Synthesis of Dimeric tetrahydro-beta-carbolines as Bivalent Receptor Ligands. An asymmetric N-Sulfinyl Pictet-Spengler Approach
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Chapter 2

Synthesis of Racemic Tetrahydro-β-carboline Dimers

Abstract

The design and synthesis of bivalent ligands allows numerous possibilities with respect to length, conformation, chemical constitution and site of attachment of the linker system. Synthesis of dimeric tetrahydro-β-carbolines can occur by the linkage of tetrahydro-β-carboline units via the C1-position. Another approach involves connection of the two benzene rings in the indole system. Tetrahydro-β-carboline dimers and trimers with hydrophobic (i.e. aliphatic and aromatic) spacers were prepared by the implementation of Bischler-Napieralski and Pictet-Spengler cyclizations. The design of more polar spacer systems (i.e. amide and ester linkages) was accomplished by the dimerization of properly protected tetrahydro-β-carbolines with amino and hydroxyl groups in the C1-substituent. Sonogashira coupling afforded a new efficient entry to the synthesis of 5,5'-linked bisindoles that can be further elaborated to give new tetrahydro-β-carboline dimers.
§ 2.1 Introduction

In many pharmacological studies towards all sorts of targets such as enzymes and receptor proteins, dimeric organic molecules show an increase in biological activity when compared to their monomeric counterparts. Many examples of this bivalent ligand effect and the mechanisms that are held responsible for it, have been discussed in chapter 1.

One of the most important factors in the bivalent ligand approach is the way in which two pharmacophoric units are linked. Extensive studies towards the nature of the pharmacological effects of dimeric species revealed the importance of the length, conformation and polarity of the linker. When dimerizing tetrahydro-β-carboline ring systems the linkersystem can be attached to different sites in the molecule. The use of the oxygen atom at the indole 5-position in serotonin (5-hydroxytryptamine, 5-HT) has for instance been reported in studies towards serotonin dimers with high biological activity (figure 2.1).\(^1\)

Another interesting site for attachment of linkers is the C1-position of the tetrahydro-β-carboline ring system. By using this position the attachment of the linker can be combined with ring-closing reactions of tryptamine derivatives (A) as is depicted in figure 2.2. Another synthetic approach for the attachment of the linker to the C1-position is the synthesis of tetrahydro-β-carboline monomers with reactive substituents that are suitable for dimerization (B). This methodology often results in the incorporation of heteroatoms in the linker system. The polarity of the linker system has a strong influence on its unfolding in aqueous solution. This plays an important role in the biological activity of the molecule for instance by the presence of charges at neutral pH.

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\(^1\) For instance, see the discussion in Chapter 1.
In § 2.2 to § 2.7 synthetic methodologies for the synthesis of racemic dimeric tetrahydro-β-carbolines, linked via the 1-position of the C-ring will be presented. In § 2.8 an approach to link indole units via the 5-position by utilizing palladium catalyzed carbon-carbon bond formations, will be described. In these compounds the C1-position of the tetrahydro-β-carbole is available for the introduction of potential pharmacophores.

§ 2.2 Synthesis of Tetrahydro-β-carbolines and -Isoquinolines

§ 2.2.1 The Pictet-Spengler Reaction

The construction of β-carboline and isoquinoline ring systems relies in the vast majority of the synthetic approaches on two classical cyclization procedures that were reported for the first time around the beginning of the 20th century. Both the Pictet-Spengler reaction and the Bischler-Napiersalski reaction were first employed for the synthesis of tetrahydroisoquinoline ring systems or analogs and were later modified to prepare tetrahydro-β-carbolines. These two reaction types will be explained in more detail in the next paragraphs.

The best known procedure for the synthesis of tetrahydroisoquinoline and -β-carboline ring systems is the Pictet-Spengler reaction. This reaction was introduced in 1911 by Amé Pictet and Theodor Spengler who condensed under acidic conditions β-phenylethyl amine with formaldehyde dimethyl acetal (scheme 2.1). Originally the Pictet-Spengler reaction was exclusively used to prepare tetrahydroisoquinoline ring systems and it was at that time considered to be the standard procedure for their synthesis. The first attempt to translate the Pictet-Spengler methodology to the synthesis of tetrahydro-β-carbolines was reported by Tatsui in 1928, who reacted tryptamine with acetaldehyde to obtain ring closed products.

Scheme 2.1

In scheme 2.2 it can be seen that the initial stage of the Pictet-Spengler reaction is in a sense related to the Mannich reaction. A reaction of tryptamine with an aldehyde under acidic conditions results in the in situ formation of an iminium ion. In this case however, the iminium ion is not attacked in an intermolecular fashion by an enolizable ketone, as is the case in the Mannich reaction. Intramolecular attack by the electrons of the pyrrole part of the indole ring system results in formation of the ring-closed product.
Cyclizations with tryptophan esters have found numerous applications as an extension of the classical Pictet-Spengler reaction. The cyclization of histidines are less common. Other substrates than aldehydes that have shown cyclization reactions with these amines are ketones, α-ketoacids, acetics, activated alkynes and cyanides under reductive conditions.

Over the last decade the quest for an enantioselective approach to the Pictet-Spengler reaction has led to many new insights with respect to the mechanism, conditions and the scope of this interesting reaction. The development of an asymmetric Pictet-Spengler reaction and its use in the synthesis of enantiopure tetrahydro-β-carboline monomers and dimers is the major subject of Chapters 3, 4, 5 and 6 of this thesis. These chapters will focus on the use of chiral auxiliaries to influence the stereochemical outcome of the Pictet-Spengler reaction. More detailed information about the mechanism and application of the Pictet-Spengler cyclization is therefore presented in these chapters.

§ 2.2.2 The Bischler-Napieralski Reaction

A reaction that is related to the Pictet-Spengler reaction both from an historical and a chemical point of view is the Bischler-Napieralski reaction. This reaction, first reported in 1893, traditionally involves the treatment of β-phenylethylamides with phosphorous oxychloride or phosphorous pentachloride which results in the formation of 3,4-dihydroisoquinolines (scheme 2.3). Reactions of tryptamides likewise lead to dihydro-β-carboline ring systems. These compounds can be transformed into tetrahydro-β-carbolines and -isoquinolines by simple hydride reduction or catalytic hydrogenation of the imine double bond.

Initially it was assumed that the mechanism of the Bischler Napieralski reaction involved the protonation of the amide carbonyl by traces of hydrogen chloride in the reaction mixture after which ring closure of the carbocation led to the product. The discovery of stabilized vinyl cations as intermediates in electrophilic aromatic substitution reactions prompted Stang et al. to question this commonly accepted mechanism for the Bischler-Napieralski reaction. Their suggestion was based on the possibility to trap the cation B (scheme 2.3) as the SbF$_6$ salt. This finding connects the Bischler-Napieralski reaction with a range of mechanistically related reactions that proceed via nitrilium salt intermediates such as the Von Braun reaction, Ritter reaction, Beckman reaction and Schmidt reaction.
The Bischler-Napieralski cyclization traditionally requires harsh conditions, e.g. treatment of the amide with POCl₃ or PCl₃ at elevated temperatures. The recognition that the cyclization proceeds by the initial formation of imidoyl chloride A opened the way for the use of better leaving groups than chloride. The POCl₄⁻ anion is believed to be a poor counterion for the nitrilium ion. This has resulted in the search for other dehydrating agents than phosphorous oxychloride and phosphorous pentachloride. Over the last decades milder reaction conditions have been reported such as the use of triphenylphosphate in carbon tetrachloride at room temperature and trifluoromethane sulfonic anhydride/DMAP at 0 °C. The improvements of the Bischler-Napieralski reaction rendered it to be one of the major synthetic handles for the synthesis of tetrahydro-β-carboline and -isoquinoline ring systems both in solution and on solid support.

§ 2.3 A Bischler-Napieralski Approach to Tetrahydro-β-carboline Dimers

§ 2.3.1 Aliphatic Linkers

Pictet-Spengler reaction of tryptamines with dialdehydes should in theory furnish a one-step synthetic route to tetrahydro-β-carboline dimers. However, the simple aliphatic bisaldehydes that are required for a Pictet-Spengler approach towards dimers with aliphatic linker systems have some disadvantages with respect to stability and commercial availability. These facts prompted us to attempt the synthesis of tetrahydro-β-carboline dimers with aliphatic linkers via a Bischler-Napieralski approach, a two-step route that is nevertheless highly advantageous since the starting dimeric tryptamides can be obtained from the corresponding aliphatic diacids that are both stable and easily available.
In order to prepare the starting dimeric tryptamides we attempted several peptide coupling reagents. The reaction was optimized with malonic acid as the diacid since this was believed to be the most challenging because of interaction between the carboxy groups. In table 2.1 the conditions of the different coupling reactions are shown.

Table 2.1

<table>
<thead>
<tr>
<th>Coupling reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Reaction time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCC</td>
<td>DMAP</td>
<td>CH₂Cl₂</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>DCC</td>
<td>HOBt</td>
<td>THF</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>DCC</td>
<td>HOBt</td>
<td>NMP</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>CDI</td>
<td>-</td>
<td>THF</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>CIP</td>
<td>DiPEA</td>
<td>CH₂Cl₂</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>CIP</td>
<td>DiPEA</td>
<td>THF</td>
<td>&lt;1</td>
<td>93</td>
</tr>
<tr>
<td>CIP</td>
<td>DiPEA</td>
<td>NMP</td>
<td>&lt;1</td>
<td>87</td>
</tr>
<tr>
<td>TCFH</td>
<td>DiPEA</td>
<td>THF</td>
<td>&lt;1</td>
<td>95</td>
</tr>
</tbody>
</table>

* After recrystallization.

The in situ formation of amino acid chlorides and fluorides has found ample precedent in peptide chemistry over the last decade. This has led to the development of efficient coupling reagents that effect peptide bond formation in more problematic cases. The use of 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate 2, CIP<sup>17</sup> in combination with DiPEA in tetrahydrofuran resulted in the efficient formation of the desired tryptamide dimer. Comparable results were obtained when using tetramethylchloroformadinium hexafluorophosphate 3 (TCFH) which was easily prepared in large quantity from tetramethylurea (scheme 2.5).<sup>18</sup>

In general, the choice of the solvent appeared to be an important factor in the coupling reaction. The low solubility of the starting dicarboxylic acid and the monocoupled...
product in dichloromethane resulted in poor yields of the desired bistryptamide 2. This problem was overcome by using tetrahydrofuran to keep the monocoupled product in solution. The desired dimer precipitated upon cooling of the reaction mixture to 0 °C. Even though the yields of the coupling reactions mediated by DCC and DMAP or HOBt were acceptable the reaction times were very long.

A range of tryptamide dimers derived from tryptamine and commercially available dicarboxylic acids was obtained by using TCFH and DiPEA. The results of these coupling reactions are summarized in table 2.2.

<table>
<thead>
<tr>
<th>Dimer</th>
<th>Linker</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−CH₂−</td>
<td>95</td>
</tr>
<tr>
<td>4a</td>
<td>−CH₂CH₂−</td>
<td>92</td>
</tr>
<tr>
<td>4b</td>
<td>−CH₂CH₂CH₂−</td>
<td>94</td>
</tr>
<tr>
<td>4c</td>
<td>−CH₂CH₂CH₂CH₂−</td>
<td>93</td>
</tr>
<tr>
<td>4d</td>
<td>−CH₂CH₂CH₂CH₂CH₂−</td>
<td>89</td>
</tr>
<tr>
<td>4e</td>
<td>−CH₂CH₂CH₂CH₂CH₂CH₂−</td>
<td>93</td>
</tr>
<tr>
<td>4f</td>
<td>−CH₂CH₂CH₂CH₂CH₂CH₂−</td>
<td>84</td>
</tr>
<tr>
<td>4g</td>
<td>−CH₂OCH₂−</td>
<td>82</td>
</tr>
<tr>
<td>4h</td>
<td>−CH₂OCH₂CH₂OCH₂−</td>
<td>86</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) TCFH, DiPEA, THF. *After recrystallization.

The dimeric tryptamides described in table 2.2 were subjected to Bischler-Napieralski cyclization by heating in phosphorus oxychloride for 1 hour yielding the dihydro-β-carbolines 5 (table 2.3). Since alkaline work-up of the reactions only in some cases allowed isolation of the dihydro-β-carbolines the products were obtained as the stable hydrochloric acid salts by evaporation of the volatiles and trituration with ethanol.
Reduction of the iminium salts proceeded smoothly with sodium borohydride in ethanol, thus furnishing a range of racemic tetrahydro-β-carboline dimers (6a-i) as a 1:1 mixture of diastereomers in good yields. The diastereomeric ratio was visible in the $^1$H-NMR spectra as a broadening of the signals of the C1-protons and characteristic splitting of the indole NH signal.

As can be seen from table 2.3 the yields of the Bischler-Napieralski cyclizations and subsequent reductions are generally good to excellent. In the reactions where no product formation was observed in the cyclization this was probably caused by the close vicinity of the two nitrilium ion intermediates. For these cases, Bischler-Napieralski cyclization was also attempted by using POCI$_3$ in toluene both at room temperature and at elevated temperatures and with trifluoromethane sulfonic anhydride in the presence of DMAP at 0 °C. Also in these cases no product formation was observed. Reactions with triphenylphosphine in carbon tetrachloride (§ 2.2.2) suffered from low solubility of the starting material.

### Table 2.3

<table>
<thead>
<tr>
<th>Bisamide</th>
<th>Dihydro-β-carboline dimer</th>
<th>Yield (%)$^a$</th>
<th>Tetrahydro-β-carboline dimer</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>-</td>
<td>6a</td>
<td>-</td>
</tr>
<tr>
<td>4a</td>
<td>5b</td>
<td>-</td>
<td>6b</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>5c</td>
<td>84</td>
<td>6c</td>
<td>88</td>
</tr>
<tr>
<td>4c</td>
<td>5d</td>
<td>67</td>
<td>6d</td>
<td>86</td>
</tr>
<tr>
<td>4d</td>
<td>5e</td>
<td>70</td>
<td>6e</td>
<td>93</td>
</tr>
<tr>
<td>4e</td>
<td>5f</td>
<td>81</td>
<td>6f</td>
<td>78</td>
</tr>
<tr>
<td>4f</td>
<td>5g</td>
<td>69</td>
<td>6g</td>
<td>83</td>
</tr>
<tr>
<td>4g</td>
<td>5h</td>
<td>-</td>
<td>6h</td>
<td>-</td>
</tr>
<tr>
<td>4h</td>
<td>5i</td>
<td>87</td>
<td>6i</td>
<td>84</td>
</tr>
</tbody>
</table>

$^a$After purification (EtOH); After column chromatography.

### § 2.3.2 Aromatic Linkers

Substituted aromatic rings find their application in numerous studies to the properties of macromolecules. This can be explained by their commercial availability and the plethora of organic reactions that allow their preparation and derivatization. The application of aromatic
rings can bring the desired rigidity in (macro)molecules. The use of aromatic tethers in template directed reactions has also found numerous applications in the literature.  

Since aromatic dialdehydes are commercially available, stable compounds, the synthesis of tetrahydro-β-carboline dimers with aromatic spacers was initially attempted using a Pictet-Spengler approach. Reacting tryptamine with terephthaldehyde under acidic conditions did not give satisfying results, even though the acidic Pictet-Spengler reaction of tryptamine with benzaldehyde is a well-described process.  

The Pictet-Spengler reaction of N-benzyltryptamine 7 (obtained by reductive amination of tryptamine with benzaldehyde) with terephthaldehyde in toluene under neutral conditions resulted in smooth formation of N-benzyl tetrahydro-β-carboline dimer 8 (scheme 2.6). Removal of the benzyl groups however appeared to be difficult without cleavage of the newly formed bond. The presence of a benzylic position at C1 led to the excessive formation of ring-opened side products. These disappointing results prompted us to try the Bischler-Napieralski approach for the synthesis of tetrahydro-β-carboline dimers with aromatic spacers.

\[
\text{Scheme 2.6}
\]

\[
\begin{align*}
7 & \xrightarrow{\text{a}} 8 \\
\text{Reagents and conditions: } & (a) \text{ terephthaldehyde, toluene, reflux, 78\%}; (b) \text{ H}_2, \text{Pd/C, HAc, EtOH, 17\%}.
\end{align*}
\]

The Bischler-Napieralski precursors were prepared starting from the corresponding commercially available aromatic diacid chlorides and tryptamine. Bischler-Napieralski cyclization was accomplished by refluxing the dimeric tryptamides 10a and 10b in POCl₃. Reducing the resulting dihydro-β-carboline hydrochloric acid salts with sodiumborohydride in ethanol (scheme 2.7) afforded tetrahydro-β-carboline dimers 9 and 11.

\[
\text{Scheme 2.7}
\]

\[
\begin{align*}
\text{Reagents and conditions: } & (a) \text{ tryptamine, CH}_2\text{Cl}_2, \text{DIPEA, 68\% (10a), 94\% (10b)}; (b) \text{ POCl}_3, \text{reflux, then NaBH}_4, \text{EtOH, 87\% (11), 82\% (9)}. \\
\end{align*}
\]
As could be expected from our results with the aliphatic linkers described above, no cyclization was observed from the 1,2-disubstituted Bischler-Napieralski precursor which is most likely due to (steric) interaction between the neighboring reactive intermediates. Switching to milder reaction conditions as is described in § 2.2.2 in order to achieve the desired ring-closed product did not give any product formation.

The same Bischler-Napieralski approach was used for the synthesis of the highly congested trimeric tetrahydro-β-carboline 13. In this case commercially available 1,3,5-benzene tricarboxylic acid chloride was reacted with tryptamine to furnish the Bischler-Napieralski precursor 12. Subsequent cyclization in refluxing POCl₃ and reduction of the resulting dihydro-β-carboline dimer gave the tetrahydro-β-carboline trimer 13 in moderate yield.

Scheme 2.8

![Scheme 2.8](image)

Reagents and conditions: (a) POCl₃, reflux, 43%; (b) NaBH₄, EtOH, 62%.

In order to obtain a balance between the rigidity of the aromatic linkers and the conformational freedom of the aliphatic linkers described in paragraph 2.3.1 compounds 19a and 19b with a two-carbon aliphatic chain between the benzene ring and the C-ring of the tetrahydro-β-carbolines were prepared (scheme 2.9).

Scheme 2.9

![Scheme 2.9](image)

Reagents and conditions: (a) malonic acid, pyridine, piperidine, reflux, 68% (14a), 78% (14b); (b) H₂, Pd/C, NaOH (aq) 96% (15a), 98% (15b); (c) SOCl₂, DMF, reflux; quant. (d) tryptamine, CH₂Cl₂, DiPEA, 75% (17a), 68% (17b); (e) POCl₃, reflux; (f) NaBH₄, EtOH; 53% (19a), 59% (19b).
The Bischler-Napieralski precursors 17 were obtained from the acid chlorides 16 that were prepared by using a Döbner reaction of the appropriate aromatic dialdehyde with malonic acid in pyridine.\textsuperscript{21} Catalytic hydrogenation under basic conditions of the $\alpha,\beta$-unsaturated dicarboxylic acids and subsequent treatment with thionyl chloride yielded the diacid chlorides which were reacted with tryptamine to give 17\textit{a} and 17\textit{b} in good yields. Bischler-Napieralski reaction and subsequent sodium borohydride reduction of the unsaturated C-ring proceeded smoothly to give the desired tetrahydro-$\beta$-carboline dimers 19\textit{a} and 19\textit{b} in good yields.

§ 2.4 A Pictet-Spengler Approach to Benzylic Linkers

The reaction of phenylacetaldehydes in a Pictet-Spengler reaction yields pharmacologically interesting tetrahydro-$\beta$-carbolines with benzylic Cl-substituents.\textsuperscript{22} Unfortunately, the stability of phenylacetaldehydes is in general extremely low, the unsubstituted phenylacetaldehyde itself being an exception. This fact has prompted synthetic organic chemists to find stable precursors that can be transformed into this important group of substrates \textit{in situ}. This strategy of using phenylacetaldehyde precursors has successfully been applied to the Pictet-Spengler reaction by Evrand and coworkers. They envisaged the conversion of benzaldehydes to phenylpyruvic acids \textit{via} the stable azalactones 19 (scheme 2.10). Pictet-Spengler reaction of the \textit{in situ} formed $\alpha$-ketoacids with tryptamine followed by decarboxylation under acidic conditions yielded the desired 1-benzyl tetrahydro-$\beta$-carbolines.\textsuperscript{23}

![Scheme 2.10](image)

The approach mentioned above resulted in the formation of an impressive amount of benzyl substituted tetrahydro-$\beta$-carbolines containing further substituents on the indole ring and benzylic ring. Some of these ring-opened yohimbine analogs appeared to have potency and selectivity towards serotonin receptors.\textsuperscript{22} All these compounds were easily obtained starting from the appropriate tryptamines and azalactones, the latter being accessible \textit{via} the huge number of commercially available substituted benzaldehydes.

The azalactone approach described above was used to develop tetrahydro-$\beta$-carboline dimers with benzylic spacers. Reaction of aromatic dialdehydes with $N$-acetylglucose and sodium acetate in acetic anhydride furnished the bisazalactones 20\textit{a} and 20\textit{b} in good yield.
These compounds were reacted with an excess of tryptamine in an aqueous solution of hydrochloric acid, thus furnishing the desired dimeric tetrahydro-β-carbolines 21 in excellent yield (scheme 2.11).

![Scheme 2.11](image)

Reagents and conditions: (a) N-acetylglycine, Ac₂O, NaOAc, 83% (20a), 76% (20b); (b) tryptamine·HCl, HCl (aq), reflux, 71% (21a), 83% (21b).

The corresponding 1,3,5-trisazalactone would lead to the formation of a less sterically congested trimeric tetrahydro-β-carboline, when compared to 13, after Pictet-Spengler reaction under acidic conditions. Formation of benzene-1,3,5-tricarboxaldehyde has been described by reduction of trisamide 26 but this procedure failed in our hands. Reduction of the corresponding triethyl ester gave the trialcohol 24 and subsequent oxidation by using pyridinium chlorochromate gave the trialdehyde 27. Formation of the desired tris-azalactone however could not be accomplished.

![Scheme 2.12](image)

Reagents and conditions: (a) EtOH, H₂SO₄, 96%; (b) LiAlH₄, THF, reflux, 67%; (c) PCC, DCM, 51%; (d) SOCl₂, pyridine, reflux; (e) 3,5-dimethylpyrazole, pyridine, toluene, 57%; (f) LiAlH₄, THF, reflux, no reaction; (g) N-acetylglycine, NaOAc, Ac₂O.

§ 2.5 Reductive Amination of Nazlinine Analogs

As was mentioned in § 2.1, the synthesis of dimeric tetrahydro-β-carbolines by combining the formation of the C-ring with the introduction of the spacer via cyclization
reactions of tryptamine analogs is just one approach to dimeric tetrahydro-β-carbolines. Another approach involves the formation of tetrahydro-β-carboline monomers with reactive centers in the C7-side chain and subsequent dimerization of these compounds. In this section we describe our efforts to find simple synthetic routes to tetrahydro-β-carboline dimers with alkylamino spacers that can be used for dimerization reactions.

An initial attempt to obtain tetrahydro-β-carboline dimers with alkylamino spacers involved the acidic Pictet-Spengler reaction of acetal protected dialdehydes. Compounds 29a and 29b were obtained by reductive amination of aromatic dialdehydes 28 (scheme 2.13). Another dimeric, protected aldehyde (31) was prepared by reaction of 5,5-diethoxypentanal 30 and piperazine under reductive conditions. Unfortunately, the deprotection of the dialdehydes and subsequent Pictet-Spengler cyclization did not give any traces of the cyclized products. Pictet-Spengler reaction under acidic conditions, which should result in the in situ liberation of the dialdehydes also did not furnish the desired dimeric tetrahydro-β-carbolines.

Scheme 2.13

![Scheme 2.13](image)

Reagents and conditions: (a) 4,4-diethoxybutylamine, toluene, reflux then NaBH₄, EtOH, 65% (29a), 78% (29b); (b) tryptamine, TFA, H₂O; (c) piperazine, NaBH₄, MeOH, 61%.

Some tetrahydro-β-carbolines with alkylamino side chains have been mentioned in the literature. The isolation and affinity for serotonergic receptors of the racemic alkaloid nazlinine 32 from the plant *Nitraria schoberi* was described in 1991. A short biomimetic synthesis and revision of the structure of this interesting alkaloid were reported from our laboratory in 1993.

Figure 2.3

![Figure 2.3](image)
The nazlinine analogue 33, lacking one methylene group in the sidechain, has been described as an intermediate in the synthesis of the biologically active alkaloid trypargine 34, isolated from the african frog *Kassina senegalensis* in optically active form.\(^\text{29}\) Compound 34 was recently isolated as the racemate from *Eudistoma* sp. ascidian.\(^\text{30}\) Nazlinine 32 was obtained by a Pictet-Spengler reaction of tryptamine with an excess of aqueous glutaric dialdehyde, furnishing the cyclic iminium salt 35 (scheme 2.14). Opening of this indoloquinolizidine using methoxyamine yielded the oxime ether 36 which was subsequently reduced with lithium aluminium hydride. The nazlinine analogue 33 was obtained in excellent yield by Pictet-Spengler condensation of tryptamine and the commercially available 4,4-diethoxybutylamine.

Scheme 2.14

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{ glutaric dialdehyde (aq); } (b) \text{ NH}_2\text{OCH}_2\text{H}_2\text{O, 90 }^\circ\text{C}; (c) \text{ LiAlH}_4, \\
& \quad \text{THF, reflux, 36\% (3 steps); (d) 4,4-diethoxybutylamine, TFA, H}_2\text{O, 90\%.}
\end{align*}
\]

Reductive amination of 32 and 33 with terephthaldehyde gave the corresponding imines which were reduced by using sodium borohydride in ethanol to yield the desired dimeric tetrahydro-\(\beta\)-carbolines 37a and 37b (scheme 2.15).

Scheme 2.15

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{ terephthaldehyde, MeOH, NaBH}_4, 82\% (37a), 73\% (37b)
\end{align*}
\]
§ 2.6 The Design of Linkers Containing Amide Functionality

§ 2.6.1 Attempted Synthesis of 1-(2-Aminoethyl)tetrahydro-β-carboline

Alkylamino substituted tetrahydro-β-carbolines, like nazlinine 32, are interesting building blocks for the synthesis of tetrahydro-β-carboline dimers with an amide functionality in the spacer. Appropriate protecting groups should however be introduced at the N-v-nitrogen in order to prevent undesired side reactions. In this section we describe some approaches to the synthesis of appropriately protected tetrahydro-β-carbolines containing an amino group in the side chain. Dimerization of these compounds, with side-chains of different dimensions should furnish a range of tetrahydro-β-carboline dimers.

Pictet-Spengler reaction of tryptamine with 3,3-diethoxypropionitrile under acidic conditions furnished in good yield the cyano alkyl substituted tetrahydro-β-carboline 38. Compound 38 was expected to provide an easy entry into the desired 1-(2-aminoethyl)tetrahydro-β-carboline by reduction of the cyano function. Very surprisingly, treatment of 38 with lithium aluminium hydride gave in excellent yield compound 39, which arises from net expulsion of acetonitrile under the reaction conditions. This interesting pathway is most likely caused by metal complexation followed by hydride reduction of the resulting imine, a reaction that also could not be suppressed at lower temperatures. Reduction of the cyanofunction by using borane dimethylsulfide in tetrahydrofuran led to the formation of an unidentifiable mixture of products.

Scheme 2.16

Reagents and conditions: (a) 3,3-diethoxypropionitrile, TFA, H_2O; (b) LiAlH_4, THF, reflux, 93%.

Since it appears that the amino hydrogen plays an important role in this extraordinary reaction under hydride reduction conditions we decided to replace this hydrogen with an alkylgroup and to investigate the effect on the outcome of the reduction. For this purpose nitrile 38 was reacted with formaldehyde and sodium cyanoborohydride to yield the N-methylamine 40a in good yield.

Reduction of 40a with lithium aluminium hydride in tetrahydrofuran did again not give any satisfying results. The use of borane dimethylsulfide in THF however gave the
desired amine 41a in moderate yield. These more encouraging results prompted us to attempt this reaction with the benzyl protected cyanide 40b in order to obtain the amine 41b, which should be a more suitable starting material for dimerization reactions than 41a because of the benzyl group that can easily be removed. For this purpose nitrile 38 was benzylated with benzylbromide and potassium carbonate in DMF to give 40b in excellent yield. Subsequent reduction with borane dimethylsulfide in tetrahydrofuran yielded amine 41b in low yield.

Scheme 2.17

In analogy, N-benzylazlinin 44 was prepared as a dimerization precursor with a butylamino C1-substituent (scheme 2.18). Pictet-Spengler reaction of N-benzyltryptamine with 5,5-dithoxypentanal 30 afforded tetrahydro-β-carboline 42 in excellent yield. Subsequent formation of the oxime ether 43 by reaction with methoxy amine and reduction of the oxime functionality by treatment with lithium aluminium hydride furnished N-benzylazlinin 44 in good yield.

Scheme 2.18

Amines 41b and 44 reacted with terephtaloyl chloride in dichlorometane in the presence of DiPEA yielding the corresponding N-benzylprotected dimeric species 45a and 45b in good yields. Removal of the N-benzylgroups by catalytic hydrogenation under acidic conditions proved to be a troublesome process, which makes the overall synthesis of amide containing spacers, based on this methodology, less efficient. For this reason we investigated a different approach, involving the use of the acid sensitive Boc-group as protection for the Nα-aminogroup, as will be described in paragraph 2.6.2.
Racemic Synthesis of Tetrahydro-\(\beta\)-carboline Dimers

\[ \text{Scheme 2.19} \]

Reagents and conditions: (a) terephthaloyl chloride, DIPEA, CH\(_2\)Cl\(_2\), 72\% (45a), 65\% (45b); (b) \(\text{H}_2\), Pd(OH)\(_2\)/C, EtOH, HOAc, 23\% (46a), 14\% (46b).

§ 2.6.2 Synthesis of \(N_2\)-Boc-1-(2-aminoethyl)tetrahydro-\(\beta\)-carboline

\(N_2\)-Boc-1-(2-aminoethyl)tetrahydro-\(\beta\)-carboline 53 should, after dimerization with a dicarboxylic acid chloride, allow easy removal of the protective group under acidic conditions. In order to circumvent the problems with the hydride reduction of the nitrile functionality that were encountered with 40a and 40b, the \(N_2\)-Boc protected nitrile was subjected to catalytic hydrogenation, which gave the desired amine 53 in an extremely slow reaction. This prompted us to develop a different strategy which involves the formation of the desired protected C1-substituent prior to introduction in the tetrahydro-\(\beta\)-carboline system by a Pictet-Spengler reaction (scheme 2.20). The synthetic approach to \(N_2\)-Boc-protected amine 53 involves the use of orthogonal protective groups such as the base labile 9-fluorenylmethyloxycarbonyl (Fmoc) and benzylxycarbonyl group (Cbz) which can be removed by catalytic hydrogenation.

\[ \text{Scheme 2.20} \]

Reagents and conditions: (a) Na, MeOH, 60\%; (b) Fmoc-OSu, Et\(_3\)N, CH\(_2\)CN, 56\%; (c) CbzCl, CH\(_2\)Cl\(_2\), K\(_2\)CO\(_3\) (aq), 95\%; (d) \(\text{H}_2\), HOAc, 85\% (50a), 99\% (50b); (e) tryptamine, TFA, CH\(_2\)Cl\(_2\), 70\%; (f) (Boc)\(_2\)O, CH\(_2\)Cl\(_2\), 95\%; (g) \(\text{H}_2\), Pd/C, EtOH.

Starting from 1-amino-3,3-diethoxypropane 48, which was obtained by dissolving metal reduction of 3,3-diethoxypropionitrile\(^{31}\) (scheme 2.20), the \(N\)-protective groups were
introduced. Treatment of 48 with 9-fluorenylmethyl-N-succinimidyl carbonate and triethyl amine yielded N-Fmoc-1-amino-3,3-dioxypropene 49a (56%). The N-Cbz analog 49b was obtained in excellent yield by treatment of 48 with benzyl chloroformate in the presence of potassium carbonate.

Hydrolysis of the acetals 49a and 49b by using aqueous acetic acid yielded the corresponding N-Fmoc protected aldehyde 50a in 85% and the N-Cbz protected aldehyde 50b quantitatively. Tryptamine proved to be very efficient in removing the N-Fmoc group from aldehyde 50a under Pictet-Spengler conditions. This fact, combined with the moderate yield in the two preceding steps prompted us to further study this pathway with the N-Cbz protected aldehyde 50b that was obtained in excellent yield over three steps.

Pictet-Spengler reaction of 50b with tryptamine under acidic conditions furnished the corresponding tetrahydro-β-carboline 51 in 70% yield. N-Boc protection of 51 yielded the double protected tetrahydro-β-carboline 52 in excellent yield and removal of the N-Cbz group by using catalytic hydrogenation gave the desired N-Boc-ethylaminotetrahydro-β-carboline 53 in an overall yield of 61% over four steps starting from 1-amino-3,3-dioxy propane.

§ 2.6.3 Dimerization of N₂-Boc-1-(2-aminoethyl)tetrahydro-β-carboline

In the preceding paragraph the synthesis of the N-Boc protected tetrahydro-β-carboline 53 was described. Reaction of this compound with diacid chlorides provides ethylamino substituted dimers 54a-54e from which the protective group was easily removed under acidic conditions (table 2.4).

<table>
<thead>
<tr>
<th>No.</th>
<th>linker</th>
<th>Yield (%)* dimerization</th>
<th>No.</th>
<th>Yield (%)* deprotection</th>
</tr>
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<td>81</td>
</tr>
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<td>54b</td>
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<td>55b</td>
<td>84</td>
</tr>
<tr>
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<td>54d</td>
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<td>89</td>
</tr>
<tr>
<td>54e</td>
<td><img src="54e.png" alt="Structure" /></td>
<td>82</td>
<td>55e</td>
<td>86</td>
</tr>
</tbody>
</table>

*Reagents and conditions: (a) dicarboxylic acid chloride or phosgene, CH₂Cl₂, K₂CO₃ (aq); (b) TFA, CH₂Cl₂. * After column chromatography.
Racemic Synthesis of Tetrahydro-β-carboline Dimers

Treatment of amine 53 with 1,3,5-benzenetricaboxylc acid chloride and subsequent removal of the Boc-group resulted in the formation of the trimeric tetrahydro-β-carboline 57 in reasonable yield (scheme 2.21).

Scheme 2.21

Reagents and conditions: (a) trimesoyl chloride, CH₂Cl₂, K₂CO₃ (aq), 65%; (b) TFA, CH₂Cl₂, 76%.

§ 2.7 Linkers Containing Ester Functionality

The presence of ester functions in biologically interesting molecules is often undesirable because of their poor pharmacological profile, due to their instability as a result of in vivo activity of esterases. Nevertheless, since we have developed an efficient synthetic route to tetrahydro-β-carboline dimers with amide functionalities and we are interested in the fundamental aspects of the in vitro activity we extended this methodology to dimers with linkers containing ester functionalities.

The starting point for the synthesis of tetrahydro-β-carboline dimers with short ester linkers was the unnatural amino acid 58. After addition of an aqueous solution of glyoxylic acid to a solution of tryptamine hydrochloride in water, a solution of potassium hydroxide was added to prevent decarboxylation which furnished 58 in quantitative yield.³²

Scheme 2.22

Reagents and conditions: (a) glyoxylic acid, KOH (aq), 92%; (b) MeOH, H₂SO₄, 92%; (c) LiAlH₄, THF, 65%; (d) (Boc)₂O, Et₃N, CH₂Cl₂, 89%; (e) isophthaloyl chloride or terephthaloyl chloride, Et₃N, CH₂Cl₂, 81% (62a), 74% (62b); (f) CH₂Cl₂, TFA, 84% (63a), 89% (63b).
Attempts to simply esterify amino acid 58 were not successful. The main reason for this is its extremely low solubility in organic solvents which limits the use of coupling reagents for esterification. Methyl ester 59 could however be obtained by overnight stirring of 58 in methanol and sulphuric acid. Reduction of 59 by using lithium aluminiumhydride in THF resulted in the formation of alcohol 60. N₂-Boc protection by treatment with di-tert-butyl dicarbonate in dichloromethane furnished the dimerization precursor 61 in good yield. Reaction of 61 with dicarboxylic acid chlorides and subsequent deprotection using trifluoroacetic acid in dichloromethane furnished tetrahydro-β-carboline dimers 63a and 63b with ester functionalities in the linker (scheme 2.22). Reaction of 61 with phosgene resulted in the formation of the carbonate 64. Deprotection under a range of acidic conditions however resulted in the decomposition of this dimer.

\[ \text{Scheme 2.23} \]

\[ \text{Reagents and conditions: (a) phosgene, DIPEA, CH₂Cl₂, 68\%.} \]

§ 2.8 Bisindoles Linked via the 5-Position

In § 2.1 several strategies for the synthesis of tetrahydro-β-carboline dimers were presented. In § 2.2 to § 2.7 we focussed on the use of dibasic cyclization strategies of tryptamines and on the dimerization of monomeric tetrahydro-β-carbolines. In this paragraph we will focus on the synthesis of some dimeric 5-5'-linked indoles that can be further elaborated to tryptamines and tetrahydro-β-carbolines.

In the literature, many examples of naturally occurring unsymmetrical bisindole and bistryptamine alkaloids, often isolated from marine sources, are mentioned. Linkages in bisindole alkaloids often occur via the reactive indole 3-position as can be seen from the natural products depicted in Figure 2.4. Another remarkable feature is the presence of bromosubstituents on the phenyrlings of many naturally occurring bisindole systems.

In hyrtiosin B, isolated from the okinawan marine sponge *Hyrtios erecta*, two 5-hydroxyindole units are connected via a simple glyoxyl linker. Nortopsin B³⁴, a cytotoxic and antifungal compound from *Spongosorites ruetzleri* shows linkage of two 6-bromoindoles by way of an imidazole ring, while the two substituted indole units in dragmacidin³⁵ are linked through a piperazine ring. The family of gelluisines³⁶, represented by the bistryptamine gelluisine F, consists of dimeric and trimeric bromo- and hydroxytryptamines with affinity for receptors in the central nervous system.
Pharmacological studies of serotonin dimers showed that dimerization of 5-hydroxytryptamine by using the 5-hydroxy substituent as an attachment for the linker, led to an increase in the serotonergic activity of the obtained dimers. This prompted us to develop a strategy to dimeric tetrahydro-β-carbolines, that are linked via the 5-position of the indole ring through carbon-carbon bonds.

Substitution reactions on the indole nucleus depend heavily on the use of palladium catalyzed reactions of haloindoles with appropriate substrates. Suzuki coupling reactions of 5- and 6-bromoindoles with arylboronic acids furnished substructures of chloropeptins and kistamicine, which are naturally occurring macropolypeptides. A Suzuki-approach to 2-aryl substituted tryptamines was reported by Wyvatt and coworkers and Stille cross-coupling of 6-haloindoles and appropriate tin reagents provided a reliable synthetic route to 6-allyl and 6-heteroaryl indoles. Another Stille approach was used to prepare bisindoles, linked via the indole 2-position.

Sonogashira couplings of aryl halides with terminal alkynes in the presence of palladium catalysts have proven to be ideal tools for the alkylation of aromatic rings. The Sonogashira conditions are an important improvement of the pioneering work by Castro and Stevens who reported the formation of biarylacetylenes from the reaction of aryl iodides with...
copper(I) acetylide in refluxing pyridine. The catalytic use of a palladium(0) species and copper(I)iodide in the presence of a base, usually an amine, allows the coupling of terminal acetylenes and arylhalides under much milder conditions. Therefore, applications of the Sonogashira reaction are widespread in organic synthesis.

In our strategy towards dimeric indoles that are linked via the indole 5-position we started from 5-bromoindole 70, which was obtained in a three-step procedure from indole. Reaction of indole with aqueous sodium bisulfite and subsequent N-acetylation produced the sodium 1-acetylindoline-2-sulfonate 69. The indoline, which is actually a substituted aniline allows electrophilic substitution at the 5-position, whereas the aromatic indole itself undergoes substitution rather at the 3-position. Bromination and basic work-up gave 5-bromoindole in excellent yield.

It was anticipated that Sonogashira reactions of 5-bromoindole require appropriate nitrogen protective groups. Efficient tosylation of 70 under phase transfer conditions furnished N-tosyl-5-bromoindole 71a in good yield. N-Boc-5-bromoindole 71b was obtained by treatment of 70 with di-tert-butyl dicarbonate (scheme 2.25).

Fukuda and coworkers have reported on the use of a Sonogashira reaction to prepare 2-carboxy substituted bisindoles as a new generation of cyclopropapyrroloindole (CPI) bisalkylators starting from 5-bromo-2-carboxylate. In a likewise procedure Sonogashira coupling of N-tosyl-5-bromoindole 71a with trimethylsilyl acetylene furnished the indole 72 in excellent yield. Removal of the trimethylsilyl group using potassium carbonate in methanol afforded the acetylene 73, which was subjected to a second Sonogashira coupling with N-tosyl-5-bromoindole to give bisindole 74 in good overall yield.
Removal of the tosyl groups and build-up of the tryptamine side-chain by using a well-established literature procedure, allows the synthesis of 5-5' linked tetrahydro-β-carbolinel dimers connected via an acetylene bridge.

Beletskaya and coworkers mentioned the synthesis of substituted propargyl alcohols by reaction of arylbromides and terminal acetylenes under Sonogashira conditions. We used hydroxyl substituted acetylenes to substitute the indole 5-position. The resulting 5-substituted indoles can be further elaborated to give dimeric indoles. The Sonogashira reactions were performed with N-tosyl and N-Boc-protected 5-bromoi ndoles 71a and 71b. The results of this approach are reported in table 2.5.

Reactions with unprotected 5-bromoi ndole 70 did not proceed to completion. The introduction of electron withdrawing N-protective groups, such as the tosyl group, turned out to be advantageous. N-Boc-5-bromoi ndole 71b suffered from unwanted thermal removal of the Boc group under the reaction conditions, which explains the lower yield of compound 77b. Propargyl alcohol was not reactive but 3-butyn-1-ol and 4-pentyn-1-ol reacted smoothly to give alcohols 77a and 78 in good yields.

Table 2.5

<table>
<thead>
<tr>
<th>no</th>
<th>R</th>
<th>n</th>
<th>Yield (%)*</th>
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</thead>
<tbody>
<tr>
<td>75</td>
<td>H</td>
<td>2</td>
<td>61</td>
</tr>
<tr>
<td>76</td>
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</tr>
<tr>
<td>77a</td>
<td>Tosyl</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>77b</td>
<td>Boc</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>78</td>
<td>Tosyl</td>
<td>3</td>
<td>89</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) Pd(PPh$_3$)$_4$, Cul, piperidine, 60 °C.

* After column chromatography.

Since reactions with terminal alkynes and N-tosyl-5-bromotryptamine 71a worked very well, we decided to further investigate this strategy by using dimeric acetylenes. Tosylation of 3-butyn-1-ol provided the O-tosylated alkyne 80 in moderate yield. Reaction of an excess of this tosylate with piperazine gave the bis-acetylene 79. Reaction of 79 with N-tosyl-5-bromoi ndole 71a under Sonogashira conditions gave only traces of the desired bisindole 81. Via a second approach Sonogashira product 77a was tosylated. Subsequent treatment of 82 with piperazine under basic conditions gave the desired product in acceptable yield (scheme 2.27).
In this paragraph some possibilities that palladium chemistry provides to prepare tetrahydro-β-carboline dimers, linked via the 5-position of the indole ring, were displayed. Further studies on this synthetic route are necessary to prepare these tetrahydro-β-carboline dimers in which the 1-position of the C-ring is free for the introduction of interesting pharmacophores.

§ 2.9 Concluding Remarks

In this chapter the synthesis of racemic tetrahydro-β-carboline dimers and trimers has been discussed. Synthetic routes that allow the efficient preparation of appropriate starting materials and introduction of various types of linker systems, have been developed. This has led to the formation of a range of dimeric and trimeric tetrahydro-β-carbolines that are connected via simple aliphatic chains and linker systems based on aromatic rings. The introduction of heteroatoms in the linker systems provided dimeric and trimeric species containing ethers, secondary amines, amide and ester linkages.

Furthermore, application of Sonogashira reactions proved to be a synthetic handle for the linkage of dimeric tetrahydro-β-carbolines via the indole 5-position thus leaving the 1-position of the C-ring open for the introduction of other substituents.
§ 2.10 Acknowledgements

Without the valuable efforts of Merijn Schenk (Bischler-Napieralski reactions, § 2.3), Mark Leemhuis (amide linkers, § 2.6), Melle Koch (ester linkers, § 2.7) and Willemijn de Nijs (palladium chemistry, § 2.8), who worked on the chemistry described here, this chapter could never have been written.

§ 2.11 Experimental Details

General information. All reactions involving moisture sensitive compounds were carried out under a dry nitrogen atmosphere and all reactions with oxygen sensitive reagents were performed under an argon atmosphere. All reagents and solvents were used without further purification unless stated otherwise. Dichloromethane (phosphorouspentoxide and calcium hydride), tetrahydrofuran (sodium/benzophenone) and light petroleum (60-80) were distilled freshly prior to use. Reactions were monitored by using TLC on silica coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated eluens. The compounds were visualized by UV light (254 nm), I$_2$ or p-anisaldehyde in methanol (20%). Column chromatography was performed under air pressure by using Acros silica gel (0.030-0.075 mm). Melting points were determined on a Leitz melting point microscope and are used uncorrected. Infrared spectra were obtained from CHCl$_3$ solutions, unless stated otherwise. Nuclear magnetic resonance spectra were determined in perdeuterated chloroform, methanol, dimethylsulfoxide and water that were obtained from Cambridge Isotope Laboratories Ltd.. $^1$H-NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer at 300 K, unless stated otherwise. $^{13}$C-NMR spectra were recorded on Bruker ARX 400 (100 MHz) or Bruker AC 200 (50 MHz) spectrometer at 300 K. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane as an internal standard. Peakshapes in the $^1$H-NMR-spectra are indicated with the symbols “q” (quartet), “t” (triplet), “d” (doublet), “s” (singlet), “bs” (broad singlet) and “m” (multiplet). Mass spectra and accurate mass measurement were performed on a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer using Fast Atom Bombardement (FAB$^+$) or Electron Ionisation (EI$^+$). Numbering of the tryptamine and tetrahydro-p-carboline ring systems is according to the numbering in the parent ring systems shown below.

![Tetramethyl chloroformamidinium hexafluorophosphate 3](image)

Tetramethyl chloroformamidinium hexafluorophosphate 3. A solution of oxalylchloride (0.19 mol, 16.50 mL) in toluene (100 mL) was added dropwise to a solution of tetramethylureum (11.60 g, 100 mmol) in toluene (100 mL). Stirring of the reaction mixture at 120 °C until gas evolution had ceased gave a white precipitate. After addition of diethyl ether (350 mL) and subsequent stirring at room temperature for 1 hour the precipitate was filtered off and dissolved in dichloromethane (500 mL). Saturated aqueous potassium hexafluorophosphate (30 mL) was added and after stirring the solution for 30 minutes the organic layer was washed with two 50 mL portions of water. Drying of the organic layer (Na$_2$SO$_4$) and coevaporation of the volatiles using ethanol in vacuo yielded 3 as a white crystalline material (16.9 g, 60%). M.p. 90 °C; $^1$H-NMR (DMSO-$d_{6}$) δ 3.34 (s, 12H).
General procedure for the preparation of bisamides 4a-i. TCFH 3 (1.74 g, 6.20 mmol) was added to a solution of tryptamine (1.0 g, 6.2 mmol) and the dicarboxylic acid (2.8 mmol) in tetrahydrofuran (30 mL). After addition of DiPEA (12.4 mmol, 2.15 mL) at 0 °C and subsequent stirring of the reaction mixture at room temperature for 15 minutes the white precipitate was filtered off. Washing of the precipitate with diethyl ether furnished the corresponding bisamides.

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{malonamide 1. White solid (95\%, 1.03 g). M.p. 161 °C; H-NMR (CD}_2\text{OD)} \delta 7.55 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.09-7.02 (m, 4H), 7.00 (t, J = 6.9 Hz, 2H), 3.53-3.41 (m, 4H), 3.16 (s, 2H), 2.98 (t, J = 7.1 Hz, 4H); IR (CHCl}_3) 1685, 1530. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{succinamide 4a. White solid (92\%, 1.04 g). M.p. 182 °C; H-NMR (CD}_2\text{OD)} \delta 7.55 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.09-7.02 (m, 4H), 6.99 (t, J = 8.2 Hz, 2H), 3.46 (t, J = 7.2 Hz, 4H), 2.92 (t, J = 7.1 Hz, 4H), 2.42 (s, 4H); IR (CHCl}_3) 1685, 1530. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{glutaramide 4b. White solid (94\%, 1.09 g). M.p. 204 °C; H-NMR (CD}_2\text{OD)} \delta 7.56 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.09-7.02 (m, 4H), 7.00 (t, J = 8.3 Hz, 2H), 3.47 (t, J = 7.2 Hz, 4H), 2.93 (t, J = 7.2 Hz, 4H), 2.12 (t, J = 7.1 Hz, 4H), 2.89-2.77 (m, 4H); IR (CHCl}_3) 1684, 1533. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{adipamide 4c. White solid (93\%, 1.12 g). M.p. 201 °C; H-NMR (CD}_2\text{OD)} \delta 7.55 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.11-7.03 (m, 4H), 7.01 (t, J = 8.3 Hz, 2H), 3.47 (t, J = 7.2 Hz, 4H), 2.93 (t, J = 7.2 Hz, 4H), 2.09 (t, J = 7.1 Hz, 4H), 2.90-2.76 (m, 4H); IR (CHCl}_3) 1685, 1529. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{pimelamide 4d. White solid (89\%, 1.11 g). M.p. 178 °C; H-NMR (CD}_2\text{OD)} \delta 7.54 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.10-7.02 (m, 4H), 6.97 (t, J = 8.0 Hz, 2H), 3.47 (t, J = 7.1 Hz, 4H), 2.92 (t, J = 7.2 Hz, 4H), 2.09 (t, J = 7.2 Hz, 4H), 1.59-1.48 (m, 4H), 1.28-1.18 (m, 2H); IR (CHCl}_3) 1682, 1530. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{suberamide 4e. White solid (93\%, 1.19 g). M.p. 192 °C; H-NMR (CD}_2\text{OD)} \delta 7.56 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.09-7.02 (m, 4H), 7.01 (t, J = 8.3 Hz, 2H), 3.46 (t, J = 7.1 Hz, 4H), 2.92 (t, J = 6.9 Hz, 4H), 2.12 (t, J = 7.1 Hz, 4H), 1.59-1.44 (m, 4H), 1.30-1.17 (m, 4H); IR (CHCl}_3) 1685, 1531. \)

\( N,N'-\text{Bis-}[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{azealamide 4f. White solid (84\%, 1.16 g). M.p. 164 °C; H-NMR (CD}_2\text{OD)} \delta 7.55 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.10-7.02 (m, 4H), 6.99 (t, J = 8.0 Hz, 2H), 3.49 (t, J = 7.1 Hz, 4H), 2.94 (t, J = 7.3 Hz, 4H), 2.15 (t, J = 7.1 Hz, 4H), 1.61-1.50 (m, 4H), 1.32-1.22 (m, 6H); IR (CHCl}_3) 1682, 1533. \)

\( N-[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{-2-2-[2-(1H\text{-indol-3-yl})\text{-ethylcarbamoyl}]methoxy} \text{acetamide 4g. White solid (82\%, 960 mg). M.p. 181 °C; H-NMR (CD}_2\text{OD)} \delta 7.56 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.10-7.02 (m, 4H), 6.99 (t, J = 8.1 Hz, 2H), 3.52 (t, J = 7.2 Hz, 4H), 3.31 (s, 4H), 2.94 (t, J = 7.2 Hz, 4H); IR (CHCl}_3) 1681, 1530. \)

\( N-[2-(1H\text{-indol-3-yl})\text{-ethyl}]\text{-2-2-[2-(1H\text{-indol-3-yl})\text{-ethylcarbamoylmethoxy} \text{acetamide 4h. White solid (86\%, 1.11 g). M.p. 209 °C; H-NMR (CD}_2\text{OD)} \delta 7.54 (d, J = 4.1 Hz, 2H), 7.31 (d, J = 4.2 Hz, 2H), 7.10-7.01 (m, 4H), 6.97 (t, J = 4.1 Hz, 2H), 3.83 (m, 4H), 3.52 (t, J = 7.2 Hz, 4H), 3.45 (s, 4H), 2.94 (t, J = 7.1 Hz, 4H); IR (CHCl}_3) 1685, 1531. \)

General procedure for the preparation of bisamides 10a and 10b and trisamide 12. To a solution of tryptamine (1.0 g, 6.24 mmol) and triethylamine (2.0 mL) in dichloromethane (30
Dihydro-β-carboline dimer 5c. White solid (84%); ¹H-NMR (CDCl₃) δ 10.43 (bs, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 8.1 Hz, 2H), 7.15 (t, J = 8.2 Hz, 2H), 4.04 (t, J = 7.9 Hz, 4H), 2.97 (t, J = 7.1 Hz, 4H), 2.82 (t, J = 7.0 Hz, 4H), 2.25 (m, 2H).

Tetrahydro-β-carboline dimer 6c. Yellow oil (88%). ¹H-NMR (D₂O) δ 7.61 (d, J = 4.0Hz, 2H), 7.45 (d, J = 4.1Hz, 2H), 7.27 (t, J = 4.1Hz, 2H), 7.18 (t, J = 4.0Hz, 2H), 4.78-4.69 (m, 2H), 3.78-3.65 (m, 2H), 3.53-3.41 (m, 2H), 3.12-3.60 (m, 4H), 2.37-2.22 (m, 2H), 2.18-2.04 (m, 2H), 1.81-1.70 (m, 2H); ¹C-NMR (D₂O) δ 139.1, 131.6, 128.4, 125.7, 122.7, 121.2, 109.2, 55.6, 44.1, 34.1, 22.9, 20.6; HRMS (EI): Calcd. for C₂₅H₂₃N₄ 384.2314, Found: 384.2322.

Dihydro-β-carboline dimer 5d. White solid (67%); ¹H-NMR (CD₃OD) δ 7.55 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.09-7.02 (m, 4H), 6.98 (t, J = 8.2 Hz, 2H), 3.48 (t, J = 6.9 Hz, 4H), 2.94 (t, J = 7.0 Hz, 4H), 2.16-2.09 (m, 4H), 1.58-1.49 (m, 4H).

Tetrahydro-β-carboline dimer 6d. Yellow oil (86%). ¹H-NMR (CDCl₃) δ 878 (bs, 2H), 8.59 (bs, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.20-7.06 (m, 4H), 4.11-3.98 (m, 2H), 3.40-3.29 (m, 2H), 3.09-2.95 (m, 2H), 2.79-2.65 (m, 4H), 1.95-1.48 (m, 8H); HRMS (EI): Calcd. for C₂₆H₂₅N₅ 398.2470, Found: 398.2467.

Dihydro-β-carboline dimer 5e. White solid (70%). ¹H-NMR (D₂O) δ 7.55 (d, J = 8.2 Hz, 2H), 7.42-7.32 (m, 4H), 7.15 (t, J = 8.2 Hz, 2H), 3.70 (t, J = 8.0 Hz, 4H), 2.96-2.88 (m, 8H), 1.88-1.75 (m, 4H), 1.27-1.22 (m, 2H).
Chapter 2

Tetrahydro-β-carboline dimer 6e. Yellow oil (93%). ^1H-NMR (CDCl3) δ 878 (bs, 2H), 8.59 (bs, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.21-7.05 (m, 4H), 4.11-3.99 (m, 2H), 3.38-3.30 (m, 2H), 3.09-2.94 (m, 2H), 2.74-2.63 (m, 4H), 1.98-1.44 (m, 10H); HRMS (EI): Calcd. for C27H37N4 412.2627, Found: 412.2636.

Dihydro-β-carboline dimer 5f. White solid (81%). ^1H-NMR (D2O) δ 7.54 (d, J = 8.2 Hz, 2H), 7.43-7.31 (m, 4H), 7.14 (t, J = 8.2Hz, 2H), 3.72 (t, J = 8.0 Hz, 4H), 2.98-2.87 (m, 8H), 1.91-1.70 (m, 6H), 1.29-1.21 (m, 2H); ^13C-NMR (DMSO-d6) δ 169.7, 140.6, 128.2, 125.5, 123.9, 123.5, 121.8, 121.2, 113.3, 41.7, 40.0, 31.8, 27.2, 26.9.

Tetrahydro-β-carboline dimer 6f. Yellow oil (78%). ^1H-NMR (CDCl3) δ 880 (bs, 2H), 8.65 (bs, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.21-7.06 (m, 4H), 4.11-4.01 (m, 2H), 3.36-3.33 (m, 2H), 3.10-2.93 (m, 2H), 2.73-2.61 (m, 6H), 2.00-1.43 (m, 10H); ^13C-NMR (CDCl3) δ 136.8, 136.2, 127.4, 122.3, 118.1, 117.3, 111.3, 108.7, 58.1, 52.8, 42.8, 29.7, 25.4, 22.6; HRMS (EI): Calcd. for C28H38N4, 426.2783, Found: 426.2789.

Dihydro-β-carboline dimer 5g. White solid (69%); ^1H-NMR (DMSO-d6) δ 125.5 (bs, 2H), 12.34 (bs, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 8.1 Hz, 2H), 7.19 (t, J = 8.3 Hz, 2H), 3.92-3.80 (m, 4H), 3.20 (t, J = 7.1 Hz, 4H), 3.11-2.98 (m, 4H), 1.77-1.67 (m, 4H), 1.58-1.31 (m, 6H).

Tetrahydro-β-carboline dimer 6g. Yellow oil (83%). ^1H-NMR (DMSO-d6) δ 878 (bs, 2H), 7.49 (d, J = 4.1Hz, 2H), 7.32 (d, J = 4.0Hz, 2H), 7.19-7.04 (m, 4H), 4.08-4.02 (m, 3H), 3.42-3.31 (m, 2H), 3.08-2.98 (m, 2H), 2.81-2.65 (m, 4H), 1.90-1.39 (m, 14H); ^13C-NMR (CDCl3) δ 138.2, 135.7, 127.4, 121.3, 119.1, 117.9, 110.7, 108.6, 57.9, 52.6, 42.5, 34.8, 29.5, 25.6, 22.6; HRMS (EI): Calcd. for C26H38N4, 440.2940, Found: 440.2933.

Dihydro-β-carboline dimer 5h. White solid (87%); ^1H-NMR (D2O) δ 7.45 (d, J = 4.1Hz, 2H), 7.38-7.30 (m, 4H), 7.04 (t, J = 4.2Hz, 2H), 4.82 (s, 4H), 4.01 (s, 4H), 3.84 (t, J = 7.1Hz, 4H), 2.98 (t, J = 4.2Hz, 4H).

Tetrahydro-β-carboline dimer 6h. Yellow oil (84%). ^1H-NMR (CD3OD) δ 7.37 (d, J = 4.0Hz, 2H), 7.28 (d, J = 4.1Hz, 2H), 7.04 (t, J = 4.1Hz, 2H), 6.69 (J = 4.2Hz, 2H), 4.24-4.18 (m, 2H), 3.86-3.70 (m, 8H), 3.28-3.19 (m, 2H), 2.97-2.89 (m, 2H), 2.74-2.65 (m, 4H); ^13C-NMR (CD3OD): δ 137.7, 133.7, 128.4, 122.3, 119.8, 118.7, 112.0, 109.6, 73.7, 53.7, 42.9, 22.7; HRMS (EI): Calcd. for C25H30N4O3, 430.2369, Found: 430.2361.

Benzyl-1-[2-[1H-indol-3-yl]-(ethyl)-amine 7. A solution of tryptamine (3.65 g, 22.8 mmol) and benzaldehyde (2.54 mL, 25.0 mmol) in methanol (30 mL) was stirred at room temperature for 2 hours. After cooling to 0 °C sodium borohydride (1.0 g, 26.4 mmol) was added and the reaction mixture was stirred for another 2 hours at room temperature. Addition of water (30 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na2SO4) and evaporation in vacuo yielded 7 (85%, 4.79 g) as a light yellow oil. ^1H-NMR (CDCl3) δ 8.16 (bs, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.37-7.17 (m, 7H), 7.11 (t, J = 8.0 Hz, 1H), 6.99 (s, 1H), 3.83 (s, 2H), 3.03 (s, 4H).

N,N'-Bis-benzyl dimer 8. A solution of 7 (2.0 g, 8.0 mmol) and terephthaldehyde (510 mg, 3.80 mmol) in toluene (50 mL) was heated to reflux for 3 hours during which time a yellow precipitate formed. Cooling to 0 °C and filtration yielded the N,N'-bisbenzyl tetrahydro-β-carboline dimer 8 (78%, 3.74 g) as a light yellow solid. M.p. 223 °C; ^1H-NMR (CDCl3) δ 7.51 (bs, 2H), 7.40-7.06 (m, 22H), 4.69 (s, 2H), 3.88 (d, J = 8.0 Hz, 2H), 3.43 (d, J = 8.1 Hz, 2H), 3.29-3.19 (m, 2H), 2.95-2.78 (m, 4H), 2.76-2.65 (m, 2H); ^13C-NMR (CDCl3) δ 141.6, 139.3, 136.0, 134.1, 128.9, 128.5, 128.0, 126.8, 121.3, 119.2, 118.1, 110.6, 108.8, 63.4, 58.1, 47.8, 20.6; HRMS (EI): Calcd. for C52H58N4, 598.3069, Found: 598.3075.
Racemic Synthesis of Tetrahydro-β-carboline Dimers

Tetrahydro-β-carboline dimer 9. Brown oil (82%). 1H-NMR (CDCl₃) δ 7.62 (bs, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.32-7.06 (m, 10H), 5.18-5.06 (m, 2H), 3.42-3.30 (m, 2H), 3.19-3.08 (m, 2H), 2.98-2.76 (m, 4H); HRMS (El): Calcd. for C₅₆H₄₅N₄ 418.2157, Found: 418.2152.

Tetrahydro-β-carboline dimer 11. Yellow oil (87%). 1H-NMR (CDCl₃) δ 7.71 (bs, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.40 (s, 1H), 7.35-7.22 (m, 2H), 7.20-7.06 (m, 5H), 5.06 (bs, 2H), 3.39-3.30 (m, 2H), 3.16-3.07 (m, 2H), 2.98-2.75 (m, 4H); HRMS (El): Calcd. for C₅₆H₄₅N₄ 418.2157, Found: 418.2163.

3-[4-(2-carboxyvinyl)-phenyl]acrylic acid 14a. A solution of 1,4 terephthalaldehyde (5.0 g, 37 mmol) and malonic acid (9.0 g, 85 mmol) in a mixture of pyridine (14 mL) and piperidine (0.5 mL) was heated to 50 °C. After 1 hour a white precipitate formed and the temperature was raised to 130 °C. Stirring was continued for another 2 hours. Subsequent filtration and washing of the residue with diethyl ether yielded dicarboxylic acid 14a (68%, 5.53 g) as a white solid. M.p. 352 °C; 1H-NMR (DMSO-d6) δ 12.45 (bs, 2H), 8.09 (s, 1H) 7.73 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 8.1 Hz, 1H), 6.69 (d, J = 8.0 Hz, 2H).

3-[4-(2-carboxyethyl)-phenyl]-propanoic acid 15a. Dicarboxylic acid 14a (9.1 mmol, 2.0 g) was dissolved in an aqueous solution of sodium hydroxide (20 mL, 1.0 M) stirred with Pd/C (10%, 100 mg) under a hydrogen atmosphere (40 psi). After completion of the reaction, as was monitored by using TLC, the catalyst was filtered off. Addition of a 2.0 M solution of hydrochloric acid (20 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and removal of the solvent in vacuo yielded the dicarboxylic acid 15a as a white solid (96%, 1.96 g). M.p. 228 °C; 1H-NMR (DMSO-d6) δ 12.22 (bs, 2H), 7.1 (t, J = 8.1 Hz, 1H), 7.15-7.02 (m, 3H), 2.79 (t, J = 6.0 Hz, 4H), 2.52 (t, J = 6.1 Hz, 4H); 13C-NMR (DMSO-d6) δ 173.7, 140.8, 128.2, 128.1, 125.8, 35.2, 30.3.

N-[2-(1H-indol-3-yl)-ethyl]-4-[4-[2-(1H-indol-3-yl)ethylcarbamoyl]-ethyl]-phenyl-butyramide 17a. Dicarboxylic acid 15a (200 mg, 0.91 mmol) was dissolved in thionyl chloride (1.0 mL). Dimethylformamide (2 drops) was added and the reaction was subsequently stirred at room temperature for 30 minutes. Evaporation in vacuo yielded dicarboxylic acid chloride 16a as a yellow solid which was dissolved in dichloromethane (5 mL). This solution was added at 0 °C to a solution of tryptamine (323 mg, 2.0 mmol) and DiPEA (1.76 mL, 10.0 mmol) in dichloromethane (10 mL). Stirring at room temperature for 2 hours resulted in the formation of a white precipitate. Filtration and washing with diethyl ether gave the tryptamide dimer 17a as a white solid (75%, 346 mg). M.p. 263 °C; 1H-NMR (DMSO) δ 10.81 (bs, 2H), 7.97-7.92 (m, 4H), 7.55 (d, J = 8.1 Hz, 2H), 7.36 (m, J = 8.0 Hz, 2H), 7.10 (s, 4H), 7.08 (t, J = 7.9 Hz, 2H), 7.00 (t, J = 8.1 Hz, 2H), 3.38-3.29 (m, 4H), 2.85-2.76 (m, 8H), 2.48 (t, J = 7.1 Hz, 4H); IR (CHCl₃) 1678.

N-[2-(1H-indol-3-yl)-ethyl]-4-[3-[2-(1H-indol-3-yl)ethylcarbamoyl]-ethyl]-phenyl-butyramide 17b. In a likewise manner as described above isophthalaldehyde (2.0 g, 14.9 mmol) was reacted with maleic acid (3.60 g, 34.6 mmol) resulting in the dicarboxylic acid 14b (78%, 2.13 g) as a white solid. M.p. 281 °C; 1H-NMR (DMSO-d6) δ 12.39 (bs, 2H), 7.74 (s, 4H), 7.62 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.1 Hz, 2H); IR (CHCl₃) 2955, 1704. Reduction of 14b as described above afforded 15b (98%) as a white solid. M.p. 145 °C; 1H-NMR (DMSO-d6) δ 12.40 (bs, 2H), 7.12 (s, 4H), 2.79 (t, J = 7.0 Hz, 4H), 2.51 (t, J = 6.9 Hz, 4H); IR (CHCl₃) 2951, 1722. Formation of the dicarboxylic acid chloride 16b and subsequent coupling to tryptamine resulted in the formation of tryptamide dimer 17b (68%) as an off-white solid. M.p. 183 °C; 1H-NMR (DMSO-d6) δ 10.82 (bs, 2H), 8.25 (t, J = 8.1 Hz, 2H), 7.61 (s, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.09 (t, J = 8.1 Hz, 2H), 7.02 (t, J = 8.1 Hz, 2H), 6.69 (d, J = 7.9 Hz, 2H), 3.57-3.48 (m, 4H), 2.97-2.88 (m, 4H); IR (CHCl₃) 1674.
Tetrahydro-β-carboline dimer 19a. A solution of bisamide 17a (500 mg, 0.98 mmol) in phosphorous oxychloride (3 mL) was stirred at 110 °C for 1 hour. Evaporation of the volatiles in vacuo and subsequent addition of ethanol yielded the dihydro-β-carboline dimer 18a hydrochloride as a white precipitate which was collected by filtration and washed with diethyl ether and immediately used. A suspension of the hydrochloride 18a in ethanol was cooled to 0 °C. Sodium borohydride (380 mg, 10 mmol) was added in small portions and the reaction mixture was stirred for 2 hours at room temperature. Evaporation in vacuo, addition of water (5 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and removal of the solvent furnished tetrahydro-β-carboline dimer 19a (59%, 275 mg). ¹H-NMR (CDCl₃) δ 7.72 (bs, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.43 (s, 1H), 7.36-7.22 (m, 2H), 7.21-7.09 (m, 5H), 5.06 (bs, 2H), 3.39-3.30 (m, 2H), 3.16-3.07 (m, 2H), 2.98-2.63 (m, 8H); 2.12 (m, 4H); HRMS (EI): Calcd. for C₃₅H₄N₄ 474.2783, Found: 474.2785.

Tetrahydro-β-carboline dimer 19b. In a similar procedure as was described above dimer 19b was obtained in 53%. ¹H-NMR (CDCl₃) δ 7.63 (bs, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.38-7.12 (m, 10H), 4.31-4.46 (m, 2H), 3.41-3.28 (m, 2H), 3.20-3.09 (m, 2H), 2.95-2.70 (m, 8H), 2.12-1.91 (m, 4H); HRMS (EI): Calcd. for C₃₅H₄N₄ 474.2783, Found: 474.2776.

Bis-azalactone 21a. Isophtaldehyde (3.0 g, 22.4 mmol) was dissolved in acetic anhydride (20 mL). After addition of N-acetylglycine (5.24 g, 45.0 mmol) and sodium acetate (3.67 g, 44.8 mmol) the reaction mixture was heated for 7 hours at 100 °C. Filtration and washing of the yellow precipitate with diethyl ether yielded bisazalactone 21a (83%, 5.50 g) as a dark yellow solid. M.p. >300 °C (decomp.); ¹H-NMR (CDCl₃) δ 8.70 (s, 1H), 8.21 (d, J = 10.1 Hz, 2H), 7.54 (t, J = 10.2 Hz, 1H), 7.21 (s, 2H), 2.46 (s, 6H); ¹³C-NMR (CDCl₃) δ 167.3, 166.5, 135.5, 133.8, 133.2, 130.0, 129.2, 15.5.

Bis-azalactone 21b. In a comparable method as described above bis-azalactone 21b was obtained in 76% as an orange solid material starting from terephtaldehyde. M.p. >300 °C (decomp.); ¹H-NMR (CDCl₃) δ 8.17 (s, 4H), 7.14 (s, 2H), 2.41 (s, 6H).

Tetrahydro-β-carboline dimer 22a. Tryptamine hydrochloride (590 mg, 3.0 mmol) and 1,3-bisazalactone 21a (444 mg, 1.50 mmol) were dissolved in 1.0 M aqueous hydrogen chloride solution (12 mL). The reaction mixture was heated under reflux for 28 hours and then quenched with aqueous sodium hydroxide (15 mL, 2.0 M). Extraction of the aqueous layer with three 20 mL portions of ethyl acetate, drying of the combined organic layers (Na₂SO₄) and removal of the solvent under reduced pressure gave a slightly yellow solid which was purified using column chromatography (Rf = 0.68, ethyl acetate/ethanol/NH₄OH (aq) 80:15:5), yielding tetrahydro-β-carboline dimer 22a (71%, 462 mg). ¹H-NMR (CD₃OD) δ 7.36 (d, J = 8.1 Hz, 2H), 7.31-7.23 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 7.65 (t, J = 8.2 Hz, 2H), 6.96 (t, J = 8.2 Hz, 2H), 4.31-4.21 (m, 2H), 3.36-3.30 (m, 2H), 3.21-3.11 (m, 2H), 2.98-2.87 (m, 2H), 2.86-2.75 (m, 2H), 2.72-2.61 (m, 4H); ¹³C-NMR (CD₃OD) δ 137.5, 135.9, 131.4, 129.7, 128.7, 128.4, 121.9, 119.5, 118.4, 111.7, 109.0, 55.1, 42.8, 41.0, 22.6; HRMS (EI): Calcd. for C₃₀H₃₀N₄ 446.2470, Found: 446.2478.

Tetrahydro-β-carboline dimer 22b. In a similar experimental procedure as described above tetrahydro-β-carboline dimer 22b (83%) was obtained as a white solid which was purified by column chromatography (Rf = 0.45 ethyl acetate/ethanol/NH₄OH (aq) 80:15:5), m.p. 180-181 °C, ¹H-NMR (CD₃OD) δ 7.39 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.24 (s, 4H), 7.06 (t, J = 8.1 Hz, 2H), 6.99 (t, J = 8.2 Hz, 2H), 4.35-4.28 (m, 2H), 3.41-3.35 (m, 2H), 3.30-3.21 (m, 2H), 2.96-2.85 (m, 4H), 2.81-2.64 (m, 4H); ¹³C-NMR (CD₃OD) δ 137.8, 137.7, 136.3, 130.8, 128.6, 122.1, 119.7, 118.6, 111.9, 109.2, 55.5, 43.3, 41.0, 22.9; HRMS (EI): Calcd. for C₃₀H₃₀N₄ 446.2470, Found: 446.2464.
**Benzene-1,3,5-tricarboxylic acid triethyl ester 23.** Trimesic acid (1.0 g, 4.66 mmol) was stirred for 3 hours in a mixture of absolute ethanol (10 mL) and sulfuric acid (1.0 mL) at room temperature. Extractive work-up (ethanol acetate), drying of the combined organic layers (Na$_2$SO$_4$) and evaporation of the solvent in vacuo yielded triethyl ester 23 (96%, 1.34 g) as a yellow oil. $^1$H-NMR (CDCl$_3$) $\delta$ 8.84 (s, 3H), 4.93 (q, $J = 8.0$ Hz, 6H), 1.44 (t, $J = 8.1$ Hz, 9H); IR (CHC$_3$) 2982, 1736.

(3,5-Bis-hydroxymethyl-phenyl)-methanol 24. Lithium aluminium hydride (1.41 g, 37.0 mmol) was added portionwise to a solution of triethyl ester 23 (1.0 g, 3.7 mmol) in tetrahydrofuran (80 mL) at 0 °C. After stirring of the reaction mixture for 3 hours at room temperature and cooling to 0 °C ethanol was added dropwise until the vigorous evolution of gas had ceased. Subsequent addition of aqueous sodium hydroxide (50 mL), concentration of the reaction mixture under reduced pressure, extractive work-up (ethanol acetate/methanol/NH$_4$O$_2$ 80:15:5) yielded bisacetate 24 (67%, 407 mg) as a yellow oil. $^1$H-NMR (CDCl$_3$) $\delta$ 7.16 (s, 3H), 4.53 (s, 6H).

**Trisamide 27.** Trimesic acid (5.0 g, 23.3 mmol) was dissolved in thionyl chloride (10 mL) by heating to reflux for 1.5 hours. Removal of the volatiles under reduced pressure yielded an off-white solid which was dissolved in toluene (30 mL). The solution of the trimesoyl chloride in toluene was added dropwise to a solution of 3,5-dimethylpyrazole (6.75 g, 70.4 mmol) in toluene (60 mL) and pyridine (8 mL). Overnight stirring of the reaction mixture at room temperature and subsequent removal of the volatiles in vacuo and recrystallization from ethanol yielded 27 (57%, 5.90 g) as a light yellow crystalline material. M.p. 243 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 8.76 (s, 3H), 6.05 (s, 3H), 2.62 (s, 9H), 2.22 (s, 9H); $^{13}$C-NMR (CDCl$_3$) $\delta$ 166.6, 152.5, 145.0, 137.2, 132.9, 111.4, 14.2, 13.7; IR (KBr) 1710, 1638.

**Benzene-1,3,5-tricarboxaldehyde 28.** Pyridinium chlorochromate (1.54 g, 7.14 mmol) was added in portions to a solution of trialcohol 25 (300 mg, 1.79 mmol) in dichloromethane (30 mL) in the presence of 3Å molecular sieves at 0 °C. After stirring for 2 hours at room temperature the reaction mixture was filtered over a short column packed with silica gel, activated carbon and hyflo. Elution of the column with diethyl ether and subsequent evaporation of the solvent in vacuo yielded the trialdehyde 28 (51%, 148 mg) as a brown oil. $^1$H-NMR (CDCl$_3$) $\delta$ 10.20 (s, 3H), 8.65 (s, 3H); IR (CHC$_3$) 1710, 1638.

(4,4-diethoxybutyl)-[4-[4,4-diethoxybutylamino]-methyl]-benzyl]-amine 29a. Terephthaldehyde (1.0 g, 7.46 mmol) and 4,4-diethoxybutylamine (3.83 mL, 22.2 mmol) were dissolved in toluene and heated to reflux in a Dean-Stark trap overnight. Evaporation of the solvent yielded the diimine as an oil which was dissolved in ethanol (30 mL) after which the solution was cooled to 0 °C. After the portionwise addition of sodium borohydride (2.85 g, 75.0 mmol) at 0 °C the reaction mixture was stirred at room temperature for 3 hours. Addition of water (30 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and evaporation of the solvent under reduced pressure yielded a brown oil. Purification by using column chromatography ($R_t = 0.24$, ethyl acetate/methanol 7:3) yielded 29a as a slightly yellow oil (65%, 1.41 g). $^1$H-NMR (CDCl$_3$) $\delta$ 7.31-7.15 (m, 4H), 4.48 (t, $J = 6.2$ Hz, 2H), 3.78 (s, 4H), 3.68-3.58 (m, 4H), 3.52-3.42 (m, 4H), 2.66 (t, $J = 7.0$ Hz, 4H), 1.69-1.50 (m, 8H), 1.19 (t, $J = 7.1$ Hz, 12H).

(4,4-diethoxybutyl)-[3-[4,4-diethoxybutylamino]-methyl]-benzyl]-amine 29b. In a similar procedure as was described above isophthaldehyde (686 mg, 5.1 mmol) was condensed with 4,4-diethoxybutylamine (1.86 mL, 10.8 mmol). Purification by using column chromatography ($R_t = 0.31$, ethyl acetate/methanol/THF (aq) 80:15:5) yielded bisacetal 29b as a yellow oil (78%, 2.46 g). $^1$H-NMR (CDCl$_3$) $\delta$ 7.27 (s, 4H), 4.48 (t, $J = 6.1$ Hz, 2H), 3.77 (s, 4H), 3.71-3.38 (m, 8H), 2.63 (t, $J = 6.0$ Hz, 4H), 1.72-1.50 (m, 8H), 1.19 (t, $J = 7.1$ Hz, 12H).
5,5-diethoxypropanal 30. A solution of aqueous glutaraldehyde (150 mL, 50%, 0.83 mol) in ethanol (1.6 L) was stirred with Dowex 50WX8 ion exchange resin (2.0 g, H\(^+\)) form for two days at room temperature. Solid NaHCO\(_3\) was added and after stirring for 1 hour the catalyst was filtered off. The resulting solution was concentrated in vacuo and the residue was subjected to column chromatography (light petroleum/ethyl acetate 3:1) to remove an apolar fraction containing glutaraldehyde and cyclic acetal. Distillation in vacuo of the fraction containing the mono-protected aldehyde gave a colourless oil (8.9%, 13.0 g). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 9.76 (t, \(J = 1.4\) Hz, 1H), 4.48 (t, \(J = 5.0\) Hz, 1H), 3.76-3.41 (m, 4H), 2.47 (dt, \(J = 7.0\) Hz, \(J = 1\) Hz, 2H), 1.71-1.61 (m, 4H), 1.19 (t, \(J = 7.1\) Hz, 6H).

1,4-Bis(5,5-diethoxypentan-1-yl)-piperazine 31. A solution of piperazine (500 mg, 5.95 mmol) and 5,5-diethoxypropanal 30 (2.34 mL, 12.75 mmol) in methanol (25 mL) was stirred at room temperature for 1 hour. After cooling to 0 °C sodium borohydride (723 mg, 19.2 mmol) was added in portions and the reaction mixture was stirred for 3 hours at room temperature. Addition of water (25 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and evaporation of the solvent in vacuo yielded 31 as an orange oil (8.9%, 13.0 g). **1H-NMR** (CDCl\(_3\)) \(\delta\) 3.41 (m, 4H), 2.47 (dt, \(J = 7.0\) Hz, \(J = 1\) Hz, 2H), 1.71-1.61 (m, 4H), 1.19 (t, \(J = 7.1\) Hz, 6H).

3-(2,3,4,9-Tetrahydro-1H-β-carboline-1-yl)propylamine 33. Trifluoroacetic acid (5 mL) was added to a solution of tryptamine (1.0 g, 6.3 mmol) in water (50 mL). After addition of 1,1-diethoxy-4-aminobutane (2.60 mL, 15.0 mmol) the reaction mixture was stirred at 95 °C for 12 hours. Cooling to room temperature, addition of saturated aqueous KO\(_2\)CO\(_3\) (20 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and removal of the solvent under reduced pressure gave a brown oil. Propylaminotetrahydro-β-carboline 33 was purified using column chromatography (R\(_f\) = 0.21 dichloromethane/methanol/NH\(_3\)OH (aq) 65:30:5) yielding a yellow oil (68%, 981 mg). **1H-NMR** (CDCl\(_3\)) \(\delta\) 8.58 (bs, 1H), 7.48 (d, \(J = 4.1\) Hz, 1H), 7.29 (d, \(J = 4.0\) Hz, 1H), 7.18-7.05 (m, 2H), 4.11-4.04 (m, 1H), 3.39-3.31 (m, 1H), 3.08-2.98 (m, 1H), 2.35-2.20 (m, 4H), 2.20-1.93 (m, 1H), 1.77-1.63 (m, 3H); HRMS (EI): Calcd. for C\(_9\)H\(_{17}\)N\(_2\) (M+H\(^+\)) 230.1657, Found: 230.1655.

Tetrahydro-β-carboline dimer 37a. A solution of terephthaldehyde (134 mg, 1.0 mmol) and 33 (481 mg, 2.1 mmol) in methanol (15 mL) was stirred at room temperature for 2 hours. After cooling to 0 °C, sodium borohydride (190 mg, 5.0 mmol) was added in portions. The reaction mixture was stirred for 2 hours at room temperature. Addition of water (15 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and evaporation of the solvent in vacuo yielded a yellow oil. Dimer 73a was purified using column chromatography (R\(_f\) = 0.10 dichloromethane/methanol/NH\(_3\)OH (aq) 65:30:5) and obtained as a slightly yellow oil (73%, 428 mg). **1H-NMR** (CD\(_3\)OD) \(\delta\) 7.42 (s, 4H), 7.38-7.28 (m, 4H), 7.07 (t, \(J = 8.0\) Hz, 2H), 6.98 (t, \(J = 8.0\) Hz, 2H), 4.22 (bs, 2H), 3.39 (s, 4H), 3.28-3.19 (m, 2H), 3.02-2.92 (m, 2H), 2.87-2.69 (m, 4H), 2.67-2.46 (m, 2H), 2.17-2.02 (m, 4H), 1.88-1.75 (m, 2H), 1.72-1.58 (m, 2H); **13C-NMR** (CD\(_3\)OD) \(\delta\) 137.5, 133.9, 130.8, 128.2, 122.6, 120.1, 118.8, 112.1, 108.8, 53.6, 52.7, 49.3, 43.0, 32.9, 25.2; HRMS (EI): Calcd. for C\(_{22}\)H\(_{34}\)N\(_4\) 558.3470, Found: 558.3474.

Tetrahydro-β-carboline dimer 37b. A solution of terephthaldehyde (134 mg, 1.0 mmol) and nazarline 32 (510 mg, 2.1 mmol) in methanol (15 mL) was stirred at room temperature for 2 hours. After cooling to 0 °C sodium borohydride (190 mg, 5.0 mmol) was added in portions. The reaction mixture was stirred for 2 hours at room temperature. Addition of water (15 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and evaporation of the solvent in vacuo yielded a brown oil. Dimer 37b was purified using column chromatography (R\(_f\) = 0.14 dichloromethane/methanol/NH\(_3\)OH (aq) 65:30:5) and
obtained as a yellow oil (82%, 458 mg). \(^{1}\)H-NMR (CDCl\(_3\)) \(\delta\) 9.33 (bs, 2H), 7.46 (d, \(J = 8.1\) Hz, 2H), 7.25 (s, 4H), 7.21 (d, \(J = 8.2\) Hz, 2H), 7.14-7.04 (m, 4H), 4.01-3.95 (m, 2H), 3.76 (s, 4H), 3.20-3.23 (m, 2H), 3.04-2.93 (m, 2H), 2.78-2.61 (m, 12H), 2.02-1.88 (m, 2H), 1.75-1.60 (m, 6H); HRMS (EI): Calcd. for C\(_{38}\)H\(_{44}\)N\(_4\) 586.3784, Found: 586.3781.

2,3,4,9-Tetrahydro-1H-\(\beta\)-carboline-1-acetonitrile 38. A solution of tryptamine (3.0 g, 18.6 mmol) and 3,3-dithioxypropionitrile (4.18 mL, 27.9 mmol) in water (50 mL) and trifluoroacetic acid (5 mL) was heated at 80 °C overnight. After cooling to room temperature, saturated aqueous K\(_2\)CO\(_3\) was added and the reaction mixture was stirred for 1 hour. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and subsequent removal of the solvent under reduced pressure yielded a brown oil which was purified by using column chromatography (R\(_f\) = 0.58 ethyl acetate/ethanol/NH\(_4\)OH 85:10:5).

2-Methyl-(2,3,4,9-tetrahydro-1H-\(\beta\)-carboline-1-acetonitrile) 40a. Formaline (2.37 mL, 40%aq, 28.0 mmol) was added at 0 °C to a solution of 38 (1.0 g, 4.74 mmol) in acetonitrile (30 mL) and acetic acid (5 mL) under a nitrogen atmosphere. To this solution sodium cyanoborohydride (1.50 g, 23.7 mmol) was added and the reaction mixture was stirred for 16 hours at room temperature. After addition of water (30 mL) the mixture was made basic by the addition of a saturated aqueous solution of K\(_2\)CO\(_3\). Extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)), removal of the solvent in vacuo and purification of the resulting oil by column chromatography (R\(_f\) = 0.28 ethyl acetate) yielded 40a as a foam (70%, 747 mmol). \(^{1}\)H-NMR (CDCl\(_3\)) \(\delta\) 8.08 (bs, 1H), 7.52 (d, \(J = 8.2\) Hz, 1H), 7.38 (d, \(J = 8.1\) Hz, 1H), 7.20 (t, \(J = 8.3\) Hz, 1H), 7.12 (t, \(J = 8.1\) Hz, 1H), 4.00-3.93 (m, 1H), 3.11-3.03 (m, 1H), 2.93-2.84 (m, 3H), 2.76-2.65 (m, 2H), 2.58 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 140.0, 134.9, 130.3, 125.0, 122.3, 121.6, 121.3, 114.5, 112.3, 60.3, 53.1, 45.1, 24.6, 22.7; IR (CHCl\(_3\)) 172.000, Found: 172.0994.

2-Benzyl-(2,3,4,9-tetrahydro-1H-\(\beta\)-carboline-1-acetonitrile) 40b. A saturated aqueous solution of K\(_2\)CO\(_3\) (1 mL) was added to a solution of 38 (25 mg, 0.12 mmol) and benzyl bromide (22.3 mg, 0.13 mmol) in DMF (3 mL). The reaction mixture was stirred at rt for 16 hours. After addition of water (10 mL) and extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)), removal of the solvent in vacuo and column chromatography (R\(_f\) = 0.58 light petroleum/ethyl acetate 3:1) 40b was obtained as a solid (95%, 34.1 mg). M.p. 115 °C; \(^{1}\)H-NMR (CDCl\(_3\)) \(\delta\) 8.02 (bs, 1H), 7.56 (d, \(J = 8.1\) Hz, 1H), 7.43-7.27 (m, 6H), 7.22 (t, \(J = 8.2\) Hz, 1H), 7.15 (t, \(J = 8.1\) Hz, 1H), 4.08 (t, \(J = 7.3\) Hz, 1H), 3.87-3.79 (m, 2H), 3.32-3.06 (m, 2H), 3.04-2.93 (m, 1H), 2.78 (dq, \(J = 12.1\) Hz, \(J = 4.2\) Hz, 2H), 2.68-2.60 (m, 1H); \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 138.2, 135.9, 131.1, 128.5, 128.3, 127.4, 126.5, 122.2, 119.5, 118.5, 118.2, 111.0, 109.1, 57.3, 53.0, 44.1, 23.2, 17.6; IR (CHCl\(_3\)) 2259.
2-(2-Methyl-2,3,4,9-tetrahydro-1H-β-carboline-1-yl)-ethylamine 41a. To a solution of 40a (100 mg, 0.44 mmol) in tetrahydrofuran (5 mL) borane dimethyl sulfide (0.53 mmol, 53 µL 10.1 M solution in THF) was added at 0 °C. The reaction mixture was heated at 65 °C for 3 hours and after cooling to 0 °C aqueous hydrochloric acid (1 mL, 2.0 M) was added dropwise. Subsequently the reaction mixture was heated to reflux for an additional two hours and then made basic with an aqueous solution of NaOH. Extractive work-up (diethyl ether), drying of the combined organic layers (Na$_2$SO$_4$) and removal of the solvent in vacuo yielded a yellow oil which was purified by using column chromatography (R$_f$ = 0.30, ethyl acetate/ methanol/ NH$_4$OH (aq) 80:15:5) yielding 41a as a white foam (30%, 30.2 mg). $^1$H-NMR (DMSO-d$_6$) δ 9.82 (s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.14-7.09 (m, 2H), 3.54-3.59 (m, 2H), 3.10-3.06 (m, 1H), 2.79-2.71 (m, 4H), 2.42 (s, 3H), 2.16-2.12 (m, 2H); $^{13}$C-NMR (DMSO-d$_6$) δ 136.1, 133.3, 126.6, 118.7, 117.6, 110.8, 107.2, 60.23, 59.1, 57.4, 37.8, 32.1, 19.0.

2-(2-Benzyl-2,3,4,9-tetrahydro-1H-β-carboline-1-yl)-ethylamine 41b. In a similar procedure as described above compound 40b (2.29 g, 7.60 mmol) was reduced to the amino compound 41b (21%, 487 mg). M.p. 114 °C; $^1$H-NMR (CDCl$_3$) δ 8.95 (bs, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.41-7.22 (m, 6H), 7.18-7.05 (m, 2H), 3.83-3.72 (m, 3H), 3.30-3.20 (m, 1H), 3.03-2.76 (m, 4H), 2.65-2.56 (m, 1H), 2.03-1.77 (m, 2H); $^{13}$C-NMR (CDCl$_3$) 139.7, 135.8, 135.0, 128.9, 128.1, 127.0, 126.9, 120.9, 119.1, 117.7, 106.8, 57.1, 53.4, 45.1, 38.3, 36.9, 17.6.

2-Benzyl-1-(4,4-dietoxybutyl)-2,3,4,9-tetrahydro-1H-β-carboline 42. A solution of 7 (1.0 g, 4.0 mmol) and 5,5-dietoxypentanal 30 (1.04 g, 6.0 g) in toluene (30 mL) was heated to reflux for 6 hours. Evaporation and purification by using column chromatography (R$_f$ = 0.56 light petroleum/ethyl acetate/triethylamine 4:2:1) yielded tetrahydro-β-carboline 42 as a yellow oil (85%, 1.38 g). $^1$H-NMR (CDCl$_3$) δ 7.94 (bs, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.41-7.23 (m, 6H), 7.18-7.07 (m, 2H), 4.51-4.43 (m, 2H), 3.81-3.72 (m, 2H), 3.70-3.58 (m, 2H), 3.54-3.43 (m, 2H), 3.01-2.85 (m, 2H), 2.64-2.55 (m, 1H), 1.87-1.44 (m, 6H).

4-(2-Benzyl-2,3,4,9-tetrahydro-1H-β-carboline-1-yl)butyraldehyde O-methyloxime 43. Acetal 42 (1.0 g, 2.46 mmol) was dissolved in a mixture of THF (10 mL) and water (30 mL). After addition of methoxamine hydrochloride (816 mg, 9.8 mmol) and sodium acetate (803 mg, 9.8 mmol) the reaction mixture was stirred at 80 °C for 16 hours. Cooling to room temperature, addition of K$_2$CO$_3$ (1.0 g), extractive work-up (ethyl acetate), drying of the solvent (Na$_2$SO$_4$) and removal of the solvent under reduced pressure gave a yellow oil. Purification by using column chromatography (R$_f$ = 0.34 ethyl acetate/light petroleum/triethylamine 6:3:1) yielded oxime ether 43 (93%, 826 mg, anti:syn = 6:4). $^1$H-NMR (CDCl$_3$) 7.84 (bs, 1H, anti), 7.77 (bs, 1H, syn), 7.53 (d, $J = 8.0$ Hz, 1H), 7.40-7.25 (m, 6H + 1H, anti), 7.19-7.09 (m, 2H), 6.59 (t, $J = 5.1$ Hz, 1H, syn), 3.88 (s, 3H, syn), 3.83 (s, 3H, anti), 3.80-3.72 (m, 3H), 3.68-3.52 (m, 2H), 3.28-3.18 (m, 2H), 2.98-2.85 (m, 2H), 2.64-2.55 (m, 2H), 2.38-2.08 (m, 2H).

4-(2-Benzyl-2,3,4,9-tetrahydro-1H-β-carboline-1-yl)butylamine 44. Lithium aluminium hydride (270 mg, 0.74 mmol) was added in portions to a solution of oxime ether 43 (500 mg, 1.39 mmol) in THF (30 mL) at 0 °C. The reaction mixture was heated to reflux for 3 hours. After cooling to room temperature ethanol was added. When gas evolution had ceased, aqueous NaOH (10 mL, 1.0 M) was added and a white precipitate formed. Filtration, concentration of the filtrate in vacuo, extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$) and removal of the solvent under reduced pressure yielded a brown oil. Purification by using column chromatography (R$_f$ = 0.18 ethyl acetate/methanol/ NH$_4$OH (aq) 75:20:5) yielded amine 44 (83%, 207 mg) as a colourless glass. $^1$H-NMR (CDCl$_3$) δ 8.22 (bs, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 7.38-7.28 (m, 6H), 7.17-7.08 (m, 2H), 3.79

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Tetrahydro-β-carboline dimer 45a. A solution of amine 41b (250 mg, 0.82 mmol) and DiPEA (286 µL, 1.64 mmol) in THF (5 mL) was cooled to 0 °C. After addition of terephthaloyl chloride the reaction mixture was stirred at room temperature for 1 hour. Addition of water (10 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na2SO4) and removal of the solvent under reduced pressure gave a brown oil. Purification by using column chromatography (Rf = 0.43 light petroleum/ethyl acetate 1:4) yielded 45a as a yellow oil (72%, 208 mg). 1H-NMR (CDCl3) δ 8.65 (bs, 2H), 7.58-7.43 (m, 6H), 7.39-7.09 (m, 16H), 3.82 (s, 4H), 3.78-3.63 (m, 2H), 3.60-3.48 (m, 2H), 3.42-3.32 (m, 2H), 3.18-3.07 (m, 2H), 3.05-2.97 (m, 2H), 2.70-2.62 (m, 2H), 2.19-2.06 (m, 2H); IR (CHCl3) ν 3636, 3451, 3300, 3069, 2922, 1710; HRMS (EI): Calcd. for C31H25N6 560.2899, Found: 560.2899.

Tetrahydro-β-carboline dimer 45b. A precooled solution of terephthaloyl chloride (27.6 mg, 0.136 mmol) in 2 mL of dichloromethane was added to a solution of 61 (100 mg, 0.30 mmol) and DiPEA (523 µL, 3.0 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. Evaporation of the volatiles under reduced pressure gave a brown oil which was subjected to column chromatography (Rf = 0.35 ethyl acetate/light petroleum 3:1), yielding dimer 45b as a yellow oil (65%, 156 mg). 1H-NMR (CDCl3) δ 8.18 (bs, 2H), 7.69 (s, 4H), 7.49 (d, J = 4.1 Hz, 2H), 7.35 (d, J = 4.0 Hz, 2H), 7.30-7.18 (m, 12H), 7.13-7.05 (m, 2H), 6.21 (bs, 2H), 3.85-3.62 (m, 6H), 3.47-3.36 (m, 4H), 3.28-3.18 (m, 2H), 2.94-2.82 (m, 4H), 2.65-2.55 (m, 2H), 195-1.76 (m, 4H), 1.57-1.45 (m, 8H); IR (CHCl3) ν 3636, 3451, 3300, 3069, 2922, 1710; HRMS (EI): Calcd. for C31H24N3O2 616.3525, Found: 616.3531.

Tetrahydro-β-carboline dimer 46a. Dimer 45a (200 mg, 0.27 mmol) was dissolved in a solution of hydrochloric acid in ethanol (10 mL, 0.1 M) and stirred vigorously under a hydrogen atmosphere (40 psi) in the presence of Pd/C (10%, 25 mg). Stirring of the reaction mixture for 16 hours and subsequent filtration over hyflo and evaporation of the solvent yielded a yellow oil. 46a was obtained by purification using column chromatography (Rf = 0.23 ethyl acetate/methanol/light petroleum 1:4) as a colourless oil (23%, 34.5 mg). 1H-NMR (DMSO-d6) δ 10.75 (bs, 2H), 8.92 (bs, 2H), 7.93 (s, 4H), 7.38 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.02 (t, J = 8.0 Hz, 2H), 6.95 (t, J = 8.2 Hz, 2H), 4.10-4.02 (m, 2H), 3.53-3.43 (m, 4H), 3.22-3.13 (m, 2H), 2.96-2.87 (m, 2H), 2.66-2.58 (m, 4H), 2.27-2.15 (m, 2H), 1.92-1.78 (m, 2H); IR (CHCl3) ν 1710; HRMS (EI): Calcd. for C34H36N4O2 560.2899, Found: 560.2893.

Tetrahydro-β-carboline dimer 46b. In a comparable procedure as was described above 46b was obtained as a yellow oil (14%). 1H-NMR (DMSO-d6) δ 10.80 (bs, 2H), 8.91 (bs, 2H), 7.97 (s, 4H), 7.36 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.06 (t, J = 8.1 Hz, 2H), 6.94 (t, J = 8.1 Hz, 2H), 4.08-3.97 (m, 2H), 4.07-4.02 (m, 2H), 3.28-3.11 (m, 8H), 2.81-2.65 (m, 4H), 1.66-1.35 (m, 12H); IR (CHCl3) ν 1710; HRMS (EI): Calcd. for C34H36N4O2 560.2899, Found: 560.2893.

3,3-diethoxypropionitrite 48. Sodium (10.0 g, 0.43 mol) was added in small portions to a solution of 3,3-diethoxypropionitrile (5.0 g, 35 mmol) in methanol (50 mL) at 0 °C. After heating of the reaction mixture under reflux for 20 minutes and cooling to room temperature the reaction was quenched by the careful addition of methanol (10 mL) and water (50 mL). Extractive work-up (MTBE), drying of the combined organic layers (Na2SO4) and removal of the solvent in vacuo gave the crude amine 48 as a colourless liquid which was purified by kugelrohr distillation (60%, 3.37 g). 1H-NMR (CDCl3) δ 4.58 (t, J = 6.1 Hz, 1H), 3.62 (m, 4H), 2.79 (t, J = 7.0 Hz, 2H), 1.76 (m, 1H), 1.17 (t, J = 6.9 Hz, 6H).
(3,3-dioethoxypropyl)-carbamic acid-9H-fluoren-9-yl methyl ester 49a. Triethyl amine (140 μL, 1.4 mmol) was added to a solution of amine 48 (205 mg, 1.39 mmol) in acetonitrile. After addition of Fmoc-OSu (471 mg, 1.40 mmol) the reaction mixture was stirred for 5 hours at room temperature. Evaporation of the volatiles in vacuo and column chromatography (Rf = 0.53 light petroleum/ethyl acetate 1:1) yielded 49a as a foam (56%, 276 mg). $^1$H-NMR (CDCl$_3$) δ 7.76 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 7.1 Hz, 2H), 7.33 (m, 4H), 5.29 (bs, 1H), 4.57 (t, J = 5.1 Hz, 1H), 4.37 (d, J = 7.0 Hz, 2H), 4.23 (m, 1H), 3.52 (m, 4H), 1.23 (t, J = 7.1 Hz, 6H).

(3,3-dioethoxypropyl)-carbamic acid benzyl ester 49b. A saturated aqueous solution of K$_2$CO$_3$ (10 mL) was added to a solution of amine 48 (1.0 g, 6.8 mmol) in dichloromethane (10 mL) and the resulting two-phase mixture was cooled to 0 °C. After dropwise addition of benzylchloroformate (10.8 mmol, 1.83 g) the reaction mixture was stirred vigorously at room temperature for 16 hours. Separation of the organic layer and subsequent extractive work-up (dichloromethane), drying of the combined organic layers (Na$_2$SO$_4$) and removal of the solvent under reduced pressure yielded a yellow oil. Cbz-protected amine 49b was obtained after column chromatography (Rf = 0.28 light petroleum/MTBE 2:1) as a colourless oil (95%, 1.79 g). $^1$H-NMR (CDCl$_3$) δ 7.34 (m, 5H), 5.12 (m, 3H), 4.55 (t, J = 5.1 Hz, 1H), 3.65 (m, 2H), 3.48 (m, 2H), 3.30 (q, J = 5.9 Hz, 2H), 1.83 (m, 2H), 4.82 (t, J = 7.2 Hz, 6H).

(3-oxo-propyl)-carbamic acid-9H-fluoren-9-yl methyl ester 50a. A solution of Fmoc-OSu (471 mg, 1.40 mmol) in water (1.0 mL) and glacial acetic acid (1.0 mL) was stirred at room temperature for 4 hours. Addition of saturated aqueous K$_2$CO$_3$, extractive work-up (ethyl acetate), drying of the combined organic layers and evaporation of the solvent under reduced pressure gave a yellow oil. Purification by using column chromatography (Rf = 0.32 light petroleum/ethyl acetate 1:1) yielded aldehyde 50a as a white foam (85%, 68.0 mg). $^1$H-NMR (CDCl$_3$) δ 9.82 (s, 1H), 7.76 (d, J = 7.3 Hz, 2H), 7.57 (d, J = 7.1 Hz, 2H), 7.36 (m, 4H), 5.23 (bs, 1H), 4.41 (d, J = 7.1 Hz, 2H), 4.22 (m, 1H), 3.53 (m, 2H), 2.75 (m, 2H).

(3-oxo-propyl)-carbamic acid benzyl ester 50b. A similar procedure as was described above was applied to the hydrolysis of acetal 49b. Aldehyde 50b was obtained after column chromatography (Rf = 0.34 light petroleum/ethyl acetate) as a white solid (99%, 696 mg). M.p. 56 °C; $^1$H-NMR (CDCl$_3$) δ 9.79 (bs, 1H), 7.33 (m, 5H), 5.18 (bs, 1H), 5.07 (s, 2H), 3.48 (q, J = 6.1 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H).

[2-(2,3,4,9-Tetrahydro-1H-b-carboline-1-yl)-ethyl]carbamic acid benzyl ester 51. A solution of tryptamine (360 mg, 2.21 mmol) and aldehyde 50b (439 mg, 2.21 mmol) in dichloromethane (18 mL) was stirred for 20 minutes at room temperature. After cooling of the reaction mixture to 0 °C trifluoroacetic acid (2.0 mL) was added. The reaction mixture was subsequently stirred for an additional 2.5 hours at room temperature. Addition of saturated aqueous K$_2$CO$_3$, extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$), removal of the solvent in vacuo and crystallization from ethyl acetate/light petroleum yielded tetrahydro-β-carboline 51 as a white crystalline solid (70%, 537 mg). M.p. 127 °C; $^1$H-NMR (CDCl$_3$) δ 8.68 (bs, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.35 (m, 6H), 7.15 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 5.63 (s, 1H), 5.12 (bs, 2H), 4.11 (t, J = 7.1 Hz, 1H), 3.57 (m, 1H), 3.39 (m, 1H), 3.26 (m, 1H), 3.11 (m, 1H), 2.75 (m, 2H), 2.06 (m, 1H), 1.91 (m, 1H); $^{13}$C-NMR (CDCl$_3$) δ 157.0, 136.3, 136.1, 135.6, 128.3, 127.9, 127.8, 127.1, 121.2, 119.0, 117.8, 110.9, 108.3, 66.6, 57.9, 50.2, 41.1, 38.4, 34.5, 22.3, 18.2.

1-(2-benzoxycarbonylaminoethyl)-1,3,4,9-tetrahydro-1H-β-carboline-2-carboxylic acid tert-butyl ester 52. Di-tert-butyl-dicarbonate (5.50 g, 25.2 mmol) was added to a solution of tetrahydro-β-carboline 51 (4.41 g, 12.6 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at room temperature for 2.5 hours. Removal of the solvent in vacuo and
column chromatography (Rf = 0.48 light petroleum/ ethyl acetate 1:2) yielded 52 as white solid (95%, 5.37 g). M.p. 145 °C; 1H-NMR (DMSO-d6, T = 350 K) δ 10.63 (bs, 1H), 7.41-7.31 (m, 7H), 7.08 (t, J = 3.9Hz, 1H), 7.00 (t, J = 4.2Hz, 1H), 5.21 (d, J = 4.1Hz, 1H), 5.07 (bs, 2H), 4.28 (d, J = 12.9Hz, 1H), 3.24-3.15 (m, 3H), 2.68-2.64 (m, 2H), 2.11-1.91 (m, 2H); 13C-NMR (CDCl3) δ 156.9, 155.4, 135.0, 134.1, 133.8, 126.6, 121.4, 119.1, 118.0, 117.8, 111.2, 107.7, 80.2, 80.0, 79.9, 79.5, 48.6, 48.0, 38.9, 37.6, 37.1, 35.5, 34.5, 28.4, 21.6, 21.2;

1-(2-aminoethyl)-1,3,4,9-tetrahydro-1H-β-carboline-2-carboxylic acid t-butyler ester 53. A solution of tetrahydro-β-carboline 52 (380 mg, 0.85 mmol) in ethanol (15 mL) was stirred for 16 hours under a hydrogen atmosphere (40 psi) in the presence of Pd/C (10%, 50 mg). Filtration over hyflo, thorough washing of the residue with ethanol and removal of the solvent under reduced pressure gave a yellow oil. Purification by using column chromatography (Rf = 0.25 ethyl acetate/ methanol/ NH4OH (aq) 80:15:5) yielded 53 as a white solid (95%, 262 mg). M.p. 114 °C; 1H-NMR (DMSO-d6, T = 350 K) δ 9.68 (bs, 1H), 7.40-7.38 (m, 1H), 7.33-7.31 (m, 1H), 7.07-7.03 (m, 1H), 6.99-6.95 (m, 1H), 5.24 (bs, 1H), 4.27 (b, J = 6.1 Hz, 1H), 3.19-3.11 (m, 2H), 2.75-2.64 (m, 4H), 1.97-1.85 (m, 2H), 1.48 (s, 9H); IR (CHCl3) 1723; HRMS (EI): Calcd. for C31H27N3O4 526.2079, Found: 526.2089.

General procedure for dimerization of amine 53. A solution of amine 53 (94.5 mg, 0.30 mmol) and triethylamine (0.40 mmol, 57 µL) in dichloromethane (3 mL) was cooled to 0 °C. After addition of a precooled solution of 0.10 mmol of the dicarboxylic acid chloride in dichloromethane (3 mL) the reaction mixture was stirred for 2 hours at room temperature. Evaporation of the volatiles under reduced pressure and flash chromatography (ethyl acetate) yielded the dimeric tetrahydro-β-carbolines.

N3-Boc protected tetrahydro-β-carboline dimer 54a. Yellow oil (65%, Rf = 0.40 ethyl acetate). 1H-NMR (DMSO-d6, T = 350 K) δ 10.78 (bs, 2H), 8.41 (bs, 2H), 8.38 (s, 1H), 7.99 (d, J = 2.4 Hz, 2H), 7.56 (t, J = 2.3 Hz, 1H), 7.93 (s, 4H), 7.42 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 8.2 Hz, 2H), 6.98 (t, J = 8.1 Hz, 2H), 5.13 (bs, 1H), 4.35-4.29 (m, 2H), 3.58-3.45 (m, 4H), 3.27-3.15 (m, 2H), 2.74-2.67 (m, 4H), 2.29-2.19 (2H), 2.12-2.00 (m, 2H), 1.45 (s, 18H); HRMS (EI): Calcd. for C41H41N3O6 764.2461, Found: 764.2465.

N3-Boc protected tetrahydro-β-carboline dimer 54b. Yellow oil (72%, Rf = 0.32 ethyl acetate) in 64%. 1H-NMR (DMSO-d6, T = 350 K) δ 10.74 (bs, 2H), 8.39 (bs, 2H), 7.93 (s, 4H), 7.42 (d, J = 4.0Hz, 2H), 7.35 (d, J = 4.1Hz, 2H), 7.08 (t, J = 4.0Hz, 2H), 6.99 (t, J = 4.2Hz, 2H), 5.25 (bs, 1H), 4.36-4.28 (m, 2H), 3.58-3.43 (m, 4H), 3.26-3.15 (m, 2H), 2.73-2.68 (m, 4H), 2.28-2.18 (2H), 2.09-2.00 (m, 2H), 1.48 (s, 18H); HRMS (EI): Calcd. for C41H41N3O6 764.2461, Found: 764.2454.

N3-Boc protected tetrahydro-β-carboline dimer 54c. Yellow oil (68%, Rf = 0.35 ethyl acetate). 1H-NMR (DMSO-d6, T = 350 K) δ 10.72 (bs, 2H), 8.23 (bs, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 8.1 Hz, 2H), 7.00 (t, J = 8.1 Hz, 2H), 5.23 (bs, 1H), 4.37-4.28 (m, 2H), 3.40-3.30 (m, 4H), 3.24-3.13 (m, 2H), 2.74-2.65 (m, 4H), 2.24-2.03 (6H), 2.01-1.91 (m, 2H), 1.48 (s, 18H); HRMS (EI): Calcd. for C41H34N4O6 716.2226, Found: 716.2430.

N3-Boc protected dimer tetrahydro-β-carboline 54d. Yellow oil (59%, Rf = 0.35 ethyl acetate). 1H-NMR (DMSO-d6, T = 350 K) δ 10.70 (bs, 2H), 8.25 (bs, 2H), 7.40 (d, J = 4.1Hz, 2H), 7.34 (d, J = 4.0Hz, 2H), 7.06 (t, J = 4.1Hz, 2H), 6.99 (t, J = 4.1Hz, 2H), 6.88 (s, 2H), 5.21 (bs, 1H), 4.34-4.23 (m, 2H), 3.40-3.29 (m, 4H), 3.20-3.09 (m, 2H), 2.73-2.64 (m, 4H), 2.19-2.08 (2H), 2.00-1.88 (m, 2H), 1.48 (s, 18H); HRMS (EI): Calcd. for C41H34N4O6 762.4105, Found: 762.4112.
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N$_2$-Boc protected tetrahydro-$\beta$-carboline dimer 54e. Yellow oil (82%, R$_f$ = 0.48 ethyl acetate).$^1$H-NMR (DMSO-d$_6$, T= 350 K) δ 10.84 (bs, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.08 (t, J = 8.1 Hz, 2H), 6.98 (t, J = 8.2 Hz, 2H), 5.98 (bs, 1H), 5.24-5.15 (m, 2H), 4.31-4.25 (m, 2H), 3.39-3.25 (m, 2H), 3.21-3.10 (m, 2H), 2.70-2.63 (m, 4 H), 2.13-1.99 (2H), 1.95-1.82 (m, 2H), 1.49 (s, 18H); HRMS (EI): Calcd. for C$_{37}$H$_{53}$N$_3$O$_3$ 660.3999, Found: 660.3993.

N$_2$-Boc protected tetrahydro-$\beta$-carboline trimer 56: Light yellow oil (65%, R$_f$ = 0.28).$^1$H-NMR (DMSO-d$_6$, T= 350 K) δ 10.76 (bs, 3H), 8.52 (bs, 3H), 8.44 (s, 3H), 7.41 (d, J = 8.1 Hz, 3H), 7.33 (d, J = 8.0 Hz, 3H), 7.08 (t, J = 8.1 Hz, 3H), 6.99 (t, J = 8.2 Hz, 3H), 5.25 (bs, 3H), 4.38-4.28 (m, 3H), 3.57-3.40 (m, 4H), 3.26-3.14 (m, 3H), 2.73-2.65 (m, 6H), 2.29-2.19 (3H), 2.11-2.02 (m, 2H), 1.47 (s, 18H); HRMS (EI): Calcd. for C$_{37}$H$_{53}$N$_3$O$_3$ 1095.5218, Found: 1095.5215.

General procedure for the deprotection of 54a-e and 56. A solution of the N-Boc protected dimeric/trimeric tetrahydro-$\beta$-carboline (0.25 mmol) in a mixture of dichloromethane (7 mL) and trifluoroacetic acid (3 mL) was stirred at room temperature for one hour. After addition of saturated aqueous K$_2$CO$_3$ (5 mL) the mixture was stirred for an additional 2 hours. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na$_2$SO$_4$), removal of the solvent under reduced pressure and subsequent purification by using column chromatography (ethyl acetate/ methanol/ NH$_4$OH (aq)) yielded the dimeric/trimeric tetrahydro-$\beta$-carbolines.

Tetrahydro-$\beta$-carboline dimer 55a. Colourless oil (81%, R$_f$ = 0.21 ethyl acetate/ methanol/ NH$_4$OH (aq)).$^1$H-NMR (DMSO-d$_6$) δ 10.78 (bs, 2H), 8.95 (bs, 2H), 8.35 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.04 (t, J = 8.2 Hz, 2H), 6.95 (t, J = 8.1 Hz, 2H), 4.18-4.07 (m, 2H), 3.57-3.40 (m, 4H), 3.26-3.16 (m, 2H), 3.00-2.90 (m, 2H), 2.71-2.58 (m, 4H), 2.28-2.17 (m, 2H), 1.95-1.82 (m, 2H); HRMS (EI): Calcd. for C$_{19}$H$_{26}$N$_2$O$_2$ 560.2899, Found: 560.2893.

Tetrahydro-$\beta$-carboline dimer 55b. Colourless oil (84%, R$_f$ = 0.18 ethyl acetate/ methanol/ NH$_4$OH (aq)).$^1$H-NMR (DMSO-d$_6$) δ 10.75 (bs, 2H), 8.92 (bs, 2H), 7.93 (s, 4H), 7.38 (d, J = 4.1Hz, 2H), 7.29 (d, J = 4.0Hz, 2H), 7.02 (t, J = 4.1Hz, 2H), 6.95 (t, J = 4.1Hz, 2H), 4.10-4.02 (m, 2H), 3.53-3.43 (m, 4H), 3.22-3.13 (m, 2H), 2.96-2.87 (m, 2H), 2.66-2.58 (m, 4H), 2.27-2.15 (m, 2H), 1.92-1.78 (m, 2H); HRMS (EI): Calcd. for C$_{19}$H$_{26}$N$_2$O$_2$ 560.2899, Found: 560.2898.

Tetrahydro-$\beta$-carboline dimer 55c. Colourless oil (92%, R$_f$ = 0.12 ethyl acetate/ methanol/ NH$_4$OH (aq)).$^1$H-NMR (DMSO-d$_6$) δ 10.70 (bs, 2H), 8.59 (bs, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 8.2 Hz, 2H), 6.94 (t, J = 8.1 Hz, 2H), 4.03-3.94 (m, 2H), 3.51-3.43 (m, 4H), 3.18-3.10 (m, 2H), 2.91-2.82 (m, 2H), 2.68-2.55 (m, 4H), 2.28-2.04 (m, 6H), 1.79-1.68 (m, 2H); HRMS (EI): Calcd. for C$_{19}$H$_{26}$N$_2$O$_2$ 512.2899, Found: 512.2905.

Tetrahydro-$\beta$-carboline dimer 55d. Light yellow oil (89%, R$_f$ = 0.15 ethyl acetate/ methanol/ NH$_4$OH (aq)).$^1$H-NMR (DMSO-d$_6$) δ 10.71 (bs, 2H), 8.55 (bs, 2H), 7.39 (d, J = 4.1Hz, 2H), 7.30 (d, J = 4.0Hz, 2H), 7.00 (t, J = 4.2Hz, 2H), 6.94 (t, J = 3.9Hz, 2H), 6.89 (s, 2H), 4.01-3.95 (m, 2H), 3.50-3.40 (m, 4H), 3.18-3.09 (m, 2H), 2.91-2.82 (m, 2H), 2.64-2.55 (m, 4H), 2.16-2.05 (m, 2H), 1.79-1.68 (m, 2H); HRMS (EI): Calcd. for C$_{19}$H$_{26}$N$_2$O$_2$ 514.3056, Found: 514.3048.

Tetrahydro-$\beta$-carboline dimer 55e. Yellow oil (86%, R$_f$ = 0.12 ethyl acetate/ methanol/ NH$_4$OH (aq)).$^1$H-NMR (DMSO-d$_6$) δ 10.71 (bs, 2H), 7.48-7.41 (m, 2H), 7.38 (d, J = 4.2Hz, 2H), 7.17 (t, J = 4.1Hz, 2H), 7.04 (t, J = 4.1Hz, 2H), 7.22-7.15 (m, 2H), 3.79-3.70 (m, 2H), 3.46-3.36 (m, 6H), 3.14-2.96 (m, 4H), 2.44-2.31 (m, 2H), 2.18-2.04 (m, 2H); HRMS (EI): 58
Racemic Synthesis of Tetrahydro-β-carboline Dimers

Tetrahydro-β-carboline trimer 57. Colourless oil (76%, \( R_t = 0.12 \) ethyl acetate/ methanol/ NH\(_4\)OH (aq)). \(^1\)H-NMR (DMSO-\(d_6\)) \( \delta \) 10.74 (bs, 3H), 9.09 (bs, 3H), 8.95 (s, 1H), 7.34 (d, \( J = 4.1\)Hz, 3H), 7.28 (d, \( J = 4.0\)Hz, 3H), 7.01 (t, \( J = 4.1\)Hz, 3H), 6.94 (t, \( J = 4.2\)Hz, 3H), 4.12-4.04 (m, 3H), 3.54-3.47 (m, 6H), 3.21-3.12 (m, 3H), 2.98-2.87 (m, 3H), 2.65-2.57 (m, 6H), 2.27-2.15 (m, 2H), 1.95-1.82 (m, 2H); HRMS (EI): Calcd. for C\(_{27}\)H\(_{39}\)N\(_6\)O 809.4115, Found: 809.4110.

2,3,4,9-Tetrahydro-1H-β-carboline-1-carboxylic acid methyl ester 59. An aqueous solution of glyoxylic acid (100 mL, 7.6% m/m) was added dropwise to a solution of tryptamine hydrochloride (20.5 g, 105 mmol) in water (200 mL). After immediate addition of an aqueous solution of potassium hydroxide (100 mL, 1.7 M) the reaction mixture was stirred. Filtration and thorough washing of the residue with ethanol and diethyl ether yielded 58 as white needles (92%, 20.9 g). M.p. 211 °C. 'H-NMR (CDCl\(_3\)) 8 8.15 (bs, 1H), 7.51 (d, \( J = 4.0\)Hz, 1H), 7.36 (d, \( J = 4.1\)Hz, 1H), 7.24-7.06 (m, 2H), 4.88 (bs, 1H), 3.39-3.26 (m, 1H), 3.23-3.07 (m, 1H), 2.83-2.71 (m, 2H); IR (CHCl\(_3\)) 1736.

2,3,4,9-Tetrahydro-1H-β-carboline-1-y1)methanol 60. Lithium aluminium hydride (1.32 g, 34.8 mmol) was added portionwise to 0 °C to a solution of ester 59 (1.60 g, 6.95 mmol) in THF (70 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 3 hours. Ethanol was carefully added at 0 °C. When gas evolution had ceased aqueous NaOH was added (30 mL) which gave a white precipitate. Filtration, concentration of the filtrate in vacuo, extractive work-up (ethyl acetate), drying of the combined organic layers (Na\(_2\)SO\(_4\)) and removal of the solvent gave a brown oil. Column chromatography (\( R_t = 0.25 \) ethyl acetate/ methanol/ NH\(_4\)OH (aq) 85:10:5) and crystallization gave 60 as a slightly yellow crystalline material (65%, 913 mg). M.p. 139 °C; \(^1\)H-NMR (CDCl\(_3\)) \( \delta \) 8.15 (bs, 7.50 (d, \( J = 4.1\)Hz, 1H), 7.29 (d, \( J = 4.0\)Hz, 1H), 7.21-7.06 (m, 2H), 4.16-4.04 (m, 1H), 3.90-3.68 (m, 2H), 3.32-3.02 (m, 2H), 2.80-2.69 (m, 2H).

1-Hydroxymethyl-1,3,4,9-tetrahydro-1H-β-carboline-2-carboxylic acid t-butyl ester 61. Di-tert-butylicarbonate (1.56 g, 7.13 mmol) was added to a solution of amino alcohol 60 (1.20 g, 5.94 mmol) in dichloromethane (50 mL). After addition of triethylamine (1.67 mL, 11.9 mmol) the reaction mixture was stirred at room temperature for 1 hour. Evaporation of the solvent and column chromatography (\( R_t = 0.43 \) light petroleum → light petroleum/ ethyl acetate 8:2) yielded 61 as a foam (89%, 1.53 g). M.p. 96 °C; \(^1\)H-NMR (DMSO-\(d_6\), T=350 K) \( \delta \) 10.55 (bs, 1H), 7.39 (d, \( J = 4.1\)Hz, 1H), 7.33 (d, \( J = 4.0\)Hz, 1H), 7.06 (t, \( J = 4.1\)Hz, 1H), 6.99 (t, \( J = 4.1\)Hz, 1H), 5.15 (bs, 1H), 4.77 (bs, 1H), 4.38-4.25 (m, 1H), 3.85-3.74 (m, 2H), 3.35-3.21 (m, 1H), 2.71-2.65 (m, 2H), 1.48 (s, 9H).

General procedure for dimerization of alcohol 61. A solution of alcohol 61 (86.7 mg, 0.30 mmol) and triethylamine (0.40 mmol, 57 \( \mu \)L) in dichloromethane (3 mL) was cooled to 0 °C. After addition of a precooled solution of 0.10 mmol of the dicarboxylic acid chloride in dichloromethane (3 mL) the reaction mixture was stirred for 2 hours at room temperature. Evaporation of the volatiles under reduced pressure and flash chromatography (ethyl acetate)
yielded the dimeric tetrahydro-β-carbolines.

N<sub>2</sub>-Boc protected tetrahydro-β-carboline dimer 62a. Brown oil (81%). ¹H-NMR (DMSO-d<sub>6</sub>, T=350 K) δ 10.88 (bs, 2H), 8.55 (s, 1H), 8.22 (d, <i>J</i> = 8.1 Hz, 2H), 7.69 (t, <i>J</i> = 8.2 Hz, 1H), 7.48 (d, <i>J</i> = 8.0 Hz, 2H), 7.36 (d, <i>J</i> = 8.1 Hz, 2H), 7.10 (t, <i>J</i> = 8.0 Hz, 2H), 7.01 (t, <i>J</i> = 8.1 Hz, 2H), 5.62 (bs, 2H), 4.81-4.68 (m, 4H), 4.40-4.29 (m, 2H), 3.40-3.29 (m, 2H), 2.77-2.68 (m, 4H), 1.34 (s, 9H); IR (CHCl<sub>3</sub>) 1743.

N<sub>2</sub>-Boc protected tetrahydro-β-carboline dimer 62b. Brown oil (74%). ¹H-NMR (DMSO-d<sub>6</sub>, T=350 K) δ 10.88 (bs, 2H), 8.55 (s, 1H), 8.22 (d, <i>J</i> = 8.1 Hz, 2H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 7.10 (t, <i>J</i> = 8.0 Hz, 2H), 7.01 (t, <i>J</i> = 8.1 Hz, 2H), 5.62 (bs, 2H), 4.81-4.68 (m, 4H), 4.40-4.29 (m, 2H), 3.40-3.29 (m, 2H), 2.77-2.68 (m, 4H), 1.34 (s, 9H); IR (CHCl<sub>3</sub>) 1743.

N<sub>2</sub>-Boc protected tetrahydro-β-carboline dimer 64: Brown oil (68%). ¹H-NMR (DMSO-d<sub>6</sub>, T=350 K) δ 10.58 (bs, 2H), 8.71 (t, <i>J</i> = 8.1 Hz, 2H), 7.36 (d, <i>J</i> = 8.1 Hz, 2H), 7.05 (t, <i>J</i> = 8.0 Hz, 2H), 6.96 (t, <i>J</i> = 8.1 Hz, 2H), 5.15 (bs, 2H), 4.35-4.26 (m, 2H), 3.85-3.78 (m, 4H), 3.35-3.21 (m, 2H), 2.71-2.62 (m, 4H), 1.49 (s, 9H); IR (CHCl<sub>3</sub>) 1732, 1734.

General procedure for removal of the Boc-group: A similar procedure as was described for the deprotection of the N-Boc protected dimers 54 was applied to the deprotection of dimers 62a and 62b.

Tetrahydro-β-carboline dimer 63a. Yellow oil (84%, R<sub>f</sub> = 0.18 ethyl acetate/ methanol/ NH<sub>4</sub>OH (aq)). ¹H-NMR (DMSO-d<sub>6</sub>) δ 10.86 (bs, 2H), 8.53 (s, 1H), 8.22 (d, <i>J</i> = 8.1 Hz, 2H), 7.72 (t, <i>J</i> = 8.0 Hz, 1H), 7.44 (d, <i>J</i> = 8.2 Hz, 2H), 7.32 (d, <i>J</i> = 8.1 Hz, 2H), 7.07 (t, <i>J</i> = 8.0 Hz, 2H), 6.98 (t, <i>J</i> = 4.1 Hz, 2H), 4.79-4.69 (m, 2H), 4.53-4.37 (m, 4H), 3.22-3.16 (m, 4H), 3.03-2.90 (m, 2H), 2.75-2.54 (m, 4H); IR (CHCl<sub>3</sub>) 1732; HRMS (EI): Caled. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> 538.2580, Found: 538.2574.

Tetrahydro-β-carboline dimer 63b. Yellow oil (89%, R<sub>f</sub> = 0.14 ethyl acetate/ methanol/ NH<sub>4</sub>OH (aq)). ¹H-NMR (DMSO-d<sub>6</sub>) δ 10.88 (bs, 2H), 8.15 (s, 4H), 7.42 (d, <i>J</i> = 8.1 Hz, 2H), 7.32 (d, <i>J</i> = 8.0 Hz, 2H), 7.08 (t, <i>J</i> = 8.2 Hz, 2H), 6.99 (t, <i>J</i> = 8.1 Hz, 2H), 4.78-4.70 (m, 2H), 2.00-1.34 (m, 4H), 3.24-3.17 (m, 4H), 3.01-2.92 (m, 2H), 2.71-2.50 (m, 4H); IR (CHCl<sub>3</sub>) 1732; HRMS (EI): Caled. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> 538.2580, Found: 538.2587.

1-Acetyl-2-indolesulfonate 69. A solution of indole (11.7 g, 100 mmol) in ethanol (25 mL) was added slowly to an aqueous solution of NaHSO<sub>3</sub> (80 mL, 2.8 M). After stirring for 20 hours at room temperature the white-green precipitate was filtered off and thoroughly washed with methanol and diethyl ether to yield a white solid. A slurry of this solid (10.0 g, 42.8 mmol) in acetic anhydride (100 mL) was stirred at 70 °C for 2 hours. The temperature was raised to 90 °C and the reaction mixture was subsequently stirred for 30 minutes to dissolve the solid. After cooling to 0 °C the precipitate was collected by filtration, thorough washing of the solid with diethyl ether afforded 69 (75%, 8.51 g) as a white solid. ¹H-NMR (D<sub>2</sub>O) δ 7.97-7.90 (m, 1H), 7.40-7.26 (m, 3H), 7.22-7.15 (m, 1H), 5.53 (d, <i>J</i> = 1.3 Hz, 1H), 3.73-3.62 (m, 1H), 3.47-3.38 (m, 1H), 2.48 (s, 3H); ¹³C-NMR (D<sub>2</sub>O) δ 143.3, 133.3, 129.2, 127.1, 126.7, 119.6, 76.4, 33.7, 24.9.

5-Bromindole 70. An aqueous solution of 69 (7.0 g, 25.7 mmol in 50 mL) was cooled to 0–5 °C. Bromine (1.46 g, 28.3 mmol) was added slowly in order to keep the temperature below 5 °C. After completion of the addition the orange solution was stirred for 1 hour at 0 °C and subsequently warmed to room temperature. Dilution of the solution with water (50 mL) and addition of sodium bisulfite to scavenge the excess bromine gave a light yellow solution. NaOH (4.3 g) was added and the reaction mixture was heated to reflux for 16 hours. Cooling of the reaction mixture to 0 °C yielded an off-white precipitate that was collected by
filtration, yielding 5-bromoindole 70 (87%, 4.07 g) as a white solid. M.p. 91 °C; 1H-NMR (CDCl₃) δ 8.23 (bs, 1H), 7.77 (s, 1H), 7.28-7.23 (m, 2H), 7.22 (s, 1H), 6.50 (bs, 1H).

5-Bromo-1-(toluene-4-sulfonyl)-1H-indole 71a. An aqueous solution of NaOH (115 mL, 2.6 M) was added to a solution of 5-bromoindole 70 (1.0 g, 5.1 mmol), tosyl chloride (1.23 g, 5.6 mmol) and tetrabutylammonium hydrogen sulphate (17 mg, 0.05 mmol) in toluene (30 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours. Separation and washing of the organic layer with water (three 50 mL portions), drying of the organic layer (Na₂SO₄) and evaporation of the solvent under reduced pressure gave 71a (95%, 1.71 g) as colourless needles. M.p. 149 °C; 1H-NMR (CDCl₃) δ 8.23 (bs, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 6.5 Hz, 1H), 2.35 (s, 3H);

5-Bromo-indole-1-carboxylic acid tert-butyl ester 71b. Di-tert-butyl dicarbonate (1.31 g, 6.0 mmol) was added in small portions to a solution of 70 (977 mg, 5.0 mmol) and DMAP (61.6 mg, 0.5 mmol) in dichloromethane (22 mL). The reaction mixture was stirred at room temperature for one hour. After cooling of the reaction mixture to 0 °C the reaction was quenched by the dropwise addition of saturated aqueous NH₄Cl (10 mL). Extractive work-up (dichloromethane), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent under reduced pressure yielded 71b (99%, 5.39 g) as a white solid. M.p. 115 °C; 1H-NMR (CDCl₃) δ 8.03 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.40 (dd, J = 8.8 Hz, J = 1.9 Hz, 1H), 6.50 (d, J = 3.7 Hz, 1H), 1.67 (s, 9H); IR (CHCl₃) 1722.

1-(Toluene-4-sulfonyl)-5-(trimethylsilyl)ethylindole 72. A solution of 71a (351 mg, 1.0 mmol), trimethylsilylacetylene (282 µL, 2.0 mmol), tetrakis(triphenylphosphine) palladium (57.6 mg, 0.05 mmol) and copper(I) iodide (9.5 mg, 0.05 mmol) in piperidine (5 mL) was heated at 60 °C for 16 hours, under an argon atmosphere. After cooling to room temperature saturated aqueous NH₄Cl (10 mL) was added. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄), evaporation of the solvent in vacuo and column chromatography (Rₛ = 0.35 ethyl acetate/ light petroleum 7:3) yielded 72 (89%, 328 mg) as a yellow oil. 1H-NMR (CDCl₃) δ 7.91 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 5.0 Hz, 2H), 7.65 (s, 1H), 7.55 (d, J = 4.7 Hz, 1H), 7.40 (d, J = 3.5 Hz, 1H), 7.20 (d, J = 5.0 Hz, 2H), 6.60 (d, J = 1.3 Hz, 1H), 2.33 (s, 3H), 0.25 (s, 9H); 13C-NMR (CDCl₃) δ 145.0, 135.0, 134.4, 130.5, 129.8, 128.3, 127.3, 125.2, 118.1, 114.8, 113.4, 108.8, 105.1, 93.1, 21.4, -0.1; HRMS (EI): Calcd. for C₉₅H₇₅NOₛ₂Si 367.1062, Found: 367.1069.

5-Ethynyl-1-(toluenesulfonyl)indole 73. A solution of 72 (283 mg, 0.77 mmol) and potassium carbonate (116 mg, 1.54 mmol) in methanol (5 mL) was stirred at room temperature for 16 hours. Addition of water (15 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and removal of the solvent under reduced pressure yielded 73 (87%, 197 mg) as a yellow oil. 1H-NMR (CDCl₃) δ 7.94 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 0.8 Hz, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.43 (dd, J = 8.3 Hz, J = 0.8 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 6.62 (d, J = 1.8 Hz, 1H), 3.03 (s, 1H), 2.34 (s, 3H).

Bisindole 74. Tetrakis(triphenylphosphine)palladium (50 mg, 0.04 mmol) was added to a solution of 73 (259 mg, 0.88 mmol), 71a (338 mg, 0.97 mmol) and copper(I) iodide (8.4 mg, 0.04 mmol) in piperidine (5 mL) and THF (3 mL) under an argon atmosphere. The reaction mixture was stirred at 50 °C for 16 hours. After cooling to room temperature saturated aqueous NH₄Cl (5 mL) was added. Extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent afforded a brown oil. Bisindole 74 (76%, 379 mg) was obtained by column chromatography (Rₛ = 0.39 ethyl acetate/ light petroleum 1:1) as a colourless oil. 1H-NMR (CDCl₃) δ 7.86 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.1Hz, 2H), 7.65 (d, J = 1.9 Hz, 1H), 7.59 (d, J = 3.8Hz, 1H), 7.39 (dd, J = 8.2
General procedure for coupling of hydroxyacetylenes: A solution of 71a or 71b (1.0 mmol), the hydroxyacetylene (2.0 mmol) and copper(I) iodide (10 mg, 0.05 mmol) in piperidine (4 mL) was heated to 60 °C under an argon atmosphere. After addition of tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) the mixture was stirred for 16 hours at 60 °C. After quenching of the reaction with saturated aqueous NH₄Cl (5 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent under reduced pressure the product was purified by column chromatography (ethyl acetate/ light petroleum 1:1).

4-1H-Indol-5-yl)-but-3-yn-1-ol 75. Brown oil (61%, Rₜ = 0.36 ethyl acetate/ light petroleum 1:1). 'H-NMR (CDCl₃) δ 8.30 (bs, 1H), 7.75 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.19 (bs, 1H), 6.53 (bs, 1H), 3.83 (t, J = 2.2 Hz, 6.1 Hz, 1H), 2.72 (t, J = 5.9 Hz, 1H).

4-[1-(toluene-4-sulfonyl)-1H-indol-5-yl]-but-3-yn-1-ol 77a. Yellow oil (99%, Rₜ = 0.42 ethyl acetate/ light petroleum 1:1). 'H-NMR (CDCl₃) δ 8.30 (bs, 1H), 7.75 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.19 (bs, 1H), 6.53 (bs, 1H), 3.83 (t, J = 2.2 Hz, 6.1 Hz, 1H), 2.72 (t, J = 5.9 Hz, 1H).

4-[1-(t-Butyl carbamoyl)-1H-indol-5-yl]-but-3-yn-1-ol 77b. Brown oil (60%, Rₜ = 0.34 ethyl acetate/ light petroleum 1:1). 'H-NMR (CDCl₃) δ 8.08 (bs, 1H), 7.62-7.56 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.54 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 1.5 Hz, 1H), 3.80 (bs, 2H), 2.68 (t, J = 6.1 Hz, 2H), 2.33 (t, 3H).

4-[1-(toluene-4-sulfonyl)-1H-indol-5-yl]-pent-3-yn-1-ol 78. Yellow oil (89%, Rₜ = 0.31 ethyl acetate/ light petroleum 1:1). 'H-NMR (CDCl₃) δ 8.30 (bs, 1H), 7.75 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.19 (bs, 1H), 6.53 (d, J = 3.9 Hz, 1H), 3.90-3.75 (m, 2H), 2.72 (t, J = 6.2 Hz, 2H), 1.67 (s, 9H).

Toluene-4-sulfonic acid but-3-ynyl ester 80. Tosyl chloride (3.60 g, 17.2 mmol) was added to a solution of butyn-1-ol (1.0 g, 14.3 mmol) in dry pyridine (20 mL). The reaction mixture was stirred for 5 hours under a nitrogen atmosphere at room temperature. After pouring the reaction mixture in water, the mixture was stirred for an additional 30 minutes. Extractive work-up (diethyl ether), drying of the combined organic layers (Na₂SO₄) and evaporation of the solvent under reduced pressure gave a light pink oil. Purification by using column chromatography (Rₜ = 0.45 ethyl acetate/ light petroleum) afforded acetylene 80 (58%, 1.81 g) as a colourless oil. 'H-NMR (CDCl₃) δ 7.55 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 4.15 (t, J = 6.9 Hz, 2H), 2.54 (dt, J = 7.6 Hz, J = 2.2 Hz, 2H), 2.46 (s, 3H), 1.92 (t, J = 2.6 Hz, 1H).

1,4-di-but-3-ynyl-piperazine 79. A solution of acetylene 80 (533 mg, 2.42 mmol), piperazine (86 mg, 1.0 mmol) and NaHCO₃ (166 mg, 2.0 mmol) in DMF (4 mL) was stirred overnight under a nitrogen atmosphere at room temperature. Addition of water (15 mL), extractive work-up (ethyl acetate), drying of the combined organic layers (Na₂SO₄) and removal of the solvent in vacuo gave a brown oil. Purification by using column chromatography (Rₜ = 0.18, ethyl acetate) gave 79 (58%, 110 mg) as a colourless oil. 'H-NMR (CDCl₃) δ 2.52 (t, J = 7.8 Hz, 4H), 2.45 (bs, 8H), 2.30 (dt, J = 8.0 Hz, 2.6 Hz, 4H), 1.92 (t, J = 2.6 Hz, 2H).
Toluene 4-sulfonic acid-4[1-(toluene-4-sulfonyl)-1H-indol-5-yl]but-3-ynyl ester 82. A solution of alcohol 77a (1.01 g, 3.0 mmol) and tosylchloride (1.71 g, 9.0 mmol) in dry pyridine (10 mL) was stirred under a nitrogen atmosphere at room temperature for 17 hours. The reaction mixture was poured in ice-water (200 mL) yielding a crystalline precipitate which was obtained by filtration and taken up in ethyl acetate. Subsequent drying of the solution (Na$_2$SO$_4$) and removal of the solvent under reduced pressure yielded 82 (73%, 1.07 g) as a white solid. M.p. 141 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 7.89 (d, $J = 8.6$ Hz, 1H), 7.81 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.56 (d, $J = 3.6$ Hz, 1H), 7.50 (s, 1H), 7.21-7.27 (m,5H), 6.59 (d, $J = 3.6$ Hz, 1H), 4.18 (t, $J = 7.0$ Hz, 2H), 2.77 (t, $J = 7.0$ Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H); HRMS (EI): Calcd. for C$_{28}$H$_{27}$NS$_2$O$_4$ 477.1068, Found: 477.1060.

Bisindole 81. A solution of 82 (493 mmol, 1.0 mmol) and K$_2$CO$_3$ (177 mg, 1.2 mmol) in dry DMF (10 mL) was heated to 70 °C and stirred overnight under a nitrogen atmosphere. Addition of water (20 mL) and extractive work-up (ethyl acetate/diethylether 1:1), drying of the combined organic layers (Na$_2$SO$_4$) and removal of the solvent under reduced pressure gave a yellow oil. Purification by using column chromatography (R$_f$ = 0.19 ethyl acetate/ NH$_4$OH (aq) 98:2) yielded 81 (35%, 255 mg) as an off-white solid. M.p. 241 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 7.89 (d, $J = 8.5$ Hz, 2H), 7.72, (d, $J = 8.0$ Hz, 4H), 7.54 (d, $J = 7.1$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.1$ Hz, 4H), 6.59 (d, $J = 1.5$ Hz, 2H), 273-274 (m, 4H), 263-254 (m, 12H), 2.35 (s, 6H); $^{13}$C-NMR (CDCl$_3$) $\delta$ 144.8, 134.9, 133.8, 130.5, 129.6, 126.9, 126.5, 124.4, 118.5, 113.2, 108.6, 87.0, 81.1, 57.0, 52.5, 21.3, 17.4; HRMS (EI): Calcd. for C$_{33}$H$_{29}$N$_7$S$_2$O$_4$ 728.2491, Found: 728.2483.

References and notes

Chapter 2

115, 3752.


