
Synthesis of chiral 2-indolyl methanamines and insight into the stereochemistry protecting effects of the 9-phenyl-9-fluorenyl protecting group

Published in:
European Journal of Organic Chemistry

DOI:
10.1002/ejoc.201500391

Published: 01/01/2015

Please cite the original version:

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Synthesis of Chiral (Indol-2-yl)methanamines and Insight into the Stereochemistry Protecting Effects of the 9-Phenyl-9-fluorenyl Protecting Group


Keywords: Asymmetric synthesis / Amino acids / Chiral pool / Protecting groups

Tetrahydro-β-carbolines, a privileged structural feature in natural products and pharmaceutically active compounds, has been the cause for considerable research interest, spanning many decades. Herein is reported the synthesis of the structurally closely related compounds denoted as (indol-2-yl)methanamines, in 99% ee using amino acid starting materials, coupled with a 9-phenyl-9-fluorenyl (Pf) protecting group strategy. Furthermore a conformational study of Pf-protected α-amino carbonyl compounds were undertaken by means of DFT refined molecular mechanics calculation, X-ray crystallography measurements and NMR experiments in order to elucidate the stereochemical protecting properties induced by the Pf group.

Introduction

Tetrahydro-β-carbolines (THβCs) comprise a large group of naturally occurring and synthetic indole alkaloids, the most simple one being tryptoline 1 (Figure 1). The THβCs represent a privileged structural family containing numerous bioactive substrates. Their pharmacological activity profile has made them an extensively studied group of compounds as well as attractive targets in organic synthesis during several decades and still today nurtures interest within the scientific community. Notable bioactivities of the THβCs include the classical antihypertensive effects induced by reserpine (not depicted), as well as antiviral,[1] antimalarial,[2] and anticancer[3] activities.[4] Additionally, the block buster drug Tadalafil® 2, used to treat erectile dysfunction, is a tryptophan derived synthetic THβC.

Herein is presented the synthesis of chiral (indol-2-yl)methanamines, structurally closely related to the THβCs, via a chiral pool approach coupled with a 9-phenyl-9-fluorenyl (Pf) protecting group strategy (Figure 2).[5]

To date, only one natural product, vinoxine 4[6] carrying the (indol-2-yl)methanamine framework, lacking the tryptamine type ethyl bridge, has been characterized. However some closely related natural products such as cinchonamine 5[7] and guettardine 6[8] along with the polyamine protocuclereine B 8[9] have been isolated. Calinol 7, a synthetic (indol-2-yl)methanamine, has also gained attention due to its high affinity towards the calcium sensing receptor (Figure 3).[10] One characteristic feature joining these seemingly quite different compounds together is the fact that they are not accessible by conventional THβC synthetic routes (such as the Pictet–Spengler or Bischler–Napieralski reaction approaches).[11,12] Therefore alternative synthetic strategies are needed.

Figure 1. A selection of THβCs and (indol-2-yl)methanamines.

Figure 2. This work: synthesis of (indol-2-yl)methanamines from amino acids; R = amino acid side chain.
Despite the (indol-2-yl)methanamines’ close connection to the THβC scaffold, only few asymmetric methodologies towards this compound class have been developed. Except for some isolated examples, the more relevant procedures include resolution of hydroxyureas,[13] diastereoselective addition of 2-lithiated indoles to either hydroazones[14] or imines[15] carrying a chiral auxiliary directing group, Sono-gashira-type cyclization reaction of chiral propargylamines and 2-iodo anilines (formally a Larock[16]-type indolization approach),[17,18] an enantioselective Friedel–Craft reaction, followed by oxidation, of 4,7-dihydroindoles with imines catalyzed by chiral phosphoric acids[19] and a three component copper catalyzed domino reaction of 2-ethynylanilines, aldehydes and secondary amines.[20]

Results and Discussion

In order to exhibit diversity and generality of the synthetic protocol we focused our attention on four structurally different amino acid starting materials. The preparation of the proline derived ketone 13d has previously been described by our group.[23] The synthesis began by preparing the Pf-protected Weinreb amides of the corresponding amino acids (Scheme 1).[24] Methyl esters 9a–b were subjected to 9-phenyl-9-fluorenlylation, following a known literature procedure developed for the dimethyl ester of aspartic acid.[25] Methyl ester 10c was synthesized according to a known literature procedure.[26,27] The esters 10a–c where then transformed into the corresponding Weinreb amides 11a–c, using a Grignard base and the HCl salt of N,N-dimethylhydroxylamine.

The Weinreb amides 11a–c were then subjected to coupling with a dilithiated Boc-protected o-toluidine 12 species (Scheme 2).[28] Initial results indicated that an excess of the lithiated substrate was necessary for the reaction to proceed. When 11a was treated with only a small excess (110 mol-%) of 12, a complicated reaction mixture was obtained. Isolation of the reaction components gave only 5% of the desired product 13a together with a large amount of unreacted starting material. Significant amounts of 14a and 15a were also observed. The same decomposition pattern of Weinreb amides[29] and Weinreb amide like derivatives[30] under strongly basic conditions has previously been observed by other research groups. When subjecting 11b to the same reaction conditions, only 3% of product was obtained and 69% of unreacted starting material could be reisolated. Interestingly, in this case we were unable to isolate the corresponding decomposition products 14b and 15b.
Increasing the amount of 12 to 250 mol-%, moderate results were obtained for the alanine amide 11a and phenylalanine amide 11b substrates, and excellent results were obtained for the serine 11c (Scheme 3).

Table 1. Temperature dependency in the alkylation of 11.[4]

<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>11a</td>
<td>–30</td>
<td>15</td>
<td>59</td>
<td>n.d.[b]</td>
</tr>
<tr>
<td>2</td>
<td>11a</td>
<td>–41</td>
<td>60</td>
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</tr>
<tr>
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<td>11a</td>
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<td>20</td>
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<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>11b</td>
<td>0</td>
<td>15</td>
<td>20</td>
<td>n.d.[b]</td>
</tr>
<tr>
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<td>11b</td>
<td>–10</td>
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</tr>
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<td>6</td>
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<td>–20</td>
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<td>38</td>
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<td>11b</td>
<td>–30</td>
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<td>62</td>
<td>n.d.[b]</td>
</tr>
<tr>
<td>8</td>
<td>11b</td>
<td>–41</td>
<td>60</td>
<td>77</td>
<td>10</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 11 (100 mol-%), sBuLi (500 mol-%). [b] Isolated yield after flash chromatography. [c] Not determined: based on crude NMR, little or no remaining starting material. [d] No 14a or 15a could be detected. [e] Crude NMR indicated mostly starting material and minor presence of 14a and 15a.

The striking difference in the reaction outcomes between entries 1 and 7 (Table 1) (250 mol-% 13) compared to the outcome discussed in Scheme 2 (110 mol-% 12), indicates that when using near equimolar amounts of the alkylating reagent almost complete quenching of the nucleophile occurs. The quenching of lithiated 12 could most likely be attributed to the free NH proton present on the substrates. In contrast, the reaction with Weinreb amide 13c and also 13d,[23] lacking free NH protons, occurs more readily (vide supra). This data suggests that the decomposition of Weinreb amide 11a into amide 14a and N,O-acetal 15a occurs through an intramolecular process instead of an intermolecular E2 pathway previously proposed.[29a] It has been suggested that the formation of amide 14a occurs via deprotonation of the methoxy carbon which then collapses, via expulsion of formaldehyde, into 14a (Scheme 4). The formation of 14a has also been accompanied by the readdition of formaldehyde, leading to the rearranged product 16.[29a,29c] Such a product was however not observed under these reaction conditions. Instead, the N,O-acetal 15a was isolated. We suggest, in accordance with previous literature,[29d] that the formation of 15a stems from the analogous deprotonation of the N-methyl group, leading to loss of a methoxide and the formation of an N-methylene intermediate. Upon readdition of the methoxide to the N-methylene compound, N,O-acetal 15a is formed.[29d]
The lack of significant amounts of Weinreb amide decomposition products $14b$ and $15b$ could also be rationalized according to an intramolecular decomposition pathway (Scheme 4 and S1). In an intramolecular pathway, the amino acid side chain would be brought into close proximity to one of the reaction centers and perhaps even more importantly, the cyclic transition states would most certainly experience extra strain with a bulkier amino acid side chain, accounting for the increased stability of $11b$ under the strongly basic reaction conditions (Scheme 4).

Based on these findings an alternative route to ketones $13a$ and $13b$ via the morpholine amides $17$ was developed. The morpholine amides, known to be less expensive substitutes for Weinreb amides, lack the possibility to decompose in the manner discussed above. Both $17a$ and $17b$ where readily synthesized from the corresponding methyl esters $10a$ and $10b$ (Scheme 5).

The less reactive morpholine amides were found to require higher reaction temperatures to achieve useful conversions. Subjecting morpholine amide $17a$ to lithiated $7d$ toluidine at $0^\circ$C satisfyingly furnished the desired ketone $13a$ in excellent 93% yield. Disappointingly, ketone $13b$ was only received in an 18% yield under the same conditions (Scheme 6). Raising the temperature to room temp increased the yield of $13b$ to 29% accompanied by severe decomposition under the strongly basic reaction conditions. The lower reactivity of $17b$ in respect to $17a$ could most likely be accounted for the significantly larger steric bulk of the phenylalanine side chain.

With access to ketones $13a$-$d$ we turned our attention to the indolization. Treatment of $13a$-$d$ with ethanolic $6$ m H$_2$SO$_4$ in CH$_2$Cl$_2$, facilitated the Boc group removal, with the subsequent ring closure of the aniline nitrogen providing indoles $18b$ and $18d$ in excellent yield and indole $18a$ in a moderate but reasonable yield (Scheme 7). Some decomposition was observed in the case of $18a$, accounting for the lower yield, most likely due to solvolysis of the Pf groups.

Cleavage of the Boc group of $13c$ was markedly slower furnishing indole $19$ in only 42% yield together with the Boc-indole $21$ in 7% yield and the rearranged indole aminal $20$ in 21% yield, due to the inherent instability of oxazolidines under acidic conditions.
(CH$_2$Cl$_2$/MeOH, 1:1 mixture) the Boc group was left intact, preventing the formation of indole aminal 20. We found it convenient at this stage also to remove the methylene group, which was readily accomplished using the HCl salt of hydroxylamine.[33] Finally, indolyl N-Boc group cleavage could be executed under both basic and acidic conditions.[34] Refluxing of 26 in MeOH together with NaOH proved superior due to a cleaner reaction profile, giving 18c in 75% yield over two steps (Scheme 8).

![Scheme 8. Indolization, aminal cleavage and boc removal of ketone 13c.](image)

The Pf-protecting group was removed via straightforward hydrolysis using 10 wt.% Pd/C (Scheme 9).[35] Compound 18a underwent clean cleavage in MeOH, giving 22a in 99% yield after work up. Compound 22c required more acidic conditions, giving excellent results in AcOH. Compound 18b suffered from low solubility in MeOH but underwent smooth Pf cleavage in AcOH. Interestingly, the hydrolysis of 18d under these conditions produced a mixture of products. However, we recently reported a hydrolysis of the Pf-protecting group on a similar system, using ammonium hypophosphite as the hydrogen source under catalytic transfer hydrogenation (CTH) conditions.[23] The Pf-cleavage under these CTH conditions provided the desired amine 22d in 86% yield.

![Scheme 9. Hydrogenolysis of the Pf protecting group on indoles 18a–d.](image)

Finally, the chiral (indol-2-yl)methanamines 22a–d could be transformed into a small compound library. Acylation of 18a, 18b, and 18d with acetyl chloride and 18e with acetic anhydride gave the corresponding amides in good yields (Scheme S2). Reductive amination of 18a–d with formaldehyde and sodium triacetoxymethyhydride gave the corresponding tertiary amines in good yields (Scheme S3).[36]

The enantiopurity of compound 22a and 13b where both determined to have an ee of 99%. The ee of compound 13d, synthesized via the same route, has previously been assigned to an ee of >99%,[23] A compound derived from 10c has previously been described as enantiopure[27] Therefore we could safely assume that the described synthetic routes to the (indol-2-yl)methanamines presented herein yields compounds with an ee of at least 99%. As a final conclusion, the successful synthesis of enantiopure (indol-2-yl)methanamines using four structurally very different amino acids shows greater generality for this substance class than previously published procedures.[14,15,17,18,19,20]

The complete retention of the stereochemical information, from the amino acid starting material to the (indol-2-yl)methanamines, under the strongly basic reaction conditions showcases yet again the Pf-protecting group’s capability of shielding the vulnerable α-amino carbonyl stereocenter from racemization. It has previously been proposed, based on molecular mechanics calculations, that the Pf group forces the α-amino carbonyl compounds to adopt a conformation which places the α-hydrogen in the carbonyl plane, a dihedral angle of 0° or 180°. The conformation would effectively minimize the overlap between the C-H$_\alpha$ σ orbital and the C=O π* orbital leading to a lowering of the α-proton acidity.[37] This stereoelectronic explanation has indeed found some support in crystallographic data.[38,39] Another important experimental result showed that treatment of Pf-protected alaninal with triethylamine in refluxing THF destroyed about 50% of the starting material. Reisolation of the remaining aldehyde however showed no deterioration of the ee. The other main reaction component was found to be 9-phenylfluorene, indicating that elimination of an aromatic 9-phenylfluorenyl anion took place preferentially over deprotonation/inversion/reprotonation of the stereogenic center on the aldehyde.[42] The lack of detailed information regarding the molecular mechanics calculations,[47] or any publications further addressing the subject, prompted us to perform the first thorough investigation of the mechanism behind the stereoregulating effects of the Pf group, by computational conformational analysis, supported by X-ray crystal structures and NMR analysis.

As a model for the calculation we chose a simple Pf-protected amino acid derivative 10a. We first set out to try to reproduce the previous calculations by performing a conformational search using an array of different force fields (MM2*,[40] MM3*,[41] MMFF[42] and OPLS-2005[43]) (Table S1). The force fields MM2* and MM3* indeed place the α-hydrogen H(4)–C(3) bond (atom numbering according to Figure 4) of 10a antiperiplanar (or alternatively synperiplanar) to the C(2)–O(1) double bond. However, when applying the more recently developed force fields, MMFF and OPLS-2005, this placement of the α-hydrogen changes noticeably. MMFF gave one dominating conformer (93% of the Boltzmann population distribution) with a dihedral angle of –155°. OPLS-2005 seemed to indicate a more conformationally flexible molecule (Scheme S1). In fact, for this particular task, OPLS-2005 seemed to be the best parameterized
Further refinement of the OPLS-2005 conformational search was performed using quantum mechanical (QM) DFT calculations at the M06-2X/6-31G** level of theory (entry 2, Table 2). Broadly speaking, the conformers arising from the QM refined conformational search could be simplified into two conformers (entry 2, conformer 1, Table 2 and entry 2, conformer 2, Table 2), with each of these two conformers having sub-conformers (entry 2, conformer 3, Table 2 and entry 2, conformer 4, Table 2, respectively) where the ester group had been rotated approximately 180 degrees with respect to the more energetically favored conformers. The minor conformer (entry 2, conformer 5, Table 2) is basically identical to one of these sub-conformers (entry 2, conformer 3, Table 2), with inversion of the nitrogen (Figure S3 and S4).

The lowest energy conformer (Figure 5) is also largely supported by the crystal structure of compound 10a (Figure 6).

To investigate the rotational barrier about the C(3)–C(2) bond of the major conformer of 10a we performed a coordinate scan, by varying the dihedral angle between the H(4) and O(1). The coordinate scan was performed using DFT calculations at the B3LYP/6-31G** level of theory. As a comparison, unprotected alanine methyl ester (free base of 9a) was also subjected to the same calculation sequence as 10a (Figure S6) (Figure 7). Not surprisingly, the bulky Pf group in 10a adds a significant amount of torsional restraints to the system, in comparison to 9a. The rotation of the C(3)–C(2) bond inadvertently forces the methyl group of the amino acid side chain closer to the fluorenyl ring structure of the Pf group, accounting for the observed energy barrier. After a certain point, the structure relaxes by rotating the C(3)–N(6) bond (Figure S8), moving the methyl group away from the fluorenyl rings. The continued rotation yet again forces the methyl group into close proximity to the fluorenyl until the structure is capable of once again relaxing by rotation of the C(3)–N(6) bond, completing the coordinate scan cycle. It is noteworthy that the alignment over the N(6)–C(7) bond is kept all throughout the coordinate scan in a staggered conformation, with the nitrogen lone pair and hydrogen antiperiplanar to the fluorenyl C(9) and C(9’).
Figure 7. Coordinate scan of 9a and 10a, rotation around the C(2)–
C(3) bond in 10° increments. Calculations performed in gas phase
using Jaguar 8.0; theory: DFT(B3LYP) with the basis set 6-31G**.
Energy: relative total electronic energy.

The conformational analysis was extended by X-ray crys-
tallography of eight structures of Pf-protected α-amino acid
derivatives, with the carbonyl at different functionality
states (Figure 8). The crystallographic data further points
to the fact that the H(4)–C(3) bond and the C(2)–O(1)
double bond do not necessarily adopt a periplanar (or anti-
periplanar) conformation as previously suggested (Table 3).

Figure 8. X-ray structures obtained from Pf-protected α-amino
carbonyl compounds.

However, the close proximity of the Pf group to the α-
hydrogen H(4) seems to be evident. In all but one of the
crystal structures (compound 10d is an exception: Table 3,
entry 7) the α-hydrogen H(4) is locked almost dead center
over the fluorenyl ring structure, which is also supported by
the lowest calculated energy conformation of 10a (Figure
5). Compound 10d seems to adopt a conformation, with
respect to the α-hydrogen and the Pf group, closely related
to the minor energy conformation of 10a (entry 2, con-
former 2, Table 2) wherein the α-hydrogen is aligned in the
conformational space between the fluorenyl ring structure
and the phenyl ring of the Pf group (Figure S4). These
observations were further supported by performing a simple
1D-CSSF-NOESY NMR experiment. Selective pulsing of the α-hydrogen H(4) of 10a gave correlation peaks with
protons on the Pf group, indicating that the Pf group, at
the very least to some extent, is in contact with the α-
hydrogen H(4) in solution. The low chemical shift of the α-
hydrogen H(4) in 10a (δ = 2.78 ppm) could also be ex-
plained by the anisotropic effect, putting the proton in close
proximity to the Pf group, to be compared with the chemi-
cal shift of the corresponding α-hydrogen in N-benzyl-
alanine methyl ester (δ = 3.37 ppm) (Figure S2).[47]

Although the Pf group does induce a significant amount
of torsional strain about the C(2)–C(3) bond, compared to
the corresponding unprotected α-amino carbonyl com-
pound, the energy barrier is not high enough to explain the
complete retention of stereochemistry the Pf-protected α-
amino carbonyl compounds experience under strongly basic
conditions through a stereoelectronic effect previously pro-
posed (Figure 7). In order to achieve maximum orbital
overlap between the C(3)–H(4) σ orbital and the C(2)–O(1)
π* orbital only 7 kJ/mol of energy is required (Figure 7).
However, even though the orbital overlap would then be
favorable, the α-hydrogen is still kept in close sterically
confined by the Pf group. In order to alleviate the steric shield-
ing, opening up for deprotonation, the C(3)–N(6) bond
would have to be rotated (with or without inversion of the
nitrogen). Such rotation would however put the Pf group in
closer proximity to the amino acid side chain R(5), increas-
ing the energy barrier further. In fact, one such unique
structure was isolated in the conformational search (Figure
S5). The relative energy level of the structure (denoted as
conformer 6) was calculated to be 18 kJ/mol higher than
the global minimum conformation (entry 2, conformer 1,
Table 2), representing a significant energy difference.

The dihedral angle between H(4) and C(7) (Table 3) (Fig-
ure S3 and S4) might help to rationalize the loss of 9-phen-
ylfluorene from Pf-protected alaninal, taking place preferen-
tially over racemization, under basic conditions.[22] The
orbitals of the H(4)–C(3) bond and of the N(6)–C(7) bond

Table 3. X-ray crystal structure data. Numbering of atoms does not conform to the crystallographic data but instead follows the num-
bering assigned in Figure 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Dihedral angle [°]</th>
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<tr>
<td></td>
<td></td>
<td>H(4)–C(3)–C(2)–O(1)</td>
<td>H(4)–C(3)–N(6)–C(7)</td>
<td>C(3)–N(6)–C(7)–C(8)</td>
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<td>172</td>
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<td>−12.5/−24 (19/15)</td>
<td>178/178 (179/177)</td>
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<td>24</td>
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<td>177</td>
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<td>−153</td>
<td>31</td>
<td>176</td>
</tr>
<tr>
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<td>29/32</td>
<td>−177/179</td>
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<td>8</td>
<td>11d</td>
<td>−161</td>
<td>28</td>
<td>174</td>
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</table>

[a] Structure data contains four crystallographically independent molecules, two in the NH/COOH state and two in the NH$_2$/COO$^-$ state (zwitterionic forms shown in brackets). [b] Angle between only one of the carboxylates oxygens presented. [c] Structure data contains two crystallographically independent molecules.
involved in the observed elimination reaction, being almost periplanar, are prealigned for a concerted E2 syn-elimination, making such a process possibly more favorable over enolization. The same rationale could be applied to the higher energy conformer, wherein the Pf group has been rotated away from the α-hydrogen H(4) (Figure S5), with the only difference that the orbitals now occupy an anti-periplanar alignment, opening up for a possible concerted anti-elimination. It is important to note that the discussion herein does not take into account the possible increased energy barrier the Pf group might induce in the enolization transition state, when the sp³ carbon rehybridizes to sp², originating from the extra allicy strain the Pf group might impose. To further probe such effects more rigorous calculations would be necessary.

Conclusions

We have successfully developed a route to chiral (indol-2-yl)methanamine derivatives in at least 99% ee. By using molecular mechanics in combination with DFT calculations, crystallographic data and NMR experiments we have also investigated the mechanism of how the 9-phenyl-fluoren-9-yl protecting group retains the stereoechemistry of α-amino carbonyl compounds. The results indicate that the α-hydrogen is kept in close proximity to the Pf group and even though an enhanced torsional strain is introduced in the substrates, stereoelectronic effects alone could not explain the complete retention of the stereoechemical information under strongly basic conditions.

Experimental Section

General Information: Compounds 12,[48] 13d,[23] 10c (experimental details are presented),[26,27] 10d,[23] 23[25] as well as 24[49] were prepared using known literature procedures. All experiments using moisture sensitive chemicals were performed in flame dried glass bottles. AcCl was distilled from CaH₂ prior to use. Pb(NO₃)₂ and K₃PO₄ were finally powdered (ambient temperature unless otherwise stated) and the peaks were scanned at 300 K. NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 250 MHz for ¹H and 62.5 MHz for ¹³C) equipped with a sodium lamp and a 10 cm quartz cuvette. HRMS spectra were recorded on a Waters Micromass LCT Premier (ESI/TOF) mass spectrometer. IR was recorded on a Bruker ALPHA ECO-ATR FT-IR spectrometer. Melting points were recorded on a Stuart SMP30.

Crystal Structure Determinations: The single-crystal X-ray diffraction studies were carried out on a Bruker-Nonius Kappa-CCD diffractometer at 90 K (λ(000) Å) (18b, 10a, 11a, 23, 10b, 11b, 10d, 11d) or a Bruker D8 Venture at 123(2) K, using Cu-Kα radiation (λ = 1.54178 Å) (24). Direct Methods (SHELXS-97[51]) were used for structure solution and refinement was carried out using SHELXL-97 or SHELXL-2013/SHELXL-2014[51] (full-matrix least-squares on F²). Hydrogen atoms were localized by difference electron density determination and refined using a riding model [H(N), H(O) free].

Semi-absorption corrections were applied for 18b, 23, 10b, 11b, 10d and 11d, a numerical absorption correction was applied for 24. An extinction correction was applied for 10a. The absolute configurations of 18b, 10a, 11a, 23, 10b, 11b, 10d, 11d could not be determined reliably by refinement of Flack’s x-parameter,[52] Parsons x-parameter[53] nor Hofft’s y-parameter,[54] using the effects of anomalous scattering. For all structures the enantiomer (absolute configuration) has been assigned by reference to an unchanging chiral centre in the synthetic procedure. In 24 the absolute configuration could be determined using the effects of anomalous scattering and in addition the enantiomer (absolute configuration) has been assigned by reference to an unchanging chiral centre in the synthetic procedure. CCDC-1036698 (for 18b), -1036699 (for 10a), -1036700 (for 11a), -1036701 (for 23), -1036702 (for 24), -1036703 (for 10b), -1036704 (for 11b), -1036705 (for 10d), and -1036706 (for 11d) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(5)-Alanine Methyl Ester Hydrochloride (9a): MeOH (240 mL) was cooled down to 0 °C after which freshly distilled AcCl (47.9 mL, 673 mmol, 200 mol-%) was added drop wise. The reaction mixture was stirred at 0 °C for 15 min and let warm to room temp. Alanine (30.0 g, 337 mmol, 100 mol-%) was added and the reaction was stirred at 0 °C after which freshly distilled AcCl (47.9 mL, 673 mmol, 200 mol-%) was added drop wise. The reaction mixture was stirred for 30 min. The suspension was filtered with Celite 535, acquired from Sigma–Aldrich. TLC monitoring was performed on Merck silica gel 60 F₂₅₄ on aluminum support. Visualization of TLC plates was done using UV light (λ = 254 nm) and/or staining the plates with ninhydrin solution (1 g of ninhydrin dissolved in 100 mL of EtOH and 0.2 mL glacial AcOH) or vanillin solution (2.4 g of vanillin dissolved in 100 mL of EtOH, 2 mL conc. H₂SO₄ and 1.2 mL glacial AcOH). NMR spectra were recorded on a Bruker Avance 400 spectrometer (at ambient temperature unless otherwise stated) and the peaks were calibrated to TMS (¹H: δ = 0.00 ppm), or residual solvent ¹H in CDCl₃ (¹H: δ = 1.94 ppm) and ¹³C in CDCl₃ (¹³C: δ = 77.0 ppm). [D₈]acetone (¹³C: δ = 29.8 ppm), CD₃OD (¹C: δ = 49.0 ppm) or [D₈]DMSO (¹³C: δ = 39.5 ppm). Optical rotations were measured with a Perkin–Elmer 343 Polarimeter equipped with a sodium lamp and a 10 cm quartz cuvette. HRMS spectra were recorded on a Waters Micromass LCT Premier (ESI/TOF) mass spectrometer. IR was recorded on a Bruker ALPHA ECO-ATR FT-IR spectrometer. Melting points were recorded on a Stuart SMP30.

(5)-Phenylalanine Methyl Ester Hydrochloride (9b): Compound 9b was prepared using the same procedure as compound 9a. The crude product was triturated from MTBE to give 9a: yield 99% (47.0 g); white solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.76 (br. s, 3 H), 4.28 (q, J = 7.3 Hz, 1 H), 3.82 (s, 3 H), 1.74 (d, J = 7.3 Hz, 3 H) ppm.

Methyl (5)-2-(9-Fluoren-9-yl)aminopropanoate (10a): Compound 9a (17.4 g, 125 mmol, 100 mol-%) was dissolved in MeCN (500 mL) in a Morton flask. K₂PO₄ (55.5 g, 262 mmol, 210 mol-%), Pb((NO₃)₂ (35.1 g, 106 mmol, 85 mol-%) and Pb-Br (50.0 g, 156 mmol, 125 mol-%) were added. The suspension was stirred vigorously at room temp. for 40 h. MeOH (50 mL) was added and the reaction mixture was stirred for 30 min. The suspension was filtered through a pad of celite which was eluted with CHCl₃ (approximately 600 mL) until no UV chromophore (λ = 254 nm) could be observed. Solvents were evaporated and the resi-
due was dissolved in EtO (480 mL). The solution was washed with H2O (360 mL) and the aqueous phase was extracted with EtO (2 × 210 mL). The combined organic layers were washed with brine, dried with Na2SO4 and filtered. The solvents were evaporated to give a light orange cake. Recrystallization from MeOH (120 mL) gave 10a: yield 82% (34.9 g); Rf 0.45 (Hex/EtOAc, 3:1; visualized by UV or ninhydrin stain); pale yellow solid; m.p. 125–128 °C. 1H NMR (400 MHz, CDCl3): δ = 7.16–7.70 (13 H), 3.29 (s, 3 H), 2.96 (br, s, 1 H), 2.78 (q, J = 7.0 Hz, 1 H), 1.12 (d, J = 7.1 Hz, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 177.1, 149.4, 148.9, 144.5, 140.8, 141.0, 128.2, 127.8, 127.4, 127.1, 126.1, 126.0, 125.0, 120.0, 119.8, 73.0, 51.5, 51.4, 21.9 ppm. IR (film): ν = 3478, 3134, 2978, 1731, 1447, 1198, 1144, 732, 699 cm⁻¹. HRMS-ESI calculated for C29H25NNaO2 [M + Na] 442.1783, found 442.1780.

(S)-3-Phenyl-2-[(9-phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxylate (10c): Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 10c: yield 86% (36.2 g); Rf 0.60 (Hex/MeOH, 3:2; visualized by UV or ninhydrin stain); white crystals; m.p. 150–151 °C. 1H NMR (400 MHz, CDCl3): δ = 7.16–7.34 (14 H), 7.04–7.34 (m, 14 H), 6.77 (app t, J = 7.4 Hz, 1 H), 6.40 (d, J = 7.3 Hz, 1 H), 3.38 (br. s, 1 H), 3.01 (br. s, 1 H), 2.81 (s, 3 H), 2.85 (s, 3 H) ppm. IR (film): ν = 3269, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm⁻¹. HRMS-ESI calculated for C30H27NNaO3 [M + Na] 442.1783, found 442.1780.

(S)-N-Methoxy-N-methyl-2-[(9-phenyl-9H-fluoren-9-yl)-amino)propanoate (10a): Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 10a: yield 86% (36.2 g); Rf 0.53 (Hex/MeOH, 3:2; visualized by UV or ninhydrin stain); white crystals; m.p. 150–151 °C. 1H NMR (400 MHz, CDCl3): δ = 7.16–7.34 (14 H), 7.04–7.34 (m, 14 H), 6.77 (app t, J = 7.4 Hz, 1 H), 6.40 (d, J = 7.3 Hz, 1 H), 3.38 (br. s, 1 H), 3.01 (br. s, 1 H), 2.81 (s, 3 H), 2.85 (s, 3 H) ppm. IR (film): ν = 3269, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm⁻¹. HRMS-ESI calculated for C30H27NNaO3 [M + Na] 442.1783, found 442.1780.

(S)-3-Phenyl-2-[(9-phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxylate (10c): Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 10c: yield 86% (36.2 g); Rf 0.60 (Hex/MeOH, 3:2; visualized by UV or ninhydrin stain); white crystals; m.p. 150–151 °C. 1H NMR (400 MHz, CDCl3): δ = 7.16–7.34 (14 H), 7.04–7.34 (m, 14 H), 6.77 (app t, J = 7.4 Hz, 1 H), 6.40 (d, J = 7.3 Hz, 1 H), 3.38 (br. s, 1 H), 3.01 (br. s, 1 H), 2.81 (s, 3 H), 2.85 (s, 3 H) ppm. IR (film): ν = 3269, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm⁻¹. HRMS-ESI calculated for C30H27NNaO3 [M + Na] 442.1783, found 442.1780.

(S)-N-Methoxy-N-methyl-2-[(9-phenyl-9H-fluoren-9-yl)-amino)propanoate (10a): Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 10a: yield 86% (36.2 g); Rf 0.53 (Hex/MeOH, 3:2; visualized by UV or ninhydrin stain); white crystals; m.p. 150–151 °C. 1H NMR (400 MHz, CDCl3): δ = 7.16–7.34 (14 H), 7.04–7.34 (m, 14 H), 6.77 (app t, J = 7.4 Hz, 1 H), 6.40 (d, J = 7.3 Hz, 1 H), 3.38 (br. s, 1 H), 3.01 (br. s, 1 H), 2.81 (s, 3 H), 2.85 (s, 3 H) ppm. IR (film): ν = 3269, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm⁻¹. HRMS-ESI calculated for C30H27NNaO3 [M + Na] 442.1783, found 442.1780.

(S)-N-Methoxy-N-methyl-3-phenyl-2-[(9-phenyl-9H-fluoren-9-yl)-amino)propanoate (11b): Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 11b: yield 70% (700 mg); Rf 0.27 (Hex/EtOAc, 5:1; visualized by UV); white foam. 1H NMR (400 MHz, CDCl3): δ = 2.24–2.4 (6 H), 1.9 (5 H), 1.8–2.2 (m, 8 H), 1.33 (d, J = 6.3 Hz, 1 H) ppm. IR (film): ν = 3269, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm⁻¹. HRMS-ESI calculated for C31H29NNaO3 [M + Na] 471.2048, found 471.2048.
suspended in THF (7 mL). The suspension was cooled to 0 °C and 
HN(OMe)Me mediated purification. The sequence was scaled up to give 
with Et2O. Combined organic layers were washed with brine, dried 
Na2SO4 and filtered. The solvents were evaporated to give a 
pale yellow solid. The crude product was recrystallized from 
EtOAc/Hex to give a white powder; yield 59% (1.35 g). The reac-
sequence from 9c to 11c could be performed without any inter-
mediate purification. The sequence was scaled up to give 11c after 
recrystallization from EtOAc/isooctane: yield 56% (22.8 g) over 
three steps; Rf 0.11 (Hex/EtOAc, 3:1; visualized by UV); white 
translucent needles; m.p. 179–182 °C dec. δ [D] = +176.0 (c = 1.0 in 
CH2Cl2). 1H NMR (400 MHz, CDCl3): δ = 7.71 (m, 1 H), 7.61 (m, 2 
H), 7.49–7.54 (m, 3 H), 7.44 (m, 1 H), 7.34 (m, 1 H), 7.16–7.27 
(m, 5 H), 4.98 (d, J = 6.6 Hz, 1 H), 4.82 (d, J = 6.6 Hz, 1 H), 3.63– 
3.71 (m, 2 H), 3.40 (m, 1 H), 3.00 (br. s, 3 H), 2.85 (br. s, 3 H) ppm. 
13C NMR (100 MHz, CDCl3): δ = 173.7, 149.4, 147.3, 144.3, 
141.2, 139.1, 128.7, 128.4, 128.2, 128.1, 128.0, 127.3, 127.1, 126.8, 125.8, 119.5, 119.4, 85.8, 77.3, 69.1, 60.2, 58.6, 31.9 ppm. IR (film): 
ν = 3057, 2966, 2938, 2972, 1660, 1449, 1176, 1021, 889, 735, 
701 cm⁻¹. HRMS-ESI calculated for C28H23NO3 [M + H] 
401.1865, found 401.1869.

(S)-1-Morpholino-2-[4-(phenyl-9H-fluoren-9-y)amino]-propan-1-one (17a): A round bottom flask was charged with dry THF (20 mL). 
10a (1.374 g, 4 mmol, 100 mol-%) and morpholine (0.52 mL, 6 mmol, 150 mol-%) and the resulting solution was cooled to 0 °C. 
To the reaction mixture was added iPrMgCl (3 mL, 6 mmol, 10 
EtOAc, 7:3) dropwise at –78 °C for 1 h. The yellow suspension 
was warmed to room temp. H2O (5 mL) and CH2Cl2 (60 mL) was 
added dropwise via a dripping funnel. The solution was stirred at 0 °C 
for 1 h. The reaction was quenched with citric acid (20 mmol, 5 wt.- 
% and the layers were separated. The aqueous layer was extracted 
with EtOAc. Combined organic layers were washed with brine, dried 
Na2SO4 and filtered. The evaporation was performed to give a 
pale yellow solid. The crude product was recrystallized from 
EtOAc/Cyclohexane, 500 mol-%) to give a white powder: yield 80% (382 mg); 
δ = 7.06–7.30 (m, 9 H), 6.90 (m, 1 H), 6.67 (m, 1 H), 3.29 (d, J = 
15.6 Hz, 1 H), 3.27 (br. s, 1 H), 2.96 (d, J = 15.4 Hz, 1 H), 2.86 (q, 
J = 7.1 Hz, 1 H), 1.53 (s, 9 H), 1.02 (d, J = 7.1 Hz, 3 H) ppm. 
13C NMR (100 MHz, CDCl3): δ = 213.6, 153.5, 149.6, 149.1, 144.2, 
144.9, 130.8, 130.3, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.2, 126.2, 126.1, 125.1, 124.1, 123.6, 119.9, 119.8, 80.1, 73.1, 57.2, 43.7, 28.4, 20.4 ppm. IR (film): ν = 3326, 3062, 2977, 2930, 
1710, 1589, 1515, 1449, 1234, 1135, 1047, 1025, 731, 699 cm⁻¹. 
HRMS-ESI calculated for C28H23NO3 [M + H] 519.2648, found 519.2642.

(S)-tert-Butyl (2-[2-Oxo-3-[4-(phenyl-9H-fluoren-9-y)amino]-butyl]phenyl)carbamate (13a): To a solution of 12 (2.59 g, 12.5 mmol, 250 mol-%) in dry THF (25 mL) was added sBuLi 
(18.4 mL, 25 mmol, 1.4 M in cyclohexane, 500 mol-%) dropwise at 
–30 °C. The solution changed color from colorless to bright yellow after approximately half the volume of sBuLi had been added. The yellow solution was left to stir at –30 °C for 1 h. The yellow suspension 
was taken to 0 °C. Compound 17a (1.993 g, 5 mmol, 100 mol-%), 
dissolved in THF (25 mL) was added to the reaction mixture. 
The reaction was quenched after 10 min with satd. NH4Cl (25 mL) and 
H2O (5 mL) and taken to room temp. The reaction mixture 
was extracted with Et2O (3 × 30 mL). The combined organic phases 
were washed with brine (50 mL) dried with Na2SO4, filtered and the solvents were evaporated affording a pale yellow syrup. 
Silica gel chromatography (Hex/EtOAc, 95:5) followed by Hex/ 
EthOAc, 90:10) gave 13a: yield 93% (2.421 g); Rf 0.65 (Hex/EtOAc, 3:1; 
visualized by UV or vanillin stain); white foam: δ [D] = +148.0 (c = 1.2 in CH2Cl2) ppm. 1H NMR (400 MHz, CDCl3): δ = 7.70 (m, 3 H), 7.34–7.42 (m, 4 H), 7.06–7.30 (m, 9 H), 6.90 (m, 1 H), 6.67 (m, 1 H), 3.29 (d, J = 15.6 Hz, 1 H), 3.27 (br. s, 1 H), 2.96 (d, J = 15.4 Hz, 1 H), 2.86 (q, 
J = 7.1 Hz, 1 H), 1.53 (s, 9 H), 1.02 (d, J = 7.1 Hz, 3 H) ppm. 
13C NMR (100 MHz, CDCl3): δ = 213.6, 153.5, 149.6, 149.1, 144.2, 
144.9, 130.8, 130.3, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.2, 126.2, 126.1, 125.1, 124.1, 123.6, 119.9, 119.8, 80.1, 73.1, 57.2, 43.7, 28.4, 20.4 ppm. IR (film): ν = 3267, 3129, 2916, 2936, 2979, 2930, 
1710, 1589, 1515, 1449, 1234, 1135, 1047, 1025, 731, 699 cm⁻¹. 
HRMS-ESI calculated for C28H23NO3 [M + H] 519.2648, found 519.2642.
(100 MHz, CDCl₃): δ = 213.2, 153.4, 149.0, 144.2, 141.0, 139.6, 137.2, 137.1, 130.5, 129.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.6, 126.5, 120.1, 125.0, 123.9, 123.3, 119.7, 119.5, 80.1, 72.9, 63.0, 45.2, 40.5, 28.4 ppm. IR (film): ν = 3311, 3062, 2978, 2930, 1716, 1450, 1155, 732, 699 cm⁻¹.

HRMS-ESI calculated for C₉₆H₇₄N₃O₅ [M + H] = 595.2961, found 595.2967.

((S)-tert-Butyl[(2-oxo-2-[9-phenyl-9H-fluoren-9-yl]oxazolidin-2-yl)ethyl]phenyl)carbamates (13c): Compound 12 (15.54 g, 67.5 mmol, 250 mol-%) was dissolved in THF (140 mL) and cooled down to −30 °C. sBuLi (102 mL, 125 mmol, 1.2 M in cyclohexane, 500 mol-%) was added dropwise. The solution changed color from colorless to bright yellow after approximately half the volume of sBuLi had been added. The reaction was stirred at −30 °C for 1 h. 1H (10.03 g, 25 mmol, 100 mol-%) in THF (65 mL) was added and the reaction was stirred for an additional 15 min. The reaction was quenched with satd. NH₄Cl (60 mL), taken to room temp. and H₂O (50 mL) was added to dissolve the white precipitate. The aqueous layer was extracted with EtOAc (2 × 150 mL) and the combined organic layers were washed with brine, dried with Na₂SO₄ and filtered. The solvents were evaporated to give a white solid. The crude product was triturated with Et₂O to give 13c yield 90% (12.3 g; R₆ 0.43 (Hex/EtOAc, 3:1; visualized by UV or by vanillin stain); white powder; mp 175–177 °C, [α]D = +139.6 (c = 1.0 in CH₂Cl₂).

1H NMR (400 MHz, CDCl₃): δ = 7.66–7.74 (m, 3 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.45–7.51 (m, 4 H), 7.18–7.36 (m, 7 H), 7.12 (br. s, 1 H), 6.99 (m, 1 H), 6.83 (m, 1 H), 5.06 (d, J = 6.4 Hz, 1 H), 4.73 (d, J = 6.6 Hz, 1 H), 3.83 (d, J = 15.6 Hz, 1 H), 3.65 (d, J = 16.6 Hz, 1 H), 3.62 (m, 1 H), 3.30 (m, 2 H), 1.52 (s, 9 H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 209.3, 153.6, 148.7, 146.0, 143.1, 141.5, 139.4, 137.3, 130.5, 129.2, 128.9, 128.7, 128.2, 128.1, 127.8, 127.7, 126.9, 125.8, 125.7, 124.3, 123.9, 120.1, 85.9, 80.3, 77.2, 67.5, 66.2, 43.3, 28.4 ppm. IR (film): ν = 3341, 3062, 2978, 2870, 1718, 1515, 1450, 1236, 1156, 734 cm⁻¹.


((S)-N-[1-(9H-Indol-2-yl)ethyl]-9-phenyl-9H-fluoren-9-amine (18a): Compound 13a (3.27 g, 6.3 mmol, 100 mol-%) was dissolved in CH₂Cl₂ (70 mL) and cooled to 0 °C. H₂SO₄ (10.5 mL, 63 mmol, 6 mol in EtOH, 1000 mol-%) was added and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with satd. NaHCO₃ (300 mL). CAUTION! Vigorous gas evolution, and the aqueous layer was extracted with CH₂Cl₂ (2 × 150 mL). Combined organic layers were dried with Na₂SO₄ and filtered. The solvents were evaporated to give a reddish foam. The crude product was purified by silica gel chromatography (Hex/EtOAc, 9:1) to give 18a: yield 65% (1.65 g); R₆ 0.47 (Hex/EtOAc, 5:1; visualized by UV or by ninhydrin staining); white powder; mp 183–186 °C. [α]D = −229.6 (c = 1.0 in CH₂Cl₂).

1H NMR (400 MHz, CDCl₃): δ = 8.25 (br. s, 1 H), 7.73 (m, 2 H), 7.38–7.44 (m, 5 H), 7.19–7.74 (m, 6 H), 7.11 (m, 1 H), 6.99–7.04 (m, 3 H), 5.93 (m, 1 H), 3.50 (br. m, 1 H), 3.37 (app t, J = 4.5 Hz, 1 H), 3.24 (dd, J = 11.0, 4.6 Hz, 1 H), 2.69 (m, 1 H), 2.55 (br. m, 1 H) ppm.

13C NMR (100 MHz, D₂O, acetone-d₆): δ = 150.9, 152.1, 148.2, 142.1, 140.5, 136.7, 129.6, 129.2, 128.9, 128.8, 128.6, 127.8, 126.7, 126.1, 126.0, 120.1, 120.9, 120.2, 119.3, 113.7, 99.9, 74.1, 66.7, 54.7 ppm. IR (film): ν = 3548, 3425, 3330, 3057, 2948, 2875, 1449, 733, 699 cm⁻¹. HRMS-ESI calculated for C₃₂H₂₉N₈NO [M + Na] = 439.1786, found 439.1788.

(S)-2-[1-(9-Phenyl-9H-fluoren-9-yl)pyrrolidin-2-yl]-1H-indole (18d): Compound 18d was prepared using the same procedure as compound 18a, giving after work up 18d: yield 99% (462 mg); R₆ 0.83 (Hex/EtOAc, 5:1, visualized by UV or by ninhydrin staining); yellow solid; mp 156–160 °C. [α]D = −94.9 (c = 1.2 in CH₂Cl₂).

1H NMR (400 MHz, CDCl₃): δ = 8.12 (br. s, 1 H), 7.75 (m, 1 H), 7.58 (m, 1 H), 6.96–7.54 (m, 14 H), 6.53 (m, 1 H), 5.70 (m, 1 H), 3.73 (m, 1 H), 3.41 (m, 1 H), 3.15 (m, 1 H), 1.69–1.90 (m, 4 H) ppm.

13C NMR (100 MHz, CDCl₃): δ = 149.0, 147.0, 144.8, 143.7, 142.2, 138.6, 135.0, 129.2, 128.5, 128.2, 127.7, 127.4, 127.2, 127.1, 127.0, 126.5, 125.8, 125.0, 119.8, 119.8, 119.2, 119.1, 110.4, 97.6, 77.2, 56.7, 50.8, 35.2, 25.2 ppm. IR (film): ν = 3448, 3056, 2965, 2868, 1449, 1285, 736, 702 cm⁻¹. HRMS-ESI calculated for C₃₆H₃₆N₄O [M + H] = 527.2174, found 527.2174.

((S)-1-(9H-Indol-2-yl)ethanamine (22a): Compound 18a (400 mg, 1 mmol, 100 mol-%) was dissolved in MeOH (8 mL) and the re-
Combined organic layers were dried with Na$_2$SO$_4$ and filtered. The reaction mixture was filtered through a pad of celite and solvents were evaporated to give 22a: yield 99% (160 mg); $R_e$ 0.19 (CH$_3$Cl/MeOH, 9:1; visualized by UV or by ninhydrin staining); pale yellow solid; m.p. 64–67 °C. $[a]_D$ (S) = +4.3 (c = 1.3 in CH$_2$Cl$_2$), (R) –3.9 (c = 1.1 in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.52 (br, s, 1 H), 7.55 (m, 1 H), 7.34 (m, 1 H), 7.14 (dd, $J$ = 8.1, 7.1, 1.1 Hz, 1 H), 7.07 (dd, $J$ = 8.0, 7.1, 1.1 Hz, 1 H), 6.30 (m, 1 H), 4.33 (br, q, $J$ = 6.6 Hz, 1 H), 1.52 (d, $J$ = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 144.1, 135.6, 128.5, 121.4, 120.1, 119.6, 110.7, 97.7, 45.3, 29.9 ppm. IR (film): $\tilde{\nu}$ = 3600, 3398, 3281, 3186, 3058, 1951, 1771, 1371, 1071 ppm. 1H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.72 (dd, $J$ = 9.1, 4.6 Hz, 1 H), 2.96–3.11 (m, 3 H), 1.77–1.97 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 141.9, 135.7, 128.7, 121.1, 120.0, 119.4, 110.7, 98.5, 96.4, 44.9 ppm. IR (film): $\tilde{\nu}$ = 3398, 2966, 2873, 1455, 1417, 1303, 1059, 784, 728, 646 cm$^{-1}$. HRMS-ESI calculated for C$_7$H$_7$N$_2$ [M + H]$^+$ 161.1079, found 161.1078.

(S)-1-(1H-Indol-2-yl)-2-phenylethanamine (22b): Compound 18b (420 mg, 0.9 mmol, 100 mol%) was dissolved in AcOH (30 mL) and degassed with argon. Pd/C (45 mg, 0.05 mmol, 10 wt.-%, 5 mol-%) was added and hydrogen (1 atm, balloon) was introduced. The reaction mixture was stirred at room temp. for 18 h. The resulting solution was degassed with argon. Pd/C (45 mg, 0.05 mmol, 10 wt.-%, 5 mol-%) was added and hydrogen (1 atm, balloon) was introduced. The reaction mixture was stirred at room temp. for 18 h. The reaction mixture was filtered through a pad of celite and the solvent was evaporated to give 22b: yield 87% (180 mg); $R_e$ 0.43 (CH$_3$Cl/MeOH, 9:1; visualized by UV or by ninhydrin staining); orange solid; m.p. 66–71 °C. $[a]_D$ = –26.6 (c = 1.6 in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.35 (br, s, 1 H), 7.53 (m, 1 H), 7.28 (m, 1 H), 7.11 (m, 1 H), 7.05 (m, 1 H), 6.30 (s, 1 H), 4.34 (m, 1 H), 2.96–3.11 (m, 2 H), 2.08–2.22 (m, 2 H), 1.77–1.97 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 141.9, 135.7, 128.7, 121.1, 120.0, 119.4, 110.7, 98.5, 56.2, 46.7, 32.6, 25.6 ppm. IR (film): $\tilde{\nu}$ = 3398, 2966, 2873, 1455, 1417, 1303, 1059, 784, 728, 646 cm$^{-1}$. HRMS-ESI calculated for C$_7$H$_7$N$_2$ [M + H]$^+$ 187.1235, found 187.1243.

Computational Information: The molecular modeling was performed using MacroModel (v. 10.0). Conformational searches were performed using force fields MM2*, MM3*, MMFF, MMFFs and OPLS-2005 using a mixed torsional/low-mode sampling method. The amount of minimization iterations was set high enough (typically 3000 iterations) so that no unconverged structures were obtained. DFT calculations were performed in Jaguar (v. 8.0). The refinement of the OPLS-2005 conformational search was performed at the M06-2X/6-31G** level of theory. Structures with high similarity to one another were judged not to be unique energy minima and therefore removed. The coordinate scan of the lowest energy conformation was performed at the B3LYP/6-31G** level of theory. All calculations were performed in the gas phase.

Supporting Information (see footnote on the first page of this article): Copies of $^1$H and $^{13}$C NMR spectra of all products; chiral HPLC spectra of compounds 25a and 13b; analytical data of compounds 14a, 15a, 19, 20 and 12-d; experimental and analytical data of a stepwise approach to 18c; experimental and analytical data of the acylation and methylation of compounds 22a-d; computational data of 9a and 10a as well as crystallographic data.

Acknowledgments

The authors are grateful for the financial support provided by the National Graduate School of Organic Chemistry and Chemical Biology, Finland and Aalto University. M. Sc. Essi Karppanen (Aalto University School of Chemical Technology) is kindly acknowledged for providing crystals of compound 24. The authors thank Bruker-AXS, Karlsruhe, Germany, for collecting the data of compound 24. Professor Antti Poso (University of Eastern Finland) and M. Sc. Marko Melander (Aalto University School of Chemical Technology) are acknowledged for valuable advice re-