirred overnight at room temperature. The majority of the methanol was removed *in vacuo*, water (60 mL) was added, and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (4 x 50 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (20 mL) and acified with aqueous hydrochloric acid (15%, 40 mL). After stirring for 1 h, the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (4 x 80 mL), dried over sodium sulphate and concentrated *in vacuo*. Purification by column chromatography (SiO\textsubscript{2}, \textit{n}-heptane:EtOAc:MeOH = 16:4:1) yielded \(\alpha\)-hydroxy ketone 32 as a yellow solid (3.35 g, 62%). mp 143-145°C; \(\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta 3.02 (s, 1H), 3.14 (dd, \textit{J} = 16.9, 4.4 Hz, 1H), 3.67 (dd, \textit{J} = 16.7, 7.5 Hz, 1H), 4.61 (dd, \textit{J} = 7.3, 4.4 Hz, 1H), 7.52 (d, \textit{J} = 8.4 Hz, 1H), 7.58 (t, \textit{J} = 7.5 Hz, 1H), 7.70 (t, \textit{J} = 7.7 Hz, 1H), 7.91 (d, \textit{J} = 8.1 Hz, 1H), 8.11 (d, \textit{J} = 8.4 Hz, 1H), 8.99 (d, \textit{J} = 8.4 Hz, 1H); \(\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \delta 35.7 (t), 74.4 (d), 124.0 (d), 124.2 (d), 127.1 (d), 128.5 (d), 128.6 (s), 129.36 (d), 129.44 (s), 133.0 (s), 137.1 (d), 154.3 (s), 206.9 (s); m/z (EI+, %): 198 (M\textsuperscript{+}, 100); HRMS (EI\textsuperscript{+}): calcd for C\textsubscript{13}H\textsubscript{11}O\textsubscript{2}: 198.0681, found: 198.0675.

**Racemic hydroxy-ketone 32**

Racemic hydroxy-ketone 32 (1.80 g, 9.08 mmol) was dissolved in a mixture of \textit{tert}-butyl methyl ether (90 mL) and tetrahydrofuran (30 mL). Isopropenyl acetate (9.12 g, 91.1 mmol) and Amano Lipase PS from \textit{Pseudomonas cepacia} (1.36 g) were added, and the mixture was stirred overnight, carefully controlling the temperature between 22-26°C. The mixture was subsequently filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\textsubscript{2}, \textit{n}-heptane:EtOAc:MeOH = 16:4:1) yielded \(\alpha\)-hydroxy ketone (S)-32 as a yellow solid (845 mg, 47%, >99% \textit{ee}). The \textit{ee} was determined by HPLC analysis: Chiralcel OB-H, \textit{n}-heptane:i-PrOH = 90:10, flow rate = 0.5 mL/min, Rt = 22.9 min (R), Rt = 33.5 min (S).
Hydroxy-ketone (S)-32 (780 mg, 3.68 mmol, >99% ee) was dissolved in iodomethane (10 mL). Calcium sulphate (2.00 g, 14.7 mmol) and silver(I) oxide (2.45 g, 10.6 mmol) were added and the mixture was stirred overnight at rt. The mixture was filtered and the residue was washed with acetone, after which the filtrate was concentrated in vacuo. Purification by column chromatography (SiO₂, CH₂Cl₂) yielded methoxy ketone (S)-31 as an orange solid (561 mg, 67%, 98% ee). mp 60-62°C; ¹H NMR (400 MHz, CDCl₃) δ 3.13 (dd, J = 17.0, 3.9 Hz, 1H), 3.59 (dd, J = 17.1, 7.2 Hz, 1H), 3.70 (s, 3H), 4.28 (dd, J = 7.3, 4.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 9.07 (d, J = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 33.6 (t), 58.2 (q), 81.4 (d), 123.8 (d), 124.1 (d), 126.8 (d), 128.2 (d), 129.1 (s), 129.2 (d), 129.4 (s), 132.8 (s), 136.7 (d), 153.8 (s), 204.2 (s); m/z (EI⁺, %) = 212 (M⁺, 25), 182 (100); HRMS (EI⁺): calcd for C₁₄H₁₂O₂: 212.0837, found: 212.0829. The ee was determined by HPLC analysis: Chiralcel OB-H, n-heptane:i-PrOH = 90:10, flow rate = 0.5 mL/min, Rt = 20.5 min (R), Rt = 24.4 min (S).

3-Chloro-1-(2,5-dimethylphenyl)propan-1-one (39)

Aluminium trichloride (34.2 g, 257 mmol) was suspended in dichloromethane (300 mL). 3-Chloropropionyl chloride (25.7 g, 202 mmol) was added and the mixture was cooled to 0°C. p-Xylene (21.3 g, 201 mmol) was added in portions over 15 min, after which the mixture was stirred overnight at rt and poured on ice (400 g). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (300 mL), dried over sodium sulphate and concentrated in vacuo, yielding 39 as a brown liquid (35.2 g, 89%). ¹H NMR (400 MHz, CDCl₃) δ 2.37 (s, 3H), 2.47 (s, 3H), 3.38 (t, J = 6.8 Hz, 2H), 3.90 (t, J = 6.8 Hz, 2H), 7.15 (d, J = 7.7 Hz, 1H), 7.21 (dd, J = 7.7, 1.5 Hz, 1H), 7.45 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.7 (q), 20.8 (q), 39.1 (t), 43.7 (t), 129.2 (d), 132.0 (d), 132.5 (d), 135.3 (s), 135.4 (s), 136.8 (s), 200.4 (s); m/z (EI⁺, %) = 196 (M⁺, 17), 133 (100); HRMS (EI⁺): calcd for C₁₁H₁₃OCl: 196.0655, found: 196.0653.
Ketone 39 (34.0 g, 173 mmol) was added dropwise to concentrated sulphuric acid (200 mL) over 40 min. The mixture was heated at 90°C for 80 min, poured over ice (1000 g) and extracted with dichloromethane (3 x 600 mL). The combined organic layers were washed with water (3 x 1000 mL), dried over sodium sulphate and concentrated in vacuo, yielding unsubstituted ketone 40 as an light brown solid (21.1 g, 76%). mp 77-78°C; 1H NMR (400 MHz, CDCl₃) δ 2.31 (s, 3H), 2.60 (s, 3H), 2.65-2.68 (m, 2H), 2.95-2.98 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H); 13C NMR (100 MHz, CDCl₃) δ 17.4 (q), 18.0 (q), 24.2 (t), 36.6 (t), 129.1 (d), 132.8 (s), 134.1 (s), 134.3 (d), 135.8 (s), 154.8 (s), 208.3 (s); m/z (EI⁺, %) = 160 (M⁺, 100); HRMS (EI⁺): calcd for C₁₁H₁₂O: 160.0888, found: 160.0879.

A solution of 41 (2.00 g, 12.5 mmol) in methanol (60 mL) was added dropwise to a solution of potassium hydroxide (2.09 g, 37.3 mmol) in methanol (30 mL) over a period of 15 min at 5°C. After the mixture was stirred for 10 min, [bis(acetoxy)iodo]benzene (4.33 g, 13.4 mmol) was added in small portions over a period of 10 min, and the mixture was stirred overnight at room temperature. The majority of the methanol was then removed in vacuo, water (30 mL) was added, and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water (4 x 30 mL), dried on sodium sulphate and concentrated in vacuo. The mixture was dissolved in tetrahydrofuran (8 mL) and acidified with aqueous hydrochloric acid (15%, 8 mL). After stirring for 3 h, the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (4 x 30 mL), dried over sodium sulphate and concentrated in vacuo. Purification by column chromatography (SiO₂, n-heptane:EtOAc = 3:1) yielded α-hydroxy ketone 41 as a white solid (621 mg, 28%). mp 113-116°C; 1H NMR (400 MHz, CDCl₃) δ 2.30 (s, 3H), 2.59 (s, 3H), 2.81 (dd, J = 16.7, 4.6 Hz, 1H), 2.91 (d, J = 1.8 Hz, 1H), 3.45 (dd, J = 16.5, 8.1 Hz, 1H), 4.45 (m, 1H), 7.06 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H); 13C NMR (100 MHz, CDCl₃) δ 17.6 (q), 18.0 (q), 33.6 (t), 74.2 (d), 129.7 (d), 131.4 (s), 132.9 (s), 135.8 (d), 136.5 (s), 150.3 (s), 207.9 (s); m/z (EI⁺, %) = 176 (M⁺, 100); HRMS (EI⁺): calcd for C₁₁H₁₂O₂: 176.0837, found: 176.0829.
(S)-2-Hydroxy-4,7-dimethyl-2,3-dihydro-1H-inden-1-one (41)

Racemic hydroxy-ketone 41 (850 mg, 4.82 mmol) was dissolved in a mixture of tert-butyl methyl ether (50 mL) and tetrahydrofuran (16 mL). Isopropenyl acetate (4.83 g, 48.2 mmol) and Amano Lipase PS from Pseudomonas cepacia (723 mg) were added, and the mixture was stirred overnight, carefully controlling the temperature between 22-26°C. The reaction was monitored by HPLC analysis (Chiralcel OB-H, n-heptane:i-PrOH = 95:5, flow rate = 0.5 mL/min, Rt = 17.4 min (S), Rt = 21.5 min (R)). Under these conditions, the highest observed ee of 41 was 34%.

1,2-Bis(tert-butyldimethylsilyl)hydrazine

Triethylamine (25 mL) was slowly added at rt to a mixture of hydrazine monohydrochloride (3.43 g, 50.0 mmol) and tert-butyldimethylsilyl chloride (15.1 g, 100 mmol), after which the mixture was stirred at 110°C for 4 h 30 min. During the reaction, additional triethylamine (10 mL each time) was added after 5 min, 50 min, 1 h 30 min, and 2 h 20 min. The mixture was extracted with n-pentane (5 x 100 mL) and the combined layers were concentrated in vacuo. Two distillations under reduced pressure (85°C at 1 mmHg) yielded the product as a colourless liquid (3.5 g, 27%). 1H NMR (400 MHz, CDCl3) δ -0.02 (s, 12H), 0.88 (s, 18H), 2.34 (s, 2H); 13C NMR (100 MHz, CDCl3) δ -5.6 (q), 18.1 (s), 26.9 (q); m/z (EI+, %): 260 (M+, 83), 83 (100); HRMS (EI+): calcd for C12H23N2Si2: 260.2104, found: 260.2103.
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(S)-1-(tert-Butyldimethylsilyl)-2-(2-methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-ylidene)hydrazine (43)

Ketone (S)-31 (40.0 mg, 0.188 mmol), 1,2-bis(tert-butyldimethylsilyl)hydrazine (98 mg, 0.380 mmol) and scandium(III) triflate (1.8 mg, 3.7 μmol) were stirred at 70°C for 45 min. The mixture was concentrated in vacuo at 80°C and TBS-hydrazone (S)-43 was used in the subsequent step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 0.29 (s, 3H), 0.31 (s, 3H), 1.02 (s, 9H), 3.12 (dd, J = 17.6, 3.3 Hz, 1H), 3.29 (s, 3H), 3.44 (dd, J = 18.0, 8.1 Hz, 1H), 5.23 (dd, J = 8.1, 3.3 Hz, 1H), 6.86 (s, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.46 (m, 1H), 7.54 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 9.30 (d, J = 8.1 Hz, 1H); m/z (EI⁺, %): 340 (M⁺, 100), 251 (76); HRMS (EI⁺): calcd for C₂₀H₂₈N₂O_Si: 340.1971, found: 340.1974. The ee was determined by HPLC analysis: Chiralcel AD, n-heptane:i-PrOH = 99.5:0.5, flow rate = 1.0 mL/min, Rt = 4.6 min (S), Rt = 5.6 min (R) and was found to be 84%. (S)-43 was dissolved in tetrahydrofuran (10 mL). Tetra-n-butylammonium fluoride (234 mg, 0.9 mmol) was added, after which the mixture was stirred for 5 min. Ethyl acetate (100 mL) was added and the mixture was washed with water (4 x 50 mL), dried over sodium sulphate and concentrated in vacuo, affording hydrazone (S)-43H as a slightly brown solid. mp 76-78°C; ¹H NMR (400 MHz, CDCl₃) δ 3.15 (dd, J = 17.6, 3.3 Hz, 1H), 3.42 (s, 3H), 3.44 (dd, J = 17.4, 7.5 Hz, 1H), 5.16 (m, 1H), 6.26 (b, 2H), 7.34 (dd, J = 8.4 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 13C NMR (100 MHz, CDCl₃) δ 34.8 (t), 54.3 (q), 77.0 (d), 123.1 (d), 125.3 (d), 125.5 (d), 127.0 (d), 128.1 (d), 128.5 (s), 129.8 (d), 131.1 (s), 133.0 (s), 142.4 (s), 153.9 (s); m/z (EI⁺, %): 226 (M⁺, 100), 165 (96); HRMS (EI⁺): calcd for C₁₄H₁₄N₂O: 226.1106, found: 226.1105. The ee was determined by HPLC analysis: Chiralcel OD-H, n-heptane:i-PrOH = 90:10, flow rate = 0.5 mL/min, Rt = 20.2 min (S), Rt = 25.5 min (R); ee: 84%.
Ketone (S)-6 (40.0 mg, 0.204 mmol, 78% ee), 1,2-bis(tert-butyldimethylsilyl)hydrazine (106 mg, 0.408 mmol) and scandium(III) triflate (2.0 mg, 4.1 μmol) were stirred at 100°C for 2 h. The mixture was concentrated in vacuo (1 mmHg) at 80°C and TBS-hydrazone (S)-44 was used in the subsequent step without further purification. 1H NMR (400 MHz, CDCl3) δ 0.22 (s, 3H), 0.27 (s, 3H), 0.96 (s, 9H), 1.22 (d, J = 6.6 Hz, 3H), 2.63 (d, J = 15.6 Hz, 1H), 3.35-3.43 (m, 2H), 5.39 (s, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.48 (t, J = 8.1 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H); m/z (EI+, %): 324 (M+, 69), 267 (100); HRMS (EI +): calcd for C20H28N2Si: 324.2022, found: 324.2023. The ee was determined by HPLC analysis: Chiralcel AD, n-heptane:i-PrOH = 99.5:0.5, flow rate = 1.0 mL/min, Rt = 4.0 min (R), Rt = 4.3 min (S); ee: 64%. (S)-44 was dissolved in tetrahydrofuran (5 mL). Tetra-n-butyrammonium fluoride (260 mg, 1.0 mmol) was added, after which the mixture was stirred for 5 min. Ethyl acetate (100 mL) was added and the mixture was washed with water (4 x 50 mL), dried over sodium sulphate and concentrated in vacuo, affording (S)-44H as a brown oil. This compound was synthesized before via a different route,17 and all spectroscopic data were according to those reported. The ee was determined by HPLC analysis: Chiralcel OD-H, n-heptane:i-PrOH = 90:10, flow rate = 0.5 mL/min, Rt = 21.3 min (S), Rt = 29.1 min (R); ee: 64%.

Ketone (S)-25 (20.0 mg, 0.088 mmol, >99% ee), 1,2-bis(tert-butyldimethylsilyl)hydrazine (91 mg, 0.35 mmol) and scandium(III) triflate (1.7 mg, 4.3 μmol) were stirred at 100 °C for 3 h. The resulting mixture was concentrated in
vacuo (1 mmHg) at 100°C and TBS-hydrazone (S)-45 was used in the subsequent step without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.17 (s, 3H), 0.19 (s, 3H), 0.95 (s, 9H), 1.23 (d, $J = 6.8$ Hz, 3H), 2.64 (dd, $J = 15.2, 12.5$ Hz, 1H), 3.17 (dd, $J = 14.8, 4.5$ Hz, 1H), 3.49 (m, 1H), 5.63 (s, 1H), 7.29 (d, $J = 8.9$ Hz, 1H), 7.37-7.42 (m, 2H), 7.58 (d, $J = 9.1$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 8.47 (d, $J = 8.4$ Hz, 1H); m/z (EI+, %): 356 (M+, 91), 299 (100); HRMS (EI$^+$): calcd for C$_{20}$H$_{28}$N$_2$SiS: 356.1743, found: 356.1735. No conditions, in terms of analytical HPLC columns and eluent combinations, for the separation of the enantiomers of 45 were found, therefore the ee of TBS-hydrazone 45 could not be determined directly. It is however assumed to be identical to the ee of the corresponding hydrazone 45H, obtained after the next step. (S)-45 was dissolved in tetrahydrofuran (5 mL). Tetra-$n$-butylammonium fluoride (117 mg, 0.45 mmol) was added, after which the mixture was stirred for 5 min. Ethyl acetate (100 mL) was added and the mixture was washed with water (4 x 50 mL), dried over sodium sulphate and concentrated in vacuo, affording (S)-45H as a brown oil. This compound was synthesized before via a different route, and all spectroscopic data were according to those reported. The ee was determined by HPLC analysis: Chiralcel OD-H, $n$-heptane:i-PrOH = 90:10, flow rate = 0.5 mL/min, Rt = 35.7 min (R), Rt = 41.5 min (S); ee: 47%.

(S)-1-(tert-Butyldimethylsilyl)-2-(3,5,8-trimethylthiochroman-4-lidene)hydrazine (46)

Ketone (S)-28 (20.0 mg, 0.0969 mmol), 1,2-bis(tert-butyldimethylsilyl)hydrazine (101 mg, 0.388 mmol) and scandium(III)triflate (4.8 mg, 9.7 μmol) were stirred at 100°C for 3 h. The resulting mixture was concentrated in vacuo (1 mmHg) at 100°C and TBS-hydrazone (S)-46 was used in the subsequent step without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.16 (s, 3H), 0.19 (s, 3H), 0.92 (s, 9H), 1.18 (d, $J = 6.4$ Hz, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 2.53 (dd, $J = 12.7, 10.5$ Hz, 1H), 3.09 (dd, $J = 12.8, 6.2$ Hz, 1H), 3.36 (m, 1H), 5.46 (s, 1H), 6.92 (s, 2H); m/z (EI+, %): 334 (M+, 58), 277 (100); HRMS (EI$^+$): calcd for C$_{18}$H$_{30}$N$_2$SiS: 334.1899, found: 334.1887. No conditions, in terms of analytical HPLC columns and eluent combinations for the separation of the enantiomers of 46 were found, therefore the ee of TBS-hydrazone 46 could not be determined directly. It is however assumed to be identical to the ee of the corresponding hydrazone 46H, obtained after the next step. (S)-46 was dissolved in tetrahydrofuran (5 mL). Tetra-$n$-butylammonium
fluoride (130 mg, 0.5 mmol) was added, after which the mixture was stirred for 5 min. Ethyl acetate (100 mL) was added and the mixture was washed with water (4 x 50 mL), dried over sodium sulphate and concentrated in vacuo. Purification by column chromatography (SiO₂, n-heptane:EtOAc = 6:1 + 1% triethylamine) yielded (S)-46H as a slightly yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (d, J = 6.6 Hz, 3H), 2.29 (s, 3H), 2.39 (s, 3H), 2.53 (dd, J = 13.0, 10.4 Hz, 1H), 3.06 (dd, J = 12.8, 6.2 Hz, 1H), 5.40 (b, 2H), 3.33-3.43 (m, 1H), 6.97 (apparent s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 15.1 (q), 20.0 (q), 21.2 (q), 34.7 (d), 36.6 (t), 128.5 (d), 128.9 (d), 133.5 (s), 134.6 (s), 135.4 (s), 138.1 (s), 151.1 (s); m/z (El⁺, %): 220 (M⁺, 100), 188 (52); HRMS (El⁺): calcd for C₁₂H₁₆N₂S: 220.1034, found: 220.1033. The ee was determined by HPLC analysis: Chiralcel OD-H, n-heptane:i-PrOH = 95:5, flow rate = 0.5 mL/min, Rt = 24.2 min (R), Rt = 36.1 min (S); ee: 30%.

(S)-Dispiro[2,3-dihydro-2-methoxy-1H-cyclopenta[a]naphthalene-1,2-thiirane-3,9-(9H-thioxanthene)] (48)

Hydrazone (S)-43, freshly prepared from ketone (S)-31 (40.0 mg, 0.188 mmol), was dissolved in DMF (2 mL) and the solution was stirred at -50°C. 9H-thioxanthene-9-thione 47 (43.0 mg, 0.188 mmol) dissolved in a 1:1 mixture of DMF and dichloromethane (2 mL) was added, and subsequently [bis(acetoxy)iodo]benzene (60.5 mg, 0.188 mmol) dissolved in dichloromethane (2 mL), pre-cooled to -50°C, was added. The mixture was allowed to slowly warm up to rt, after which stirring was continued for 1 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (3 x 15 mL), dried over sodium sulphate and concentrated in vacuo. Purification by column chromatography (SiO₂, toluene) yielded episulfide (S)-48 as a yellow solid (26.4 mg, 33% over 2 steps from ketone (S)-31). The ee determination was performed by HPLC analysis: Chiralcel AD, n-heptane:i-PrOH = 99:1, flow rate = 1.0 mL/min, Rt = 13.7 min (S), Rt = 15.9 min (R); ee: 84%. Part of this product (14.8 mg) was recrystallized twice from ethyl acetate, thereby affording episulfide (S)-48 as a white solid (6.1 mg, 41%) in a total yield of 14% from ketone (S)-31; ee: >99%. mp 212-214°C; ¹H NMR (400 MHz, CDCl₃) δ 2.87 (d, J = 16.5 Hz, 1H), 2.95 (d, J = 4.4 Hz, 1H), 3.25 (s, 3H), 3.43 (dd, J = 16.3, 4.6 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 7.14-7.26 (m, 4H), 7.34 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 8.92 (d, J = 8.8 Hz, 1H); ¹³C NMR (100 MHz,
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CDCl₃ δ 36.8 (t), 57.0 (q), 60.8 (s), 67.5 (s), 86.5 (d), 123.3 (d), 124.4 (d), 124.6 (d), 124.9 (d), 126.2 (d), 126.8 (d), 126.9 (2xd), 127.1 (d), 127.3 (d), 127.8 (d), 128.8 (d), 129.8 (d), 130.9 (s), 131.0 (d), 131.4 (s), 133.0 (s), 134.3 (s), 136.1 (s), 136.8 (s), 138.9 (s), 141.4 (s); m/z (EI+, %): 424 (M⁺, 16), 392 (100); HRMS (EI⁺): calcd for C₂₇H₂₀O₂S₂: 424.0956, found: 424.0943.

(S)-9-(2-Methoxy-2,3-dihydro-1H-cyclopent[a]naphthalen-1-ylidene)-9H-thioxanthene (49)

A solution of episulfide (S)-48 (6.1 mg, 14.4 μmol, >99% ee) and triphenylphosphine (38 mg, 0.14 mmol) in p-xylene (4 mL) was stirred overnight at 125°C, after which the mixture was concentrated in vacuo. The crude product was redissolved in dichloromethane (5 mL) and iodomethane (2 mL) was added, after which the mixture was stirred at room temperature for 1 h in order to convert the excess triphenylphosphine to the corresponding phosphonium ylide. After concentration in vacuo, the residue was pulled over a short plug of silica using diethyl ether as the eluent to remove the phosphonium salts formed, and again concentrated in vacuo. The product was further purified by column chromatography (SiO₂, n-heptane:EtOAc = 1:1), giving (S)-49 as a white solid (5.0 mg, 87% yield). mp 156-158°C; ¹H NMR (400 MHz, CDCl₃) δ 2.83 (s, 3H), 3.03 (d, J = 16.1 Hz, 1H), 3.61 (dd, J = 15.9, 3.8 Hz, 1H), 5.67 (d, J = 4.0 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.79-6.86 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.64 (apparent d, J = 8.1 Hz, 3H), 7.70 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 39.8 (t), 55.3 (q), 80.3 (d), 123.7 (d), 124.4 (d), 125.1 (d), 126.3 (d), 126.4 (d), 126.5 (d), 126.8 (d), 126.9 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.9 (s), 129.0 (d), 130.4 (d), 133.3 (s), 133.7 (s), 134.8 (s), 135.4 (s), 136.0 (s), 137.6 (s), 139.4 (s), 139.5 (s), 144.9 (s); m/z (EI⁺, %) = 392 (M⁺, 56), 212 (100); HRMS (EI⁺): calcd for C₂₇H₂₀O₂S: 392.1235, found: 392.1238. The ee determination was performed by HPLC analysis: Chiralcel AD, n-heptane:i-PrOH = 99:1, flow rate = 1.0 mL/min, Rt = 10.7 min (S), Rt = 14.0 min (R) (separation conditions found using racemic 49, synthesized starting with racemic α-methoxy ketone 31); ee: >99%.
Hydrazone (S)-43, freshly prepared from ketone (S)-31 (40.0 mg, 0.188 mmol), was dissolved in DMF (2 mL) and the solution was stirred at -50°C. Thioketone 50 (72.0 mg, 0.188 mmol), dissolved in a 1:1 mixture of DMF and dichloromethane (2 mL), and subsequently [bis(acetoxy)iodo]benzene (60.5 mg, 0.188 mmol), dissolved in dichloromethane (2 mL) and pre-cooled to -50°C, were added. The mixture was allowed to slowly warm up to room temperature, after which stirring was continued for 1 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (3 x 15 mL), dried over sodium sulphate and concentrated in vacuo. The crude product was re-dissolved in chloroform (2 mL) and hydrazine monohydrate (0.1 mL) was added, after which the mixture was stirred at rt for 1 min. After concentration in vacuo, the product was purified by column chromatography (SiO₂, n-heptane:EtOAc = 3:1), yielding episulfide (S)-51 as a yellow solid (61.0 mg, 56% over 2 steps from ketone (S)-31). The ee determination was performed by HPLC analysis: Chiralcel OD, n-heptane:i-PrOH = 95:5, flow rate = 1.0 mL/min, Rt = 12.0 min (S), Rt = 26.7 min (R); ee: 84%. This product was recrystallized twice from isopropanol to afford episulfide (S)-51 as a white solid (31.8 mg, 52%) in a total yield of 29% from ketone (S)-31; ee: >99%. mp 144-145°C; ¹H NMR (400 MHz, CDCl₃) δ 1.48-1.86 (m, 5H), 2.11 (m, 1H), 2.51-2.64 (m, 2H), 2.76 (d, J = 17.6 Hz, 1H), 2.93 (dd, J = 17.8, 5.0 Hz, 1H), 3.25 (d, J = 5.1 Hz, 1H), 3.32 (s, 3H), 3.58 (s, 3H), 3.65 (s, 3H), 6.85 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.99-7.02 (m, 2H), 7.24 (t, J = 7.0 Hz, 1H), 7.32-7.53 (m, 6H), 8.05 (d, J = 7.3 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 9.32 (d, J = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 29.2 (t), 29.4 (t), 29.9 (t), 36.0 (t), 39.0 (t), 45.4 (s), 51.6 (q), 51.7 (q), 56.6 (q), 60.0 (s), 69.4 (s), 83.9 (d), 123.0 (d), 124.3 (d), 124.8 (d), 124.9 (d), 125.5 (d), 125.6 (d), 125.9 (d), 126.3 (d), 127.68 (d), 127.74 (d), 127.9 (d), 128.7 (d), 129.8 (d), 131.3 (s), 131.6 (s), 132.4 (d), 133.4 (s), 133.6 (s), 133.7 (s), 140.7 (s), 141.2 (s), 142.6 (s), 173.3 (s), 174.2 (s); m/z (EI⁺, %) = 578 (M⁺, 5), 459 (100); m/z (Cl⁺, %) = 596 (M NH₄⁺, 100), 564 (39); HRMS (EI⁺): calcd for C₃₆H₃₄O₅S: 578.2127, found: 578.2116.
A solution of episulfide $\text{(S)}$-51 (31.8 mg, 54.9 μmol, >99% ee) and triphenylphosphine (144 mg, 0.549 mmol) in p-xylene (4 mL) was stirred overnight at 125°C, after which the mixture was concentrated in vacuo. The crude product was redissolved in dichloromethane (5 mL) and iodomethane (2 mL) was added, after which the mixture was stirred at room temperature for 1 h in order to convert the excess triphenylphosphine to the corresponding phosphonium ylide. After concentration in vacuo, the residue was pulled over a short plug of silica using diethyl ether as the solvent to remove the phosphonium salts formed, and again concentrated in vacuo. The product was further purified by column chromatography (SiO$_2$, n-heptane:EtOAc = 3:1), giving $\text{(S)}$-52 as a yellow solid (15.6 mg, 52%, >99% ee). mp 173-174°C; $^1$H NMR (400 MHz, CDCl$_3$) δ 2.14 (t, $J = 8.3$ Hz, 2H), 2.46-2.67 (m, 4H), 2.85 (s, 3H), 2.76-2.91 (m, 2H), 3.03 (d, $J = 15.8$ Hz, 1H), 3.50 (s, 3H), 3.60 (dd, $J = 15.6$, 3.9 Hz, 1H), 3.70 (s, 3H), 5.93 (d, $J = 3.7$ Hz, 1H), 6.60 (t, $J = 7.5$ Hz, 1H), 6.70-6.82 (m, 3H), 7.11-7.19 (m, 2H), 7.33-7.39 (m, 2H), 7.47-7.53 (m, 3H), 7.70-7.75 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 27.6 (t), 29.5 (t), 30.6 (t), 36.7 (t), 39.9 (t), 47.0 (s), 51.8 (q), 51.9 (q), 56.1 (q), 80.5 (d), 123.8 (d), 124.4 (d), 124.7 (d), 125.7 (d), 125.8 (d), 126.0 (d), 126.1 (d), 126.4 (d), 127.1 (2xd), 128.3 (d), 128.5 (d), 128.7 (d), 129.0 (s), 130.2 (d), 132.8 (s), 133.3 (s), 135.7 (s), 138.9 (s), 139.4 (s), 139.6 (s), 139.9 (s), 141.5 (s), 144.9 (s), 173.3 (s). m/z (EI$^+$, %) = 546 (M$^+$, 59), 427 (100); HRMS (EI$^+$): calcd for C$_{36}$H$_{34}$O$_5$: 546.2406, found: 546.2389. The ee determination was performed by HPLC analysis: Chiralcel OD, n-heptane:i-PrOH = 95:5, flow rate = 1.0 mL/min, Rt = 16.3 min (S), Rt = 39.5 min (R) (separation conditions found using racemic 52, synthesized starting with racemic α-methoxy ketone 31); ee: >99%.
Chapter 4

4.8 References


8 R. Hoen, Ph.D. Thesis, University of Groningen, 2006, Ch. 5.


12 Unpublished result.

13 This methodology towards α-hydroxylation was developed by Moriarty, see: R. M. Moriarty, H. Hu, S. C. Gupta, *Tetrahedron Lett.* 1981, 22, 1283-1286.


15 To prevent racemization, non-basic conditions are required, therefore this procedure developed by Pearlman was employed, see: B. A. Pearlman, *J. Am. Chem. Soc.* 1979, 101, 6404-6408.

