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Published in: European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201500391

Published: 01/01/2015

Document Version Peer-reviewed accepted author manuscript, also known as Final accepted manuscript or Post-print

Please cite the original version:

Lood, C. S., Laine, A. E., Högnäsbacka, A., Nieger, M., & Koskinen, A. M. P. (2015). Synthesis of chiral 2-indolyl methanamines and insight into the stereochemistry protecting effects of the 9-phenyl-9-fluorenyl protecting group. *European Journal of Organic Chemistry*, 2015(17), 3793-3805. https://doi.org/10.1002/ejoc.201500391

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This is the peer reviewed version of the following article: Lood, CS, Laine, AE, Högnäsbacka, A, Nieger, M & Koskinen, AMP 2015, 'Synthesis of chiral 2-indolyl methanamines and insight into the stereochemistry protecting effects of the 9phenyl-9-fluorenyl protecting group' EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol 2015, no. 17, pp. 3793-3805, which has been published in final form at DOI: 10.1002/ejoc.201500391. This article may be used for noncommercial purposes in accordance With Wiley-VCH Terms and Conditions for self-archiving.

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

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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) protect-

ing group strategy. Furthermore a conformational study of Pfprotected  $\alpha$ -amino carbonyl compounds were undertaken by means of DFT refined molecular mechanics calculation, Xray 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 TH $\beta$ Cs 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 THBCs include the classical antihypertensive effects induced by reserpine (not depicted), as well as antiviral,<sup>[1]</sup> antimalarial,<sup>[2]</sup> and anticancer<sup>[3]</sup> activities.<sup>[4]</sup> Additionally, the block buster drug Tadalafil<sup>®</sup> 2, used to treat erectile dysfunction, is a tryptophan derived synthetic TH $\beta$ C.

Herein is presented the synthesis of chiral (indol-2-yl)methanamines, structurally closely related to the TH $\beta$ Cs, via a chiral pool approach coupled with a 9-phenyl-9-fluorenyl (Pf) protecting group strategy, starting from amino acids (Figure 2).<sup>[5]</sup>

To date, only one natural product, vinoxine 4,<sup>[6]</sup> 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

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



Figure 2. this work: synthesis of (indol-2-yl)methanamines from amino acids; R = amino acid side chain.

 $5^{[7]}$  and guettardine  $6^{[8]}$  along with the polyamine protoaculeine B 8<sup>[9]</sup> have been isolated. Calindol 7, a synthetic (indol-2-yl)methanamine, has also gained attention due to its high affinity towards the calcium sensing receptor (Figure 3).<sup>[10]</sup> One characteristic feature joining these seemingly quite different compounds together is the fact that they are not accessible by conventional TH $\beta$ C synthetic routes (such as the Pictet-Spengler or Bischler-Napieralski reaction approaches).<sup>[11,12]</sup> Therefore alternative synthetic strategies are needed.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500391.



Figure 3. Examples of (indol-2-yl)methanamines.

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,<sup>[13]</sup> diastereoselective addition of 2-lithiated indoles to either hydroazones<sup>[14]</sup> or imines<sup>[15]</sup> carrying a chiral auxiliary directing group, Sonogashira-type cyclization reaction of chiral propargylamines and 2-iodo anilines (formally a Larock<sup>[16]</sup>-type indolization approach),<sup>[17,18]</sup> an enantioselective Friedel–Craft reaction, followed by oxidation, of 4,7-dihydroindoles with imines catalyzed by chiral phosphoric acids<sup>[19]</sup> and a three component copper catalyzed domino reaction of 2-ethynylanilines, aldehydes and secondary amines.<sup>[20]</sup> Due to the propensity for  $\alpha$ -amino carbonyl compounds to racemize/epimerize, the Pf group was introduced as a more acid stable alternative to the trityl protecting group.<sup>[21,22]</sup> The exact mechanism behind this stereochemical protecting effect has however not yet been elucidated and no thorough mechanistic investigations have yet to be undertaken. Therefore, within the framework of this work, we also aim to offer insight into the stereochemical protecting effects of the Pf-protecting group.

#### **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.<sup>[23]</sup> The synthesis began by preparing the Pf-protected Weinreb amides of the corresponding amino acids (Scheme 1).<sup>[24]</sup> Methyl esters **9a–b** were subjected to 9-phenyl-9-fluorenylation, following a known literature procedure developed for the dimethyl ester of aspartic acid.<sup>[25]</sup> Methyl ester **10c** was synthesized according to a known literature procedure,<sup>[26,27]</sup> The esters **10a–c** where then transformed into the corresponding Weinreb amides **11a–c**, using a Grignard base and the HCl salt of *N*,*O*-dimethylhydroxylamine.

The Weinreb amides 11a-c were then subjected to coupling with a dilithiated Boc-protected o-toluidine 12 species (Scheme 2).<sup>[28]</sup> 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<sup>[29]</sup> and Weinreb amide like derivatives<sup>[30]</sup> 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.



Scheme 1. Preparation of the Pf-protected Weinreb amides 9a-c.



Scheme 2. Lithiation coupling of toluidine 12 and Weinreb amides 11a–b. *Reaction conditions:* 12 (110 mol-%) stirred together with *s*BuLi (220 mol-%) for 1 h at -30 °C. 11 (100 mol-%) was added and the reaction stirred for 1 h. Isolated yields after silica gel chromatography. n.d. = not determined.

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.<sup>[a]</sup>

NHBoc			1) sBuLi 2) <b>11a-b</b> THF, <i>T</i>	NHF NH Boc	
	1	2		13a: R = Me 13b: R = Bn	
Entry	11	Т	t	Yield 13 <sup>[b]</sup>	Yield 11 <sup>[b]</sup>
		[°C]	[min]	[%]	[%]
1	11a	-30	15	59	n.d. <sup>[c]</sup>
2 <sup>[d]</sup>	11a	-41	60	64	6
3 <sup>[e]</sup>	11a	-78	20	0	n.d.
4	11b	0	15	20	n.d. <sup>[c]</sup>
5	11b	-10	15	30	n.d. <sup>[c]</sup>
6	11b	-20	15	38	n.d. <sup>[c]</sup>
7	11b	-30	15	62	n.d. <sup>[c]</sup>
8	11b	-41	60	77	10

Scheme 3. Lithiation coupling between toludine 12 and Weinreb amides 11a–c. *Reaction conditions:* 12 (250 mol-%) stirred together with *s*BuLi (500 mol-%) for 1 h at -30 °C. 11 (100 mol-%) was added and the reaction stirred for 15 min after it was quenched. Isolated yields after purification.

The low yield of ketones 13a and 13b and the decomposition of Weinreb amide 11a, prompted us to investigate the reaction further. We first performed a simple deuterium quenching experiment, to investigate the degree of benzylic lithiation under the reaction conditions. Quenching the dianion of 12 with MeOD and analyzing the crude reaction mixture by NMR revealed >95% deuterium incorporation at the benzylic position (Figure S1).

The formation of ketone 13a-b was shown to be strongly dependent on the reaction temperature (Table 1). Higher temperature seemed to cause large amounts of decomposition (entries 1 and 4–7). At low temperature, -78 °C, the reaction suffered from low conversions. Interestingly, the Weinreb amide decomposition seems to take place, albeit at a low rate (entry 3). At -41 °C the observed rate of the Weinreb amide decomposition was markedly lower than the conversion of the Weinreb amides 11a-b to the desired ketone 13a-b enabling us to obtain 13b in a good 77% yield (entry 8) as well as a minor yield improvement for 13a (entry 2).

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

[a] Reaction conditions: **11** (100 mol-%), **12** (250 mol-%), *s*BuLi (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**.

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,<sup>[23]</sup> 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.<sup>[29a]</sup> 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.<sup>[29a,29c]</sup> 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,<sup>[29d]</sup> 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.<sup>[29d]</sup>



Scheme 4. a) Decomposition of Weinreb amide 11a into amide 14a.
b) Decomposition of Weinreb amide 11a into N,O-acetal 15a. c)
Steric repulsion in the cyclic transition states of 11b.

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.<sup>[31]</sup> Both **17a** and **17b** where readily synthesized from the corresponding methyl esters **10a** and **10b**. (Scheme 5).



Scheme 5. Formation of morpholine amides 17a and 17b.

The less reactive morpholine amides were found to require higher reaction temperatures to achieve useful conversions. Subjecting morpholine amide **17a** to lithiated **7d** toluidine **12** at 0 °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.



Scheme 6. Alkylation of morpholine amides 17a and 17b.

With access to ketones 13a-d we turned our attention to the indolization. Treatment of 13a-d with ethanolic 6 M H<sub>2</sub>SO<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub>, 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 group.<sup>[32]</sup> 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.



Scheme 7. a) Indolization of ketones **13a–d**. b) Biproducts from the indolization of **13c**.

We recognized that when performing the indolization reaction on compound **13c** in a less acidic reaction medium (CH<sub>2</sub>Cl<sub>2</sub>/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.<sup>[33]</sup> Finally, indolyl *N*-Boc group cleavage could be executed under both basic and acidic conditions.<sup>[34]</sup> 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**.

The Pf-protecting group was removed via straightforward hydrogenolysis using 10 wt.-% Pd/C (Scheme 9).<sup>[35]</sup> 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 hydrogenolysis of **18d** under these conditions produced a mixture of products. However, we recently reported a hydrogenolysis of the Pf-protecting group on a similar system, using ammonium hypophosphite as the hydrogen source under catalytic transfer hydrogenation (CTH) conditions.<sup>[23]</sup> 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.

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 **18c** with acetic anhydride gave the corresponding amides in good yields (Scheme S2). Reductive amination of **18a–d** with formaldehyde and sodium triacetoxyborohydride gave the corresponding tertiary amines in good yields (Scheme S3).<sup>[36]</sup>

The enantiopurity of compound 22a and 13b were assigned using chiral HPLC. (*R*)-22a was synthesized from D-alanine and (*R*)-13b was synthesized from D-phenylalanine, by the same routes as the corresponding enantiomers.

Compounds **22a** and **13b** where both determined to have an *ee* of 99%. The *ee* of compound **13d**, synthesized via the same route, has previosly been assigned to an *ee* of >99%.<sup>[23]</sup> A compound derived from **10c** has previously been described as enantiopure.<sup>[27]</sup> Therefore we could safely assume that the described synthetic routes to the (indol-2yl)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.<sup>[14,15,17,18,19,20]</sup>

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  $\alpha$ -amino carbonyl stereocenter from racemization. It has previously been proposed, based on molecular mechanics calculations, that the Pf group forces the  $\alpha$ -amino carbonyl compounds to adopt a conformation which places the  $\alpha$ -hydrogen in the carbonyl plane, a dihedral angle of 0° or 180°. The conformation would effectively minimize the overlap between the C-H<sub>a</sub>  $\sigma$ orbital and the C=O  $\pi^*$  orbital leading to a lowering of the α-proton acidity.<sup>[37]</sup> This stereoelectronic explanation has indeed found some support in crystallographic data.<sup>[38,39]</sup> 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.<sup>[22]</sup> The lack of detailed information regarding the molecular mechanics calculations,<sup>[37]</sup> or any publications further addressing the subject, prompted us to perform the first thorough investigation of the mechanism behind the stereoprotecting 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 Pfprotected 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\*,<sup>[40]</sup> MM3\*,<sup>[41]</sup> MMFF<sup>[42]</sup> and OPLS-2005<sup>[43]</sup>) (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  $\alpha$ -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 complicated system, giving several conformers with a narrow energy difference (entry 1, Table 2). In fact, for this particular task, OPLS-2005 seemed to be the best parameterized

force field examined.<sup>[44]</sup> 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).<sup>[45]</sup> 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).



Figure 4. Generic Pf-protected  $\alpha$ -amino carbonyl compound and **10a**. Numbering (does not follow IUPAC guidelines) of relevant atoms to simplify the conformational (computational and crystallographic) discussion.

Table 2. Conformational investigation of **10a**, using force field OPLS-2005, showing data for the 5 lowest energy conformations.

Entry	Conformer	Dihedral angle <sup>[a]</sup> [°]	Population distribution <sup>[b]</sup> [%]
1 <sup>[c]</sup>	1	10	35.4
	2	-139	29.8
	3	-155	12.4
	4	-143	10.1
	5	16	2.8
2 <sup>[d]</sup>	1	-162	69.6
	2	-151	11.2
	3	19	10.5
	4	35	7.4
	5	16	0.5

[a] Dihedral angle between H(4)–C(3)–C(2)–O(1). [b] Determined as the Boltzmann distribution at T = 298.15 K. [c] Calculations performed in gas phase with force field OPLS-2005 using Macro-Model 10.0 without any constraints; electrostatic treatment was set to constant dielectric. [d] Calculations performed in gas phase using Jaguar 8.0; theory: DFT (M06–2X) with the basis set 6-31G\*\*++.

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.<sup>[46]</sup> 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,



Figure 5. Lowest energy conformation of **10a** (entry 2, conformer 1, Table 2).



Figure 6. Crystal structure of 10a (entry 1, Table 3). Displacement parameters are drawn at 50% probability level. Note that the crystallographic numbering presented in this Figure is not used in the conformational discussion.

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 S9).



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 crystallography of eight structures of Pf-protected  $\alpha$ -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 antiperiplanar) conformation as previously suggested (Table 3).



Figure 8. X-ray structures obtained from Pf-protected  $\alpha$ -amino carbonyl compounds.

However, the close proximity of the Pf group to the  $\alpha$ -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  $\alpha$ -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  $\alpha$ -hydrogen and the Pf group, closely related

to the minor energy conformation of **10a** (entry 2, conformer 2, Table 2) wherein the  $\alpha$ -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  $\alpha$ -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  $\alpha$ -hydrogen H(4) in **10a** ( $\delta = 2.78$  ppm) could also be explained by the anisotropic effect, putting the proton in close proximity to the Pf group, to be compared with the chemical shift of the corresponding  $\alpha$ -hydrogen in *N*-benzyl-L-alanine methyl ester ( $\delta = 3.37$  ppm) (Figure S2).<sup>[47]</sup>

Although the Pf group does induce a significant amount of torsional strain about the C(2)–C(3) bond, compared to the corresponding unprotected a-amino carbonyl compound, the energy barrier is not high enough to explain the complete retention of stereochemistry the Pf-protected aamino carbonyl compounds experience under strongly basic conditions through a stereoelectronic effect previously proposed (Figure 7). In order to achieve maximum orbital overlap between the C(3)–H(4)  $\sigma$  orbital and the C(2)–O(1)  $\pi^*$  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 steric confinement by the Pf group. In order to alleviate the steric shielding, 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), increasing 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) (Figure S3 and S4) might help to rationalize the loss of 9-phenylfluorene from Pf-protected alaninal, taking place preferentially over racemization, under basic conditions.<sup>[22]</sup> 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 numbering assigned in Figure 4.

Entry	Compound	Dihedral angle [°] H(4)–C(3)–C(2)–O(1)	Dihedral angle [°] H(4)–C(3)–N(6)–C(7)	Dihedral angle [°] C(3)–N(6)–C(7)–C(8)
1	10a	-120	5	-175
2	11a	-147	23	172
3	<b>23</b> <sup>[a]</sup>	19/23 (44/45) <sup>[b]</sup>	-12.5/-24 (19/15)	178/178 (179/177)
4	24	-149	26	177
5	10b	-153	31	176
6	11b <sup>[c]</sup>	-153/-150	29/32	-177/179
7	10d	-149	3	61
8	11d	-161	28	174

[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  $\alpha$ -hydrogen H(4) (Figure S5), with the only difference that the orbitals now occupy an antiperiplanar 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 sp<sup>3</sup> carbon rehybridizes to sp<sup>2</sup>, originating from the extra allylic 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)methanamines giving compounds 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 9phenyl-fluoren-9-yl protecting group retains the stereochemistry of  $\alpha$ -amino carbonyl compounds. The results indicate that the  $\alpha$ -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 stereochemical information under strongly basic conditions.

# **Experimental Section**

General Information: Compounds 12,<sup>[48]</sup> 13d,<sup>[23]</sup> 10c (experimental details are presented),<sup>[26,27]</sup> 10d,<sup>[23]</sup> 23<sup>[25]</sup> as well as 24<sup>[49]</sup> were prepared using known literature procedures. All experiment using moisture sensitive chemicals were performed in flame dried glass ware under argon atmosphere. Dry solvents (THF, MeCN and CH<sub>2</sub>Cl<sub>2</sub>) were obtained from a solvent drying system (MB SPS-800, using neutral alumina as desiccant). Other solvents used were of P.A. quality, with the exception of HPLC grade hexane for the intended use of HPLC analysis, and used as such straight from the bottles. TMSCl was distilled from CaH<sub>2</sub> prior to use. AcCl was distilled prior to use. Pb(NO<sub>3</sub>)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub> were finally powdered and dried in oven prior to use. sBuLi was titrated from N-benzylbenzamide.<sup>[50]</sup> Reagents were obtained from Sigma Aldrich, TCI Europe and Johnson Matthey Chemicals Limited. Celite used for filtration was 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 ( $\lambda$ = 254 nm) and/or staining the plates with ninhydrin solution (1 g of ninhydrin dissolved in 100 mL of EtOH and 0.2 mLglacial AcOH) or vanillin solution (2.4 g of vanillin dissolved in 100 mL of EtOH, 2 mL conc. H<sub>2</sub>SO<sub>4</sub> 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 (<sup>1</sup>H:  $\delta$  = 0.00 ppm), or residual solvent <sup>1</sup>H in CD<sub>3</sub>CN (<sup>1</sup>H:  $\delta$  = 1.94 ppm) and <sup>13</sup>C in CDCl<sub>3</sub> (<sup>13</sup>C:  $\delta$  = 77.0 ppm),  $[D_6]$ acetone (<sup>13</sup>C:  $\delta$  = 29.8 ppm), CD<sub>3</sub>OD (<sup>13</sup>C:  $\delta$  = 49.0 ppm) or  $[D_6]DMSO$  (<sup>13</sup>C:  $\delta$  = 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.

**Crystal Structure Determinations:** The single-crystal X-ray diffraction studies were carried out on a Bruker-Nonius Kappa-CCD diffractometer at 123(2) K using Mo- $K_{\alpha}$  radiation ( $\lambda = 0.71073$  Å) (**18b, 10a, 11a, 23, 10b, 11b, 10d, 11d**), or a Bruker D8 Venture at 123(2) K, using Cu- $K_{\alpha}$  radiation ( $\lambda = 1.54178$  Å) (**24**). Direct Methods (SHELXS-97<sup>[51]</sup>) were used for structure solution and refinement was carried out using SHELXL-97 or SHELXL-2013/SHELXL-2014<sup>[51]</sup> (full-matrix least-squares on  $F^2$ ). 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,<sup>[52]</sup> Parsons *x*-parameter<sup>[53]</sup> nor Hofft's *y*-parameter,<sup>[54]</sup> 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.

(*S*)-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 room temp. for 18 h. Solvents were evaporated to yield a white solid. The crude product was triturated from MTBE to give 9a: yield 99% (47.0 g); white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.76$  (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.

(*S*)-Phenylalanine Methyl Ester Hydrochloride (9b): Compound 9b was prepared using the same procedure as compound 9a. The crude product was triturated from Et<sub>2</sub>O: yield 99% (34.1 g); light green solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 7.26–7.39 (m, 5 H), 4.33 (dd, *J* = 7.2, 6.3 Hz, 1 H), 3.80 (s, 3 H), 3.27 (dd, *J* = 14.3, 6.2 Hz, 1 H), 3.19 (dd, *J* = 14.3, 7.1 Hz, 1 H) ppm.

Methyl (*S*)-2-[(9-Phenyl-9*H*-fluoren-9-yl)amino]propanoate (10a): Compound 9a (17.4 g, 125 mmol, 100 mol-%) was dissolved in MeCN (500 mL) in a Morton flask. K<sub>3</sub>PO<sub>4</sub> (55.5 g, 262 mmol, 210 mol-%), Pb(NO<sub>3</sub>)<sub>2</sub> (35.1 g, 106 mmol, 85 mol-%) and Pf-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 CHCl<sub>3</sub> (approximately 600 mL) until no UV chromophore ( $\lambda$  = 254 nm) could be observed. Solvents were evaporated and the resi-

due was dissolved in Et<sub>2</sub>O (480 mL). The solution was washed with  $H_2O$  (360 mL) and the aqueous phase was extracted with Et<sub>2</sub>O (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 crystals; m.p. 88-90 °C.  $[a]_{D}(S) = -226.4$  (c = 0.55 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +225.4 (c 0.55 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.16–7.70 (m, 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 177.1, 149.4, 148.9, 144.5, 140.8, 140.1, 128.2, 127.8, 127.4, 127.1, 126.1, 126.0, 125.0, 120.0, 119.8, 73.0, 51.5, 51.4, 21.5 ppm. IR (film):  $\tilde{\nu}$  $= 3478, 3314, 3061, 2978, 1731, 1447, 1198, 1144, 732, 699 \text{ cm}^{-1}$ . HRMS-ESI calculated for C<sub>23</sub>H<sub>21</sub>NNaO<sub>2</sub> [M + Na] 366.1470, found 366.1473.

**Methyl (S)-3-Phenyl-2-[(9-phenyl-9***H***-fluoren-9-yl)amino]propanoate (10b):** Compound 10b was prepared using the same procedure as compound 10a. The crude product was recrystallized from EtOH to give 10b: yield 86% (36.2 g);  $R_f$  0.53 (Hex/EtOAc, 3:1; visualized by UV or ninhydrin stain); white crystals; m.p. 150–151 °C. [*a*]<sub>D</sub> (*S*) = -206.7 (*c* = 1.2 in CH<sub>2</sub>Cl<sub>2</sub>), (*R*) +208.3 (*c* 1.1 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.66 (m, 1 H), 7.61 (m, 1 H), 7.31–7.36 (m, 3 H), 7.14–7.28 (m, 9 H), 7.02–7.07 (m, 2 H), 6.96 (m, 1 H), 6.63 (m, 1 H), 3.20 (s, 3 H), 2.64–2.92 (m, 4 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.2, 148.6, 148.5, 144.6, 141.0, 140.0, 137.6, 129.7, 128.2, 128.2, 128.1, 128.0, 127.8, 127.2, 127.1, 126.4, 126.2, 126.1, 125.0, 119.8, 119.6, 72.9, 57.5, 51.4, 41.4 ppm. IR (film):  $\tilde{v}$  = 3312, 3061, 3028, 2948, 1733, 1449, 1169, 733, 698 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>29</sub>H<sub>25</sub>NNaO<sub>2</sub> [M + Na] 442.1783, found 442.1780.

(S)-N-Methoxy-N-methyl-2-[(9-phenyl-9H-fluoren-9-yl)amino]propanamide (11a): Compound 10a (22.1 g, 64 mmol, 100 mol-%) and HN(OMe)Me·HCl (7.5 g, 77 mmol, 120 mol-%) were suspended in THF (80 mL). The suspension was cooled to 0 °C and iPrMgCl (77 mL, 154 mmol, 2 м in Et<sub>2</sub>O, 240 mol-%) was added dropwise via dropping funnel. The reaction was stirred at 0 °C for 3 h before being quenched with citric acid (200 mL, 5 wt.-%). The layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$ 150 mL). The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give 11a: yield 99% (23.9 g); R<sub>f</sub> 0.18 (Hex/EtOAc, 3:1; visualized by UV); pale yellow solid; m.p. 125–128 °C.  $[a]_D = -236.0$  (c = 1.3in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.65 (m, 2 H), 7.40–7.46 (m, 3 H), 7.15–7.33 (m, 8 H), 3.56 (br. s, 1 H), 2.86–2.93 (br. m, 7 H), 1.06 (d, J = 7.0 Hz, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$ 177.2, 150.3, 149.4, 144.9, 141.2, 139.9, 128.2, 128.2, 128.1, 128.0, 127.5, 127.0, 126.8, 126.1, 125.4, 119.6, 119.5, 73.3, 60.3, 48.2, 31.9, 21.9 ppm. IR (film): v = 3298, 3061, 2935, 1650, 1446, 1382, 1178, 991, 727, 698 cm<sup>-1</sup>. HRMS-ESI calculated for  $C_{24}H_{25}N_2O_2$  [M + H] 373.1916, found 373.1907.

(S)-N-Methoxy-N-methyl-3-phenyl-2-[(9-phenyl-9H-fluoren-9-yl)amino]propanamide (11b): Compound 10b (804 mg, 2 mmol, 100 mol-%) and HN(OMe)Me·HCl (234 mg, 2.4 mmol, 120 mol-%) were suspended in THF (2.4 mL). The suspension was cooled to 0 °C and *i*PrMgCl (2.4 mL, 4.8 mmol, 2 M in Et<sub>2</sub>O, 240 mol-%) was added drop wise via a dropping funnel. The reaction was stirred at 0 °C for 1 h and at room temp. for 3 h. The reaction mixture was cooled down to 0 °C and HN(OMe)Me·HCl (234 mg, 2.4 mmol, 120 mol-%) and *i*PrMgCl (2.4 mL, 4.8 mmol, 2 M in Et<sub>2</sub>O, 240 mol-%) were added. The reaction mixture was stirred at room temp. for 3 h. The reaction was quenched with citric acid

(10 mL, 5 wt.-%) and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O ( $2 \times 10$  mL). The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give a yellow foam. The crude product was purified by silica gel column chromatography (Hex/EtOAc, 5:1) to give 11b: yield 70% (700 mg);  $R_{\rm f}$  0.27 (Hex/EtOAc, 5:1; visualized by UV); white foam.  $[a]_D$  (S) = -224.4 (c = 1.1 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +225.0 (c = 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta = 7.59$  (d, J = 7.3 Hz, 1 H), 7.51 (d, J = 7.5 Hz, 1 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), 2.47–2.71 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 176.0, 149.2, 148.8, 145.2, 141.3, 139.2, 138.8, 130.1, 128.0, 128.0, 127.9, 127.8, 127.5, 127.1, 126.9, 126.0, 126.0, 125.3, 119.3, 118.9, 73.0, 60.2, 54.4, 41.4, 31.8 ppm. IR (film): v = 3296, 3061, 3027, 2936, 1655, 1449, 1178, 732, 698 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>30</sub>H<sub>28</sub>N<sub>2</sub>NaO<sub>2</sub> [M + Na] 471.2048, found 471.2048.

(S)-Methyl 3-(9-Phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxylate (10c): Compound 9c (1.55 g, 10 mmol, 100 mol-%) was dissolved in CH2Cl2 (30 mL) in a Morton flask. TMSCl (3.2 mL, 25 mmol, 250 mol-%) was added and the solution was cooled to 0 °C. Et<sub>3</sub>N (4.9 mL, 35 mmol, 350 mol-%) was added dropwise. The reaction mixture was refluxed for 1 h and cooled to 0 °C. MeOH (0.75 mL, 18.5 mmol, 185 mol-%) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added and the reaction mixture was warmed to room temp. and stirred for 1 h. Et<sub>3</sub>N (1.4 mL, 10 mmol, 100 mol-%),  $Pb(NO_3)_2$  (3.00 g, 9 mmol, 90 mol-%) and Pf-Br (4.01 g, 12.5 mmol, 125 mol-%) were added. The suspension was stirred vigorously for 72 h. The suspension was filtered through a pad of celite which was subsequently washed with CHCl<sub>3</sub> until no UV chromophore ( $\lambda = 254$  nm) in the filtrate was detected. Solvents were evaporated. Citric acid (40 mL, 10 wt.-% in MeOH) was added and the solution was stirred for 1 h after which the solvents were evaporated. The residue was dissolved in EtOAc (80 mL). The solution was washed with  $H_2O$  (40 mL) and the aqueous phase was extracted with EtOAc ( $2 \times 60 \text{ mL}$ ). The combined organic layers were washed with brine, dried with Na2SO4 and filtered. The solvents were evaporated to yield a brown syrup. The crude could be purified by flash chromatography (Hex/EtOAc, 1:1), to give the intermediate Pf-protected serine methyl ester, or used in the next step without further purification: yield 76% (2.71 g);  $R_{\rm f}$ 0.17 (Hex/EtOAc, 3:1; visualized by UV); white solid.  $[a]_{D} = -321.9$  $(c = 1.0 \text{ in } CH_2Cl_2)$ . <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.66-7.72$ (m, 2 H), 7.31-7.42 (m, 5 H), 7.21-7.28 (m, 6 H), 3.44 (m, 1 H), 3.42 (s, 3 H), 3.31 (br. s, 1 H), 3.27 (m, 1 H), 2.77 (dd, J = 5.7, 4.8 Hz, 1 H), 2.67 (br. t, J = 6.3 Hz, 1 H) ppm. <sup>13</sup>C NMR  $(100 \text{ MHz}, \text{ CDCl}_3)$ :  $\delta = 174.2, 148.7, 148.4, 144.0, 141.2, 139.9,$ 128.7, 128.6, 128.4, 128.3, 127.7, 127.4, 125.9, 125.7, 125.0, 120.2, 120.0, 72.6, 63.8, 57.1, 52.1 ppm. IR (film):  $\tilde{v} = 3462$ , 3310, 3060, 2951, 1730, 1600, 1447, 1334, 1175, 1052 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>23</sub>H<sub>21</sub>NNaO<sub>3</sub> [M + Na] 382.1419, found 382.1414. The white solid (2.58 g, 7.2 mmol, 100 mol-%) was dissolved in THF (72 mL). pTsOH·H<sub>2</sub>O (83 mg, 0.43 mmol, 6 mol-%) and CH<sub>2</sub>O (8.1 mL, 108 mmol, aq. 37 wt.-%, 1500 mol-%) were added and the solution was stirred at room temp. for 20 h. The reaction mixture was washed with satd. aq. NaHCO<sub>3</sub> ( $2 \times 50$  mL) and brine. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated to give 10c: yield 99% (2.69 g);  $R_{\rm f}$  0.54 (Hex/ EtOAc, 3:1; visualized by UV); white foam.  $[a]_D = +258.0$  (c = 1.0in CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.70 (m, 1 H), 7.63 (m, 1 H), 7.55 (m, 1 H), 7.41-7.51 (m, 4 H), 7.16-7.34 (m, 6 H), 4.93 (d, J = 6.4 Hz, 1 H), 4.74 (d, J = 6.4 Hz, 1 H), 3.62 (d, J =7.5 Hz, 1 H), 3.62 (d, J = 6.3 Hz, 1 H), 3.56 (s, 3 H), 3.30 (dd, J = 7.5, 6.2 Hz, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.5,

148.7, 146.7, 143.9, 141.5, 139.1, 128.9, 128.5, 128.0, 127.8, 127.5, 127.1, 126.5, 125.8, 119.8, 119.7, 85.0, 77.1, 69.0, 60.8, 51.9 ppm. IR (film):  $\tilde{\nu}$  = 3063, 2952, 2870, 1746, 1450, 1173, 723, 646 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>24</sub>H<sub>22</sub>NO<sub>3</sub> [M + H] 372.1600, found 372.1614.

(S)-N-Methoxy-N-methyl-3-(9-phenyl-9H-fluoren-9-yl)oxazolidine-4-carboxamide (11c): Compound 10c (2.13 g, 5.7 mmol, 100 mol-%) and HN(OMe)Me·HCl (670 mg, 6.9 mmol, 120 mol-%) were suspended in THF (7 mL). The suspension was cooled to 0 °C and *i*PrMgCl (6.9 mL, 13.8 mmol, 2 м in Et<sub>2</sub>O, 240 mol-%) was added dropwise via a dropping funnel. The solution was stirred at 0 °C for 1 h. The reaction was quenched with citric acid (20 mL, 5 wt.-%) and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O. Combined organic layers were washed with brine, dried with  $Na_2SO_4$  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 reaction sequence from 9c to 11c could be performed without any intermediate purification. The sequence was scaled up to give 11c after recrystallization from EtOAc/isooctane: yield 56% (22.8 g) over three steps;  $R_f 0.11$  (Hex/EtOAc, 3:1; visualized by UV); white translucent needles; m.p. 179–182 °C dec.  $[a]_D = +176.0$  (c = 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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), 2.88 (br. s, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 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):  $\tilde{v} = 3057, 2966, 2938, 2972, 1660, 1449, 1176, 1021, 889, 735,$ 701 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>25</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M + H] 401.1865, found 401.1869.

(S)-1-Morpholino-2-[(9-phenyl-9H-fluoren-9-yl)amino]propan-1-one (17a): A round bottomed 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, 2 M in Et<sub>2</sub>O, 150 mol-%) dropwise. The solution was stirred for 2 h. Citric acid (20 mL, 5 wt.-%) was added and the resulting suspension was warmed to room temp. H<sub>2</sub>O (5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added and the phases separated. The aqueous phase was extracted with  $CH_2Cl_2$  (2 × 100 mL) and the combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated. The pale yellow solid was subjected to silica gel chromatography (Hex/ EtOAc, 1:1) to give 17a: yield 93% (1.488 g);  $R_{\rm f}$  0.15 (Hex/EtOAc, 3:1; visualized by UV); white solid; m.p. 189–195 °C dec.  $[a]_D$  (S) = -256.2 (c = 0.86 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +252.9 (c 0.58 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.68 (m, 2 H), 7.16–7.44 (m, 11 H), 3.74 (br. s, 1 H), 3.44 (m, 1 H), 3.22-3.32 (m, 4 H), 2.98 (m, 1 H), 2.80 (m, 2 H), 2.49 (ddd, J = 13.3, 6.26, 2.96 Hz, 1 H), 1.02 (d, J = 7.0 Hz, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 175.2, 150.1, 149.3, 144.5, 141.0, 139.7, 128.2, 128.2, 128.1, 127.5, 127.0, 126.8, 126.0, 125.3, 119.6, 119.5, 73.2, 66.5, 65.9, 47.0, 44.9, 41.9, 21.8 ppm. IR (film):  $\tilde{v} = 3286, 2964, 2921, 2859, 1631, 1427, 1114,$ 1028, 733, 702 cm  $^{-1}$ . HRMS-ESI calculated for  $C_{26}H_{27}N_2O_2$  [M + H] 399.2073, found 399.2072.

(*S*)-1-Morpholino-3-phenyl-2-[(9-phenyl-9*H*-fluoren-9-yl)amino]propan-1-one (17b): Prepared in the same manner as 17a. Reaction time: 20 h. Product purified by silica gel chromatography (Hex/ EtOAc, 7:3): yield 80% (382 mg);  $R_f$  0.23 (Hex/EtOAc, 3:1, visualized by UV); white solid; m.p. 150–152 °C.  $[a]_D = -220.8$  (c = 0.86in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.66$  (m, 1 H), 7.62 (m, 1 H), 7.08–7.39 (m, 14 H), 6.89 (m, 2 H), 3.61 (br. d, J = 9.0 Hz, 1 H), 3.34 (ddd, J = 13.4, 5.4, 3.0 Hz, 1 H), 3.24 (ddd, J = 11.3, 5.5, 3.3 Hz, 1 H), 3.12 (ddd, J = 11.3, 7.7, 3.1 Hz), 2.69–2.93 (m, 5 H), 2.35 (ddd, J = 11.3, 7.5, 3.4 Hz, 1 H), 2.04 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 173.9$ , 149.5, 149.4, 144.6, 141.0, 139.4, 137.8, 129.6, 128.3, 128.2, 128.2, 128.1, 127.5, 127.1, 126.6, 126.4, 126.0, 125.3, 119.5, 119.5, 73.0, 66.2, 65.3, 53.0, 44.7, 43.1, 41.6 ppm. IR (film):  $\tilde{v} = 3300$ , 3061, 3024, 2964, 2922, 2858, 1632, 1423, 1113, 697, 646 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>32</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub> [M + H] 475.2386, found 475.2396.

(S)-tert-Butyl (2-{2-Oxo-3-[(9-phenyl-9H-fluoren-9-yl)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. NH<sub>4</sub>Cl (25 mL) and H<sub>2</sub>O (5 mL) and taken to room temp. The reaction mixture was extracted with Et<sub>2</sub>O ( $3 \times 30$  mL). The combined organic phases were washed with brine (50 mL) dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated affording a pale yellow syrup. Silica gel chromatography (Hex/EtOAc, 95:5 followed by Hex/ EtOAc, 90:10) gave 13a: yield 93% (2.421 g); Rf 0.65 (Hex/EtOAc, 3:1; visualized by UV or vanillin stain); white foam.  $[a]_D(S) =$ -148.0 (c = 1.2 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +143.6 (c 0.57 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 213.6, 153.5, 149.6, 149.1, 144.2, 140.9, 140.0, 137.1, 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):  $\tilde{v} = 3326$ , 3062, 2977, 2930, 1710, 1589, 1515, 1449, 1234, 1153, 1047, 1025, 731, 699 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>34</sub>H<sub>35</sub>N<sub>2</sub>O<sub>3</sub> [M + H] 519.2648, found 519.2642.

(S)-tert-Butyl (2-{2-Oxo-4-phenyl-3-[(9-phenyl-9H-fluoren-9-yl)aminolbutyl}phenyl)carbamate (13b): To a solution of 12 (1.55 g, 7.5 mmol, 250 mol-%) in dry THF (22.5 mL) was added sBuLi (11.5 mL, 15 mmol, 1.3 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 cooled to -41 °C. 11b (1.35 g, 3 mmol, 100 mol-%) dissolved in THF (7.5 mL) was added to the reaction mixture. After 1 h the reaction was quenched with satd. NH<sub>4</sub>Cl (30 mL) and H<sub>2</sub>O (5 mL) and taken to room temp. The reaction mixture was extracted with Et<sub>2</sub>O ( $3 \times 30$  mL). The combined organic phases were washed with brine (60 mL) dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated affording a pale yellow syrup. Silica gel chromatography (Hex/EtOAc, 9:1) gave 13b: yield 77% (1.38 g);  $R_{\rm f}$ 0.62 (Hex/EtOAc, 3:1; visualized by UV or by vanillin stain); white foam; Chiral HPLC analysis [Chiralpak IB, 99:1 Hexane/EtOH, 1 mL/min, retention times: (*R*)-enantiomer = 8.0 min, (*S*)-enantiomer = 8.9 min], (S) >99% ee, (R) = 99% ee.  $[a]_D$  (S) = -146.7 (c = 1.2 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +148.9 (c 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.65 (m, 3 H), 6.85–7.38 (m, 18 H), 6.64 (m, 1 H), 6.48 (m, 1 H), 3.20 (br. s, 1 H), 2.99 (d, J = 15.9 Hz, 1 H), 2.93 (br. m, 1 H), 2.73 (d, J = 15.9 Hz, 1 H), 2.57 (dd, J = 13.8, 5.9 Hz, 1 H), 2.51 (dd, *J* = 13.6, 8.3 Hz, 1 H), 1.53 (s, 9 H) ppm. <sup>13</sup>C NMR

(100 MHz, CDCl<sub>3</sub>):  $\delta$  = 213.2, 153.4, 149.0, 148.8, 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, 127.2, 126.6, 126.5, 126.0, 125.1, 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):  $\tilde{v}$  = 3311, 3062, 3027, 2978, 2930, 1716, 1450, 1155, 732, 699 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>40</sub>H<sub>39</sub>N<sub>2</sub>O<sub>3</sub> [M + H] 595.2961, found 595.2967.

(S)-tert-Butyl(2-{2-oxo-2-[3-(9-phenyl-9H-fluoren-9-yl)oxazolidin-4yl]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. 11c (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. NH<sub>4</sub>Cl (60 mL), taken to room temp. and H<sub>2</sub>O (50 mL) was added to dissolve the white precipitate. The aqueous layer was extracted with EtOAc ( $2 \times 150 \text{ mL}$ ) and the combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give a white solid. The crude product was triturated with  $Et_2O$  to give 13c: yield 90% (12.3 g); R<sub>f</sub> 0.43 (Hex/EtOAc, 3:1; visualized by UV or by vanillin stain); white powder; m.p. 175–177 °C.  $[a]_{D}$  = +139.6 (c = 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 =15.6 Hz, 1 H), 3.62 (m, 1 H), 3.30 (m, 2 H), 1.52 (s, 9 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 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, 128.0, 127.7, 127.0, 126.9, 125.8, 125.7, 124.3, 123.9, 120.1, 119.8, 85.0, 80.3, 77.2, 67.5, 66.2, 43.3, 28.4 ppm. IR (film):  $\tilde{v} = 3341$ , 3062, 2978, 2870, 1718, 1515, 1450, 1236, 1156, 734 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>35</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub> [M + H] 547.2597, found 547.2597.

(S)-N-[1-(1H-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 м 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. NaHCO<sub>3</sub> (300 mL), CAUTION! vigorous gas evolution, and the aqueous layer was extracted with  $CH_2Cl_2$  (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); Rf 0.47 (Hex/EtOAc, 5:1; visualized by UV or by ninhydrin staining); white foam.  $[a]_D$  (S) = -147.2 (c = 1.0 in CH<sub>2</sub>Cl<sub>2</sub>), (R) +145.7 (c 0.67 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.05 (br. s, 1 H), 7.74 (m, 1 H), 7.64 (m, 1 H), 7.16– 7.46 (m, 11 H), 7.04–7.10 (m, 2 H), 6.99 (m, 1 H), 6.88 (m, 1 H), 5.88 (m, 1 H), 3.47 (q, J = 6.8 Hz, 1 H), 2.32 (br. s, 1 H) 1.17 (d, J = 6.8 Hz, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 150.2$ , 149.0, 144.9, 144.1, 141.0, 139.9, 135.1, 128.7, 128.4, 128.3, 128.1, 127.9, 127.5, 127.2, 126.0, 125.1, 124.8, 120.9, 120.0, 119.9, 119.9, 119.3, 110.5, 97.7, 73.1, 46.8, 24.0 ppm. IR (film): v = 3429, 3057, 2966, 2867, 1616, 1599, 1449, 1295, 1156, 732, 699 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>29</sub>H<sub>25</sub>N<sub>2</sub> [M + H] 401.2018, found 401.2014.

(S)-N-[1-(1H-Indol-2-yl)-2-phenylethyl]-9-phenyl-9H-fluoren-9amine (18b): Compound 18b was prepared using the same procedure as compound 18a, giving, after work up 18b as a yellow solid with acceptable purity: yield 99% (710 mg);  $R_f$  0.38 (Hex/ EtOAc, 9:1; visualized by UV or by ninhydrin staining); An X-ray structure was obtained of **18b**. Crystals obtained by recrystallization from EtOAc/Hex: white translucent crystals; m.p. 172–174 °C. [a]<sub>D</sub> = -127.9 (c = 1.1 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.86 (br. s, 1 H), 7.70 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.7 Hz, 1 H), 7.31–7.38 (m, 4 H), 7.15–7.21 (m, 7 H), 6.09–7.09 (m, 4 H), 6.89 (m, 2 H), 6.74 (d, J = 7.7 Hz, 1 H), 6.57 (d, J = 7.6 Hz, 1 H), 6.50 (m, 1 H), 5.73 (m, 1 H), 3.40 (dd, J = 8.0, 6.1 Hz, 1 H), 2.88 (dd, J = 13.5, 6.1 Hz, 1 H), 2.84 (dd, J = 13.5, 8.0 Hz, 1 H), 2.62 (br. s, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 148.9, 148.4, 144.8, 142.6, 141.1, 139.5, 138.1, 135.0, 129.4, 128.7, 128.5, 128.3, 128.1, 127.8, 127.7, 127.1, 127.0, 126.5, 126.0, 125.3, 124.7, 120.8, 119.9, 119.4, 119.4, 119.1, 110.5, 98.6, 73.0, 53.1, 44.8 ppm. IR (film):  $\tilde{v}$  = 3433, 3312, 3058, 3026, 2922, 2857, 1454, 1287, 729, 698 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>35</sub>H<sub>29</sub>N<sub>2</sub> [M + H] 477.2331, found 477.2325.

(R)-2-(1H-Indol-2-yl)-2-[(9-phenyl-9H-fluoren-9-yl)amino]ethanol (18c): Compound 13c (1.09 g, 2 mmol, 100 mol-%) was dissolved in MeOH/CH2Cl2 (1:1, 20 mL) and the resulting solution was cooled to 0 °C. H<sub>2</sub>SO<sub>4</sub> (3.4 mL, 20 mmol, 6 м in EtOH, 1000 mol-%) was added and the reaction mixture was stirred at 0 °C for 1 h and at room temp. for 1 h. NH2OH·HCl (1.40 g, 20 mmol, 1000 mol-%) was added and the reaction was stirred at room temp. for 1.5 h. The reaction mixture was poured very carefully to satd. NaHCO<sub>3</sub> (60 mL), CAUTION! vigorous gas evolution, and the aqueous layer was extracted with  $CH_2Cl_2$  (2 × 50 mL). Combined organic layers were dried with Na2SO4, filtered and the solvent were evaporated. The residual was dissolved in MeOH (20 mL) and NaOH (5.0 mL, 10 mmol, aq. 5 M, 500 mol-%) was added. The reaction mixture was refluxed for 0.5 h after which H<sub>2</sub>O (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (40 mL) were added. The layers were separated and the aqueous layer was extracted with  $CH_2Cl_2$  (2 × 40 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated. The crude product was purified by trituration from MeOH to give 18c: yield 75% (630 mg) over two steps;  $R_{\rm f}$  0.22 (Hex/EtOAc, 3:1; visualized by UV or by ninhydrin staining); white powder; m.p. 183–186 °C dec.  $[a]_D = -229.6$  (c = 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (br. s, 1 H), 7.73 (m, 2 H), 7.38–7.44 (m, 5 H), 7.19–7.34 (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 (br. m, 1 H), 2.55 (br. m, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, [D<sub>6</sub>]acetone):  $\delta$  = 150.9, 150.1, 146.8, 142.2, 142.1, 140.5, 136.9, 129.6, 129.2, 128.9, 128.6, 128.4, 127.8, 127.6, 127.1, 126.3, 126.0, 121.0, 120.6, 120.3, 120.2, 119.3, 111.7, 99.6, 74.1, 66.7, 54.7 ppm. IR (film):  $\tilde{v} = 3548$ , 3425, 3330, 3057, 2948, 2875, 1449, 733, 699 cm<sup>-1</sup>. HRMS-ESI calculated for  $C_{29}H_{24}N_2NaO$  [M + Na] 439.1786, found 439.1788.

(S)-2-[1-(9-Phenyl-9*H*-fluoren-9-yl)pyrrolidin-2-yl]-1*H*-indole (18d): Compound 18d was prepared using the same procedure as compound 18a, giving after work up 18d: yield 99% (462 mg);  $R_f$  0.83 (Hex/EtOAc, 5:1, visualized by UV or by ninhydrin staining); yellow solid; m.p. 156–160 °C.  $[a]_D = -49.4$  (c = 1.2 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.12$  (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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 149.0$ , 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, 120.5, 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):  $\tilde{v} = 3448$ , 3056, 2965, 2868, 1449, 1285, 736, 702 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>31</sub>H<sub>27</sub>N<sub>2</sub> [M + H] 427.2174, found 427.2174.

(S)-1-(1*H*-Indol-2-yl)ethanamine (22a): Compound 18a (400 mg, 1 mmol, 100 mol-%) was dissolved in MeOH (8 mL) and the re-

sulting 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 and the reaction was stirred for 18 h at room temp. The reaction mixture was filtered through a pad of celite and the solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1 M) and Et<sub>2</sub>O (100 mL) and the phases were separated. The organic phase was extracted with HCl (50 mL, aq. 1 M). The combined aqueous phases were basified with NaOH (aq. 1 M) until pH >8. The aqueous phase was extracted with  $Et_2O$  (3 × 100 mL). Combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give 22a: yield 99% (160 mg);  $R_{\rm f}$  0.19 (CH<sub>2</sub>Cl<sub>2</sub>/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<sub>2</sub>Cl<sub>2</sub>), (R) -3.9 (c 1.1 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.52 (br. s, 1 H), 7.55 (m, 1 H), 7.34 (m, 1 H), 7.14 (ddd, J = 8.1, 7.1, 1.1 Hz, 1 H), 7.07 (ddd, 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.1, 135.6, 128.5, 121.4, 120.1, 119.6, 110.7, 97.7, 45.3, 24.9 ppm. IR (film):  $\tilde{v} = 3600, 3398$ , 3150-3350, 3050, 2969, 2869, 1587, 1457, 1341, 1302, 943, 789, 751 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>10</sub>H<sub>13</sub>N<sub>2</sub> [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 (16 mL) and degassed with argon. Pd/C (46 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 solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1 M) and Et<sub>2</sub>O (100 mL). The phases were separated and the organic phase was extracted with HCl (50 mL, aq. 1 M). The combined aqueous phases were basified with NaOH (aq. 1 M) until pH >8. The aqueous phase was extracted with  $CH_2Cl_2$  (3 × 100 mL). Combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give **22b**: yield 87% (180 mg);  $R_{\rm f}$ 0.43 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1; visualized by UV or by ninhydrin staining); orange solid; m.p. 66–71 °C.  $[a]_D = +20.1$  (c = 0.9 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.91 (br. s, 1 H), 7.55 (m, 1 H), 7.05–7.33 (m, 8 H), 6.34 (m, 1 H), 4.35 (dd, J = 9.1, 4.6 Hz, 1 H), 3.23 (dd, J = 13.4, 4.6 Hz, 1 H), 2.85 (dd, J = 13.4, 9.2 Hz, 1 H), 1.96 (br. m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.1, 138.2, 135.6, 129.3, 128.6, 128.4, 126.7, 121.4, 120.2, 119.6, 110.8, 98.5, 51.3, 44.9 ppm. IR (film):  $\tilde{v} = 3403$ , 3345, 3281, 3186, 3058, 2919, 2854, 1584, 1455, 1289, 750, 699 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub> [M + H] 237.1392, found 237.1391.

(R)-2-Amino-2-(1H-indol-2-yl)ethanol (22c): Compound 18c (1.67 g, 4 mmol, 100 mol-%) was dissolved in AcOH (32 mL) and degassed with argon. Pd/C (180 mg, 0.2 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 solvents were evaporated. The residue was partitioned between HCl (50 mL, aq. 1 M) and Et<sub>2</sub>O (100 mL). The phases were separated and the organic phase was extracted with HCl (25 mL, aq. 1 M). The combined aqueous phases were basified with NaOH (aq. 1 M) until pH > 8. The aqueous phase was extracted with CHCl<sub>3</sub>/2-propanol (4:1,  $5 \times$ 200 mL). Combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvents were evaporated to give 22c: yield 95% (670 mg);  $R_f$  0.05 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1; visualized by UV or by ninhydrin staining); light grey solid; m.p. 96–98 °C.  $[a]_D = -21.7$  (c = 1.1 in MeOH). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 7.45 (m, 1 H), 7.30 (m, 1 H), 7.04 (ddd, J = 8.1, 7.0, 1.3 Hz, 1 H), 6.95 (ddd, J = 8.2, 7.0, 0.9 Hz, 1 H), 6.35 (m, 1 H), 4.13 (dd, J = 7.2, 4.7 Hz, 1 H), 3.85 (dd, J = 10.8, 4.8 Hz, 1 H), 3.70 (dd, J = 10.8, 7.3 Hz, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD):  $\delta = 141.2$ , 137.8, 129.7, 122.0, 120.9, 120.1, 111.8, 99.5, 67.7, 53.0 ppm. IR (film):  $\tilde{v} = 3392$ , 3347, 3284, 3082, 3055, 2918, 2869, 1587, 1456, 1342, 1289, 1035, 792, 743 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>O [M + H] 177.1028, found 177.1027.

(S)-2-(Pyrrolidin-2-yl)-1H-indole (22d): Compound 18d (427 mg, 1 mmol, 100 mol-%) was suspended together with NH<sub>4</sub>H<sub>2</sub>PO<sub>2</sub> (498 mg, 6 mmol, 600 mol-%) in EtOH (10 mL). Pd/C (53 mg, 0.05 mmol, 10 wt.-%, 5 mol-%) was added. The reaction mixture was refluxed for 1.5 h after which it was cooled to room temp. The suspension was filtered through a pad of celite and eluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and MeOH (30 mL). The solvents were evaporated and the crude mixture portioned between Et<sub>2</sub>O (50 mL) and HCl (30 mL, aq., 1 M). The aqueous phase was washed once with Et<sub>2</sub>O (10 mL). The aqueous phase was basified with NaOH (aq., 1 M), until pH = 12, and extracted with  $CH_2Cl_2$  (3 × 20 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents were evaporated. One portion of hexane (10 mL) was added and the solvent was evaporated to give 22d: yield 86% (160 mg); R<sub>f</sub> 0.19 [CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (aq., 25 wt.-%), 90:10:1; visualized by UV or by ninhydrin staining]; beige solid; m.p. 105-107 °C.  $[a]_{D} = -26.6$  (c = 1.6 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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. <sup>13</sup>C NMR  $(100 \text{ MHz}, \text{ CDCl}_3)$ :  $\delta = 141.9, 135.7, 128.7, 121.1, 120.0, 119.4,$ 110.7, 98.0, 56.2, 46.7, 32.6, 25.6 ppm. IR (film):  $\tilde{v} = 3398$ , 2966, 2873, 1455, 1417, 1303, 1059, 784, 728, 646 cm<sup>-1</sup>. HRMS-ESI calculated for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub> [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 <sup>1</sup>H and <sup>13</sup>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<sub>2</sub>; 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 regarding the molecular mechanics and DFT calculations. CSC is kindly acknowledged for providing the license to Maestro 9.4.

- Exemplified by: a) K. L. Rinehart, J. Kobayashi, G. C. Harbour, R. G. Hughes Jr., S. A. Mizsak, T. A. Scahill, J. Am. Chem. Soc. 1984, 106, 1524–1526; b) K. L. Rinehart Jr., J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield, F. Lafargue, J. Am. Chem. Soc. 1987, 109, 3378–3387.
- [2] Exemplified by: a) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russel, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science* 2010, *329*, 1175–1180; b) S. T. S. Chan, A. N. Pearce, M. J. Page, M. Kaiser, B. R. Copp, *J. Nat. Prod.* 2011, *74*, 1972–1979.
- [3] Exemplified by: a) S. Hotha, J. C. Yarrow, J. G. Yang, S. Garrett, K. V. Renduchintala, T. U. Mayer, T. M. Kapoor, *Angew. Chem. Int. Ed.* 2003, 42, 2379–2382; *Angew. Chem.* 2003, 115, 2481; b) N. Sunder-Plassmann, V. Sarli, M. Gartner, M. Utz, J. Seiler, S. Huemmer, T. U. Mayer, T. Surrey, A. Giannis, *Bioorg. Med. Chem.* 2005, 13, 6094–6111.
- [4] For a review regarding pharmacological activities of THβCs, see: A. E. Laine, C. Lood, A. M. P. Koskinen, *Molecules* 2014, 19, 1544–1567.
- [5] For a review regarding Pf-protecting group chemistry, see: E. J. Karppanen, A. M. P. Koskinen, *Molecules* 2010, 15, 6515– 6547.
- [6] a) Z. Votický, E. Grossmann, P. Potier, Collec. Czech. Chem. Commun. 1977, 42, 548–552; b) J. Bosch, M.-L. Bennasar, E. Zulaica, M. Feliz, Tetrahedron Lett. 1984, 25, 3119–3122.
- [7] a) M. Arnaud, C. R. Hebd. Acad. Sci. 1881, 93, 593–595; b)
   G. Grethe, H. L. Lee, M. R. Uskoković, Helv. Chim. Acta 1976, 59, 2268–2272.
- [8] M. H. Brillanceau, C. Kan-Fan, S. K. Kan, H.-P. Husson, *Tetrahedron Lett.* 1984, 25, 2767–2770.
- [9] S. Matsunaga, R. Kishi, K. Otsuka, M. J. Fujita, M. Oikawa, R. Sakai, Org. Lett. 2014, 16, 3090–3093.
- [10] A. Kessler, H. Faure, C. Petrel, M. Ruat, P. Dauban, R. H. Dodd, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3345–3349.
- [11] A. Pictet, T. Spengler, Ber. Dtsch. Chem. Ges. 1911, 44, 2030– 2036.
- [12] A. Bischler, B. Napieralski, Ber. Dtsch. Chem. Ges. 1893, 26, 1903–1908.
- [13] R. S. Garigipati, M. E. Sorenson, K. F. Erhard, J. L. Adams, *Tetrahedron Lett.* **1993**, *34*, 5537–5540.
- [14] D. Enders, G. D. Signore, *Tetrahedron: Asymmetry* 2004, 15, 747–751.
- [15] L. Cheng, L. Liu, Y. Sui, D. Wang, Y.-J. Chen, *Tetrahedron: Asymmetry* 2007, 18, 1833–1843.
- [16] R. C. Larock, E. K. Yum, M. D. Refvik, J. Org. Chem. 1998, 63, 7652–7662.
- [17] F. Messina, M. Botta, F. Corelli, C. Villani, *Tetrahedron: Asym*metry 2000, 11, 1681–1685.
- [18] K. Goswami, I. Duttagupta, S. Sinha, J. Org. Chem. 2012, 77, 7081–7085.
- [19] Q. Kang, X.-J. Zheng, S.-L. You, Chem. Eur. J. 2008, 14, 3539– 3542.
- [20] Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, J. Org. Chem. 2009, 74, 7052–7058.
- [21] B. D. Christie, H. Rapoport, J. Org. Chem. 1985, 50, 1239– 1246.
- [22] W. D. Lubell, H. Rapoport, J. Am. Chem. Soc. 1987, 109, 236– 239.

- [23] C. S. Lood, A. M. P. Koskinen, Eur. J. Org. Chem. 2014, 11, 2357–2364.
- [24] For a seminal publication of the use of Weinreb amides in the synthesis of ketones, see: S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* 1981, 22, 3815–3818.
- [25] T. F. Jamison, H. Rapoport, Org. Synth. 1993, 71, 226-235.
- [26] W. D. Lubell, H. J. Rapoport, J. Org. Chem. 1989, 54, 3824-3831
- [27] J. E. Dettwiler, L. Bélec, W. D. Lubell, Can. J. Chem. 2005, 83, 793–800.
- [28] R. D. Clarke, J. M. Muchowski, L. E. Fisher, L. A. Flippin, D. B. Repke, M. Souchet, *Synthesis* 1991, 871–878.
- [29] For selected examples, see: a) S. L. Graham, T. H. Scholz, *Tetrahedron Lett.* 1990, *31*, 6269–6272; b) G. E. Keck, S. F. McHardy, J. A. Murry, *Tetrahedron Lett.* 1993, *34*, 6215–6218; c) S. Hirner, D. K. Kirchner, P. Somfai, *Eur. J. Org. Chem.* 2008, 5583–5589; d) O. Labeeuw, P. Phansavath, J.-P. Genêt, *Tetrahedron Lett.* 2004, *45*, 7107–7110.
- [30] W. D. Lubell, T. F. Jamison, H. Rapoport, J. Org. Chem. 1990, 55, 3511–3522.
- [31] For the use of morphiline amides as ketone precursors, see: R. Martin, P. Romea, C. Tey, F. Urpí, J. Vilarrasa, *Synlett* 1997, 12, 1414–1416.
- [32] R. Bolton, N. B. Chapman, J. Shorter, J. Chem. Soc. 1964, 1895–1906.
- [33] V. Banphavichit, W. Bhanthumnavin, T. Vilaivan, *Tetrahedron* 2007, 63, 8727–8734.
- [34] I. Hassan, E. R. Marinelli, L.-C. C. Lin, F. W. Fowler, A. B. Levy, J. Org. Chem. 1981, 46, 157–164.
- [35] J. A. Campbell, W. K. Lee, H. Rapoport, J. Org. Chem. 1995, 60, 4602–4616.
- [36] For a seminal publication on NaBH(OAc)<sub>3</sub> in reductive aminations, see: A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849– 3862.
- [37] M. M. Paz, F. J. Sardina, J. Org. Chem. 1993, 58, 6990-6995.
- [38] J. M. Humphrey, R. J. Bridges, J. A. Hart, A. R. Chamberlin, J. Org. Chem. 1994, 59, 2467–2472.
- [39] S. J. K. Sauerland, J. A. Castillo-Meléndez, K. Nättinen, K. Rissanen, A. M. P. Koskinen, *Synthesis* 2010, 757–762.
- [40] N. L. Allinger, J. Am. Chem. Soc. 1977, 99, 8127–8134.
- [41] N. L. Allinger, Y. H. Yuh, J.-H. Lii, J. Am. Chem. Soc. 1989, 111, 8551–8566.
- [42] T. A. Halgren, J. Comput. Chem. 1996, 17, 490-519.
- [43] For a seminal publication on the OPLS force field, see: W. L. Joergensen, J. Tirado-Rives, J. Am. Chem. Soc. 1988, 110, 1657–1666.
- [44] Evaluated by the quality of stretch, bend and torsional parameters generated by the force fields in MacroModel 10.0.
- [45] Y. Zhao, D. G. Truhlar, Acc. Chem. Res. 2008, 41, 157-167.
- [46] A. D. Becke, J. Chem. Phys. 1993, 98, 5648.

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- [47] M. K. Ghorai, K. Ghosh, A. K. Yadav, Y. Nanaji, S. Halder, M. Sayyad, J. Org. Chem. 2013, 78, 2311–2326.
- [48] J. M. Muchowski, M. C. Venuti, J. Org. Chem. 1980, 45, 4798– 4801.
- [49] M. R. Paleo, M. I. Calaza, F. J. Sardina, J. Org. Chem. 1997, 62, 6862–6869.
- [50] A. F. Burchat, J. M. Chong, N. Nielsen, J. Organomet. Chem. 1997, 542, 281–283.
- [51] G. M. Sheldrick, Acta Crystallogr., Sect. A 2008, 64, 112-122.
- [52] H. D. Flack, Acta Crystallogr., Sect. A 1983, 39, 876–881.
- [53] S. Parsons, H. D. Flack, Acta Crystallogr., Sect. A 2004, 60,
- [54] R. W. W. Hooft, L. H. Straver, A. L. Spek, J. Appl. Crystallogr. 2008, 41, 96–103.

Received: March 24, 2015 Published Online: May 1, 2015