Synthesis of Dimeric tetrahydro-beta-carbolines as Bivalent Receptor Ligands. An asymmetric N-Sulfinyl Pictet-Spengler Approach

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Abstract
The influence of chiral $N$-sulfinyl groups on the stereochemistry of the Pictet-Spengler reactions has been investigated. $(R)$-$N$-$p$-Tolylsulfynyl tryptamine was obtained in one step from tryptamine and the commercially available Andersen reagent. $N$-Sulfinyl Pictet-Spengler reaction of this compound with aliphatic aldehydes in the presence of camphorsulfonic acid or $\text{BF}_3\cdot\text{OEt}_2$ resulted in the efficient formation of $N$-sulfinyl tetrahydro-β-carbolines with moderate to good diastereoselectivity. The optimisation of the reaction conditions for the $N$-sulfinyl Pictet-Spengler cyclization will be described in this chapter. Efficient separation of the diastereomers and removal of the $N$-sulfinyl group under mild acidic conditions furnished a new route to enantiopure tetrahydro-β-carbolines with aliphatic and benzylic substituents.
§ 4.1 Introduction

Many naturally occurring alkaloids and their synthetic analogs contain tetrahydro-β-carboline ring systems. This has resulted in a large amount of efforts to influence the stereochemistry of the Pictet-Spengler cyclization, one of the main synthetic procedures for the preparation of tetrahydro-β-carboline ring systems. In chapter 3 of this thesis, we have reviewed some chiral auxiliary approaches to the Pictet-Spengler reaction that have been described in the literature. Furthermore, we described some of our efforts to influence the stereochemistry by the introduction of chiral auxiliaries at different sites in the molecule.

It was shown that substituents on the \( N\)-nitrogen of tryptamine can have a strong effect on the reactivity and stereoselectivity of the Pictet-Spengler reaction. In § 3.6.3, the \( N\)-sulfinyl group was introduced as a chiral auxiliary for the Pictet-Spengler reaction. The enhanced reactivity of the intermediate \( N\)-sulfinyl iminium ion 1 combined with the good synthetic availability of \( N\)-sulfinyl tryptamines make this group potentially interesting. However, the main advantage of the \( N\)-sulfinyl group as a chiral auxiliary is that the chiral sulfur atom is connected directly to the iminium nitrogen atom. It may therefore be expected that it has a strong effect on the stereoselectivity of the Pictet-Spengler cyclization (scheme 4.1). In this chapter the development of \( N\)-sulfinyl groups as effective chiral auxiliaries in the Pictet-Spengler reaction will be presented.

![Scheme 4.1](image)

§ 4.2 Chiral Sulfinyl Groups in Organic Synthesis

The use of chiral sulfoxides in organic synthesis has found ample precedent in the literature. Apart from many other applications, they have especially found their application as chiral auxiliaries in the synthesis of enantiopure amines. The pioneering work of Davis and coworkers has revealed that enantiopure amines are very well accessible, starting from \( N\)-sulfinyl imines.

The addition of organometallic reagents to the imine double bond is an important pathway to the synthesis of amine derivatives. However, this approach usually suffers from the low electrophilicity of the unsubstituted imine. Therefore, the use of chiral \( N\)-sulfinyl imines as electrophiles is advantageous since the enhanced electrophilicity of \( N\)-sulfinyl imines over the nonsubstituted analogs drastically increases the reactivity of the C-N double bond. More importantly, the stereochemical outcome of the reaction is directed by the chiral sulfur atom that is located closely to the reactive center.
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

Treatment of the enantiopure N-sulfinyl imine 2 with organometallic reagents furnishes N-sulfinyl amines 3 in often excellent diastereoselectivity. The lability of the N-S bond in the resulting N-sulfinyl amine under acidic conditions allows for the hydrolytic cleavage after separation of the diastereoisomers to afford a primary amine with a new stereocenter (scheme 4.2). By making use of this methodology, the use of N-sulfinyl imines has found numerous applications in the synthesis of enantiopure building blocks for asymmetric synthesis of complex molecules.

Scheme 4.2

\[
\begin{align*}
R_1 & \quad N \quad S \quad Ar \\
R & \\
\rightarrow \\
R_1 & \quad H \\
R_2 & \\
\rightarrow \\
R_1 & \quad NH_2 \\
R_2 & \\
\end{align*}
\]

Scheme 4.2 gives a short overview of the different enantiopure building blocks that have been prepared starting from N-sulfinyl imines. Enantiopure α-amino acids can be obtained by an asymmetric Strecker reaction of enantiopure N-sulfinyl imines 5. These building blocks have for instance been used for the synthesis of the Astatins A, B and C, a class of cytotoxic pentapeptides isolated from \textit{A. tataricus}.

Scheme 4.3
The unnatural amino acid (R)-(4-methoxy-3,5-dihydroxyphenyl)glycine, a central building block for the glycopeptide antibiotic vancomycin, was also prepared by using the N-sulfinyl imine Strecker protocol in stead of previously reported inefficient synthetic routes. Cyclization of enantiopure oxo-amino acids that were obtained from N-sulfinyl imines resulted in enantiopure proline and piperolic acid derivatives. Asymmetric addition of ester enolates to N-sulfinyl imines resulted in the formation of enantiopure $\beta$-amino acids.

Enantiopure substituted aziridines that are obtained by a Darzens type reaction of the lithium enolate of methyl bromoacetate or dimethylsulfoxonium methylide with enantiopure N-sulfinyl imines 5 have found many applications in asymmetric synthesis. Ring-opening of the aziridine ring has provided a valuable building block for the synthesis of the antibiotic (+)-thiamphenicol. Other applications of these enantiopure aziridines are the syntheses of $\alpha$-alkyl-$\beta$-amino acids and the C13-side chain of taxol. Oxidation of the aziridine ring provided a synthetic entry to the antibiotic (-)-dysdazirine. In a different approach chiral non-racemic 2-arylpyrrolidines were prepared via a [3+2] cycloaddition reaction of N-sulfinyl imines.

From scheme 4.3 it can be concluded that enantiopure N-sulfinyl imines of type 5 are excellent starting materials for the synthesis of enantiopure building blocks. The synthesis of 5 was initially attempted by asymmetric oxidation of N-sulfinimines with oxaziridines (scheme 4.4). However, the asymmetric induction for aliphatic and aromatic sulfinimines 6 reaches a maximum of 90% enantiomeric excess, which makes this method insufficient. Another synthetic route to N-sulfinimines with enhanced optical purity involves the partial reduction of nitriles to the metalaldimines which are activated as the ate complex 8 by addition of methyl lithium. Subsequent reaction with the commercially available Andersen reagent (-)-9, an enantiomerically pure menthyl ester of $p$-toluene-sulfonic acid, affords enantiopure aromatic and $\alpha$- and $\beta$-unsaturated N-sulfinyl imines in moderate yields but is not applicable to the synthesis of aliphatic N-sulfinyl imines.
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

The most efficient and generally applicable synthetic route towards enantiopure N-sulfinyl imines also starts from the Andersen reagent. Treatment of (-)-9 with LiHMDS at low temperature and subsequent addition of an appropriate aldehyde or ketone affords the desired N-sulfinyl imine in excellent yield and enantiopurity (scheme 4.5).

§ 4.3 Racemic N-Sulfinyl Pictet-Spengler Cyclizations

§ 4.3.1 Optimization of the Reaction Conditions

The development of the N-sulfinylimine chemistry described above has furnished a reliable route to enantiopure amines. Even though the reactivity of the imine double bond is good, in most cases strong nucleophiles were used in the addition reactions. The \textit{in situ} formation of an N-sulfinyliminium ion drastically increases the electrophilicity of the imine double bond and thus facilitates the addition of weaker nucleophiles (scheme 4.6).
In § 3.6.3 it was shown that racemic N₆-p-tolylsulfinyltryptamine 10 reacts with hexanal in the presence of trifluoroacetic acid to afford the tetrahydro-β-carboline 11. The yield of the reaction is however only moderate, which can be explained by the hydrolysis of the starting material under the protic acidic reaction conditions. Furthermore, the diastereoselectivity of the reaction was low. In the following paragraphs the optimization of the reaction conditions of the N-sulfinyliminium ion cyclization of 10, that was obtained by reaction of tryptamine with p-tolylsulfinyl chloride, will be discussed.

One of the first approaches was to study the N-sulfinyl Pictet-Spengler reaction of 10 under neutral conditions, in order to avoid the problems with its stability under acidic conditions. However, condensation of N₆-sulfinyl tryptamines with aldehydes did not proceed under neutral conditions, even at elevated temperatures. The N-sulfinyl tryptamine 10 was stable under these conditions. The failure of the cyclization under neutral conditions can be explained by the low nucleophilicity of the N₆-amino group due to the presence of the electronwithdrawing sulfinyl substituent. Formation of the iminium ion can be accomplished by activation of the aldehyde under acidic conditions, as was already shown (scheme 4.6).

Since it was shown that catalysis by trifluoroacetic acid furnished the cyclization product as a 52:48 mixture of diastereoisomers and in moderate yield, we attempted the reaction under milder acidic conditions, and at lower temperatures. Anticipating on the lability of the N-sulfinyl group under acidic conditions we first attempted the N-sulfinyl Pictet-Spengler reaction in the presence of the weakly acidic PPTS. Under these conditions only the starting material was recovered, even at elevated temperatures (e.g. toluene reflux). Reactions in the presence of acetic acid at room temperature resulted in hydrolysis of the starting material. Also reaction with p-toluenesulfonic acid did not give satisfying results (i.e. low yield and diastereoselectivity).

The best results for the N-sulfinyl Pictet-Spengler reaction of 10 with hexanal were obtained with 10-camphorsulfonic acid (CSA) as the acid catalyst in a 1:1 mixture of dry chloroform and dichloromethane at -78 °C, which gave an optimal balance between the reaction time and the diastereoselectivity. This solvent system was used since pure chloroform solidifies at -78 °C and the solubility of the sulfinyltryptamine in pure dichloromethane is low at this temperature. As can be seen from table 4.1, the reaction of aliphatic aldehydes proceeds smoothly under these reaction conditions. With branched aldehydes the reactions were slower and substoicheometric concentrations of CSA were required. Further increase of the amount of the acid catalyst to shorten the reaction time resulted in hydrolysis of the starting material. The steric effect of the bulky alkylsubstituent strongly decreased the rate of the reaction, but showed only a marginal effect on the diastereoselectivity.

The reaction was quenched by the addition of an excess of triethylamine at -78 °C and subsequent warming of the reaction mixture to room temperature. After evaporation of the solvents, the major diastereomer was obtained in pure form by a single crystallization from ethyl acetate.
Table 4.1

<table>
<thead>
<tr>
<th>No</th>
<th>R</th>
<th>Time (h)</th>
<th>CSA (eq)</th>
<th>Yield (%)</th>
<th>Ratio</th>
<th>Yield major isomer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Methyl</td>
<td>4</td>
<td>0.2</td>
<td>75</td>
<td>76:24</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>Ethyl</td>
<td>4</td>
<td>0.2</td>
<td>82</td>
<td>73:27</td>
<td>58</td>
</tr>
<tr>
<td>14</td>
<td>Propyl</td>
<td>4</td>
<td>0.2</td>
<td>80</td>
<td>78:22</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>Butyl</td>
<td>4.5</td>
<td>0.2</td>
<td>84</td>
<td>81:19</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>Penty l</td>
<td>4.5</td>
<td>0.2</td>
<td>69</td>
<td>83:17</td>
<td>55</td>
</tr>
<tr>
<td>16</td>
<td>Isobu ty l</td>
<td>8</td>
<td>0.6</td>
<td>71</td>
<td>81:19</td>
<td>54</td>
</tr>
<tr>
<td>17</td>
<td>Isopropyl</td>
<td>20</td>
<td>0.6</td>
<td>78</td>
<td>86:14</td>
<td>65</td>
</tr>
<tr>
<td>18</td>
<td>Cyclohexyl</td>
<td>20</td>
<td>0.6</td>
<td>73</td>
<td>88:12</td>
<td>62</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) CSA, CH$_2$Cl$_2$, CHCl$_3$, -78 °C.
* After column chromatography * Diastereomeric ratio as determined by $^1$H-NMR * After crystallization.

When aromatic aldehydes were used as substrates no cyclization was observed under proptic acidic conditions. This is most likely caused by the resonance stabilization of N-sulfinyl iminium ions of type 20 (scheme 4.7). Reactions with benzaldehyde and furfural did not proceed, even at higher temperatures and higher concentrations of the acid catalyst. Decomposition of the starting material was a competitive side-reaction at -20 °C and 0.2 equivalents of CSA. As can be seen from table 4.1, the amount of the acid catalyst could be raised to 0.6 equivalents at -78 °C before decomposition occurred.

Scheme 4.7

Reactions with nitrosubstituted benzaldehydes with increased electrophilicity of the resulting iminium salt also did not lead to product formation. It seems unlikely that the unreactivity of the aromatic aldehydes can be attributed solely to the steric bulk of the
aromatic ring, since the sterically demanding cyclohexyl substituted iminium ion 21 does undergo cyclization.

Isoprenyl substituents at the C1-position of tetrahydro-β-carbolines can be found in numerous natural products. The influence of resonance stability of the iminium ion is also reflected in the reactions that were attempted with α,β-unsaturated aldehydes. Acrolein, crotonaldehyde and 3-methylcrotonaldehyde were condensed with $N_{\alpha \beta}$-p-tolylsulfinyl tryptamine 10 in the presence of varying concentrations of CSA and at temperatures ranging from -78 °C to 0 °C. Unfortunately, in all these reactions no cyclization products could be isolated.

Pictet-Spengler reactions with other substrates than aldehydes have found ample precedent in the literature, as is described in chapter 2. From condensation of methylethyl ketone with 10 no cyclization products could be isolated (scheme 4.8). In another approach propionaldehyde dimethylacetal was reacted with $N_{\alpha \beta}$-p-tolylsulfinyl tryptamine in the presence of CSA but no products could be isolated.

![Scheme 4.8](image)

**Reagents and conditions:** (a) CSA or BF$_3$·OEt$_2$, CH$_2$Cl$_2$, CHCl$_3$, -78 to -60 °C; (b) CSA, CH$_2$Cl$_2$, CHCl$_3$, -78 to -60 °C.

There can be several reasons for the failure of the reactions that were mentioned above. Cyclization might be prevented for electronic or steric reasons. The first requirement for the cyclization is the successful formation of the intermediate $N$-sulfinyl iminium ion. In order to investigate their formation, we attempted to trap the intermediate imines by reduction to the corresponding amines (scheme 4.9). Since the solvent system (dichloromethane/chloroform) is not suitable for the use of sodium borohydride we attempted the reduction of the *in situ* formed $N$-sulfinyl iminium ion with other reducing agents. Addition of phenylsilane or diisobutyl aluminiumhydride to the reaction mixtures of the Pictet-Spengler cyclizations with benzaldehydes, α,β-unsaturated aldehydes, methylethyl ketone and propionaldehyde dimethylacetal however did not furnish amines of type 23.

![Scheme 4.9](image)
§ 4.3.2 Cyclizations Under Lewis Acidic Conditions

In principle, Pictet-Spengler reactions of \( N \)-sulfinyl tryptamines in the presence of protic acids conflict with the well-described lability of the \( N \)-sulfinyl group under protic acidic conditions. As was shown above, this lability is an important limitation in the optimization of the reaction conditions of the \( N \)-sulfinyl Pictet-Spengler reaction. For this reason we studied the effect of Lewis acids on the cyclization reaction.

In general, the use of Lewis acids led to the formation of enamine products in stead of the desired \( N \)-sulfinyl iminium ions. In most cases, even at -78 °C, complex mixtures of products were obtained from reactions with \( \text{Et}_2\text{AlCl} \), \( \text{Sc(OTf)}_3 \) and \( \text{Yb(OTf)}_3 \), probably due to intermolecular reactions of the reactive enamines. This can possibly be explained by the absence of a proton donor which would shift the imine-enamine equilibrium to the side of the imine. The use of \( \text{TiCl}_4 \), \( \text{SnCl}_4 \) and \( \text{ClTi(O-Pr)}_4 \) resulted in the decompostion of the starting material. Reactions in the presence of \( \text{ZnCl}_2 \) and \( \text{Ti(O-Pr)}_4 \) did not give any product formation. The use of the chiral Lewis acid diisopinocampheylchloro borane also resulted in the formation of an unidentifyable mixture of products.

Very surprisingly, reaction of \( N \)-2-p-tolylsulfinyltryptamine \( 10 \) with hexanal in the presence of 2 equivalents of \( \text{BF}_3\text{-OEt}_2 \) at -78 °C resulted in the formation of the cyclization product \( 11 \) (scheme 4.10). Tetrahydro-\( \beta \)-carboline \( 11 \) was obtained as a 1:1 mixture of diastereoisomers in excellent yield.

Scheme 4.10

![Scheme 4.10](image)

Reagents and conditions: (a) hexanal, \( \text{CH}_2\text{Cl}_2 \), \( \text{CHCl}_3 \), -78 °C, 86 %.

The low stereoselectivity of this reaction was attributed to the relatively high rate of the reaction, even at -78 °C. The Lewis acidic conditions were also applied to the reaction of \( 10 \) with benzaldehyde and methyl ethyl ketone. Also, the activation of propionaldehyde dimethyl acetal by \( \text{BF}_3\text{-OEt}_2 \), in reaction with \( 10 \) at -78 °C was attempted. Unfortunately, all these reactions did not result in the formation of cyclization products. Decomposition of \( 10 \) became a competitive side reaction at -20 °C and higher temperatures.
§ 4.4 Variation of the Sulfinyl Group

One of the limitations of Np-tolylsulfinyl tryptamine 10 is its lability under protic acidic conditions, which prevents the increase of temperature and amount of catalyst. It was anticipated that the electronic character of the sulfinyl group plays an important role in the stability of the N-sulfinyl tryptamine and its reactivity in the Pictet-Spengler reaction. Via the introduction of electron-withdrawing and electron-donating substituents (e.g. NO2 and OMe) on the aromatic ring, the influence of the electronic character was investigated. Furthermore, the effect of alkylsulfinyl groups, such as the methylsulfinyl group and the tert-butyldisulfynyl group on the reactivity and stereoselectivity of the reaction was studied.

One of the most obvious ways for the introduction of N-sulfinyl substituents is the reaction of tryptamine with the corresponding sulfinyl chlorides (scheme 4.12). p-Tolylsulfinyl chloride was obtained by treatment of the commercially available sulfinic acid with thionyl chloride. The synthesis of other sulfinyl chlorides is less straightforward since the corresponding sulfinic acids are not easily available.

2-Ethoxynaphthyl sulfinyl chloride 27 was obtained as a stable solid in good yield by treatment of β-ethoxynaphthalene with thionyl chloride.19 Oxidation of tert-butyl disulfide with m-CPBA20 furnished the thiosulfinate 28 in excellent yield. Subsequently, gaseous chlorine was passed through a solution of 28 in dichloromethane to afford the sulfinyl chloride 3021.
which was immediately reacted with tryptamine to give 25 in good overall yield. \(N_s\)-methylsulfinyl tryptamine 26 was prepared according to a similar route starting from dimethyl disulfide.

![Scheme 4.13](image)

Reagents and conditions: (a) SOCl₂, 86%; (b) m-CPBA, CHCl₃; (c) Cl₂, CH₂Cl₂.

\(N_s\)-o-Nitrophenylsulfinyl tryptamine and its \(p\)-nitro isomer were obtained by the oxidation of the corresponding \(N_s\)-sulfeny l tryptamines 32 and 33 since the corresponding sulfinyl chlorides could not be prepared by methods similar to those described above. The nitrosulfinylchlorides are commercially available and were reacted with tryptamine under basic conditions to furnish 32 and 33 in good yield. Subsequent oxidation with m-CPBA yielded the \(N_s\)-nitrophenyl sulfinyl tryptamines 34 and 35 in moderate yield.

![Scheme 4.14](image)

Reagents and conditions: (a) tryptamine, \(K_2CO_3\) (aq), CH₂Cl₂, 66% (32), 72% (33); (b) m-CPBA, CH₂Cl₂, 54% (34), 48% (35).

The synthesis of analogs with electron donating aromatic substituents (e.g. \(p\)-Cl and \(p\)-OMe) via the methods that are described above, proved to be troublesome. Formation of \(p\)-chloro- and \(p\)-methoxyphenylsulfinylchlorides could not be accomplished by oxidation and chlorination of the appropriate disulfides (scheme 4.13). Treatment with sulfuryl chloride was also not successful. Furthermore, synthesis of the corresponding sulfinylchlorides by alternative chlorination of the disulfides failed in our hands. Therefore, the sulfinylation-
oxidation pathway as it has been described for the nitrosubstituted sulfinylamines 34 and 35 (scheme 4.14) was not applicable.

A different approach involves the reaction of the appropriate disulfides with tryptamine to afford the sulfenylamine in one step. Activation of p-chlorophenyl disulfide with silver nitrate\(^24\) in the presence of tryptamine resulted in the formation of sulfenyl tryptamine 36 in good yield (scheme 4.15). This method also provided the p-nitrophenylsulfenyltryptamine 33 in better yield than described above. This procedure was not successful for the synthesis of the p-methoxy analog. Oxidation by using m-CPBA resulted in the formation of \(N_p\)-p-chlorophenylsulfinyl tryptamine 37 in good yield.

![Scheme 4.15](image)

Reagents and conditions: (a) tryptamine, AgNO\(_3\), MeOH, 73% (36), 85% (33); (b) m-CPBA, CH\(_2\)Cl\(_2\), 67% (37), 48% (35).

In table 4.2 the results of \(N\)-sulfinyl Pictet-Spengler reactions with the \(N_p\)-sulfinyl tryptamines 24-26, 34, 35 and 37 under protic acidic conditions are summarized.

<table>
<thead>
<tr>
<th>Amine</th>
<th>R</th>
<th>Time (h)</th>
<th>CSA (equiv.)</th>
<th>No</th>
<th>Yield (%)*</th>
<th>Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>p-tolyl</td>
<td>4.5</td>
<td>0.2</td>
<td>38</td>
<td>69</td>
<td>83 : 17</td>
</tr>
<tr>
<td>24</td>
<td>2-EtO-naphtyl</td>
<td>8</td>
<td>0.2</td>
<td>39</td>
<td>50(^4)</td>
<td>81 : 19</td>
</tr>
<tr>
<td>37</td>
<td>p-Cl-phenyl</td>
<td>6</td>
<td>0.2</td>
<td>40</td>
<td>71</td>
<td>80 : 20</td>
</tr>
<tr>
<td>34</td>
<td>o-NO(_2)-phenyl</td>
<td>6</td>
<td>0.2</td>
<td>41</td>
<td>38</td>
<td>85 : 15</td>
</tr>
<tr>
<td>35</td>
<td>p-NO(_2)-phenyl</td>
<td>6</td>
<td>0.2</td>
<td>42</td>
<td>24</td>
<td>61 : 39</td>
</tr>
<tr>
<td>25</td>
<td>t-butyl</td>
<td>18</td>
<td>0.6</td>
<td>43</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>methyl</td>
<td>18</td>
<td>0.6</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) CSA, CH\(_2\)Cl\(_2\), CHCl\(_3\), -78 °C.

*After column chromatography. *Diastereomeric ratio as determined by \(^1\)H-NMR. *Starting material recovered.
From Table 4.2 it can be seen that the presence of the 2-ethoxynaphthylsulfinyl group in 24 gives diastereoselectivities comparable to that of the p-tolyl analog 10 in the cyclization reaction. The presence of this sterically demanding substituent only has negative influence on the rate of the reaction. The stability of 24 was found to be comparable to that of N-p-tolylsulfinyl tryptamine 10 under protic acidic reaction conditions. A more electron-donating substituent than the p-methyl group in the aromatic ring was believed to increase the stability of the N-S bond. However, p-chlorophenyl N-sulfinyl tryptamine 37 gives results that are comparable to those obtained with 10 with respect to stability and stereoselectivity.

The introduction of electron-withdrawing nitro substituents (34 and 35) has a negative effect on the stability under acidic conditions which is reflected in the poor yields of the cyclization reactions. O-nitrophenylsulfinyltryptamine 34 shows the highest diastereoselectivity which is most likely caused by steric effects of the o-nitrosubstituent. Unfortunately the N-alkylsulfinyl substituted analogs 25 and 26 did not afford any cyclized products, even at temperatures up to -10 °C and higher concentrations of the acid catalyst. The stability of these compounds in acidic media however proved to be much better.

§ 4.5 Enantiopure Tetrahydro-β-carbolines

§ 4.5.1 Synthesis of Enantiopure N₆-p-Tolylsulfinyl Tryptamine

To obtain enantiopure tetrahydro-β-carbolines by using N-sulfinyl iminium ion cyclizations, an efficient synthetic route to the appropriate enantiopure N₆-sulfinyl tryptamines is required. From § 4.3 describing the optimization of the N-sulfinyl Pictet-Spengler cyclization, it was obvious that the best candidates were the p-chlorophenyl- and p-tolylsulfinyl tryptamines 10 and 37. Compound 37 was only accessible via oxidation of N-p-chlorosulfonyl tryptamine 36 and since asymmetric sulfoxidation might be a difficult procedure with these substrates, the better available N₆-p-tolylsulfinyl tryptamine 10 was selected.

Scheme 4.16

Reagents and conditions: (a) n-BuLi, THF then TMSCl then n-BuLi, THF, -78 °C; (b) (-)-9, THF, 73%.
Enantiopure 10 was prepared from the Andersen reagent \((1R,2S,5R)-(S)\)-menthyl \(p\)-toluenesulfinate (-)-9 and its optical antipode, both of which are commercially available. These menthy1 esters of \(p\)-toluenesulfinic acid can be prepared by reaction of (-)- or (+)-menthol with \(p\)-toluenesulfinyl chloride and subsequent efficient separation of the diastereoisomers.\(^{25}\) The optically pure Andersen reagents are the major starting materials for the synthesis of enantiopure \(N\)-sulfinyl imines as was described in § 4.2.

Reaction of tryptamine and (-)-9 in refluxing toluene, \(N,N\)-dimethyl formamide or dimethylsulfoxide, did not afford the desired products. A melt reaction of (-)-9 and tryptamine resulted in the efficient formation of the desired compound 10. However, the product did not show any optical rotation, probably as a result of thermal racemization of the sulfoxide.\(^{26}\)

One of the main problems in the synthesis of \(N\)-substituted tryptamines via the anion is the presence of the indole proton. Addition of two equivalents of \(n\)-butyl lithium and subsequent reaction of the dianion with (-)-9 did not afford the desired \(N\text{-}p\text{-}p\text{-}tolylsulfinyl\) tryptamine 10.\(^{27}\) A recent publication of Meanwell et al. on the selective benzylation of primary amines in the presence of secondary amines generated the idea to protect the indole nitrogen \textit{in situ}.\(^{28}\) Treatment of tryptamine with two equivalents of \(n\)-butyl lithium, subsequent addition of two equivalents of chlorotrimethylsilane and addition of an extra equivalent of \(n\)-butyl lithium afforded the anion \(45\) (scheme 4.16). Reaction of this anion with (-)-9 furnished (+)-10 in good yield (73%) and excellent enantiopurity as was determined by chiral HPLC. Likewise, the enantiomer (-)-10 was obtained starting from the (+)-Andersen reagent (68%).

\section*{4.5.2 \(N\)-Sulfinyl Pictet-Spengler Reactions}

The Pictet-Spengler condensations of (+)-10 were performed under the same conditions as mentioned in table 4.1. The results of these reactions were comparable to the results that were obtained from reactions with racemic 10, as expected. The major isomers were all obtained diastereomerically pure after a single crystallization (table 4.3).

In principle, the stereochemical outcome of the Pictet-Spengler reaction can be influenced by the chiral \(10\text{-}p\text{-}camphorsulfonate\) counterion of the iminium salt. Since no change in the diastereomeric ratio was observed using (+)-CSA instead of the racemic catalyst, this possibility was excluded. When compared to the use of trifluoroacetic acid, the diastereoselectivity of the cyclization is enhanced. Most likely, this is the consequence of the decreased rate of the reaction and the steric bulk of the counterion. The configuration of the \(10\text{-}p\text{-}camphorsulfonate\) counterion however has no influence on the stereochemical outcome of the cyclization. The use of (+)-10-camphorsulfonic acid has been reported in the Dutch resolution of 4-hydroxy- and 4-fluorophenylglycine. The use of this relatively cheap resolving agent, that is used on a multi-ton scale for the resolution of phenylglycine, allowed the use of D-enantiomers of these amino acids for the production of semi-synthetic antibiotics.\(^{29}\)
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

Table 4.3

<table>
<thead>
<tr>
<th>No</th>
<th>R</th>
<th>Yield (%)</th>
<th>[α]₀ °</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-12</td>
<td>methyl</td>
<td>57</td>
<td>+212</td>
<td>205-207</td>
</tr>
<tr>
<td>(+)-13</td>
<td>ethyl</td>
<td>61</td>
<td>+196</td>
<td>229-233</td>
</tr>
<tr>
<td>(+)-14</td>
<td>propyl</td>
<td>58</td>
<td>+190</td>
<td>204-206</td>
</tr>
<tr>
<td>(+)-15</td>
<td>butyl</td>
<td>60</td>
<td>+167</td>
<td>208-211</td>
</tr>
<tr>
<td>(+)-16</td>
<td>pentyl</td>
<td>57</td>
<td>+158</td>
<td>179-182</td>
</tr>
<tr>
<td>(+)-17</td>
<td>isobutyl</td>
<td>59</td>
<td>+190</td>
<td>190-193</td>
</tr>
<tr>
<td>(+)-18</td>
<td>isopropyl</td>
<td>63</td>
<td>+215</td>
<td>222-224</td>
</tr>
<tr>
<td>(+)-19</td>
<td>cyclohexyl</td>
<td>57</td>
<td>+196</td>
<td>240-241</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) CSA, CH₂Cl₂, CHCl₃, -78 °C.

* After crystallization. ** Acetone, c = 0.5-1.0, values ± 3°.

Removal of the p-tolylsulfinyl chiral auxiliary was accomplished in high yield and without racemization by using a 2% solution of hydrochloric acid in ethanol at 0 °C, which afforded the enantiopure tetrahydro-β-carbolines (-)-46 to (-)-53 in excellent yield and enantiopurity (table 4.4).

Table 4.4

<table>
<thead>
<tr>
<th>No</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee °</th>
<th>[α]₀ °</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-46</td>
<td>methyl</td>
<td>89</td>
<td>&gt;98%</td>
<td>-44.0f</td>
</tr>
<tr>
<td>(-)-47</td>
<td>ethyl</td>
<td>93</td>
<td>&gt;98%</td>
<td>-62.6</td>
</tr>
<tr>
<td>(-)-48</td>
<td>propyl</td>
<td>91</td>
<td>&gt;98%</td>
<td>-30.0</td>
</tr>
<tr>
<td>(-)-49</td>
<td>butyl</td>
<td>93</td>
<td>&gt;98%</td>
<td>-65.8</td>
</tr>
<tr>
<td>(-)-50</td>
<td>pentyl</td>
<td>82</td>
<td>&gt;98%</td>
<td>-40.0</td>
</tr>
<tr>
<td>(-)-51</td>
<td>isobutyl</td>
<td>90</td>
<td>&gt;98%</td>
<td>-47.1</td>
</tr>
<tr>
<td>(-)-52</td>
<td>isopropyl</td>
<td>93</td>
<td>&gt;98%</td>
<td>-58.3</td>
</tr>
<tr>
<td>(-)-53</td>
<td>cyclohexyl</td>
<td>86</td>
<td>&gt;98%</td>
<td>-68.5</td>
</tr>
</tbody>
</table>

Reagents and conditions: HCl (aq), EtOH, 0 °C.

* After chromatography. ** As determined with 1H-NMR by using (R)-1-(9-anthryl)-2,2,2-trifluoro ethanol.

* Acetone, c = 0.5-1.0, values ± 3°. ** Lit. [α]₀ = -51.0 ° (CHCl₃, c = 1.0).
The alkyl substituted tetrahydro-β-carbolines that are depicted in table 4.3 have found ample reference in the literature. The racemic isobutyl substituted analog rac-51 has been found in the root bark of the Canadian silverberry (Elaeagnus commutata). Its cyclohexyl substituted analog rac-53 was prepared by Cook et al. in a carboxyl mediated Pictet-Spengler cyclization. Other racemic, alkyl substituted tetrahydro-β-carbolines were obtained by racemic Pictet-Spengler condensations of tryptamine with aliphatic aldehydes. The racemic synthesis of most of these compounds is well-described but none of them have been prepared in enantiopure form. Noyori et al. have reported the synthesis of tetrahydro-β-carbolines with high optical purity via asymmetric transfer hydrogenation of dihydro-β-carbolines, catalyzed by chiral ruthenium complexes. They were able to prepare tetrahydroharman (-)-46 in good yield and 93% enantiomeric excess. Other reductive approaches furnished 46 in lower enantiopurity. The absolute stereochemistry of the enantiopure tetrahydro-β-carbolines described in table 4.4 was related to the S-stereochemistry of the major product in these asymmetric reductions.

Since acidic deprotection in the presence of ethanol yields the tetrahydro-β-carboline and the ethyl ester of p-toluenesulfonic acid, it is in principle possible to regenerate the Andersen reagent. Reaction of N-sulfinyltetrahydro-β-carboline (-)-49 with hydrochloric acid in tetrahydrofuran in the presence of (-)-menthol yielded the Andersen reagent after 8 hours at room temperature. The optical purity of the chiral compound however was lower, as indicated by a reduction of the specific rotation from -198° to -112°.

§ 4.5.3 Enantiopure 1-Benzyltetrahydro-β-carbolines

Audia and coworkers found that C1-benzyl substituted tetrahydro-β-carbolines, which they envisaged to be ring-opened analogs of yohimbine (57), have a strongly increased affinity for the 5HT2B serotonin receptor when compared to yohimbine itself (scheme 4.17).
Their interest in finding structure-activity relationships for these compounds was further raised when 1-benzylsubstituted tetrahydro-β-carbolines showed strongly increased selectivity when compared to yohimbine. The synthesis of a large library of these racemic compounds by making use of azalactones 54 as phenylacetaldehyde equivalents in the Pictet-Spengler cyclizations has led to new potent and selective antagonists of the 5HT<sub>2B</sub> contractile receptor in the rat stomach fundus. The synthesis of enantiopure 1-benzyltetrahydro-β-carbolines was investigated by using N-sulfinyl Pictet-Spengler reactions. Unfortunately, the use of the azalactone approach, as reported by Evrard and coworkers, was not applicable in combination with our system. The liberation of the α-ketoacids from the azalactones 54 takes place under strongly acidic conditions at increased temperatures under which N<sub>p</sub>-tolylsulfinyl tryptamine 10 is not stable. The reaction of commercially available phenylacetaldehyde with 10 in the presence of CSA was alternatively attempted. Under these protic acidic conditions no cyclization products could be isolated.

Scheme 4.18

In § 4.3.2 we discussed the use of Lewis acids as catalysts for the N-sulfinyl Pictet-Spengler reaction. In general, Lewis acids gave a lot of side-products in these reactions. One positive exception was BF<sub>3</sub>·OEt<sub>2</sub>, which resulted in the rapid formation of cyclization product in high yield but low diastereoselectivity. Surprisingly, N-sulfinyl Pictet-Spengler reaction of 10 with phenylacetaldehyde in the presence of BF<sub>3</sub>·OEt<sub>2</sub> resulted in the rapid formation of 1-benzyl-N-sulfinyltetrahydro-β-carboline in a 82:18 mixture of diastereoisomers. Separation of the major diastereoisomer (+)-58 and subsequent removal of the chiral auxiliary resulted in the formation of enantiopure 1-benzyltetrahydro-β-carboline (-)-59 (scheme 4.18).

In principle, it is possible to realize the enantioselective synthesis of other 1-benzyl substituted tetrahydro-β-carbolines via this BF<sub>3</sub>·OEt<sub>2</sub> mediated N-sulfinyl iminium ion cyclization. The instability of phenylacetaldehyde derivatives however, is one of the main obstacles in this approach. Methoxy substituted phenylacetaldehydes<sup>37</sup> 63, 64 and 65 were obtained in poor yield by reduction of the corresponding phenylacetic acids to the alcohols, followed by Swern oxidation. No cyclization products could be isolated from immediate reaction of these compounds with (+)-10 in the presence of BF<sub>3</sub>·OEt<sub>2</sub>. It was anticipated that
enolization of the aldehyde was the main problem in this reaction. Reactions with a mixture of CSA and BF$_3$OEt$_2$ also did not result in the formation of the desired products.

Scheme 4.19

\[
\begin{align*}
\text{Y} & \quad \text{Y} \\
\text{OH} & \quad \text{OH} \\
\text{10} & \quad \text{no product formation}
\end{align*}
\]

60 $Y = 3$-$\text{OCH}_3$
61 $Y = 4$-$\text{OCH}_3$
62 $Y = 3$,4-$\text{OCH}_3$$_2$
63 $Y = 3$-$\text{OCH}_3$
64 $Y = 4$-$\text{OCH}_3$
65 $Y = 3$,4-$\text{OCH}_3$$_2$

Reagents and conditions: (a) LIAIH$_4$, THF, 67% (60), 73% (61), 67% (62); (b) (COCl)$_2$, DMSO, -65 °C, 43% (63), 56% (64), 48% (65); (c) BF$_3$OEt$_2$, CH$_2$Cl$_2$, CHCl$_3$, -78 °C; (d) BF$_3$OEt$_2$, CSA, CH$_2$Cl$_2$, CHCl$_3$, -78 °C.

In order to circumvent the use of instable phenylacetaldehydes, cyclization with enol ether 66 was attempted. The enol ether was obtained as a mixture of E/Z isomers by Wittig reaction of 3,4-dimethoxy benzaldehyde with (methoxymethyl)triphenylphosphonium chloride. However, N-sulfinyl Pictet-Spengler reaction of this compound under the conditions mentioned above, did not give any cyclization products (scheme 4.20).

Scheme 4.20

\[
\begin{align*}
\text{H$_3$CO} & \quad \text{H$_3$CO} \\
\text{OCH$_3$} & \quad \text{OCH$_3$} \\
\text{66} & \quad \text{no product formation}
\end{align*}
\]

Reagents and conditions: a) KHMDS, THF, (methoxymethyl)triphenylphosphonium chloride, 90%; b) 10, CSA or BF$_3$OEt$_2$, CH$_2$Cl$_2$, CHCl$_3$, -78 °C.

The synthesis of biologically interesting enantiopure 1-benzyltetrahydro-β-carbolines via N-sulfinyl Pictet-Spengler reactions is at this moment limited to the formation of the unsubstituted 1-benzyl compound (-)-59. This limitation can be attributed to the lability of substituted phenylacetaldehydes, a problem that has been mentioned several times in the literature.

§ 4.6 Concluding Remarks

The application of N-sulfinyliminium ion chemistry to the Pictet-Spengler reaction of tryptamine provided a practical synthesis of enantiopure tetrahydro-β-carbolines. The influence of different N-sulfinyl groups on the diastereoselectivity of the Pictet-Spengler
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

reaction has been studied. It was shown that the p-tolylsulfinyl group was superior with respect to yields and diastereoselectivity. Furthermore, both (R)- and (S)-N-tolylsulfinyl tryptamine are accessible in one step from the commercially available (R)- and (S)-Andersen reagent.

N-sulfinyl Pictet-Spengler reactions of unbranched, α- and β-branched aliphatic aldehydes and phenyl acetaldehyde have been optimized for both protic (CSA) and Lewis acidic (BF₃·OEt₂) conditions. Efficient separation of the major diastereoisomers from the crude reaction mixtures by crystallization and mild cleavage of the chiral auxiliary furnished a range of tetrahydro-β-carbolines in excellent enantiopurity. The S-stereochemistry of the products was related to literature data by comparison of the optical rotations.

§ 4.7 Acknowledgements

Bianca Willemse is kindly acknowledged for her efforts in studying Lewis acid catalyzed N-sulfinyl Pictet-Spengler reactions, as described in § 4.4.2.

§ 4.8 Experimental Details

General methods. For general experimental details see §2.11. Chlorine gas was prepared by dropwise addition of concentrated hydrochloric acid to potassium permanganate (1.0 g of potassium permanganate requires 6.2 mL of hydrochloric acid to give 16 mmol of chlorine gas) and subsequently passing through water and concentrated sulfuric acid before it was bubbled through the reaction mixture. Chloroform was distilled from phosphorous pentoxide and stored over 4Å molecular sieves in the dark. Acetaldehyde, propionaldehyde, butyraldehyde and isobutyraldehyde were distilled prior to use. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in acetone (c = 0.6-1.0), unless stated otherwise. Chiral HPLC was performed on a LKB HPLC-apparatus by using a chiral OD Daicel column with elution of hexanes and isopropyl alcohol.

2-Ethoxynaphtalene-1-sulfinyl chloride 27. β-Ethoxynaphtalene (3.44 g, 20.0 mmol) was stirred with thionyl chloride (40 mL) for 1 hour at room temperature. Evaporation of the volatiles under reduced pressure, addition of diethyl ether and filtration yielded 27 (86%, 4.38 g) as a white solid that was used without further purification. ¹H-NMR (CDCl₃) δ 9.03 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 4.35-4.22 (m, 2H), 1.49 (t, J = 7.0 Hz, 3H).

tert-Butyl sulfinyl chloride 30. A solution of m-CPBA (3.50 g, 18.1 mmol) in chloroform (60 mL) was added dropwise to a solution of tert-butyl disulfide (3.25 g, 18.1 mmol) in chloroform (60 mL) at 0 °C. After stirring of the reaction mixture for 3 hours at room temperature a saturated aqueous solution of NaHCO₃ (40 mL) was added. Separation of the organic layer, extractive work-up (chloroform) drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent yielded 28 (91%, 3.22 g) as a colourless oil that was used without further purification. ¹H-NMR (CDCl₃) δ 1.65 (s, 9H), 1.39 (s, 9H). Chlorine gas (prepared from 10 mmol of concentrated hydrochloric acid) was bubbled through a solution of 28 (960 mg, 4.94 mmol) in dichloromethane (30 mL) at room temperature. After bubbling
nitrogen through the yellow solution it was used immediately for coupling to tryptamine without further purification.

**Methylsulfinyl chloride**: In a similar procedure as was described above for 30 we obtained methyl thiosulfinate 29 (68%) as a colourless oil and sulfinyl chloride 31 as a yellow solution in dichloromethane that was used immediately for reaction with tryptamine without further purification.

**General procedure for the preparation of racemic sulfamines**: A solution of the sulfinyl chloride (22 mmol) in dichloromethane (50 mL) was added dropwise to a vigorous stirred mixture of saturated aqueous K₂CO₃ (25 mL), dichloromethane (35 mL) and tryptamine (3.2 g, 20 mmol) at 5 °C. After stirring for 2 hours at ambient temperature the product partially precipitated as a white crystalline material, which was obtained by filtration and washed thoroughly with water (30 mL), acetone (30 mL) and ethyl acetate (three times 30 mL). The layers of the filtrate were separated and after drying (Na₂SO₄), removal of the solvents in vacuo and recrystallization, additional product was obtained.

**4-Methyl-benzenesulfinic acid-[2-(1H-indol-3-yl)-ethyl]-amide**: Compound 10 (75%) was obtained as a white solid. M.p. 109 °C; ¹H-NMR (CDCl₃) δ 8.07 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.20 (t, J = 2.1 Hz, 1H), 7.08 (t, J = 2.2 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 4.15 (t, J = 4.1 Hz, 1H), 3.42 (m, 1H), 3.16 (m, 1H), 2.98 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H); IR (CHCl₃) 3479, 1057; HRMS (EI): Calcd. for C₁₅H₁₉N₂O₂ 298.1136, Found: 298.1143.

**2-Ethoxynaphtalene-1-sulfinic acid-[2-(1H-indol-3-yl)-ethyl]-amide**: Compound 24 (70%) was obtained as a white solid. M.p. 93-95 °C; ¹H-NMR (CDCl₃) δ 8.67 (d, J = 8.0 Hz, 1H), 8.10 (bs, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.56-7.49 (m, 2H), 7.39 (t, J = 6.2 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.23-7.15 (m, 2H), 7.21-7.03 (m, 2H), 5.78 (bs, 1H), 4.23-4.04 (m, 2H), 3.74-3.65 (m, 1H), 3.65-3.54 (m, 1H), 3.19-3.03 (m, 2H), 1.22 (t, J = 6.1 Hz, 3H); IR (CHCl₃) 3479, 1057; HRMS (EI): Calcd. for C₂₁H₂₃N₃SO 363.1562, Found: 363.1568.

**t-Butyl sulfonic acid-[2-(1H-indol-3-yl)-ethyl]-amide**: Compound 25 (65%) was obtained as a white solid. M.p. 114-117 °C; ¹H-NMR (CDCl₃) δ 8.33 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 6.3 Hz, 1H), 7.12 (t, J = 6.2 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 3.58-3.48 (m, 1H), 3.46-3.28 (m, 2H), 3.15-2.98 (m, 2H), 1.18 (s, 9H); IR (CHCl₃) 3479, 1057; HRMS (EI): Calcd. for C₁₄H₂₀N₂SO 264.1292, Found: 264.1288.

**Methyl sulfonic acid-[2-(1H-indol-3-yl)-ethyl]-amide**: Compound 26 (72%) was obtained as a white solid. M.p. 163 °C; ¹H-NMR (CDCl₃) δ 8.11 (bs, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.25-7.11 (m, 2H), 7.08 (s, 1H), 3.88 (bs, 1H), 3.52-3.42 (m, 2H), 3.11-3.05 (m, 2H), 2.58 (s, 3H); ¹³C-NMR (CDCl₃) δ 127.3, 122.4, 122.2, 19.5, 118.7, 112.4, 111.3, 42.8, 42.0, 26.6.

**N-[2-(1H-indol-3-yl)-ethyl]-S-(2-nitrophenyl) thio hydroxylamine**: An aqueous solution of sodium hydroxide (40 mL, 5.0 M) was added to a solution of tryptamine (3.2 g, 20.0 mmol) in dichloromethane (75 mL). After cooling to 0 °C nitrrophenylsulfinyl chloride (4.0 g, 20.5 mmol, recrystallized from light petroleum/ dichloromethane) was added in small portions. After vigorous stirring of the reaction mixture for 2 hours at 0 °C, separation of the organic layer and extraction of the aqueous layer (ethyl acetate), drying of the combined organic layers and evaporation of the solvent in vacuo, the residue was triturated with diethyl ether to afford 32 (66%, 4.13 g). ¹H-NMR (CDCl₃) δ 8.25 (d, J = 8.3 Hz, 1H), 8.06 (bs, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.42-7.37 (m, 2H), 7.26-7.13 (m, 3H), 7.11 (s, 1H), 3.32 (t, J = 6.6 Hz, 1H), 3.10 (t, J = 6.6 Hz, 2H).
N-[2-(1H-indol-3-yl)-ethyl]-S-(4-nitrophenyl) thio hydroxylamine 33: A solution of p-nitrophenylsulfenyl chloride (6.22 g, 31.2 mmol) in dichloromethane (50 mL) was added in small portions to a vigorously stirred mixture of tryptamine (5.0 g, 31.2 mmol) in dichloromethane (50 mL) and saturated aqueous \( \text{K}_2\text{CO}_3 \) at 0 °C. The reaction mixture was stirred at room temperature for 4 hours after which the organic layer was separated. Extractive work-up of the aqueous layer (ethyl acetate), drying of the combined organic layers (\( \text{Na}_2\text{SO}_4 \)) and evaporation of the solvent under reduced pressure gave a brown oil which was crystallized from ethyl acetate to yield 33 (72%, 7.03 g) as a yellow solid. \(^1\text{H-}
MR (\text{CDCl}_3) \delta 8.02 (\text{bs}, 1\text{H}), 7.82 (\text{d}, J = 8.2 \text{ Hz}, 2\text{H}), 7.65 (\text{d}, J = 8.2 \text{ Hz}, 2\text{H}), 7.35-7.12 (\text{m}, 6\text{H}), 6.99 (\text{s}, 1\text{H}), 3.39-3.32 (\text{m}, 2\text{H}), 3.07 (\text{t}, J = 7.1 \text{ Hz}, 2\text{H}), 3.86 (\text{bs}, 1\text{H}).

2-Nitrobenzenesulfinic acid [2-(1H-indol-3-yl)-ethyl]amide 34: m-CPBA (107 mg, 0.56 mmol) was added to a solution of 33 (159 mg, 0.51 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 2 hours after which saturated aqueous NaHCO\(_3\) (10 mL) was added. Removal of the organic layer and extractive work-up of the water layer (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and evaporation of the solvents under reduced pressure gave a yellow oil. Column chromatography (R\(_f\) = 0.37, ethyl acetate/ light petroleum 1:1) and recrystallization (diethyl ether) yielded 35 (54%) as a yellow solid. M. p. 154 °C; \(^1\text{H-NMR} (\text{CDCl}_3) \delta 8.27 (\text{bs}, 1\text{H}), 8.21 (\text{d}, J = 8.1 \text{ Hz}, 1\text{H}), 8.03 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 7.78 (\text{t}, J = 8.1 \text{ Hz}, 1\text{H}), 7.55 (\text{t}, J = 8.1 \text{ Hz}, 1\text{H}), 7.38 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 7.31 (\text{d}, J = 8.1 \text{ Hz}, 1\text{H}), 7.15 (\text{t}, J = 8.1 \text{ Hz}, 1\text{H}), 7.03 (\text{t}, J = 8.1 \text{ Hz}, 1\text{H}), 6.92 (\text{s}, 1\text{H}), 4.21 (\text{bs}, 1\text{H}), 3.40-3.30 (\text{m}, 1\text{H}), 3.04-2.94 (\text{m}, 1\text{H}), 2.89-2.79 (\text{m}, 2\text{H}); HRMS (EI): Calcd. for C\(_{19}\)H\(_{16}\)N\(_2\)SO\(_3\) 329.0834, Found: 329.0829.

4-Nitrobenzenesulfinic acid [2-(1H-indol-3-yl)-ethyl]amide 35. In a similar procedure as described above 35 was obtained by oxidation of \( \text{N}_2\text{-o-nitrosulfenyl tryptamine} \) 32 (48%). M. p. 122 °C; \(^1\text{H-NMR} (\text{CDCl}_3) \delta 8.32 (\text{bs}, 1\text{H}), 8.19 (\text{d}, J = 8.2 \text{ Hz}, 2\text{H}), 7.74 (\text{d}, J = 8.2 \text{ Hz}, 2\text{H}), 7.43 (\text{d}, J = 8.0 \text{ Hz}, 1\text{H}), 7.35 (\text{d}, J = 8.1 \text{ Hz}, 1\text{H}), 7.28 (\text{t}, J = 8.0 \text{ Hz}, 1\text{H}), 7.07 (\text{t}, J = 8.1 \text{ Hz}, 1\text{H}), 7.01 (\text{s}, 1\text{H}), 4.48 (\text{bs}, 1\text{H}), 3.48-3.39 (\text{m}, 1\text{H}), 3.11-2.92 (\text{m}, 3\text{H}); HRMS (EI): Calcd. for C\(_{19}\)H\(_{16}\)N\(_2\)SO\(_3\) 329.0834, Found: 329.0839.

N-[2-(1H-indol-3-yl)-ethyl]-S-(4-chlorophenyl) thio hydroxylamine 36. A solution of tryptamine (1.12 g, 6.96 mmol) in methanol (10 mL) was added to a solution of p-chlorophenyl disulfide (1.0 g, 3.48 mmol) and silver nitrate (595 mg, 3.50 mmol) in methanol (10 mL). The reaction mixture was stirred for 48 hours after which the solvent was removed. Column chromatography (R\(_f\) = 0.21, ethyl acetate/ light petroleum 1:1) yielded 36 (73%, 769 mg) as a light yellow oil. \(^1\text{H-NMR} (\text{CDCl}_3) \delta 7.99 (\text{bs}, 1\text{H}), 7.59 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 7.38 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 7.26-7.05 (\text{m}, 6\text{H}), 7.03 (\text{s}, 1\text{H}), 3.29-3.22 (\text{m}, 2\text{H}), 3.06 (\text{t}, J = 7.1 \text{ Hz}, 2\text{H}), 3.90 (\text{bs}, 1\text{H}); HRMS (EI): Calcd. for C\(_{16}\)H\(_{14}\)N\(_2\)SCI 302.0644, Found: 302.0638.

4-Chlorobenzenesulfinic acid [2-(1H-indol-3-yl)-ethyl]amide 37. In a similar oxidation procedure as described above 37 was obtained by oxidation of 36 (54%) as a white solid. M. p. 96 °C; \(^1\text{H-NMR} (\text{CDCl}_3) \delta 8.18 (\text{bs}, 1\text{H}), 7.58 (\text{d}, J = 8.2 \text{ Hz}, 2\text{H}), 7.49 (\text{d}, J = 8.1 \text{ Hz}, 1\text{H}), 7.42 (\text{d}, J = 8.1 \text{ Hz}, 2\text{H}), 7.37 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 7.21 (\text{t}, J = 8.0 \text{ Hz}, 1\text{H}), 7.11 (\text{t}, J = 8.0 \text{ Hz}, 1\text{H}), 7.03 (\text{s}, 1\text{H}), 4.24 (\text{m}, 1\text{H}), 3.48-3.39 (\text{m}, 1\text{H}), 3.17-3.08 (\text{m}, 1\text{H}), 2.98 (\text{t}, J = 6.8 \text{ Hz}, 2\text{H}); HRMS (EI): Calcd. for C\(_{16}\)H\(_{15}\)N\(_2\)SCI 318.0594, Found: 318.0601.

(+)-4-Methyl-benzenesulfinic acid-[2-(1H-indol-3-yl)-ethyl]-amide (+)-10. A solution of n-butyllithium (25.6 mL, 41 mmol 1.6 M \(^\text{solution}) in hexanes was added to a solution of tryptamine (20 mmol, 3.2 g) in THF (200 mL) at -78 °C. The reaction mixture was allowed to warm to ambient temperature before chlorotrimethylsilane (21 mmol, 2.66 mL) was added. After
stirring for 30 min n-butyllithium (21 mmol, 13.1 mL) in hexanes was added and the reaction mixture was stirred for an additional 45 min. The reaction mixture was added to a solution of \((S,2R,5S)-(S)-\text{menthy}-p\text{-toluenesulfinate (10 mmol)}\) in THF. The reaction was quenched after 1 hour by the addition of an aqueous solution of \(\text{NaHPO}_4\) (200 mL, 0.1 M). The organic layer was separated and the aqueous layer was extracted with three 100 mL portions of ethyl acetate. The combined organic layers were dried (\(\text{Na}_2\text{SO}_4\)) and the solvents were removed \textit{in vacuo}. Column chromatography (ethyl acetate/light petroleum 1:1) and recrystallisation (ethyl acetate) yielded \((R)-(-)-10\) (4.2 g, 73%). M. p. 109 °C; \([\alpha]_D = 102^\circ\). Following the same procedure starting from \((S,2R,5S)-(R)-\text{menthy}-p\text{-toluenesulfinate (5)-10}\) was obtained in 68 %. M. p. 109 °C; \([\alpha]_D = -108^\circ\).

**General procedure for N-sulfinyl Pictet-Spengler reactions.** A solution of \((+)-10\) (60 mg, 0.20 mmol) and the aldehyde (1.0 mmol) in a mixture of dichloromethane/chloroform (2 mL, 1:1) was cooled to -78 °C. The indicated quantity of 10-camphorsulfonic acid was added and the reaction mixture was stirred at -78 °C for the indicated time (table 4.3). The reaction was quenched with triethylamine (0.7 mL, 5 mmol) at -78 °C and allowed to warm to room temperature. The solvents were removed \textit{in vacuo} and flash chromatography (ethyl acetate/light petroleum 1:1) yielded the mixture of products from which the major diastereomer was obtained by crystallization (diethyl ether or ethyl acetate).

1-Methyl-2(\text{toluene-4-sulfinyl})-2,3,4,9-tetrahydro-\beta-carboline (+)-12. Compound (+)-12 (57 %) was obtained as a white solid. M. p. 205-207 °C; \([\alpha]_D = 212^\circ\); \(^1\)H-NMR (CDCl₃) δ 7.82 (bs, 1H), 7.60 (d, \(J = 8.1\) Hz, 2H), 7.44 (d, \(J = 8.0\) Hz, 1H), 7.32-7.28 (m, 3H), 7.15 (t, \(J = 6.3\) Hz, 1H), 7.08 (t, \(J = 3\) Hz, 1H), 4.78 (q, \(J = 3.2\) Hz, 1H), 3.52-3.39 (m, 2H), 2.94-2.86 (m, 1H), 2.68 (d, \(J = 7.0\) Hz, 1H), 2.43 (s, 3H), 1.69 (d, \(J = 3.1\) Hz, 3H); IR (CHCl₃) 3470, 1466, 1060; HRMS (EI) Calcd. for C₁₉H₁₂NO₂ 324.1292, Found: 324.1297.

1-Ethyl-2(\text{toluene-4-sulfinyl})-2,3,4,9-tetrahydro-\beta-carboline (+)-13. Compound (+)-13 (61 %) was obtained as a white solid. M. p. 229-233 °C; \([\alpha]_D = 196^\circ\); \(^1\)H-NMR (CDCl₃) δ 7.77 (bs, 1H), 7.61 (d, \(J = 8.0\) Hz, 2H), 7.42 (d, \(J = 8.1\) Hz, 1H), 7.33-7.27 (m, 3H), 7.13 (t, \(J = 6.2\) Hz, 1H), 7.08 (t, \(J = 6.4\) Hz, 1H), 4.71 (t, \(J = 3.2\) Hz, 1H), 3.51-3.45 (m, 1H), 3.29-3.22 (m, 1H), 3.00-2.94 (m, 1H), 2.67-2.62 (m, 1H), 2.42 (s, 3H), 2.17-2.14 (m, 1H), 2.11-1.91 (m, 1H), 1.09 (t, \(J = 5.8\) Hz, 3H); \(^1\)C-NMR (CDCl₃) δ 158.9, 141.3, 140.8, 136.1, 133.5, 129.7, 127.0, 126.4, 121.8, 119.4, 118.2, 110.8, 109.3, 58.2, 40.5, 28.3, 22.9, 21.4, 10.5; IR (CHCl₃) 3470, 1466, 1060; HRMS (EI) Calcd. for C₁₉H₁₂NO₂SO 338.1448, Found: 338.1454.

1-Propyl-2(\text{toluene-4-sulfinyl})-2,3,4,9-tetrahydro-\beta-carboline (+)-14. Compound (+)-14 (58 %) was obtained as a white solid. M. p. 204-206 °C; \([\alpha]_D = 190^\circ\); \(^1\)H-NMR (CDCl₃) δ 7.80 (s, 1H), 7.60 (d, \(J = 8.0\) Hz, 2H), 7.41 (d, \(J = 8.0\) Hz, 1H), 7.33-7.28 (m, 3H), 7.14 (t, \(J = 8.1\) Hz, 1H), 7.09 (t, \(J = 8.1\) Hz, 1H), 4.77 (t, \(J = 3.3\) Hz, 1H), 3.52-3.46 (m, 1H), 3.29-3.21 (m, 1H), 3.03-2.96 (m, 1H), 2.63 (d, \(J = 7.1\) Hz, 1H), 2.43 (s, 3H), 2.05-1.87 (m, 2H), 1.63-1.52 (m, 2H), 1.00 (t, \(J = 3.9\) Hz, 3H); IR (CHCl₃) 3470, 1466, 1060; HRMS (EI) Calcd. for C₂₁H₁₄NO₂SO 352.1604, Found: 352.1602.

1-Butyl-2(\text{toluene-4-sulfinyl})-2,3,4,9-tetrahydro-\beta-carboline (+)-15. Compound (+)-15 (60 %) was obtained as a white solid. M. p. 208-211 °C; \([\alpha]_D = 167^\circ\); \(^1\)H-NMR (CDCl₃) δ 7.88 (bs, 1H), 7.61 (d, \(J = 8.0\) Hz, 2H), 7.42 (d, \(J = 8.1\) Hz, 1H), 7.33-7.28 (m, 3H), 7.13 (t, \(J = 8.0\) Hz, 1H), 7.07 (t, \(J = 8.1\) Hz, 1H), 4.76 (t, \(J = 3.8\) Hz, 1H), 3.50-3.45 (m, 1H), 3.28-3.21 (m, 1H), 3.02-2.95 (m, 1H), 2.63 (d, \(J = 7.1\) Hz, 1H), 2.42 (s, 3H), 2.06-2.02 (m, 1H), 2.00-1.86 (m, 1H), 1.58-1.34 (m, 4H), 0.94 (t, \(J = 7.1\) Hz, 3H); \(^1\)C-NMR (CDCl₃) δ 158.9, 141.3, 140.8, 136.0, 133.9, 129.7, 127.0, 126.4, 121.7, 119.3, 118.1, 110.9, 108.9, 57.2, 40.3, 35.2, 28.1, 23.0, 22.6, 21.3, 14.1; IR (CHCl₃) 3471, 1468, 1060; HRMS (EI) Calcd. for C₂₃H₂₆NO₂SO 366.1760, Found: 366.1764.
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

1-Pentyl-2(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-β-carboline (+)-16. Compound (+)-16 (57 %) was obtained as an off-white solid. M.p. 179-182 °C; [α]_D = 158 °; 1^H-NMR (CDCl₃) δ 7.87 (bs, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.33-7.27 (m, 3H), 7.12 (t, J = 6.3 Hz, 1H), 7.05 (t, J = 6.3 Hz, 1H), 4.75 (t, J = 3.5 Hz, 1H), 3.51-3.45 (m, 1H), 3.28-3.20 (m, 1H), 3.02-2.95 (m, 1H), 2.63 (d, J = 7.2 Hz, 1H), 2.43 (s, 3H), 2.05-1.87 (m, 2H), 1.57-1.49 (m, 2H), 1.40-1.34 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H). Calcd. for C24H22SNO: 380.1916. Found: 380.1913. 1H-NMR (CDCl₃) δ 8.15 (J = 7.2 Hz, 1H), 8.05 (J = 7.0 Hz, 1H), 7.15 (t, J = 6.3 Hz, 1H), 7.05 (t, J = 6.2 Hz, 1H), 4.63 (bs, 1H), 3.40-3.31 (m, 1H), 3.24-3.01 (m, 3H), 2.40 (s, 1H), 1.98-1.94 (m, 1H), 1.65-1.47 (m, 2H), 1.06 (d, J = 4.2 Hz, 3H), 1.97 (d, J = 4.1 Hz, 3H). IR (CHCl₃) 3470, 1466, 1059; HRMS (EI) Calcd. for C24H22N2S0 380.1916, Found: 380.1913.

1-Thenyl-2(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-β-carboline (+)-17. Compound (+)-17 (59 %) was obtained as a white solid. M.p. 190-193 °C; [α]_D = 190 °; 1H-NMR (CDCl₃) δ 7.80 (bs, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.40-7.31 (m, 3H), 7.15 (t, J = 6.3 Hz, 1H), 7.05 (t, J = 6.2 Hz, 1H), 4.63 (bs, 1H), 3.40-3.31 (m, 1H), 3.24-3.01 (m, 3H), 2.40 (s, 1H), 1.98-1.94 (m, 1H), 1.65-1.47 (m, 2H), 1.06 (d, J = 4.2 Hz, 3H). IR (CHCl₃) 3470, 1466, 1061; HRMS (EI) Calcd. for C24H22N2S0 366.1750. Found: 366.1754.

1-Isopropyl-2(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-β-carboline (+)-18. Compound (+)-18 (63 %) was obtained as a white solid. M.p. 222-224 °C; [α]_D = 215 °; 1H-NMR (CDCl₃) δ 7.76 (bs, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.35-7.28 (m, 3H), 7.17 (t, J = 6.0 Hz, 1H), 7.08 (t, J = 6.0 Hz, 1H), 4.59 (d, J = 4.1 Hz, 1H), 3.61-3.54 (m, 1H), 3.26-3.16 (m, 1H), 3.08-2.98 (m, 1H), 2.65 (d, J = 7.1 Hz, 1H), 2.42 (s, 3H), 2.31-2.21 (m, 1H), 1.20 (d, J = 5.1 Hz, 3H), 1.10 (d, J = 5.2 Hz, 3H), 1.10 (d, J = 5.2 Hz, 3H). IR (CHCl₃) 3471, 1465, 1058; HRMS (EI) Calcd. for C11H14N2S0 252.0760. Found: 252.0760.

1-Cyclohexyl-2(toluene-4-sulfinyl)-tetrahydro-β-carboline (+)-19. Compound (+)-19 (57 %) was obtained as a white solid. M.p. 240-241 °C; [α]_D = 196 °; 1H-NMR (CDCl₃) δ 7.75 (bs, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.35-7.27 (m, 3H), 7.18 (t, J = 6.1 Hz, 1H), 7.08 (t, J = 6.1 Hz, 1H), 4.55 (d, J = 4.1 Hz, 1H), 3.63-3.52 (m, 1H), 3.26-3.16 (m, 1H), 3.09-2.98 (m, 1H), 2.65 (d, J = 7.0 Hz, 1H), 2.42 (s, 3H), 1.96-1.78 (m, 4H), 1.77-1.68 (m, 1H), 1.43-1.14 (m, 6H); IR (CHCl₃) 3468, 1466, 1060; HRMS (EI) Calcd. for C24H22N2S0 352.1917. Found: 352.1917.

General procedure for removal of the p-tolylsulfinyl chiral auxiliary. Concentrated aqueous hydrochloric acid (50 μL) was added to a solution of the Pictet-Spengler product (50 mg) in ethanol (1 mL) at 0 °C. The reaction mixture was stirred for 5 min and made alkaline with saturated K₂CO₃ solution. After addition of ethyl acetate (5 mL) and stirring for an additional 15 min the organic layer was removed. The aqueous layer was extracted with two 5 mL portions of ethyl acetate. The combined organic layers were dried (MgSO₄) and the solvent was evaporated in vacuo. Flash chromatography (ethyl acetate/ethanol/NH₄OH(aq) 85:10:5) yielded the corresponding tetrahydro-β-carboline.

1-Methyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-46. Compound (-)-46 (89 %) was obtained as a yellow oil. [α]_D = -44.0 °; 1H-NMR (CDCl₃) δ 8.05 (bs, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.18-7.09 (m, 2H), 4.17 (q, J = 3.4 Hz, 1H), 3.41-3.35 (m, 1H), 3.10-3.03 (m, 1H), 2.83-2.70 (m, 2H), 1.45 (d, J = 4.2 Hz, 3H). IR (CHCl₃) 3473, 1467; HRMS (EI) Calcd. for C16H14N2 186.1154, Found: 186.1157.

1-Ethyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-47. Compound (-)-47 (93 %) was obtained as a yellow oil. [α]_D = -62.6 °; 1H-NMR (CDCl₃) δ 7.72 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.31...
Chapter 4

(d, J = 8.0 Hz, 1H), 7.18-7.05 (m, 2H), 4.06-3.99 (m, 1H), 3.42-3.31 (m, 1H), 3.09-2.99 (m, 1H), 2.81-2.68 (m, 2H), 2.00-1.89 (m, 1H), 1.78-1.67 (m, 1H), 1.08 (t, J = 5.1 Hz, 3H); IR (CHCl$_3$) 3473, 1469; HRMS (EI): Calcd. for C$_{13}$H$_{14}$N$_2$ 200.1310, Found: 200.1303.

1-Propyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-48. Compound (-)-48 (91 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -30.0°; 1H-NMR (CDCl$_3$) δ 7.80 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.16-7.07 (m, 2H), 4.09-4.06 (m, 1H), 3.39-3.33 (m, 1H), 3.06-2.99 (m, 1H), 2.80-2.70 (m, 2H), 1.89-1.80 (m, 1H), 1.72-1.45 (m, 3H), 1.00 (t, J = 7.0 Hz, 3H); IR (CHCl$_3$) 3471, 1466; HRMS (EI): Calcd. for C$_{14}$H$_{21}$N$_2$ 214.1466, Found: 214.1458.

1-Butyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-49. Compound (-)-49 (93 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -65.8°; 1H-NMR (CDCl$_3$) δ 7.79 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.18-7.06 (m, 2H), 4.11-4.03 (m, 1H), 3.41-3.34 (m, 1H), 3.08-2.98 (m, 1H), 2.80-2.70 (m, 2H), 1.96-1.84 (m, 2H), 1.75-1.63 (m, 1H), 1.58-1.36 (m, 3H), 0.94 (t, J = 5.1 Hz, 3H); IR (CHCl$_3$) 3473, 1466; HRMS (EI): Calcd. for C$_{15}$H$_{22}$N$_2$ 228.1622, Found: 228.1614.

1-Pentyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-50. Compound (-)-50 (82 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -40.0°; 1H-NMR (CDCl$_3$) δ 7.79 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.17-7.06 (m, 2H), 4.13-4.06 (m, 1H), 3.42-3.33 (m, 1H), 3.10-2.99 (m, 1H), 2.83-2.69 (m, 2H), 1.95-1.82 (m, 1H), 1.78-1.65 (m, 1H), 1.62-1.42 (m, 2H), 1.42-1.38 (4H), 0.91 (t, J = 5.2 Hz, 3H); IR (CHCl$_3$) 3473, 1465; HRMS (EI): Calcd. for C$_{16}$H$_{25}$N$_2$ 242.1778, Found: 242.1770.

1-Isobutyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-51. Compound (-)-51 (90 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -47.1°; 1H-NMR (CDCl$_3$) δ 7.76 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.18-7.07 (m, 2H), 4.18-4.09 (m, 1H), 3.40-3.31 (m, 1H), 3.09-3.00 (m, 1H), 2.81-2.69 (m, 2H), 2.05-1.94 (m, 1H), 1.68-1.59 (m, 2H), 1.04 (d, J = 3.1 Hz, 3H), 0.98 (d, J = 3.0 Hz, 3H); IR (CHCl$_3$) 3471, 1466; HRMS (EI): Calcd. for C$_{15}$H$_{22}$N$_2$ 228.1622, Found: 228.1620.

1-Isopropyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-52. Compound (-)-52 (93 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -58.3°; 1H-NMR (CDCl$_3$) δ 7.76 (bs, 1H), 7.48 (d, J = 4 Hz, 1H), 7.30 (d, J = 4 Hz, 1H), 7.19-7.07 (m, 2H), 4.07 (bs, 1H), 3.36-3.29 (m, 1H), 3.15-3.07 (m, 1H), 2.78-2.96 (m, 2H), 1.81-1.87 (m, 1H), 1.04 (t, J = 4 Hz, 3H), 0.95 (t, J = 4 Hz, 3H); IR (CHCl$_3$) 3473, 1467; HRMS (EI): Calcd. for C$_{14}$H$_{21}$N$_2$ 214.1466, Found: 214.1470.

1-Cyclohexyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-53. Compound (-)-53 (86 %) was obtained as a yellow oil. [$\alpha$]$_D$ = -68.5°; 1H-NMR (CDCl$_3$) δ 7.78 (bs, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.18-7.07 (m, 2H), 4.00 (bs, 1H), 3.42-3.34 (m, 1H), 3.05-2.95 (m, 1H), 2.79-2.68 (m, 2H), 1.88-1.67 (m, 4H), 1.59-1.11 (m, 7H); IR (CHCl$_3$) 3473, 1464; HRMS (EI): Calcd. for C$_{15}$H$_{21}$N$_2$ 254.1778, Found: 254.1769.

1-Benzyl-2-(toluene-4-sulfanyl)-2,3,4,9-tetrahydro-β-carboline (+)-58. BF$_3$-OEt$_2$ (50 µL, 0.4 mmol) was added to a solution of (+)-9 (60 mg, 0.2 mmol) and phenylacetaldehyde (40.6 µL, 0.4 mmol) in a mixture of dichloromethane (1.0 mL) and chloroform (1.0 mL) at -78 °C. After stirring for 1 hour the reaction was quenched by the addition of triethylamine (100 µL) and stirred for 15 minutes at room temperature. Removal of the volatiles in vacuo, column chromatography (ethyl acetate/ light petroleum) and crystallization (ethyl acetate) yielded (+)-58 as a white crystalline material. M.p. = 206 °C; [$\alpha$]$_D$ = 103°; 1H-NMR (CDCl$_3$) δ 7.48-7.04 (m, 14H), 5.01 (t, J = 7.1 Hz, 1H), 3.61-3.53 (m, 1H), 3.38-3.22 (m, 3H), 3.09-2.98 (m, 1H), 2.73-2.65 (m, 1H), 2.41 (s, 3H); 13C-NMR (CDCl$_3$) δ 148.9, 141.2, 140.6, 137.8, 135.8, 133.3, 129.6, 128.7, 126.8, 126.4, 121.9, 119.4, 118.2, 110.8, 109.2, 58.1, 42.4, 40.6, 23.2.
Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions

21.3; HRMS (EI): Calcd. for C_{18}H_{24}N_{2}SO 401.1687, Found: 401.1683.

1-Benzyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-59: Tetrahydro-β-carboline (-)-59 (92%) was obtained as a yellow oil after deprotection under acidic conditions as was described above. [α]_D = -52.1 °; 1H-NMR (CDCl₃) δ 7.55 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.39-7.23 (m, 5H), 7.19 (d, J = 7.9 Hz, 1H), 7.13-7.04 (m, 2H), 4.40 (bs, 1H), 3.39 -3.31 (m, 1H), 3.15-2.97 (m, 3H), 2.79-2.68 (m, 2H); HRMS (EI): Calcd. for C_{18}H_{16}N_{2} 262.1470, Found: 262.1474.

General procedure for the reduction of phenylacetic acids. Lithium aluminium hydride (76.0 mg, 2.0 mmol) was added in small portions to a solution of the phenylacetic acid (1.0 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Upon dropwise addition of ethanol until gas evolution had ceased and addition of aqueous sodium hydroxide (25 mL, 1.0 M) a white precipitate formed. Filtration and concentration of the filtrate, extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent under reduced pressure afforded the alcohol as a yellow syrup.

2-(3-Methoxy-phenyl)ethanol 60. (67%); 1H-NMR (CDCl₃) δ 7.26-7.19 (m, 1H), 6.84-6.75 (m, 3H), 3.83-3.72 (m, 5H), 2.82 (t, J = 7.3 Hz, 2H).

2-(4-Methoxy-phenyl)ethanol 61. (73%); 1H-NMR (CDCl₃) δ 7.16 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 3.88-3.76 (m, 5H), 2.84 (t, J = 7.2 Hz, 2H);

2-(3,4-Dimethoxy-phenyl)ethanol 62. (67%); 1H-NMR (CDCl₃) δ 6.83-6.72 (m, 3H), 3.89-3.81 (m, 8H), 2.80 (t, J = 7.2 Hz, 2H);

General procedure for the Swern oxidation of alcohols 60-62. Oxalyl chloride (0.55 mmol, 48 µL) was added dropwise to a solution of DMSO (0.82 mmol, 85.5 µL) in dichloromethane (2.0 mL) at -60 °C. After stirring for 30 minutes at -60 °C the mixture was cooled to -78 °C and a precooled solution of the alcohol (0.275 mmol) in dichloromethane was added. Stirring of the reaction mixture for an additional 1.5 hours and subsequent addition of triethylamine (150 µL), warming to room temperature, addition of light petroleum and flash chromatography (ethyl acetate/ light petroleum 3:7) afforded the phenylacetaldehyde as a yellow oil that was immediately used.

2-(3-Dimethoxy-phenyl)acetaldehyde 63. (43%); 1H-NMR (CDCl₃) δ 9.73 (t, J = 2.3 Hz, 1H), 6.71 (s, 1H), 6.69-6.43 (m, 3H), 3.87 (s, 3H), 3.62 (d, J = 2.3 Hz, 2H).

2-(4-Dimethoxy-phenyl)acetaldehyde 64. (56%); 1H-NMR (CDCl₃) δ 9.72 (t, J = 2.3 Hz, 1H), 7.13 (d, J = 6.9 Hz, 2H), 6.94 (d, J = 6.8 Hz, 2H), 3.80 (s, 3H), 3.69 (d, J = 2.4 Hz, 2H); IR (CHCl₃) 1725, 1610.

2-(3,4-Dimethoxy-phenyl)acetaldehyde 65. (48%); 1H-NMR (CDCl₃) δ 9.71 (t, J = 2.3 Hz, 1H), 6.71-6.88 (m, 3H), 3.83 (s, 6H), 3.65 (d, J = 2.3 Hz, 2H).

1,2-Dimethoxy-4-(2-methoxy-vinyl)bezen 66. A solution of KHMDS (12.0 mL, 0.5M) in toluene was added to a solution of (methoxymethyl)triphenylphosphonium chloride (2.1 g, 6.0 mmol) in tetrahydrofuran (30 mL). After stirring for 30 minutes at room temperature a solution of 3,4-dimethoxybenzaldehyde (831 mg, 5.0 mmol) in tetrahydrofuran (15 mL) was added. After stirring of the reaction mixture for 16 hours water (10 mL) was added. Concentration of the reaction mixture in vacuo, extractive work-up (ethyl acetate), drying of
the combined organic layers (Na₂SO₄) and evaporation of the solvent under reduced pressure yielded a yellow oil. Purification by using flash chromatography (light petroleum/ethyl acetate 9:1) afforded 66 (90%, 900 mg) as a colorless oil in a 6:4 mixture of geometric isomers. H-NMR (CDCl₃) δ 7.24 (d, J = 0.9 Hz, 1H, minor), 7.07 (dd, J = 3.2 Hz, J = 0.9 Hz, 1H, minor), 6.94 (d, J = 6.6 Hz, 1H, major), 6.81-6.75 (m, 4H, major + minor), 6.06 (d, J = 3.5 Hz, 1H, minor), 5.78 (d, J = 6.6 Hz, 1H, major), 5.16 (d, J = 3.5 Hz, 1H, minor), 3.90-3.85 (m, 12H, major + minor), 3.76 (s, 3H, minor), 3.66 (s, 3H, major).

References and Notes

Enantiopure Tetrahydro-β-carbolines via N-Sulfinyl Pictet-Spengler Reactions
