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First Asymmetric Synthesis of (Un)saturated 1-Alkylbenzo[*c*]azepin-3-ones: Extension to the Corresponding Benzazepines

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A flexible route for the stereoselective synthesis of a variety of structurally diverse (*1R*)-1-alkyldihydro and tetrahydrobenzazepin(ones) has been developed. The key step is a highly diastereoselective 1,2-addition process applied to a stereopure aromatic hydrazone combined with a ring-closing metathesis reaction to secure the formation of the seven-membered azaheterocycle ring system.

Introduction

The synthesis of 1-substituted 2-benzazepines is a topic of continuing interest because these ring systems lie at the heart of a great number of poly- and diversely functionalized compounds that have gained considerable attention due to their profound chemotherapeutic properties.[1] Thus compounds of this class have been found to be potent platelet anti-aggregatory drugs, anticonvulsants, antidiabetics, CNS agents[2] and specific ligands for serotonin and dopamine receptor sub-types.[2] Compounds containing the 1-substituted 2-benzazepine skeleton are also known to exhibit PNMT inhibitory activity and α_2-adrenoreceptor affinity.[3] They have also been shown to display potent inhibitory activities against AChE and SERT,[4] broncho-relaxing activity[5] and also to promote the healing of skin wounds.[6] The 1-alkyl-2-benzazepine nucleus is also found in a number of *Cephalotoxus* and *Homoerythrina* alkaloids.[7] Synthetic routes to the construction of these heterobicyclic compounds have mainly been based on Bischler–Napieralski[8] or Pictet–Spengler[9]-type cyclization reactions of activated 3-phenylpropylamine derivatives under acidic catalysis. However, besides the fact that the formation of a seven-membered ring by cyclization of an aliphatic chain often proceeds in low yields,[10] these annulation reactions are also fraught with difficulties associated with the absence of electron-donating substituents, for example, OH and OMe, on the basic aromatic nucleus, which renders the electrophilic ring-closure less selective and thus it requires more drastic conditions.[2b,11] Alternative methods have thus been developed and tetrahydro-2-benzazepines have been accessed through the reduction of products of modified Schmidt ring-expansion reactions from derivatives of 1-tetralone.[5,12] However, the success of these ring-expansion methodologies, which require the use of hazardous reagents (e.g. azides), is highly dependent upon the nature of the substrate and in all cases a mixture of isomeric compounds is obtained. Above all, none of these annulation techniques allows control of the stereogenic centre at C1. Despite the great progress made in asymmetric synthesis in recent decades, few flexible methods are available for the asymmetric synthesis of 1-alkylbenzazepines in high enantiomeric excess. To the best of our knowledge these chiral compounds have been only obtained by a multistep sequence involving metallation/alkylation/hydrazinolysis reactions applied to a variety of chiral benzazepine formamidines[12] derived from a free NH model.[5] As a consequence, the development of synthetic methodologies that may have generality for the construction of a variety of substituted or unsubstituted benzazepines equipped with alkyl appendages at C1 in a stereo- and enantioselective manner is an area of current interest and alternative methods are currently the object of synthetic endeavour. In this context, the corresponding saturated or α,β-unsaturated ε-benzolactams can serve a key role as advanced intermediates prior to the conversion to the benzazepine derivatives as they possess the requisite structure and functional group location to be easily converted into the seven-membered azaheterocyclic models through rather simple chemical manipulation.

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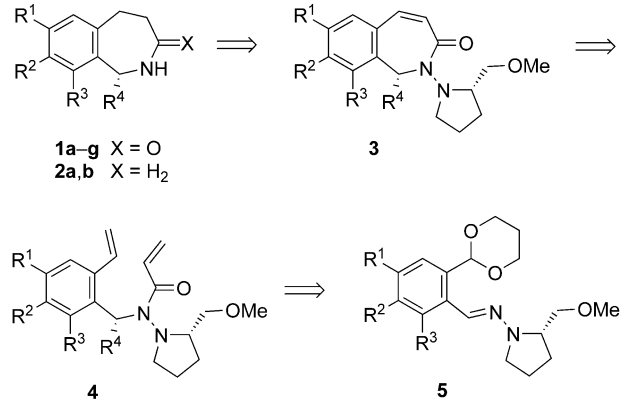
Results and Discussion

Herein we wish to report a conceptually new asymmetric approach to an array of poly- and diversely substituted 1-alkyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-ones **1**, immediate

precursors of the corresponding chiral 1-alkyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines **2** (Table 1). This new synthetic route, which is depicted retrosynthetically in Scheme 1, is based upon the use of diastereopure benzo-fused enehydrazides **3** as substrates for catalytic hydrogenation. Ensuing manipulation of the latent functionalities would provide an efficient and flexible route to optically active 1-alkylbenzazepinones **1** and benzazepines **2**. Assembly of these seven-membered cyclic enehydrazides would be secured by ring-closure metathesis (RCM) of the diastereochemically pure styrenic enehydrazides **4**. The creation of the stereogenic centre would be ensured early in the sequence by taking advantage of the high degree of diastereoselectivity observed upon nucleophilic 1,2-addition to chiral aromatic hydrazones.[13] This operation would be performed on the diversely substituted aromatic hydrazones **5** equipped with appropriate functionalities to secure installation of the mandatory diolefinic unit.

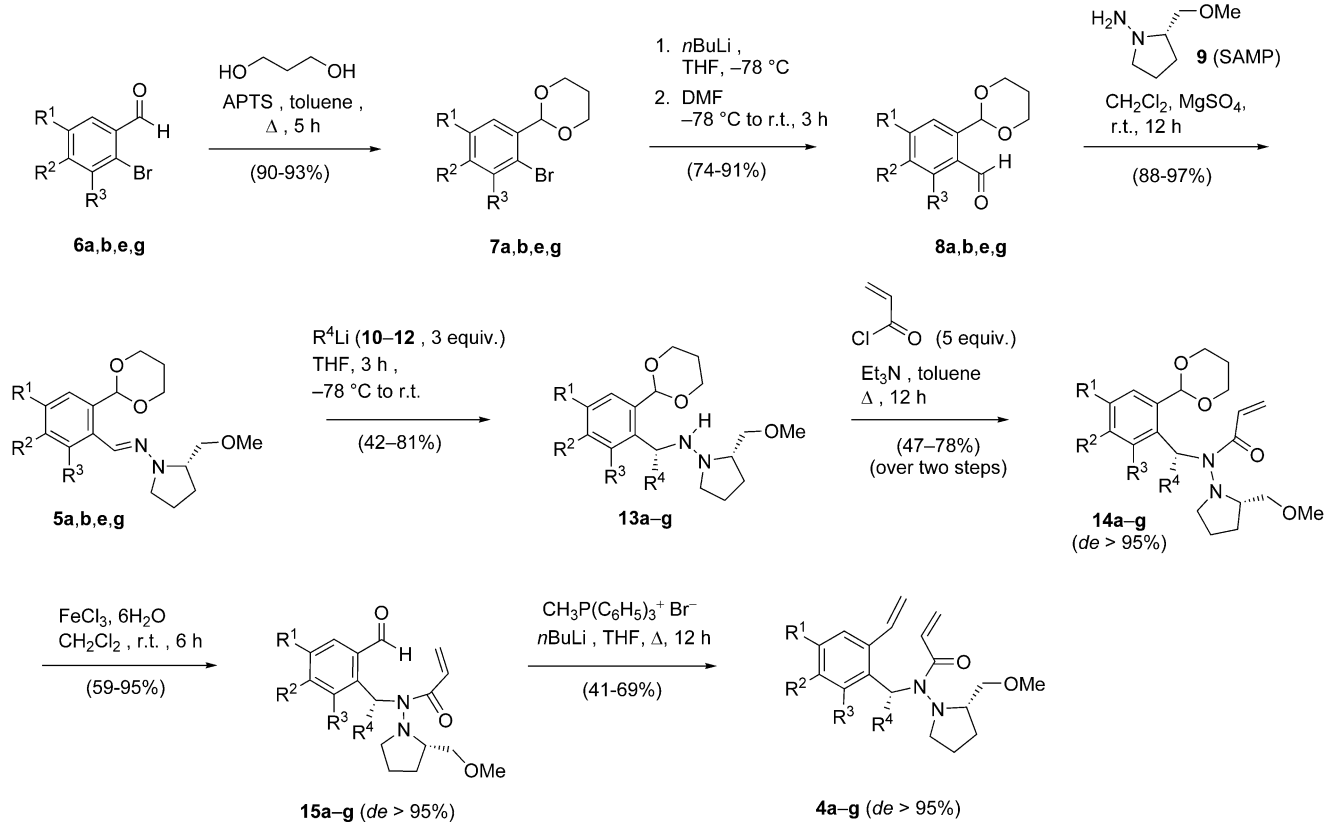
Table 1. Compounds prepared.

1–**8**, **13**–**17**	R^1	R^2	R^3	R^4
a	OMe	OMe	OMe	$CH_3(CH_2)_3$
b	H	H	H	Me
c	H	H	H	$CH_3(CH_2)_3$
d	H	H	H	$CH_3(CH_2)_5$
e	OCH_2O		H	$CH_3(CH_2)_3$
f	OCH_2O		H	Me
g	OMe	OMe	H	Me



Scheme 1. Retrosynthetic analysis of chiral benzazepin(on)es.

The first facet of the synthesis was the elaboration of the monoprotected aromatic hydrazones **5a**,**b**,**e**,**g**. These compounds were easily obtained by the three-step sequence depicted in Scheme 2 (Table 1). Initially the 2-bromobenzaldehydes **6a**,**b**,**e**,**g** were protected to give the corresponding acetals **7a**,**b**,**e**,**g** and subsequently exposed to *n*BuLi and then DMF. This technique allowed the installation of two differentiated carbaldehyde functions onto the symmetrically or unsymmetrically substituted models **8a**,**b**,**e**,**g**. The monoprotected aromatic carbaldehydes were converted into the corresponding chiral hydrazones (*S*)-**5a**,**b**,**e**,**g** by simply mixing the enantiomerically pure hydrazine (*S*)-(–)-1-amino-2-



Scheme 2. Synthesis of the styrenic enehydrazides **4a**–**g**.

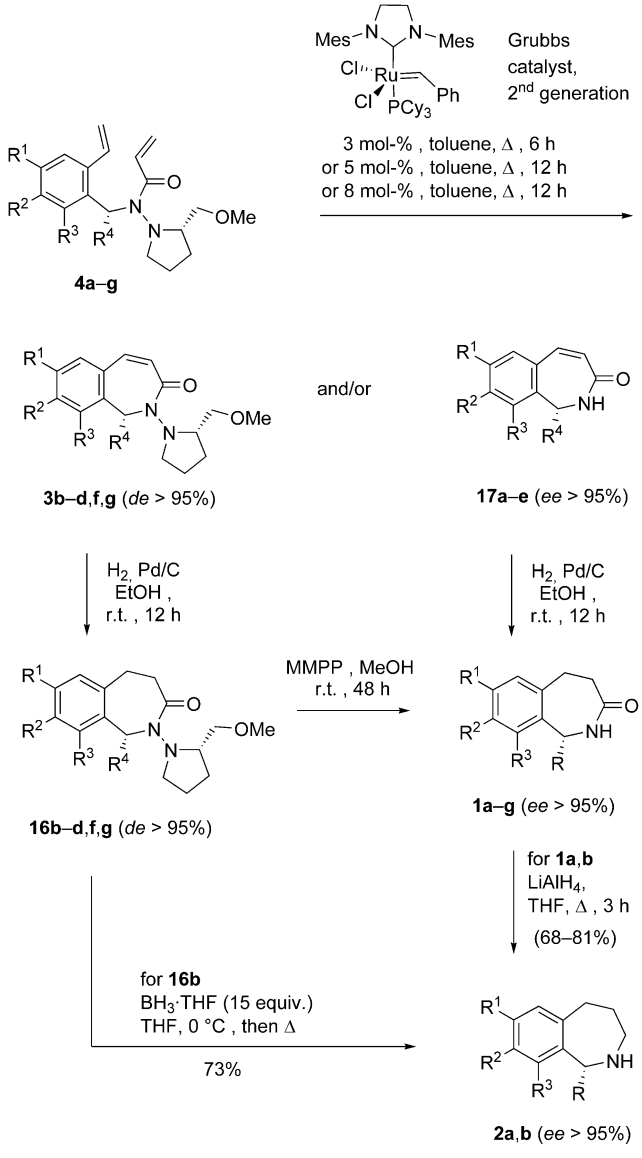
(methoxymethyl)pyrrolidine (SAMP; **9**) with aromatic carbaldehydes **8a**,**b**,**e**,**g**. Owing to the high degree of stereoselectivity observed upon reaction of the SAMP-hydrazones with organometallic reagents, a property aptly exploited by Enders and co-workers,[13] the SAMP-hydrazones were allowed to react with a variety of lithiated reagents **10**–**12** to afford the alkylated hydrazines **13a**–**g**, which were subsequently acylated with acryloyl chloride under basic conditions to afford the diastereochemically pure enehydrazides **14a**–**g** with varying degrees of success, probably due to their rather congested structure (Scheme 2, Table 2). These precursors were obtained essentially as single diastereoisomers detectable by NMR (*de* ≥ 96% after chromatographic treatment), thus revealing the excellent selectivity of the diastereofacial 1,2-addition process.[13] This procedure allowed the introduction, early in the sequence, of the absolute configuration at the benzylic α position with respect to the nitrogen atom, that is, at C1 in the final compounds **1** and **2**, one of the major challenging tasks in the synthesis of the targeted compounds.

Table 2. Yields of the precursors **8**, **5**, **14**, **15** and **4**.

	% Yield				
	8	**5**	**14**[a]	**15**[b]	**4**
a	87	97	48	66	56
b	85	88	78	74	69
c	–	–	63	95	47
d	–	–	71	84	41
e	74	91	47	70	57
f	–	–	58	72	66
g	91	88	53	59	48

[a] Over two steps. [b] Yield of the crude product.

Regeneration of the retained formyl functionality proceeded uneventfully to afford satisfactory yields of the highly functionalized models **15a**–**g** and a final Wittig reaction delivered the opened aromatic dienehydrazides **4a**–**g**, suitable candidates for the ring-closing metathesis reaction. The olefin metathesis reaction ranks high in the hierarchy of synthetic approaches for the elaboration of small, medium and large unsaturated heterocycles,[14] and the propulsion of the RCM reaction to the forefront of contemporary organic chemistry stems mainly from the advent of efficient homogeneous catalysts.[15] For the ring-closing metathesis of the styrenic enehydrazides **4a**–**g** we observed that the outcome of the annulation reaction was strongly conditioned by the structures of the constitutionally diverse dienic precursors (Scheme 3, Table 3). Thus, for the methylated compounds **4b**,**f**,**g**, the best results were obtained by employing 3 mol-% of the second-generation Grubbs catalyst at reflux for 6 h in toluene, which gave significantly better results than the usual solvent CH_2Cl_2. This operation delivered satisfactory yields of the virtually diastereochemically pure benzazepinones (*R*,*S*)-**3b**,**f**,**g**. Annulation of the bulkier models **4c**,**d** required an increased amount of ruthenium catalyst, that is, 5 mol-%, and an extended reaction time, that is, 12 h. In these cases we observed that the expected diastereopure benzazepinones (*R*,*S*)-**3c**,**d** were obtained along with the NH-free (*R*)-benzazepinones **17c**,**d** released from the chiral appendage. We surmised that the formation of these lactams could be attributed to the N–N bond cleavage catalysed by the efficient homogeneous ruthenium catalyst. The activity of the ruthenium complex in the cleavage of the N–N bonds has indeed been demonstrated for a number of aromatic hydrazines and hydrazides.[16] To corroborate this hypothesis, the polysubstituted models **4a**,**e** were in turn exposed to 8 mol-% of the second-generation Grubbs catalyst in toluene for 12 h, which delivered exclusively the chiral unsaturated benzolactams **17a**,**e** in excellent yield and enantiopurity. Despite the fact that the RCM reaction could be a priori performed with the concomitant release of the chiral auxiliary we opted to isolate and characterize the easily separable cyclic enehydrazides **3**. It was indeed anticipated that the olefinic moiety of such compounds equipped with a stereocontrolling agent could serve



Scheme 3. Asymmetric synthesis of benzazepinones **1a**–**g** and benzazepines **2a**,**b**.

as a chemical handle for alternative functionalization chemistry. Furthermore, the formation of compounds **3** and **17** was not detrimental to the outcome of the synthetic process liable to give access to the targeted titled compounds. Thus, catalytic hydrogenation of **3b**–**d**,**f**,**g** proceeded uneventfully to provide excellent yields of the saturated hydrazides **16b**–**d**,**f**,**g**, a class of compounds endowed with an interesting synthetic profile. Indeed treatment of **16b**–**d**,**f**,**g** with magnesium monoperoxyphthalate (MMPP)[17] triggered off the exclusive release of the chiral appendage and this operation delivered very satisfactory yields of the virtually enantiopure NH-free 1-alkylbenzazepin-2-ones **1b**–**d**,**f**,**g**. As far as we are aware, this synthetic approach can be regarded as the first asymmetric synthesis of these monoalkylated benzazepinones as well as their unsaturated congeners **17a**–**e**. Finally, the reductive N–N bond cleavage by the BH_3·THF complex could be accomplished with the simultaneous reduction of the lactam carbonyl functionality of **16b** to complete the synthesis of the chiral 1-alkylbenzazepine (*R*)-**2b**. Alternatively the chiral seven-membered azaheterocycles (*R*)-**2a**,**b** could be accessed by $LiAlH_4$ reduction of the corresponding lactams **1a**,**b**.

Table 3. Yields of the benzazepinones **3**, **17**, **16** and **1** and the benzazepines **2**.

	% Yield					
	3 and/or **17**[a]	**1**(from **17**)	**16**[b](from **3**)	**1**(from **16**)	**2**	
a	–	50	90	–	–	68[c]
b	72	–	–	91	81	81[c]
b	38	41	90	–	–	73[d]
c	43	48	92	85	66	–
d	11	42	95	88	59	–
e	–	48	90	–	–	–
f	41	–	–	82	78	–
g	54	–	–	87	57	–

[a] After an extended reaction time (12 h). [b] Yield of the crude product. [c] $LiAlH_4$ reduction of **1a**,**b**. [d] Treatment of **16b** with BH_3·THF.

The absolute configurations of the stereogenic centres as well as the enantiopurities of compounds **1** and **2** were confirmed to be *R* by comparison of the sign, the optical rotation value and the spectroscopic data with that of an authentic sample assembled by a conceptually different synthetic approach, for example, $[\alpha]_D^{25}$ = –13.2 (*c* = 1.05, $CHCl_3$) for (*R*)-**2b** and $[\alpha]_D$ = +13.3 (*c* = 9.0, EtOH) for (*S*)-**2b**.[12]

Conclusions

We have developed a flexible and efficient route for the stereoselective synthesis of a variety of structurally diverse 1-alkyldihydro and tetrahydro-2-benzazepin(on)es. The key steps are the highly diastereoselective nucleophilic 1,2-addition process applied to a diastereopure aromatic hydrazone combined with RCM to form the seven-member azaheterocycle ring system. The synthetic utility of this approach has been further enhanced by its extension to the synthesis of the corresponding benzazepines. We also believe that the formation of unsaturated hydrazide intermediates provides a strong incentive for the elaboration of structurally modified congeners.

Experimental Section

General Methods: Tetrahydrofuran (THF) was predried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, Et_3N and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry argon. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. The melting points were obtained with a Reichert-Thermopan apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. Elemental analyses were obtained by using a Carlo–Erba CHNS-11110 instrument. NMR spectra were recorded with a Bruker AM 300 (300 and 75 MHz for ^1H, and ^{13}C, respectively) using $CDCl_3$ as the solvent and TMS as the internal standard.

Starting Materials: The *o*-bromobenzaldehydes **6b**,**e**,**g** are commercially available and 2-bromo-3,4,5-trimethoxybenzaldehyde (**6a**) was prepared according to a reported procedure.[18] *o*-Bromobenzaldehyde acetals **7a**,[19] **7b**[20] and **7e**[21] were synthesized following literature methods.

2-(2-Bromo-4,5-dimethoxyphenyl)-1,3-dioxane (7g): A stirred solution of 2-bromo-4,5-dimethoxybenzaldehyde (**6g**; 4.90 g, 20 mmol), 1,3-propanediol (4.75 g, 60 mmol) and *p*-toluenesulfonic acid (PTSA, 20 mg, catalytic amount) in dry toluene (60 mL) was heated at reflux in a Dean–Stark apparatus for 5 h. After evaporation of the solvent under reduced pressure, the crude residue was purified by flash column chromatography (ethyl acetate/hexanes, 40:60, as eluent) to afford the title compound **7g** as a white solid (5.46 g, 90%); m.p. 121–122 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 13.5 Hz, 1 H, CH_2), 2.18–2.34 (m, 1 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.04 (t, *J* = 10.1 Hz, 2 H, OCH_2), 4.20–4.41 (m, 2 H, OCH_2), 5.71 (s, 1 H, OCHO), 6.99 (s, 1 H, H_{arom}), 7.21 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (CH_2), 55.9 (2 OCH_3), 67.4 (OCH_2), 67.5 (OCH_2), 100.7 (OCHO), 109.4 (CH), 111.8 (CH), 113.2 (C), 130.6 (C), 147.1 (C), 148.4 (C) ppm. $C_{12}H_{15}BrO_4$ (303.1): calcd. C 47.54, H 4.99; found C 47.35, H 4.89.

General Procedure for the Synthesis of 2-(1,3-Dioxan-2-yl)benzaldehyde Derivatives 8a,b,e,g: *n*BuLi (6.6 mL, 16.5 mmol, 2.5 M solution in hexanes) was slowly added to a stirred solution of the appropriate protected 2-bromobenzaldehyde **7a**,**b**,**e**,**g** (15 mmol) in dry THF (50 mL) at –78 °C under argon. The mixture was warmed to –50 °C for 40 min and then cooled to –78 °C. DMF (1.28 mL, 1.20 g, 16.5 mmol) was added and the solution was warmed to room temp. and then stirred for 3 h. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography (ethyl acetate/hexanes, 40:60, as eluent) to give compounds **8a**,**b**,**e**,**g** as colourless oils.

6-(1,3-Dioxan-2-yl)-2,3,4-trimethoxybenzaldehyde (8a): Yield 3.68 g, 87%. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 13.6 Hz, 1 H, CH_2), 2.15–2.35 (m, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.99 (s, 6 H, 2 OCH_3), 4.10 (t, *J* = 12.2 Hz, 2 H, OCH_2), 4.25 (dd, *J* = 10.7, 5.1 Hz, 2 H, OCH_2), 6.35 (s, 1 H, OCHO), 7.26 (s, 1 H, H_{arom}), 10.40 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ

= 25.8 (CH_2), 56.2 (OCH_3), 61.0 (OCH_3), 62.5 (OCH_3), 67.6 (2 OCH_2), 97.3 (OCHO), 105.7 (CH), 119.1 (C), 133.7 (C), 151.5 (C), 155.5 (2 C), 190.6 (CHO) ppm. $C_{14}H_{18}O_6$ (282.3): calcd. C 59.57, H 6.43; found C 59.41, H 6.18.

2-(1,3-Dioxan-2-yl)benzaldehyde (8b):[22] Yield 2.45 g, 85%.

6-(1,3-Dioxan-2-yl)benzo[1,3]dioxole-5-carbaldehyde (8e): Yield 2.62 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, J = 13.6 Hz, 1 H, CH_2), 2.16–2.34 (m, 1 H, CH_2), 4.02 (t, J = 9.9 Hz, 2 H, OCH_2), 4.17–4.31 (m, 2 H, OCH_2), 5.91 (s, 1 H, OCHO), 6.01 (s, 2 H, OCH_2O), 7.13 (s, 1 H, H_{arom}), 7.34 (s, 1 H, H_{arom}), 10.30 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (CH_2), 67.5 (OCH_2), 67.5 (OCH_2), 100.0 (OCHO), 101.1 (OCH_2O), 110.5 (CH), 114.7 (CH), 129.6 (C), 140.2 (C), 147.4 (C), 152.3 (C), 190.0 (CHO) ppm. $C_{12}H_{12}O_5$ (236.3): calcd. C 61.02, H 5.12; found C 61.27, H 4.99.

2-(1,3-Dioxan-2-yl)-4,5-dimethoxybenzaldehyde (8g): Yield 3.44 g, 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, J = 13.4 Hz, 1 H, CH_2), 2.20–2.37 (m, 1 H, CH_2), 3.96 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.07 (t, J = 9.9 Hz, 2 H, OCH_2), 4.26–4.34 (m, 2 H, OCH_2), 6.04 (s, 1 H, OCHO), 7.28 (s, 1 H, H_{arom}), 7.47 (s, 1 H, H_{arom}), 10.39 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8 (CH_2), 55.9 (2 OCH_3), 67.5 (OCH_2), 67.6 (OCH_2), 100.1 (OCHO), 114.4 (CH), 119.1 (CH), 130.5 (C), 139.1 (C), 148.8 (C), 153.4 (C), 189.9 (CHO) ppm. $C_{13}H_{16}O_5$ (252.3): calcd. C 61.90, H 6.39; found C 61.68, H 6.44.

General Procedure for the Synthesis of the SAMP-Hydrazones 5a,b,e,g: A solution of the appropriate 2-(1,3-dioxan-2-yl)benzaldehyde derivative **8a**,**b**,**e**,**g** (0.10 mmol), SAMP (1.56 g, 0.12 mmol) and $MgSO_4$ (500 mg) in CH_2Cl_2 (50 mL) was stirred at room temp. for 12 h. $MgSO_4$ was filtered off and the solvent was evaporated under vacuum. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes, 50:50, as eluent) to yield hydrazones **5a**,**b**,**e**,**g** as a yellow viscous oil.

{(*E*)-1-[6-(1,3-Dioxan-2-yl)-2,3,4-trimethoxyphenyl]methylidene}-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amine (5a): Yield 3.83 g, 97%. $[a]_D^{25}$ = –97.3 (c = 1.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, J = 13.4 Hz, 1 H, CH_2), 1.81–2.13 (m, 4 H, 2 CH_2), 2.16–2.39 (m, 1 H, CH_2), 3.05 (q, J = 8.5 Hz, 1 H, CH), 3.44 (s, 3 H, OCH_3), 3.51–3.63 (m, 2 H, CH_2N), 3.65–3.79 (m, 2 H, CH_2O), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.02 (t, J = 10.2 Hz, 2 H, OCH_2), 4.21–4.37 (m, 2 H, OCH_2), 6.30 (s, 1 H, OCHO), 7.19 (s, 1 H, H_{arom}), 7.52 (s, 1 H, CH=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 (CH_2), 25.7 (CH_2), 26.8 (CH_2), 49.1 (NCH_2), 55.9 (OCH_3), 56.0 (OCH_3), 59.4 (OCH_3), 60.8 (OCH_3), 63.6 (CH), 67.3 (OCH_2), 67.4 (OCH_2), 74.9 (OCH_2), 99.0 (OCHO), 102.9 (CH), 121.3 (C), 129.6 (CH=N), 131.5 (C), 134.3 (C), 151.2 (C), 153.2 (C) ppm. $C_{20}H_{30}N_2O_6$ (394.46): calcd. C 60.90, H 7.67, N 7.10; found C 61.09, H 7.77, N 7.46.

{(*E*)-1-[2-(1,3-Dioxan-2-yl)phenyl]methylidene}[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amine (5b): Yield 2.68 g, 88%. $[a]_D^{25}$ = –68.9 (c = 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, J = 13.4 Hz, 1 H, CH_2), 1.86–2.07 (m, 4 H, 2 CH_2), 2.16–2.37 (m, 1 H, CH_2), 3.10 (q, J = 8.5 Hz, 1 H, CH), 3.40 (s, 3 H, OCH_3), 3.52 (t, J = 7.9 Hz, 2 H, CH_2N), 3.68 (dd, J = 3.5, 10.2 Hz, 2 H, OCH_2), 3.97 (t, J = 10.1 Hz, 2 H, OCH_2), 4.26 (dd, J = 5.0, 6.0 Hz, 2 H, OCH_2), 5.75 (s, 1 H, CH), 7.22 (sext., J = 6.1 Hz, 2 H, H_{arom}), 7.52 (dd, J = 1.1, 7.7 Hz, 1 H, H_{arom}), 7.63 (s, 1 H, CH=N), 7.85 (dd, J = 1.6, 7.8 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 49.1 (NCH_2), 59.2 (OCH_3), 63.0 (CH), 67.4 (OCH_2), 67.5 (OCH_2), 74.7 (OCH_2), 101.0 (OCHO), 125.1 (CH), 126.1 (CH=N), 126.5 (CH), 128.7 (CH), 130.7 (CH), 134.4 (C), 134.7 (C) ppm. $C_{17}H_{24}N_2O_3$ (304.4): calcd. C 67.08, H 7.95, N 9.20; found C 67.19, H 7.86, N 9.39.

{(*E*)-1-[6-(1,3-Dioxan-2-yl)benzo[1,3]dioxol-5-yl]methylidene}[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amine (5e): Yield 3.17 g, 91%. $[a]_D^{25}$ = –63.6 (c = 0.73, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, J = 13.5 Hz, 1 H, CH_2), 1.81–2.09 (m, 4 H, 2 CH_2), 2.12–2.28 (m, 1 H, CH_2), 3.08 (q, J = 8.4 Hz, 1 H, CH), 3.38 (s, 3 H, OCH_3), 3.54 (t, J = 7.9 Hz, 2 H, CH_2N), 3.66 (d, J = 9.8 Hz, 2 H, OCH_2), 3.95 (t, J = 10.2 Hz, 2 H, OCH_2), 4.19–4.29 (m, 2 H, OCH_2), 5.64 (s, 1 H, OCHO), 5.91 (s, 2 H, OCH_2O), 7.04 (s, 1 H, H_{arom}), 7.37 (s, 1 H, H_{arom}), 7.53 (s, 1 H, CH=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 49.3 (NCH_2), 59.3 (OCH_3), 63.1 (CH), 67.5 (OCH_2), 67.5 (OCH_2), 74.6 (OCH_2), 100.0 (OCHO), 101.0 (OCH_2O), 104.7 (CH), 106.5 (CH), 129.0 (C), 129.5 (C), 130.4 (C), 130.5 (CH=N), 146.7 (C), 148.0 (C) ppm. $C_{18}H_{24}N_2O_5$ (348.4): calcd. C 62.05, H 6.94, N 8.04; found C 61.92, H 6.69, N 8.28.

{(*E*)-1-[2-(1,3-Dioxan-2-yl)-4,5-dimethoxyphenyl]methylidene}[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amine (5g): Yield 3.21 g, 88%. $[a]_D^{25}$ = –65.3 (c = 0.93, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, J = 13.5 Hz, 1 H, CH_2), 1.74–2.02 (m, 4 H, 2 CH_2), 2.11–2.24 (m, 1 H, CH_2), 3.04 (q, J = 8.5 Hz, 1 H, CH), 3.33 (s, 3 H, OCH_3), 3.43 (t, J = 8.0 Hz, 2 H, CH_2N), 3.60 (d, J = 10.0 Hz, 2 H, OCH_2), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.89 (t, J = 10.3 Hz, 2 H, OCH_2), 4.09–4.27 (m, 2 H, OCH_2), 5.64 (s, 1 H, OCHO), 7.02 (s, 1 H, H_{arom}), 7.36 (s, 1 H, H_{arom}), 7.50 (s, 1 H, CH=N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 49.5 (NCH_2), 55.8 (2 OCH_3), 59.3 (OCH_3), 63.1 (CH), 67.5 (OCH_2), 67.5 (OCH_2), 74.8 (OCH_2), 100.1 (OCHO), 107.4 (CH), 108.8 (CH), 127.6 (CH=N), 130.8 (C), 130.9 (C), 149.4 (C), 157.1 (C) ppm. $C_{19}H_{28}N_2O_5$ (364.4): calcd. C 62.62, H 7.74, N 7.69; found C 62.45, H 7.87, N 7.41.

General Procedure for the Synthesis of the Protected (1*R*)-Alkylenehydrazides 14a–g: Methyllithium (**10**, 3.75 mL, 6 mmol, 1.6 M in diethyl ether), *n*-butyllithium (**11**, 3.75 mL, 6 mmol, 1.6 M solution in hexanes) or hexyllithium (**12**, 2.6 mL, 6 mmol, 2.3 M solution in hexane) was added dropwise to a stirred solution of the appropriate hydrazone **5a**,**b**,**e**,**g** (2 mmol) in dry THF (10 mL) at –78 °C under argon. The mixture was then warmed to room temp. and stirred for a further 3 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to give the corresponding crude hydrazine **13a**–**g** as a brown oil, which was used without further purification in the next step. Acryloyl chloride (545 mg, 0.48 mL, 6 mmol) was added dropwise to a stirred solution of hydrazine **13a**–**g** (1.2 mmol) and Et_3N (5 mL) in dry toluene (12 mL) under argon and the mixture was heated at reflux for 12 h. The cooled solution was washed with water (3 × 15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), the solvent was evaporated under vacuum and the crude product was purified by flash column chromatography (ethyl acetate/hexanes, 40:60, as eluent) to yield the corresponding enehydrazide **14a**–**g** as a pale brown-orange oil.

***N*-{(*R*)-1-[6-(1,3-Dioxan-2-yl)-2,3,4-trimethoxyphenyl]pentyl}-*N*-[(S)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14a):** Yield 292 mg, 48%. $[a]_D^{25}$ = –66.6 (c = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.9 Hz, 3 H, CH_3), 1.09–1.52 (m, 5 H, 4 H, 2 CH_2 + 1 H, CH_2), 1.53–1.79 (m, 4 H, 2 CH_2), 1.81–1.99 (m, 2 H, CH_2), 2.03–2.27 (m, 1 H, CH_2), 2.47–2.74 (m, 1 H, CH_2N), 2.77–2.98 (m, 1 H, CH_2N), 3.01–3.17 (m, 2 H, OCH_2), 3.11 (s, 3 H, OCH_3), 3.35–3.51 (m, 1 H, CH), 3.74–4.02 (m, 2 H, OCH_2), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3),

4.09–4.31 (m, 2 H, OCH_2), 5.39–5.48 (m, 1 H, ArCHN), 5.55 (s, 1 H, OCHO), 5.61 (dd, *J* = 2.2, 10.3 Hz, 1 H, CH_2=), 6.35 (dd, *J* = 2.2, 15.1 Hz, 1 H, CH_2=), 7.06 (dd, *J* = 6.9, 10.3 Hz, 1 H, CH=), 7.09 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.6 (CH_2), 22.5 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 29.8 (CH_2), 33.9 (CH_2), 50.8 (NCH_2), 55.8 (OCH_3), 55.9 (OCH_3), 56.6 (ArCHN), 57.8 (OCH_3), 58.4 (CH), 60.8 (OCH_3), 67.5 (OCH_2), 67.6 (OCH_2), 72.9 (OCH_2), 100.2 (OCHO), 103.2 (CH), 121.3 (C), 126.2 (CH_2=), 129.4 (CH=), 131.7 (C), 134.6 (C), 150.8 (C), 152.1 (C), 170.8 (CO) ppm. $C_{27}H_{42}N_2O_7$ (506.6): calcd. C 64.01, H 8.36, N 5.53; found C 63.78, H 8.13, N 5.38.

***N*-{(*R*)-1-[2-(1,3-Dioxan-2-yl)phenyl]ethyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14b):** Yield 350 mg, 78%. $[\alpha]_D^{25}$ = –55.8 (*c* = 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 13.6 Hz, 1 H, CH_2), 1.51–1.69 (m, 4 H, 2 CH_2), 1.82 (d, *J* = 7.3 Hz, 3 H, CH_3), 2.12–2.43 (m, 1 H, CH_2), 2.63 (q, *J* = 7.75 Hz, 1 H, CH_2N), 2.78–2.92 (m, 1 H, CH_2N), 3.05 (d, *J* = 11.6 Hz, 2 H, OCH_2), 3.06 (s, 3 H, OCH_3), 3.38–3.51 (m, 1 H, CH), 3.82–4.11 (m, 2 H, OCH_2), 4.17–4.31 (m, 2 H, OCH_2), 5.61 (dd, *J* = 2.2, 9.9 Hz, 1 H, CH_2=), 5.62 (s, 1 H, OCHO), 5.72 (q, *J* = 7.2 Hz, 1 H, ArCH), 6.37 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 7.07 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.23–7.40 (m, 2 H, H_{arom}), 7.51 (d, *J* = 7.7 Hz, 1 H, H_{arom}), 7.87 (d, *J* = 7.8 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.8 (CH_2), 25.9 (CH_2), 27.1 (CH_2), 50.9 (NCH_2), 51.5 (CH), 58.1 (OCH_3), 58.6 (CH), 67.6 (OCH_2), 67.7 (OCH_2), 73 (OCH_2), 101.1 (OCHO), 126.4 (CH_2=), 126.8 (CH), 127.4 (CH), 128.6 (CH=), 129.4 (CH), 130.0 (CH), 135.2 (C), 141.2 (C), 170.3 (CO) ppm. $C_{21}H_{30}N_2O_4$ (374.5): calcd. C 67.36, H 8.07, N 7.48; found C 67.63, H 8.14, N 7.69.

***N*-{(*R*)-1-[2-(1,3-Dioxan-2-yl)phenyl]pentyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14c):** Yield 315 mg, 63%. $[\alpha]_D^{25}$ = –59.4 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.12–1.42 (m, 4 H, 2 CH_2), 1.45 (d, *J* = 13.5 Hz, 1 H, CH_2), 1.51–1.82 (m, 4 H, 2 CH_2), 1.83–2.04 (m, 2 H, CH_2), 2.13–2.34 (m, 1 H, CH_2), 2.60–2.79 (m, 1 H, CH_2N), 2.81–2.94 (m, 1 H, CH_2N), 2.93–3.06 (m, 5 H, OCH_2, OCH_3), 3.25–3.38 (m, 1 H, CH), 3.84–4.11 (m, 2 H, OCH_2), 4.14–4.32 (m, 2 H, OCH_2), 5.43 (q, *J* = 5.6 Hz, 1 H, ArCHN), 5.58 (dd, *J* = 2.3, 10.2 Hz, 1 H, CH_2=), 5.59 (s, 1 H, OCHO), 6.34 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 7.08 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.23–7.28 (m, 2 H, H_{arom}), 7.47 (d, *J* = 7.6 Hz, 1 H, H_{arom}), 7.92 (d, *J* = 7.4 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 21.6 (CH_2), 22.5 (CH_2), 25.9 (CH_2), 26.8 (CH_2), 29.8 (CH_2), 33.8 (CH_2), 50.6 (NCH_2), 56.4 (ArCHN), 57.7 (OCH_3), 58.3 (CH), 67.5 (OCH_2), 67.6 (OCH_2), 72.8 (OCH_2), 101.6 (OCHO), 126.1 (CH_2=), 127.0 (CH), 127.1 (CH), 128.8 (CH=), 129.3 (CH), 130.2 (CH), 134.8 (C), 140.1 (C), 170.6 (CO) ppm. $C_{24}H_{36}N_2O_4$ (416.5): calcd. C 69.20, H 8.71, N 6.72; found C 69.38, H 8.84, N 6.99.

***N*-{(*R*)-1-[2-(1,3-Dioxan-2-yl)phenyl]heptyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14d):** Yield 379 mg, 71%. $[\alpha]_D^{25}$ = –57.5 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72–0.93 (m, 3 H, CH_3), 1.12–1.41 (m, 8 H, 4 CH_2), 1.46 (d, *J* = 13.6 Hz, 1 H, CH_2), 1.51–1.79 (m, 4 H, 2 CH_2), 1.82–2.03 (m, 2 H, CH_2), 2.05–2.32 (m, 1 H, CH_2), 2.58–2.79 (m, 1 H, CH_2N), 2.81–2.93 (m, 1 H, CH_2N), 2.94–3.04 (m, 5 H, OCH_2, OCH_3), 3.34 (m, 1 H, CH), 3.82–4.08 (m, 2 H, OCH_2), 4.13–4.34 (m, 2 H, OCH_2), 5.44 (q, *J* = 5.6 Hz, 1 H, ArCHN), 5.58 (dd, *J* = 2.3, 9.9 Hz, 1 H, CH_2=), 5.60 (s, 1 H, OCHO), 6.34 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 7.08 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.18–7.39 (m, 2 H, H_{arom}), 7.47 (d, *J* = 7.5 Hz, 1 H, H_{arom}), 7.91 (d, *J* = 7.5 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.7 (CH_2), 22.6 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 34.1 (CH_2), 50.7 (NCH_2), 56.3 (ArCHN), 57.8 (OCH_3), 58.3 (CH), 67.5 (OCH_2), 67.6 (OCH_2), 72.9 (OCH_2), 101.5 (OCHO), 126.1 (CH_2=), 127.0 (CH), 127.1 (CH), 128.9 (CH=), 129.3 (CH), 130.2 (CH), 134.9 (C), 142.3 (C), 170.6 (CO) ppm. $C_{26}H_{40}N_2O_4$ (444.6): calcd. C 70.24, H 9.07, N 6.30; found C 70.27, H 8.88, N 6.18.

***N*-{(*R*)-1-[6-(1,3-Dioxan-2-yl)benzo[1,3]dioxol-5-yl]pentyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14e):** Yield 260 mg, 47%. $[\alpha]_D^{25}$ = –18.6 (*c* = 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.11–1.51 (m, 5 H, 4 H, 2 CH_2 + 1 H, CH_2), 1.53–1.81 (m, 4 H, 2 CH_2), 1.83–2.01 (m, 2 H, CH_2), 2.07–2.31 (m, 1 H, CH_2), 2.48–2.76 (m, 1 H, CH_2N), 2.78–2.96 (m, 1 H, CH_2N), 3.09 (dd, *J* = 4.1, 8.9 Hz, 2 H, OCH_2), 3.11 (s, 3 H, OCH_3), 3.37–3.50 (m, 1 H, CH), 3.77–4.09 (m, 2 H, OCH_2), 4.11–4.35 (m, 2 H, OCH_2), 5.39–5.48 (m, 1 H, ArCHN), 5.55 (s, 1 H, OCHO), 5.61 (dd, *J* = 2.2, 10.4 Hz, 1 H, CH_2=), 5.88 (s, 2 H, OCH_2O), 6.35 (dd, *J* = 2.2, 15.1 Hz, 1 H, CH_2=), 7.05 (s, 1 H, H_{arom}), 7.06 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.45 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.3 (CH_2), 22.6 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 29.6 (CH_2), 34.1 (CH_2), 50.8 (NCH_2), 56.0 (ArCHN), 58.1 (OCH_3), 58.5 (CH), 67.5 (OCH_2), 67.5 (OCH_2), 73.0 (OCH_2), 100.3 (OCHO), 101.1 (OCH_2O), 107.1 (CH), 109.0 (CH), 126.4 (CH_2=), 128.7 (C), 130.1 (CH=), 132.3 (C), 146.5 (C), 148.1 (C), 170.4 (CO) ppm. $C_{25}H_{36}N_2O_6$ (460.6): calcd. C 65.20, H 7.88, N 6.08; found C 64.99, H 7.74, N 6.19.

***N*-{(*R*)-1-[6-(1,3-Dioxan-2-yl)benzo[1,3]dioxol-5-yl]ethyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14f):** Yield 291 mg, 58%. $[\alpha]_D^{25}$ = –15.4 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 13.7 Hz, 1 H, CH_2), 1.40–1.68 (m, 4 H, 2 CH_2), 1.73 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.0–2.28 (m, 1 H, CH_2), 2.63 (q, *J* = 7.6 Hz, 1 H, CH_2N), 2.68–2.93 (m, 1 H, CH_2N), 3.02 (dd, *J* = 3.0, 9.7 Hz, 2 H, OCH_2), 3.03 (s, 3 H, OCH_3), 3.38–3.51 (m, 1 H, CH), 3.62–3.97 (m, 2 H, OCH_2), 4.07–4.24 (m, 2 H, OCH_2), 5.49 (s, 1 H, OCHO), 5.54 (dd, *J* = 2.8, 9.6 Hz, 1 H, CH_2=), 5.59–5.77 (m, 1 H, CH), 5.86 (s, 2 H, OCH_2O), 6.29 (dd, *J* = 2.5, 15.2 Hz, 1 H, CH_2=), 6.98 (s, 1 H, H_{arom}), 7.01 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.33 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.8 (CH_2), 25.7 (CH_2), 27.1 (CH_2), 50.9 (NCH_2), 51.3 (CH), 58.2 (CH), 58.5 (OCH_3), 67.4 (OCH_2), 67.5 (OCH_2), 73.0 (OCH_2), 100.0 (OCHO), 101.1 (OCH_2O), 107.0 (CH), 108.6 (CH), 126.4 (CH_2=), 129.4 (C), 129.8 (CH=), 135.3 (C), 146.6 (C), 148.0 (C), 170.1 (CO) ppm. $C_{22}H_{30}N_2O_6$ (418.5): calcd. C 63.14, H 7.23, N 6.69; found C 63.29, H 7.05, N 6.51.

***N*-{(*R*)-1-[2-(1,3-Dioxan-2-yl)-4,5-dimethoxyphenyl]ethyl}-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (14g):** Yield 276 mg, 53%. $[\alpha]_D^{25}$ = –29.1 (*c* = 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 13.4 Hz, 1 H, CH), 1.49–1.76 (m, 4 H, 2 CH_2), 1.81 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.1–2.33 (m, 1 H, CH_2), 2.65 (q, *J* = 7.6 Hz, 1 H, CH_2N), 2.83–2.96 (m, 1 H, CH_2N), 2.97–3.06 (m, 2 H, OCH_2), 3.07 (s, 3 H, OCH_3), 3.31–3.5 (m, 1 H, CH), 3.76–4.06 (m, 2 H, OCH_2), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.13–4.31 (m, 2 H, OCH_2), 5.57 (dd, *J* = 1.9, 8.2 Hz, 1 H, CH_2=), 5.58 (s, 1 H, OCHO), 5.69 (q, *J* = 7.2 Hz, 1 H, CH), 6.32 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 7.04 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.05 (s, 1 H, H_{arom}), 7.49 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.8 (CH_2), 25.7 (CH_2), 27.0 (CH_2), 50.8 (NCH_2), 51.2 (CH), 55.8 (OCH_3), 55.9 (OCH_3), 58.2 (CH), 58.7 (OCH_3), 67.5 (OCH_2), 67.6 (OCH_2), 73.2 (OCH_2), 100.4 (OCHO), 109.1 (CH), 111.6 (CH), 126.2 (CH_2=), 127.8 (C), 130.1 (CH=), 134.0 (CH), 147.7 (C), 149.1 (C), 170.3 (CO) ppm. $C_{23}H_{34}N_2O_6$ (434.5): calcd. C 63.57, H 7.89, N 6.45; found C 63.79, H 7.89, N 6.65.

General Procedure for the Deprotection of the Benzaldehyde Moiety of the (1*R*)-Alkyl-enehydrazides 14a–g: A mixture of the protected enehydrazide **14a**–**g** (1 mmol) and $FeCl_3·6H_2O$ (946 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) was stirred at room temp. for 3 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under vacuum. The resulting oily solution was filtered through a short pad of silica gel to remove any remaining iron species. The deprotected aldehydes were eluted by using an EtOAc/hexanes (60:40) mixture. Evaporation of the solvent delivered benzaldehyde derivative **15a**–**g** as a yellow-orange oil, which was used in the next step without further purification.

***N*-[(*R*)-1-(6-Formyl-2,3,4-trimethoxyphenyl)pentyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15a):** Yield 296 mg, 66%. $[\alpha]_D^{25}$ = –73.5 (*c* = 0.88, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.7 Hz, 3 H, CH_3), 1.04–1.41 (m, 4 H, 2 CH_2), 1.56–1.91 (m, 2 H, CH_2), 1.93–2.35 (m, 4 H, 2 CH_2), 2.82 (s, 3 H, OCH_3), 2.87–3.39 (m, 2 H, CH_2N), 3.49–3.73 (m, 2 H, OCH_2), 3.79–4.01 (m, 1 H, CH), 3.88 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.77 (dd, *J* = 1.9, 8.5 Hz, 1 H, CH_2=), 5.92–6.12 (m, 1 H, ArCHN), 6.44 (dd, *J* = 2.2, 14.2 Hz, 1 H, CH_2=), 6.96 (dd, *J* = 6.7, 10.4 Hz, 1 H, CH=), 7.35 (s, 1 H, H_{arom}), 10.60 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.9 (CH_2), 22.6 (CH_2), 28.1 (CH_2), 29.5 (CH_2), 36.8 (CH_2), 50.6 (NCH_2), 55.9 (OCH_3), 56.0 (OCH_3), 56.8 (ArCHN), 58.2 (OCH_3), 58.6 (CH), 60.8 (OCH_3), 73.8 (OCH_2), 106.4 (CH), 126.6 (C), 127.8 (CH_2=), 128.3 (C), 129.6 (CH=), 133.7 (C), 151.6 (C), 152.9 (C), 170.8 (CO), 193.2 (CHO) ppm. $C_{24}H_{36}N_2O_6$ (448.5): calcd. C 64.26, H 8.09, N 6.25; found C 64.14, H 8.31, N 6.49.

***N*-[(*R*)-1-(2-Formylphenyl)ethyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15b):** Yield 234 mg, 74%. $[\alpha]_D^{25}$ = –228.6 (*c* = 0.81, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49–1.67 (m, 2 H, CH_2), 1.70–1.89 (m, 2 H, CH_2), 1.83 (d, *J* = 7.0 Hz, 3 H, CH_3), 2.72–2.87 (m, 1 H, CH_2N), 3.08 (s, 3 H, OCH_3), 2.95–3.03 (m, 2 H, CH_2N in part + CH), 3.04–3.18 (m, 2 H, CH_2O), 5.64 (dd, *J* = 2.2, 8.2 Hz, 1 H, CH_2=), 6.00 (q, *J* = 7.0 Hz, 1 H, CH), 6.39 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 7.18 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.44 (t, *J* = 6.4 Hz, 1 H, H_{arom}), 7.58 (td, *J* = 1.3, 6.3 Hz, 1 H, H_{arom}), 7.76 (dd, *J* = 1.3, 6.3 Hz, 1 H, H_{arom}), 8.03 (d, *J* = 7.75 Hz, 1 H, H_{arom}), 10.10 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.6 (CH_2), 27.0 (CH_2), 50.9 (NCH_2), 51.3 (CH), 58.6 (CH), 58.7 (OCH_3), 73.3 (OCH_2), 126.8 (CH_2=), 127.4 (CH), 129.7 (CH), 129.9 (CH=), 131.1 (CH), 134.3 (CH), 136.1 (C), 146.8 (C), 171.6 (CO), 194.2 (CHO) ppm. $C_{18}H_{24}N_2O_3$ (316.4): calcd. C 68.33, H 7.65, N 8.85; found C 68.57, H 7.83, N 8.69.

***N*-[(*R*)-1-(2-Formylphenyl)pentyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15c):** Yield 340 mg, 95%. $[\alpha]_D^{25}$ = –111.2 (*c* = 0.74, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.14–1.41 (m, 4 H, 2 CH_2), 1.51–1.66 (m, 2 H, CH_2), 1.68–1.83 (m, 2 H, CH_2), 1.85–2.06 (m, 2 H, CH_2), 2.61–2.81 (m, 1 H, CH_2N), 2.96–3.07 (m, 2 H, CH_2O), 2.99 (s, 3 H, OCH_3), 3.13 (q, *J* = 8.0 Hz, 1 H, CH_2N), 3.3–3.42 (m, 1 H, CH), 5.61 (dd, *J* = 2.2, 10.4 Hz, 1 H, CH_2=), 5.89 (q, *J* = 5.3 Hz, 1 H, ArCHN), 6.38 (dd, *J* = 2.2, 14.9 Hz, 1 H, CH_2=), 7.16 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.33 (t, *J* = 6.4 Hz, 1 H, H_{arom}), 7.57 (td, *J* = 1.2, 6.3 Hz, 1 H, H_{arom}), 7.74 (dd, *J* = 1.4, 6.2 Hz, 1 H, H_{arom}), 8.22 (d, *J* = 7.75 Hz, 1 H, H_{arom}), 10.09 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 21.6 (CH_2), 22.5 (CH_2), 26.8 (CH_2), 29.8 (CH_2), 33.8 (CH_2), 50.9 (NCH_2), 55.3 (ArCHN), 58.4 (OCH_3), 58.5 (CH), 73.9 (OCH_2), 126.4 (CH_2=), 127.1 (CH), 130.1 (CH), 130.2 (CH=), 131.2 (CH), 134.3 (CH), 136.1 (C), 147.2 (C), 170.8 (CO), 194.3 (CHO) ppm. $C_{21}H_{30}N_2O_3$ (358.5): calcd. C 70.36, H 8.44, N 7.81; found C 70.69, H 8.68, N 7.58.

***N*-[(*R*)-1-(2-Formylphenyl)heptyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15d):** Yield 325 mg, 84%. $[\alpha]_D^{25}$ = –104.1 (*c* = 0.64, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.11–1.42 (m, 8 H, 4 CH_2), 1.51–1.64 (m, 2 H, CH_2), 1.67–1.83 (m, 2 H, CH_2), 1.87–2.04 (m, 2 H, CH_2), 2.58–2.79 (m, 1 H, CH_2N), 2.85–2.96 (m, 2 H, CH_2O), 2.92 (s, 3 H, OCH_3), 3.12 (q, *J* = 7.8 Hz, 1 H, CH_2N), 3.28–3.41 (m, 1 H, CH), 5.61 (dd, *J* = 2.2, 10.2 Hz, 1 H, CH_2=), 5.87 (q, *J* = 5.4 Hz, 1 H, ArCHN), 6.36 (dd, *J* = 2.2, 15.0 Hz, 1 H, CH_2=), 7.13 (dd, *J* = 6.8, 10.5 Hz, 1 H, CH=), 7.32 (t, *J* = 6.5 Hz, 1 H, H_{arom}), 7.57 (td, *J* = 1.2, 6.3 Hz, 1 H, H_{arom}), 7.72 (dd, *J* = 1.4, 6.1 Hz, 1 H, H_{arom}), 8.18 (d, *J* = 7.7 Hz, 1 H, H_{arom}), 10.08 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.7 (CH_2), 22.6 (CH_2), 26.9 (CH_2), 27.6 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 34.1 (CH_2), 50.8 (NCH_2), 55.9 (ArCHN), 58.1 (OCH_3), 58.3 (CH), 73.3 (OCH_2), 126.1 (CH_2=), 127.0 (CH), 129.8 (CH), 130.1 (CH=), 131.3 (CH), 134.4 (CH), 136.9 (C), 147.3 (C), 170.6 (CO), 194.2 (CHO) ppm. $C_{23}H_{34}N_2O_3$ (386.5): calcd. C 71.47, H 8.87, N 7.25; found C 71.20, H 8.94, N 6.97.

***N*-[(*R*)-1-(2-Formylbenzo[1,3]dioxol-5-yl)pentyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15e):** Yield 282 mg, 70%. $[\alpha]_D^{25}$ = –172.8 (*c* = 1.39, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.7 Hz, 3 H, CH_3), 1.02–1.44 (m, 4 H, 2 CH_2), 1.53–1.68 (m, 2 H, CH_2), 1.70–1.91 (m, 4 H, 2 CH_2), 2.53–2.72 (m, 1 H, CH_2N), 2.79–2.93 (m, 1 H, CH_2N), 2.97 (d, *J* = 9.8 Hz, 2 H, OCH_2), 3.05 (s, 3 H, OCH_3), 2.94–3.15 (m, 1 H, CH), 5.63 (dd, *J* = 2.2, 8.3 Hz, 1 H, CH_2=), 5.88 (q, *J* = 5.8 Hz, 1 H, ArCHN), 6.06 (s, 2 H, OCH_2O), 6.36 (dd, *J* = 14.9–2.3 Hz, 1 H, CH_2=), 7.13 (dd, *J* = 6.7, 10.4 Hz, 1 H, CH=), 7.16 (s, 1 H, H_{arom}), 7.80 (s, 1 H, H_{arom}), 9.94 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.4 (CH_2), 22.6 (CH_2), 26.8 (CH_2), 29.6 (CH_2), 34.7 (CH_2), 50.7 (NCH_2), 55.2 (ArCHN), 58.7 (OCH_3), 58.7 (CH), 73.3 (OCH_2), 102.1 (OCH_2O), 110.8 (CH), 113.4 (CH), 126.0 (C), 126.6 (CH_2=), 130.1 (CH=), 144.9 (C), 152.5 (C), 170.9 (CO), 191.4 (CHO) ppm. $C_{22}H_{30}N_2O_5$ (402.5): calcd. C 65.65, H 7.51, N 6.96; found C 65.49, H 7.68, N 6.98.

***N*-[(*R*)-1-(2-Formylbenzo[1,3]dioxol-5-yl)ethyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15f):** Yield 259 mg, 72%. $[\alpha]_D^{25}$ = –183.6 (*c* = 0.44, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29–1.68 (m, 2 H, CH_2), 1.79 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.71–1.92 (m, 2 H, CH_2), 2.79–2.94 (m, 1 H, CH_2N), 3.09 (s, 3 H, OCH_3), 2.97–3.16 (m, 4 H, 2 H, CH_2O + 1 H, CH_2N + 1 H, CH), 5.63 (dd, *J* = 2.2, 8.2 Hz, 1 H, CH_2=), 6.02 (q, *J* = 7.0 Hz, 1 H, CH), 6.06 (s, 2 H, OCH_2O), 6.36 (dd, *J* = 2.2, 15.1 Hz, 1 H, CH_2=), 7.13 (dd, *J* = 6.9, 10.4 Hz, 1 H, CH=), 7.16 (s, 1 H, H_{arom}), 7.60 (s, 1 H, H_{arom}), 9.92 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.7 (CH_2), 26.9 (CH_2), 50.9 (NCH_2), 51.2 (CH), 58.7 (OCH_3), 58.8 (CH), 73.4 (OCH_2), 102.1 (OCH_2O), 110.3 (CH), 113.5 (CH), 125.7 (C), 126.8 (CH_2=), 129.9 (CH=), 144.5 (C), 146.8 (C), 152.4 (C), 170.6 (CO), 191.2 (CHO) ppm. $C_{19}H_{24}N_2O_5$ (360.4): calcd. C 63.32, H 6.71, N 7.77; found C 63.52, H 7.02, N 7.54.

***N*-[(*R*)-1-(2-Formyl-4,5-dimethoxyphenyl)ethyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (15g):** Yield 222 mg, 59%. $[\alpha]_D^{25}$ = –170.0 (*c* = 1.69, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43–1.66 (m, 2 H, CH_2), 1.68–1.88 (m, 2 H, CH_2), 1.82 (d, *J* = 7.0 Hz, 3 H, CH_3), 2.78–2.94 (m, 1 H, CH_2N), 3.03 (s, 3 H, OCH_3), 2.95–3.15 (m, 4 H, 2 H, CH_2O + 1 H, CH_2N + 1 H, CH), 3.94 (s, 6 H, 2 OCH_3), 5.60 (dd, *J* = 2.1, 8.3 Hz, 1 H, CH_2=), 6.00 (q, *J* = 7.0 Hz, 1 H, CH), 6.33 (dd, *J* = 2.1, 15.2 Hz, 1 H, CH_2=), 7.14

(dd, J = 6.9, 10.4 Hz, 1 H, CH=), 7.19 (s, 1 H, H_{arom}), 7.78 (s, 1 H, H_{arom}), 10.0 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.6 (CH_2), 26.9 (CH_2), 50.8 (CH), 50.9 (NCH_2), 56.0 (OCH_3), 56.2 (OCH_3), 58.7 (OCH_3), 58.8 (CH), 73.6 (OCH_2), 112.8 (CH), 116.4 (CH), 124.2 (C), 126.3 (CH_2=), 130.2 (CH=), 142.3 (C), 147.6 (C), 153.7 (C), 170.8 (CO), 191.7 (CHO) ppm. $C_{20}H_{28}N_2O_5$ (376.4): calcd. C 63.81, H 7.50, N 7.44; found C 63.52, H 7.61, N 7.66.

General Procedure for the Synthesis of the (1*R*)-Alkyl-dienehydrazides 4a–g: *n*BuLi (0.5 mL, 0.8 mmol, 1.6 M solution in hexanes) was added slowly to a stirred suspension of methyl(triphenyl)phosphonium bromide (286 mg, 0.8 mmol) in dry degassed THF (8 mL) at room temp. under argon. The yellowish solution was stirred for an additional 30 min. Enehydrazide **15a**–**g** (0.8 mmol) in dry degassed THF (4 mL) was then added and the resulting solution was heated at reflux for 12 h. Saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and water (2 × 10 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum the crude residue was purified by flash column chromatography (ethyl acetate/hexanes, 20:80, as eluent) to afford dienehydrazide **4a**–**g** as a pale-yellow oil.

***N*-[(*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(2,3,4-trimethoxy-6-vinylphenyl)pentyl]acrylamide (4a):** Yield 200 mg, 56%. $[\alpha]_D^{25}$ = –63.2 (c = 2.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.0 Hz, 3 H, CH_3), 1.08–1.41 (m, 4 H, 2 CH_2), 1.56–1.83 (m, 2 H, CH_2), 1.85–2.08 (m, 4 H, 2 CH_2), 2.25–2.42 (m, 1 H, CH_2N), 2.64–2.83 (m, 1 H, CH_2N), 2.90 (s, 3 H, OCH_3), 3.01–3.31 (m, 3 H, OCH_2 + CH), 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.31 (dd, J = 1.2, 10.2 Hz, 1 H, CH_2=), 5.42 (t, J = 5.7 Hz, 1 H, ArCHN), 5.53 (dd, J = 1.2, 15.8 Hz, 1 H, CH_2=), 5.69 (dd, J = 2.2, 8.2 Hz, 1 H, CH_2=), 6.22–6.44 (m, 1 H, CH_2=), 6.74 (s, 1 H, H_{arom}), 6.79–7.04 (m, 2 H, 2 CH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.0 (CH_2), 22.6 (CH_2), 27.6 (CH_2), 29.8 (CH_2), 34.2 (CH_2), 49.9 (NCH_2), 55.7 (OCH_3), 56.2 (OCH_3), 56.8 (ArCHN), 58.2 (OCH_3), 58.4 (CH), 60.7 (OCH_3), 73.6 (OCH_2), 105.6 (CH), 114.0 (CH_2=), 126.2 (CH_2=), 127.0 (C), 127.8 (C), 129.9 (CH=), 130.0 (C), 134.1 (CH=), 150.9 (C), 152.9 (C), 167.5 (CO) ppm. $C_{25}H_{38}N_2O_5$ (446.6): calcd. C 67.24, H 8.58, N 6.27; found C 67.32, H 8.29, N 6.47.

***N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(2-vinylphenyl)-ethyl]acrylamide (4b):** Yield 174 mg, 69%. $[\alpha]_D^{25}$ = –81.7 (c = 1.59, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.36 (m, 2 H, CH_2), 1.53–1.68 (m, 2 H, CH_2), 1.82 (d, J = 7.2 Hz, 3 H, CH_3), 2.64 (q, J = 8.0 Hz, 2 H, CH_2N), 2.83–2.98 (m, 2 H, OCH_2), 3.10 (s, 3 H, OCH_3), 3.19–3.32 (m, 1 H, CH), 5.23–5.42 (m, 2 H, 1 H, CH_2= +1 H, CH), 5.63 (dd, J = 2.3, 8.2 Hz, 1 H, CH_2=), 6.39 (dd, J = 2.2, 15.1 Hz, 1 H, CH_2=), 6.84–7.13 (m, 2 H, CH_2= + CH=), 7.20–7.36 (m, 3 H, CH= + 2 H_{arom}), 7.42 (dd, J = 2.3, 6.7 Hz, 1 H, H_{arom}), 7.72 (d, J = 7.7 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 21.7 (CH_2), 27.3 (CH_2), 51.2 (NCH_2), 52.3 (CH), 58.5 (CH), 58.7 (OCH_3), 73.2 (OCH_2), 117.3 (CH_2=), 126.2 (CH), 126.9 (CH_2=), 127.6 (CH), 127.9 (2 CH), 128.1 (C), 128.6 (CH=), 129.4 (C), 129.4 (CH=), 170.8 (CO) ppm. $C_{19}H_{26}N_2O_2$ (314.4): calcd. C 72.58, H 8.33, N 8.91; found C 72.46, H 8.63, N 8.97.

***N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(2-vinylphenyl)-pentyl]acrylamide (4c):** Yield 134 mg, 47%. $[\alpha]_D^{25}$ = –149.7 (c = 1.51, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.15–1.48 (m, 4 H, 2 CH_2), 1.51–1.86 (m, 4 H, 2 CH_2), 1.89–2.21 (m, 2 H, CH_2), 2.52–2.68 (m, 1 H, CH_2N), 2.70–2.82 (m, 1 H, CH_2N), 2.84–2.99 (m, 2 H, OCH_2), 3.02 (s, 3 H, OCH_3), 3.08–3.23 (m, 1 H, CH), 5.0 (t, J = 7.6 Hz, 1 H, ArCHN), 5.39 (dd, J = 1.2, 9.7 Hz, 1 H, CH_2=), 5.57–5.69 (m, 2 H, 2 × 1 H, 2 CH_2=), 6.38 (dd, J = 2.3, 14.9 Hz, 1 H, CH_2=), 6.91–7.17 (m, 2 H, H_{arom}), 7.19–7.37 (m, 2 H, 2 CH=), 7.41 (dd, J = 2.1, 6.6 Hz, 1 H, H_{arom}), 7.88 (d, J = 7.7 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.6 (CH_2), 22.6 (CH_2), 27.1 (CH_2), 29.7 (CH_2), 33.9 (CH_2), 50.9 (NCH_2), 57.0 (ArCHN), 58.2 (CH), 58.5 (OCH_3), 72.9 (OCH_2), 117.5 (CH_2=), 126.4 (CH), 126.6 (CH_2=), 127.5 (2 CH), 128.1 (C), 128.3 (CH + CH=), 129.8 (C), 134.4 (CH=), 170.3 (CO) ppm. $C_{22}H_{32}N_2O_2$ (356.5): calcd. C 74.12, H 9.05, N 7.86; found C 74.32, H 8.87, N 8.10.

***N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(2-vinylphenyl)-heptyl]acrylamide (4d):** Yield 132 mg, 41%. $[\alpha]_D^{25}$ = –88.3 (c = 1.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.7 Hz, 3 H, CH_3), 1.14–1.51 (m, 8 H, 4 CH_2), 1.51–1.85 (m, 4 H, CH_2), 1.87–2.16 (m, 2 H, CH_2), 2.51–2.66 (m, 1 H, CH_2N), 2.73 (q, J = 7.6 Hz, 1 H, CH_2N), 2.84–2.97 (m, 2 H, OCH_2), 3.01 (s, 3 H, OCH_3), 3.08–3.21 (m, 1 H, CH), 5.0 (t, J = 7.9 Hz, 1 H, ArCHN), 5.40 (dd, J = 1.3, 9.6 Hz, 1 H, CH_2=), 5.57–5.68 (m, 2 H, 2 × 1 H, 2 CH_2=), 6.39 (dd, J = 2.2, 15.0 Hz, 1 H, CH_2=), 6.92–7.16 (m, 2 H, H_{arom}), 7.18–7.37 (m, 2 H, 2 CH=), 7.42 (dd, J = 2.2, 6.5 Hz, 1 H, H_{arom}), 7.88 (d, J = 7.6 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.7 (CH_2), 22.6 (CH_2), 27.1 (CH_2), 27.5 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 34.2 (CH_2), 50.9 (NCH_2), 57.0 (ArCHN), 58.2 (CH), 58.5 (OCH_3), 72.9 (OCH_2), 117.5 (CH_2=), 126.4 (CH), 126.6 (CH_2=), 127.5 (CH), 128.3 (CH + CH=), 129.8 (C), 134.3 (CH=), 136.1 (CH), 139.9 (C), 170.3 (CO) ppm. $C_{24}H_{36}N_2O_2$ (384.6): calcd. C 74.96, H 9.44, N 7.28; found C 74.88, H 9.29, N 7.11.

***N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(6-vinylbenzo-[1,3]dioxol-5-yl)pentyl]acrylamide (4e):** Yield 183 mg, 57%. $[\alpha]_D^{25}$ = –48.0 (c = 1.03, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.12–1.48 (m, 4 H, 2 CH_2), 1.53–1.83 (m, 4 H, 2 CH_2), 1.85–2.08 (m, 2 H, CH_2), 2.46–2.63 (m, 1 H, CH_2N), 2.72–2.86 (m, 1 H, CH_2N), 2.89–3.01 (m, 2 H, OCH_2), 3.09 (s, 3 H, OCH_3), 3.11–3.23 (m, 1 H, CH), 4.92 (t, J = 5.6 Hz, 1 H, ArCHN), 5.30 (dd, J = 1.2, 10.2 Hz, 1 H, CH_2=), 5.51 (dd, J = 1.2, 15.9 Hz, 1 H, CH_2=), 5.62 (dd, J = 2.2, 8.2 Hz, 1 H, CH_2=), 5.95 (s, 2 H, OCH_2O), 6.36 (dd, J = 2.3, 14.9 Hz, 1 H, CH_2=), 6.79–6.97 (m, 1 H, CH=), 6.90 (s, 1 H, H_{arom}), 7.05 (dd, J = 6.9, 10.4 Hz, 1 H, CH=), 7.28 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 21.6 (CH_2), 22.6 (CH_2), 27.1 (CH_2), 29.6 (CH_2), 33.8 (CH_2), 51.1 (NCH_2), 56.9 (ArCHN), 58.3 (CH), 58.6 (OCH_3), 73.0 (OCH_2), 101.2 (OCH_2O), 106.0 (CH), 108.7 (CH), 116.1 (CH_2=), 126.7 (CH_2=), 129.8 (CH=), 130.1 (C), 133.9 (CH=), 134.0 (C), 147.8 (C), 154.3 (C), 170.1 (CO) ppm. $C_{23}H_{32}N_2O_4$ (400.5): calcd. C 68.97, H 8.05, N 6.99; found C 68.74, H 7.92, N 6.71.

***N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-*N*-[(*R*)-1-(6-vinylbenzo-[1,3]dioxol-5-yl)ethyl]acrylamide (4f):** Yield 189 mg, 66%. $[\alpha]_D^{25}$ = –56.5 (c = 2.23, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.73 (m, 4 H, 2 CH_2), 1.77 (d, J = 7.2 Hz, 3 H, CH_3), 2.71 (q, J = 7.75 Hz, 1 H, NCH_2), 2.87–3.02 (m, 2 H, OCH_2), 3.04–3.11 (m, 1 H, CH_2N), 3.18 (s, 3 H, OCH_3), 3.20–3.31 (m, 1 H, CH), 5.17–5.33 (m, 1 H, CH), 5.28 (d, J = 9.6 Hz, 1 H, CH_2=), 5.51 (d, J = 17.1 Hz, 1 H, CH_2=), 5.62 (dd, J = 2.2, 8.2 Hz, 1 H, CH_2=), 5.95 (s, 2 H, OCH_2O), 6.39 (dd, J = 2.2, 15.1 Hz, 1 H, CH_2=), 6.78–6.93 (m, 1 H, CH=), 6.91 (s, 1 H, H_{arom}), 7.05 (dd, J = 6.9, 10.4 Hz, 1 H, CH=), 7.34 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3), 21.8 (CH_2), 27.3 (CH_2), 51.1 (NCH_2), 52.2 (CH), 58.5 (OCH_3), 58.8 (CH), 73.2 (OCH_2), 101.1 (OCH_2O), 105.9 (CH), 108.3 (CH), 115.9 (CH_2=), 126.9 (CH_2=), 129.5 (CH=),

130.0 (C), 133.7 (*C*H=), 134.0 (C), 147.6 (C), 154.4 (C), 170.0 (CO) ppm. $C_{20}H_{26}N_2O_4$ (358.4): calcd. C 67.02, H 7.31, N 7.82; found C 66.84, H 7.23, N 7.75.

***N*-[(*R*)-1-(4,5-Dimethoxy-2-vinylphenyl)ethyl]-*N*-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (4g):** Yield 144 mg, 48%. $[\alpha]_D^{25}$ = –73.4 (*c* = 1.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.71 (m, 4 H, 2 CH_2), 1.83 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.65 (q, *J* = 8.0 Hz, 1 H, NCH_2), 2.89–2.98 (m, 2 H, OCH_2), 3.02–3.20 (m, 4 H, 1 H, CH_2N + 3 H, OCH_3), 3.21–3.32 (m, 1 H, CH), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.24–5.42 (m, 2 H, 1 H, CH + 1 H, CH_2=), 5.41–5.61 (m, 1 H, CH_2=), 5.64 (dd, *J* = 1.8, 10.8 Hz, 1 H, CH_2=), 6.35 (dd, *J* = 2.3, 14.9 Hz, 1 H, CH_2=), 6.89–7.04 (m, 2 H, H_{arom} + CH=), 7.07 (dd, *J* = 6.8, 10.5 Hz, 1 H, CH=), 7.44 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.7 (CH_2), 27.2 (CH_2), 51.0 (NCH_2), 51.7 (CH), 55.9 (OCH_3), 56.0 (OCH_3), 58.5 (OCH_3), 58.7 (CH), 73.3 (OCH_2), 108.6 (CH), 111.2 (CH), 115.5 (CH_2=), 126.5 (CH_2=), 128.3 (C), 129.7 (CH=), 132.9 (C), 133.6 (CH=), 148.1 (C), 148.9 (C), 170.2 (CO) ppm. $C_{21}H_{30}N_2O_4$ (374.5): calcd. C 67.36, H 8.07, N 7.48; found C 67.61, H 7.98, N 7.14.

General Procedure for the Synthesis of the (1*R*)-Alkyl-(*S*)-*N*-SMP-benzo[*c*]azepinones 3b–d,f,g and (1*R*)-Alkylbenzo[*c*]azepinones 17a–e: A stirred mixture of the dienehydrazide **4a**,**f**,**g** (0.6 mmol) and the second-generation Grubbs catalyst (15 mg, 3 mol-%) in dry toluene (8 mL) was heated at reflux for 6 h under argon. Further of the second-generation Grubbs catalyst (10 mg, 2 mol-% for the dienehydrazides **4b**–**d** or 25 mg, 5 mol-% for **4a**,**e**) was added after cooling, and the reaction mixture was heated at reflux for an additional 6 h. The solution was then filtered through a pad of Celite that was washed with dichloromethane (20 mL). Evaporation of the solvent left a dark oil, which was separated by flash column chromatography. Compounds **3b**–**d**,**f**,**g** eluted first (ethyl acetate/hexanes, 30:70, as eluent) followed by compounds **17a**–**e** (ethyl acetate/hexanes, 70:30, as eluent).

(1*R*)-1-Butyl-7,8,9-trimethoxy-1,2-dihydrobenzo[*c*]azepin-3-one (17a): After an extended reaction time. Yield 92 mg, 50%. $[\alpha]_D^{25}$ = –168.3 (*c* = 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.09–1.39 (m, 4 H, 2 CH_2), 1.53–1.95 (m, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 5.07–5.22 (m, 1 H, ArCHN), 6.18 (d, *J* = 12.0 Hz, 1 H, =CHCO), 6.62 (s, 1 H, H_{arom}), 6.88 (d, *J* = 12.2 Hz, 1 H, ArCH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 55.8 (ArCHN), 55.9 (2 OCH_3), 60.8 (OCH_3), 109.0 (CH), 126.9 (=CH), 127.1 (C), 127.9 (C), 131.2 (C), 135.9 (ArCH=), 148.9 (C), 152.3 (C), 168.2 (CO) ppm. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 67.02, H 7.67, N 4.86.

(1*R*)-2-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-1,2-dihydrobenzo[*c*]azepin-3-one (3b): Yield 124 mg, 72%. After an extended reaction time a mixture of **3b** (66 mg, 38%) and **17b** was obtained. $[\alpha]_D^{25}$ = –105.5 (*c* = 0.97, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.3 Hz, 2 H, CH_2), 1.71 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.82–1.98 (m, 2 H, CH_2), 2.43–2.52 (m, 1 H, CH_2N), 2.53–2.64 (m, 1 H, CH_2N), 3.05 (s, 3 H, OCH_3), 3.02–3.14 (m, 1 H, OCH_2), 3.28–3.41 (m, 1 H, OCH_2), 3.51 (q, *J* = 7.8 Hz, 1 H, CH), 4.40 (q, *J* = 7.0 Hz, 1 H, CH), 6.32 (d, *J* = 12.0 Hz, 1 H, =CHCO), 7.01 (d, *J* = 12.0 Hz, 1 H, ArCH=), 7.21–7.32 (m, 2 H, H_{arom}), 7.33–7.42 (m, 2 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 23.0 (CH_2), 27.5 (CH_2), 52.9 (CH_2N), 58.5 (OCH_3), 58.5 (CH), 58.7 (CH), 74.8 (OCH_2O), 124.0 (=CH), 127.4 (CH), 128.0 (CH), 128.9 (CH), 129.3 (ArCH=), 130.1 (CH), 130.7 (C), 136.1 (C), 165.0 (CO) ppm. $C_{17}H_{22}N_2O_2$ (286.4): calcd. C 71.30, H 7.74, N 9.78; found C 71.53, H 7.91, N 9.66.

(1*R*)-1-Methyl-1,2-dihydrobenzo[*c*]azepin-3-one (17b): From the mixture of **3b** and **17b** (42 mg, 41%). $[\alpha]_D^{25}$ = –92.4 (*c* = 0.74, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 7.0 Hz, 3 H, CH_3), 4.40 (q, *J* = 6.3 Hz, 1 H, CH), 6.35 (d, *J* = 12.0 Hz, 1 H, =CHCO), 6.83 (br. s, 1 H, NH), 7.17 (d, *J* = 12.1 Hz, 1 H, ArCH=), 7.23–7.48 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1 (CH_3), 48.3 (CH), 123.8 (=CH), 126.2 (CH), 127.7 (CH), 129.7 (CH), 130.0 (CH), 134.8 (C), 138.7 (ArCH=), 141.3 (C), 168.6 (CO) ppm. $C_{11}H_{11}NO$ (173.2): calcd. C 76.28, H 6.40, N 8.09; found C 76.04, H 6.22, N 8.27.

(1*R*)-1-Butyl-2-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1,2-dihydrobenzo[*c*]azepin-3-one (3c): After an extended reaction time a mixture of **3c** (85 mg, 43%) and **17c** was obtained. $[\alpha]_D^{25}$ = –94.5 (*c* = 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.07–1.51 (m, 4 H, 2 CH_2), 1.53–1.92 (m, 4 H, 2 CH_2), 1.93–2.31 (m, 2 H, CH_2), 2.52 (dd, *J* = 3.7, 6.0 Hz, 1 H, CH_2N), 2.63 (dd, *J* = 2.5, 7.0 Hz, 1 H, CH_2N), 2.93 (s, 3 H, OCH_3), 3.12–3.51 (m, 3 H, CH_2O + CH), 4.23 (t, *J* = 7.0 Hz, 1 H, ArCHN), 6.42 (d, *J* = 11.9 Hz, 1 H, =CHCO), 6.99 (d, *J* = 12.2 Hz, 1 H, ArCH=), 7.21–7.30 (m, 1 H, H_{arom}), 7.31–7.49 (m, 3 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.4 (CH_2), 23.0 (CH_2), 27.4 (CH_2), 27.8 (CH_2), 29.3 (CH_2), 53.6 (NCH_2), 59.4 (ArCHN), 60.1 (CH), 60.4 (OCH_3), 74.7 (OCH_2), 124.5 (=CH), 127.3 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 129.4 (ArCH=), 130.5 (C), 136.1 (C), 164.7 (CO) ppm. $C_{20}H_{28}N_2O_2$ (328.5): calcd. C 73.14, H 8.59, N 8.53; found C 73.39, H 8.65, N 8.55.

(1*R*)-1-Butyl-1,2-dihydrobenzo[*c*]azepin-3-one (17c): From the mixture of **3b** and **17b** (62 mg, 48%). $[\alpha]_D^{25}$ = –89.7 (*c* = 0.67, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.13–1.62 (m, 4 H, 2 CH_2), 1.96–2.11 (m, 2 H, CH_2), 4.14 (t, *J* = 7.0 Hz, 1 H, ArCHN), 6.32 (dd, *J* = 10.4, 1.75 Hz, 1 H, =CHCO), 6.90 (br. s, 1 H, NH), 7.14 (d, *J* = 12.1 Hz, 1 H, ArCH=), 7.23–7.31 (m, 1 H, H_{arom}), 7.32–7.49 (m, 3 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.4 (CH_2), 28.9 (CH_2), 30.8 (CH_2), 53.9 (ArCHN), 125.0 (=CH), 126.4 (CH), 127.6 (CH), 129.6 (CH), 130.2 (CH), 134.8 (C), 138.5 (ArCH=), 140.7 (C), 168.4 (CO) ppm. $C_{14}H_{17}NO$ (215.3): calcd. C 78.10, H 7.96, N 6.51; found C 77.97, H 8.17, N 6.66.

(1*R*)-1-Hexyl-2-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1,2-dihydrobenzo[*c*]azepin-3-one (3d): After an extended reaction time a mixture of **3d** (23 mg, 11%) and **17d** was obtained. $[\alpha]_D^{25}$ = –112.2 (*c* = 0.42, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.04–1.45 (m, 6 H, 3 CH_2), 1.46–1.92 (m, 6 H, 3 CH_2), 1.93–2.04 (m, 2 H, CH_2), 2.49–2.61 (m, 1 H, CH_2N), 2.63–2.74 (m, 1 H, CH_2N), 3.01 (s, 3 H, OCH_3), 3.07–3.57 (m, 3 H, OCH_2O + CH), 4.15 (t, *J* = 6.9 Hz, 1 H, ArCHN), 6.32 (d, *J* = 11.9 Hz, 1 H, =CHCO), 7.13 (d, *J* = 12.0 Hz, 1 H, ArCH=), 7.23–7.44 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.5 (CH_2), 23.0 (CH_2), 26.7 (CH_2), 27.3 (CH_2), 29.1 (CH_2), 30.9 (CH_2), 31.7 (CH_2), 53.1 (NCH_2), 58.9 (OCH_3), 59.0 (ArCHN), 59.3 (CH), 74.8 (OCH_2), 124.8 (=CH), 126.9 (CH), 127.7 (CH), 128.4 (CH), 128.9 (CH), 129.4 (ArCH=), 130.2 (C), 136.0 (C), 168.4 (CO) ppm. $C_{22}H_{32}N_2O_2$ (356.5): calcd. C 74.12, H 9.05, N 7.86; found C 74.01, H 9.32, N 7.69.

(1*R*)-1-Hexyl-1,2-dihydrobenzo[*c*]azepin-3-one (17d): From the mixture of **3d** and **17d** (61 mg, 42%). $[\alpha]_D^{25}$ = –99.5 (*c* = 1.22, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.04–1.46 (m, 7 H, 6 H, 3 CH_2 + 1 H, CH_2), 1.48–1.64 (m, 1 H, CH_2), 1.91–2.04 (m, 2 H, CH_2), 4.13 (t, *J* = 7.0 Hz, 1 H, ArCHN),

6.32 (dd, J = 1.5, 10.7 Hz, 1 H, =CHCO), 7.13 (d, J = 12.0 Hz, 1 H, ArCH=), 7.23–7.44 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 29.0 (CH_2), 31.0 (CH_2), 31.7 (CH_2), 54.0 (ArCHN), 125.0 (=CH), 126.4 (CH), 127.6 (CH), 129.6 (CH), 130.2 (CH), 134.8 (C), 138.4 (Ar*C*H=), 140.7 (C), 168.4 (CO) ppm. $C_{16}H_{21}NO$ (243.4): calcd. C 78.97, H 8.70, N 5.76; found C 79.13, H 8.47, N 6.01.

(5*R*)-5-Butyl-5,6-dihydro-1,3-dioxa-6-azacyclohepta[*f*]inden-7-one (17e): After an extended reaction time. Yield 75 mg, 48%. $[\alpha]_D^{25}$ = –114.4 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75–1.03 (m, 3 H, CH_3), 1.14–1.48 (m, 4 H, 2 CH_2), 1.89–2.08 (m, 2 H, CH_2), 4.02–4.18 (m, 1 H, ArCHN), 6.03 (s, 2 H, OCH_2O), 6.05–6.17 (br. s, 1 H, NH), 6.25 (dd, J = 1.4, 10.6 Hz, 1 H, =CHCO), 6.82 (s, 1 H, H_{arom}), 7.02 (d, J = 12.0 Hz, 1 H, ArCH=), 7.28 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 22.5 (CH_2), 29.8 (CH_2), 33.6 (CH_2), 54.1 (ArCHN), 101.6 (OCH_2O), 104.9 (CH), 108.7 (CH), 126.4 (=CH), 129.1 (C), 129.3 (C), 135.7 (ArCH=), 135.8 (C), 141.2 (C), 166.4 (CO) ppm. $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.58, H 6.54, N 5.22.

(5*R*)-6-[(*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-5-methyl-5,6-dihydro-1,3-dioxa-6-azacyclohepta[*f*]inden-7-one (3f): Yield 81 mg, 41%. $[\alpha]_D^{25}$ = –129.6 (c = 0.63, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.69 (m, 2 H, CH_2), 1.73 (d, J = 7.0 Hz, 3 H, CH_3), 1.88–2.05 (m, 2 H, CH_2), 2.70 (dd, J = 1.0, 4.4 Hz, 1 H, CH_2N), 3.05 (s, 3 H, OCH_3), 3.11–3.22 (m, 1 H, CH_2N), 3.23–3.51 (m, 2 H, OCH_2), 5.58 (q, J = 7.75 Hz, 1 H, CH), 4.39 (q, J = 7.2 Hz, 1 H, ArCHN), 6.02 (s, 2 H, OCH_2O), 6.31 (d, J = 12.0 Hz, 1 H, =CHCO), 6.83 (s, 1 H, H_{arom}), 6.93 (s, 1 H, H_{arom}), 6.96 (d, J = 12.0 Hz, 1 H, ArCH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 23.0 (CH_2), 27.3 (CH_2), 52.9 (NCH_2), 54.9 (CH), 58.7 (CH), 58.8 (OCH_3), 74.6 (OCH_2), 101.5 (OCH_2O), 104.9 (CH), 108.7 (CH), 126.5 (=CH), 129.3 (2 C), 135.8 (ArCH=), 136.5 (C), 141.3 (C), 164.8 (CO) ppm. $C_{18}H_{22}N_2O_4$ (330.4): calcd. C 65.44, H 6.71, N 8.48; found C 65.21, H 6.58, N 8.15.

(1*R*)-7,8-Dimethoxy-2-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-1,2-dihydrobenzo[*c*]azepin-3-one (3g): Yield 112 mg, 54%. $[\alpha]_D^{25}$ = –107.3 (c = 0.88, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.69 (m, 2 H, CH_2), 1.78 (d, J = 7.1 Hz, 3 H, CH_3), 1.89–2.04 (m, 2 H, CH_2), 2.58–2.73 (m, 2 H, CH_2N), 2.99 (s, 3 H, OCH_3), 3.10–3.21 (m, 1 H, CH), 3.26–3.52 (m, 2 H, CH_2O), 3.92 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.42 (q, J = 7.0 Hz, 1 H, ArCHN), 6.33 (d, J = 11.9 Hz, 1 H, =CHCO), 6.87 (s, 1 H, H_{arom}), 6.93 (s, 1 H, H_{arom}), 7.01 (d, J = 12.0 Hz, 1 H, ArCH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 23.0 (CH_2), 27.3 (CH_2), 53.0 (NCH_2), 54.9 (CH), 56.0 (OCH_3), 56.1 (OCH_3), 58.8 (CH), 59.1 (OCH_3), 74.8 (OCH_2), 107.1 (C), 111.7 (C), 126.3 (=CH), 128.1 (C), 132.6 (C), 134.8 (C), 135.9 (ArCH=), 148.0 (C), 165.3 (CO) ppm. $C_{19}H_{26}N_2O_4$ (346.4): calcd. C 65.88, H 7.56, N 8.09; found C 66.07, H 7.47, N 7.83.

General Procedure for the Synthesis of (1*R*)-Alkyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-ones 1a–e Starting from (1*R*)-Alkyl-2-benzo-[*c*]azepinones 17a–e: A solution of the appropriate benzazepinone **17a**–**e** (0.3 mmol) in anhydrous EtOH (8 mL) was stirred with activated Pd/C (10%, 5 mg) at room temp. under hydrogen for 12 h after which time TLC indicated complete consumption of the starting material. The mixture was filtered through a pad of Celite, which was further eluted with EtOH (10 mL) and then CH_2Cl_2 (20 mL). Evaporation of the solvent furnished an oily product, which was purified by flash column chromatography using ethyl acetate as eluent to afford the corresponding **1a**–**e** as a viscous yellow oil.

(1*R*)-1-Butyl-7,8,9-trimethoxy-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1a): Yield 70 mg, 90%. $[\alpha]_D^{25}$ = –36.2 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66–0.99 (m, 3 H, CH_3), 1.04–1.51 (m, 4 H, 2 CH_2), 1.53–1.94 (m, 2 H, CH_2), 2.46–2.64 (m, 1 H, CH_2CO), 2.75–3.19 (m, 3 H, 1 H, CH_2CO + 2 H, $ArCH_2$), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.09–5.23 (m, 1 H, ArCHN), 6.06–6.27 (br. s, 1 H, NH), 6.61 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 32.6 ($ArCH_2$), 37.0 (*C*H_2CO), 55.8 (ArCHN), 55.9 (OCH_3), 56.0 (OCH_3), 59.0 (OCH_3), 108.5 (CH), 127.4 (C), 127.6 (C), 129.9 (C), 149.1 (C), 151.2 (C), 171.3 (CO) ppm. $C_{17}H_{25}NO_4$ (307.4): calcd. C 66.43, H 8.20, N 4.56; found C 66.56, H 8.24, N 4.35.

(1*R*)-1-Methyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1b): Yield 47 mg, 90%. $[\alpha]_D^{25}$ = –15.1 (c = 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (d, J = 7.0 Hz, 3 H, CH_3), 2.49–2.68 (m, 1 H, CH_2CO), 2.79–3.04 (m, 2 H, $ArCH_2$), 3.19–3.41 (m, 1 H, CH_2CO), 4.85–5.01 (m, 1 H, CH), 6.16–6.44 (br. s, 1 H, NH), 7.05–7.31 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_3), 29.4 ($ArCH_2$), 35.3 (*C*H_2CO), 47.7 (ArCHN), 124.0 (C), 126.8 (C), 128.2 (C), 128.9 (C), 139.9 (C), 140.4 (C), 173.9 (CO) ppm. $C_{11}H_{13}NO$ (175.2): calcd. C 75.40, H 7.48, N 7.99; found C 75.62, H 7.77, N 8.11.

(1*R*)-1-Butyl-1,2,4,5-tetrahydro-2-benzazepin-3-one (1c): Yield 59 mg, 92%. $[\alpha]_D^{25}$ = –18.1 (c = 0.64, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61–1.02 (m, 3 H, CH_3), 1.04–1.65 (m, 4 H, 2 CH_2), 1.81–2.14 (m, 2 H, CH_2), 2.49–2.73 (m, 1 H, CH_2CO), 2.75–3.01 (m, 2 H, $ArCH_2$), 3.04–3.41 (m, 1 H, CH_2CO), 4.49–4.69 (m, 1 H, ArCHN), 6.26–6.51 (br. s, 1 H, NH), 7.06–7.51 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 28.9 (CH_2), 33.3 ($ArCH_2$), 35.6 (*C*H_2CO), 53.4 (ArCHN), 125.1 (CH), 126.7 (CH), 128.0 (CH), 129.2 (CH), 139.8 (C), 140.0 (C), 174.1 (CO) ppm. $C_{14}H_{19}NO$ (217.3): calcd. C 77.38, H 8.81, N 6.45; found C 77.21, H 8.54, N 6.54.

(1*R*)-1-Hexyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1d): Yield 58 mg, 95%. $[\alpha]_D^{25}$ = –16.9 (c = 0.71, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.8 Hz, 3 H, CH_3), 1.03–1.66 (m, 8 H, 4 CH_2), 1.80–2.15 (m, 2 H, CH_2), 2.55–2.73 (m, 1 H, CH_2CO), 2.78–3.01 (m, 2 H, $ArCH_2$), 3.09–3.32 (m, 1 H, CH_2CO), 4.50–4.68 (m, 1 H, ArCHN), 6.26–6.57 (br. s, 1 H, NH), 7.09–7.32 (m, 1 H, H_{arom}), 7.35–7.51 (m, 2 H, H_{arom}), 7.58–7.67 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 33.5 ($ArCH_2$), 35.5 (*C*H_2CO), 53.4 (ArCHN), 126.8 (CH), 128.6 (2 CH), 129.1 (CH), 137.1 (C), 139.8 (C), 174.0 (CO) ppm. $C_{16}H_{23}NO$ (245.4): calcd. C 78.32, H 9.45, N 5.71; found C 78.53, H 9.51, N 5.56.

(5*R*)-5-Butyl-5,6,8,9-tetrahydro-1,3-dioxa-6-azacyclohepta[*f*]inden-7-one (1e): Yield 70 mg, 90%. $[\alpha]_D^{25}$ = –36.2 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76–1.02 (m, 3 H, CH_3), 1.09–1.49 (m, 4 H, 2 CH_2), 1.87–2.09 (m, 2 H, CH_2), 2.52–2.77 (m, 1 H, CH_2CO), 2.78–3.28 (m, 3 H, 1 H, CH_2CO + 2 H, $ArCH_2$), 4.42–4.69 (m, 1 H, ArCHN), 6.03 (s, 2 H, OCH_2O), 6.09–6.32 (br. s, 1 H, NH), 6.83 (s, 1 H, H_{arom}), 6.96 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3 (CH_3), 22.5 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 32.8 ($ArCH_2$), 35.4 (*C*H_2CO), 53.9 (ArCHN), 101.2 (OCH_2O), 104.9 (CH), 108.6 (CH), 129.1 (C), 129.3 (C), 136.1 (C), 141.2 (C), 172.8 (CO) ppm. $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 68.98, H 7.07, N 5.14.

General Procedure for the Synthesis of the (1*R*)-Alkyltetrahydro-3*H*-benzo[*c*]azepinones 1b–d,f,g Starting from (1*R*)-Alkyl-(*S*)-*N*-SMP-2-benzazepinones 3b–d,f,g: Catalytic hydrogenation as described previously delivered the appropriate alkyltetrahydro-2-benzazep-

inone **16b**–**d**,**f**,**g** as pale-grey oils, which was used in the next step without further purification. Magnesium monoperoxyphthalate hexahydrate (MMPP) (247 mg, 0.5 mmol) was added to a solution of the alkyltetrahydro-2-benzazepinone **16b**–**d**,**f**,**g** (0.2 mmol) in MeOH (5 mL) and the resulting mixture was then stirred at room temp. under argon for 48 h. The mixture was then poured into CH_2Cl_2 (20 mL) and treated with a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined extracts washed successively with water (10 mL) and brine (10 mL) and finally dried ($MgSO_4$). Evaporation of the solvent furnished an oily product, which was purified by flash column chromatography using ethyl acetate as eluent to yield the corresponding **1b**–**d**,**f**,**g** as a viscous yellow oil.

(1*R*)-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (16b): Yield 66 mg, 91%. $[\alpha]_D^{25}$ = –17.3 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.30 (m, 1 H, CH_2), 1.51–1.65 (m, 1 H, CH_2), 1.70 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.80–1.94 (m, 1 H, CH_2), 1.96–2.13 (m, 1 H, CH_2), 2.67–3.02 (m, 5 H, 1 H,CH_2N + 4 H, 2 CH_2), 3.07 (s, 3 H, OCH_3), 3.09–3.18 (m, 2 H, OCH_2), 3.23–3.44 (m, 1 H, CH_2N), 3.51–3.76 (m, 1 H, CH), 4.98–5.11 (m, 1 H, CH), 7.06–7.22 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_3), 22.9 (CH_2), 27.3 (CH_2), 29.4 ($ArCH_2$), 35.3 (*C*H_2CO), 47.7 (ArCHN), 52.9 (NCH_2), 58.6 (CH), 58.8 (OCH_3), 74.7 (OCH_2O), 124.0 (CH), 126.7 (CH), 128.2 (CH), 128.8 (CH), 139.8 (C), 140.1 (C), 173.6 (CO) ppm.

(1*R*)-1-Butyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (16c): Yield 84 mg, 85%. $[\alpha]_D^{25}$ = –19.7 (*c* = 0.74, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.02–1.64 (m, 6 H, 3 CH_2), 1.80–1.91 (m, 1 H, CH_2), 1.94–2.33 (m, 3 H, 1 H, CH_2 + 2 H, CH_2), 2.67–3.02 (m, 5 H, 1 H, CH_2N + 4 H, 2 CH_2), 3.08 (s, 3 H, OCH_3), 3.12–3.31 (m, 3 H, 1 H, CH_2N + 2 H, OCH_2), 3.51–3.76 (m, 1 H, CH), 4.89–5.06 (m, 1 H, ArCHN), 7.02–7.26 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.5 (CH_2), 22.8 (CH_2), 27.4 (CH_2), 28.4 (CH_2), 28.9 (CH_2), 33.3 ($ArCH_2$), 35.6 (*C*H_2CO), 53.0 (NCH_2), 53.4 (ArCHN), 58.8 (CH), 58.9 (OCH_3), 74.5 (OCH_2), 125.1 (CH), 126.7 (CH), 128.0 (CH), 129.2 (CH), 139.8 (C), 140.0 (C), 174.1 (CO) ppm.

(1*R*)-1-Hexyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (16d): Yield 95 mg, 88%. $[\alpha]_D^{25}$ = –21.4 (*c* = 0.64, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.03–1.72 (m, 8 H, 4 CH_2), 1.74–1.93 (m, 3 H, 1 H, CH_2 + 2 H, CH_2), 1.96–2.29 (m, 3 H, 1 H, CH_2 + 2 H, CH_2), 2.62–3.01 (m, 5 H, 1 H, CH_2N + 4 H, 2 CH_2), 3.05 (s, 3 H, OCH_3), 3.09–3.26 (m, 3 H, 1 H, CH_2N + 2 H, OCH_2), 3.44–3.62 (m, 1 H, CH), 4.77–4.96 (m, 1 H, ArCHN), 6.98–7.23 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 26.7 (CH_2), 27.5 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 33.5 ($ArCH_2$), 35.4 (*C*H_2CO), 52.9 (NCH_2), 53.6 (ArCHN), 58.7 (CH), 58.8 (OCH_3), 74.6 (OCH_2), 126.8 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 137.1 (C), 139.8 (C), 174.0 (CO) ppm.

(5*R*)-6-[(*S*)-(2-(methoxymethyl)pyrrolidin-1-yl]-5-methyl-5,6,8,9-tetrahydro-1,3-dioxa-6-azacyclohepta[*f*]inden-7-one (16f): Yield 82 mg, 82%. $[\alpha]_D^{25}$ = –36.9 (*c* = 0.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.63 (m, 2 H, CH_2), 1.74 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.86–2.05 (m, 2 H, CH_2), 2.51–2.64 (m, 1 H, CH_2N), 2.68–3.09 (m, 5 H, 4 H, 2 CH_2 + 1 H, CH_2N), 3.06 (s, 3 H, OCH_3), 3.10–3.48 (m, 3 H, CH + OCH_2), 4.77–4.95 (m, 1 H, ArCHN), 6.01 (s, 2 H, OCH_2O), 6.86 (s, 1 H, H_{arom}), 6.93 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7 (CH_3), 23.0 (CH_2), 27.3 (CH_2), 32.1 ($ArCH_2$), 35.4 (*C*H_2CO), 52.9 (NCH_2), 54.7 (CH), 58.7 (CH), 58.8 (OCH_3), 74.6 (OCH_2), 101.4 (OCH_2O), 105.2 (CH), 108.4 (CH), 129.2 (C), 129.3 (C), 136.2 (C), 141.8 (C), 169.8 (CO) ppm.

(1*R*)-7,8-Dimethoxy-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (16g): Yield 91 mg, 87%. $[\alpha]_D^{25}$ = –19.6 (*c* = 0.83, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39–1.58 (m, 2 H, CH_2), 1.72 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.84–1.99 (m, 1 H, CH_2), 2.02–2.17 (m, 1 H, CH_2), 2.54–2.67 (m, 1 H, CH_2N), 2.69–3.03 (m, 5 H, 4 H, 2 CH_2 + 1, CH_2N), 3.07 (s, 3 H, OCH_3), 3.11–3.22 (m, 1 H, CH), 3.23–3.51 (m, 2 H, CH_2O), 3.88 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.87–5.02 (m, 1 H, ArCHN), 6.88 (s, 1 H, H_{arom}), 6.94 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH_3), 22.9 (CH_2), 27.4 (CH_2), 31.4 ($ArCH_2$), 35.4 (*C*H_2CO), 52.9 (NCH_2), 54.2 (*C*HCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 58.9 (CH), 59.0 (OCH_3), 74.9 (OCH_2O), 107.2 (CH), 111.5 (CH), 128.0 (C), 132.6 (C), 134.7 (C), 148.1 (C), 171.9 (CO) ppm.

(1*R*)-1-Methyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1b): Yield 28 mg, 81%.

(1*R*)-1-Butyl-1,2,4,5-tetrahydro-2-benzazepin-3-one (1c): Yield 28 mg, 66%.

(1*R*)-1-Hexyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1d): Yield 24 mg, 59%.

(5*R*)-5-Methyl-5,6,8,9-tetrahydro-1,3-dioxa-6-azacyclohepta[*f*]inden-7-one (1f): Yield 34 mg, 78%. $[\alpha]_D^{25}$ = –25.5 (*c* = 0.47, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.52–2.72 (m, 1 H, CH_2CO), 2.75–3.01 (m, 2 H, $ArCH_2$), 3.04–3.28 (m, 1 H, CH_2CO), 4.62–4.81 (m, 1 H, CH), 6.01 (s, 2 H, OCH_2O), 6.04–6.27 (br. s, 1 H, NH), 6.88 (s, 1 H, H_{arom}), 6.92 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (CH_3), 32.1 ($ArCH_2$), 35.9 (*C*H_2CO), 50.9 (ArCHN), 101.1 (OCH_2O), 104.8 (CH), 108.8 (CH), 129.4 (C), 129.5 (C), 136.2 (C), 141.5 (C), 172.9 (CO) ppm. $C_{12}H_{13}NO_3$ (219.22): calcd. C 65.74, H 5.98, N 6.39; found C 65.48, H 6.12, N 6.65.

(1*R*)-7,8-Dimethoxy-1-methyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (1g): Yield 27 mg, 57%. $[\alpha]_D^{25}$ = –17.4 (*c* = 0.51, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.51–2.69 (m, 1 H, CH_2CO), 2.76–2.99 (m, 2 H, $ArCH_2$), 3.12–3.31 (m, 1 H, CH_2CO), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.82–5.03 (m, 1 H, CH), 6.72 (s, 1 H, H_{arom}), 6.74 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6 (CH_3), 29.3 ($ArCH_2$), 36.1 (*C*H_2CO), 48.3 (ArCHN), 55.9 (OCH_3), 56.1 (OCH_3), 110.6 (CH), 111.2 (CH), 128.0 (C), 132.8 (C), 146.8 (C), 147.3 (C), 174.9 (CO) ppm. $C_{13}H_{17}NO_3$ (235.3): calcd. C 66.36, H 7.28, N 5.95; found C 66.56, H 7.58, N 6.11.

Synthesis of (1*R*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (2b) from 10b by Concomitant Cleavage of the N–N Bond and Reduction of the Lactam: BH_3·THF (3.3 mL, 3.3 mmol, 1 M solution in THF) was added to an ice-cooled stirred solution of tetrahydrobenzazepinone **16b** (65 mg, 0.22 mmol) in dry THF (4 mL) under argon. The mixture was stirred at 0 °C for 1 h and then heated at reflux for 24 h. Aqueous 6 N HCl (2 mL) was added to the cooled reaction mixture and the resulting mixture was stirred at room temperature for 1 h and then heated at reflux for 1 h. The mixture was concentrated under vacuum, the residue was made basic with aqueous 2 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under vacuum. Purification by flash column chromatography (acetone/MeOH, 95:5, as eluent) delivered (1*R*)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (**2b**). Yield 26 mg, 73% as a light-yellow oil. The structure of (*R*)-**2b** was clearly established

from the optical rotation value {$[\alpha]_D^{25}$ = –13.2 (c = 1.05, $CHCl_3$)} and from the spectroscopic data which matched those reported for (*S*)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine {$[\alpha]_D$ = +13.3 (c = 9.0, EtOH)}, but with the opposite sign.[12]

Synthesis of (1*R*)-1-Alkyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines 2a,b by Reduction of Lactams 1a,b: A solution of lactam **1a**,**b** (0.2 mmol) in THF (2 mL) was added slowly at 0 °C under Ar to a suspension of $LiAlH_4$ (15 mg, 0.4 mmol, 1.5 equiv.) in anhydrous THF (5 mL). The resulting mixture was stirred under reflux for 3 h. After careful hydrolysis with ice-water (0.5 mL) the resulting suspension was filtered. The residue was washed thoroughly with Et_2O (5 mL) and CH_2Cl_2 (5 mL). The filtrate was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under vacuum. Purification by flash column chromatography (acetone/MeOH, 95:5, as eluent) afforded benzazepine **2a**,**b** as a pale-yellow oil.

(1*R*)-1-Butyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (2a): Yield 44 mg, 68%. $[\alpha]_D^{25}$ = –21.4 (c = 0.43, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.01 (m, 3 H, CH_3), 1.12–1.63 (m, 7 H, 3 CH_2 + NH), 1.56–1.97 (m, 3 H, 2 H, CH_2 + 1 H, CH_2), 2.69–3.12 (m, 3 H, CH_2 + 1H from CH_2), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.87–4.03 (m, 1 H, ArCHN), 6.17 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 29.2 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 35.2 ($ArCH_2$), 51.1 (NCH_2), 55.8 (OCH_3), 55.8 (ArCHN), 55.9 (OCH_3), 57.9 (OCH_3), 105.7 (CH), 123.1 (C), 127.7 (C), 132.6 (C), 148.2 (C), 150.1 (C) ppm. $C_{17}H_{27}NO_3$ (293.4): calcd. C 69.59, H 9.28, N 4.77; found C 69.55, H 9.54, N 4.58.

(1*R*)-1-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (2b): Yield 26 mg, 81%.

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