Synthesis of Dimeric tetrahydro-beta-carbolines as Bivalent Receptor Ligands. An asymmetric N-Sulfinyl Pictet-Spengler Approach
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Chapter 3

Approaches to Asymmetric Pictet-Spengler Cyclizations

Abstract
The Pictet-Spengler reaction is one of the well-described synthetic tools for the preparation of tetrahydro-β-carboline ring systems. The presence of enantiopure tetrahydro-β-carbolines in many alkaloids and compounds with biological activity has resulted in a vivid interest in asymmetric Pictet-Spengler reactions over the last decade. Many of these approaches involve the use of chiral auxiliaries, attached to the tryptamine NH$_2$-group. In this chapter attempts to introduce chiral auxiliary groups at other sites in the tryptamine molecule, an approach that is limited by long synthetic routes and instability of the resulting Pictet-Spengler precursors, will be presented. The introduction of nitrogen, phosphor and sulfur containing chiral groups at the tryptamine NH$_2$ appeared to be more promising. N-sulfinyl groups were found to combine stability, good synthetic availability and increased reactivity and influence on the stereochemical outcome of the Pictet-Spengler reaction.
§ 3.1 Introduction

Tetrahydro-β-carboline ring systems can be found in numerous natural compounds that often have interesting biological activities. For this reason these ring systems and analogs have drawn a lot of attention from a pharmacochemical and biosynthetic point of view. In Figure 3.1 two complex natural products with tetrahydro-β-carboline ring systems derived from tryptamine are depicted.

![Figure 3.1](image)

Obviously the synthesis of tetrahydro-β-carbolines has found ample precedent in the literature. In chapter 2 the Bischler-Napieralski reaction and the Pictet-Spengler reaction, two classical cyclization reactions that were discovered around 1900, have been discussed in some detail. Since the Pictet-Spengler reaction plays an important role in the chemistry that is described in this thesis, some more detailed information about the mechanism and scope of this reaction will be provided.

Pictet-Spengler cyclizations of tryptamines and phenylethylamines, the classical substrates, yield tetrahydro-β-carbolines and -isoquinolines in which a new asymmetric carbon atom is formed. Not surprisingly, many approaches to asymmetric Pictet-Spengler reactions have been reported in the literature, since the synthesis of enantiopure tetrahydro-β-carbolines and analogs is of interest for both synthetic organic chemistry and medicinal chemistry. In § 3.3 asymmetric approaches to the Pictet-Spengler reaction that have been mentioned in the literature are described. Furthermore, a number of our approaches towards a chiral auxiliary mediated Pictet-Spengler reaction will be discussed in § 3.4 to § 3.6.

§ 3.2 The Pictet-Spengler Reaction

§ 3.2.1 Mechanism of the Pictet-Spengler Reaction

An accepted mechanism of the acid-catalyzed Pictet-Spengler reaction is depicted in scheme 3.1. The protonated Schiff-base A, that is formed upon reaction of tryptamine with an aldehyde, can be attacked by electrons from the pyrrole ring, forming a new carbon-carbon bond either on the 2- or the 3-position. It is commonly accepted that attack from the 3-position is more likely for electronic reasons.
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A theoretical study by Kowalski et al. based on MNDO calculations indeed supports some earlier concepts\(^1\) that the Pictet-Spengler reaction involves both spiroindolenine B and the intermediate C that eventually leads to product formation.\(^2\) The heat of formation of spiroindolenine B is only 1 kcal/mol lower than that of the intermediate C while both are calculated to be thermodynamically favoured over the protonated Schiff base A.

![Scheme 3.1](image1)

Initially it was believed that the spiroindolenine B was transformed into the intermediate C via a 1,2- alkylshift (pathway III), which would make B an important intermediate in the reaction. However, the energy barrier of this reaction is calculated to be 43.8 kcal/mol. It is therefore anticipated that the conversion of B to C via this pathway proceeds extremely slow. It is most likely that spiroindolenine B is in equilibrium with the protonated Schiff base A which is also in equilibrium with the intermediate C. Deprotonation of C leads to progress of the reaction in the direction of the tetrahydro-β-carbol ine products.

![Scheme 3.2](image2)

Experiments by Nakagawa and coworkers towards the total synthesis of the naturally occurring alkaloid eudistomin L showed that the formation of the spiroindolenine F (scheme
3.2) is, at least in their Pictet-Spengler cyclization, an important side-process.\textsuperscript{3} Reaction of $N_b$-hydroxytryptamine 3 with $N$-Boc-cysteine yielded the imine D which was cyclized with trifluoroacetic acid. The formation of the tetracyclic side-product 4, which arises from intramolecular attack of the Boc-protected amino group onto the spiro-indolenine F, could only be suppressed at $-78^\circ$ C. In this case efficient trapping of the spiroindolenine makes its formation irreversible and thus prevents the formation of the tetrahydro-$\beta$-carboline product.

§ 3.2.2 Biosynthetic Relevance of Pictet-Spengler Reaction

The Pictet-Spengler cyclization of tryptamine with secologanin\textsuperscript{4} 5, catalyzed by strictosidine synthase, is considered to be an important starting point for the biosynthesis of a variety of naturally occurring monoterpene indole alkaloids such as strychnine\textsuperscript{5} and vindoline.\textsuperscript{6}

![Scheme 3.3](image)

Moreover it is believed that the presence of tryptamine and its derivatives serotonin and 5-methoxytryptamine leads to the in vivo formation of tetrahydro-$\beta$-carbolines in the mammalian central nervous system.\textsuperscript{7} These compounds are known to inhibit the biosynthesis of mono amine oxidases\textsuperscript{8} and interact with the 5HT-reuptake receptor.\textsuperscript{9} The biogenetic Pictet-Spengler reaction is thus believed to have a significant influence on the metabolism of serotonin and its neuronal reuptake and is therefore a crucial reaction in mammalian species.

§ 3.3 Enantioselective Pictet-Spengler Reactions in the Literature

§ 3.3.1 Introduction

The formation of a new stereocenter in the Pictet-Spengler products has prompted many research groups to study asymmetric approaches to the Pictet-Spengler reaction. Although there have been many reports on the use of catalytic C-C bond forming reactions using imines,\textsuperscript{10} a catalytic asymmetric approach to the Pictet-Spengler reaction has not been reported.
Approaches to Asymmetric Pictet-Spengler Cyclizations

Figure 3.2

Asymmetric approaches to the Pictet-Spengler reaction involve the use of chiral auxiliary groups in the starting material, that can either be removed after the cyclization or can further be elaborated to synthesize structurally more complex tetrahydro-\(\beta\)-carbolines. Substituents that have an influence on the stereoselectivity of the reaction can be introduced at different positions in the starting tryptamine skeleton, as can be seen in figure 3.2.

Substitution of the aromatic ring has severe effects on the feasibility of the Pictet-Spengler cyclization since the electronic character of the pyrrole ring is dramatically changed when electron-donating or electron-withdrawing groups are introduced. Obviously, substitution of the \(N_o\)-nitrogen atom has an effect on the geometry of the ring closure and the organization of the iminium ion. In § 3.3.2 some literature approaches that involve chiral \(N_o\)-substituted tryptamines are discussed while some of our own studies regarding this approach are mentioned in § 3.6.

When enantiopure tryptophan derivatives are used as starting materials for the Pictet-Spengler reaction there is a strong effect, both on the reactivity and on the stereoselectivity of the cyclization. Some aspects with regard to the reactivity and stereochemical outcome of Pictet-Spengler cyclizations of tryptophan derivatives will be reviewed shortly in § 3.3.3. In § 3.4 we will describe our attempts to introduce heteroatom substituents at the benzylic \(\alpha\)-position of the tryptamine sidechain. Approaches that involve the introduction of chiral auxiliaries at the indole nitrogen will be described in § 3.5.

§ 3.3.2 Chiral \(N_o\)-substituted Tryptamines

In 1996 Nakagawa et al. reported asymmetric Pictet-Spengler reactions of tryptamine using an \(\alpha\)-methylbenzyl group as a chiral auxiliary. Tryptamines 7 were obtained, according to the literature, by treatment of indole with oxalylchloride, amination with \((S)\)-\(\alpha\)-methylbenzylamine or \((S)\)-\(\alpha\)-methyl-naphthylamine and subsequent reduction of the carbonyl groups (scheme 3.4). Pictet-Spengler reaction with benzaldehyde in the presence of trifluoroacetic acid yielded the tetrahydro-\(\beta\)-carboline 8 as a 86:14 mixture of diastereoisomers in 71% yield. Substitution of the phenyl group for a naphtyl group resulted in a 93:7 mixture of diastereoisomers.
Unfortunately, this reaction only gave satisfying results when benzaldehydes were used. Pictet-Spengler condensation with aliphatic aldehydes gave low diastereoselectivity. Another drawback of this procedure is the problematic removal of the chiral auxiliary after the reaction. The new benzylc C-N bond in the product leads to the excessive formation of ring-opened products upon hydrogenolysis.

Scheme 3.4

\[
\begin{align*}
7 & \quad \text{Ar = phenyl, naphthyl} \\
8 & \quad \text{Ar = phenyl, naphthyl}
\end{align*}
\]

Reagents and conditions: (a) benzaldehyde, TFA, benzene reflux; (b) H₂, Pd(OH)₂, EtOAc

The use of \(N,N\)-phthaloyl amino acids as chiral auxiliaries was first mentioned by Waldmann and coworkers in asymmetric Mannich reactions. This methodology has also been applied to the chemically related Pictet-Spengler reaction. Formation of the imines 9 and subsequent reaction with protected amino acid chlorides gives an intermediate \(N\)-acyliminium ion 10. Intramolecular attack by electrons of the pyrrole ring of the indole system results in the formation of \(N\)-acyl-tetrahydro-\(\beta\)-carbolines 11 with high diastereoselectivity (scheme 3.5). This reaction proceeds only in high diastereoselectivity with specific aldehydes and is therefore not generally applicable. Furthermore, removal of the \(N\)-acylsubstituent by using lithium aluminium hydride reduction furnished the corresponding tetrahydro-\(\beta\)-carbolines in only moderate yield.

Scheme 3.5

\[
\begin{align*}
9 & \quad R = \text{iPr, Ph} \\
10 & \quad R_1 = \text{iPr, tBu} \\
11 & \quad R_1 \quad \text{NPht}
\end{align*}
\]

In another approach Waldmann et al. reported the \(N\)-acyliminium ion Pictet-Spengler cyclization of \(N\)-(3-indolyl)ethyl amino acid esters 12 and substituted aromatic aldehydes in the presence of acetic acid. Despite the excellent diastereoselectivity that was reached with some aromatic aldehydes, the removal of the \(N\)-substituent involves multiple steps under harsh conditions (i.e. \textit{retro} Strecker reaction).
§ 3.3.3 Pictet-Spengler Cyclizations of Tryptophan Derivatives

Pictet-Spengler reactions of tryptophan derivatives have found ample precedent in the literature.\(^\text{16}\) The investigation towards the ratios of cis to trans diastereoisomers in the Pictet-Spengler reaction of tryptophan derivatives has been an important issue over the last decades. It seems obvious that the β-carboxysubstituent plays an important role in the stereochemical outcome of the reaction. Numerous studies have however shown that substitution of the indole NH and tryptamine \(\text{NH}_2\)-groups also plays an important role in the stereochemistry of the Pictet-Spengler cyclization.

In a typical example, Ungemach and coworkers have reported that \(N_b^\text{-benzyltryptophan methyl ester 14 reacts with salicylaldehyde and propionaldehyde to provide the trans-1,3-disubstituted β-carboline 16 in favor of the cis diastereoisomer (scheme 3.7).}\(^\text{16}\) Nagasaka and coworkers have shown that \(N_a^\text{-methyl substitution drastically increases the diastereoselectivity of the cyclization in favor of the trans diastereoisomer.}
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It was shown that the stereoselectivity of the cyclization is influenced for an important part by the \(N_\alpha\)-benzyl substituent and not solely by the \(A^{(1,2)}\) strain on the system. An explanation of this phenomenon can be found in the transition state of the benzyliminium ions 15A and 15B (\(R = \text{ethyl}\)). The \(N\)-benzylsubstituent has a drastic effect on the conformation of the iminium ion which is forced so that unfavorable interactions of the \(R\)-group and the carboxygroup in 15A are absent. Secondly, attack of the electrons from the pyrrole ring is believed to occur antiperiplanar to the methyl ester. This remarkable stereoselectivity is however also dependent on the electronic character of the iminium ion since Pictet-Spengler reactions with \(N_\alpha\)-benzoxoxytryptophan methyl ester under similar conditions show a decrease in stereoselectivity.

A detailed understanding of the steric and electronic requirements of the Pictet-Spengler reaction of tryptophan esters can result in the diastereoselective formation of \(\beta\)-carboxytetrahydro-\(\beta\)-carbolines. These compounds have found ample application in the synthesis of many natural products such as (-)-suaveoline (\textit{Rauwolfia suaveolens}) and (-)-alstonerine (\textit{Alstonia muelleriana}).\(^{17}\) Understanding of the mechanism of epimerization of \(cis\)-\(\beta\)-carboxy-tetrahydro-\(\beta\)-carbolines towards the more stable \(trans\) diastereoisomers has found application in the enantioselective synthesis of tetrahydro-\(\beta\)-carboline alkaloids.\(^{18}\)

One of the advantages of the use of enantiopure tryptophan esters in Pictet-Spengler cyclizations is that they are easily available. Although stereoselective formation of \(\beta\)-carboxy substituted tetrahydro-\(\beta\)-carbolines can be accomplished starting from commercially available tryptophan esters, this methodology is not a suitable entry for the synthesis of tryptamine derived tetrahydro-\(\beta\)-carbolines. Methods for removal of the \(\beta\)-carboxy substituent have been described in the literature but require multiple steps under harsh conditions (scheme 3.8).\(^{19}\)

\[\text{Scheme 3.8}\]

\[\text{Reagents and conditions: (a) NH}_3/\text{MeOH; (b) BnBr, NaHCO}_3, \text{EtOH; (c) PCl}_3, \text{DMF; (d) NaBH}_4, \text{EtOH, pyridine; (e) H}_2, \text{Pd(OH)}_2/C, \text{EtOH.}}\]

§ 3.4 Tryptamine Derivatives with \(\alpha\)-Substituents

Numerous synthetic applications of tryptamine derivatives with substituents at the \(\beta\)-position in the ethylamino sidechain are mentioned in the literature. Substituents on the \(\alpha\)-position are much less common in tryptamine derivatives. In view of our interest in asymmetric approaches to the synthesis of tetrahydro-\(\beta\)-carbolines we evaluated the influence of substituents at the \(\alpha\)-position on the Pictet-Spengler reaction and related cyclizations.
The α-position of the ethylamino side-chain has substantial benzylic character. In theory, the presence of heteroatoms attached to the α-position would allow the easy removal of these substituents and therefore the α-position seems to be an interesting position for the introduction of chiral groups that can influence the diastereoselectivity of the Pictet-Spengler cyclization.

Only few studies of cyclization reactions with carbon substituents at the tryptamine α-position have been reported in the literature. Good diastereoselectivity was observed by Maryanoff and coworkers who studied the influence of α-substituents on N-acyl iminium ion cyclizations. Imide reduction of α,α'-phenylsubstituted tryptamine derivative 17 under acidic conditions at room temperature yielded the product 18 in nearly quantitative yield and in a 92:8 mixture of diastereoisomers.

Scheme 3.9

![Scheme 3.9](image)

Reagents and conditions: (a) NaBH₄, CH₃SO₃H, THF, EtOH, 98%.

In recent years, Pictet-Spengler reactions of conformationally restricted tryptamine derivatives, in which the secondary aminogroup and the α-carbon atom are bridged via either a propylamino or ethylamino bridge, have been studied in our laboratory. These cyclizations proceed in good yield and moderate to good diastereoselectivity which can be explained by the conformational restriction of the transition state (scheme 3.10).

Scheme 3.10

![Scheme 3.10](image)

Reagents and conditions: RCHO, toluene, reflux.

The presence of α-substituents and reduction of the conformational freedom in the transition state obviously has an influence on the stereochemical outcome of cyclization reactions towards tetrahydro-β-carbolines. As was already noticed by other research groups,
the benzylic character of the α-position accounts for low stability of heteroatoms at this position. We envisaged that esters of type 21 could be appropriate starting materials for an asymmetric approach to the Pictet-Spengler reaction when stability of the starting material and influence of the substituent on the cyclization could be optimized (scheme 3.11).

![Scheme 3.11]

Selective oxidation of 3-alkylindoles by DDQ was first described by Yonemitsu et al. in the oxidation of tetrahydrocarbazoles. Application of the same reaction conditions to tryptamine did not give the desired product, probably due to the effect of the primary amingroup in the side-chain. DDQ oxidation of N-Boc protected tryptamine 23 in a water/tetrahydrofuran mixture gave smooth conversion to the desired β-amino ketone 24 from which the N-Boc group was efficiently cleaved in methanolic hydrogen chloride to give the stable ketone 25 as the hydrochloride salt. Reduction of the ketones 24 and 25 to the corresponding secondary alcohols 26 and 27 with sodium borohydride proceeded smoothly (scheme 3.12).

![Scheme 3.12]

Reagents and conditions: (a) (Boc)₂O, CH₂Cl₂, 86%; (b) DDQ, THF/H₂O, 64%; (c) HCl/MeOH, 98%; (d) NaBH₄, MeOH, 91%.

Esterification of alcohol 26 turned out to be extremely difficult, which was mainly caused by its instability under neutral, acidic and basic conditions. Tryptamine derivatives with ester functionalities at the α-position had scarcely been mentioned before in the literature, but also in these cases the compounds suffered from low stability.

In order to rule out the influence of the amino group on the instability another approach was studied. Vilsmeijer-Haack type carboxylation of indole with 2-chloro-N,N-diethyl acetamide and phosphorous oxychloride yielded the α-chloro ketone 28 in moderate
yield (scheme 3.13). Attempts to optimize the yield of this reaction by applying other solvent systems however failed. With N-methylpyrrolidone as the cosolvent, complete conversion of the starting material was observed, leading to the efficient formation of amino ketone 30. Reduction of the ketone function in 28 by using sodium borohydride furnished the alcohol 29 in good yield. Although this α-chloro alcohol appeared to be more stable under neutral conditions than its β-amino analog 27, esterification under a range of basic conditions failed, due to decomposition of the starting material.

Scheme 3.13

Reagents and conditions: (a) 2-chloro-N,N-diethyl acetamide, POCl₃, THF, H₂O, reflux, 53%; (b) NaBH₄, MeOH, 34%; (c) 2-chloro-N,N-diethyl acetamide, NMP, POCl₃, 67%

§ 3.5 Substituents at the Indole Nitrogen

The influence of chiral groups attached to the indole nitrogen atom on the stereochemistry of the Pictet-Spengler condensation did not attract much attention in the literature. This can be explained by the influence of electronwithdrawing N₆-substituents on the electronic character of the enamine system. Electronwithdrawing substituents reduce the electron density of the pyrrole ring and make cyclization less feasible.²⁶ Electron donating N₆-substituents have a positive effect but a disadvantage of their use is that they are often difficult to install and, more importantly, to remove.²⁷

We envisaged that a more challenging approach towards asymmetric Pictet-Spengler reactions involves the hemiaminals 31 (Scheme 3.14). These N₆-substituted tryptamine
derivatives are potentially interesting since the hydroxyalkyl substituent does not have a negative effect on the electronic character of the indole nucleus and can be cleaved under basic conditions after the reaction. Furthermore, the chirality of the Pictet-Spengler cyclization can be induced either by the asymmetric hemiaminal carbon atom or by an appropriate chiral R-substituent.

Hydroxyalkylation of the indole nitrogen and subsequent introduction of the ethylamino sidechain was envisaged to be an approach to the hemiaminals 31. It is however unlikely that the hydroxyalkyl substituent will survive the harsh conditions that are required for the construction of the tryptamine skeleton. We attempted the synthesis of 31 via N-acylation of N-protected tryptamines and subsequent deprotection and reduction to the hemiaminal (scheme 3.15).

**Scheme 3.15**

\[
\begin{array}{c}
\text{NH} \\
\text{R} = \text{H} \\
33 \quad R = \text{Cbz}
\end{array}
\quad \xrightarrow{b} \quad
\begin{array}{c}
\text{O} \\
\text{NH} \text{Cbz}
\end{array}
\quad \xrightarrow{c} \quad
\begin{array}{c}
\text{NH} \\
\text{R}
\end{array}
\]

Reagents and conditions: (a) benzyl chloroformate, CH\(_2\)Cl\(_2\), K\(_2\)CO\(_3\), 85%; (b) valeryl chloride, CH\(_2\)Cl\(_2\), K\(_2\)CO\(_3\), 67%; (c) H\(_2\), Pd/C, EtOH, 98%.

N-Cbz-protection of tryptamine and N-acylation with valeryl chloride yielded compound 34 (scheme 3.15). Unfortunately, treatment of 34 with DiBAL at -78 °C gave a mixture of unidentifiable products, a result that was also obtained by using other reduction conditions. Deprotection of the N-nitrogen by catalytic hydrogenation gave the transamidated product 35 in nearly quantitative yield. Due to these disappointing results, the approach to asymmetric Pictet-Spengler reactions via induction by substituents at the indole nitrogen was abandoned.

**§ 3.6 Cyclizations of Tryptamines with N-hetero Atoms**

Some literature examples of Pictet-Spengler reactions of tryptamines with chiral N-substituents have been mentioned in § 3.3. It was shown that chiral N-substituents can have a strong influence on the diastereoselectivity of the cyclization. The removal of the carbon (e.g. benzyl, carbonyl) substituents that was discussed in § 3.4 is a major drawback of this methodology. N-heteroatom substituted imines are characterized by increased reactivity towards the addition of carbon nucleophiles. Furthermore, diastereoselective additions to N-heteroatom substituted imines with chiral substituents are an attractive approach to enantiopure amine derivatives.

In this paragraph the reactivity of N-heteroatom substituted tryptamines in the Pictet-Spengler cyclization is discussed (scheme 3.16). Furthermore the influence of chiral N-heteroatom substituents on the diastereoselectivity of the Pictet-Spengler reaction will be
worked. In § 3.6.1 the influence of chiral nitrogen substituents will be discussed while § 3.6.2 involves the use of chiral phosphorous substituents on the Pictet-Spengler cyclization. The application of oxygen and sulfur substituted \( N \)-tryptamines as substrates for the Pictet-Spengler reaction will be dealt with in § 3.6.3.

\[ \text{Scheme 3.16} \]

\[ \text{Scheme 3.17} \]

§ 3.6.1 \( N \)-Nitrogen Substituted Tryptamines

Enders and coworkers have reported numerous examples of addition of nucleophiles to the carbon nitrogen double bond of hydrazones. A wide range of enantiomerically pure hydrazones, obtained from the condensation of aldehydes and (S)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) or (R)-1-amino-2-(methoxymethyl)pyrrolidine 36 (RAMP) reacts with organometallic reagents in a highly stereoselective manner. Reductive cleavage of the hydrazine furnishes the corresponding primary amines in good yield and enantioselectivity (scheme 3.17).
The impressive results that were reported from the application of the Enders RAMP/SAMP hydrazone method prompted us to investigate the influence of the chiral 2-(methoxymethyl)pyrrolidine (RMP/SMP) group on the stereochemical outcome of the Pictet-Spengler cyclization.

A synthetic route to $N_b$-RMP substituted tryptamine via indole-3-acetaldehyde 40 has been developed. Oxidation of 2-(indole-3-yl)ethanol, that was obtained by lithium aluminium hydride reduction of 2-indolylacetic acid, did not result in formation of the desired aldehyde under a variety of conditions (e.g. TPAP/NMO, pyridinium chlorochromate and Swern oxidation). However, reduction of the ester 39 with DiBAL at $-78\,^\circ C$ afforded the desired aldehyde 40, which was condensed with RAMP to give the hydrazone 41 in good yield. Subsequent hydride reduction of the hydrazone led to the hydrazine 42. Pictet-Spengler reactions with 42, using both protic (e.g. trifluoroacetic acid) and Lewis acids (e.g. BF$_3$-OEt$_2$), in different solvents and at a variety of temperatures did not give any cyclization products.

§ 3.6.2 $N$-Phosphorus Substituted Tryptamines

In our quest for chiral $N_b$-heteroatom substituents on tryptamines and their effect on reactivity and stereoselectivity in Pictet-Spengler reactions, we also focussed on phosphorus-substituents. The ease of functionalization of the phosphor atom and effective chelating properties of phosphines with transition metals have resulted in numerous applications for phosphor-based ligands, such as BINAP, a fully arylated chiral diphosphine,\textsuperscript{32} in catalytic asymmetric synthesis.
Since their discovery nearly 20 years ago TADDOL and its derivatives have revealed themselves as true chiral auxiliary systems. Their accessibility via commercially available tartrates has led to numerous structural variations and applications. The successful implementation of TADDOLates as ligands for transition state metals resulted in the formation of TADDOL-based cyclic phosphorous esters. These compounds have found numerous applications in asymmetric synthesis.\(^3\)

Reagents and conditions: (a) PCl\(_3\), THF then diisopropyl amine, 63% (47a), 55% (47b); (b) tryptamine tetrazole, CH\(_3\)CN, 47% (43), 52% (44).

We have attempted the coupling of cyclic tartrate- and TADDOLate esters to the tryptamine \(\text{N}_1\)-nitrogen in order to study their reactivity in and possible effect on the stereoselectivity of the Pictet-Spengler cyclization (scheme 3.19). The commercially available \((2R, 3R)\)-diethyl and \((2R, 3R)\)-diisopropyl tartrate esters were first converted with phosphorous trichloride to give the intermediate phosphoryl chloride esters (scheme 3.20). In the second step, these were reacted with diisopropyl amine to give the corresponding phosphoramidite esters 47. Transamidation with the tetrazole salt of tryptamine yielded the desired tartrate esters 43 and 44 in moderate yield.

The synthesis of TADDOL derivative 45 was attempted by using the same protocol, but the yield of this approach was remarkably lower than that of the tartrates 43 and 44. Treatment of TADDOL with hexamethylphosphorous triamide in the presence of a catalytic amount of tetrazole however, furnished the dimethyl phosphoramidite 48a in much better yield. Compound 45 was obtained by subsequent transamidation with tryptamine (scheme 3.21).
Pictet-Spengler reactions of tartrate substituted tryptamine derivatives 43 and 44 under acidic conditions resulted in efficient hydrolysis of the starting material. Reaction with hexanal in the presence of diisopropylethylamine at room temperature resulted in the formation of the imine 50 (scheme 3.22). Heating of 43 with hexanal under neutral conditions in toluene at reflux for 3 hours gave a mixture of tryptamine and tetrahydro-β-carboline 49, while no N-phosphorus substituted products or starting material were found. Obviously, the nitrogen-phosphorus bond is too unstable under Pictet-Spengler reaction conditions. Also the tryptamine TADDOLate 45 proved to be highly unstable under both neutral and acidic conditions.

§ 3.6.3 N-Oxygen and N-Sulfur Substituted Tryptamines

In the approaches towards new chiral auxiliaries for the Pictet-Spengler reaction that were presented so far, the reactivity and stability of the N₅-substituted tryptamine appeared to play an important role. The hydrazines described in § 3.6.1 are shown to be inactive under cyclization conditions while phosphor substituted tryptamine analogs (§ 3.6.2) are too unstable. In this paragraph we will focus on Pictet-Spengler reactions with the group VI elements oxygen and sulfur as substituents, since these elements should combine stability, enhanced reactivity and synthetic availability.

Pictet-Spengler cyclizations of N₅-hydroxytryptamines have found numerous applications in the synthesis of natural products. The eudistominols that were isolated from the
colonic tunicate *Eudistoma olivaceum* were synthesized by applying the Pictet-Spengler reaction of $N_\beta$-hydroxy tryptamines. These compounds display potent antitumour activity, besides antiviral activity against *Herpes simplex* and *Polio* vaccine type I viruses.

Two common approaches towards the intriguing tetracyclic ring system of eudistomins are the *inter*molecular Pictet-Spengler condensation of $N_\beta$-hydroxytryptamines with the appropriate cysteinal and an *intram*olecular condensation of $N_\beta$-alkoxytryptamines.

The latter approach is an excellent application of the pioneering work of Plate et al. on the Pictet-Spengler cyclization of $N_\beta$-hydroxy- and $N_\beta$-alkoxytryptamines and shows the enhanced reactivity of these substrates when compared to unsubstituted tryptamines.

Nakagawa et al. have used the excellent reactivity of $N_\beta$-hydroxytryptamines in an asymmetric Pictet-Spengler reaction that was catalyzed by chiral Lewis acids (scheme 3.24). The imine of $N_\beta$-hydroxytryptamine and benzaldehyde (51) was reacted with (+)-diisopinocampheylchloroborane at $-78 \degree C$ to give $N_\beta$-hydroxy-1-phenyltetrahydro-β-carboline 53 in moderate enantiomeric excess (83%). To the best of our knowledge, Pictet-Spengler reactions between $N_\beta$-alkoxytryptamines with chiral alkoxygroups and aldehydes in an *inter*molecular fashion have never been reported.
The increased reactivity and high stability of the \( \text{N}_6 \)-hydroxy- and \( \text{N}_6 \)-alkoxytryptamines that were mentioned above opened the way for the investigation of the reactivity of analogous \( \text{N}_6 \)-sulfur substituted tryptamines. One of the advantages of this approach is that \( \text{N}_6 \)-sulfenyl tryptamines can be prepared in one step from the corresponding sulfenyl chlorides and tryptamine while the synthesis of \( \text{N}_6 \)-alkoxytryptamines involves multiple steps.\(^{39}\)

The \( o \)-nitrophenylsulfenyl group (Nps) is a protective group for amino acids and nucleosides that can be cleaved under acidic conditions and by desulfurization with Raney nickel.\(^{40}\) \( \text{N}_6 \)-Nps tryptamine 54, which was obtained by sulfenylation of tryptamine with the commercially available \( o \)-nitrophenylsulfenyl chloride, proved to be a highly reactive amine for Pictet-Spengler cyclizations.

Scheme 3.25

Reagents and conditions: (a) \( o \)-nitrophenylsulfenyl chloride, \( \text{CH}_2\text{Cl}_2 \), NaOH (aq) 66%; (b) hexanal, CSA, \( \text{CH}_2\text{Cl}_2 \); (c) \( \text{EtOH} \), conc. HCl, 83% (2 steps).

Pictet-Spengler reaction of aqueous glutaric dialdehyde with a stoichiometric amount of \( \text{N}_6 \)-Nps-tryptamine 54 furnished, after deprotection, the dimeric tetrahydro-\( \beta \)-carbol ine 60 (see also § 2.3.1). When an excess of the dialdehyde was used, the monocoupled Pictet-Spengler product 56 was obtained which could efficiently be cyclized and deprotected under neutral conditions to give the azaepine 58, a racemic arborescidine alkaloid.\(^{41}\)

Scheme 3.26

Reagents and conditions: (a) glutaric dialdehyde (aq), 1 equiv, PTFA, \( \text{CaCl}_2 \), \( \text{CH}_2\text{Cl}_2 \); (b) \( \text{Et}_3\text{N} \), \( \text{CH}_2\text{Cl}_2 \), 100%; (c) RanNi, THF, 40%; (d) glutaric dialdehyde (aq) (10 equiv), PTFA, \( \text{CaCl}_2 \), \( \text{CH}_2\text{Cl}_2 \), 56% (57); (e) RanNi, THF, 50%.
Approaches to Asymmetric Pictet-Spengler Cyclizations

$N_\text{sulfur}$ and $N_\text{oxygen}$ substituted tryptamines show excellent reactivity and high stability in Pictet-Spengler reactions. The introduction of chiral alkoxy and sulfenyl groups to the tryptamine $N_\text{s}$-nitrogen atom would in principle be an attractive approach to asymmetric Pictet-Spengler reactions.

Chiral $N$-sulfanyl groups have some interesting characteristics for use as chiral auxiliaries in the Pictet-Spengler reaction. $N$-sulfanyl groups can easily be introduced at the tryptamine $N_\text{s}$-nitrogen atom, either by oxidation of the corresponding sulfenyl tryptamine or by reaction of tryptamine with an appropriate sulfanyl chloride. The electronwithdrawing effect of the sulfanyl group is believed to increase the electrophilic character of the intermediate $N$-sulfenyliminium ion (scheme 3.27). But more importantly, it may be expected that the chiral sulfur has a strong influence on the stereocchemical outcome of the reaction since it is located in close vicinity of the reactive center. Removal of the $N$-sulfanyl group can be accomplished under both reductive and mild acidic conditions.\(^{42}\)

![Scheme 3.27](image)

Racemic $N_\text{s}$-$p$-tolylsulfanyl tryptamine 61 was obtained by reaction of tryptamine with $p$-tolylsulfanyl chloride. Subsequent reaction of 61 with hexanal in the presence of trifluoroacetic acid in dichloromethane at 0 °C furnished $N_\text{s}$-$p$-tolylsulfanyl tetrahydro-$\beta$-caroline 62 in moderate yield as a 52:48 mixture of diastereoisomers (scheme 3.28). This encouraging result prompted us to select the sulfanyl group for further studies as a chiral auxiliary in the Pictet-Spengler cyclization.

![Scheme 3.28](image)

*Reagents and conditions: (a) $p$-tolylsulfanyl chloride, $\text{CH}_2\text{Cl}_2$, $\text{K}_2\text{CO}_3$ (aq), 75%; (b) hexanal, TFA, $\text{CH}_2\text{Cl}_2$, 0 °C, 43%.*

Detailed information concerning the use of optically pure $N_\text{s}$-sulfanyltryptamines and $N_\text{s}$-sulfanylphenylethylamines in Pictet-Spengler reactions and the application of this approach to the synthesis of enantiopure tetrahydro-$\beta$-carbolines and -isoquinolines will be presented in chapter 4, 5 and 6 of this thesis.
§ 3.7 Concluding Remarks

Chiral auxiliary mediated Pictet-Spengler reactions have found ample precedent in the literature. Although the diastereoselectivity of these asymmetric approaches is often good, the removal of the chiral auxiliary without racemization is in most cases a limiting factor. In this chapter we studied the effect of the introduction of chiral auxiliaries at different sites in the molecule.

The introduction of chiral \( N_\alpha \)-substituents appeared to be advantageous since the chiral centre is located in close vicinity of the reactive C-N double bond. The Pictet-Spengler cyclization of \( N_\alpha \)-nitrogen-, \( N_\alpha \)-phosphor-, \( N_\alpha \)-oxygen and \( N_\alpha \)-sulfur substituted tryptamines was studied in detail. It was found that the \( p \)-tolysulfinyl group has encouraging properties with respect to reactivity and diastereoselectivity.

§ 3.8 Acknowledgements

Martin Wanner is kindly acknowledged for the work he did on the chemistry concerning the synthesis of \( N \)-phosphor and \( N \)-sulfur substituted tryptamines (§ 3.6.2 and § 3.6.3). I am grateful to Dr. Floris van Delft for stimulating ideas and discussions regarding asymmetric Pictet-Spengler reactions, that initiated the research described in this chapter and thesis.

§ 3.9 Experimental Details

General methods. For general experimental details see § 2.11.

\[ \text{[2-(1H-indol-3-yl)-ethyl]carbamic acid t-butyl ester 23.} \]
A solution of di-tert-butyl dicarbonate (29.7 g, 136 mmol) in dichloromethane (50 mL) was added dropwise to a solution of tryptamine (8.0 g, 68.4 mmol) in dichloromethane (250 mL). After stirring for 3 hours at room temperature, the solvent was removed in vacuo. Column chromatography (\( R_f = 0.21 \)) yielded 23 as a yellow solid (86%, 15.2 g). \( ^1 \)H-NMR (CDCl\(_3\)) \( \delta \) 8.21 (bs, 1H), 7.62 (d, \( J = 8.1 \) Hz, 1H), 7.39 (d, \( J = 8.2 \) Hz, 1H), 7.26-7.07 (m, 2H), 7.06-7.01 (bs, 1H), 4.64 (bs, 1H), 3.55-3.39 (m, 2H), 3.03-2.90 (m, 2H), 1.45 (s, 9H); IR (CHCl\(_3\)) 1723.

\[ \text{[2-(1H-indol-3-yl)-2-oxo-ethyl]carbamic acid t-butyl ester 24.} \]
DDQ (6.90 g, 30.4 mmol) was added in small portions to a solution of 23 (3.72 g, 15.2 mmol) in a mixture of tetrahydrofuran and water (150 mL, 9:1 v/v) at 0 °C. After stirring for two hours at room temperature the reaction mixture was concentrated to 25% of its original volume. Addition of ethyl acetate (100 mL) resulted in the formation of a thick white precipitate which was collected by filtration and purified by recrystallization (ethyl acetate) to give 24 (64%, 2.51 g) as a white crystalline material. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)), evaporation of the solvent in vacuo and recrystallization from ethyl acetate yielded another 15% (588 mg) of 20. M.p. 213 °C; \( ^1 \)H-NMR (CDCl\(_3\)) \( \delta \) 8.82 (bs, 1H), 8.34-8.29 (m, 1H), 7.44 (d, \( J = 0.8 \) Hz, 1H), 7.48-7.41 (m, 1H), 7.35-7.30 (m, 2H), 5.67 (bs, 1H), 4.56 (d, \( J = 2.1 \) Hz, 2H), 1.49 (s, 9H); \( ^13 \)C-NMR (CD\(_3\)OD) \( \delta \) 190.8, 156.0, 136.4, 133.3, 125.4, 122.8, 121.7, 121.2, 113.9, 112.2, 77.9, 46.8, 28.2; IR (CHCl\(_3\)) 1728, 1673; HRMS (El): Calcd. for C\(_{10}\)H\(_{10}\)N\(_2\)O 174.0793; Found: 174.0798.
2-Amino-1-(1H-indol-3-yl)-ethanone 25. Ketone 24 (1.0 g, 3.88 mmol) was stirred for 1 hour at room temperature in saturated methanolic hydrogen chloride (20 mL). After evaporation of the volatiles and coevaporation with ethanol, ethyl acetate (20 mL) was added and the resulting solution was stirred at 0 °C for two hours. Filtration and washing of the residue with diethyl ether yielded 25 (98%, 747 mg) as a white solid. M.p. 283 °C; $^1$H-NMR (D$_2$O) $\delta$ 8.31-8.15 (m, 2H), 7.71-7.77 (m, 1H), 7.48-7.35 (m, 2H), 4.48 (bs, 2H); IR (KBr) 1674.

2-Amino-1-(1H-indol-3-yl) ethanol 26. Sodium borohydride (590 mg, 15.6 mmol) was added in small portions to a solution of 24 (1.0 g, 3.88 mmol) in methanol (50 mL) at 0 °C. After stirring of the reaction mixture for 2 hours at room temperature the volatiles were removed by evaporation in vacuo. Addition of water (50 mL) and extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and purification by column chromatography (R$_f$ = 0.44 ethyl acetate/ ethanol/ NH$_4$OH (aq) 85:10:5, note R$_f$(24) = 0.46) yielded 26 (91%, 918 mg) as a yellow oil that was stored under a nitrogen atmosphere at -20 °C. $^1$H-NMR (CDCl$_3$) $\delta$ 8.20 (bs, 1H), 7.72 (d, $J$ = 8.3 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.25-7.18 (m, 2H), 7.15-7.10 (t, $J$ = 8.1 Hz, 1H), 5.18-5.12 (m, 1H), 4.99 (bs, 1H), 3.72-3.61 (m, 1H), 3.57-3.47 (m, 1H), 1.46 (s, 9H).

2-Chloro-1-(1H-indol-3-yl)-ethanone 28. 2-Chloro-N,N-diethyl acetamide (1.40 mL, 10.2 mmol) was added to a solution of indole (1.0 g, 8.54 mmol) in phosphorous oxychloride (30 mL) at 40 °C. The reaction mixture was heated to reflux for 30 minutes after which the volatiles were removed under reduced pressure. Upon addition of water (10 mL) and saturated aqueous K$_2$CO$_3$ (3 mL) the reaction mixture was stirred for another 30 minutes. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$), evaporation of the solvent in vacuo and purification by column chromatography (R$_f$ = 0.35 ethyl acetate/ light petroleum 1:1) yielded 28 (53%, 876 mg) as a yellow solid. M.p. 182 °C; $^1$H-NMR (CDCl$_3$/ CD$_3$OD) $\delta$ 8.17-8.12 (m, 1H), 7.89 (s, 1H), 7.34-7.29 (m, 1H), 7.17-7.12 (m, 2H), 4.47 (s, 2H); IR (CHCl$_3$) 1679.

2-Chloro-1-(1H-indol-3-yl)-ethanol 29. Sodium borohydride was added in portions to a solution of 28 (193 mg, 1.0 mmol) in ethanol (10 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 30 minutes at room temperature, after which water (10 mL) was added and stirring was continued for an additional 10 minutes. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$), evaporation of the solvent in vacuo and purification by using column chromatography (R$_f$ = 0.42 ethyl acetate/ light petroleum 1:1, note R$_f$(28) = 0.45) yielded 29 (34%, 66 mg) as a brown oil that was stored under a nitrogen atmosphere at -20 °C. $^1$H-NMR (CDCl$_3$) $\delta$ 8.52 (bs, 1H), 7.68 (d, $J$ = 8.3 Hz, 1H), 7.32 (d, $J$ = 8.1 Hz, 1H), 7.21 (t, $J$ = 8.1 Hz, 1H), 7.15 (t, $J$ = 8.2 Hz, 1H), 7.05 (bs, 1H), 5.21 (t, $J$ = 6.1 Hz, 1H), 3.85 (d, $J$ = 6.0 Hz, 12H); $^1$C-NMR (CD$_3$OD) $\delta$ 138.2, 127.1, 123.7, 122.7, 120.3, 120.0, 116.5, 112.7, 69.9, 50.4.

1-(1H-indol-3-yl)-4-methylamino butan-1-one 30. 2-Chloro-N,N-diethyl acetamide (170 mg, 1.2 mmol) was added to a solution of indole (117 mg, 1.0 mmol) and phosphorous oxychloride (190 µL, 2.0 mmol) in N-methylpyrrolidone (5 mL). After stirring at room temperature for 2 hours the reaction mixture was cooled to 0 °C. A white precipitate was filtered off and recrystallized from diethyl ether yielding 30 (67%, 144 mg) as a white solid. M.p. 205 °C; $^1$H-NMR (DMSO-$d_6$) $\delta$ 8.67 (d, $J$ = 1.8 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 1H), 6.78 (d, $J$ = 8.2 Hz, 1H), 7.43-7.32 (m, 2H), 4.19 (t, $J$ = 3.2 Hz, 2H), 3.76 (t, $J$ = 3.4 Hz, 2H), 3.66 (s, 3H), 2.33-2.22 (m, 2H); IR (CHCl$_3$) 1671.

[2-(1H-indol-3-yl)-ethyl] carbamic acid benzyl ester 33. Benzyl chloroformate (0.98 mL, 6.78 mmol) was added slowly to a solution of tryptamine (1.0 g, 6.24 mmol) in a mixture of
dichloromethane (20 mL) and saturated aqueous NaHCO₃ at 0 °C. The reaction mixture was stirred for 3 hours at room temperature, after which the organic layer was separated. Extractive work-up of the aqueous layer (ethyl acetate), drying of the combined organic layers and removal of the solvent under reduced pressure yielded 33 as a yellow oil which was used without further purification. ¹H-NMR (CDCl₃) δ 8.02 (bs, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.41-7.36 (m, 6H), 7.21 (t, J = 8.3 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 7.01 (s, 1H), 5.09 (s, 2H), 4.82 (bs, 1H), 3.58-3.49 (m, 2H), 2.97 (t, J = 7.1 Hz, 2H); IR (CHCl₃) 1723.

[2-(1-pentanoyl-1H-indol-3-yl)-ethyl]-carbamic acid benzyl ester 34. Valeryl chloride (45 µL, 0.37 mmol) was added to a solution of 33 (100 mg, 0.34 mmol) in a mixture of dichloromethane (5 mL) and saturated aqueous K₂CO₃ at 0 °C. After stirring of the reaction mixture at room temperature for 3 hours the organic layer was separated. Extractive work-up of the aqueous layer (ethyl acetate), drying of the combined organic layers and removal of the solvent under reduced pressure gave a brown oil. Compound 34 was obtained after column chromatography (Rₗ = 0.45 ethyl acetate/ light petroleum 1:3) as a yellow oil (67%, 86.2 mg).

¹H-NMR (CDCl₃) δ 8.45 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.38-7.23 (m, 8H), 5.12 (s, 2H), 4.88 (bs, 1H), 3.61-3.51 (m, 2H), 3.93 (t, J = 6.1 Hz, 1H), 2.84 (t, J = 7.3 Hz, 2H), 1.85-1.76 (m, 2H), 1.51-1.42 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); IR (CHCl₃) 3136, 1684.

(1H-indol-3-yl)-acetic acid methyl ester 38. A solution of indole-3-acetic acid (1.75 g, 10.0 mmol) in saturated methanolic hydrochloric acid was stirred at room temperature for two hours. Evaporation of the solvent yielded 38 (99%, 1.89 g) as a brown oil. ¹H-NMR (CDCl₃) δ 8.12 (bs, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 7.21 (d, J = 8.2 Hz, 1H), 7.18-7.12 (m, 2H), 3.81 (s, 2H), 3.72 (s, 3H); ¹³C-NMR (CDCl₃) δ 145.7, 136.5, 133.6, 127.3, 125.8, 124.4, 122.3, 119.5, 118.8, 114.2, 112.8, 111.3, 51.2, 26.5; IR (CHCl₃) 1742.

(1H-indol-3-yl)-acetaldehyde 40. A solution of diisobutyl aluminium hydride (4.6 mL, 25% m/m in toluene) was added dropwise to a solution of ester 39 (1.02 g, 5.39 mmol) in a mixture of dichloromethane (20 mL) and dimethoxyethane (20 mL) at -78 °C. After stirring of the reaction mixture for 12 hours at room temperature it was poured into an aqueous solution of hydrochloric acid (40 mL, 10%). Extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvents in vacuo gave a brown oil. Column chromatography (Rₗ = 0.28 ethyl acetate/ light petroleum 1:1) yielded 40 (64%, 548 mg) as a yellow oil. ¹H-NMR (CDCl₃) δ 9.78 (s, 1H), 8.29 (bs, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H) 7.25 (t, J = 8.3 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 7.09 (bs, 1H), 3.82 (d, J = 1.0 Hz, 1H); IR (CHCl₃) 1728.

[2-(1H-indol-3-yl)-ethylidene]-[2-methoxymethylpyrrolidine-1-yl]-amine 41. Sulfuric acid, (98%, 1 drop) was added to a solution of aldehyde 40 (50 mg, 0.31 mmol) and RAMP (44 µL, 0.33 mmol) in ethanol (3 mL). The dark brown reaction mixture was stirred for 10 minutes at room temperature. Addition of triethylamine (100 µL), evaporation of the volatiles under reduced pressure and column chromatography (Rₗ = 0.24 ethyl acetate/ light petroleum 1:1) yielded hydrazine 41 (87%, 73 mg) as a brown oil. ¹H-NMR (CDCl₃) δ 8.17 (bs, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.02 (bs, 1H), 6.79 (t, J = 2.9 Hz, 1H), 3.70 (d, J = 3.0 Hz, 1H), 3.67-3.59 (m, 1H), 3.52-3.44 (m, 2H), 3.39 (s, 3H), 3.36-3.29 (m, 1H), 2.74 (q, J = 4.1 Hz, 1H), 2.00-1.74 (m, 4H); HRMS (EI): Calcd. for C₁₆H₁₇N₂O 271.1685, Found: 271.1676.

[2-(1H-indol-3-yl)-ethyl]-[2-methoxymethylpyrrolidine-1-yl]-amine 42. Sodium cyanoborohydride (46 mg, 0.74 mmol) was added to a solution of hydrazine 41 (20 mg, 74 µmol) in methanol (3 mL) at 0 °C. Stirring of the reaction mixture for 5 hours at room temperature, addition of water (3 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent in vacuo yielded hydrazine 42 (75%, 15.1 mg) as a yellow oil. ¹H-NMR (CDCl₃) δ 8.01 (bs, 1H), 7.65 (d, J = 8.1 Hz,
1H), 7.38 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 8.1 Hz, 1H), 7.12 (t, J = 8.1 Hz, 1H), 7.08 (s, 1H), 3.55-3.49 (m, 1H), 3.48-3.36 (m, 2H), 3.27 (s, 3H), 3.25-3.13 (m, 2H), 3.05-2.89 (m, 2H), 2.71-2.62 (bs, 1H), 2.25 (q, J = 7.0 Hz, 1H), 1.95-1.86 (m, 1H), 1.80-1.71 (m, 2H), 1.65-1.50 (m, 2H); HRMS (EI): Calcd. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{3}O\textsubscript{273.1841}, Found: 273.1847.

2-[2-(1H-indole-3-yl)-ethylamino]-[1,3,2]-dioxaphospholane-4,5-dicarboxylic acid diethyl ester 43. A solution of 2-[2R,3R]-diethyltartrate (2.06 g, 10.0 mmol) in tetrahydrofuran (30 mL) was added slowly to a solution of phosphorus trichloride (0.88 mL, 10.0 mmol) in tetrahydrofuran (25 mL) at 0°C. The reaction mixture was heated to reflux for 30 minutes after which diisopropyl amine (5.61 mL, 40.0 mmol) was added dropwise at 0°C. Stirring of the reaction mixture for an additional 3 hours at room temperature, subsequent heating to reflux for 20 minutes, cooling and addition of light petroleum gave a white precipitate. Purification by using column chromatography (R<sub>f</sub> = 0.32 ethyl acetate/ light petroleum 1:2:1) yielded 47a (63%), 2.11 g. A solution of tryptamine tetrozole salt (690 mg, 2.98 mmol) and 47a (1.0 g, 2.98 mmol) in acetonitrile (50 mL) was heated under reflux for 2 hours. After cooling of the reaction mixture to 0°C, removal of a crystalline byproduct (diisopropyamine tetrozole salt) by filtration and concentration of the filtrate in vacuo, 43 (47%) was obtained by column chromatography (R<sub>f</sub> = 0.25 ethyl acetate/ light petroleum/ triethylamine 70:25:5).

1H-NMR (CDCl<sub>3</sub>) δ 8.02 (bs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 7.10 (t, J = 8.2 Hz, 1H), 7.07 (s, 1H), 4.82 (q, J = 1.2 Hz, 1H), 4.61 (q, J = 2.5 Hz, 1H), 4.39-4.18 (m, 4H), 3.83 (m, 1H), 3.34-3.25 (m, 2H), 3.00-2.88 (m, 4H). 

2-[2-(1H-indole-3-yl)-ethylamino]-[1,3,2]-dioxaphospholane-4,5-dicarboxylic acid diisopropyl ester 44. In a similar procedure as was described above 44 (55%) was obtained as a white solid. 1H-NMR (CDCl<sub>3</sub>) δ 7.99 (bs, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.06 (s, 1H), 5.15-5.04 (m, 2H), 4.73 (q, J = 1.2 Hz, 1H), 4.54 (q, J = 2.4 Hz, 1H), 3.85 (bs, 1H), 3.35-3.26 (m, 2H), 2.91 (t, J = 7.0 Hz, 1H), 1.31-1.22 (m, 12H).

(2,2-dimethyl-4,8,8-tetraphenyl-tetrahydro[1,3]-dioxolo-[4,5-e][1,3,2]-dioxaphosphepin-6-yl)-[2-(1H-indol-3-yl)-ethyl] amine 45. A solution of 48a (108 mg, 0.20 mmol) and tryptamine tetrozole salt (46 mg, 0.20 mmol) in acetonitrile (1.0 mL) was heated under reflux for 16 hours. Cooling of the reaction mixture, filtration and column chromatography of the concentrated filtrate (R<sub>f</sub> = 0.22 ethyl acetate/ light petroleum 2:1) yielded 45 (23%, 30.1 mg) as a yellow oil. 1H-NMR (CDCl<sub>3</sub>) δ 8.14 (bs, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.67-7.60 (m, 6H), 7.55-7.28 (m, 16H), 7.13 (t, J = 8.3 Hz, 1H), 7.02 (s, 1H), 5.22 (dd, J = 2.5 Hz, J = 0.6 Hz, 1H), 4.86 (d, J = 2.1 Hz, 1H), 3.65-3.57 (m, 1H), 3.55-3.48 (m, 1H), 3.04 (t, J = 7.1 Hz, 2H), 1.32 (s, 3H), 0.34 (s, 3H).

[2,2-dimethyl-4,8,8-tetraphenyl-tetrahydro[1,3]-dioxolo-[4,5-e][1,3,2]-dioxaphosphepin-6-yl] dimethyamine 48a. A solution of hexamethylphosphorous triamide (0.362 mL, 2.0 mmol), TADDO (934 mg, 1.0 mmol) and tetrozole (5 mg) in acetonitrile (5 mL) was stirred at reflux for 16 hours. Cooling of the reaction mixture and filtration yielded 48a (56%) as a white solid. 1H-NMR (CDCl<sub>3</sub>) δ 7.73 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.32-7.18 (m, 12H), 5.18 (J = 2.1 Hz, J = 0.6 Hz, 1H), 4.82 (d, J = 2.3 Hz, 1H), 2.71 (d, J = 5.6 Hz, 6H), 1.28 (s, 3H), 0.30 (s, 3H).

[2,2-dimethyl-4,8,8-tetraphenyl-tetrahydro[1,3]-dioxolo-[4,5-e][1,3,2]-dioxaphosphepin-6-yl]-dilisopropylyamine 48b. A solution of TADDO (467 mg, 1.0 mmol), PCl<sub>3</sub> (0.88 mL, 1.0 mmol) and triethylamine (0.48 mL, 3.5 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature. Upon addition of diisopropylamine (0.28 mL, 3.8 mmol) the reaction mixture was heated to reflux for 2 hours. Cooling, addition of light petroleum (20 mL), filtration and column chromatography (R<sub>f</sub> = 0.43 ethyl acetate/ light
petroleum 5:1) yielded 48b (13%, 80 mg). 1H-NMR (CDCl3) δ 7.90 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.55-7.45 (m, 4H), 7.36-7.19 (m, 12H), 5.27 (dd, J = 2.5 Hz, J = 0.6 Hz, 1H), 4.69 (d, J = 2.5 Hz, 1H), 4.12-4.01 (m, 2H), 1.51 (s, 3H), 1.33 (d, J = 3.4 Hz, 3H), 1.25 (d, J = 3.3 Hz, 1H), 0.29 (s, 3H).

N-[2-(1H-indole-3-yl)-ethyl]-S-(2-nitrophenyl)thio hydroxylamine 54. 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 o-nitrophenylsulfenyl 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 54 (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).

1-Pentyl-2,3,4,9-tetrahydro-β-carboline 55. Camphorsulfonic acid (5.0 mg, 0.02 mmol) was added to a solution of 54 (63 mg, 0.20 mmol) and hexanal (60 μL, 0.50 mmol) at −78 °C in dichloromethane (2.0 mL). The reaction mixture was stirred at −78 °C for 2 hours after which it was quenched with triethylamine (2 drops). Concentration in vacuo and column chromatography (Rf = 0.26, ethyl acetate/ light petroleum 4:1) yielded a brown oil which was dissolved in ethanol (1.0 mL). After addition of concentrated hydrochloric acid (2 drops) and stirring for 10 minutes the reaction was quenched by the addition of saturated aqueous sodium carbonate (1 mL). Extractive work-up (diethyl ether), drying of the combined etheral extracts (Na2SO4) and concentration in vacuo yielded 55 (83%, 40.1 mg) as a yellow oil. 1H-NMR (CDCl3) δ 7.78 (bs, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.17-7.07 (m, 2H), 4.10-4.04 (m, 1H), 3.41-3.34 (m, 1H), 3.08-2.99 (m, 1H), 2.80-2.71 (m, 2H), 1.92-1.83 (m, 1H), 1.72-1.62 (m, 1H), 1.60-1.28 (m, 6H), 0.93 (t, J = 6.8 Hz, 3H).

4-[2-(2-nitrophenylsulfonyl)-2,3,4,9-tetrahydro-β-carboline-1-yl]-butanal 56. Calcium chloride (25 g), and aqueous glutaric dialdehyde (9 mL, 5.0 M) were added to a solution of 53 (1.57 g, 5.0 mmol) and pyridinium trifluoroacetate (293 mg, 1.52 mmol) in dichloromethane (100 mL). The reaction mixture was stirred vigorously at 0 °C for 1 hour and at room temperature for 4 hours. Water (100 mL) and light petroleum (100 mL) were added and the layers were separated. The organic layer was washed with water, dried (Na2CO3) and the solvent was removed in vacuo yielding a yellow oil. Purification by column chromatography (light petroleum/ ethyl acetate 75:25 → 25:75) yielded 56 (56%, 1.10 g). 1H-NMR (CDCl3) δ 9.73 (bs, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.30-8.27 (bs, 1H), 8.11-8.07 (bs, 1H), 7.81-7.56 (bs, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.22-7.10 (m, 2H), 4.23 (bs, 1H), 2.80-2.40 (bs, 4H), 2.57-2.36 (bs, 2H), 2.10-1.67 (bs, 2H).

1,2,3,3a,4,5,6,7-octahydro-3,7a-diazacycloheptal[4,5]fluoren-7-ol 58. A solution of aldehyde 57 (0.41 g, 1.03 mmol) in a mixture of dichloromethane (10 mL) and triethylamine (1 mL) was stirred at room temperature for 18 hours. After evaporation of the solvents the remaining glass was dissolved in tetrahydrofuran (10 mL). After portionwise addition of excess Raney nickel the reaction mixture was stirred for 45 minutes at room temperature. Addition of light petroleum (5 mL) and diethyl ether (5 mL), drying of the reaction mixture (Na2SO4), evaporation of the solvent under reduced pressure and trituration with ethyl acetate yielded 58 (50%, 121 mg) as colourless needles. M.p. 160-161 °C; 1H-NMR (CDCl3/ CD2OD 95:5) δ 7.36 d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.14 (d, J = 7.4 Hz, 1H), 4.12 (dJ = 5.7 Hz, 1H), 3.21-3.17 (m, 1H), 2.88-2.81 (m, 1H), 2.71-2.59 (m, 2H), 2.30-2.21 (m, 1H), 2.18-2.14 (m, 1H), 1.99-1.95 (m, 1H), 1.79-1.72 (m, 1H), 1.68-1.61 (m, 1H), 1.51-1.41 (m, 1H).
Tetrahydro-β-carboline dimer 60. Crushed calcium chloride (20 g), and aqueous glutaric dialdehyde (363 μL, 5.0 M) were added to a solution of 54 (1.25 g, 4.0 mmol) and pyridinium trifluoroacetate (100 mg, 0.5 mmol) in dichloromethane (75 mL). After stirring for 16 hours at room temperature the reaction mixture was filtered. Concentration of the filtrate in vacuo and addition of tetrahydrofuran (50 mL) yielded a yellow solution to which an excess of Raney nickel was added in portions. After stirring of the reaction mixture for an additional 45 minutes at room temperature, light petroleum (5 mL) and diethyl ether (5 mL) were added. The resulting mixture was dried (Na₂SO₄) and the solvent removed in vacuo to give an oil. Purification by using column chromatography (dichloromethane/methanol/NH₄OH (aq) 90:8:2 → ethyl acetate) yielded 60 (305 mg, 40%).

4-Methylbenzenesulfonic acid[2-(1H-indol-3-yl)-ethyl]-amide 61. Sodium p-tolylsulfinate (10.0 g, 0.56 mol) was added portionwise to thionyl chloride (25 mL) under cooling and vigorous stirring. The mixture was stirred for 2 hours at room temperature during which the evolved gases were trapped in an aqueous solution of sodium hydroxide (0.5 M). The volatiles were evaporated in vacuo and the resulting oil was coevaporated twice with diethyl ether. The residual p-tolylsulfinyl chloride was dissolved in dichloromethane (100 mL). This solution was added dropwise to a solution of tryptamine (8.2 g, 51.0 mmol) in a mixture of aqueous saturated potassium carbonate (75 mL) and dichloromethane (75 mL). Removal of the organic layer, extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvents under reduced pressure yielded a yellow oil. Recrystallization from ethyl acetate yielded 61 as white crystals (75%, 11.4 g). M.p. 109 °C; 1H-NMR (CDCl₃) δ 8.07 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 2.1 Hz, 1H), 7.08 (t, J = 2.0 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 4.15 (t, J = 8.0 Hz, 1H), 3.42 ((m, 1H), 3.16 (m, 1H), 2.98 (t, J = 7.1 Hz, 2H), 2.40 (s, 3H); IR (CHCl₃): 3479, 1059; HRMS (EI): Calcd. for C₁₇H₁₄N₂SO 298.1136, Found: 298.1143.

References and Notes