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Asymmetric synthesis of two new conformationally constrained lysine derivatives

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Abstract—The asymmetric synthesis of the conformationally constrained L- and D-lysine derivatives methyl (1*S*,8*S*)-1-amino-8-tert-butoxycarbonylamino-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate (**4**) and methyl (1*R*,8*S*)-1-amino-8-tert-butoxycarbonylamino-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate (**5**), respectively are described. Application of the Bucherer hydantoin synthesis to the carbonyl group of 2′,3′,4′,5′,6′,7′-hexahydrospiro[1,3-ethylenedithiole-2,1′-anthracen]-8′-one (**18**), which was prepared from 1,8-dichloroanthraquinone (**14**) in nine steps and the deprotection of the masked second ketone of **18** yields *rac*-21. The latter is the precursor for a novel asymmetric reductive amination protocol using (*R*)-phenylglycinol as a chiral amino auxiliary and $NaBH(OAc)_3$ as a reducing agent. Using this procedure, the asymmetric reductive amination of α-tetralone derivatives and indanone proceeds with >95% de. Lower diastereomeric excesses are observed for benzosuberone (16.7% de) and acetophenone (27.3% de). *rac*-21 gave (1′*S*,8′*S*,1(*R*)-**25a** (38% yield) and (1′*R*,8′*S*,1(*R*)-**25b** (44.5% yield) with greater than 52 and 78% de, respectively. Cleavage of the amino auxiliary of (1′*S*,8′*S*,1(*R*)-**25a** and of (1′*R*,8′*S*,1(*R*)-**25b** with lead(IV) tetraacetate and hydrolysis of the hydantoin ring yields the unprotected analogs of **4** and **5**. The latter are transformed into the selectively protected target molecules **4** and **5** through standard protection procedures. The overall yield of the 17- and 18-step synthesis starting from **13** was 0.3% yield for each constrained lysine derivative.

1. Introduction

The design and synthesis of conformationally constrained amino acids[1] and peptidomimetics[2] is of special interest for medicinal and bio-organic chemistry in view of their possible application as potency-enhanced ligands for biological receptors,[3] as probes for mimicry of peptide secondary structures,[4] and as novel structural elements of relevance to bio-materials.[5] Efforts to design and synthesize scaffolds that mimic parts of peptide folds and induce an increased conformational stability have mainly focused on the α-helix and β-hairpin.[1,2,4,6,7]

In particular constrained di- and tripeptides have been used to mimic turn structures, which are parts of these motifs. In addition, the incorporation of α,α-disubstituted glycines into the peptide backbone has led to stabilized helices.[8,9] We have designed the conformationally constrained amino

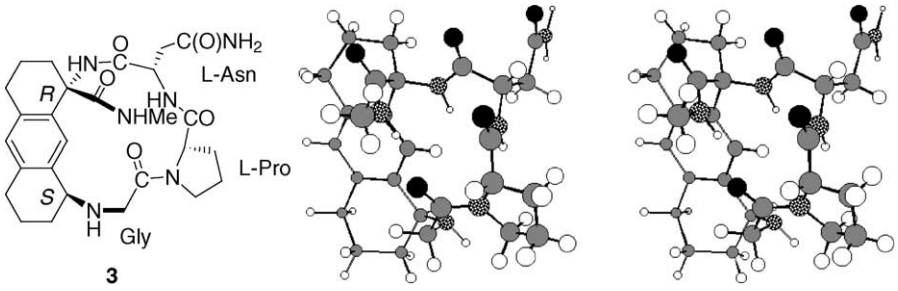

Figure 1. Stereoview of energy-minimized structure of helix-nucleation site **3** (OPLS-AA*,[31] GB/SA water solvation model[25c]); atom coloring: C grey; H white; N dotted; O black.

Keywords: asymmetric reductive amination; constrained amino acid; lysine.

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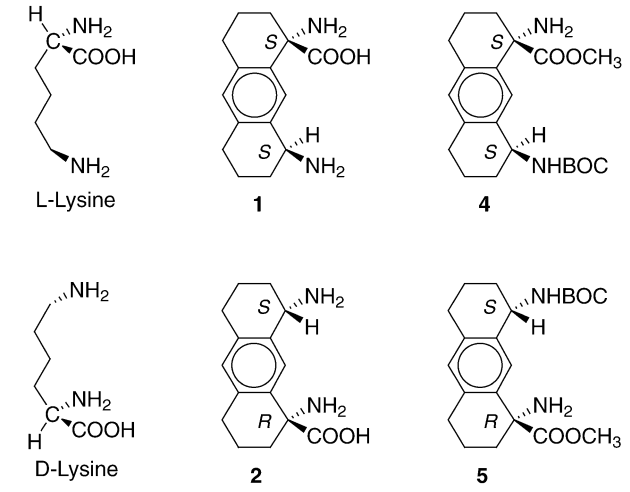
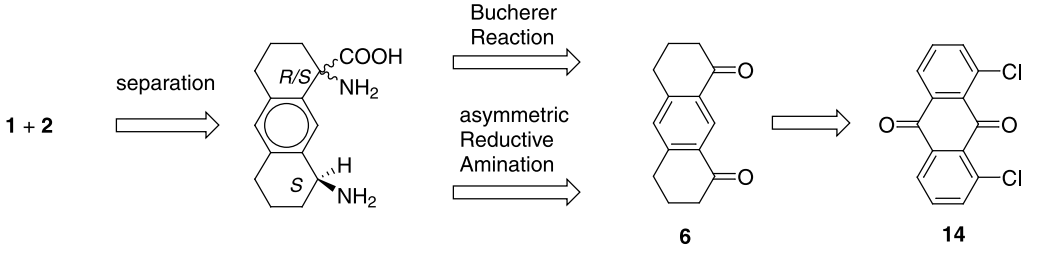


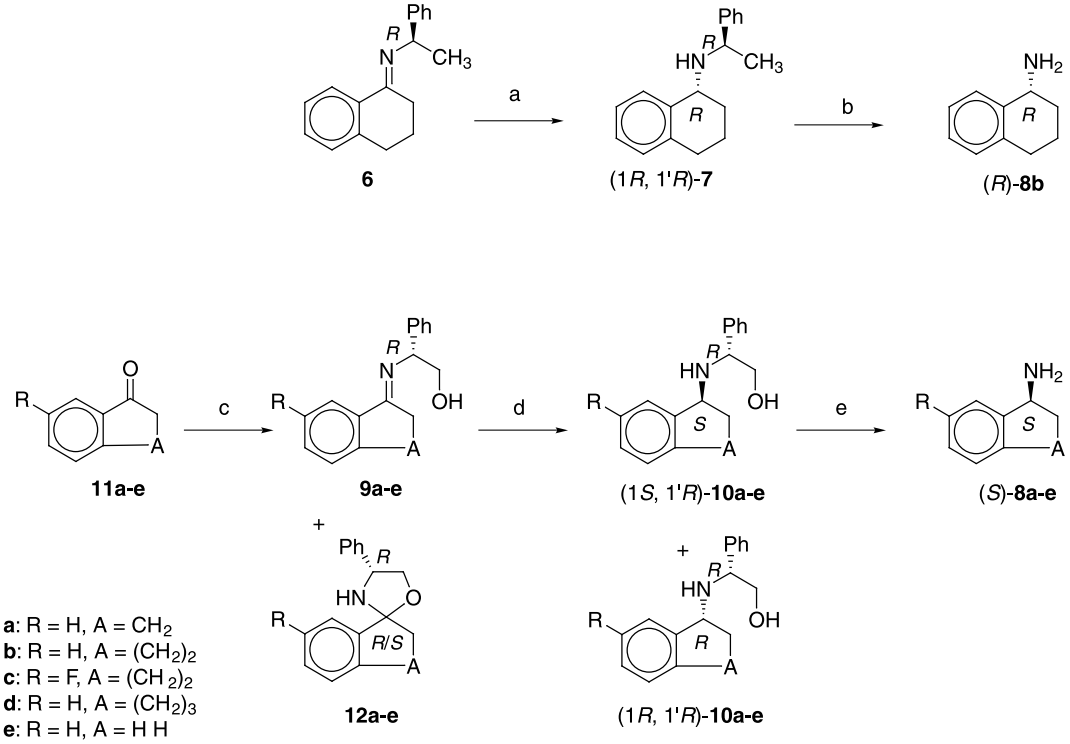
Chart 1.

acids **1** and **2**, which belong to the family of α,α-disubstituted glycines. Our motivation for the design and synthesis of **1** and **2** was twofold. (1) Both **1** and **2** are conformationally constrained L- and D-lysines, respectively,[10] with a completely constrained side chain in the $(+)g$, t, t, $(-)g$ conformation for **1** and $(-)g$, t, t, $(-)g$ conformation for **2**. In lieu of the importance of the lysine side chain for the stability of the α-helix[11] both amino acids are interesting targets for extended studies related to this aspect. For example, model studies show that the protonated ϵ-amino group of **1** can undergo an $(i, i-3)$-electrostatic interaction with a backbone carbonyl group of an α-helix. (2) Both constrained lysines are interesting rigid building blocks for the design of novel C- and N-terminal peptide helix nucleation sites.[7,11] For example, linking both amino groups of **1** with a Gly-(L)-Pro-(L)-Asn tripeptide leads to a macrocycle **3** that mimics the first turn of an α-helix (Fig. 1) and could strongly stabilize the α-helical conformation of a covalently attached peptide.

In this report, we describe the asymmetric synthesis of **4** and



Scheme 1. Synthetic strategy towards the conformationally constrained lysines **1** and **2**.



Scheme 2. Model studies on the reductive amination of α-tetralone **12**. *Conditions*: (a) $NaBH_4$, EtOH, toluene, −10°C; (b) $Pd/C/H_2$, MeOH, HCl (1N) (c) (*R*)-phenylglycinol, *p*-TsOH, xylenes, reflux; (d) $NaBH(OAc)_3$ THF, 0°C; (e) 1.$Pb(OAc)_4$, MeOH, 0°C; 2. HCl (6N), EtOH, reflux.

Table 1. Asymmetric reductive amination of ketones **12a–e**

Entry	Ketone	Ratio[a,b] **10**:**13**	Reducing agent/solvent	Temperature (°C)	Ratio[c] (1*S*,1′*R*)-**11**/(1*R*,1′*R*)-**11** (de)	Yield[d] **11** (%)
1	**12a**	>40:1[e]	$NaBH(OAc)_3$/THF	0	>40:1 (>95%)	84
2	**12b**	86:14[e,f]	$NaBH_4$/EtOH	24	9.5:1 (80.7%)	85
3	**12b**	86:14[e,f]	$NaBH_4$/EtOH	0	9.95:1 (81.7%)	83
4	**12b**	86:14[e,f]	$NaBH_4$/EtOH	−10	9.85:1 (81.6%)	85
5	**12b**	86:14[e,f]	$NaBH(OAc)_3$/THF	0	40:1 (95.1%)	87
6	**12c**	89:11[e,g]	$NaBH(OAc)_3$/THF	24	>40:1 (>95%)	48
7	**12d**	[h]	$NaBH(OAc)_3$/THF	24	1.4:1 (16.7%)	84
8	**12e**	22:78[d,i]	$NaBH(OAc)_3$/THF	0	7:4 (27.3%)	90

[a] Determined from the integrals of the 1′ methine proton signals of the products in the ^1H NMR spectrum of the reaction mixture.
[b] See Ref. 24d,e.
[c] Determined by HPLC.
[d] Yield of isolated product (mixture).
[e] Only *E*-imine was detected.
[f] 10:4 Ratio of diastereomeric 1,3-oxazolidines **13b**.
[g] 7:4 Ratio of diastereomeric 1,3-oxazolidines **13c**.
[h] Complex mixture of *E*-**10**, *Z*-**10**, and two diastereomeric 1,3-oxazolidines (1*S*,1′*R*)-**13** and (1*R*,1′*R*)-**13**.
[i] 2.1:1 Ratio of diastereomeric 1,3-oxazolidines **13e**.

5, which are selectively protected derivatives of **1** and **2** and which are suitable to be incorporated into short host peptides for such model studies (Chart 1).

2. Results and discussion

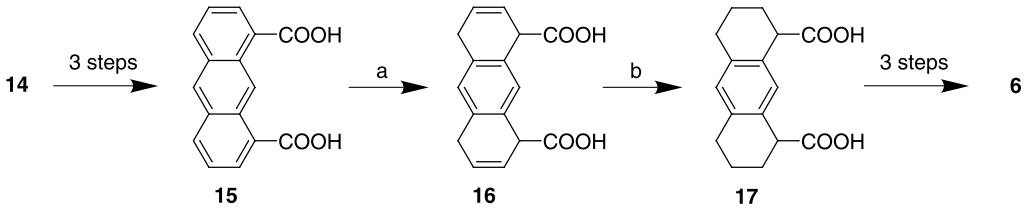
2.1. Synthetic strategy

Our strategy for the synthesis of **1** and **2** involves the regioselective conversion of the carbonyl groups of 1,2,3,4,5,6,7,8-tetrahydroanthracene-1,8-dione **6**,[12] into an amino acid group and an amine, respectively (Scheme 1). For the first key transformation, we choose the *Bucherer hydantoin synthesis* followed by the hydrolysis of the hydantoin ring. Even though no asymmetric protocol has been developed for the *Bucherer* reaction, it has been proven highly reliable and high yielding for the synthesis of benzocyclic aryl- and alkyl-amino acids.[13] The subsequent enantioselective reductive amination of the second ketone group of **7** would yield both diastereomeric **1** and **2**, which would have to be separated chromatographically or through crystallization.

2.2. Model study of the asymmetric reductive amination

Based on our outlined synthetic strategy, the reductive amination is a very important step in the reaction sequence. We undertook an investigation using α-tetralone as model compound (Scheme 2). Several methods for the asymmetric reductive amination of ketones had been developed earlier.[14] These include the reduction of imines, oximes, or enamines in the presence of a chiral reducing reagent,[15,16] a chiral hydrogenation catalyst,[17,18] or a hydrosilylation catalyst,[19] asymmetric transaminations,[20] enzymatic methods,[21] and the selective reduction of chiral imines formed from chiral amino auxiliaries and the ketone.[22,23] The latter method has the advantage to yield diastereomeric product mixtures. Often, these mixtures can be separated through column chromatography or crystallization to yield enantiopure amines after cleavage of the auxiliary. A recent investigation of the reduction of (*R*)-α-methylbenzylamine derived imine **7** by Gutman et al. caught our attention (Scheme 2).[23]

Under optimal conditions, the reduction proceeded with excellent 97:3 diastereofacial selectivity. Unfortunately, the subsequent debenzylation using catalytic hydrogenation showed a marginally regioselectivity of 3.5:1 in favor of cleaving the C1′–N bond of **7**. Nevertheless, the high facial selectivity of this reduction lured us to investigate the related reduction of the (*R*)-α-phenylglycinol derived imine **10b**. The use of (*R*)-α-phenylglycinol as the chiral amino auxiliary is very attractive since the C1′–N bond of the expected product **11b** is selectively cleaved with lead (IV) tetraacetate.[24] Imine **10b** was prepared as an equilibrium mixture with the two diastereomeric 1,3-oxazolidines **13b** in greater 90–95% yield by refluxing tetralone and (*R*)-α-phenylglycinol in xylenes in the presence of catalytic amounts of *p*-tolylsulfonic acid.[24e] The reduction of this mixture with $NaBH_4$ in ethanol at room temperature gave in greater than 85% yield a 9.5:1-mixture of diastereomeric amines (1*S*,1′*R*)-**11b** and (1*R*,1′*R*)-**11b** (80.7% de) (Table 1, entry 2). The diastereomeric excess (de) showed little temperature dependence (Table 1, entries 3–4). We reckoned that an increased bulkiness of the reducing agent would improve the facial selectivity. Indeed, reduction of the **10b/13b** mixture with freshly prepared $NaBH(OAc)_3$ in THF at 0°C strongly increased the diastereomeric ratio (dr) of (1*S*,1′*R*)-**11b**/(1*R*,1′*R*)-**11b** to 40:1 (95.1 de; 87% isolated yield) (Table 1, entry 5). The subsequent oxidative cleavage of (1*S*,1′*R*)-**11b** using $Pb(OAc)_4$ gave (*S*)-**9** in 63% yield. Thus, this method proved to be a suitable alternative to Gutman's method as well as other asymmetric reductive amination protocols. The stereochemical outcome of the reduction was determined by X-ray crystallography. The use of (*R*)-α-phenylglycinol gives (*S*)-stereochemistry at the new stereogenic center of the major product diastereomer **11b**. This outcome is consistent with the lowest energy conformation of **10b** obtained from a Monte Carlo conformational search (MM2; GB/SA $CHCl_3$ solvent model),[25] which shows a better accessibility of the imine bond from the *re*-face of **10b** to give (*S*)-**9b**.

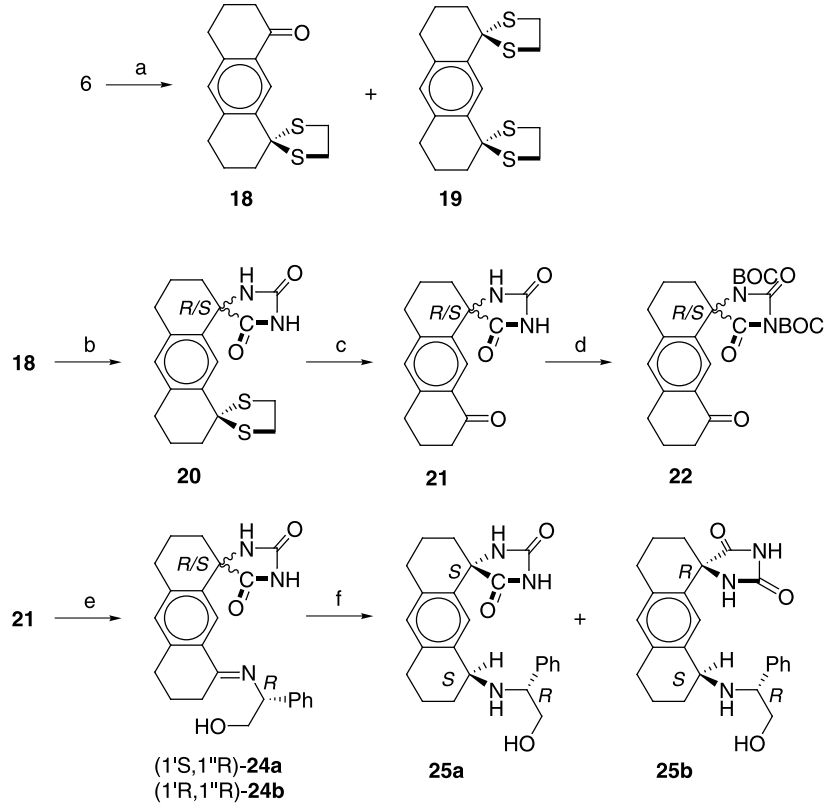


Scheme 3. Synthesis of 1,2,3,4,5,6,7,8-tetrahydroanthracene-1,8-dione **6**. *Conditions*: (a) 1. Li/NH_3 liq.; 2. NH_4Cl; (b) EtOH; $Pd/C/H_2$ 67% yield over 2 steps.

We further tested this approach for the asymmetric reductive amination of other arylketones **12a** and **12c–e** (Table 1, entries 1, 6–8). In each case, the major product diastereomer had (*S*)-stereochemistry at the new stereogenic center, as determined by comparing the optical rotation of the amines **9** after cleavage of the auxiliary with $Pb(OAc)_4$ (47–75% yield) with those reported in the literature.[23] For five and six-membered benzocycloalkanones, we obtained excellent diastereomeric excesses >95%. These high diastereomeric excesses clearly show that the two diastereomeric 1,3-oxazolidines **13** have no negative influence on the diastereofacial selectivity of the reduction. Poor diastereomeric ratios were obtained for benzosuberone **12d** and acetophenone **12e**, which is consistent with similar results for the TMSCN addition to these imines.[24d,e] Whereas the condensation of **12d** with (*R*)-α-phenylglycinol **12a–c** and **12e** yields only the corresponding (*E*)-imine, the formation of both (*E*)-**13d** and (*Z*)-**13d** might contribute to the lower de observed in the reductive amination of **12d**. Both isomeric imines **13d** will have different and most likely opposite diastereofacial selectivities in their reaction with $NaBH(OAc)_3$.

2.3. Synthesis of constrained lysines derivatives

As briefly discussed in Section 1, our strategy for the synthesis of the constrained lysine derivatives **1** and **2** involved the conversion of one carbonyl group of **6** into a racemic fully protected amino acid moiety. Subsequently, application of our asymmetric reductive amination would result in a pair of diastereomers, which we would try to separate chromatographically. For the synthesis of dione **6**, we chose a literature procedure,[12a] which we slightly modified during the course of our investigations (Scheme 3). 1,8-Dichloroanthraquinone **14** was converted in three steps into anthracene-1,8-dicarboxylic acid **15**.[26] We experienced major difficulties in converting **15** into **17** according to the reported three-step literature procedure.[12a] In particular, the Birch reduction of **15** under the published conditions gave very unreliable results in our laboratory. Thus, we modified the conditions of this step.[27] Quenching the Birch reduction with excess solid ammonium chloride gave 1,4,5,8-tetrahydroanthracene-1,8-dicarboxylic acid **16**, which was immediately subjected to a catalytic hydrogenation on Pd/C to afford **17** as a mixture of diastereomers.



Scheme 4. *Conditions*: (a) $HSCH_2CH_2SH$; $BF_3{\cdot}Et_2O$; CH_2Cl_2. (b) KCN; $(NH_4)_2CO_3$; EtOH; H_2O; 130°C. (c) $AgNO_3$; EtOH; THF; H_2O. (d) $(BOC)_2O$; DMAP cat.; THF; rt. (e) (*R*)-phenylglycinol; xylenes; *p*-TsOH cat.; reflux. (f) $NaBH(OAc)_3$; THF; 0°C.

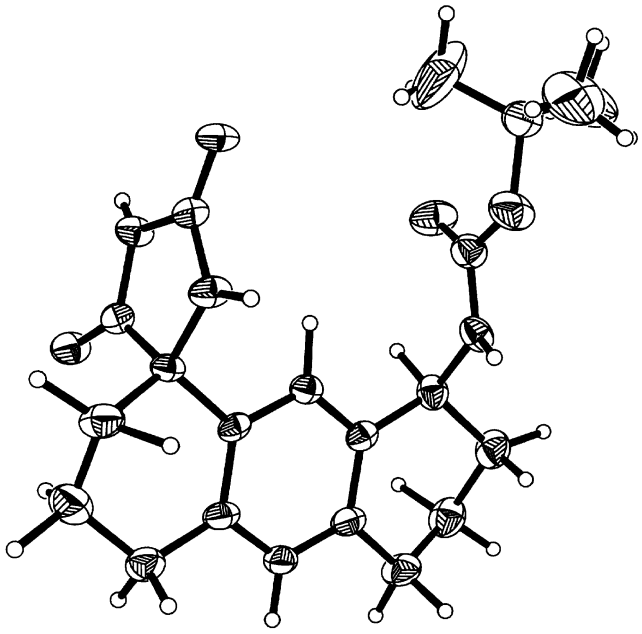
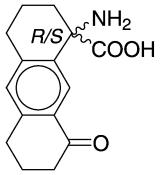


Figure 2. X-Ray crystal structure of diastereomer **26b**.

The total yield of converting **15** to **17** was very reproducible and is comparable to the yield of the reported three-step synthesis. Diacid **17** was further converted into **6** in three steps as described by Caluwe and Pepper.[12a]

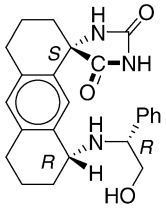
Monoprotection of one carbonyl group of **6** using one equivalent of ethane-1,2-dithiol in the presence of the Lewis acid $BF_3{\cdot}Et_2O$ gave **18** together with small amounts of the diprotected bis-dithiane **19** which could be easily separated by chromatography (Schemes 3 and 4).

Subjection of **18** to typical conditions of a Bucherer hydantoin synthesis (KCN, $(NH_4)_2CO_3$, EtOH, water, 130°C)[13] gave almost quantitatively the racemic hydantoin **20**. The protected carbonyl group of **20** was unmasked using $AgNO_3$ in an ethanol/water/THF (5:3:1) mixture (65% yield). Unfortunately, the arylketone group of **21** was too unstable under the harsh conditions ($Ba(OH)_2$/120°C) required for the hydrolysis of the hydantoin moiety. Thus, we tested a mild hydantoin hydrolysis procedure reported by Rebek and co-workers in which they successfully hydrolyzed a *N*,*N*-bis-BOC-protected hydantoin at room temperature with aqueous LiOH.[28] The BOC protection of **21** using $(BOC)_2O$ in the presence of catalytic amounts of DMAP afforded **22** in 79% yield. However, treatment of **22** at room temperature with 2N LiOH in THF/water reverted **22** back to **21** rather than forming the desired amino acid **23**.

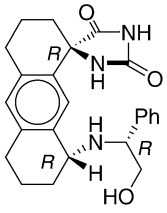


23

After the failure to hydrolyze the hydantoin on this stage of the synthesis, we decided that the conversion of the carbonyl group of **21** into an amino group would render the molecule stable enough. For the reductive amination of **21**, we applied our protocol described above. Heating a solution of **21** and 1.5 equiv. of (*R*)-phenylglycinol in xylenes in the presence of catalytic amounts of *p*-tolylsulfonic acid under constant removal of condensation water afforded a 1:1 mixture of diastereomeric imines **24a** and **24b** in about 80–85% yield as determined from the ^1H NMR spectrum of the crude reaction mixture. Reduction of both imines with $NaBH(OAc)_3$ in THF yielded a 1:1-mixture of two major products. Both products were isolated in 38 and 44.5% yield using normal phase gravity chromatography followed by reversed phase HPLC. Their spectroscopic properties are consistent with those of the diastereomeric amines **25a** and **25b**, which are the expected stereoisomers according to our model investigation. The other two possible diastereomers **25c** and **25d** could not be isolated and must be formed, if at all, in very low yields.



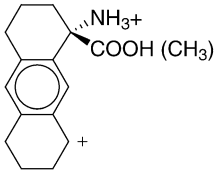
25c



25d

The assignment of the stereochemical relationship between the hydantoin ring at C1′ and the amino group at C8′ of **25a** and **25b** was determined after the cleavage of the chiral auxiliary using lead (IV) acetate. *N*-BOC protection of the generated amino group gave **26a** from **25a** and **26b** from **25b** in 65 and 62% yield, respectively. Fortunately, we were able to grow crystals of **26b** that were suitable for X-ray crystal structure analysis. The crystal structure of **26b** is illustrated in Fig. 2 and shows *R*-configuration at the stereogenic carbon C1′.

In order to complete the synthesis of **4** (Scheme 5), the hydantoin ring of **26a** was hydrolyzed with aqueous $Ba(OH)_2$ at 125°C. Subsequent heating of crude **1** in methanol in the presence of $SOCl_2$ for 24 h afforded the methyl ester **27a** in 40.5% yield. Selective BOC-protection of the more reactive secondary amine of **27a** under standard conditions gave the desired constrained L-lysine derivative **4**, which is suitably protected to allow its incorporation into a short peptide. The yield of the esterification of crude **1** was disappointingly low. This might result from an acid catalyzed deamination of **1** or **27a** during the esterification as a consequence of the stability of carbocation **28**.



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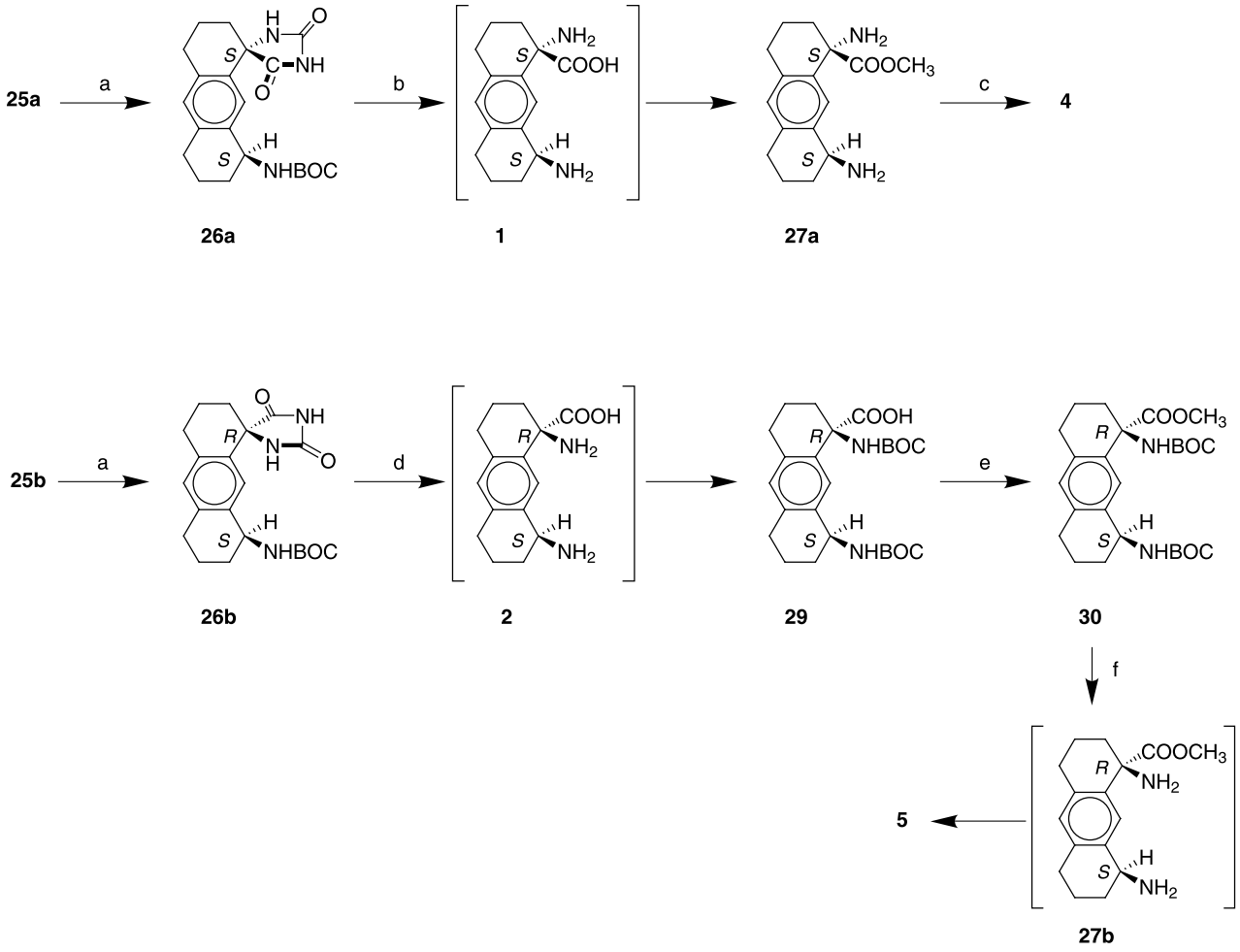
Thus, for the synthesis of the constrained D-lysine derivative **5** (Scheme 5), we choose a slightly different route in the hope to improve the overall yield. After hydrolysis of



Scheme 5. Final steps of the synthesis of **4** and **5**. *Conditions*: (a) 1. $Pb(OAc)_4$; CH_2Cl_2/MeOH (2:1); 0°C; 2. HCl (2N) reflux; 3. Na_2CO_3, $(BOC)_2O$; dioxane/water (1:1); **26a**: 62% yield, **26b**: 65% yield. (b) 1. $Ba(OH)_2$; water; 125°C; 2. H_2SO_4; 3. $SOCl_2$; MeOH; reflux; 4. Na_2CO_3; 40.5% yield. (c) $(BOC)_2O$; dioxane; 78% yield. (d) 1. $Ba(OH)_2$; water; 125°C; 2. H_2SO_4; 3. $(BOC)_2O$; Na_2CO_3; dioxane/water (1:1); 45% yield. (e) CH_2N_2; ether; quantitative. (f) 1. TFA; 0°C; 2. Na_2CO_3 3. $(BOC)_2O$; dioxane; 65% yield.

hydantoin **26b**, both amino groups of **2** were first protected with a BOC group through the reaction of crude **2** with excess $(BOC)_2O$. The subsequent reaction of **29** with diazomethane afforded **30** quantitatively. Deprotection of both amino groups with trifluoroacetic acid and subsequent selective BOC-protection of the secondary amine of **27b** gave **5** in 65% yield. Unfortunately, the total yield of this sequence did not lead to an improved yield as compared to the shorter sequence used for the preparation of **4** from **26a**.

3. Conclusions

In summary, we have developed a new asymmetric reductive amination protocol for arylalkylketones in which α-phenylglycinol is used as chiral auxiliary and $NaBH(OAc)_3$ as reducing agent. Particularly high diastereomeric excesses are obtained for indanone and tetralone derivatives. This reductive amination protocol was a key step in our synthesis of the new conformationally constrained L-lysine and D-lysine derivatives **4** and **5**, which were prepared starting from 1,8-dichloroanthraquinone **14** through a 17- and 18-step reaction sequence. Both amino acids derivatives are interesting scaffolds to test the important role of the lysine side chain in the conformational stability of secondary peptide structures. They are also useful building blocks for the design and synthesis of novel C- and N-terminal α-helix nucleation sites. Such studies are currently underway in our laboratories.

4. Experimental

4.1. General

1-Indanone, 1-tetralone, and 1-benzosuberone were obtained from Aldrich Chemical Company, and were distilled under reduced pressure prior to use when necessary. 7-Fluoro-α-tetralone was synthesized from fluorobenzene and succinnic anhydride in three steps.[29,30] Dichloromethane, methanol and tetrahydrofuran were freshly distilled from calcium hydride, magnesium methoxide or benzophenone ketyl respectively, under an inert atmosphere. All other reagents were used without further purification. All reactions were conducted under an argon atmosphere unless otherwise stated. ^1H and ^{13}C NMR spectra were obtained using a 400 MHz Varian FT NMR spectrometer or a Varian 200 MHz FT NMR spectrometer.

^{1}H NMR spectra were referenced to the residual $CHCl_3$, CHD_2OD, $CHCl_2CDCl_2$, $C_6D_5CD_2H$ or HDO, signals at δ 7.26, 3.31, 5.91, 2.09 or 4.81, respectively. ^{13}C NMR spectra were referenced to the residual $CDCl_3$, $CDCl_2CDCl_2$, or CD_3OD signals at δ 77.3, 74.2, or 49.5, respectively. MALDI-TOF mass spectra were obtained on an IonSpec HiRes MALDI mass spectrometer. High resolution FAB-MS were determined on a ZAB SE instrument with 3-nitrobenzyl alcohol (NOBA) matrix from the mass spectrometry laboratory at the University of Kansas, Lawrence, Kansas. CHN analyses were obtained from Desert Analytics, Tucson, Arizona. Gravity chromatography was performed on Bodman silica gel (70–230 mesh). HPLC was performed on Rainin Varian Dual Pump System. Melting points are uncorrected.

4.2. X-Ray crystallography

Crystalline samples of (1*S*,1′*R*)-**11b** and **26b** were placed in inert oil, mounted on a glass pin, and transferred to the cold gas stream of the diffractometer. Crystal data were collected and integrated using a Bruker SMART 1000 system, with graphite monochromated Mo Kα (λ=0.71073 Å) radiation at 173 K. The structures were solved by direct methods using SHELXS-97 and refined using SHELXL-97 (Sheldrick, G. M., University of Göttingen). Non-hydrogen atoms were found by successive full matrix least squares refinement on F^2 and refined with anisotropic thermal parameters. Hydrogen atom positions were located from difference Fourier maps, and a riding model with fixed thermal parameters (u_{ij}=1.2U_{ij}(eq) for the atom to which they are bonded), was used for subsequent refinements.

4.3. Asymmetric reductive amination of α-tetralone using (*R*)-2-phenylglycinol (*procedure A*)

To a stirred solution of α-tetralone **12b** (15 mmol) in xylenes (30 mL) was added (*R*)-2-phenylglycinol (16.5 mmol) and *p*-tolylsulfonic acid monohydrate (0.5 mol%). The resulting mixture was heated to reflux and maintained there until ^{1}H NMR spectroscopy showed less than 5% **12b** (3–8 h). The reaction mixture is diluted with 15 mL toluene, washed with 10% $NaHCO_3$ (2×10 mL), water (5×10 mL), and brine (10 mL) and is dried over $MgSO_4$. Solvent was removed in vacuo to give a mixture of imine **10b**, oxazolidines **13b** and unreacted **12b** (86:10:4:5 ratio).[24e] For the reduction with $NaBH(OAc)_3$, the crude imine/oxazolidine mixture (1.3 g, 4.8 mmol) was taken up in anhydrous THF (10 mL) and cooled to 0°C under argon. $NaBH_4$ (2.1 g, 5.5 mmol) and glacial acetic acid (0.95 mL, 16.5 mmol) were added and the reaction mixture was stir at 0°C for 2 h. Dichloromethane (10 mL) and saturated $NaHCO_3$ (2 mL) was added. The organic phase was separated and washed with saturated $NaHCO_3$ (4×2 mL), dried over $MgSO_4$ and concentrated to yield 1.3 g of the crude product. The crude diastereomeric mixtures of amines were purified by column chromatography (Silica gel, CH_2Cl_2) to give a mixture of diastereomeric amines (1*S*,1′*R*)-**11b**/(1*R*,1′*R*)-**11b** (1.16 g, 87%). For the reduction with $NaBH_4$, the imine/oxazolidine mixture (100 mg, 0.38 mmol) was dissolved in absolute ethanol (10 mL). The solution was thermally equilibrated at the desired reaction temperature (24, 0, or −10°C) and $NaBH_4$ (3 equiv.) was added. The solution was stirred until all imine and oxazolidines had been reduced (TLC control) and was worked up as described above. The diastereomeric ratio of each reaction was determined by reversed phase HPLC of the crude reaction products (Higgins TARGA C18 column, 4,6×250 mm, 100 mM phosphate buffer pH 2.74/MeOH (55:45), 1 mL/min flow rate, detection at 270 nm). Retention time of major isomer: 26.5 min; retention time of minor isomer: 31.2 min. Both diastereomers were separated by preparative reversed phase HPLC on a TARGA C18 column (250×20 mm) (Higgins Analytical) using 40 mM phosphate buffer pH 2.85/MeOH (60:40) as the mobile phase (15 mL/min flow rate, detection at 285 nm). The product fractions were concentrated, basified with saturated Na_2CO_3 and extracted twice with ether. The combined organic layers were washed with water and with brine, dried over $MgSO_4$ and concentrated to yield the pure diastereomers.

4.3.1. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-1,2,3,4,-tetrahydronaphthalene (1*S*,1′*R*)-11b (major diastereomer). Colorless solid; mp 84–86°C; $[\alpha]_D^{24}$=−95.2° (*c* 3.14, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 6H), 7.2–7.14 (m, 2H), 7.12–7.07 (m, 1H), 3.98 (dd, *J*=4.6, 7.9 Hz, 1H), 3.80 (t, *J*=4.5 Hz, 1H), 3.72 (dd, *J*=4.6, 10.7 Hz, 1H), 3.51 (dd, *J*=7.9, 10.7 Hz, 1H), 2.86–2.64 (m, 2H), 1.94–1.60 (m, 4H) 2.4–1.7 (svb, 2H); ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 142.2, 139.3, 137.4, 129.3, 129.2, 128.8, 127.7, 127.4, 127.0, 125.8, 66.9, 63.2, 54.3, 30.2, 29.1, 18.8; HR-MALDI MS *m/z* ($M+Na^+$) 290.154 (calcd for $C_{18}H_{21}NONa$, 290.152). Anal. calcd for $C_{18}H_{21}NO$: C, 81.16; H, 7.57; N, 5.26. Found: C, 81.17; H, 7.89; N, 5.33.

4.3.2. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*R*)-1-amino-1,2,3,4,-tetrahydronaphthalene (1*R*,1′*R*)-11b (minor diastereomer). Colorless oil; $[\alpha]_D^{24}$=+3.5° (*c* 0.34, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 7.16–7.06 (m, 4H), 3.99 (dd, *J*=4.6, 9.0 Hz, 1H), 3.71–3.66 (m, 2H), 3.51 (dd, *J*=9.0, 10.8 Hz, 1H), 2.88–2.79 (m, 1H), 2.74–2.60 (m, 1H), 2.4–1.7 (svb, 2H), 2.15–1.9 (m, 2H), 1.77–1.65 (m, 2H); ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 141.0, 139.2, 137.9, 129.4, 129.14, 129.07, 128.1, 127.7, 127.2, 126.2, 67.1, 62.2, 51.7, 29.6, 27.4, 18.5; HR-MALDI MS *m/z* ($M+Na^+$) 290.153 (calcd for $C_{18}H_{21}NONa^+$, 290.152).

4.3.3. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*R*)-1-amino-8-fluoro-1,2,3,4,-tetrahydronaphthalene (1*S*,1′*R*)-11c. Application of procedure A to 8-fluoro-1,2,3,4-tetrahydro-1-naphthalone **12c** and (*R*)-phenylglycinol gave crude (1*S*,1′*R*)-**11c**, which was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH (50:1)) to afford (1*S*,1′*R*)-**11c** as a single diastereomer by ^{1}H NMR in 48% yield. Pale yellow oil; $[\alpha]_D^{24}$=−51.8° (*c* 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4–7.28 (m, 5H), 7.08 (dd, *J*=2.4, 9.6 Hz, 1H), 7.03 (dd, *J*=6.0, 7.6 Hz, 1H), 6.86 (dt, *J*=2.4, 8.4 Hz, 1H), 3.97 (dd, *J*=4.1, 8.0 Hz, 1H), 3.78–3.70 (m, 2H), 3.52 (dd, *J*=8.0, 10.8 Hz, 1H), 2.80–2.60 (m, 2H), 2.5 (svb, 2H), 1.90–1.77 (m, 2H), 1.74–1.58 (m, 2H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 161.1 (d, $^1J_{CF}$=242 Hz), 142.0, 141.3 (d, $^3J_{CF}$=6.1 Hz), 132.8 (d, $^4J_{CF}$=3.1 Hz), 130.5 (d, $^3J_{CF}$=7.6 Hz), 128.9, 127.8, 127.6, 115.2 (d, $^2J_{CF}$=20.9 Hz), 114.0 (d, $^2J_{CF}$=21.2 Hz), 67.0, 65.2, 54.3 (d, $^4J_{CF}$=1.2 Hz),

30.1, 28.4, 19.0; HR-FAB MS *m/z* ($M+H^+$) 285.1606 (calcd for $C_{18}H_{21}NOF^+$, 285.1607).

4.3.4. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocyclopentane (1*S*,1′*R*)-11a. Application of procedure A to 1-indanone **12a** and (*R*)-phenylglycinol gave crude (1*S*,1′*R*)-**11a**, which was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc (1:1)) to afford (1*S*,1′*R*)-**11a** as a single diastereomer by ^1H NMR in 84% yield. Yellowish oil; $[\alpha]_D^{24}=-53.2°$ (*c* 0.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (m, 6H), 7.22–7.18 (m, 3H), 4.21 (t, *J*=6.8 Hz, 1H, C*H*NH), 4.03 (dd, *J*=4.4, 8.4 Hz, 1H), 3.73 (dd, *J*=4.4, 10.4 Hz, 1H), 3.54 (dd, *J*=10.4, 8.4 Hz, 1H), 3.5–1.4 (svb, 2H, N*H*, O*H*), 2.91 (ddd, *J*=4.8, 8.4, 11.6 Hz, 1H), 2.76–2.66 (m, 1H), 2.26–2.15 (m, 1H), 1.66–1.63 (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 145.8, 143.7, 142.1, 128.9 127.7, 127.5, 126.4, 125.0, 124.5, 66.8, 63.7, 36.0, 30.6; HR-FAB-MS *m/z* ($M+H^+$) 254.1544 (calcd for $C_{17}H_{20}NO^+$, 254.1545).

4.4. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocycloheptane (1*S*,1′*R*)-11d and *N*-[(*R*)-2′-hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocycloheptane (1*R*,1′*R*)-11d

Application of procedure A to 1-benzosuberone **12d** and (*R*)-phenylglycinol gave crude **11d**, which was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc (1:1) to afford a (1:1.4)-mixture of diastereomers (1*R*,1′*R*)-**11d** and (1*S*,1′*R*)-**11d** as determined by HPLC (Higgins Analytical TARGA C18 column, 4,6×250 mm, 0.1% TFA in H_2O/MeOH (65:35), 2 mL/min flow rate, detection at 254 nm; retention time of minor isomer: 16.7 min; retention time of major isomer: 19.8 min) in 84% yield. A small portion (40 mg) was separated via preparative HPLC (TARGA C18 column (250×20 mm) (Higgins Analytical); 0.1% TFA in H_2O/MeOH (65:35); 20 mL/min flow rate, detection at 254 nm) to afford the pure diastereomers.

4.4.1. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocycloheptane ((1*S*,1′*R*)-11d) (major diastereomer). Colorless oil; $[\alpha]_D^{24}=-151.4°$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.4–7.0 (m, 9H), 7.22–7.18 (m, 3H), 3.76 (d, *J*=7.2 Hz, 1H), 3.68–3.53 (m, 3H), 3.13 (t, *J*=7.8 Hz, 1H), 2.8–2.1 (svb, 2H, N*H*, O*H*), 2.70 (dd, *J*=7.8, 14.2 Hz, 1H), 2.1–1.7 (m, 5H), 1.58–1.43 (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 142.8, 141.9, 140.6, 130.6, 129.0, 127.9, 127.8, 127.6, 126.3, 67.4, 61.9, 59.7, 36.1, 34.7, 28.3, 26.9; HR-FAB-MS *m/z* ($M+H^+$) 282.1846 (calcd for $C_{19}H_{24}NO^+$, 282.1858).

4.4.2. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocycloheptane ((1*R*,1′*R*)-11d) (minor diastereomer). Colorless oil; $[\alpha]_D^{24}=-15.2°$ (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 7.16–7.05 (m, 4H), 3.93 (dd, *J*=4.8, 8.8 Hz, 1H), 3.81 (d, *J*=7.2 Hz, 1H), 3.76 (dd, *J*=4.4, 11.0 Hz, 1H), 3.56 (dd, *J*=8.8, 11.0 Hz, 1H), 3.14–3.03 (m, 1H), 2.7–2.1 (svb, 2H, N*H*, O*H*), 2.67 (dd, *J*=8.0, 13.6 Hz, 1H), 2.12–1.7 (m, 5H), 1.58–1.50 (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 143.8, 142.8, 140.5, 130.4, 129.0, 128.0, 127.4, 127.2, 126.4, 66.9, 61.4, 59.6, 36.3, 31.7, 28.3, 26.7; HR-FAB-MS *m/z* ($M+H^+$) 282.1858 (calcd for $C_{19}H_{24}NO^+$, 282.1858).

4.4.3. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-phenyl-1-ethylamine ((1*S*,1′*R*)-11e) and *N*-[(*R*)-2′-hydroxy-1′-phenylethyl]-(*R*)-1-phenyl-1-ethylamine ((1*R*,1′*R*)-11e). Application of procedure A to acetophenone **12e** and (*R*)-phenylglycinol gave crude **11e**, which was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc (2:3) to afford a (4:7)-mixture of diastereomers (1*R*,1′*R*)-**11e** and (1*S*,1′*R*)-**11e** (determined by ^1H NMR) as a colorless oil in 90% yield. $[\alpha]_D^{24}=-112.4°$ (*c* 1.31 MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.4–7.2 (m, 10H major, 10H minor), 3.90 (dd, *J*=4.4, 7.8 Hz, 1H minor), 3.77 (q, *J*=6.4 Hz, 1H, C*H*CH_3 minor), 3.74 (dd, *J*=4.8, 10.4 Hz, 1H minor), 3.77 (qt, *J*=6.4 Hz, 1H, C*H*CH_3 major), 3.58–3.46 (m, 1H minor, 3H major), 2.44 (svb, 2H, N*H*, O*H* minor and major), 1.38 (d, *J*=6.4 Hz, 3H, CHC*H*$_3$ minor), 1.33 (d, *J*=6.4 Hz, 3H, CHC*H*$_3$ major); ^{13}C NMR (100.56 MHz, $CDCl_3$): major diastereomer δ 145.3, 141.2, 128.8, 128.7, 127.7, 127.5, 127.3, 127.0, 67.2, 61.8, 55.1, 25.3; minor diastereomer δ 146.0, 141.4, 128.8, 128.7, 127.7, 127.4, 127.3, 126.8, 66.4, 61.8, 55.0, 22.7; HR-FAB-MS *m/z* ($M+H^+$) 242.1544 (calcd for $C_{16}H_{20}NO^+$, 242.1545).

4.4.4. (*S*)-1,2,3,4-Tetrahydro-1-naphthylamine ((*S*)-8b) (*procedure B*). Lead (IV) acetate 95% (2.43 g, 5.2 mmol) was dissolved at 0°C in dry methanol (55 mL). To this solution was drop wise added over 30 min a solution of (1*S*,1′*R*)-**11b** (1.07 mg, 4 mmol) in dry methanol (30 mL) under argon. The solution was stirred at 0°C for further 10 min before it was diluted with dichloromethane (105 mL) and quenched by the addition of 10% Na_2CO_3 (35 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over magnesium sulfate, filtered and concentrated in vacuo. The remaining yellowish oil was taken up in ethanol (135 mL) and conc. HCl (3 mL) and heated to reflux for 22 h. After cooling to room temperature, the reaction mixture was concentrated and partitioned between water (100 mL) and ether (15 mL). The aqueous layer was separated, basified with solid K_2CO_3 to pH 9.1 and extracted with ether (3×40 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated in vacuo to leave a brown oil (0.5 g). This oil was taken up in the minimum volume of ethyl acetate and purified by silica gel column chromatography (SiO_2, ethyl acetate/MeOH (9:1)) to yield (*S*)-**9b** (370 mg, 63% yield) as a yellowish oil. $[\alpha]_D^{24}=+27°$ (*c* 1.7 MeOH); ((*R*)-**9b**: $[\alpha]_D^{24}=-26°$ (*c* 1.32 MeOH));[23] δ_H (400 MHz, $CDCl_3$) 7.41 (d, *J*=7.2 Hz, 1H), 7.23–7.02 (m, 3H), 3.99 (t, *J*=5.8 Hz, 1H), 2.90–2.70 (m, 2H), 2.14–1.90 (m, 2H), 1.88–1.64 (m, 2H), 1.55 (sb, 2H); δ_C (100.6 MHz, $CDCL_3$) 141.0, 137.0, 129.2, 128.3, 126.8, 126.3, 49.6, 33.6, 29.8, 19.8; MALDI MS *m/z* ($M+H^+$) 148.1 (calcd for $C_{10}H_{14}N$, 148.1).

4.4.5. (*S*)-8-Fluoro-1,2,3,4-tetrahydro-1-naphthylamine ((*S*)-9c). Application of procedure B to (1*S*,1′*R*)-**11c** afforded (*S*)-**8c** as a colorless oil in 70% yield. $[\alpha]_D^{24}=+31.3°$ (*c* 0.48 $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 7.12 (dd, *J*=2.4, 9.6 Hz, 1H), 7.02 (dd, *J*=6.0, 8.4 Hz, 1H), 6.84 (td, *J*=2.4, 8.4 Hz, 1H), 3.94 (t, *J*=5.4 Hz, 1H), 2.80–2.64

(m, 2H), 2.12 (sb, 2H), 2.1–1.6 (m, 4H); δ_C (100.56 MHz, $CDCl_3$) δ 161.1 (d, $^1J_{CF}$=243 Hz), 142.8 (d, $^3J_{CF}$=6.1 Hz), 132.5 (d, $^4J_{CF}$=3.0 Hz), 130.5 (d, $^3J_{CF}$=7.7 Hz), 114.4 (d, $^2J_{CF}$=21.0 Hz), 114.0 (d, $^2J_{CF}$=21.3 Hz), 49.9 (d, $^4J_{CF}$= 1.1 Hz), 33.5, 29.0, 20.0; HR-FAB MS *m/z* ($M+H^+$) 166.1027 (calcd for $C_{10}H_{13}FN$, 166.1032).

4.4.6. (*S*)-1-Indanamine ((*S*)-9a). Application of procedure B to (1*S*,1′*R*)-**11a** afforded (*S*)-**9a** as a colorless oil in 47% yield. $[\alpha]_D^{24}$=+16.4° (*c* 1.4, MeOH) ((*R*)-**9a**: $[\alpha]_D^{20}$=−17 (*c* 1.5, MeOH));[23] δ_H(400 MHz, $CDCl_3$) 7.33 (d, *J*=7.6 Hz, 1H), 7.26–7.18 (m, 3H), 4.36 (t, *J*=7.4 Hz, 1H), 3.00–2.86 (m, 1H), 2.83–2.76 (m, 1H), 2.58–2.44 (m, 1H), 1.63 (s, 2H), 1.74–1.65 (m, 1H); δ_C (100.56 MHz, $CDCl_3$) δ 147.7, 143.3, 127.4, 126.7, 124.9, 123.5, 57.5, 37.6, 30.3; HR-FAB MS *m/z* ($M+H^+$) 134.0988 (calcd for $C_9H_{12}N$, 134.0988).

4.4.7. 1-Aminobenzocycloheptane (9d). Application of procedure B to (1*S*,1′*R*)-**11d**/(1*R*,1′*R*)-**11d** (1.4:1) afforded **9d** as a colorless oil in 61% yield. $[\alpha]_D^{24}$=−1.4° (*c* 1.5, MeOH) ((*R*)-**9d**: $[\alpha]_D^{20}$=+26 (*c* 1.125, MeOH));[23] δ_H(400 MHz, $CDCl_3$) 7.42 (d, *J*=7.6 Hz, 1H), 7.21 (dt, *J*=1.6, 5.7 Hz, 1H), 7.15–7.05 (m, 2H), 4.22 (d, *J*= 8.8 Hz, 1H), 2.86–2.78 (m, 2H), 2.04–1.93 (m, 1H), 1.91–1.75 (m, 3H), 1.70–1.38 (m, 4H); δ_C (100.56 MHz, $CDCl_3$) δ 146.0, 141.7, 129.7, 126.6, 126.4, 124.4, 55.0, 37.5, 36.1, 29.1, 27.8.

4.4.8. 1-Phenyl-1-ethylamine (9e). Application of procedure B to (1*S*,1′*R*)-**11e**/(1*R*,1′*R*)-**11e** (7:4) afforded (*S*)-**8e** (23% ee) as a colorless oil (75% yield). $[\alpha]_D^{24}$=−8.0° (*c* 2.36, MeOH) ((*R*)-**9e** (Aldrich Chemical Company, 99%ee): $[\alpha]_D^{20}$=+34.4 (*c* 3.52, MeOH)); δ_H(400 MHz, $CDCl_3$) 7.37–7.22 (m, 5H), 4.12 (q, *J*= 6.6 Hz, 1H, C*H*CH_3), 1.48 (sb, 2H), 1.39 (d, *J*=6.6 Hz, 3H, CH*C*H_3); δ_C (100.56 MHz, $CDCl_3$) δ 148.0, 128.7, 127.0, 125.9, 51.5, 25.9.

4.5. 1,2,3,4,5,6,7,8-Octahydroanthracene-1,8-dicarboxylic acid (17)

Dry tetrahydrofuran (20 mL) was added under argon into a 3-necked, 250 mL flask fitted with a dry ice condenser, gas inlet and low temperature thermometer and was cooled to −70°C using an acetone/dry ice bath. The dry ice condenser was charged with a acetone/dry ice slurry and dry ammonia gas was passed through the cold tetrahydrofuran until the flask was approximately half-full. To this solution, solid anthracene-1,8-dicarboxylic acid[26] (1.21 g, 4.55 mmol) was added under stirring in one portion. The acetone/dry ice bath was removed. Lithium wire (190 mg, 27 mmol) was added in eight portions. Caution: exothermic reaction. Enough time was given to allow each lithium piece to dissolve before the next portion was added. After the addition was complete, the reaction mixture was refluxed for 1 h and was quenched by the addition of solid ammonium chloride (3 g). Caution: the addition of ammonium chloride is very exothermic. The ammonium chloride should be added carefully in small portions. After the addition, the reaction mixture was further stirred at room temperature until all of the ammonia had been evaporated. The tetrahydrofuran was removed under vacuum. The residual solid was suspended in water (20 mL) and was cooled with an ice bath to 0°C. Ice-cold aqueous HCl (6N) was added until pH<1. The precipitated crude 1,4,5,8-tetrahydroanthracene-1,8-dicarboxylic acid **15** was filtered off, washed with water until the filtrate was pH neutral, sucked dry and was used for the next step without further purification. The crude **15** (1.2 g) was dissolved in ethanol (150 mL). Hydrogenation catalyst, 5% Pd on activated charcoal, (1.2 g) was added and the solution degassed twice and purged with hydrogen gas. The solution was shaken under a hydrogen atmosphere (70 psi) for 12 h. After completion of the hydrogenation, the solution was degassed and filtered through a pad of celite. The ethanol was removed in vacuo to leave **17** as a white solid, which was 90 to 95% pure by ^{1}H NMR spectroscopy. It was further purified by crystallization from boiling xylenes to give **17**[12a] as colorless solid (0.83 g, 66.2% yield).

4.5.1. 2′,3′,4′,5′,6′,7′-Hexahydrospiro[1,3-ethylenedithiole-2,1′-anthracen]-8′-one (18) and 2′,3′,4′,5′,6′,7′-hexahydrodispiro[1,3-dithiolane-2,1′-anthracen-8′,2″-[1,3]dithiolane] (19). 3,4,5,6-Tetrahydro-1(2*H*),8(7*H*)-anthracenedione 6 (365 mg, 1.7 mmol) was dissolved in 50 mL dry dichloromethane under argon and cooled to 0°C. Ethane-1,2-dithiol (90%, 0.14 mL, 1.7 mmol) was added via syringe followed by the addition of $BF_3{\cdot}Et_2O$ (86 μL, mmol). The solution was stirred at room temperature under argon. After 24 h, the reaction solution was washed with 5% Na_2CO_3 solution (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residual solid was dissolved in the minimum amount of dichloromethane and was purified by flash-column chromatography on silica gel. The diprotected anthracenedione **19** was eluted with CH_2Cl_2 (192 mg, 37% based on consumed **6**) followed by the monoprotected anthracenedione **17** (214 mg, 52% based on consumed **6**). Unreacted **6** (56 mg) was eluted with CH_2Cl_2/MeOH (9:1). **18**: colorless solid mp 138°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 6.89 (s, 1H), 3.7–3.42 (m, 4H), 2.88 (t, *J*=6.1 Hz, 2H), 2.81 (t, *J*= 6.4 Hz, 2H), 2.62 (dd, *J*=6.2, 6.9 Hz, 2H), 2.42–2.37 (m, 2H), 2.14–1.98 (m, 4H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 197.8, 143.1, 142.9, 139.0, 131.4, 130.4, 128.9, 68.3, 43.8, 41.2, 39.4, 30.0, 29.5, 23.4, 22.9; HR-MALDI MS *m/z* ($M+Na^+$) 313.070 (calcd for $C_{16}H_{18}S_2ONa^+$, 313.069). Anal. calcd for $C_{16}H_{18}OS_2$: C, 66.16; H, 6.25. Found: C, 66.12; H, 6.19. 19: colorless solid mp 236–238°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 6.65 (s, 1H), 3.7–3.42 (m, 8H), 2.73 (t, *J*=6.2 Hz, 4H), 2.40–2.37 (m, 4H), 2.01–1.95 (m, 4H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 137.4, 136.6, 133.7, 128.7, 68.9, 43.8, 41.0, 29.3, 23.2; HR-MALDI MS *m/z* ($M+Na^+$) 389.051 (calcd for $C_{18}H_{22}S_4Na^+$, 389.050). Anal. calcd for $C_{18}H_{22}S_4$: C, 58.96; H, 6.05. Found: C, 58.37; H, 6.02.

4.5.2. *rac*-2′,3′,4′,5′,6′,7′-Hexahydrodispiro[imidazolidine-4,1′-anthracene-8′,2″-[1,3]dithiolane]-2,5-dione (20). A suspension of **18** (2 g, 6.85 mmol), KCN (2.5 g, mmol) and $(NH_4)_2CO_3$ (13.6 g, mmol) in ethanol/water (4:1) (100 mL) was placed in a steel reactor fitted with a glass liner. The reactor was sealed and the content heated to 130–140°C for 48 h with stirring. After the reactor had cooled to room temperature it was carefully vented in a fume hood and opened. The content was poured into water (400 mL). The precipitated product was filtered off and washed with water (200 mL). The precipitate was dried

and suspended in boiling dichloromethane (100 mL). After cooling and standing for 1 h, the suspension was filtered to give 1.8 g of pure **20** as a white solid. The filtrate contained some unreacted **18**, **20** and an unidentified byproduct. All three compounds were separated by silica gel column chromatography. Unreacted **18** (252 mg) was eluted first with CH_2Cl_2, followed by the byproduct (50 mg) with CH_2Cl_2/EtOAc (9:1), followed by **20** (420 mg) with CH_2Cl_2/EtOAc (6:4). The total yield of **20** was 97% based on reacted **18**. Mp 251°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.49 (sb, 1H), 6.8 (s, 1H), 5.6 (s, 1H), 3.6–3.38 (m, 4H), 2.86–2.7 (m, 4H), 2.4–2.25 (m, 4H), 2.08–1.94 (m, 3H), 1.84–1.74 (m, 1H); ^{13}C NMR (100.56 MHz, CD_3OD/$CDCl_3$ (1:2)) δ 178.5, 157.7, 137.7, 137.6 136.8, 130.8, 129.3, 128.8, 68.3, 64.1, 43.4, 40.5, 34.0, 29.0, 28.2, 22.5, 18.7; HR-FABMS *m/z* ($M+H^+$) 361.1033 (calcd for $C_{18}H_{21}N_2O_2S_2$, 361.1044). Anal. calcd for $C_{18}H_{20}N_2O_2S_2$: C, 59.97; H, 5.59; N, 7.77. Found: C, 60.01; H, 5.53; N, 7.78.

4.5.3. *rac*-2′,3′,4′,5′,6′7′-Hexahydrospiro[imidazolidine-4,1′-anthracen-8′-one]-2,5-dione (21). Compound **20** (569 mg, 1.58 mmol) was dissolved in ethanol/water/THF (5:3:1) (90 mL) under gentle warming. To this solution was added a solution of silver(I) nitrate (1.07 g, 6.3 mmol) in ethanol/water/THF (5:3:1) (30 mL). Immediately after the addition, a yellowish precipitate forms. The suspension was stirred in the dark at 45°C for 1 h. Brine (10 mL) was added. The precipitate was filtered off and washed with hot ethanol (30 mL). The filtrate was concentrated to 20 mL and extracted with ethyl acetate (4×30 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give the crude product as a slightly yellowish solid. The crude product was purified by crystallization from boiling ethanol/ethyl acetate to give **21** as a colorless solid (305 mg, 68% yield): mp 274°C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.15 (s, 1H), 2.95 (t, *J*=6.4 Hz, 2H), 2.88 (t, *J*=6.0 Hz, 2H), 2.61 (t, *J*=6.0 Hz, 2H), 2.3–2.0 (m, 5H), 1.94–1.82 (m, 1H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.38 (sb, 1H), 7.07 (s, 1H), 5.54 (sb, 1H), 2.95–2.81 (m, 4H), 2.62 (t, *J*=6.4 Hz, 2H), 2.40–2.30 (m, 2H), 2.15–2.0 (m, 3H), 1.88–1.77 (m, 1H); ^{13}C NMR (100.56 MHz, CD_3OD/DMF_{d7} (1:1)) δ 199.1, 179.5, 158.7, 146.0, 145.7, 134.4, 132.5, 131.1, 126.4, 65.0, 40.0, 35.0, 30.3, 30.2, 24.4, 19.8; HR-FABMS *m/z* ($M+H^+$) 285.1223 (calcd for $C_{16}H_{17}N_2O_3$, 285.1239). Anal. calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.49; H, 5.64; N, 9.88.

4.5.4. *rac*-*N*,*N*′-bis[*tert*-Butyloxycarbonyl]-2′,3′,4′,5′,6′,7′-hexahydrospiro[imidazolidine-4,1′-anthracen-8′-one]-2,5-dione (22). Ketone **21** (50 mg, 0.176 mmol) was dissolved in dry THF (7 mL) under argon. $(BOC)_2O$ (150 mg, 0.69 mmol) was added and the solution was refluxed for 3 h. The solvent was removed in vacuo. The residual crude product was purified by column chromatography on silica gel (eluant: dichloromethane/ethyl acetate (9:1)) to give **22** as a colorless oil (67 mg, 79% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.09 (s, 1H), 295–2.78 (m, 3H), 2.66–2.55 (m, 2H), 2.61 (t, *J*=6.0 Hz, 2H), 2.3–2.0 (m, 5H), 1.94–1.82 (m, 1H), 1.63 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$ (1:1)) δ 197.5, 168.3, 147.8, 147.7, 145.4, 144.8, 144.5, 131.6, 31.1, 130.4, 123.9, 87.0, 84.8, 65.5, 39.2, 32.1, 29.5, 29.3, 27.94, 27.92 23.3, 19.3; HR-MALDI MS *m/z* 407.159 ($M-CO_2-CH_2=C(CH_3)_2+Na^+$) (calcd for $C_{21}H_{24}N_2O_5Na^+$, 407.158).

4.5.5. (1′*S*,8′*S*,1″*R*)-*N*-[2″-Hydroxy-1″-phenylethyl]-8′-amino-2′,3′,4′,5′,6′,7′,8′-heptahydrospiro[imidazolidine-4,1′-anthracene]-2,5-dione (25a) and (1′*R*,8′*S*,1″*R*)-*N*-[2″-hydroxy-1″-phenylethyl]-8′-amino-2′,3′,4′,5′,6′,7′,8′-heptahydrospiro[imidazolidine-4,1′-anthracene]-2,5-dione (25b). Application of procedure A using **21** (300 mg, 1.06 mmol), (*R*)-phenylglycinol (299 mg, 1.7 mmol), and *p*-tolylsulfonic acid monohydrate (28 mg, 0.13 mmol) to form the intermediate imines (1′*S*,1″*R*)-**24a** and (1′*R*,1″*R*)-**24b**, and $NaBH(OAc)_3$ as reducing agents afforded the crude amines **25a** and **25b**. Column chromatography (silica gel; eluant: $CHCl_3$/ethyl acetate) afforded unreacted **21** (50 mg) and a 1:1-mixture of the diastereomeric amines (336 mg). Both diastereomers were further separated by preparative reversed phase HPLC on a TARGA C18 column (250×20 mm; Higgins Analytical) using water/methanol (20:35) containing 0.1% TFA as the mobile phase (20 mL/min flow rate, detection at 254 nm; retention time of **25a**: 19.6 min, retention time of **25b**: 17.3 min). The product fractions were concentrated by rotavaporation. The residual TFA salts of **25a** and of **25b** were partitioned between saturated aqueous Na_2CO_3 (20 mL) and ethyl acetate (20 mL). The organic layers were separated off. The aqueous layers were extracted with ethyl acetate (4×25 mL each). The combined organic layers were dried over $MgSO_4$, concentrated to give **25a** and **25b**, respectively as white solids. Both diastereomers were recrystallized from ethyl acetate. **25a**: (136 mg, 38% yield) colorless needles; mp 224–226°C; $[\alpha]_D^{24}=-52°$ (*c* 0.31 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4–7.16 (m, 5H), 7.10 (s, 1H), 7.03 (sb, 1H), 6.81 (s, 1H), 5.4–3.9 (svb, 3H), 3.86 (dd, *J*=3.8, 9.0 Hz, 1H), 3.58–3.51 (m, 1H), 3.52 (dd, *J*=3.8, 11.2 Hz, 1H), 3.33 (m, 1H), 2.8–2.5 (m, 4H), 2.3–2.14 (m, 2H), 1.95–1.5 (m, 6H); ^{13}C NMR (100.56 MHz, $CDCl_3$; 60°C) δ 177.27, 157.05, 142.14, 138.8, 138.51, 136.55, 130.53, 130.28, 128.96, 127.8, 127.75, 126.95, 67.55, 64.87, 64.2, 54.03, 34.57, 30.8, 28.93, 28.76, 19.5, 19.17; HR-FABMS *m/z* ($M+H^+$) 406.2125 (calcd for $C_{24}H_{28}N_3O_3$, 406.2131). Anal. calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.54; H, 6.50; N, 10.20. **25b**: (159 mg, 44.5% yield) colorless needles; mp 208°C; $[\alpha]_D^{24}=-39.1°$ (*c* 1.39, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.16 (m, 5H), 7.18 (s, 1H), 6.83 (s, 1H), 6.66 (sb, 1H), 6.4–3.0 (svb, 3H), 3.80 (dd, *J*=3.6, 8.8 Hz, 1H), 3.60–3.55 (m, 1H), 3.51 (dd, *J*=3.6, 11.0 Hz, 1H), 3.33 (dd, *J*=8.8, 11.0 Hz, 1H), 2.8–2.5 (m, 4H), 2.3–2.18 (m, 2H), 2.0–1.9 (m, 1H), 1.86–1.64 (m, 2H), 1.64–1.50 (m, 3H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 178.2, 157.6, 142.0, 136.6, 138.3, 136.4, 130.4, 130.1, 128.8, 127.6, 127.2, 67.2, 64.6, 64.3, 54.2, 34.2, 30.5, 28.8, 28.7, 19.5, 18.9; HR-FABMS *m/z* ($M+H^+$) 406.2131 (calcd for $C_{24}H_{28}N_3O_3$, 406.2131). Anal. calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.28; H, 6.49; N, 10.40.

4.5.6. (1′,8′*S*)-*N*-[*tert*-Butyloxycarbonyl]-8′-amino-2′,3′,4′,5′,6′,7′,8′-heptahydrospiro[imidazolidine-4,1′-anthracene]-2,5-dione (26b). Application of procedure B to **25b** (133 mg, 0.32 mmol) using dichloromethane/methanol (2:1) as solvent mixture instead of pure methanol, afforded

the crude amine **31**, which was *N*-BOC protected without purification. Thus, crude **31** was dissolved in THF (6 mL), methanol (3 mL) and triethylamine (0.5 mL). Solid $(BOC)_2O$ (110 mg, mmol) was added and the solution was stirred at room temperature for 13 h. The solvent was evaporated in vacuo. The residual solid was participated between water (10 mL) and ethyl acetate (10 mL). The organic layer was separated off. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residual solid was purified by column chromatography (SiO_2, ethyl acetate/dichloromethane (1:2)) to yield pure **26b** (82 mg, 65% yield), which was further recrystallized from chloroform/hexane (1:3). Mp 224°C; $[\alpha]_D^{24}=-23.4°$ (*c* 1.49, MeOH); ^{1}H NMR (400 MHz, $CDCl_2CDCl_2$; 353 K) δ 8.2 (svb, 1H), 7.12 (s, 1H), 6.83 (s, 1H), 6.1 (svb, 1H), 5.0 (svb, 1H), 4.66 (sb, 1H), 2.8–2.6 (m, 4H), 2.25–2.10 (m, 2H), 2.0–1.85 (m, 2H), 1.82–1.71 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_2CDCl_2$, 353 K) δ 176.88, 156.50, 155.92, 138.50, 137.00, 136.69, 131.14, 130.15, 126.83, 80.03, 64.54, 49.45 (sb), 34.54, 30.59, 29.17, 28.72, 28.66, 20.1, 19.24; HR-FABMS *m/z* ($M+H^+$) 386.2056 (calcd for $C_{21}H_{28}N_3O_4$, 386.2080).

4.5.7. (1′*S*,8′*S*)-*N*-[*tert*-Butyloxycarbonyl]-8′-amino-2′,3′,4′,5′,6′,7′,8′-heptahydrospiro[imidazolidine-4,1′-anthracene]-2,5-dione (26a). This compound was prepared from **25a** in 62% yield as described for the synthesis of **26b** from **25b**. Colorless solid; mp 248°C; $[\alpha]_D^{24}=-17.0°$ (*c* 0.84, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (sb, 1H), 7.15 (s, 1H), 6.88 (s, 1H), 5.78 (sb, 1H), 4.75–4.55 (m, 2H), 2.9–2.2 (m, 4H), 2.38–2.2 (m, 2H), 2.1–1.1 (m, 6H), 1.47 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3/CD_3OD$ (5:1)) δ 178.7, 157.3, 156.3, 138.0, 136.8, 136.0, 130.9, 130.0, 126.3, 79.7, 64.3, 48.7, 34.3, 30.4, 28.9, 28.5, 28.3, 20.1, 18.9, 18.9; HR-FABMS *m/z* ($M+H^+$) 386.2061 (calcd for $C_{21}H_{28}N_3O_4$, 386.2080).

4.5.8. Methyl (1*S*,8*S*)-1,8-diamino-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate (27a) (*Procedure C*). Hydantoin **26a** (173 mg, 0.61 mmol) and $Ba(OH)_2{\cdot}8H_2O$ (5.85 g, 18.5) were suspended in water (14 mL) and were heated to 120°C for 24 h in a Teflon-lined steel-reactor. After cooling the reactor to room temperature, it was vented, opened and the content was poured into 50 mL of water. The solution is carefully acidified with 1.4 M H_2SO_4 aq. The precipitated $BaSO_4$ was filtered off and washed with water. The filtrate was concentrated. The partially solidified crude **1**. $n H_2SO_4$ was taken up in the minimum amount of methanol and was precipitated with ether, filtered off, washed with ether and dried at high vacuum: ^{1}H NMR (400 MHz, D_2O) δ 7.27 (s, 1H), 7.16 (s, 1H), 4.56 (sb, 1H), 3.0–2.75 (m, 4H), 2.5–2.4 (m, 1H), 2.35–1.8 (m, 7H). The crude $\mathbf{1}{\cdot}H_2SO_4$ was dissolved in dry methanol (20 mL) and was cooled to 0°C under argon. Thionyl chloride (4 mL, mmol) was dropwise added to this stirred solution. After the addition was complete, the reaction solution was refluxed for 24 h. The solvent was evaporated in vacuo. The remaining solid was participated between ethyl acetate and 10% aqueous Na_2CO_3. The organic layer was separated off. The aqueous layer was extracted with ethyl acetate (4×20 mL). The combined organic layers were washed with 10 mL brine, dried over $MgSO_4$ and concentrated. The residual oil was purified by reversed phase HPLC (TARGA C18 20×250 mm (Higgins Analytical); MeOH/water (6:4); flow 20 mL/min, detection at 254 nm; retention time of **27a**=4.5 min) to yield **27a** as a yellowish oil (50 mg, 40.5% yield). $[\alpha]_D^{24}=+60°$ (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $C_6D_5CD_3$) δ 7.38 (s, 1H), 6.60 (s, 1H), 3.66 (t, *J*=5.6 Hz, 1H), 3.34 (s, 3H), 2.64–2.4 (m, 4H), 2.24–2.16 (m, 1H), 2.05–1.95 (m, 1H), 1.88–1.63 (m, 4H), 1.56–1.43 (m, 1H), 1.4–1.3 (m, 1H), 1.0 (ssb, 4H (NH_2), 4H (H_2O)); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 178.12, 139.24, 136.51, 136.36, 135.23, 129.91, 126.55, 59.84, 52.85, 49.29, 36.66, 33.35, 29.40, 29.33, 19.80, 19.34; HR-MALDI-MS *m/z* 297.159 ($M+Na^+$) (calcd for $C_{16}H_{22}N_2O_2Na^+$, 297.157).

4.5.9. Methyl (1*S*,8*S*)-1-amino-8-*tert*-butoxycarbonylamino-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate (4). $(BOC)_2O$ (34 mg, 0.156 mmol) was added at room temperature to a solution of **27a** (48 mg, 0.134 mmol) in dry THF (3 mL). The solution was stirred for 10 h at room temperature under argon. The solvent was evaporated in vacuo. The remaining solid was washed with hexanes (2×2 mL) to leave **4** as a slightly yellowish solid (49 mg, 78% yield).

Mp 170°C; $[\alpha]_D^{24}=-14.4°$ (*c* 0.23, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$; 60°C) δ 7.15 (s, 1H), 6.83 (s, 1H), 4.76 (sb, 1H), 4.62 (sb, 1H), 3.71 (s, 3H), 2.82–2.62 (m, 4H), 2.3–2.2 (m, 1H), 2.08–1.74 (m, 9H), 1.49 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 60°C) δ 177.91, 155.73, 137.28, 136.88, 136.22, 135.89, 129.96, 127.33, 79.60, 60.10, 52.58, 48.99, 36.73, 31.00, 29.51, 29.23, 28.82, 20.32, 19.41; HR-MALDI-MS *m/z* 397.212 ($M+Na^+$) (calcd for $C_{21}H_{30}N_2O_4Na^+$, 397.210).

4.5.10. (1*R*,8*S*)-1,8-bis(*tert*-Butyloxycarbonylamino)-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylic acid (29). Application of procedure C to **26b** (141 mg, 0.37 mmol) gave crude $\mathbf{2}{\cdot}n H_2SO_4$: ^{1}H NMR (400 MHz, D_2O) δ 7.27 (s, 1H), 7.16 (s, 1H), 4.56 (sb, 1H), 3.0–2.75 (m, 4H), 2.5–2.4 (m, 1H), 2.35–1.8 (m, 7H). Crude $\mathbf{2}{\cdot}n H_2SO_4$, was dissolved in dioxane/1N NaOH (1:1, 10 mL). This solution was cooled to 0°C. $(BOC)_2O$ (600 mg, 2.75 mmol) was added and the solution stirred at room temperature for 20 h. The solution was concentrated to half of its initial volume. Ethyl acetate (20 mL) was added and the aqueous layer cooled to 0°C and acidified to pH 3 with aqueous citric acid (10%). The organic layer was separated off and the aqueous layer extracted with ethyl acetate (5×25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate 2:1 to 0:1). The product fractions were concentrated. The remaining solid was crystallized form dichloromethane/hexanes (1:10) to yield **29** as colorless crystals (76 mg, 45% yield). mp 185°C; $[\alpha]_D^{24}=-55.3°$ (*c* 1.36, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$; 60°C) δ 7.37 (s, 1H), 6.83 (s, 1H), 5.7 (sb, 1H), 5.9–3.8 (svb, 1H), 4.9–4.6 (m, 2H), 2.82–2.5 (m, 4H), 2.4–2.32 (m, 1H), 2.12–2.02 (m, 1H), 1.92–1.7 (m, 4H), 1.48 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$; 60°C) δ 176.14, 156.06, 154.68, 137.69, 137.28, 135.53, 133.93, 130.07, 127.19, 80.14, 60.85, 49.12, 32.89, 30.44, 29.33, 29.18, 28.98, 28.79, 28.69, 20.34, 19.71;

HR-MALDI-MS *m/z* 483.247 ($M+Na^+$) (calcd for $C_{25}H_{36}N_2O_6Na^+$, 483.247). Anal. calcd for $C_{25}H_{36}N_2O_6$: C, 65.20; H, 7.88; N, 6.08. Found: C, 65.43; H, 7.77; N, 6.03.

4.5.11. Methyl (1*R*,8*S*)-1,8-bis(*tert*-butyloxycarbonylamino)-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate 30). Carboxylic acid **29** (75 mg, 0.163 mmol) was dissolved in diethyl ether (6 mL) and was cooled to 0°C. Into this solution was condensed an approximately 0.4 M solution of diazomethane in diethyl ether (9 mL), which was prepared from diazald (1 g, 4.6 mmol) using a commercially available Mini-Diazald Kit (Aldrich Chemical Company). The reaction flask was sealed with a rubber septum and was left standing inside a metal can in the back of a well-ventilated fume hood. After 12 h, excess diazomethane was decomposed via the drop-wise addition of glacial acetic acid (100 μL). The solvent was removed under high vacuum to yield **30** as a colorless oil (77 mg, quantitative). $[\alpha]_D^{24}=-32.5°$ (*c* 1.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$; 60°C) δ 7.33 (s, 1H), 6.83 (s, 1H), 5.45 (sb, 1H), 4.75–4.65 (m, 1H), 4.58 (sb, 1H), 3.72 (s, 3H), 2.82–2.5 (m, 5H), 2.38–2.30 (m, 1H), 2.07–1.75 (m, 8H), 1.51 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$; 60°C) δ 173.97, 155.69, 154.26, 137.51, 137.45, 136.15, 133.86, 130.14, 126.92, 79.83, 79.68, 61.18, 52.94, 49.12, 32.50, 30.78, 29.36, 29.2, 28.82, 28.70, 20.15, 20.03; HR-MALDI-MS *m/z* 497.263 ($M+Na^+$) (calcd for $C_{26}H_{38}N_2O_6Na^+$, 497.262)

4.5.12. Methyl (1*R*,8*S*)-1-amino-8-*tert*-butoxycarbonylamino-1,2,3,4,5,6,7,8-octahydroanthracene-1-carboxylate (5). Ice-cold trifluoroacetic acid (0.5 mL) was added to **30** (27 mg, 0.056 mmol) at 0°C. This solution was left standing in an ice bath for 1 h. The solvent was removed in vacuo. The remaining **27b**·$2CF_3COOH$ was taken up in aqueous saturated Na_2CO_3 (2 mL) and was extracted with ethyl acetate (2×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The remaining crude **27b** was redissolved in dioxane (1 mL). A solution of $(BOC)_2O$ (12.5 mg, 0.057 mmol) dissolved in dioxane (0.2 mL) was added via syringe. The reaction mixture was stirred at room temperature for 2 h until which all **27b** had been consumed (TLC control: SiO_2; mobile phase: ethyl acetate/*n*-butanol/acetic acid/water (2:1:1:1; R_F(**27b**)=0.3; R_F(**5**)=0.8). The solution was concentrated in vacuo. The residual crude product was purified by reversed phase HPLC (TARGA C18 20×250 mm (Higgins Analytical); MeOH/water (7:3); flow 20 mL/min, detection at 254 nm; retention time of **5**=13.9 min) to give **5** as a colorless foam (13 mg, 61% yield). $[\alpha]_D^{24}=-21°$ (*c* 0.32, MeOH); ^1H NMR (400 MHz, $CDCl_3$; 60°C) δ 7.13 (s, 1H), 6.83 (s, 1H), 4.73 (sb, 1H), 4.64 (sb, 1H), 3.71 (s, 3H), 2.8–2.62 (m, 4H), 2.3–2.21 (m, 1H), 2.03–1.75 (m, 9 H), 1.49 (s, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$; 60°C) δ 179.07, 155.79, 137.16, 137.02, 136.07, 135.96, 130.04, 127.07, 79.73, 60.09, 52.82, 49.17, 36.79, 30.86, 29.59, 29.27, 28.83, 20.22, 19.47; HR-MALDI-MS *m/z* 397.212 ($M+Na^+$) (calcd for $C_{21}H_{30}N_2O_4Na^+$, 397.210).

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