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

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The N-Sulfinyl Pictet-Spengler Reaction: Applications and Mechanism

Abstract
The \(N\)-sulfinyl Pictet-Spengler reaction appears to be an excellent handle for the introduction of hydroxyalkyl- and aminoalkyl C1-substituents. Reactions of \(N\)-sulfinyltryptamine with acetal-, ester- and halide substituted aldehydes allows the formation of enantiopure building blocks for the efficient asymmetric synthesis of naturally occurring ring systems. Dimerization strategies of tetrahydro-\(\beta\)-carbolines based on the \(N\)-sulfinyl Pictet-Spengler reaction involve reactions of dialdehydes and indole substituted aldehydes. These reactions and some mechanistic considerations concerning the \(N\)-sulfinyl Pictet-Spengler reaction are described in this chapter.
§ 6.1 Introduction

In chapter 4 and 5 of this thesis an efficient synthetic route to enantiopure tetrahydro-β-carbolines and -isoquinolines was described. The asymmetric formation of these pharmacologically interesting ring systems was accomplished by the \( N \)-sulfinyl Pictet-Spengler reaction, which allows the introduction of aliphatic and benzylic C1-substituents. The nature of the substituents at the C1-position plays an important role in the biological activity of these tetrahydroisoquinolines and tetrahydro-β-carbolines. In this chapter the introduction of more complex substituents by reactions with functionalized aldehydes will be described. Furthermore, some mechanistic considerations with respect to the stereochemical outcome of the reaction will be discussed.

§ 6.2. \( N \)-sulfinyl Pictet-Spengler Cyclizations with Functionalized Aldehydes

§ 6.2.1 Tetrahydro-β-carbolines with Aminogroups in the C1-Substituent

Tetrahydro-β-carbolines with C1-substituents containing an amino group are interesting from a pharmacological point of view. In chapter 2 of this thesis we discussed the formation of tetrahydro-β-carboline dimers with linkers containing aminogroups by the dimerization of racemic amines of type 3 (scheme 6.1). The formation of the enantiopure monomers of type 2 by means of \( N \)-sulfinyl Pictet-Spengler cyclizations, which would lead to enantiopure tetrahydro-β-carboline dimers, was investigated.

Scheme 6.1

For the synthesis of the enantiopure monomers 2 some appropriate aminoaldehydes were first synthesized. In scheme 6.2 the synthesis of a number of \( N \)-protected \( \alpha \)- and \( \beta \)-aminoaldehydes with protective groups that can be removed under different conditions is depicted. Commercially available \( N \)-Fmoc-glycine 5 was reacted with \( N,O \)-dimethylhydroxylamine hydrochloride to obtain the Weinreb amide 6. Subsequent reduction with lithium
aluminium hydride afforded N-Fmoc-glycinol 7 in excellent yield over two steps. The N-Boc and N-ethyl carbamate protected aldehydes 11 and 12 were obtained by protection and reduction of glycine methylester 8 and subsequent oxidation to the aldehydes. The synthesis of N-Boc and N-Cbz protected 1,3-aminoaldehydes 13 and 14 was described in § 2.6.2.

\[ \text{Scheme 6.2} \]

\[ \begin{align*}
\text{HO} & \text{C} \quad \text{NH} \quad \text{Fmoc} \\
\text{H}_3\text{C} & \text{N} \quad \text{NH} \quad \text{Fmoc} \\
\text{H}_2\text{CO} & \text{NH}_2 \\
\text{H}_3\text{CO} & \text{NH} \quad \text{R} \\
\text{H}_3\text{CO} & \text{NH} \quad \text{R} \\
\text{O} & \text{C} \quad \text{O} \quad \text{R} \\
\text{O} & \text{C} \quad \text{O} \quad \text{R} \\
\text{N} & \text{Boc} \\
\text{N} & \text{Cbz} \\
\end{align*} \]

\text{Reagents and conditions:} \text{(a): N,O-dimethylhydroxylamine.HCl, DIPCDI, HOBT, DiPEA, CH}_2\text{Cl}_2, 96\%; \text{(b): LiAlH}_4, \text{THF}, 85\%; \text{(c): (Boc)$_2$O, CH}_2\text{Cl}_2, K_2\text{CO}_3 \text{(aq)}, 95\%; \text{(d): ethyl chloroformate, CH}_2\text{Cl}_2, K_2\text{CO}_3 \text{(aq)}, 79\%; \text{(e): NaBH}_4, \text{MeOH}; \text{(f): PCC, CH}_2\text{Cl}_2, 63\% (11), 72\% (12); \]

\( N\)-Sulfinyl Pictet-Spengler cyclization with aminoaldehydes 7 and 11-14 did not afford the desired Cl-aminoalkyl substituted tetrahydro-\( \beta \)-carbolines under both protic acidic (CSA) and Lewis acidic (BF\(_3\)-OEt\(_2\)) conditions (scheme 6.3). The reactions were performed with amounts of CSA ranging from 0.2 equivalents to 0.6 equivalents at temperatures from \(-78\) °C to \(0\) °C. BF\(_3\)-OEt\(_2\) was used in a 5 equivalent excess at the same temperature range. Decomposition of the starting material was the only reaction that took place at higher temperatures and with increased concentrations of the acid catalyst.

\[ \text{Scheme 6.3} \]

\[ \begin{align*}
\text{[+]1} & \quad \text{CSA or BF}_3\text{-OEt}_2, \\
\text{CH}_2\text{Cl}_2, \text{CHCl}_3, -78^\circ \text{C} & \quad \text{no product formation} \\
\end{align*} \]

\[ \begin{align*}
7 \quad \text{R = Fmoc} & \quad 13 \quad \text{R = Boc} \\
11 \quad \text{R = COOC}_2\text{H}_5 & \quad 14 \quad \text{R = Cbz} \\
12 \quad \text{R = Boc} & \quad \end{align*} \]
It was believed that the presence of the NH-group in the aldehyde could interfere with the use of the acid catalysts in the reactions depicted in scheme 6.3. Furthermore the relatively close vicinity of the amino functionality, with a bulky protective group, to the reactive centre was expected to inhibit cyclization. To overcome these problems \(N\)-phtalimido protected \(\gamma\)-aminoaldehyde 17 and glutaraldehyde monooxime 19 were prepared (Scheme 6.4).

Treatment of potassium phtalimide with methylchloroformate in the presence of 18-crown-6 afforded 16 in 68\%.\(^3\) Subsequent reaction with 4,4-diethoxybutylamine and hydrolysis under acidic conditions gave aldehyde 17 in good yield over two steps. Oximaldehyde 19 was obtained in 35\% by reaction of excess aqueous glutaric aldehyde with \(O\)-methylhydroxylamine. The low yield of this reaction can be explained by the formation of the di-oxim 20, which was efficiently removed by flash chromatography. Unfortunately also these aldehydes did not react with \(N\)-sulfinyl tryptamine (+)-1 under both protic and Lewis acidic conditions. In the case of the oximaldehyde 19 this can be explained by the lability of this compound under acidic reaction conditions.\(^4\)

\[
\begin{align*}
15 & \xrightarrow{a} 16 \quad b, c \quad 17 \\
18 & \xrightarrow{d} 19 + 20
\end{align*}
\]

Reagents and conditions: (a) methylchloroformate, 18-crown-6, toluene; (b) 4,4-diethoxybutylamine, \(\text{Et}_3\text{N}, \text{THF}, 68\%\) (2 steps); (c) \(\text{H}_2\text{O}, \text{HOAc}, 99\%\); (d) \(O\)-methylhydroxylamine.HCl, 35\% (19).

Since the presence of nitrogen containing functional groups seems to interfere with the \(N\)-sulfinyl Pictet-Spengler reaction, the introduction of \(Cl\)-substituents with functional groups serving as amine precursors was attempted. The \textit{in situ} hydrolysis of acetal 21 and subsequent formation of oximether 22 was succesfully applied to the synthesis of conformationally restricted nazlinine analogs 23 in our laboratory (scheme 6.5).\(^2\) Treatment of acetal 21 with \(O\)-methylhydroxylamine hydrochloride in the presence of sodium acetate afforded 22 in excellent yield after which reduction with lithium aluminium hydride furnished the bridged nazlinine analog 23.
The N-sulfinyl Pictet-Spengler Reaction: Applications and Mechanism

Scheme 6.5

**Reagents and conditions:** (a) O-methylhydroxylamine.HCl, NaOAc, THF, H₂O, 95%; (b) LiAlH₄, THF, reflux, 66%.

In analogy, the N-sulfinyl Pictet-Spengler cyclization of (+)-1 with 5,5-diethoxypentanal in the presence of substoechiometric CSA at -78 °C afforded the tetrahydro-β-carboline 24 as a 82:18 mixture of diastereomers. The major diastereoisomer (R,R)-24 was obtained diastereomerically pure after a single crystallization from ethyl acetate in 67% yield (scheme 6.6). Treatment of acetal 24 with O-methylhydroxylamine hydrochloride and sodium acetate in a mixture of water and tetrahydrofuran however led to the formation of a complex mixture of products. Most likely this is caused by the concomittant removal of the N-sulfinyl group which leads to inter- and intramolecular condensation reactions between the aldehyde and N2-aminogroup.

Scheme 6.6

**Reagents and conditions:** (a) 5,5-diethoxypentanal, CH₂Cl₂, CHCl₃, -78 °C, 67%.

The problem of the two acid-labile protective groups in compound 24 could be solved by the oxidation of the sulfinyl group to the much more stable sulfonamide. This methodology was described by Davis et al. in the synthesis of enantiopure diaminopimelic acids from enantiopure bis-sulfinylimines. Subsequent *in situ* hydrolysis of the acetal, formation of the oxime ether and hydride reduction would then furnish enantiopure nazlinine 26, after removal of the N-tosyl group (scheme 6.7). Oxidation of 24 was attempted with m-CPBA and with dimethyldioxirane in dichloromethane. Both procedures however led to the formation of multiple products, probably due to the oxidation and subsequent rearrangement of the indole ring.
Reagents and conditions: (a) m-CPBA, CH$_2$Cl$_2$ or DMDO, CH$_2$Cl$_2$.

§ 6.2.2 Enantiopure Tetrahydro-β-carbolines with C1-Alkenyl Substituents

In the preceding chapter it was shown that the introduction of functionalized C1-substituents via the N-sulfinyl Pictet-Spengler reaction was troublesome. In this paragraph the introduction of alkenyl C1-substituents and further functionalization of the double bond is discussed. The synthesis and reactivity of N-sulfinyltetrahydro-β-carbolines with an alkyne substituent is described in § 6.4.2.

5-Hexen-1-yl 28 was prepared by PCC-oxidation of the corresponding alcohol 27 (scheme 6.8). N-sulfinyl Pictet-Spengler cyclization of 5-hexen-1-yl with N-p-tolylsulfinyltryptamine (+)-1 in the presence of CSA at -78 °C afforded a 86:14 mixture of diastereomers of which the major isomer (+)-29 was obtained after recrystallization from ethyl acetate. Acid catalyzed deprotection of (+)-29 afforded the enantiopure tetrahydro-β-carboline (-)-30.

Reagents and conditions: (a) PCC, CH$_2$Cl$_2$, 85%; (b) (+)-1, CSA, CH$_2$Cl$_2$, CHCl$_3$, -78 °C, 70%; (c) HCl, MeOH, 0 °C, 92%.

Dimerization of biologically active molecules by ruthenium catalyzed cross metathesis has found ample precedent in the literature.\(^7\) Attempts to subject the enantiopure N-p-tolylsulfinyl protected tetrahydro-β-carboline (+)-29 to cross metathesis in the presence
of ruthenium catalysts 31 and 32 failed. This can be rationalized by interaction of the catalyst with the sulfanyl group. Protection of the secondary aminogroup by making the hydrochloride salt of the tetrahydro-β-carboline (-)-30 and subsequent cross metathesis failed, due to the unexpected low solubility of (-)-30 and its hydrochloride salt.

Scheme 6.9

![Scheme 6.9](image)

Reagents and conditions: (a) 31, CH₂Cl₂, 20 °C; (b) 32, CH₂Cl₂, reflux.

C1-allyl substituted tetrahydro-β-carboline (+)-34 is a key intermediate in the asymmetric synthesis of enantiopure pseudoyohimbanes of type 36, as reported by Meyers et al. Alkylation of the lithium salt of tetrahydro-β-carboline 33 with allyliodide at -100 °C, separation of the diastereoisomers and subsequent removal of the chiral auxiliary affords (+)-34. N-acylation of MOM-protected derivative (+)-34 with 2,4-pentadienoic acid furnishes 35 which was subjected to Diels-Alder cyclization and reduction and deprotection steps to give (+)-36 in 40% overall yield, starting from 33 (scheme 6.10).

Scheme 6.10

![Scheme 6.10](image)

Reagents and conditions: (a) t-BuLi, CH₂=CHCH₂I, THF, -100 °C; (b) N₂H₄, HOAc, MeOH, 77% (two steps); (c) 2,4-pentadienoyl chloride, NaH, THF, 0°C.
Until now, one of the more successful asymmetric approaches to unprotected 1-allyltetrahydro-β-carboline (+)-42 was reported by Itoh and coworkers, who studied the addition of allyltributyltin to β-carboline 38, substituted with a proline derived chiral auxiliary at the indole nitrogen atom (scheme 6.11). Subsequent removal of the chiral auxiliary, hydride reduction of the 3,4-dihydro-β-carboline 40 and removal of the Troc group afforded 1-propenyl-tetrahydro-β-carboline (+)-42 (scheme 6.11).

Scheme 6.11

\[ \text{(+)42} \]

Reagents and conditions: (a) allyltributyltin, Troc-Cl, SnCl₄; (b) NaOH (aq), THF, 91% (2 steps); (c) Et₃SiH, TFA, CH₂Cl₂, 76%; (d) Zn, HOAc, THF, H₂O, 85%.

This route requires 8 steps to prepare (+)-42 in 86% enantiopurity and 55% overall yield starting from 38. Nakamura et al. reported on the synthesis of (+)-42 in comparable overall yield and optical purity by using enantioselective allylzinc addition in the presence of bis-oxazoline ligands. Other asymmetric approaches furnished compound (+)-42 in lower enantiopurity.

The desired (+)-enantiomer of compound 42 can easily be prepared starting from the appropriate (-)-N-p-tolylsulfinyltryptamine (-)-1. Treatment of (-)-1 with 3-buten-1-al 45 at -78 °C in the presence of CSA did not give formation of the cyclization product. Since it was shown in § 4.5.3 that α,γ-unsaturated aldehydes such as phenylacetaldehyde react smoothly in the presence of BF₃·OEt₂, the reaction was attempted under Lewis acidic conditions. Reaction at -78 °C with BF₃·OEt₂ afforded 1-allyl-N-sulfinyltetrahydro-β-carboline (-)-43 in good yield as a single diastereomer by crystallization. After removal of the sulfinyl group with aqueous hydrochloric acid in ethanol (+)-42 was obtained in 89% yield (ee > 98%). Starting from tryptamine enantiopure 1-allyltetrahydro-β-carboline (+)-42 was obtained in 36% yield over 3 steps. Aldehyde 45 was obtained by acidic hydrolysis of the commercially available 3-buten-1-al diethyl acetal 44.
The N-sulfinyl Pictet-Spengler Reaction: Applications and Mechanism

Scheme 6.12

(-)-1 $\xrightarrow{a}$ (-)-43 [α]₀ = -78.5°

(-)-43 $\xrightarrow{b}$ (+)-42 [α]₀ = 132°

Reagents and conditions: (a) 45, BF₃·OEt₂, CH₂Cl₂, CHCl₃, -78 °C, 56%; (b) HCl (aq), EtOH, 89%; (c) 2% HCl (aq), 99%.

§ 6.3 Synthesis of Enantiopure Alkaloids and Derivatives

Vinca alkaloids comprise a large group of biologically active compounds isolated from several plants of the Vinca family. Among these compounds vincamine (+)-48, the major alkaloid encountered in Vinca minor L. Apocynaceae, appears to be a particularly attractive synthetic target (scheme 6.13). The best established pharmacological property of 48 and less complex derivatives like apovincinate 49 is the cerebroprotective activity by dilation of brain arteries. Biological applications of these compounds are proposed for the treatment of vascular dementia and of the sensorineural impairment of hearing.¹⁴

Scheme 6.13
Synthetic approaches to *Vinca*-alkaloids involve for instance elaboration of indoloquinolizidines of type 47 that are obtained starting from Bischler-Napieralski cyclizations of lactam 46.\(^5\) The parent tetracyclic indoloquinolizidine 50 was isolated as the (-)-enantiomer in 1966.\(^6\) The racemate was isolated more recently from *Nitraria schoberi*.\(^7\) Its brominated analog arborescideine A (51) was found in the marine tunicate *Pseudodistoma arborescens*, also in racemic form.\(^8\) Arylquinolizidines like 50 show affinity for α-adrenergic receptors in the central nervous system.\(^9\) Meyers and coworkers described succesful racemic and asymmetric methodologies for the synthesis of (-)-50.\(^10\)

A short and efficient route towards compound (-)-50 involves the N-sulfinyl Pictet-Spengler reaction of N-p-tolylsulfinyltryptamine (+)-1 and 5-chloropentanal 54. The latter compound was obtained by lithium aluminium hydride reduction of 5-chloropentanoic acid to 5-chloropentanol and subsequent PCC oxidation of the alcohol.\(^11\) Treatment of aldehyde 54 with N-sulfinyltryptamine (+)-1 in the presence of CSA afforded N-p-tolylsulfinyltetrahydro-β-carboline 52 as a 76:24 mixture of diastereoisomers (yield 83%). Crystallization afforded the major isomer (+)-52 in diastereomerically pure form (63% yield). Deprotection under acidic conditions and basic work-up furnished the enantiopure indoloquinolizidine (-)-50 in 94% yield (ee > 98%) by efficient nucleophilic displacement of the chlorine (scheme 6.14). The optical rotation of (-)-50 obtained via this route ([α]_D = -104°) is substantially higher than that reported in the literature ([α]_D = -80.9°, ee = 96%).\(^10\)

![Scheme 6.14](image)

The enantiopure tetrahydroisoquinoline analog (+)-57 of indoloquinolizidine (-)-50 was obtained in a similar fashion by N-sulfinyl Pictet-Spengler cyclization of 5-chloropentanal 54 under Lewis acidic conditions (diastereomeric ratio 91:9) and subsequent deprotection and cyclization (scheme 6.15). The tricyclic ring system in 57 is found in protoberberines, a large family of naturally occurring compounds characterized by a tetracyclic ring skeleton and a tetrahydroisoquinoline core.\(^22\)
The N-sulfinyl Pictet-Spengler Reaction: Applications and Mechanism

Scheme 6.15

\[
\begin{align*}
&\text{Reagents and conditions: (a) 54, BF}_3\text{OEt}_2, \text{CH}_2\text{Cl}_2, \text{CHCl}_3, -78 \text{ °C, 68%; (b) HCl (aq), EtOH then K}_2\text{CO}_3 \text{ (aq), 89%.}
\end{align*}
\]

Recently, Davis and coworkers have reported the asymmetric synthesis of (-)-xylopinine 63b, a prototypical member of the family of protoberberine alkaloids, by application of N-sulfinylimine chemistry. This laborious synthesis prompted us to apply the N-sulfinyl Pictet-Spengler reaction to develop an alternative synthetic route to (-)-xylopinine. Reaction of (+)-55 with phenylacetaldehyde 60 in the presence of BF$_3$OEt$_2$ afforded tetrahydroisoquinoline 61 as a 85:15 mixture of diastereoisomers. Further elaboration of 61 by deprotection and cyclization and subsequent reduction of the lactam should furnish the enantiopure core structure of xylopinine (63a). A synthetic route to (-)-xylopinine 63b, based on this chemistry demands N-sulfinyl Pictet-Spengler reaction of the 3,4-dimethoxy analog of aldehyde 60 and is currently under research. Even though the stability of these compounds is in general low, the presence of the carboxy group might be advantageous. Aldehyde 60 was prepared by a modified literature procedure, starting from indene.

Scheme 6.16

\[
\begin{align*}
&\text{Reagents and conditions: (a) NBS, MeOH, 68%; (b) KO-t-Bu, t-BuOH, reflux, 74%; (c) O}_3, \text{CH}_2\text{Cl}_2, 47%;
\end{align*}
\]

In another approach a fused 5-membered ring was attached to the tetrahydro-β-carboline ring system by N-sulfinyl Pictet-Spengler reaction of (+)-1 with 4-oxobutyric
methyl ester 66 in the presence of BF₃·OEt₂ affording compound (+)-67 as a single diastereoisomer after crystallization (59%, scheme 6.17). This enantiopure N-sulfinyltetrahydro-β-carboline is an ideal precursor for the synthesis of the tetracyclic alkaloid harmicine (+)-64, a compound that was recently isolated in optically active form from leaf extracts of *Kopsia griffithii*.²⁶

![Scheme 6.17](image)

Harmicine derivative 65, containing the same ring system, was recently reported as a cytotoxic compound.²⁷ Deprotection of (+)-67 under acidic conditions and subsequent basic work-up results in efficient lactamization to furnish compound (-)-68 in 49% overall yield (ee > 98%). Harmicine (+)-64 can be obtained from this compound by the well-described reduction of the lactam.²⁸

§ 6.4 Approaches to Enantiopure Tetrahydro-β-carboline Dimers

§ 6.4.1 N-Sulfinyl Pictet-Spengler Reactions with Dialdehydes

The N-sulfinyl Pictet-Spengler reaction has proven to be an effective tool for the asymmetric introduction of aliphatic C1-substituents in tetrahydro-β-carbolines and tetrahydroisoquinolines.²⁹ In chapter 2 of this thesis, the synthesis of racemic tetrahydro-β-carboline dimers as potential bivalent receptor ligands has been discussed. In this paragraph an asymmetric approach to the synthesis of these dimeric species based on the N-sulfinyl Pictet-Spengler reaction will be presented.

The first step is the synthesis of some appropriate aliphatic dialdehydes. Octanedral 70 was obtained in good yield by straightforward PCC oxidation of 1,8-octanediol.

146
Dialdehyde 73, based on a 1,3-disubstituted benzene ring was obtained via Döbner reaction of isophthalldialdehyde with malonic acid.\textsuperscript{29} Subsequent catalytic hydrogenation of the double bond, lithium aluminium hydride reduction to the diol and PCC-oxidation afforded 73 in good overall yield (scheme 6.18).

\textbf{Scheme 6.18}

![Chemical structure](image)

\textit{Reagents and conditions:} (a) PCC, CH\textsubscript{2}Cl\textsubscript{2}, 64%; (b) malonic acid, pyridine, piperidine, reflux, 76%; (c) H\textsubscript{2}, Pd-C, NaOH (aq), 98%; (d) LiAlH\textsubscript{4}, THF, 92%; (e) PCC, CH\textsubscript{2}Cl\textsubscript{2}, 62%.

Racemic \textit{N}-p-tolylsulfinyltryptamine 1 was reacted in a 3 equivalent excess both with octanediol 70, in the presence of CSA, and with dialdehyde 73, in the presence of BF\textsubscript{3}·OEt\textsubscript{2}. Subsequent removal of the \textit{N}-sulfinyl groups afforded tetrahydro-\textit{β}-carboline dimers 74 and 75 in 67% and 59% respectively (scheme 6.19). The synthesis of these compounds has already been described in chapter 2 of this thesis by making use of the Bischler-Napieralski reaction and reduction of the resulting 3,4-dihydro-\textit{β}-carboline dimers.

\textbf{Scheme 6.19}

![Chemical structure](image)

\textit{Reagents and conditions:} (a) 70 (0.3 eq), CSA, CH\textsubscript{2}Cl\textsubscript{2}, CHCl\textsubscript{3}, -78 °C then HCl (aq), EtOH, 67% (2steps); (b) 73 (0.3 eq), BF\textsubscript{3}·OEt\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, CHCl\textsubscript{3}, -78 °C then HCl (aq), EtOH, 59% (2 steps).
Since racemic 1 was used the dimeric species 74 and 75 were found as racemic mixtures of diastereoisomers. To prepare dimeric compounds of this type with a determined stereochemistry, a stepwise reaction of enantiopure (+)-1 or (-)-1 with an excess of the dialdehyde had to be performed. Reaction of (+)-1 with an excess of dialdehydes 70 and 73 should allow stepwise formation of tetrahydro-β-carboline dimers of type 74 and 75.

N-Sulfinyl Pictet-Spengler cyclization with CSA as the acid catalyst afforded the aldehyde 76 as a 78:22 mixture of diastereoisomers (scheme 6.20). Flash chromatography furnished the major diastereomer (+)-76 in 43% yield. In a comparable reaction under Lewis acidic conditions (+)-1 was reacted with dialdehyde 73 to give N-sulfinyl tetrahydro-β-carboline (+)-77 as the major diastereomer after chromatographic separation of the 73:27 mixture of diastereomers in 40% yield.

This efficient formation of the enantiopure aldehydes (+)-76 and (+)-77 allows the application of the N-sulfinyl Pictet-Spengler reaction to the synthesis of enantiopure tetrahydro-β-carboline dimers. Further experiments in this direction were not performed however, due to lack of time.

§ 6.4.2 Towards C1-C5-linked Tetrahydro-β-carboline Dimers

In chapter 2 of this thesis some synthetic approaches to tetrahydro-β-carbolines of which the monomers are linked via the 5-position of the indole ring have been reported. In this way the C1-position, that is particularly interesting with respect to the biological activity of tetrahydro-β-carbolines, is free for the introduction of pharmacophores. Carbon-carbon
bond formation at the indole 5-position was achieved by Sonogashira coupling of 5-bromooindoles with several alkynes. In this section a strategy to combine the Sonogashira coupling with the N-sulfinyl Pictet-Spengler reaction will be presented.

Reaction of N-p-tolylsulfinyltryptamine (+)-1 with 1-hexyn-1-al 79 (scheme 6.21), that was obtained by oxidation of the corresponding alcohol, afforded alkynes (+)-80 (53%) as a single diastereomer after crystallization. Deprotection of (+)-80 under acidic conditions gave the enantiopure tetrahydro-β-carboline (-)-81 in good yields. Sonogashira reaction of N-sulfinyl protected alkyn (+)-80 with 5-bromo-N-tosylindole 83 in the presence of catalytic palladium tetrakistriphenylphosphine in piperidine at 50 °C did not afford the desired bisindole 82 under a variety of other reaction conditions (variations in solvent, base and temperature).

In another approach towards products that are comparable to bisindole 82, the alkyme 84, that was obtained by Sonogashira coupling of N-tosyl-5-bromooindole 83 with 3-buten-1-ol (§ 2.8), was subjected to catalytic hydrogenation in the presence of palladium on carbon (scheme 6.22). When the reaction was performed with ethanol as the solvent quantitative formation of the over-reduced product 88 was observed, while reaction in ethyl acetate furnished the desired alcohol 85 in quantitative yield.

Swern oxidation of alcohol 85 gave aldehyde 86 which was subjected to N-sulfinyl Pictet-Spengler cyclization with (+)-1 in the presence of BF₃·OEt₂, furnishing compound 87 as a 82:18 mixture of diastereoisomers. In principle this compound can be further elaborated by removal of the sulfinyl and tosyl group and construction of the tryptamine sidechain.
Reagents and conditions: (a) H\(_2\), Pd-C, EtOAc, 100%; (b) (COCI\(_2\), DMSO, , 67%; (c) (+)-1, BF\(_3\)OEt\(_2\), CH\(_2\)Cl\(_2\), CHCI\(_3\), -78 °C, 57%.

§ 6.5 The Mechanism of the N-Sulfinyl Pictet-Spengler Reaction

The Pictet-Spengler reactions of N-sulfinyltryptamine (+)-1 and N-sulfinyl- 3,4-dimethoxyphenylethylamine (+)-55 show some remarkable differences with respect to reaction conditions and stereochemical outcome (scheme 6.23). N-p-Tolylsulfinyltryptamine reacts with aliphatic aldehydes in the presence of substoechiometric amounts of CSA with reaction times of several hours to afford N-sulfinyltetrahydro-β-carbolines in moderate to good diastereoselectivity. Reactions in the presence of BF\(_3\)-OET\(_2\) lead to extremely rapid product formation but low diastereoselectivity.

BF\(_3\)-OET\(_2\) has proven to be ideal for the N-sulfinyl Pictet-Spengler cyclization of N-p-tolylsulfinyl-3,4-dimethoxyphenylethylamines (R)-55. The products were obtained in very good diastereoselectivity after short reaction times while reactions of this substrate catalyzed by CSA did not proceed. One of the most remarkable differences between the two reactions is the stereochemistry of the respective products 89 and 90. Starting from (R)-N-sulfinyltryptamine (+)-1, the carbon atom at the 1 position in the tetrahydro-β-carbolines has the (S)-configuration while the tetrahydroisoquinolines are characterized by (R)-stereochemistry at C1 in the major diastereoisomer (scheme 6.23). These unexpected differences in stereochemical outcome of the reaction demand a more detailed understanding of the mechanism of the N-sulfinyl Pictet-Spengler reaction.
A structural comparison of the two respective starting materials led to an experiment to investigate the influence of the indole NH on the stereochemistry. The indole NH was protected with a methyl group which does not decrease the electron density of the pyrrole ring and was believed to have a low steric influence on the cyclization. For reasons of simplicity this experiment was carried out with a racemic model compound.

\[ \text{Reagents and conditions: (a) (COCl)}_2, \text{Et}_2\text{O, 87%; (b) NH}_4\text{OH (aq); (c) BH}_3\text{DMS, THF, reflux, 67%; (d) p-tolylsulfanyl chloride, CH}_2\text{Cl}_2, \text{K}_2\text{CO}_3 (aq), 65%; (e) hexanal, CSA, CH}_2\text{Cl}_2, \text{CHCl}_3, \text{-78 °C, 65%}. \]

\(N\text{,methyl tryptamine 93 was obtained by starting with treatment of commercially available N-methylindole 91 with oxalyl chloride and subsequent reaction with aqueous ammonia (scheme 6.24). Reduction of the glyoxylamide 92 with BH}_3\text{DMS afforded 93 which was reacted with p-tolylsulfanyl chloride under basic conditions to give racemic } N\text{-methyl tryptamine 93.} \)
methyl-N₆-p-tolylsulfinyltryptamine 94 in good yield. N-Sulfinyl Pictet-Spengler reaction of 94 with hexanal smoothly furnished the N-sulfinyl tetrahydro-β-carboline 95 in good yield and as a 76:24 mixture of diastereoisomers. The major diastereoisomer had the (R) configuration at C1, and also the diastereomeric ratio is comparable to that of the unprotected product. Thus, any influence of the indole NH on the diastereoselectivity of the reaction, for instance by formation of a hydrogen bridge, was excluded by methylation of the indole NH.

In the N-sulfinyl Pictet-Spengler reaction, the cyclization products are obtained by an intramolecular nucleophilic attack on an activated aromatic ring on an N-sulfinyliminium ion. A more detailed consideration of the steric factors that play a role in the transition state of the reaction can explain the differences in stereochemical outcome with the different starting materials (R)-1 and (R)-55 (scheme 6.25). Attack of the 3,4-dimethoxyphenyl ring on the energetically favourable E-iminium ion with the sterically least congested orientation of the sulfinyl group (transition state A) results in formation of (R,R)-90 (si-face attack). In contrast, the cyclization of p-tolyl-N-sulfinyltryptamine (R)-1 gives compound 89 with (R)-stereochemistry on C1 as the major product. This can be explained by attack on the Z-iminium ion, as depicted in transition state B2. Sterical hindrance between the bulky p-tolyl group and the substituent R in transition state B1 results in rotation of the p-tolyl group out of the plane of the iminium ion.

Scheme 6.25

\[ \text{E-iminium ion: si-face attack} \quad \text{Z-iminium ion: re-face attack} \]

Attack of the incoming aromatic nucleophile occurs antiperiplanar from the p-tolyl group (B2). The influence of the steric bulk of the p-tolyl group on the intermolecular nucleophilic attack on N-sulfinyl imines has been described by Shimizu et al. They studied the diastereofacial selectivity of attack of lithium enolates on N-sulfinyl imine 91 and found that under non-chelating conditions (3S)-92 was formed as the major product (re-face attack,
scheme 6.26). Also in this reaction the nucleophilic attack occurs in an antiperiplanar fashion with respect to the $p$-tolyl group.

**Scheme 6.26**

From scheme 6.25 it can be gathered that the most important factor that influences the stereochemical outcome of the reaction is the formation of either the $E$ or the $Z$-sulfinyliminium ion. To the best of our knowledge, studies on the formation of $N$-sulfinyl iminium ions have not been mentioned in the literature. With respect to the reactivity of the intermediate, the $N$-sulfinyliminium ion reaction has close resemblance to the well-described $N$-acyliminium ion chemistry.$^{31}$ $N$-Acyliminium ions are generated by elimination reactions of $\alpha$-hydroxy or $\text{--}$alkoxyamides or carbamates of type 100 and can react with a variety of nucleophiles to form new C-C bonds. An understanding of the underlying mechanism of the formation of $N$-acyliminium ions possibly allows a more detailed understanding of the factors that influence the stereochemistry of the $N$-sulfinyliminium ion cyclization.

**Scheme 6.27**

The instability and high reactivity of $N$-acyliminium ions makes detailed studies on the mechanism of their formation troublesome. It is generally accepted that the $N$-acyliminium ion 101 and its precursor 100 are in equilibrium. Experimental evidence that the treatment of 100 with a Lewis acid leads to 101 and that there is an equilibrium between these
two species was first presented by Yamamoto et al.\textsuperscript{32} \textsuperscript{1}H- and \textsuperscript{13}C-NMR experiments detected \textit{N}-acyliminium ion intermediates of type 104 and NOE experiments revealed both the existence of the equilibrium and the \textit{E}-geometry of the iminium ion (scheme 6.27). The geometry of the intermediate \textit{N}-acyliminium ion only plays a role in reactions of acyclic iminium salts. The lack of detailed studies on \textit{E}- and \textit{Z}-iminium ions can largely be attributed to the fact that many \textit{N}-acyliminium ion reactions are endocyclic.

In order to gain a more detailed understanding of the geometry of the intermediates in the \textit{N}-sulfinyl Pictet-Spengler reaction, \textsuperscript{1}H-NMR analysis of the reaction mixture of the condensation of \textit{N}-\textit{p}-tolysulfinylphenylethylamine 105 with acetaldehyde in the presence of BF\textsubscript{3}OEt\textsubscript{2} was conducted. In chapter 5 it was shown that the aromatic ring in \textit{N}-sulfinylamine 105 is not nucleophilic enough for Pictet-Spengler cyclization, which should result in the accumulation of the reactive \textit{N}-sulfinyliminium ion.

The \textsuperscript{1}H-NMR spectrum of a solution of 105 and acetaldehyde in the presence of BF\textsubscript{3}OEt\textsubscript{2} in CDCl\textsubscript{3} at \textdegree C shows the H1-proton in the \textit{N}-sulfinyliminium ion 106 as a broadened quartet at 8.83 ppm (scheme 6.28). This observation is in agreement with the work of Yamamoto et al. who found the \textit{N}-acyliminium proton in 104 around 9 ppm, depending on the nature of the substituent \textit{R}\. Unfortunately, NOE experiments on the H1-proton in 106 did not give a clear indication of the geometry of the iminium ion. This can possibly be attributed to the complicated set-up of this experiment (i.e. a water-free, degassed and low temperature reaction mixture on a \textmu m scale).

\begin{center}
\textbf{Scheme 6.28}
\end{center}

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

In scheme 6.25 a rationale for the formation of the major diastereomers of the cyclization products of the \textit{N}-sulfinyliminium Pictet-Spengler condensation based on \textit{E}- and \textit{Z}-iminium ions was depicted. The formation of either the \textit{E}- or the \textit{Z}-iminium ion is the most important factor that influences the stereochemical outcome of the reaction. Just as the formation of olefines, the formation of iminium ions involves an E2-type elimination that most likely takes place in an \textit{anti}-fashion.\textsuperscript{33}

The steric demands of the sulfinyl group, the nucleophile (e.g. the 3,4-dimethoxyphenylethyl group or the 3-ethylindole group), the presence of either an \textalpha-
hydroxyl group or its BF$_3$-adduct and the type of aldehyde used, influence the orientation of the elimination precursors. Furthermore the geometry of the iminium ion may depend on $E/Z$ isomerization in the presence of a suitable nucleophile that has been described in the literature (scheme 6.29). This reaction involves the nucleophilic addition of a water molecule and subsequent rotation and elimination. The use of either BF$_3$OEt$_2$ or CSA can have a completely different influence on this isomerization. In order to gain a more detailed understanding of the factors that govern the stereochemical outcome of $N$-sulfinyl Pictet-Spengler reactions extensive mechanistic studies of the intermediates are required.

Scheme 6.29

\[
\begin{align*}
\text{R} & \quad \text{H} & \quad \text{Nu} \quad \text{OCH}_3 \\
\text{R}^1 & \quad \text{OCH}_3
\end{align*}
\]

§ 6.6 Concluding Remarks

In this chapter some applications of the $N$-sulfinyl Pictet-Spengler reaction of $N$-$p$-tolylsulfinyltryptamine and $N$-$p$-tolylsulfinyl-3,4-dimethoxyphenylethylamine were discussed. Reactions with acetal-, ester and halide substituted aldehydes resulted in the formation of enantiopure building blocks for the efficient asymmetric synthesis of naturally occurring ring systems. Dimerization strategies of tetrahydro-$\beta$-carbolines based on the $N$-sulfinyl Pictet-Spengler reaction involve reactions of dialdehydes and indole substituted aldehydes. The efficient formation of these enantiopure compounds allows further elaboration to enantiopure dimeric tetrahydro-$\beta$-carbolines with different types of linker systems.

The differences in the stereochemical outcome of the Pictet-Spengler reaction with the two different $N$-sulfinyl starting materials can be rationalized by accepting nucleophilic attack on either the $E$- or $Z$-iminium salt with a preference for attack antiperiplanar to the $p$-tolyl group. The geometry of the iminium ion is probably dependent both on the type of nucleophilic aromatic ring and on the catalyst used. Preliminary experimental studies and theoretical considerations on the formation of $N$-sulfinyliminium ions did not provide unambiguous evidence to understand their formation.

§ 6.7 Acknowledgements

Mandy Vink is kindly acknowledged for constantly supplying me with 4-oxobutyric acid methyl ester 60. I am grateful to Jan Geenevasen for keeping his head and the NMR-spectrometer cool during the NMR-experiments described in § 6.5. Martin Wanner is acknowledged for his last minute efforts towards to (-)-xylopinine.
§ 6.8 Experimental Details

General information. For general experimental details see §2.10. Chloroform was distilled from phosphorous pentoxide and stored over 4Å molecular sieves in the dark. Dichloromethane was distilled from phosphorus pentoxide, stored over calcium hydride and distilled freshly prior to use. Dimethylidioxirane was prepared by the portionwise addition of potassium monopersulfate to a vigorously stirred solution of NaHCO₃ in a mixture of reagent grade acetone and distilled water at 5 °C and subsequent distillation of the dimethylidioxirane-acetone solution under reduced pressure. After preliminary drying over Na₂SO₄, the solution of dimethylidioxirane was stored over 4Å molecular sieves at -20 °C. The synthesis of the enantiopure N-sulfinyltryptamine (+)-I and (-)-I and N-sulfinyl-3,4-dimethoxyphenylethyl amine (+)-55 was described in § 4.8 and § 5.7, respectively. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in acetone (c = 0.6-1.0), unless stated otherwise.

(2-oxo-ethyl)-carbamic acid 9H-fluoren-9-yI methyl ester 7. A solution of N-Fmoc-glycinal (5.95 g, 20.0 mmol), N,O-dimethylhydroxylamine hydrochloride (2.15 g, 22.0 mmol), DIPCDDI (3.44 mL, 22.0 mmol), HOBT (0.30 g, 2.2 mmol) and diisopropylethylamine (3.83 mL, 22.0 mmol) in dichloromethane (150 mL, peptide grade) was stirred for 2 hours at room temperature. The organic layer was subsequently washed with two portions of aqueous hydrochloric acid (3.0 M), two portions of saturated aqueous NaHCO₃, and one portion of saturated aqueous NaCl. Drying of the organic layer (Na₂SO₄) and evaporation of the solvent in vacuo afforded a yellow oil. Addition of hot ethyl acetate and cooling to room temperature gave a white precipitate that was removed by filtration. Evaporation of the solvent in vacuo and subsequent crystallization from ethyl acetate afforded the Weinreb amide 6 (96%, 6.57 g) as white needles. Lithium aluminium hydride (712 mg, 18.8 mmol) was added in portions to a solution of 6 (5.11 g, 15.0 mmol) in tetrahydrofuran (150 mL) at 0 °C. After stirring of the reaction mixture for 30 minutes at 0 °C the reaction was quenched by the careful addition of aqueous KH₂PO₄ (100 mL, 0.26 M) and stirred for 15 minutes. Extractive work-up (diethyl ether), washing of the organic layer with subsequently aqueous hydrochloric acid (two 75 mL portions, 10%), saturated aqueous NaHCO₃ and saturated aqueous NaCl. Drying of the organic layer (Na₂SO₄) and evaporation of the solvent in vacuo gave a yellow oil. Trituration in a mixture of tetrahydrofuran and light petroleum afforded 7 (85%, 3.57 g) as a white solid.

1H-NMR (CDCl₃) δ 9.69 (s, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 5.45 (bs, 1H), 4.48-4.40 (m, 2H), 4.25 (t, J = 4.2 Hz, 1H), 4.20 (d, J = 4.2 Hz, 2H); IR (CHCl₃) 1743, 1712.

Ethoxycarbonylamino acetic acid ethyl ester 9. Ethyl chloroformate (4.0 mL, 43.8 mmol) was added to a solution of glycine methyl ester (5.0 g, 39.8 mmol) in a mixture of saturated aqueous potassium carbonate (20 mL) and dichloromethane (30 mL). After stirring of the reaction mixture for 2 hours at room temperature the organic layer was removed. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent in vacuo gave an oil that was purified by flash chromatography (light petroleum/ethyl acetate 2:1) affording 9 (79%, 5.1 g) as a colourless oil.1H-NMR (CDCl₃) δ 5.20 (bs, 1H), 4.14 (q, J = 6.1 Hz, 2H), 3.96 (d, J = 5.4 Hz, 2H), 3.79 (s, 3H), 1.26 (t, J = 6.1 Hz, 3H); IR (CHCl₃) 1740, 1712.

(2-Oxo-ethyl)-carbamic acid ethyl ester 11. Sodium borohydride (1.17 g, 31.1 mmol) was added at 0 °C to a solution of 9 (1.0 g, 6.2 mmol) in methanol (20.0 mL) under an argon atmosphere. After stirring of the reaction mixture for 30 minutes at room temperature water (30 mL) was added. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent in vacuo yielded the alcohol (71%, 585 mg) as a
The N-sulfinyl Pictet-Spengler Reaction: Applications and Mechanism

colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 5.68 (bs, 1H), 4.11 (q, $J = 6.1$ Hz, 2H), 3.69 (t, $J = 5.5$ Hz, 2H), 3.38-3.29 (m, 2H), 1.23 (t, $J = 6.1$ Hz, 3H); IR (CHCl$_3$) 1714. Pyridinium chlorochromate (1.42 g, 5.64 mmol) was added at 0°C to a solution of the alcohol (500 mg, 3.76 mmol) in dichloromethane (15 mL) in the presence of 4Å molecular sieves. The reaction mixture was stirred for two hours at room temperature after which it was filtered through a short column packed with hyflo, activated carbon and silica. The resulting solution was concentrated under reduced pressure (T <45°C) to give 11 (63%, 310 mg) as a colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 9.98 (s, 1H), 5.51 (bs, 1H), 4.13 (q, $J = 6.1$ Hz, 2H), 3.49 (d, $J = 2.1$ Hz, 2H), 1.20 (t, $J = 6.1$ Hz, 3H); IR (CHCl$_3$) 1738.

Tert-Butoxycarbonylamino acetic acid ethyl ester 10. Di-tert-butylidicarbonate (10.4 g, 47.7 mmol) was added to a solution of glycine methyl ester (5.0 g, 39.8 mmol) in a mixture of saturated aqueous potassium carbonate (20 mL) and dichloromethane (30 mL). After stirring of the reaction mixture for 3 hours at room temperature the organic layer was removed. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and evaporation of the solvent in vacuo gave an oil that was purified by flash chromatography (light petroleum/ ethyl acetate 4:1) affording 10 (95%, 7.15 g) as a colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 5.01 (bs, 1H), 3.91 (bs, 2H), 3.73 (s, 3H), 1.45 (s, 9H); IR (CHCl$_3$) 1742, 1712.

(2-Oxo-ethyl)-carbonyl amino acid tert-buty1 ester 12. Sodium borohydride (100.2 mg, 2.65 mmol) was added at 0°C to a solution of N-Boc-glycine methyl ester (100.0 mg, 0.53 mmol) in methanol (2.0 mL) under an argon atmosphere. After stirring of the reaction mixture at room temperature for 20 minutes water (5 mL) was added. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and evaporation of the solvent in vacuo yielded the alcohol (76%, 58.4 mg) as a colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 5.14 (bs, 1H), 3.69-3.64 (m, 2H), 3.30-3.21 (m, 2H), 1.41 (s, 9H); IR (CHCl$_3$) 1714.

Pyridinium chlorochromate (117 mg, 0.47 mmol) was added at 0°C to a solution of the alcohol (50.0 mg, 0.31 mmol) in dichloromethane (3.0 mL) in the presence of 4Å molecular sieves. The reaction mixture was stirred for two hours at room temperature after which it was filtered through a short column packed with hyflo, activated carbon and silica. The resulting solution was concentrated under reduced pressure (T <45°C) to give 12 (72%, 35.5 mg) as a colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 9.88 (s, 1H), 5.45 (bs, 1H), 4.53 (d, $J = 2.3$ Hz, 2H), 1.42 (s, 9H); IR (CHCl$_3$) 1737.

4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-butyraldehyde 17. Methyl chloroformate (1.19 mL, 15.4 mmol) was added dropwise at 0°C to a solution of potassium pthalimide (3.0 g, 12.8 mmol) and 18-crown-6 (340 mg, 1.3 mmol) in toluene (25.0 mL). The reaction mixture was stirred for 3 hours at 50°C. After cooling to room temperature the solvents were removed in vacuo yielding 16 as a brown oil that was taken up in tetrahydrofuran (20 mL). After addition of 4,4-diethoxybutylamine (1.12 mL, 4.63 mmol) and triethylamine (1.17 mL, 8.42 mmol) the reaction mixture was heated to reflux for 3 hours. Evaporation of the volatiles in vacuo and flash chromatography (light petroleum/ ethyl acetate 4:1) yielded the acetal (68%, 2.54 g) as a yellow oil. $^1$H-NMR (CDCl$_3$) $\delta$ 7.84, 7.79 (2H, 2H), 7.71-7.64 (m, 2H), 4.49 (t, $J = 6.1$ Hz, 2H), 3.69 (t, $J = 6.8$ Hz, 2H), 3.65-3.58 (m, 2H), 3.51-3.41 (m, 2H), 1.79-1.70 (m, 2H), 1.69-1.60 (m, 2H), 1.18 (t, $J = 7.1$ Hz, 6H); IR (CHCl$_3$) 1764.

A mixture of the acetal (779 mg, 2.68 mL) in acetic acid (3.0 mL) and water (3.0 mL) was stirred for 2 hours at room temperature. Addition of saturated aqueous potassium carbonate (5 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and evaporation of the solvent in vacuo yielded 17 (99%, 578 mg) as a colourless oil. $^1$H-NMR (CDCl$_3$) $\delta$ 9.73 (s, 1H), 7.81-7.76 (m, 2H), 7.72-7.67 (m, 2H), 3.69 (t, $J = 6.2$ Hz, 2H), 2.51 (t, $J = 6.3$ Hz, 2H), 2.02-1.94 (m, 2H); IR (CHCl$_3$) 1765, 1730.

Pentanedialmono-(O-methyloxime) 19. Methoxyamine hydrochloride (50 mg) was added to an aqueous solution of glutaric dialdehyde (1.3 M, 40 mL). After cooling to 5°C an aqueous
solution of methoxyamine (3.2 M, 20 mL) was added dropwise over a period of 30 minutes. Stiring for an additional 2 hours yielded a yellow reaction mixture to which NaHCO₃ (10.0 g), NaCl (10.0 g) and diethyl ether (30 mL) were added after which the mixture was stirred for 1 hour. Exctactive work-up (diethyl ether), drying of the combined organic layers (Na₂SO₄), and evaporation of the solvents under reduced pressure yielded a yellow oil. Flash chromatography (Rᵣ = 0.36 ethyl acetate/light petroleum 3:1 → 4:6) yielded a mixture of syn- and anti-19 (35%, 2.35 g) as a yellow oil. ¹H-NMR (CDCl₃) δ 7.97 (s, 1H), 7.38 (t, J = 6.1 Hz, 1H, anti), 6.62 (t, J = 6.1 Hz, 1H, syn), 3.92 (s, 1H, syn), 3.81 (s, 1H, anti), 2.50 (t, J = 6.1 Hz, 2H), 2.26-2.19 (m, 2H), 1.86-1.78 (m, 2H); IR (CHCl₃) 3454.2290, found 3454.2297.

1-(4,4-Diethoxybutyl)-2-(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carboline (R,R)-24. A mixture of 5,5-diethoxypentanal (183 µL, 1.0 mmol) and N-p-tolylsulfinyltryptamine (+)-1 (60.0 mg, 0.2 mmol) in dichloromethane (1.0 mL) and chloroform (1.0 mL) was cooled to -78 °C. After addition of CSA (9.2 mg, 0.04 mmol) the reaction mixture was stirred at -78 °C for 6 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography afforded an oil. Crystallization (ethyl acetate/light petroleum) afforded (R,R)-24 (45%, 41.0 mg) as a white crystalline material. ¹H-NMR (CDCl₃) δ 8.22 (bs, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.35-7.24 (m, 4H), 7.14 (t, J = 8.1 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 4.80-4.75 (m, 1H), 4.52-4.49 (m, 1H), 3.71-3.60 (m, 2H), 3.53-3.42 (m, 2H), 3.31-3.20 (m, 1H), 2.92 (m, 1H), 2.69-2.60 (m, 1H), 2.44 (s, 3H), 2.11-1.91 (m, 2H), 1.80-1.59 (m, 5H), 1.22 (t, J = 7.1 Hz, 6H); HRMS (EI) calculated for C₂₃H₂₃NO₄S, 545.2290, found 545.2297.

5-hexen-1-ol 28. Pyridinium chlorochromate (2.42 g, 11.2 mmol) was added to a solution of 5-hexen-1-ol (7.5 mmol, 740 mg) in dichloromethane (65 mL) in the presence of 4Å molecular sieves at 0 °C. The reaction mixture was stirred for 2 hours at room temperature after which it was passed through a column packed with Hyflo, activated carbon and silica. The slightly green solution was concentrated under reduced pressure (T <45 °C) to give 28 (85%, 574 mg) as a green oil. ¹H-NMR (CDCl₃) δ 7.97 (s, 1H), 5.82-5.70 (m, 1H), 5.09-4.96 (m, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.15-2.06 (m, 2H), 1.80-1.71 (m, 2H); IR (CHCl₃) 3172.5.

1-Pent-4-enyl-2-(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carboline (+)-29. A mixture of 5-hexenal 28 (98 mg, 1.0 mmol) and N-p-tolylsulfinyltryptamine (+)-1 (60.0 mg, 0.2 mmol) in dichloromethane (1.0 mL) and chloroform (1.0 mL) was cooled to -78 °C. After addition of (+)-CSA (28.0 mg, 0.12 mmol) the reaction mixture was stirred at -78 °C for 6 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography afforded an oil. Crystallization (ethyl acetate/light petroleum) afforded (+)-29 (56%, 42.3 mg) as a white crystalline material. 1H-NMR (CDCl₃) δ 9.79 (s, 1H), 5.82-5.70 (m, 1H), 5.09-4.96 (m, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.15-2.06 (m, 2H), 1.80-1.71 (m, 2H); IR (CHCl₃) 3172.5.

1-Pent-4-enyl-2,3,4,9-tetrahydro-1H-β-carboline (-)-30. Compound (+)-29 (40.0 mg, 0.11 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (1.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes at 0 °C after which saturated aqueous potassium carbonate (1.0 mL) was added. Additional stirring for 20 minutes, extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/methanol/aqueous ammonia 85:10:5) yielded (-)-30 (92%, 24.3 mg) as a yellow oil. 1H-NMR (CDCl₃) δ 11.18 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 7.9 Hz, 1H), 5.96-5.82 (m, 1H), 5.15-5.00 (m, 2H), 4.68 (bs, 1H), 3.62-3.51 (m,
hydrochloric acid (10.0 mL, 2%) was stirred for 6 hours at 0 °C. Addition of saturated aqueous potassium carbonate (2.0 mL), extractive work-up, drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent in vacuo afforded 45 (99%, 488 mg) as a colourless oil. (¹H-NMR (CDCl₃) δ 9.71 (s, 1H), 5.99-5.86 (m, 1H), 5.31-5.18 (m, 2H), 3.20 (d, J = 2.1 Hz, 2H); IR (CHCl₃) 1728.

1-Allyl-2-(toluene-4-sulfonyl)-2,3,4,9-tetrahydro-1H-β-carboline (-)-43. A mixture of 3-butene-1-ol 45 (24.2 mg, 0.35 mmol) and N-p-tolylsulfinyltryptamine (-)-1 (20.0 mg, 0.07 mmol) in dichloromethane (0.5 mL) and chloroform (0.5 mL) was cooled to -78 °C. After addition of BF₃·OEt₂ (16.7 µL, 0.14 mmol) the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography afforded an oil. Crystallization (ethyl acetate/light petroleum) gave (-)-43 (56%, 13.7 mg) as a white crystalline material. [α]D = -78.5 °; M.p. 214 °C; ¹H-NMR (CDCl₃) δ 7.83 (bs, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.37-7.28 (m, 3H), 7.18 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.01-5.90 (m, 1H), 5.26-5.9 (m, 2H), 4.80 (t, J = 7.1 Hz, 1H), 3.58-3.49 (m, 1H), 3.39-3.29 (m, 1H), 3.02-2.93 (m, 1H), 2.90-2.80 (m, 2H), 2.71-2.61 (m, 1H), 2.43 (s, 3H); ¹³C-NMR (CDCl₃) δ 141.0, 140.5, 135.7, 134.3, 133.0, 129.4, 126.6, 126.3, 121.7, 119.2, 118.4, 117.9, 110.6, 109.1, 55.9, 40.7, 39.9, 22.7, 21.1; HRMS (EI) calculated for C₁₄H₁₂N₂OS 350.1453, found 350.1460.

1-Allyl-2,3,4,9-tetrahydro-1H-β-carboline (+)-42. Compound (+)-43 (10.0 mg, 0.03 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (1.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes after which saturated aqueous potassium carbonate (1.0 mL) was added. Additional stirring for 20 minutes, extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/ methanol/ aqueous ammonia 85:10:5) yielded (+)-33 (89%, 5.7 mg) as a yellow oil. [α]D = 132 °; ¹H-NMR (CDCl₃) δ 8.19 (bs, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 5.96-5.83 (m, 1H), 5.32-5.20 (m, 2H), 4.31 (bs, 1H), 3.45-3.39 (m, 1H), 3.15-3.06 (m, 1H), 3.40-3.34 (m, 2H), 3.21-3.11 (m, 2H); HRMS (EI) calculated for C₁₆H₁₆N₂ 240.1625, found 240.1626.

5-Chloropentanal 54. Lithium aluminium hydride (1.67 g, 44.1 mmol) was added portionwise to 0 °C to a solution of 5-chloropentanoic acid 53 (2.0 g, 14.7 mmol) in tetrahydrofuran (50 mL). The reaction mixture was stirred at room temperature for 3 hours after which it was quenched by the careful addition of ethanol at 0 °C until the vigorous evolution of hydrogen had ceased. Addition of aqueous sodium hydroxide (50 mL, 1.0 M) afforded a white precipitate which was removed by filtration. Extractive work-up (ethylacetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvents in vacuo yielded a yellow oil that was taken up in dichloromethane (50 mL). Pyridiniumchlorochromate (4.75 g, 22.1 mmol) was added portionwise at 0 °C in the presence of 4Å molecular sieves. After stirring of the reaction mixture for 3 hours at room temperature the dark brown suspension was filtered over a short column with hyflo, activated carbon and silica. Evaporation of the solvent in vacuo afforded a green oil which was purified by flash chromatography (light petroleum/ ethyl acetate 9:1) to yield 54 (67%, 1.19 g) as a colourless oil. ¹H-NMR (CDCl₃) δ 9.79 (s, 1H), 3.55 (t, J = 4.1 Hz, 2H), 2.52-2.45 (m, 2H), 1.86-1.75 (m, 4H); IR (CHCl₃) 1728.
\[ \text{Chapter 6} \]

\begin{align*}
\text{1-(4-Chlorobutyl)-2-(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carboline (±)-52.} & \quad \text{A mixture of 5-chloropentanal 54 (24.2 mg, 0.35 mmol) and \(N\)-p-tolysulfanyltryptamine (±)-1 (150.0 mg, 0.50 mmol) in dichloromethane (2.0 mL) and chloroform (2.0 mL) was cooled to -78 °C. After addition of CSA (70 mg, 0.30 mmol) the reaction mixture was stirred at -78 °C for 4 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography afforded an oil. Crystalization (ethyl acetate) afforded (±)-52 (50%, 100 mg) as a white crystalline material.} \\
\text{[\(\alpha\)]D = 179.6 °; m.p. 238 °C; \(^1\)H-NMR (CDCl\(_3\)) \(\delta 7.84, (bs, 1H), 7.61 (d, \(J = 8.0\) Hz, 2H), 7.48 (d, \(J = 8.0\) Hz, 1H), 7.35-7.28 (m, 3H), 7.15 (t, \(J = 8.1\) Hz, 1H), 7.08 (t, \(J = 8.0\) Hz, 1H), 4.78 (t, \(J = 7.1\) Hz, 1H), 3.59 (t, \(J = 6.1\) Hz, 2H), 3.55-3.48 (m, 1H), 3.31-3.22 (m, 1H), 3.04-2.94 (m, 1H), 2.69-2.61 (m, 1H), 2.42 (s, 3H), 2.11-2.02 (m, 1H), 2.00-1.65 (m, 5H); HRMS (EI) calculated for \(C_{23}H_{23}N_2Cl\) 400.1376, found 400.1376.} \\
\text{1,2,3,4,6,7,12,12b-Octahydro-indolo[2-3a]quinolizidine (-)-50.} & \quad \text{Compound (±)-52 (23.0 mg, 0.06 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (1.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes at 0 °C after which saturated aqueous potassium carbonate (1.0 mL) was added. Additional stirring for 2 hours at room temperature, extractive work-up (ethyl acetate, drying of the combined organic layers (Na\(_2SO_4\)), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/ methanol/ aqueous ammonia 85:10:5) yielded (±)-50 (94%, 12.8 mg) as a yellow oil.} \\
\text{[\(\alpha\)]D (acetone, \(c = 0.8\)) = 104.3 °; \(^1\)H-NMR (CDCl\(_3\)) \(\delta 8.29, (bs, 1H), 7.45 (d, \(J = 8.1\) Hz, 1H), 7.32 (d, \(J = 8.0\) Hz, 1H), 7.17-7.05 (m, 2H), 3.37 (bs, 1H), 3.30-3.12 (m, 1H), 3.10-3.00 (m, 2H), 2.76-2.64 (m, 2H), 2.48-2.40 (m, 1H), 2.11-2.05 (m, 1H), 1.79-1.65 (m, 3H), 1.62-1.39 (m, 2H); HRMS (EI) calculated for \(C_{16}H_{19}NO\) 226.1470, found 226.1478.} \\
\text{1-(4-chlorobutyl)-6,7-dimethoxy-2-(toluene-4-sulfinyl)-1,2,3,4-tetrahydroisoquinoline (±)-56.} & \quad \text{A mixture of 5-chloropentanal 54 (141.6 mg, 1.20 mmol) and \(N\)-p-tolysulfanyl-3,4-dimethoxyphenylethylamine (±)-55 (150.0 mg, 0.47 mmol) in dichloromethane (2.0 mL) and chloroform (2.0 mL) was cooled to -78 °C. After addition of BF\(_3\)OEt\(_2\) (75 mg, 0.30 mmol) the reaction mixture was stirred at -78 °C for 4 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography (light petroleum → ethyl acetate/light petroleum 1:1) afforded (±)-56 (68%, 138 mg) as an oil.} \\
\text{[\(\alpha\)]D (acetone, \(c = 0.8\)) = 86.4 °; \(^1\)H-NMR (CDCl\(_3\)) \(\delta 7.54 (d, \(J = 8.0\) Hz, 2H), 7.29 (d, \(J = 7.9\) Hz, 2H), 6.53 (s, 1H), 6.49 (s, 1H), 4.36-4.31 (m, 1H), 8.85 (s, 3H), 3.82 (s, 3H), 3.62-3.54 (m, 1H), 3.51-3.40 (m, 3H), 2.93-2.82 (m, 1H), 2.63-2.55 (m, 1H), 2.41 (s, 3H), 1.84-1.73 (m, 1H), 1.65-1.40 (m, 4H), 1.21-1.09 (m, 1H); HRMS (EI) calculated for \(C_{23}H_{23}NO_2\) 433.1478, found 433.1474.} \\
\text{9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2-pyrido-[2,1-a]isoquinoline (±)-57.} & \quad \text{Compound (±)-56 (21.0 mg, 0.05 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (1.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes at 0 °C, after which saturated aqueous potassium carbonate (1.0 mL) was added. Additional stirring for 1 hour at room temperature, extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2SO_4\)), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/ methanol/ aqueous ammonia 85:10:5) yielded (±)-56 (89%, 10.6 mg) as a yellow oil.} \\
\text{[\(\alpha\)]D (acetone, \(c = 0.8\)) = 113 °; \(^1\)H-NMR (CDCl\(_3\)) \(\delta 6.68 (s, 1H), 6.57 (s, 1H), 3.84 (s, 6H), 3.31-3.23 (m, 1H), 3.21-3.04 (m, 4H), 2.71-2.59 (m, 2H), 2.50-2.39 (m, 1H), 2.31-2.25 (m, 1H), 1.94-1.88 (m, 1H), 1.82-1.69 (m, 2H), 1.61-1.49 (m, 1H); HRMS (EI) calculated for \(C_{15}H_{19}NO_2\) 247.1572, found 247.1577.} \\
\text{2-[6,7-Dimethoxy-2-(toluene-4-sulfinyl)-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl]-benzoic acid methyl ester (±)-61.} & \quad \text{A solution of (±)-55 (100 mg, 0.31 mmol) and aldehyde 60 (167 mg, 0.94 mmol) in dichloromethane (2.0 mL) and chloroform (2.0 mL) was cooled to -78 °C. BF\(_3\)OEt\(_2\) (75 µL, 0.63 mmol) was added and the reaction mixture was stirred for 1} 
\end{align*}
hour at -78 °C. The reaction was quenched by the addition of triethylamine and allowed to warm to room temperature. Evaporation of the solvent and flash chromatography yielded (−)-61 as a colourless oil (45 %, 66.8 mg). 1H-NMR (CDCl3) δ 7.79 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.04-6.96 (m, 3H), 6.68 (s, 1H), 6.55 (s, 1H), 4.78-4.75 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.67-3.53 (m, 1H), 3.23-2.99 (m, 2H), 2.74-2.68 (m, 1H), 2.33 (s, 3H).

2,3-Dimethoxy-5,6,13a-tetrahydroisoquinoline[3,2a]isoquinolin-8-one (−)-62a. Aqueous concentrated hydrochloric acid (20 µL) was added to a solution of (−)-61 (19 mg, 0.04 mmol) in ethanol (0.5 mL) at 0 °C. After stirring of the reaction mixture for 30 minutes at 0 °C aqueous saturated potassium carbonate was added (0.5 mL) and the mixture was stirred for an additional 2 hours at room temperature. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na2SO4) and evaporation of the solvent in vacuo yielded (−)-62a as a white solid material (96%, 11.9 mg). M. p. 162-165 °C; [α]D = -395 °; 1H-NMR (CDCl3) δ 8.14 (d, J = 8.1 Hz, 1H), 7.48-7.46 (m, 2H), 7.27-7.24 (m, 1H), 6.70 (d, J = 9.4 Hz, 2H), 5.02-4.97 (m, 1H), 4.86 (dd, J = 10.1 Hz, J = 3.5 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.24-3.19 (m, 1H), 3.01-2.91 (m, 3H), 2.80-2.75 (m, 1H).

3-[2-(Toluenesulfinyl)-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl]-propionic acid methyl ester (−)-67. A mixture of 4-oxobutyric acid methyl ester 66 (370 µL, 3.46 mmol) and N-p-tolylsulfinyltritylmethane (+)-1 (200 mg, 0.69 mmol) in dichloromethane (2.0 mL) and chloroform (2.0 mL) was cooled to -78 °C. After addition of BF3·OEt2 (167 µL) the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography (light petroleum → ethyl acetate/light petroleum 1:1) afforded (+)-67 (59%, 161 mg) as an oil. [α]D = 60.1 °; 1H-NMR (CDCl3) δ 8.20 (bs, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 7.9 Hz, 1H), 7.33-7.22 (m, 3H), 7.16 (t, J = 7.9 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 4.68-4.61 (m, 1H), 3.69 (s, 3H), 3.62-3.54 (m, 1H), 3.40-3.31 (m, 1H), 3.05-2.93 (m, 1H), 2.82-2.65 (m, 3H), 2.56-2.46 (m, 3H), 2.39 (s, 3H), 2.37-2.29 (m, 1H), 2.23-2.14 (m, 1H); IR (CHCl3) 1742; HRMS (EI) calculated for C23H19N3O5S 396.1508, found 396.1513.

1,2,5,6,11,11b-hexahydro-indolozino[8,7-b]indole-3-one (−)-68. Compound (+)-66 (40.0 mg, 0.10 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (2.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes after which saturated aqueous potassium carbonate (2.0 mL) was added. Additional stirring for 1 hour, extractive work-up (ethyl acetate), drying of the combined organic layers (Na2SO4), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/methanol/aqueous ammonia 85:10:5) yielded (−)-68 (83%, 18.8 mg) as a yellow oil. [α]D (acetone, c = 0.8) = -46.2°; 1H-NMR (CDCl3) δ 7.96, 7.51 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 4.98-4.91 (m, 1H), 4.60-4.51 (m, 1H), 3.10-2.99 (m, 1H), 2.90-2.83 (m, 2H), 2.70-2.51 (m, 3H), 2.04-1.91 (m, 1H); 13C-NMR (CDCl3) δ 194.3, 173.2, 136.0, 132.9, 126.2, 122.1, 119.7, 118.2, 110.7, 54.0, 37.4, 31.4, 25.5, 20.8; IR (CHCl3) 1653; HRMS (EI) calculated for C14H13N3O 226.1106, found 226.1101.

1,8-Octanediol 70. Pyridinium chlorochromate (7.42 g, 34.4 mmol) was added at 0 °C to a solution of 1,8-octanediol (1.0 g, 8.6 mmol) in dichloromethane (50 mL) in the presence of 4 Å molecular sieves. The reaction mixture was stirred for two hours at room temperature after which it was filtered through a short column packed with hyflo, activated carbon and silica. The resulting solution was concentrated under reduced pressure (T <45 °C) to give 70 (64%, 793 mg) as a colourless oil. 1H-NMR (CDCl3) δ 9.27 (s, 2H), 2.41 (dt, J = 7.3 Hz, J = 1.2 Hz, 4H), 1.74-1.54 (m, 4H), 1.44-1.29 (m, 4H); IR (CHCl3) 1728.

3-[3-(3-Oxo-propyl)phenyl]propionaldehyde 73. Lithium aluminium hydride (464 mg, 11.6 mmol) was added in small portions to a solution of 3-[3-(2-carboxy-ethyl]propionic acid (see
§ 2.3.2, 516 mg, 2.32 mmol) in tetrahydrofuran (50 mL) at 0 °C. The reaction mixture was stirred for 2 hours at room temperature. Addition of ethanol until vigorous evolution of hydrogen had ceased and aqueous sodium hydroxide (100 mL, 1.0 M) gave a white precipitate. Filtration, concentration of the resulting yellow solution in vacuo, extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation under reduced pressure yielded the diol (92%, 414 mg) as a yellow oil. ¹H-NMR (CDCl₃) δ 7.21 (t, J = 7.8 Hz, 1H) 7.07-7.01 (m, 3H), 3.67 (t, J = 6.4 Hz, 4H), 2.69 (t, J = 7.5 Hz, 4H), 1.92-1.84 (m, 4H).

Pyridinium chlorochromate (507 mg, 2.35 mmol) was added at 0 °C to a solution of the dialcohol (152 mg, 0.78 mmol) in dichloromethane (5 mL) in the presence of 4Å molecular sieves. The reaction mixture was stirred for two hours at room temperature after which it was filtered through a short column packed with Hyflo, activated carbon and silica. The resulting solution was concentrated under reduced pressure (T <45 °C) to give 73 (62%, 92.0 mg) as a yellow oil. [a] (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.35-7.23 (m, 3H), 7.17-7.02 (m, 2H), 4.79-4.72 (m, 1H), 3.52-3.44 (m, 1H), 3.30-3.21 (m, 1H), 3.04-2.61 (m, 7H), 2.42 (s, 3H), 2.10-1.85 (m, 2H), 1.71-1.18 (m, 7H); IR (CHCl₃) 1731; HRMS (EI) calculated for C₂₃H₂₉N₂O₂S 422.2028, found 422.2036.

7-[2-(Toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl]-heptanal (+)-76. A mixture of 1,8-octanediol 70 (47 mg, 0.33 mmol) and N-p-tolysulfinyltryptamine (+)-1 (20 mg, 0.07 mmol) in dichloromethane (0.5 mL) and chloroform (0.5 mL) was cooled to -78 °C. After addition of (+)-CSA (9.6 mg, 0.04 mmol) the reaction mixture was stirred at -78 °C for 4 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature.

Evaporation of the volatiles and flash chromatography (light petroleum → ethyl acetate/light petroleum 1:1) afforded (+)-76 (43%, 12.7 mg) as an oil. [α]D = 112°; ¹H-NMR (CDCl₃) δ 9.78 (s, 1H), 8.01 (bs, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.35-7.23 (m, 3H), 7.17-7.02 (m, 2H), 4.79-4.72 (m, 1H), 3.52-3.44 (m, 1H), 3.30-3.21 (m, 1H), 3.02-2.92 (m, 1H), 1.71-1.62 (m, 1H), 2.41 (s, 3H), 2.10-1.85 (m, 2H), 1.71-1.18 (m, 7H); IR (CHCl₃) 1731; HRMS (EI) calculated for C₂₃H₂₉N₂O₂S 422.2028, found 422.2036.

3-[2-(Toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl][ethyl]-phenyl)-propionaldehyde (+)-77. A mixture of dialdehyde 73 (63 mg, 0.33 mmol) and N-p-tolysulfinyltryptamine (+)-1 (20 mg, 0.07 mmol) in dichloromethane (0.5 mL) and chloroform (0.5 mL) was cooled to -78 °C. After addition of BF₃·OEt₂ (18 µL, 0.14 mmol) the reaction mixture was stirred at -78 °C for 2 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the volatiles and flash chromatography (light petroleum → ethyl acetate/light petroleum 1:1) afforded (+)-77 (40%, 13.2 mg) as an oil. [α]D = 88.6°; ¹H-NMR (CDCl₃) δ 9.80 (s, 1H), 7.92 (bs, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.36-7.15 (m, 7H), 7.12-6.99 (m, 2H), 4.76-4.71 (m, 1H), 3.64-3.49 (m, 1H), 3.39-3.28 (m, 1H), 3.04-2.61 (m, 7H), 2.42 (s, 3H), 2.38-2.24 (m, 1H), 1.38-1.24 (m, 2H); IR (CHCl₃) 1741; HRMS (EI) calculated for C₂₅H₂₉N₂O₄S 470.2028, found 470.2036.

5-hexyn-1-ol 79. Pyridinium chlorochromate (13.2 g, 61.2 mmol) was added to a solution of 5-hexyn-1-ol 78 (4.0 g, 40.8 mmol) in dichloromethane (180 mL) in the presence of 4Å molecular sieves at 0 °C. The reaction mixture was stirred for two hours at room temperature after which it was filtered through a column packed with Hyflo, activated carbon and silica. The slightly green solution was concentrated under reduced pressure (T <45 °C) to give 79 (67%, 2.62 g) as a green oil. ¹H-NMR (CDCl₃) δ 9.81 (s, 1H), 2.59 (t, J = 4.5 Hz, 2H), 2.31-2.19 (m, 3H), 1.98 (s, 1H), 1.90-1.81 (m, 2H).

1-Pent-4-ynyl-2-(toluene-4-sulfinyl)-2,3,4,9-tetrahydro-1H-β-carboline (+)-80. A mixture of 5-hexynol 79 (96.0 mg, 1.0 mmol) and N-p-tolysulfinyltryptamine (+)-1 (60.0 mg, 0.2 mmol) in dichloromethane (1.0 mL) and chloroform (1.0 mL) was cooled to -78 °C. After addition of (+)-CSA (28.0 mg, 0.12 mmol) the reaction mixture was stirred at -78 °C for 6 hours. The reaction was quenched with triethylamine and allowed to warm to room
1-Pent-4-ynyl-2,3,4,9-tetrahydro-1H-β-carboline(-)-81. Compound (+)-80 (30.0 mg, 0.08 mmol) was dissolved in a solution of aqueous hydrochloric acid in ethanol (1.0 mL, 2%) at 0 °C. The reaction mixture was stirred for 5 minutes at 0 °C after which saturated aqueous potassium carbonate (1.0 mL) was added. Additional stirring for 20 minutes at room temperature, extraction work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄), evaporation of the solvent under reduced pressure and flash chromatography (ethyl acetate/methanol/aqueous ammonia 85:10:5) yielded (-)-81 (95%, 18.1 mg) as a yellow oil. [α]D = -46 °; 'H-NMR (CDCl₃) δ 7.80 (bs, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.20-7.08 (m, 2H), 4.19-4.10 (m, 1H), 3.41-3.32 (m, 1H), 3.10-3.02 (m, 1H), 2.81-2.71 (m, 2H), 2.43-2.38 (m, 2H), 2.20 (s, 1H), 2.09-1.99 (m, 2H), 1.89-1.71 (m, 2H); HRMS (EI) calculated for C₁₆H₁₄NO₂S 376.1609, found 376.1618.

The N-sulfinyl Pictet-Spengler Reaction: Applications and Mechanism
4-[1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-butan-1-ol 88. A solution of alkyne 77 (30 mg, 0.9 mmol) in ethanol (1.0 mL) was hydrogenated (1 atm.) under vigorous stirring in the presence of palladium on carbon (5 mg, 10%). After 16 hours the catalyst was removed by filtration over hyflo and the solvent was removed in vacuo yielding 88 (100%, 30.5 mg) as a colourless glass. 1H-NMR (CDCl3) δ 7.66 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.99 (bs, 1H), 6.89 (s, 1H), 3.88 (t, J = 8.3 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 8.3 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.69-1.56 (m, 4H); HRMS (EI) calculated for C18H19NO2S 343.1242, found 343.1237.

2-(1-Methyl-1H-indol-3-yl)-2-oxo-acetamide 92. Oxalyl chloride (4.0 mL, 45.7 mmol) was added dropwise at 0 °C to a solution of N-methylindole (5.0 g, 38.1 mmol) in diethyl ether (500 mL). Upon stirring of the reaction mixture for 30 minutes at room temperature a yellow precipitate formed which was collected by filtration affording the glyoxyl chloride as yellow needles. Portionwise addition of the glyoxyl chloride to an aqueous solution of ammonia (50 mL, 25%) at 0 °C afforded a white precipitate. Filtration and washing of the white crystalline material with water (100 mL), ethanol (50 mL) and diethyl ether (50 mL) yielded 92 (87%, 33.3 mmol) as a white crystalline material. 1H-NMR (DMSO-d6) δ 8.75 (bs, 1H), 8.25 (d, J = 1.5 Hz, 1H), 8.09 (bs, 1H), 7.74 (bs, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.39-7.30 (m, 2H), 3.94 (s, 3H).

2-(1-methyl-1H-indol-3-yl)ethylamine hydrochloride 93. Borane dimethylsulfide solution in tetrahydrofuran (65.0 mL, 10.1 M) was added dropwise at 0 °C to a solution of glyoxylamide 92 (6.7 g, 33.2 mmol) in tetrahydrofuran (80 mL). The reaction mixture was stirred under reflux for 3 hours. After cooling to room temperature aqueous hydrochloric acid (50 mL) was added carefully and the reaction mixture was stirred for an additional 2 hours at 50 °C. After cooling to room temperature, addition of saturated aqueous potassium carbonate (25 mL), extractive work-up (ethyl acetate), drying of the combined organic layers and evaporation of the solvent in vacuo yielded a yellow solid. Addition of saturated methanolic hydrochloric acid (10 mL), evaporation of the volatiles and addition of ethyl acetate afforded 93 (57%, 4.0 g) as a white solid. 1H-NMR (D2O) δ 7.41 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 3.79 (s, 3H), 3.05 (s, 4H).

4-methylbenzenesulfinic acid [2-(1-methyl-1H-indol-3-yl)ethyl]-amide 94. A solution of p-tolylsulfinyl chloride (3.49 g, 20.0 mmol) in dichloromethane (30 mL) was added dropwise at 0 °C to a vigorously stirred solution of N-methyltryptamine hydrochloride 93 (3.97 g, 18.9 mmol) in a mixture of dichloromethane (20 mL) and saturated aqueous potassium carbonate (20 mL). After stirring of the reaction mixture for 2 hours at 0 °C the organic layer was separated. Extractive work-up of the aqueous layer (ethyl acetate), drying of the combined organic layers (Na2SO4) and evaporation of the solvents gave a yellow oil. Crystalization (ethyl acetate) afforded 94 (65%, 3.83 g) as a white crystalline material. M.p. 174 °C; 1H-NMR (CDCl3) δ 7.57 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 8.1 Hz, 1H), 7.30-7.19 (m, 3H), 7.09 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.89 (s, 1H), 4.18 (bs, 1H), 3.75 (s, 3H), 3.47-3.38 (m, 2H), 3.20-3.10 (m, 1H), 2.96 (t, J = 6.7 Hz, 2H), 2.42 (s, 3H); HRMS (EI) calculated for C16H15N3O2S 312.1296, found 312.1302.

1-Methyl-1-pentyl-2-(toluene-4-sulfonyl)-2,3,4,9-tetrahydro-1H-β-carboline 95. A mixture of 94 (62.4 mg, 0.20 mmol) and hexanal (120 μL, 1.0 mmol) in dichloromethane (1.0 mL) and chloroform (1.0 mL) was cooled -78 °C. After addition of CSA (9.6 mg, 0.04 mmol) the reaction mixture was stirred for 5 hours. The reaction was quenched with triethylamine and allowed to warm to room temperature. Evaporation of the solvents in vacuo, flash chromatography (light petroleum/ethyl acetate 1:1) and crystallization (ethylacetate) afforded 95 (56%, 44.1 mg) as a white crystalline material. M.p. 229 °C; 1H-NMR (CDCl3) δ 7.61 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.35-7.22 (m, 3H), 7.19 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 4.80-4.72 (m, 1H), 3.62 (s, 3H), 3.63-3.50 (m, 1H), 3.30-3.20 (m, 1H), 3.14-
3.04 (m, 1H), 2.70-2.61 (m, 1H), 2.43 (s, 3H), 1.90-1.78 (m, 2H), 1.73-1.20 (m, 6H), 0.99 (t, J = 6.1 Hz, 3H); 13C-NMR (CDCl3) δ 153.3, 141.2, 141.1, 137.3, 135.5, 129.6, 126.8, 126.2, 121.4, 119.0, 118.2, 108.7, 107.8, 56.8, 38.9, 35.1, 31.4, 29.8, 26.4, 23.1, 22.7, 21.3, 14.0; HRMS (EI) calculated for C9H16O2S: 194.0649, found 194.0649.

Low temperature NMR-experiment. Argon was passed through a solution of p-tolyl-N-sulfinylphenylethyl amine 105 (10.0 mg, 0.04 mmol) and freshly distilled acetaldehyde (11 μL, 0.20 mmol) in deuterated chloroform (0.7 mL, filtrated over basic aluminium oxide) in a dry NMR-tube. The resulting solution was cooled to −55 °C and BF₃·ΟEt₃ (10.0 μL, 0.08 mmol) was added under an argon atmosphere. ¹H-NMR spectra were subsequently recorded at −55 °C on a Varian Inova (500 MHz) spectrometer.

References and Notes


