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Article

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Synthesis of Shld derivatives, their binding the Destabilizing Domain and influence on protein accumulation in transgenic plants

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Abstract

A series of 35 analogues of **Shld** with modifications in the A-residue and the C-residues were prepared and investigated for binding to FKBP and GFP accumulation in transgenic plants. The modifications investigated explored variations that was supposedly inside or outside the receptor binding site with the latter being important by influencing the overall polarity of the compounds in order to improve the absorption in plants. The binding of the new compounds to the destabilizing domain was determined using a fluorescence polarization competition assay and the GFP expression in engineered *Arabidopsis thaliana* was studied. The results showed that modifications of the C-building block phenol with acidic, basic and neutral groups led to better ligands with some being better that **Shld** in the plant. Generally small, polar substituents showed the best GFP accumulation.

Introduction

The compound **Shld** (or Shield1, Figure 1)[1] is a truncated synthetic[2] analogue[3,4] of the natural compounds Rapamycin and FK506, that present strong affinity for FK binding proteins, but only when the binding site is mutated. **Shld** binds to a F36V mutant of FKBP12 with a 3 orders of magnitude selectivity over the wild type.[5] **Shld** is employed to stabilize destabilized protein domains attached to a protein of interest – when **Shld** binds the protein-conjugate it is not degraded. Hence, **Shld** can be used to induce the accumulation of a protein-of-interest in a genetically engineered cell and has been used in mammalian cells,[6] parasites[7] and plants.[8] In a project where we needed to use **Shld** in plants it became apparent that **Shld** might not have an optimal structure for absorption in plants. The propensity of which a small organic compound like **Shld** penetrates a plant cell can be very different from what is observed for mammalian cells, due to the plant cell's fundamentally different structure.[9] To protect the plant from environmental stress and water loss, the outer-layer of cells (epidermis) is covered by a hydrophobic wax layer called the cuticle, which small molecules applied on the leaf must penetrate. This penetration is heavily impacted by the size of the molecule.[10,11] For the ionic species this tendency is not as pronounced as they are believed to cross the cuticles in hydration shells via aqueous polar pores.[10] The acid/base properties of the compound is also important as it after having passed the cuticle, has to cross the slightly acidic (pH

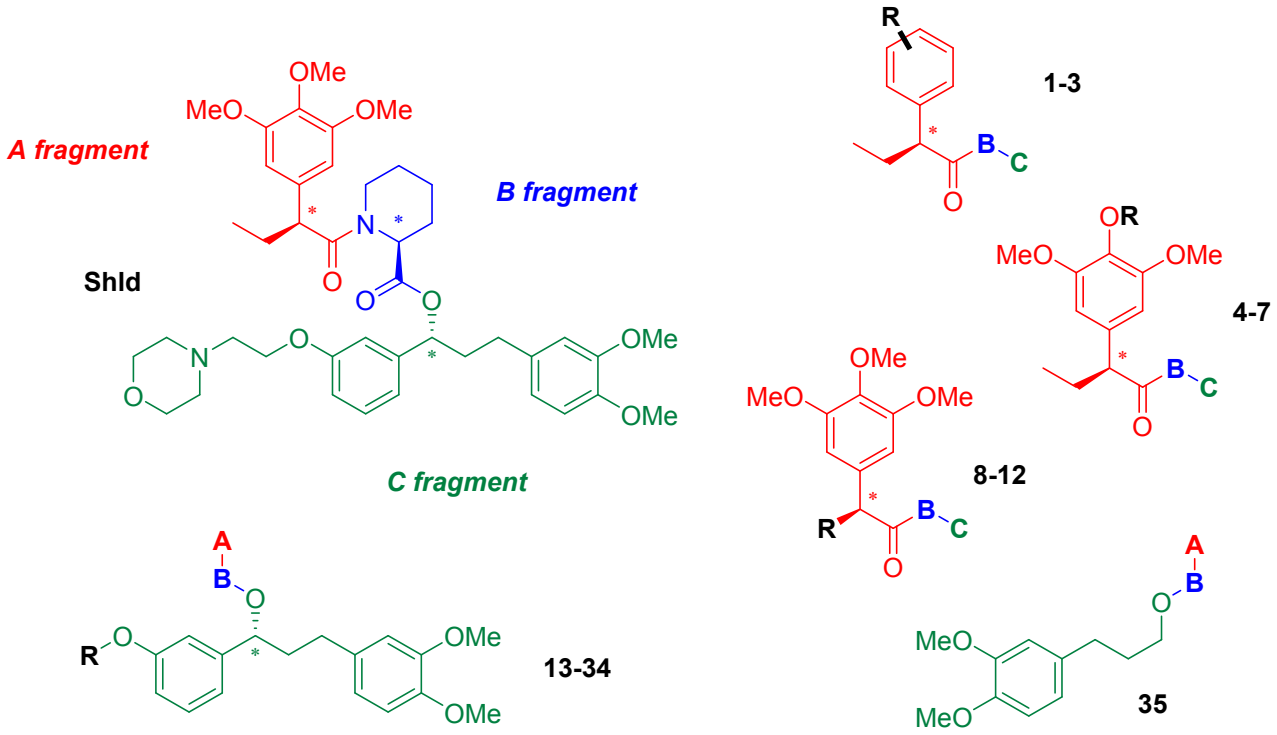


Figure 1. Structure of **Shld** and target compounds **1-35**. The structure is conveniently divided into fragments A-C.

5.5) cell wall or apoplasm before crossing the cell membrane (Figure 2). This is potentially beneficial for acidic compounds as they more readily penetrate from the outside and become trapped inside in the more basic cytosol (Figure 2B).[12] The reverse is true for the basic compounds such as **Shld** (Figure 2C), which more readily penetrate the cell-membrane from the inside. However such compound can accumulate in the acidic vacuoles inside the cell and be slowly released complicating matters further. A neutral compound obviously penetrates the cell without being affected of the unusual pH phenomena (Figure 2A).

The purpose of the present study was to investigate whether a **Shld** derivative with better properties for plant cell penetration could be found. The **Shld** A fragment has previously been identified as very important for DD binding (Figure 1),[3] but only a limited number of **Shld** structures have been investigated. We have therefore decided to explore modifications of the A-

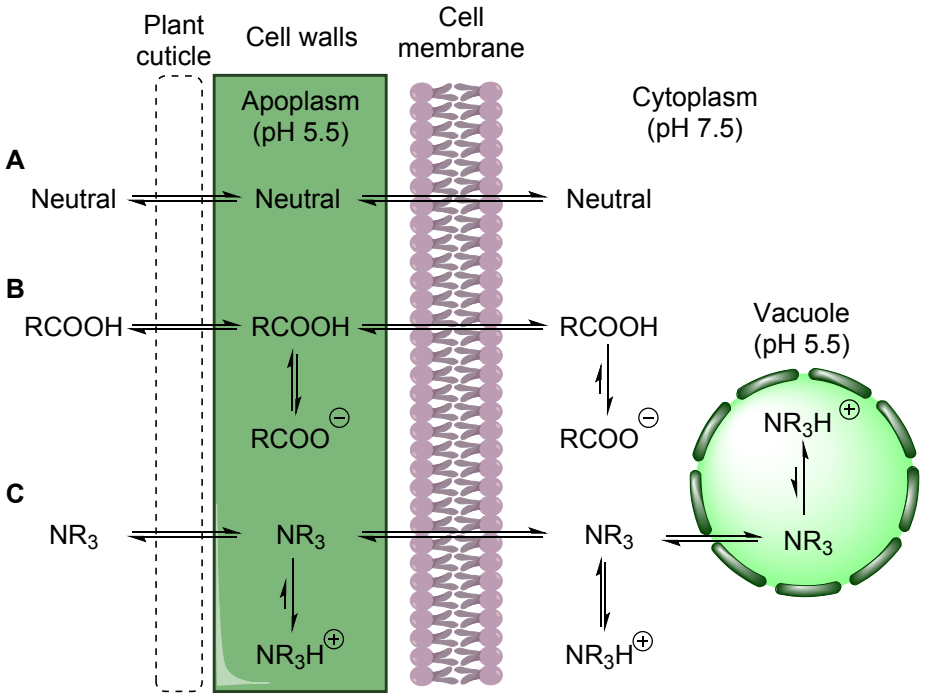
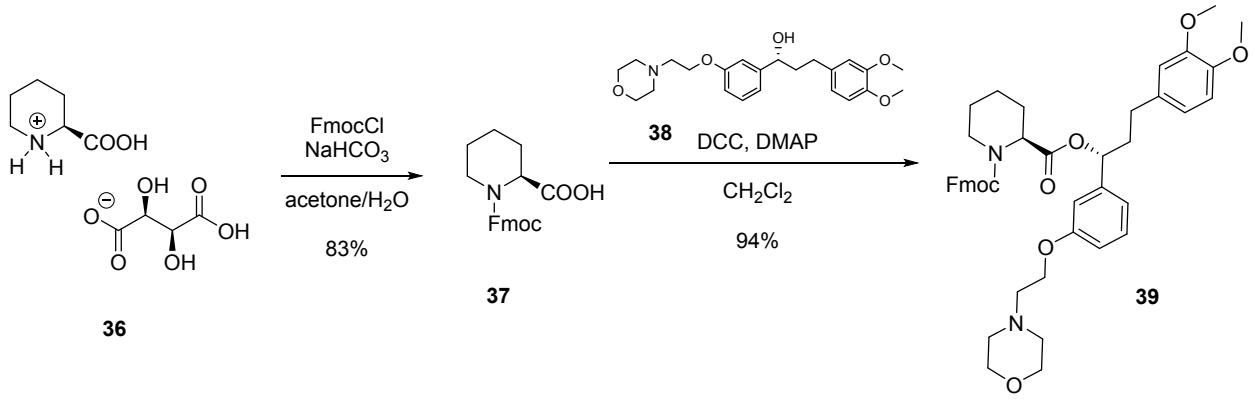


Figure 2. Schematic representation of organic compounds access to a plant cell (bottom). A) Diffusion of neutral lipophilic compound. B) Diffusion of organic carboxylic acid as protonated form, followed by deprotonation in the cytoplasm (ion-trapping). C) Diffusion of deprotonated amine into the vacuole where it is protonated (ion-trapping).

fragment (Figure 1, compounds **1**-**12**). Furthermore the above mentioned pH conditions in the plant cell made it obvious to investigate compounds that were acidic rather than a base such as **Shld**. Indeed the ethylmorpholino-group of **Shld** is believed to be outside the receptor,[1] and thus replacing this moiety with different acidic (or basic) groups was an obvious choice. Therefore the series of **Shld** derivatives **13**-**35** (Figure 1) with a wide range of different acidic and basic substituents were prepared. In this paper we describe the synthesis of these compounds, their receptor binding as measured by a fluorescence polarization assay developed to the purpose and their protein stabilization when applied to transgenic plants. We find that some of the derivatives have improved efficacy compared to **Shld**.

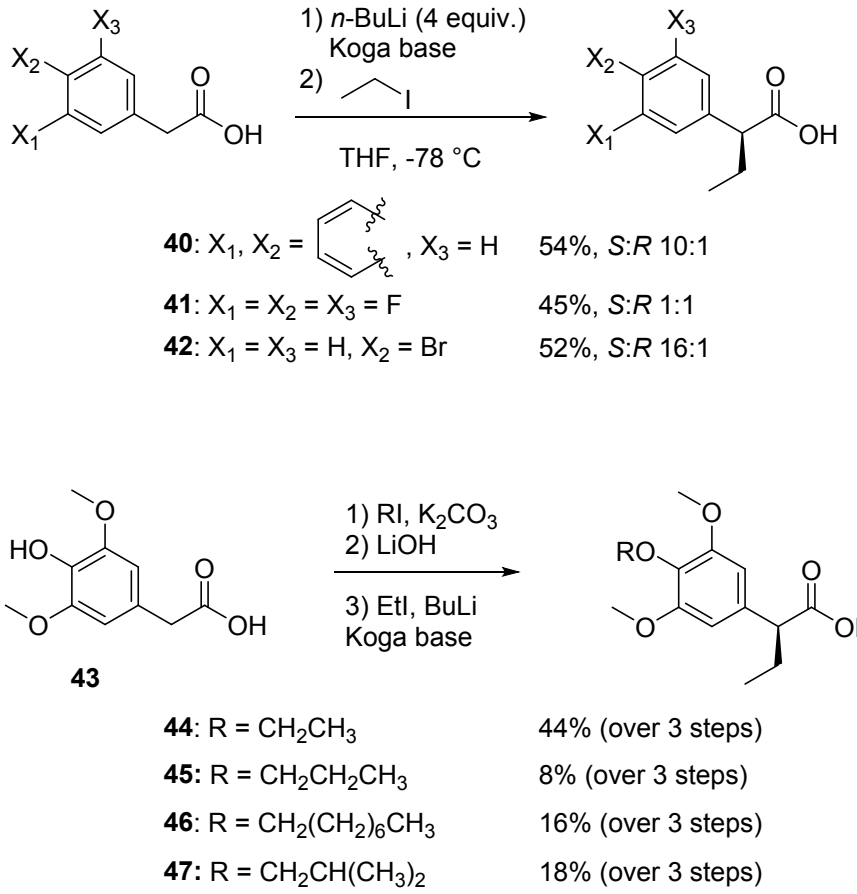
Results and discussion

Previous modifications of the A-fragment (Figure 1) found that removal of the three methoxy-substituents on the aromatic ring led to a 20-fold decrease in affinity to the mutant, while a change of stereochemistry at the stereocenter led to a 100-fold decrease in affinity.[3] These observation prompted synthesis of two sets of derivatives. In the first set, we changed the aromatic group by either making it electronically different in derivatives **1-3** or changing its steric impact in derivatives **4-7** (Figure 1). In a second set of derivatives, **8-12**, we varied the ethyl substituent – this was based on *molecular modelling* studies which indicated that the size of this substituent could be expanded slightly.



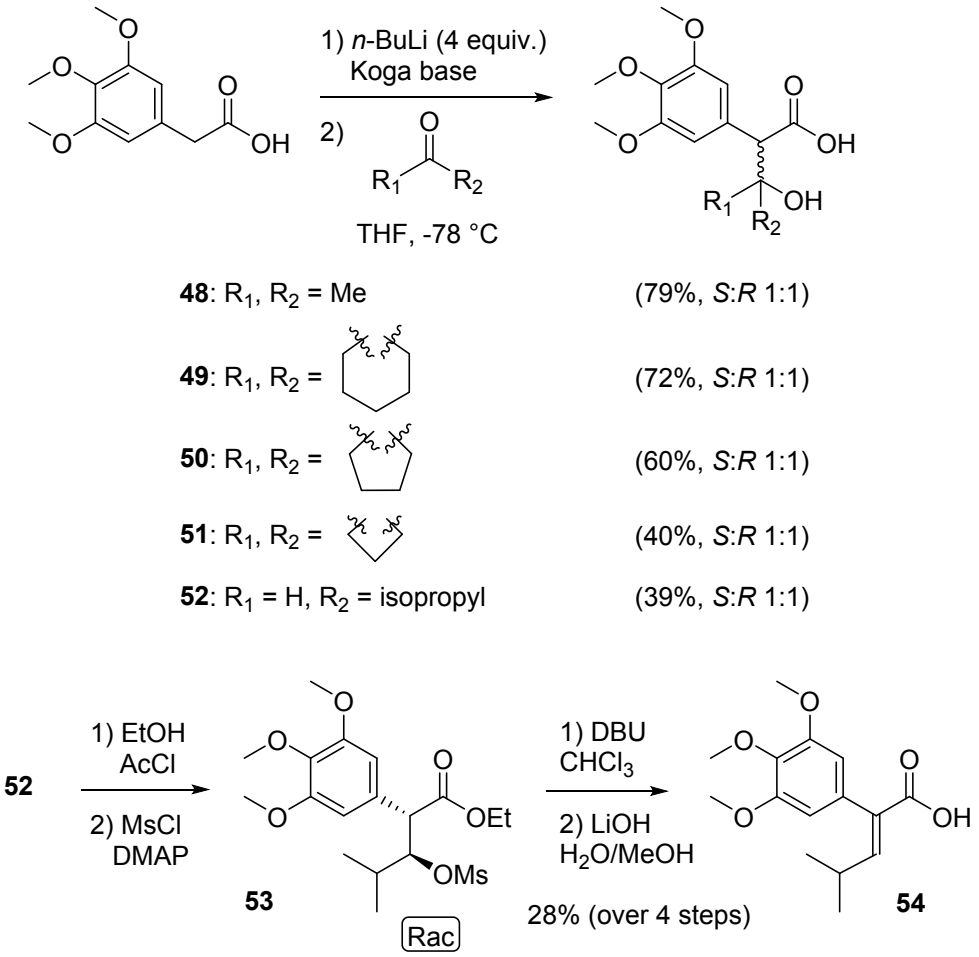
Scheme 1. Synthesis of B-C fragment **39**

Synthesis of the derivatives was carried out as follows: The C-fragment **38** was prepared enantiomerically pure as previous described.[2] Resolution of inexpensive racemic pipecolic acid gave the tartrate **36**.[13] Direct Fmoc protection of **36** gave **37** in 83% yield (Scheme 1), which subsequently was esterified with **38** using DCC and DMAP to give **39** in 94% yield. Compound **39** is the B-C fragment of the molecule and, after removal of the Fmoc group with DBU, it was ready, to be coupled with fragment A acids. The fragment A acids that were precursors for **1-3** were prepared as outlined in scheme 2. Using the enantioselective alkylation method described by Stivala and Zakarian,[Error! Bookmark not defined.] 2-



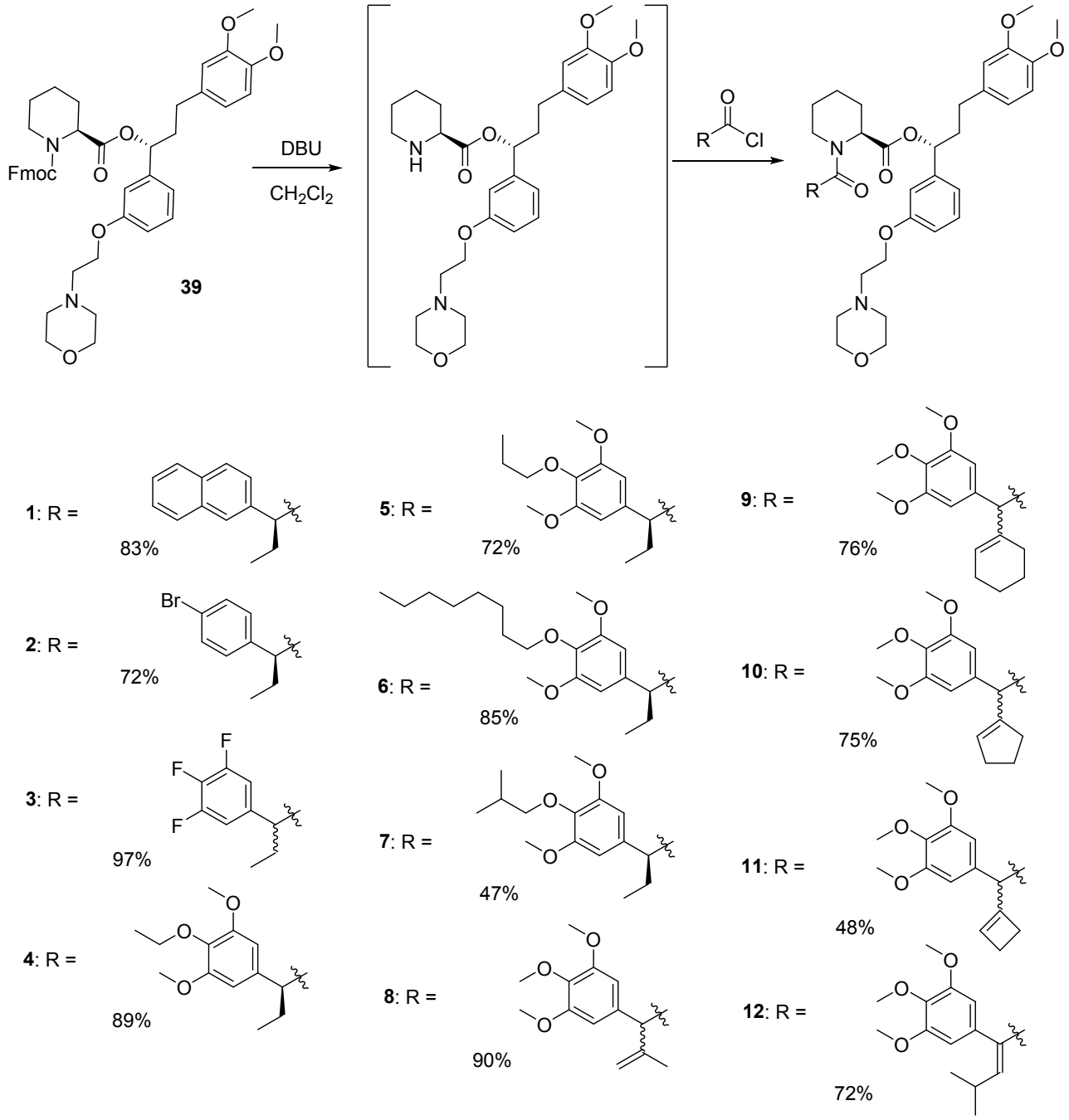
Scheme 2. Synthesis of fragment A precursors **40**-**42** and **44**-**47**. In the synthesis of **45** Cs_2CO_3 was used in place of K_2CO_3. In the synthesis of **46**-**47** the alkyl bromides rather than the iodides were used. Koga base is N^1,N^3-bis((*R*)-1-phenyl-2-(piperidin-1-yl)ethyl)propane-1,3-diamine.

naphtylacetic acid was ethylated using butyl lithium and Koga's base giving the *S*-derivative **40** in 54% yield. The stereoselectivity was 10:1. From the 3,4,5-trifluorophenylacetic acid this reaction gave the ethyl derivative **41** in 45% yield, but with no stereoselectivity. Similar ethylation of 4-bromophenylacetic acid gave the *S*-ethyl derivative **42** in 52% yield and with a stereoselectivity of 15:1. The stereochemical purity of the products was determined by comparing the optical rotation with literature values of enantiopure samples.



Scheme 3. Synthesis of **48-52** and **54**

Modification of the substituents of the trimethoxyphenyl group was done by taking advantage of the commercial availability of 4-hydroxy-3,5-dimethoxyphenylacetic acid **43** (Scheme 2). This compound was alkylated with ethyl iodide and potassium carbonate giving the 4-ethoxy 3,5-dimethoxyphenyl acetic ethyl ester. The ester was hydrolysed with LiOH to the corresponding acid that was then ethylated using Stivala and Zakarian's method to give the *S*-ethyl derivative **44**. The yield was 44% over the three steps. Similarly, this transformative sequence was performed with propyl iodide, octyl iodide and isobutyl iodide giving the 4-propoxy acid **45** in 8% yield, the 4-octyloxy acid **46** in 16% yield and the isobutoxy acid **47** in 18% yield (Scheme 2).



Scheme 4. Synthesis of **Shld** analogues **1-12**

The A-fragments for **8-12** were made by alkylation of the 3,4,5-trimethoxyphenylacetic acid with various carbonyl derivatives (Scheme 3). Reaction with acetone gave alcohol **48** in 79% yield. Similarly, alkylation of the phenylacetic acid with butyl lithium, Koga's base and cyclohexanone, cyclopentantone or cyclobutanone gave **49**, **50,** and **51** in 72, 60, and 40% yield, respectively. None

of the reactions displayed any enantioselectivity presumably, because the crossed Claisen-aldol adduct equilibrates in the strong base.

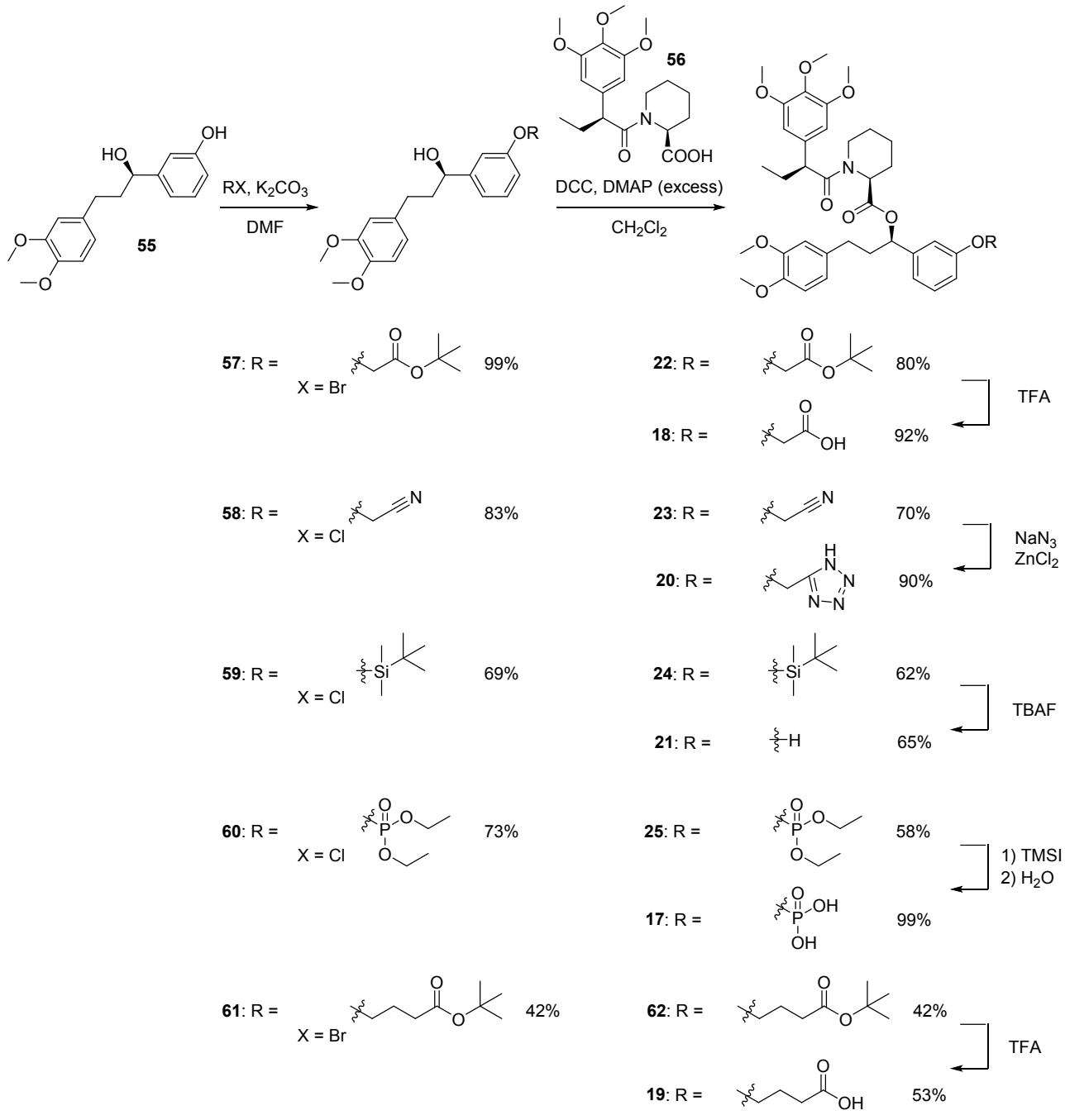
Alkylation with an aldehyde, isobutyraldehyde, was also attempted. This gave alcohol **52** in 39% yield as a single diastereomeric pair (Scheme 3) in accordance with the reaction going through a cyclic transition state.[14] The alcohol was eliminated by first converting the acid to the ethyl ester and mesylating the alcohol to obtain **53** (Scheme 3). Subsequent anti-elimination with DBU and reconversion to the acid with LiOH gave unsaturated acid **54** in 28% yield over these 4 steps (Scheme 3). The configuration of **54** was determined from the ^{13}C-^{1}H coupling constant between the vinyl proton and the carbonyl carbon. It was 6.9 Hz while model compounds *E*-diphenyl acrylic acid had a coupling of 7.3 Hz, while the Z-isomer had 12.5 Hz.[15]

The synthesis of **Shld** analogues **1**-**12** was completed as shown in Scheme 4. The Fmoc protective group was removed from B-C-fragment **39** using DBU and the resulting amine was reacted with acid chlorides formed from each of the acids **40**-**47** formed *via* reaction with thionyl chloride at 40^{o}C. This led to smooth amide bond formation and resulted in 12 **Shld** derivatives in 47-97% yield. Since the acid chlorides formed from **41** & **48**-**51** were racemic, **3** & **8**-**11** were 1:1 diastereomeric mixtures and were tested as such (see below).

The analogues with C-fragment modifications were made using the synthesis strategy recently reported[2] where the fragments are assembled in order from A to C (i.e. A+B → AB + C →ABC). The phenol group substituent was attached to the C-fragment **55** (Scheme 5) that was then attached to the AB fragment (**56**) by esterification. Depending on the derivative some late state deprotection/ or modification of the side chain was necessary. First a series of acidic analogues were prepared with a broad range of pK_a values (Scheme 5). The idea behind these derivatives was to investigate if the ion-trapping mechanism described above (Figure 2, B) could work for these compounds.

Normally a protected version of the acidic group was used. Thus alkylation of the phenolic position of **55**[2] with *tert*-butyl bromoacetate afforded **57** in 99% yield. Similar alkylation with chloroacetonitrile gave **58** in 83% yield. To silyl protect the phenol of **55**, *tert*-butyldimethylsilyl chloride was used together with DMAP and triethylamine in dichloromethane to obtain **59** in 69% yield. Phosphorylation of **55** was performed with diethylchlorophosphate to acquire the arylphosphoric ester **60** in 58% yield. Finally, alkylation of **55** with *tert*-butyl 4-bromobutanoate afforded **61** in 42% yield.

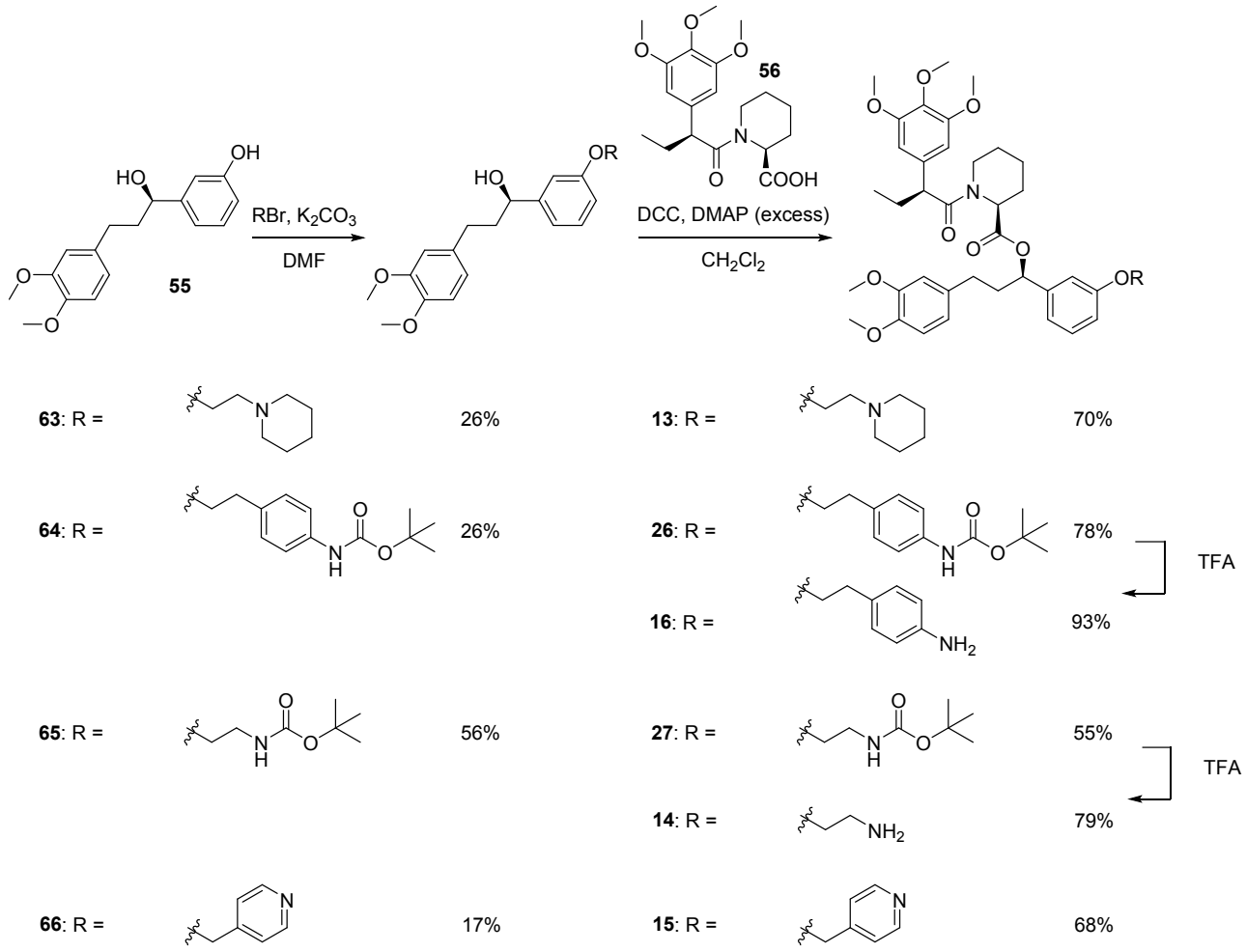
The *O*-substituted phenols **57**, **58**, **59**, **60** and **61** was coupled to **56**[2] using DCC and DMAP. This gave the protected **Shld** analogues **22**, **23**, **24**, **25** and **62** in 80%, 70%, 62%, 58% and 42% yield respectively (Scheme 5). These products were then modified/deprotected as follows: The *tert*-butyl analogues **22** and **62** were treated with TFA in dichloromethane to afford the carboxylic acid analogues **18** and **19** in 92% and 53% yield, respectively (Scheme 5). The silyl protected phenol **24** was deprotected using TBAF under slightly acidic conditions to furnish the phenol derivative **21**. Deprotection of the ethyl groups of the phosphoric ester **25** was performed using trimethylsilyl iodide (TMSI) as described by Blackburn and Ingleson, by first generating the O-TMS phosphoric ester, followed by addition of water affording the phosphoric acid analogue **17**.[16] It turned out that the ester hydrolysis with TMSI was exceptionally prone to formation of byproducts. Initially, addition of TMSI was performed at -78 ºC and the reaction allowed to heat to ambient temperature overnight before hydrolysis with water. LC-MS and NMR revealed that a mixture of two products



Scheme 5. Synthesis of acidic **Shld** analogues. **59** was synthesized using DMAP and Et_3N in CH_2Cl_2.

were obtained, where one was the desired deprotected phosphoric acid **17**, while the other was a sideproduct resulting from hydrolysis of one of the five methoxy groups present in the structure. To avoid hydrolysis of the methoxy groups, it was attempted to keep the reaction at -78 ºC for 5 hours

before addition of water. Unfortunately, this resulted in incomplete deprotection of the phosphoric ester. Eventually, it was found that adding TMSI at -40 ºC and slowly heating the reaction to ambient temperature over 4 hours before addition of water afforded the desired phosphoric acid **17** in quantitative yield. The nitrile analogue **23** was converted into the acidic tetrazole by a 1,3-dipolar cycloaddition with sodium azide facilitated by $ZnCl_2$ in i-PrOH, conditions reported by Vorona *et al.*[17] affording the tetrazole analogue **20** in 90% yield (Scheme 5).

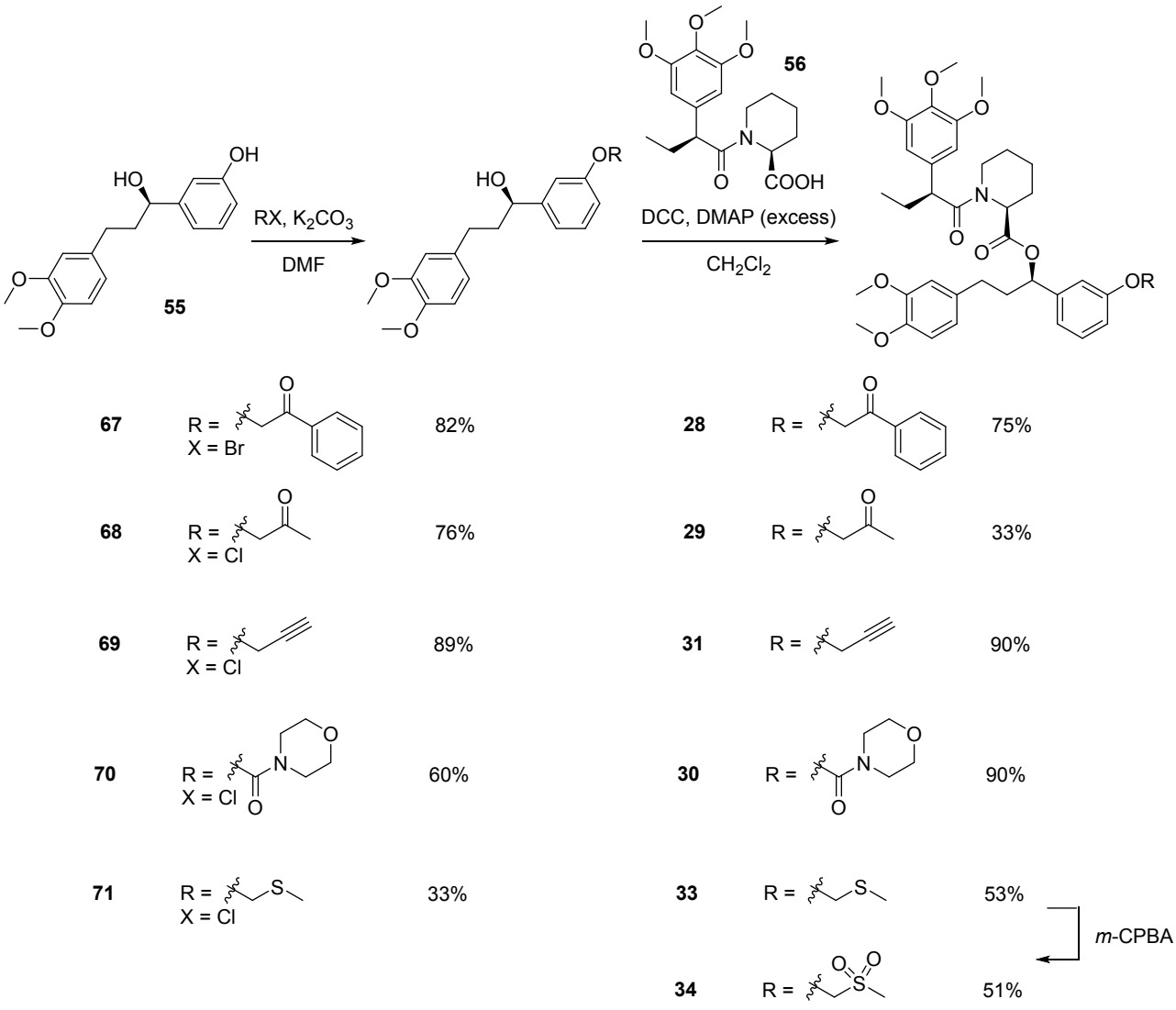


Scheme 6. Synthesis of basic **Shld** analogues.

To explore the effect of variations of pK_a in the base of **Shld** and the potential of the vacuole trapping hypothesis (figure 2, C), four other basic **Shld** analogues were prepared: A piperidine, a pyridine, a primary amine and an aromatic amine (Scheme 6). The latter two had to protected with Boc-groups during the synthesis. In order to prepare the piperidine analogue the alkylation of the phenolic position of **55** were carried out using potassium carbonate and *N*-(2-bromoethyl)piperidine affording **63** in 26% yield. Similar alkylation of **55** with Boc-protected *p*-(2-bromoethyl)aniline, with Boc-protected 2-bromoethylamine and with 4-(bromomethyl)pyridine gave **64**, **65** and **66** in 26% yield, in 56% yield and in 17% yield, respectively (Scheme 6). These four O-alkylated phenols were then coupled to **56** using DCC and DMAP giving **13**, **26**, **27**, and **15** in 70%, 78%, 55% and 68% yields, respectively. Deprotection of the Boc-group of **26** and **27** were carried out with TFA in dichloromethane to afford the aniline derivative **16** and the primary amine **14** in 93% and 79% respectively (Scheme 6).

A series of neutral analogues with differing size and polarity were also synthesized. Two ketone containing analogues were prepared (Scheme 7) by alkylation of the phenolic position of **1** with bromoacetophenone and chloroacetone affording **67** and **68** in 82% and 76%, respectively. Subsequent DCC coupling with **56** furnished **Shld** analogues **28** and **29** in 75% and 33%, respectively. An alkyn derivative was also prepared by alkylation with propargyl chloride and K_2CO_3 to give **69** in 89% yield. Coupling with **56** in the usual way gave **31** in 90% yield. Sulphur containing **Shld** analogues were synthesized: Alkylation of **1** was performed using chloromethyl methyl sulfide to give **71** in 33% yield (Scheme 7). Coupling to **56** afforded the sulfide analogue **39** in 53% yield and finally oxidation using *m*-chloroperbenzoic acid (*m*-CPBA) of the sulfide gave the corresponding sulfone **34** in 51% yield.

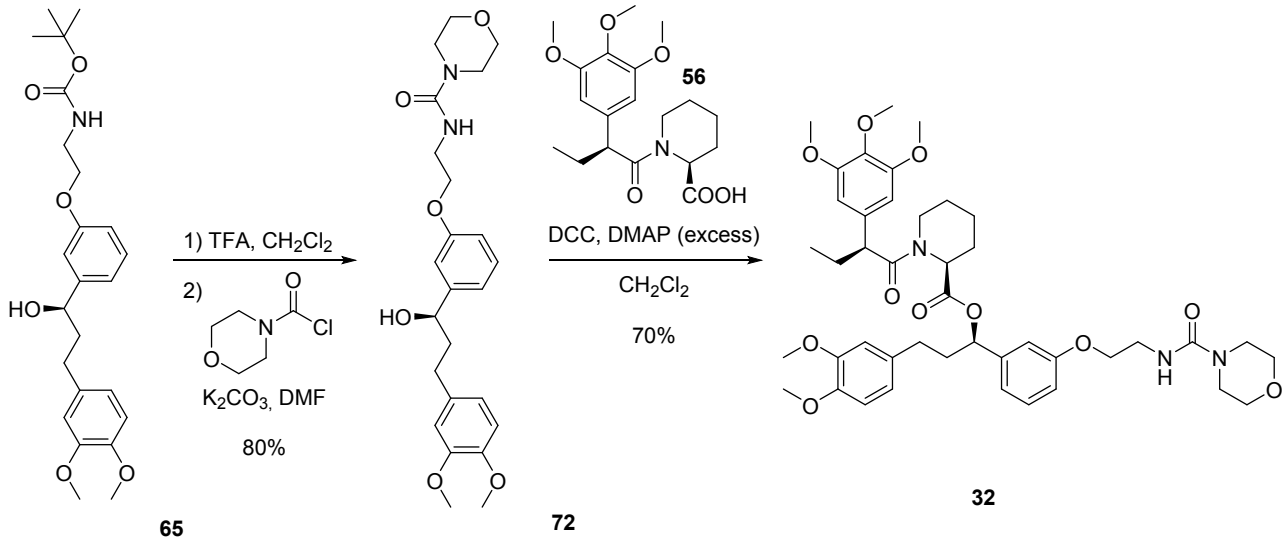
Neutral analogues resembling the shape of **Shld** were also prepared by replacing the amine with



Scheme 7. Synthesis of neutral **Shld** analogues with differing size and polarity

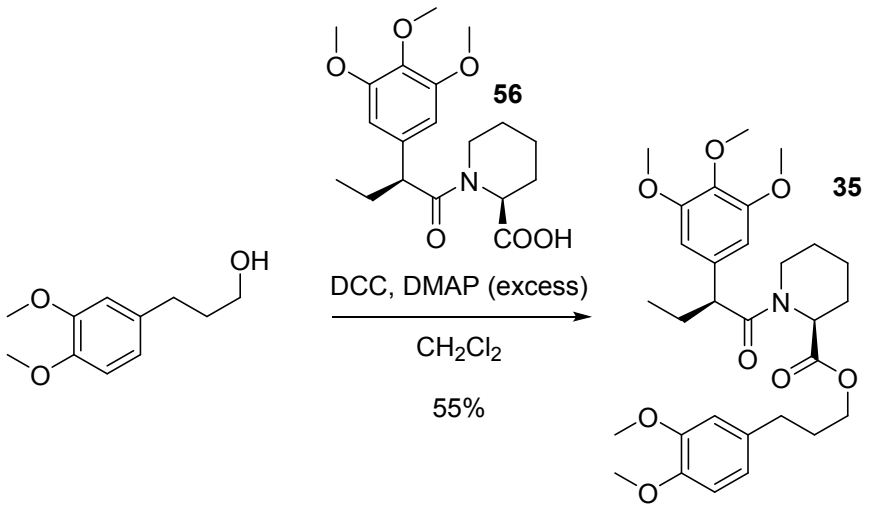
a carbamide or carbamate. Reaction of **55** with 4-morpholinecarbonyl chloride under basic conditions gave **70** in 60% yield, which was subjected to DCC-coupling with **56** affording the carbamate **30** in 90% yield (Scheme 7). To closer mimic the structure of **Shld** the ethyl linker attaching the morpholine and the phenolic position was included in the structure which was done by using the precursor for the primary amine analogue **65** as a starting point (Scheme 8). Deprotection with TFA and reaction with 4-morpholinecarbonyl chloride and potassium carbonate in DMF gave

carbamide **72** in 80% yield. Yet again, coupling to **56** using the developed DCC/DMAP conditions afforded the carbamide analogue **32** in 70% yield.



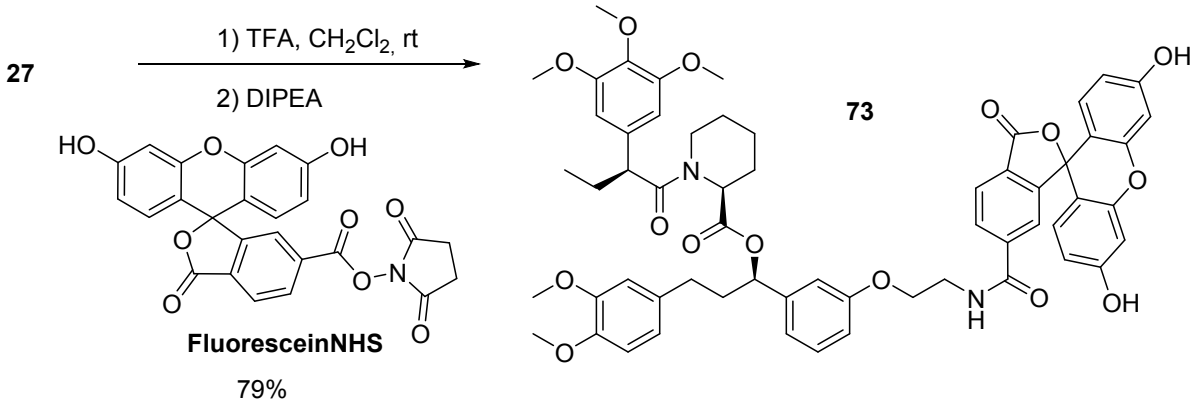
Scheme 8. Synthesis of **Shld** analogue with morpholine scaffold but as a carbamide unable to act as a base in the aqueous buffer

The hypothesis that small molecules more readily penetrate the cuticle led us to prepare a smaller truncated **Shld** analogue. The synthesis was simply carried out by coupling of commercially available 3-(3,4-dimethoxyphenyl)propanol with **56** giving **35** in 55% yield (Scheme 9).



Scheme 9. Synthesis of truncated **Shld** analogue **35**.

In order to test the *in vitro* binding of the new compounds a fluorescence polarization competition assay was devised. A fluorescein labeled version of the known SLF compound has been widely used in fluorescence polarization assays for high throughput screening studies of



Scheme 10. Synthesis of a Fluorescein-labeled Shld derivative **73**

inhibitors towards the FKBPs.[18] For the binding studies of the DD protein, we synthesized an adapted fluoresceinated version of **Shld** as outlined in scheme 10. From the ester **27** the Boc group was removed with TFA and the resulting amine was coupled with commercial 6-carboxyfluorescein succinimide (6-**Fluorescein-NHS**, Scheme 10) in the presence of Hünigs base to give the fluorescein-labeled **Shld** conjugate **73** in 79 % yield.

A binding curve was generated in a saturation binding study of the fluorescent probe **73** with a maltose-binding protein fused DD protein (MBP-DD, Figure 3 left). A binding constant of 3.01 ± 1.02 nM was observed, which were in the expected area for binding to the DD.[3,18] In order to identify the binding affinity of ligands for the DD protein, the binding of the novel fluorescent probe (**73**) was tested in competition with **Shld**. A K_i value of 7.49 ± 1.21 nM was obtained (Figure 3, right). With the fluorescence polarity assay established we determined the binding of the **Shld**

derivatives to the DD protein *in vitro*. The modifications in residue A gave the K_i values shown in Table 1 & 2.

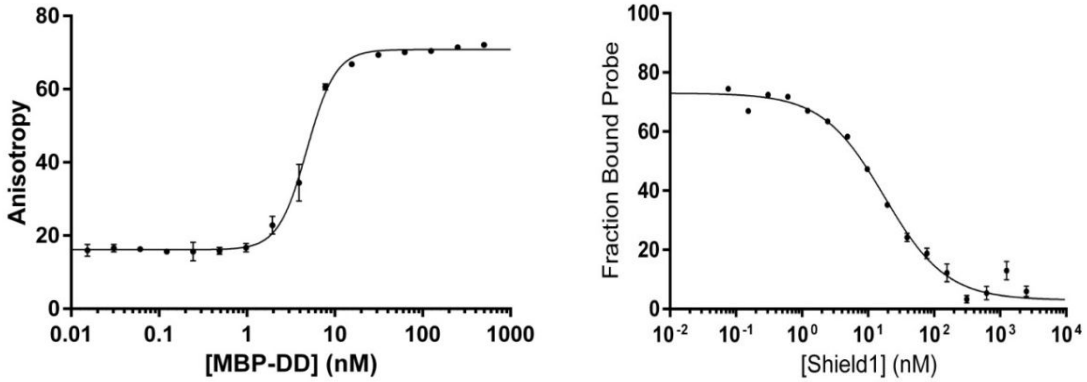


Figure 3. Fluorescence polarization anisotropy versus His-MBP-DD-FKBP12 added to fluorescent ligand **73** (left) & Shld replacement of fluorescent probe **73** from His-MBP-DD-FKBP12 (right)

The effect of the compounds in transgenic plants of species *Arabidopsis* with the 35S::DD–EGFP mutation[8] was also investigated. Plants were sprayed with solutions of **1-35** and immunoblot analyses revealed various levels of accumulation of RDDKeGFP (Figure 4). The results were compared to RDDKeGFP accumulation from **Shld** and untreated plants and the value relative effectiveness (E_{rel}) was determined as the percentage of RDDKeGFP stabilization compared to **Shld**

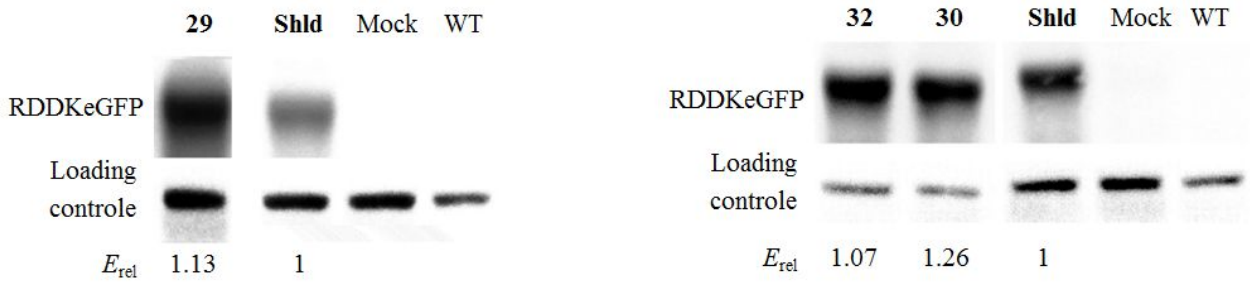
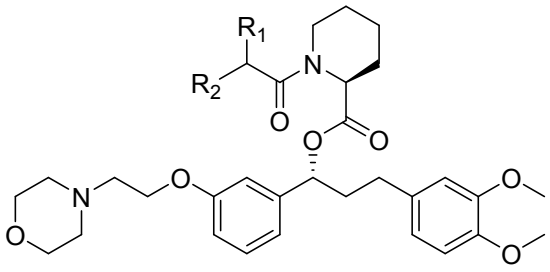


Figure 4. Accumulation of RDDKeGFP in transgenic Arabidopsis treated with **Shld** derivatives **29,30 & 32**

(Table 1 & 2). E_{rel} was calculated as $(I_x-I_u)/(I_{shld}-I_u)$, where I_x is the relative intensity from the derivative investigated, I_{shld} is the intensity from **Shld** and I_u is the intensity in untreated plant.

The naphtyl derivative **1** bound with about three hundred fold less affinity than **Shld** while the trifluorophenyl derivative **3** bound 4000 fold less. The 4-bromophenyl compound **2** was slightly better with a K_i about 100 fold greater than **Shld** (Table 1). The relative affinity of **Shld**, **2** and **3** (pK_i = 8.1, 6.2 and 4.5) reflects the impact of the substituents on the electron density in the aromatic



Compound	R_1-group	R_2-group	K_i	K_i(shld)/K_i	E_{rel}
Shld	3,4,5-$(MeO)_3C_6H_2$-	Et	7.49 ± 1.21	1.0	100%
1	2-Naphtyl-	Et	2101 ± 1820	0.00	0%
2	4-BrC_6H_5-	Et	635 ± 248	0.01	0%
3*	3,4,5-$F_3C_6H_2$-	Et	>10000	0.00	0%
4	4-EtO-3,5-$(MeO)_2C_6H_2$-	Et	13.9 ± 3.63	0.54	50.0%
5	4-PrO-3,5-$(MeO)_2C_6H_2$-	Et	13.9 ± 1.53	0.54	36.0%
6	4-OktO-3,5-$(MeO)_2C_6H_2$-	Et	1581 ± 1132	0.00	5.8%
7	4-iBuO-3,5-$(MeO)_2C_6H_2$-	Et	37.8 ± 4.16	0.20	10.5%
8*	3,4,5-$(MeO)_3C_6H_2$-	2-allyl	35.0 ± 7.82	0.21	0%
9*	3,4,5-$(MeO)_3C_6H_2$-	1-cyclohexenyl	217 ± 32.3	0.03	0%
10*	3,4,5-$(MeO)_3C_6H_2$-	1-cyclopentenyl	151 ± 21.8	0.05	0%
11*	3,4,5-$(MeO)_3C_6H_2$-	1-cyclobutenyl	104 ± 8.27	0.07	18.8%
12	3,4,5-$(MeO)_3C_6H_2$-	Isobutylene	>10000	0.00	2.2%

Table 1. Dissociation constants (K_i) of shld derivatives modified in the A-residue binding to His-MBP-DD-FKBP12 determined by fluorescence polarization and relative accumulation of DD-EGFP (E_{rel}) induced by the derivatives **1-12** compared to **Shld**. $E_{rel}=(I_x-I_u)/(I_{shld}-I_u)$, where I_x, I_{shld} and I_u are the fluorescence intensity of DD-EFGP in the presences of the derivatives investigated, **Shld** or untreated plant, respectively.

* Compound is 1:1 mixture of diastereomers

ring (σ_{sum} = -0.03, 0.23 and 0.74) according to the equation pK_i = -4.5σ_{sum} + 7.7, where σ_{sum} is the sum of the Hammett constants (i.e. σ_{sum}(OMe) = 2 x 0.12-0.27; σ_{sum}(Br) = 0.23 ; σ_{sum}(F) = 2 x 0.34+0.06). The very high affinity of the trimethoxyphenyl group has been ascribed to formation of two hydrogen bonds.[3] Yet, fluorine can also act as hydrogen bond acceptor[19] so the very poor binding of **3** compared to **Shld** or **2** does not fit well with this explanation. An alternative explanation more consistent with our results would be that this aromatic ring is involved in a π interaction whose strength would depend on electron density. However, an x-ray structure of a **Shld**-analogue bound to F36V-FKBP indicates only a intramolecular T-shape π-π interaction with

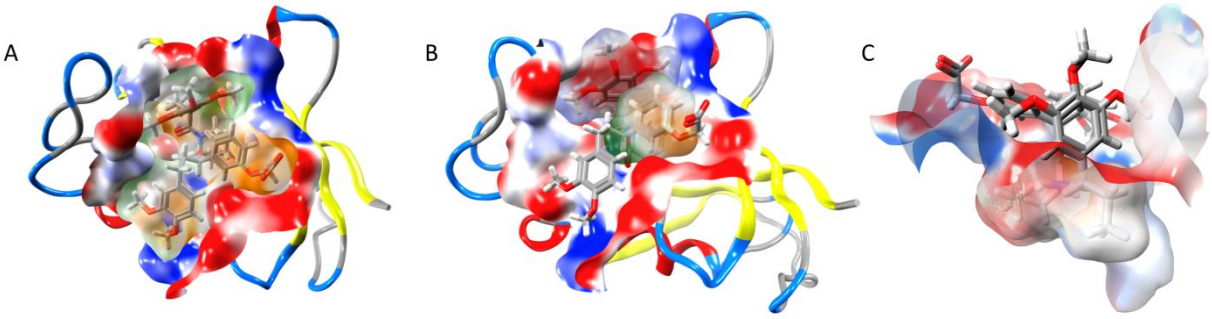


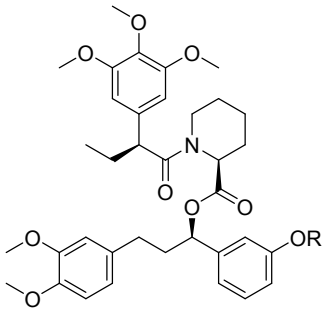
Figure 5. The interaction of shld with the DD (F36V) mutant of FKBP. A) Illustrates the tight fit of a shld-analogue in the binding site of FKBP, B) Presents the important T-π stacking of the trimethoxyphenyl with the carboxymethyloxyphen-3-yl group of the shld-analogue likely to facilitate preorganization of the ligand. C) Shows the exact and tight fitting of the ethyl group and the pipercolic acid at the bottom of the binding pocket. The volume surrounding the ethyl group does not appear to allow favorable modifications as seen from the crystal structure perspective. The models were made from the PDB structure 1BL4[20]

one of the benzene rings in the C-fragment (Figure 5).[20] Perhaps the huge difference in binding affinity of the various aromatic derivatives is a result of different conformations of the ligand due to a difference in strength of this interaction. This is supported by previous NMR experiments, which indicated that different Shld analogues are bound in different conformations.[4]

The 4-*O*-alkylated derivatives **4**-**7** exhibited decreasing levels of binding with size of the substituent. The ethyl and propyl derivatives **4** and **5** had only slightly reduced affinity, while isobutyl derivative **7** was 4 times less potent than **Shld** (Table 1). A very big drop in binding was observed for the octyl derivative **6**, which binds 200 times weaker than **Shld**. The crystal structure of F36V-FKBP shows there is plenty of space for substituents in this area, which suggests that the low binding of **6** could be related to its lipophilicity in the assay.

For compounds **1**-**7** the E_{rel} value generally follows the results of the *in vitro* tests very well. Compounds **1**-**3**, which have close to no affinity *in vitro* show 0% of the increase in accumulation of RDDKeGFP[21] compared to **Shld**, while **4**, **5** and **7** show *in vivo* effectiveness that very closely mimics the *in vitro* values. An exception is the octyl derivative **6** which has 5% of the effectiveness of **Shld** in the plant – yet in vitro the K_i is very high. As discussed above the poor efficacy of **6** *in vitro* could be related to the assay and its solubility.

Similarly the R_2 substituted derivatives **8**-**12** (Table 1) generally decreased in affinity with increasing size: Allyl (**8**) had 4 times the K_i of **Shld**, cyclobutenyl (**11**) a 15-fold lower affinity, cyclopentenyl (**10**) a 20-fold lower affinity and cyclohexenyl (**9**) a 25-fold lower affinity. Only the isobutylene compound **12** was significantly different by having an extremely low affinity. An explanation for these results is that the protein affinity for **8**-**11** fit more and more poorly into the protein cavity with increased bulk of the substituent. The very low binding of **12** is probably due to a wrong geometry as the α-carbon is sp^2 hybridized. There is comparatively poor agreement between the protein accumulation in plant and *in vitro* binding constants for these compounds. Compound **8**-**10** have E_{rel} of 0% yet particularly **8** shows relatively good *in vitro* binding. For compound **11** there is however a rough agreement between the *in vitro* and *in vivo* data (Table 1).



Entry	Cmp	R-group	Type	pK_a	K_i (nM)	K_i(Shld)/K_i	E_{rel}
1	**13**	$-CH_2CH_2N(CH_2CH_2)_2CH_2$	base	10.5	8.78 ± 1.05	0.85	74%
2	**14**	$-CH_2CH_2NH_2$	base	9.8	4.08 ± 0.37	1.84	70%
3	**Shld**	$-CH_2CH_2N(CH_2CH_2)_2O$	base	7.8	7.49 ± 1.21	1.0	100%
4	**15**	$-CH_2C(CHCH)_2N$	base	6.3	56.0 ± 30.5	0.13	11%
5	**16**	$-CH_2CH_2$-*p*-C_6H_4-NH_2	base	5.1	150 ± 55.0	0.05	35%
6	**17**	$-PO_3H_2$	acid	0.5	228 ± 33.2	0.03	18%
7	**18**	$-CH_2COOH$	acid	3.2	18.7 ± 3.90	0.40	84%
8	**19**	$-CH_2CH_2CH_2COOH$	acid	4.4	38.0 ± 5.05	0.20	77%
9	**20**	$-CH_2C(=N)(N=N)NH$	acid	4.7	37.2 ± 2.34	0.20	18%
10	**21**	-H	acid	10.0	30.5 ± 11.4	0.24	89%
11	**22**	$-CH_2COOC(CH_3)_3$	neutral		109 ± 18.2	0.07	15%
12	**23**	$-CH_2CN$	neutral		31.2 ± 7.47	0.24	58%
13	**24**	$-Si(CH_3)_2C(CH_3)_3$	neutral		1650 ± 906	0.00	10%
14	**25**	$-PO(OEt)_2$	neutral		16.0 ± 3.31	0.47	83%
15	**26**	$-CH_2CH_2$-*p*-C_6H_4-$NHCOOC(CH_3)_3$	neutral		> 10000	0.00	19%
16	**27**	$-CH_2CH_2NHCOOC(CH_3)_3$	neutral		109 ± 15.1	0.07	2%
17	**28**	$-CH_2COC_6H_5$	neutral		91.8 ± 13.7	0.08	21%
18	**29**	$-CH_2COCH_3$	neutral		16.6 ± 2.37	0.45	113%
19	**30**	$-CON(CH_2CH_2)_2O$	neutral		16.8 ± 5.84	0.45	126%
20	**31**	$-CH_2CCH$	neutral		56.9 ± 11.8	0.13	62%
21	**32**	$-CH_2CH_2NHCON(CH_2CH_2)_2O$	neutral		9.09 ± 0.97	0.82	107%
22	**33**	$-CH_2SCH_3$	neutral		28.1 ± 8.38	0.27	86%
23	**34**	$-CH_2SO_2CH_3$	neutral		8.19 ± 2.25	0.91	76%
24	**35**	See scheme 9	neutral		261 ± 59.8	0.03	80%

Table 2. Dissociation constants (K_i) of **Shld** derivatives modified at the C-residue binding to His-MBP-DD-FKBP12 determined by fluorescence polarization and relative accumulation of RDDKeGFP (E_{rel}) induced by the derivatives **13-35**. pK_a values listed are not the pK_a values of the compound but of similar, simpler, compounds containing the same functional group.

The test results of the C-residue modifications are shown in Table 2, where they are listed according to their acid-base properties and their pK_a values. The primary amine analogue **14** (Table 2, entry 2) showed the strongest binding towards the protein (K_i = 4.08 nM) of all the tested

compounds in the *in vitro* assay, providing a twofold increase in binding affinity compared to **Shld**. The piperidine derivative **13** (entry 1) gave a binding affinity similar to **Shld**, whereas the pyridine **15** (entry 4) and aniline **16** (entry 5) derivative afforded a 7-fold and 20-fold decrease in binding affinity respectively compared to **Shld**. The significant change in binding affinity for the base analogues suggests that the phenolic substituent does indeed influence the binding towards the protein. The higher pK_a bases are more protonated in the buffer (pH 8.0) suggesting that having an positive charge in this area is favorable. The *in vivo* assay only **13** and **14** provided stabilization and accumulation of the RDDKeGFP protein similar to **Shld** (E_{rel} 70% and 74% respectively) and overall the protein accumulation crudely follows *in vitro* binding.

The acid analogues **18**-**20** (entry 6-10) generally showed weaker (than **Shld**) and individually similar binding affinities (*in vitro*). The short-chained carboxylic acid **18** is the strongest binding ligand (K_i = 18.7 nM) of the five while the arylphosphoric acid **17** (entry 6) was the weakest with a 5-10 fold decrease in binding affinity (K_i = 228 nM), compared to the other acid analogues. Since all these derivatives are negatively charged at pH 8 and the phosphate particularly so the results suggest that negative charge cause repulsion from the protein much in line with positive charge causing stronger binding. On the other hand in the plant based assay, the five acid analogues generally show much better protein accumulation than anticipated based on receptor binding which suggest that the ion-trapping mechanism (Figur 2B) is working with these derivatives. Best stabilization of the RDDKeGFP protein was observed for **18**, **19** and **21** (E_{rel} of 84%, 77% and 89% respectively), while the tetrazole analogue **20** and the phosphate **17** had a lower effect (E_{rel} of 18%). It should be noted that the higher pK_a acids **19** and **21** are superior at accessing the plant cell compared to **Shld** (E_{rel} 89% and 77% respectively) when taking into account their receptor binding

affinity is lower **Shld** (K_i(**Shld**)/K_i = 0.24 and 0.20 respectively). For **21** there could be an influence of this compound being of smaller size and possible more likely superior at penetrating the cuticle.

The neutral analogues **22**-**35** (entries 11-24) had a surprisingly large span in binding affinities given the supposition that the modification is outside the receptor binding site. The most potent derivatives, **25**,**29**-**30**,**32** and **34**, have polar and typically small substituents and a binding as **Shld** or twofold lower. In contrast the derivatives with the bulky, lipophilic derivatives **24** and **26** (entry 13 and 15) showed the weakest *in vitro* binding of the entire assay. The other bulky *tert*-butyl ester or carbamates **22** and **27** also gave relatively poor binding affinities. In the plant assay GFP accumulation roughly followed receptor affinity. The best analogues **29**-**30** (entry 18-19) and the carbamide **32** (entry 21) exhibited better protein accumulation that **Shld** (E_{rel} = 113%, 126% and 107% respectively). In contrast, the large and bulky groups gave the low GFP protein. Overall the results show that **Shld**'s ability to act as a base is not required neither for binding to the receptor or for biological uptake in the plant.

The truncated analogue **35** showed poor receptor binding (261 nM), yet very respectable GFP accumulation (E_{rel} 80%). It is probable that the effectiveness of the compound is a result of the more effective penetration of the cuticle by a small compound such as **35**.

Conclusions

In conclusion this study has shown that the electron rich nature of aromatic group in **Shld** is important for binding and that only minor modifications in the A-fragment are allowed to retain affinity. Modifications in the C-fragment had a surprisingly large variation in receptor binding affinities which appears to contradict the statement[1] that the phenolic substituent is not related to binding. The results showed that it is beneficial for receptor binding to have a positive charge in this

area while negative charge is bad. Strongly basic derivative **14** had twice the affinity of **Shld**. In the plant **Shld** derivatives with acidic and basic groups did not show better protein accumulation that the parent. In contrast analogous with small neutral substituents, **29**, **30** and **32**, gave slightly better GFP production than **Shld**. This is probably due to better penetration. This was supported by the observation that the simplified **Shld** analogue **35** despite being a comparatively weak binder, showed 80% of the effect of **Shld** in plants.

Experimental

General information.

Air and water sensitive reactions were carried out under nitrogen. All commercial available chemicals and solvents were used as received. ^{1}H NMR spectra were measured on a Bruker instrument with cryo-probe at 500 MHz. ^{13}C NMR was measured on the same instrument but at 126 MHz. ^{19}F NMR was recorded on a Bruker instrument with inverse probe at 470 MHz. NMR solvents used were $CDCl_3$ (D 99.8%, referenced to δ_H = 7.26 ppm ($CHCl_3$) and δ_C = 77.16 ppm ($CDCl_3$)) and DMSO-d_6 (D 99.8%, referenced to δ_H = 2.50 ppm (DMSO-d_5) and δ_C = 39.52 ppm (DMSO-d_6)). Fluorine NMR were carried out in $CDCl_3$ with a lock tube containing TFA (referenced to δ_F = -76.55 ppm). Coupling constants (*J*) was given in Hertz (Hz). $CDCl_3$ was passed through activated Al_2O_3 (basic) prior to use. Anhydrous solvents were collected from an IT (Innovative Technology) installation of the model PS-MD-05. Thin-layer chromatography (TLC) was performed on precoated (silica 60) aluminum plates with fluorescence indicator. Flash column chromatography was on silica (SiO_2) with particle size 40-63 μm from ROTH. Optical rotation was measured on an Anton Paar MCP 300 polarimeter with a 50 x 5 mm cuvette. UPLC-MS (Ultra Performance Liquid Chromatography - Mass Spectrometry) was performed on a Dionex UltiMate

3000 RS with an Acclaim™ RSLC 120 C18 column (2.2 μm, 120 Å, 2.1 x 100 mm) connected to a Bruker micrOTOF Q-III mass spectrometer. High resolution mass spectrometry (HR-MS) was on a FT-ICR spectrometer using either matrix assisted laser desorption ionization (MALDI) with dithranol as matrix or electrospray ionization (ESI+) with methanol + 1% TFA. Melting points are uncorrected. Koga's base is N^1,N^3-bis((*R*)-1-phenyl-2-(piperidin-1-yl)ethyl)propane-1,3-diamine and was prepared as previously described.[22] For simplicity, the integrals in ^{1}H NMR of rotamers (when both rotamers are distinguishable) are reported as the sum of the major- and minor contributor (e.g. for rotamer ratio of 1:0.7), 1 proton reported as 1H and 0.7H instead of 0.59H and 0.41H). Tested compounds were analyzed with LCMS confirming ≥ 95% purity.

General procedure for amide bond formation. (R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (S)-1-((S)-2-naphtylbutanoyl)piperidine-2-carboxylate (1)

To flask A, a solution of **40** (100 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (4 mL) was added thionyl chloride (0.25 mL, 3.4 mmol) and the solution was heated to reflux and kept at this temperature for 2 hours. The contents of the reaction vessel were concentrated *in vacuo* and redissolved in anhydrous CH_2Cl_2 (3 mL). In a separate flask B, a solution of **39** (100 mg, 0.136 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DBU (22 μL, 0.15 mmol). After 1 hour TLC analysis indicated complete cleavage of Fmoc. To flask B, Et_3N (0.1 mL, 0.7 mmol) was added followed by the contents of flask A. The resulting solution was left stirring 30 min before it was concentrated *in vacuo* and subjected to flash column chromatography (30% acetone in toluene + 1% Et_3N) to yield **1** (80 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers, 1:0.4, **A**:**B**): δ 7.83 – 7.79 (m, 1.4H, **A** + **B**), 7.77 – 7.68 (m, 3.8H, **A** + **B**), 7.66 (d, *J* = 1.8 Hz, 0.4H, **B**), 7.50 – 7.44 (m, 1.8H, **A** + **B**) 7.44 – 7.39 (m, 2H, **A**), 7.38 (dd, *J* = 8.5, 1.8 Hz, 0.4H, **B**), 7.31 (t, *J* = 7.9 Hz, 0.4H, **B**), 6.95 (d, *J* = 7.7 Hz, 0.4H, **B**), 6.93 – 6.89 (m, 0.4H, **B**), 6.90 – 6.85 (m, 0.4H, **B**), 6.82 – 6.74 (m, 2.4H,

A + **B**), 6.70 (dd, *J* = 8.2, 2.1 Hz, 0.4H, **B**), 6.70 – 6.64 (m, 2H, **A**), 6.65 (s, 1.4H, **A** + **B**), 6.62 – 6.58 (m, 1H, **A**), 6.23 (d, *J* = 7.6 Hz, 1H, **A**), 5.82 (dd, *J* = 7.8, 6.0 Hz, 0.4H, **B**), 5.62 (dd, *J* = 8.2, 5.6 Hz, 1H, **A**), 5.54 (d, *J* = 4.2 Hz, 1H, **A**), 4.69 (d, *J* = 5.7 Hz, 0.4H, **B**), 4.64 (d, *J* = 13.9 Hz, 0.4H, **B**), 4.14 (t, *J* = 5.5 Hz, 0.8H, **B**), 3.96 – 3.91 (m, 3H, **A**), 3.87 (s, 1.2H, **B**), 3.86 (s, 4.2H, **A** + **B**), 3.84 (s, 4H, **A**), 3.77 – 3.69 (m, 5.6H, **A** + **B**), 3.55 (t, *J* = 7.1 Hz, 0.4H, **B**), 2.86 – 2.81 (m, 0.8H, **B**), 2.74 – 2.69 (m, 2H, **A**), 2.69 – 2.47 (m, 8.8H, **A** + **B**), 2.45 – 2.36 (m, 1H, **A**), 2.33 – 2.26 (m, 1.4H, **A** + **B**), 2.25 – 2.15 (m, 1.4H, **A** + **B**), 2.14 – 2.06 (m, 0.4H, **B**), 2.04 – 1.95 (m, 1H, **A**), 1.96 – 1.90 (m, 0.4H, **B**), 1.91 – 1.83 (m, 1H, **A**), 1.84 – 1.75 (m, 1.4H, **A** + **B**), 1.69 – 1.60 (m, 2H, **A**), 1.57 – 1.52 (m, 1.4H, **A** + **B**), 1.49 – 1.39 (m, 1.8H, **A** + **B**), 1.28 – 1.14 (m, 1.8H, **A** + **B**), 0.91 (t, *J* = 7.3 Hz, 3H, **A**), 0.84 (t, *J* = 7.3 Hz, 1.2H, **B**) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers, 1:0.4, **A**:**B**): δ 172.70 (**B**), 172.41 (**A**), 170.77 (**A**), 170.67 (**B**), 159.09 (**B**), 158.60 (**A**), 149.10 (**B**), 148.99 (**A**), 147.62 (**B**), 147.43 (**A**), 141.73 (**A**), 141.63 (**B**), 137.90 (**B**), 137.34 (**A**), 133.82 (**A**), 133.71 (**B**), 133.64 (**A**), 133.41 (**B**), 132.61 (**A**), 132.59 (**B**), 129.92 (**B**), 129.47 (**A**), 128.89 (**B**), 128.59 (**A**), 127.87 (**A**), 127.86 (**B**), 127.81 (**B**), 127.78 (**A**), 127.01 (**A**), 126.37 (**B**), 126.36 (**A**), 126.32 (**B**), 126.21 (**A**), 125.95 (**B**), 125.87 (**B**), 125.80 (**A**), 120.36 (**A**), 120.27 (**B**), 119.21 (**B**), 118.90 (**A**), 114.36 (**B**), 114.06 (**A**), 113.16 (**B**), 113.01 (**A**), 111.95 (**A**), 111.80 (**B**), 111.51 (**B**), 111.45 (**A**), 76.94 (**B**), 76.05 (**A**), 66.98 (**A** + **B**), 65.98 (**B**), 65.68 (**A**), 57.81 (**B**), 57.71 (**A**), 56.08 (**A** + **B**), 56.00 (**B**), 55.96 (**A**), 55.88 (**B**), 54.25 (**B**), 54.16 (**A**), 52.18 (**A**), 51.30 (**B**), 50.89 (**A**), 43.77 (**A**), 39.80 (**B**), 38.15 (**B**), 38.08 (**A**), 31.67 (**B**), 31.29 (**A**), 28.51 (**B**), 28.34 (**A**), 26.84 (**A**), 26.60 (**B**), 25.57 (**A**), 24.55 (**B**), 21.11 (**A**), 20.80 (**B**), 12.72 (**B**), 12.55 (**A**) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{43}H_{52}N_2O_7Na^+$ 731.3667; Found 731.3664.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(4-bromophenyl)butanoyl)piperidine-2-carboxylate (2)

The reaction was carried out as described for **1**, using **42** (100 mg, 0.41 mmol) and anhydrous THF as solvent. Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **2** as a slightly yellow oil (79 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers, 1:0.25, **A**:**B**): δ 7.46 – 7.42 (m, 0.5H, **B**), 7.39 – 7.35 (m, 2H, **A**), 7.17 – 7.12 (m, 2H, **A**), 7.13 – 7.08 (m, 0.5H, **B**), 6.92 (d, J = 7.7 Hz, 0.25H, **B**), 6.89 – 6.83 (m, 1H, **A**), 6.82 – 6.77 (m, 2.5H, **A** + **B**), 6.69 – 6.64 (m, 4H, **A** + **B**), 6.56 (d, J = 7.6 Hz, 1H, **A**), 5.82 – 5.77 (m, 0.25H, **B**), 5.67 (dd, J = 8.1, 5.8 Hz, 1H, **A**), 5.47 (d, J = 4.7 Hz, 1H, **A**), 4.57 (d, J = 13.6 Hz, 0.25H, **B**), 4.53 (d, J = 5.0 Hz, 0.25H, **B**), 4.11 (t, J = 5.7 Hz, 0.5H, **B**), 4.06 (t, J = 5.7 Hz, 1H, **A**), 4.05 (t, J = 5.7 Hz, 1H, **A**), 3.85 (br s, 7.5H, **A** + **B**), 3.80 – 3.76 (m, 1H, **A**), 3.75 – 3.71 (m, 5H, **A** + **B**), 3.63 (t, J = 7.2 Hz, 1H, **A**), 3.33 (t, J = 7.1 Hz, 0.25H, **B**), 2.82 – 2.77 (m, 2.5H, **A** + **B**), 2.72 (td, J = 13.4, 3.0 Hz, 1H, **A**), 2.59 – 2.56 (m, 5H, **A** + **B**), 2.57 – 2.49 (m, 1.75H, **A** + **B**), 2.44 (ddd, J = 14.0, 9.7, 6.5 Hz, 1H, **A**), 2.33 – 2.25 (m, 1H, **A**), 2.25 – 2.22 (m, 0.25H, **B**), 2.12 – 2.01 (m, 2.75H, **A** + **B**), 1.97 – 1.87 (m, 1H, **A**), 1.78 – 1.68 (m, 1.25H, **A** + **B**), 1.68 – 1.59 (m, 2H, **A**), 1.59 – 1.52 (m, 1.5H, **A** + **B**), 1.41 (qt, J = 12.8, 3.8 Hz, 1H, **A**), 1.31 – 1.16 (m, 1.5H, **A** + **B**), 1.02 (tdd, J = 12.9, 5.5, 3.7 Hz, 0.25H, **B**), 0.86 (t, J = 7.3 Hz, 3H, **A**), 0.77 (t, J = 7.3 Hz, 0.75H, **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers, 1:0.25, **A**:**B**): δ 172.25 (**B**), 172.06 (**A**), 170.66 (**A**), 170.42 (**B**), 159.07 (**B**), 158.81 (**A**), 149.06 (**B**), 148.98 (**A**), 147.59 (**B**), 147.42 (**A**), 141.70 (**A**), 141.50 (**B**), 139.42 (**B**), 138.83 (**A**), 133.69 (**A**), 133.32 (**B**), 132.13 (**B**), 131.87 (**A**), 129.98 (**A**), 129.89 (**B**), 129.70 (**A**), 129.42 (**B**), 120.99 (**B**), 120.84 (**A**), 120.27 (**A**), 120.23 (**B**), 119.13 (**B**), 118.98 (**A**), 114.30 (**B**), 114.06 (**A**), 113.16 (**A** + **B**), 111.84 (**A**), 111.75 (**B**), 111.46 (**A** + **B**), 77.00 (**B**), 76.14 (**A**), 67.03 (**A** + **B**), 65.96 (**B**), 65.80 (**A**), 57.79 (**A** + **B**), 56.04 (**A**), 55.97 (**B**), 55.96 (**B**), 55.95 (**A**), 55.85 (**B**), 54.24 (**B**), 54.22 (**A**), 52.18 (**A**), 50.42 (**B**), 50.04 (**A**), 43.68 (**A**), 39.76 (**B**), 38.13 (**A**), 38.05 (**B**), 31.62 (**B**), 31.30 (**A**), 28.38 (**B**), 28.26 (**A**), 26.80 (**A**), 26.70 (**B**), 25.52 (**A**),

24.47 (**B**), 21.05 (**A**), 20.79 (**B**), 12.52 (**B**), 12.40 (**A**). HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd. for $C_{39}H_{50}BrN_2O_7^+$ 737.2796; Found 737.2776.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-(2-(3,4,5-trifluorophenyl)butanoyl)piperidine-2-carboxylate (3)

The reaction was carried out as described for **1**, using **41** (100 mg, 0.46 mmol). Purification was performed by flash column chromatography (25% acetone in toluene + 1% Et_3N) yielding **3** as a slightly yellow oil (103 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.20) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 7.26 (t, *J* = 7.9 Hz, 1H, **A** *or* **B**), 7.17 (t, *J* = 7.9 Hz, 1H, **A** *or* **B**), 6.93 (dd, *J* = 8.2, 6.6 Hz, 4H, **A** + **B**), 6.93 – 6.88 (m, 1H, **A** *or* **B**), 6.87 – 6.86 (m, 1H, **A** *or* **B**), 6.84 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H, **A** *or* **B**), 6.82 – 6.76 (m, 3H, **A** + **B**), 6.71 – 6.62 (m, 6H, **A** + **B**), 5.75 (dd, *J* = 7.9, 5.8 Hz, 1H, **A** *or* **B**), 5.70 (dd, *J* = 8.0, 5.9 Hz, 1H, **A** *or* **B**), 5.49 (d, *J* = 4.9 Hz, 1H, **A** *or* **B**), 5.45 (d, *J* = 5.1 Hz, 1H, **A** *or* **B**), 4.11 (t, *J* = 5.7 Hz, 2H, **A** *or* **B**), 4.07 (t, *J* = 5.7 Hz, 2H, **A** *or* **B**), 3.86 (s, 3H, **A** *or* **B**), 3.85 (s, 9H, **A** + **B**), 3.77 (br d, *J* = 13.4 Hz, 2H, **A** + **B**), 3.75 – 3.72 (m, 8H, **A** + **B**), 3.63 (t, *J* = 7.2 Hz, 1H, **A** *or* **B**), 3.62 (t, *J* = 7.2 Hz, 1H, **A** *or* **B**), 3.20 (td, *J* = 13.1, 2.9 Hz, 1H, **A** *or* **B**), 2.86 – 2.81 (m, 1H, **A** *or* **B**), 2.81 (t, *J* = 5.7 Hz, 2H, **A** *or* **B**), 2.79 (t, *J* = 5.7 Hz, 2H, **A** *or* **B**), 2.61 – 2.55 (m, 8H, **A** + **B**), 2.55 – 2.42 (m, 4H, **A** + **B**), 2.34 – 2.27 (m, 2H, **A** + **B**), 2.26 – 2.19 (m, 1H, **A** *or* **B**), 2.14 – 2.00 (m, 4H, **A** + **B**), 1.95 (ddt, *J* = 13.8, 9.8, 6.4 Hz, 1H, **A** *or* **B**), 1.76 – 1.59 (m, 6H, **A** + **B**), 1.59 – 1.48 (m, 2H, **A** + **B**), 1.44 (qt, *J* = 13.3, 4.2 Hz, 1H, **A** *or* **B**), 1.36 – 1.22 (m, 2H, **A** + **B**), 0.95 (qt, *J* = 12.9, 4.2 Hz, 1H, **A** *or* **B**), 0.88 (t, *J* = 7.3 Hz, 3H, **A** *or* **B**), 0.87 (t, *J* = 7.3 Hz, 3H, **A** *or* **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.20) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 171.94 (**A** *or* **B**), 171.48 (**A** *or* **B**), 170.63 (**A** *or* **B**), 170.47 (**A** *or* **B**), 159.03 (**A** *or* **B**), 158.92 (**A** *or* **B**), 152.48 – 150.20 (m, J_{C-}

$_F$ = 250.7 Hz, **A** + **B**), 149.05 (**A** *or* **B**), 149.00 (**A** *or* **B**), 147.53 (**A** *or* **B**), 147.46 (**A** *or* **B**), 141.61 (**A** *or* **B**), 141.59 (**A** *or* **B**), 138.86 (dt, *J* = 250.9, 15.0 Hz, **A** + **B**), 136.85 – 136.02 (m, **A** + **B**), 133.60 (**A** + **B**), 129.79 (**A** *or* **B**), 129.65 (**A** *or* **B**), 120.30 (**A** *or* **B**), 120.27 (**A** *or* **B**), 119.07 (**A** *or* **B**), 118.86 (**A** *or* **B**), 114.10 (**A** *or* **B**), 113.97 (**A** *or* **B**), 113.34 (**A** *or* **B**), 113.31 (**A** *or* **B**), 112.22 (ddd, *J* = 34.5, 16.3, 5.1 Hz), 111.85 (**A** *or* **B**), 111.83 (**A** *or* **B**), 111.46 (**A** *or* **B**), 111.44 (**A** *or* **B**), 76.52 (**A** *or* **B**), 76.21 (**A** *or* **B**), 67.10 (**A** *or* **B**), 67.09 (**A** *or* **B**), 65.95 (**A** *or* **B**), 65.89 (**A** *or* **B**), 57.84 (**A** *or* **B**), 57.77 (**A** *or* **B**), 56.07 (**A** *or* **B**), 56.06 (**A** *or* **B**), 55.99 (**A** *or* **B**), 55.93 (**A** *or* **B**), 54.28 (**A** *or* **B**), 54.25 (**A** *or* **B**), 52.47 (**A** *or* **B**), 52.37 (**A** *or* **B**), 49.56 (**A** *or* **B**), 49.52 (**A** *or* **B**), 43.77 (**A** *or* **B**), 43.59 (**A** *or* **B**), 38.15 (**A** *or* **B**), 37.92 (**A** *or* **B**), 31.43 (**A** *or* **B**), 31.29 (**A** *or* **B**), 28.31 (**A** *or* **B**), 28.15 (**A** *or* **B**), 26.81 (**A** *or* **B**), 26.66 (**A** *or* **B**), 25.55 (**A** *or* **B**), 25.29 (**A** *or* **B**), 21.05 (**A** *or* **B**), 21.04 (**A** *or* **B**), 12.37 (**A** *or* **B**), 12.34 (**A** *or* **B**). ^{19}F NMR (470 MHz, $CDCl_3$) δ -132.53 – -132.73 (m), -161.10 – -161.42 (m) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{39}H_{48}F_3N_2O_7^+$ 713.3408; Found 713.3405.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (S)-1-(((S)-2-(4- ethoxy-3,5-dimethoxyphenyl)butanoyl)oxy)piperidine-2-carboxylate (4)

The reaction was carried out as described for **1**, using **44** (167 mg, 0.635 mmol). Purification was performed by flash column chromatography (40% acetone in toluene + 1% Et_3N) yielding **4** as a colorless oil (99 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.33).Only major rotamer is reported here): δ 7.26-7.22 (m, 2H), 7.19 – 7.11 (m, 2H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.63 (m, 1H), 6.40 (s, 2H), 5.60 (dd, *J* = 8.2, 5.5 Hz, 1H), 5.46 (d, *J* = 5.1 Hz, 1H), 4.12 (s, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.65 (2xs, 6H), 3.79 – 3.72 (m, 5H), 3.67 (s, 6H), 3.57 (dd, *J* = 7.9, 6.3 Hz, 1H), 2.82 (dt, *J* = 13.3, 3.1 Hz, 2H), 2.65 – 2.38 (m, 8H), 2.30 (d, *J* = 13.8, 1H), 2.17 – 2,02 (m, 1H), 1.74 – 1.50 (m, 8 H), 1.41 (tt, *J* = 13.5, 4.1 Hz, 1H), 1.32 (t, *J* = 7.1, 3H), 0.9 (t, *J* = 7.3

Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.33). Only major rotamer is reported here): δ 172.77, 170.70, 153.50, 149.01, 147.57, 142.06, 141.57, 135.81, 135.24, 133.64, 129.69, 129.17, 129.17, 128.36, 125.43, 120.34, 114.01, 113.27, 111.87, 111.43, 105.17, 76.01, 68.90, 67.01, 65.90, 57.77, 56.80, 56.00, 54.19, 52.17, 50.95, 43.55, 38.36, 31.43, 28.54, 27.03, 25.51, 21.10, 15.71, 12.74 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{43}H_{59}N_2O_{10}^+$ 763.41553; Found 763.41553.

(R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (S)-1-(((S)-2-(3,5-dimethoxy-4-propoxyphenyl)butanuyl)oxy)piperidine-2-carboxylate (5)

The reaction was carried out as described for **1**, using **45** (75 mg, 0.266 mmol). Purification was performed by flash column chromatography (40% acetone in toluene + 1% Et_3N) yielding **5** as a colorless oil (82 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.25). Only major rotamer is reported here): *δ* 7.14 (dd, *J* = 9.0, 7.6 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 3H), 6.67 – 6.56 (m, 2H), 6.39 (s, 2H), 5.60 (dd, *J* = 8.2, 5.5 Hz, 1H), 5.47 – 5.42 (m, 1H), 4.17 – 4.06 (m, 2H), 3.9 (t, *J* = 6.9, 2H), 3.84 (d, *J* = 2.8, 2H), 3.84 (2xs, 6H), 3.73 (t, *J* = 4.7 Hz, 5H), 3.66 (s, 6H), 3.56 (dd, *J* = 7.8, 6.2 Hz, 1H), 2.80 (d, *J* = 5.3 Hz, 2H), 2.58 (s, 5H), 2.55 – 2.41 (m, 2H), 2.35 – 2.19 (m, 1H), 2.13 – 2.02 (m, 1H), 1.98 – 1.87 (m, 1H), 1.79 – 1.71 (m, 4H), 1.60 – 154 (m, 2H), 1.47 – 1.34 (m, 1H), 1.34 – 1.17 (m, 1H), 0.99 (td, *J* = 7.4, 2.0 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.32). Only major rotamer is reported here): *δ* 173.72, 176.65, 158.76, 153.50, 148.96, 147.42, 136.17, 135.83, 133.61, 129.63, 120.29, 118.66, 113.94, 112.78, 111.83, 111.39, 105.27, 75.96, 75.08, 66.98, 66.74, 57.77, 56.15, 56.03, 55.95, 54.19, 52.11, 50.89, 43.50, 38.29, 31.37, 28.48, 26.98, 25.46, 23.43, 21.06, 12.69, 10.43 ppm 172.75, 170.66, 158.77, 153.51, 148.96, 147.42, 142.00, 136.18, 135.07, 133.62, 129.64, 120.30, 118.67, 113.94, 112.78, 111.83, 111.40, 105.27, 75.96, 75.08, 66.97, 65.74, 57.77, 56.15,

56.03, 55.95, 54.19, 52.11, 50.89, 43.50, 38.28, 31.37, 28.48, 26.98, 25.46, 23.43, 21.05, 12.68, 10.43 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{61}N_2O_{10}^+$ 777.43207; Found 777.43153.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (S)-1-((S)-2-(3,5-dimethoxy-4-(octyloxy)phenyl)butanoyl)piperidine-2-carboxylate (6)

The reaction was carried out as described for **1**, using **46** (132 mg, 0.375 mmol). Purification was performed by flash column chromatography (40% EtOAc in toluene + 1% Et_3N) yielding **6** as a brown oil (103 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.43). Only major rotamer is reported here): δ 7.15 (m, 1H), 6.77 (m, 3H), 6.65 (m, 4H), 6.39 (s, 2H), 5.60 (dd, *J*=8.3, 5.4 Hz, 1H), 5.45 (d, *J*=5.4, 1H), 4.20 (br s, 4H), 3.94 (t, *J*=6.7 Hz, 2H), 3.86 (s, 3H), 3.85, (s, 3H), 3.81 (s, 3H), 3.66 (s, 6H), 3.57 (dd, *J*=7.9, 6.5 Hz, 1H), 2.94 (br s,2H), 2.81 (td, *J*=13.3, 3.0 Hz, 2H), 2.73 (br s,2H), 2.56 (ddd, *J*=14.7, 9.8, 5.7 Hz, 3H), 2.48 (m, 2H), 2.30 (d, *J*=13.4 Hz, 1H), 2.22 (m, 1H), 2.07 (m, 4H), 1.93 (m, 2H), 1.71 (m, 4H), 1.40 (m,2H), 1.28 (m,6H), 0.88 (m,6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): *δ* 172.84, 170.73, 153.58, 149.03, 147.49, 135.14, 134.84, 133.64, 129.75, 129.24, 124.49, 120.36, 114.26, 114.08, 113.30, 111.89, 111.45, 105.32, 75.97, 73.57, 57.52, 56.50, 56.20, 56.08, 56.01, 52.18, 50.95, 43.57, 38.37, 32.01, 31.45, 30.27, 29.56, 29.46, 29.45, 28.55, 27.02, 26.01, 22.50, 22.82, 21.09, 14.26, 12.73 ppm. (1 signal less due to overlapping $\underline{C}H_2$). HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{49}H_{71}N_2O_{10}^+$ 847.51032; Found 847.50834.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-(((*S*)-2-(3,5-dimethoxy-4-isobutoxyphenyl)butanuyl)oxy)piperidine-2-carboxylate (7)

The reaction was carried out as described for **1**, using **47** (167 mg, 0.630 mmol). Purification was performed by flash column chromatography (40% acetone in toluene + 1% Et_3N) yielding **7** as a colorless oil (55 mg, 47%). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.28). Only major rotamer is reported here): δ 7.18 – 7.12 (m, 1H), 6.81 – 6.74 (m, 2H), 6.66 – 6.61 (m 2H), 6.38 (s, 2H), 5.60 (dd, J = 8.1, 5.4 Hz, 1H), 5.45 (d, J = 4.1 Hz, 1H), 4.12 (s, 4H), 3.88 (d, J = 9.8 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 2H), 3.74 (m, 6H), 3.70 (dd, J = 6.7, 1.7 Hz, 1H), 3.65 (s, 6H) 3.65 (dd, J = 7.9, 6.4 Hz, 1H), 3.56 (dd, J = 7.9, 6.4 Hz, 1H), 2.82 (q, J = 4.1, 3.1 Hz, 2H), 2.60 (br s, 4 H), 2.55 – 2.40 (m, 2H), 2.32 – 2.26 (m, 1H), 2.14 – 1.98 (m, 5H), 1.74 – 1.64 (m, 4H), 1.57 (t, J = 12.5 Hz, 2H), 1.02 – 0.99 (m, 3H), 0.98 (dd, J = 6.7, 2.6 Hz, 6H), 0.89 (t, J = 7.3 Hz, 3H) ppm. ^{13}C-NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.33). Only major rotamer is reported here): δ 172.78, 170.67, 158.74, 153.49, 148.98, 147.44, 142.04, 136.63, 134.96, 133.63, 120.67, 120.23, 118.75, 113.89, 111.85, 111.41, 107.48, 105.49, 80.08, 75.97, 66.93, 61.25, 57.76, 56.22, 56.05, 55.97, 54.20, 52.13, 50.93, 46.72, 43.51, 38.31, 31.40, 29.14, 28.48, 27.00, 25.48, 21.07, 19.40, 12.69 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{45}H_{63}N_2O_{10}^+$ 791.44772; Found 791.44680.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (2*S*)-1-(3-methyl-2-(3,4,5-trimethoxyphenyl)but-3-enoyl)piperidine-2-carboxylate (8)

The reaction was carried out as described for **1**, using **48** (246 mg, 0.87 mmol) and **39** (150 mg, 0.204 mmol). Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **8** as a slightly yellow oil (140 mg, 90%). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.25) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 7.25 (t, J = 7.9 Hz, 1H, **A** *or* **B**), 7.20 (t, J = 7.9 Hz, 1H, **A** *or* **B**), 6.95 – 6.75 (m, 8H, **A** + **B**), 6.69 – 6.61 (m, 4H, **A** + **B**), 6.48 (s, 2H, **A** *or* **B**), 6.40 (s, 2H, **A** *or* **B**), 5.77 (dd, J

= 7.7, 5.9 Hz, 1H, **A** *or* **B**), 5.66 (dd, *J* = 7.9, 5.6 Hz, 1H, **A** *or* **B**), 5.53 – 5.47 (m, 2H, **A** + **B**), 5.03 (s, 1H, **A** *or* **B**), 5.00 (s, 1H, **A** *or* **B**), 4.87 (s, 1H, **A** *or* **B**), 4.73 (s, 1H, **A** *or* **B**), 4.41 (s, 1H, **A** *or* **B**), 4.36 (s, 1H, **A** *or* **B**), 4.12 – 4.07 (m, 4H, **A** + **B**), 3.85 (s, 3H, **A** *or* **B**), 3.845 (s, 3H, **A** *or* **B**), 3.841 (s, 3H, **A** *or* **B**), 3.837 (s, 3H, **A** *or* **B**), 3.83 (s, 9H, **A** + **B**), 3.80 (s, 3H, **A** *or* **B**), 3.74 – 3.71 (m, 8H, **A** + **B**), 3.71 (s, 6H, **A** *or* **B**), 3.68 – 3.62 (m, 2H, **A** + **B**), 3.17 (td, *J* = 13.2, 2.9 Hz, 1H, **A** *or* **B**), 3.08 (td, *J* = 13.1, 3.0 Hz, 1H, **A** *or* **B**), 2.79 (t, *J* = 5.8 Hz, 2H, **A** *or* **B**), 2.78 (t, *J* = 5.8 Hz, 2H, **A** *or* **B**), 2.63 – 2.46 (m, 12H, **A** + **B**), 2.33 (d, *J* = 13.1 Hz, 2H, **A** + **B**), 2.29 – 2.14 (m, 2H, **A** + **B**), 2.12 – 1.97 (m, 2H, **A** + **B**), 1.81 – 1.52 (m, 12H, **A** + **B**), 1.49 – 1.14 (m, 4H, **A** + **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.25) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 171.47 (**A** *or* **B**), 171.26 (**A** *or* **B**), 170.71 (**A** *or* **B**), 170.69 (**A** *or* **B**), 158.96 (**A** *or* **B**), 158.95 (**A** *or* **B**), 153.18 (**A** *or* **B**), 153.16 (**A** *or* **B**), 149.01 (**A** *or* **B**), 148.99 (**A** *or* **B**), 147.48 (**A** *or* **B**), 147.47 (**A** *or* **B**), 144.43 (**A** *or* **B**), 143.16 (**A** *or* **B**), 141.85 (**A** *or* **B**), 141.63 (**A** *or* **B**), 137.21 (**A** *or* **B**), 136.92 (**A** *or* **B**), 133.64 (**A** *or* **B**), 133.60 (**A** *or* **B**), 133.43 (**A** *or* **B**), 132.79 (**A** *or* **B**), 129.72 (**A** *or* **B**), 129.67 (**A** *or* **B**), 120.24 (**A** + **B)**, 119.14 (**A** *or* **B**), 118.80 (**A** *or* **B**), 114.72 (**A** *or* **B**), 114.30 (**A** *or* **B**), 114.04 (**A** *or* **B**), 113.90 (**A** *or* **B**), 113.33 (**A** *or* **B**), 112.90 (**A** *or* **B**), 111.85 (**A** *or* **B**), 111.80 (**A** *or* **B**), 111.42 (**A** + **B)**, 106.45 (**A** *or* **B**), 106.25 (**A** *or* **B**), 76.38 (**A** *or* **B**), 76.30 (**A** *or* **B**), 67.04 (**A** + **B)**, 65.91 (**A** *or* **B**), 65.83 (**A** *or* **B**), 60.94 (**A** *or* **B**), 60.87 (**A** *or* **B**), 57.80 (**A** + **B)**, 56.93 (**A** *or* **B**), 56.88 (**A** *or* **B**), 56.25 (**A** + **B**), 56.06 (**A** + **B**), 56.04 (**A** + **B**), 55.96 (**A** + **B**), 54.23 (**A** + **B**), 52.34 (**A** *or* **B**), 52.14 (**A** *or* **B**), 44.02 (**A** *or* **B**), 43.81 (**A** *or* **B**), 38.36 (**A** *or* **B**), 38.18 (**A** *or* **B**), 31.47 (**A** *or* **B**), 31.40 (**A** *or* **B**), 27.07 (**A** *or* **B**), 26.96 (**A** *or* **B**), 25.38 (**A** + **B**), 22.48 (**A** *or* **B**), 22.18 (**A** *or* **B**), 21.17 (**A** *or* **B**), 21.08 (**A** *or* **B**) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{43}H_{57}N_2O_{10}^+$ 761.4008; Found 761.4004.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-(2-(cyclohex-1-en-1-yl)-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (9)

The reaction was carried out as described for **1**, using **49** (136 mg, 0.419 mmol) and **39** (120 mg, 0.163 mmol). Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **9** as a slightly yellow oil (100 mg, 76%). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.20) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 7.26 – 7.24 (m, 1H, **A** *or* **B**), 7.19 – 7.15 (m, 1H, **A** *or* **B**), 6.94 – 6.90 (m, 1H, **A** *or* **B**), 6.88 – 6.81 (m, 5H, **A** + **B**), 6.78 (dd, J = 8.1, 3.4 Hz, 2H, **A** + **B**), 6.71 – 6.61 (m, 4H, **A** + **B**), 6.46 (s, 2H, **A** *or* **B**), 6.40 (s, 2H, **A** *or* **B**), 5.78 (dd, J = 7.9, 5.8 Hz, 1H, **A** *or* **B**), 5.67 (dd, J = 8.1, 5.5 Hz, 1H, **A** *or* **B**), 5.58 – 5.55 (m, 1H, **A** *or* **B**), 5.51 (br t, J = 6.5 Hz, 2H, **A** + **B**), 5.49 – 5.44 (m, 1H, **A** *or* **B**), 4.31 (s, 1H, **A** *or* **B**), 4.29 (s, 1H, **A** *or* **B**), 4.13 – 4.08 (m, 4H, **A** + **B**), 3.86 (s, 3H, **A** *or* **B**), 3.854 (s, 3H, **A** *or* **B**), 3.850 (s, 3H, **A** *or* **B**), 3.84 (s, 3H, **A** *or* **B**), 3.84 (s, 9H, **A** + **B**), 3.81 (s, 3H, **A** *or* **B**), 3.75 – 3.72 (m, 14H, **A** + **B**), 3.72 – 3.68 (m, 2H, **A** *or* **B**), 3.18 (td, J = 13.3, 2.9 Hz, 1H, **A** *or* **B**), 3.09 (td, J = 13.1, 3.0 Hz, 1H, **A** *or* **B**), 2.80 (q, J = 5.9 Hz, 4H, **A** + **B**), 2.64 – 2.47 (m, 12H, **A** + **B**), 2.35 – 2.30 (m, 2H, **A** + **B**), 2.28 – 2.16 (m, 2H, **A** + **B**), 2.14 – 2.01 (m, 6H, **A** + **B**), 1.98 – 1.82 (m, 4H, **A** + **B**), 1.77 – 1.52 (m, 15H, **A** + **B**), 1.46 – 1.28 (m, 3H, **A** + **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.20) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 171.95 (**A** *or* **B**), 171.71 (**A** *or* **B**), 170.80 (**A** *or* **B**), 170.73 (**A** *or* **B**), 158.97 (**A** + **B**), 153.12 (**A** *or* **B**), 153.10 (**A** *or* **B**), 149.04 (**A** *or* **B**), 149.03 (**A** *or* **B**), 147.51 (**A** *or* **B**), 147.50 (**A** *or* **B**), 141.87 (**A** *or* **B**), 141.81 (**A** *or* **B**), 137.06 (**A** *or* **B**), 136.88 (**A** *or* **B**), 136.81 (**A** *or* **B**), 135.76 (**A** *or* **B**), 134.09 (**A** *or* **B**), 133.71 (**A** *or* **B**), 133.65 (**A** *or* **B**), 133.40 (**A** *or* **B**), 129.74 (**A** *or* **B**), 129.71 (**A** *or* **B**), 125.47 (**A** *or* **B**), 125.36 (**A** *or* **B**), 120.29 (**A** *or* **B**), 120.27 (**A** *or* **B**), 119.11 (**A** *or* **B**), 118.92 (**A** *or* **B**), 113.98 (**A** *or* **B**), 113.91

(**A** *or* **B**), 113.39 (**A** *or* **B**), 113.06 (**A** *or* **B**), 111.89 (**A** *or* **B**), 111.84 (**A** *or* **B**), 111.45 (**A** + **B**), 106.55 (**A** *or* **B**), 106.40 (**A** *or* **B**), 76.30 (**A** *or* **B**), 76.27 (**A** *or* **B**), 67.07 (**A** + **B**), 65.93 (**A** *or* **B**), 65.85 (**A** *or* **B**), 60.97 (**A** *or* **B**), 60.90 (**A** *or* **B**), 57.82 (**A** + **B**), 57.12 (**A** *or* **B**), 57.07 (**A** *or* **B**), 56.27 (**A** + **B**), 56.12 (**A** + **B**), 56.07 (**A** + **B**), 55.99 (**A** + **B**), 54.26 (**A** *or* **B**), 54.25 (**A** *or* **B**), 52.33 (**A** *or* **B**), 52.11 (**A** *or* **B**), 43.97 (**A** *or* **B**), 43.80 (**A** *or* **B**), 38.38 (**A** *or* **B**), 38.32 (**A** *or* **B**), 31.52 (**A** *or* **B**), 31.40 (**A** *or* **B**), 28.40 (**A** *or* **B**), 28.30 (**A** *or* **B**), 27.15 (**A** *or* **B**), 27.05 (**A** *or* **B**), 25.52 (**A** + **B**), 25.48 (**A** *or* **B**), 25.46 (**A** *or* **B**), 23.15 (**A** *or* **B**), 23.14 (**A** *or* **B**), 22.43 (**A** *or* **B**), 22.39 (**A** *or* **B**), 21.23 (**A** *or* **B**), 21.21 (**A** *or* **B**) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{46}H_{61}N_2O_{10}^+$ 801.4321; Found 801.4324.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-(2-(cyclopent-1-en-1-yl)-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (10)

The reaction was carried out as described for **1**, using **50** (100 mg, 0.32 mmol). Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **10** as a slightly yellow oil (80 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.23) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 7.25 (t, J = 7.9 Hz, 1H, **A** *or* **B**), 7.19 (d, J = 7.9 Hz, 1H, **A** *or* **B**), 6.92 (d, J = 7.6 Hz, 1H, **A** *or* **B**), 6.87 – 6.76 (m, 7H, **A** + **B**), 6.70 – 6.61 (m, 4H, **A** + **B**), 6.47 (s, 2H, **A** *or* **B**), 6.40 (s, 2H, **A** *or* **B**), 5.78 (dd, J = 7.6, 5.9 Hz, 1H, **A** *or* **B**), 5.65 (dd, J = 7.9, 5.5 Hz, 1H, **A** *or* **B**), 5.56 – 5.54 (m, 1H, **A** *or* **B**), 5.49 (br t, J = 5.6 Hz, 2H, **A** + **B**), 5.42 – 5.40 (m, 1H, **A** *or* **B**), 4.54 (s, 1H, **A** *or* **B**), 4.49 (s, 1H, **A** *or* **B**), 4.16 – 4.05 (m, 4H, **A** + **B**), 3.86 (s, 3H, **A** *or* **B**), 3.85 (s, 3H, **A** *or* **B**), 3.846 (s, 3H, **A** *or* **B**), 3.842 (s, 3H, **A** *or* **B**), 3.83 (s, 9H, **A** + **B**), 3.81 (s, 3H, **A** *or* **B**), 3.77 – 3.70 (m, 16H, **A** + **B**), 3.17 (td, J = 13.3, 2.8 Hz, 1H, **A** *or* **B**), 3.06 (td, J = 12.9, 2.8 Hz, 1H, **A** *or* **B**), 2.85 – 2.76 (m, 4H, **A** + **B**), 2.64 – 2.47 (m, 12H, **A** + **B**), 2.38 – 2.29 (m, 6H, **A** + **B**), 2.28 – 2.16 (m, 6H, **A** + **B**), 2.10

– 1.97 (m, 2H, **A** + **B**), 1.93 – 1.84 (m, 4H, **A** + **B**), 1.76 – 1.59 (m, 5H, **A** + **B**), 1.57 – 1.50 (m, 1H, **A** *or* **B**), 1.47 – 1.27 (m, 3H, **A** + **B**), 1.23 – 1.10 (m, 1H, **A** *or* **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.23) and diastereoisomers (1:1, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 171.61 (**A** *or* **B**), 171.42 (**A** *or* **B**), 170.78 (**A** *or* **B**), 170.71 (**A** *or* **B**), 158.89 (**A** + **B**), 153.20 (**A** *or* **B**), 153.17 (**A** *or* **B**), 149.03 (**A** + **B**), 147.51 (**A** + **B**), 143.27 (**A** *or* **B**), 142.10 (**A** *or* **B**), 141.93 (**A** *or* **B**), 141.75 (**A** *or* **B**), 137.11 (**A** *or* **B**), 136.84 (**A** *or* **B**), 134.03 (**A** *or* **B**), 133.67 (**A** *or* **B**), 133.63 (**A** *or* **B**), 133.38 (**A** *or* **B**), 129.77 (**A** *or* **B**), 129.71 (**A** *or* **B**), 128.63 (**A** *or* **B**), 128.36 (**A** *or* **B**), 120.27 (**A** + **B**), 119.20 (**A** *or* **B**), 118.94 (**A** *or* **B**), 114.03 (**A** *or* **B**), 113.95 (**A** *or* **B**), 113.34 (**A** *or* **B**), 113.23 (**A** *or* **B**), 111.87 (**A** *or* **B**), 111.84 (**A** *or* **B**), 111.45 (**A** + **B**), 106.25 (**A** *or* **B**), 106.06 (**A** *or* **B**), 76.31 (**A** *or* **B**), 76.28 (**A** *or* **B**), 66.94 (**A** + **B**), 65.77 (**A** + **B**), 60.97 (**A** *or* **B**), 60.91 (**A** *or* **B**), 57.76 (**A** + **B**), 56.30 (**A** + **B**), 56.13 (**A** + **B**), 56.07 (**A** + **B**), 55.99 (**A** + **B**), 54.18 (**A** + **B**), 52.37 (**A** *or* **B**), 52.18 (**A** *or* **B**), 51.73 (**A** *or* **B**), 51.68 (**A** *or* **B**), 44.01 (**A** *or* **B**), 43.84 (**A** *or* **B**), 38.36 (**A** *or* **B**), 38.26 (**A** *or* **B**), 34.75 (**A** *or* **B**), 34.59 (**A** *or* **B**), 32.64 (**A** *or* **B**), 32.45 (**A** *or* **B**), 31.50 (**A** *or* **B**), 31.43 (**A** *or* **B**), 27.09 (**A** *or* **B**), 27.01 (**A** *or* **B**), 25.43 (**A** *or* **B**), 25.40 (**A** *or* **B**), 23.77 (**A** *or* **B**), 23.67 (**A** *or* **B**), 21.22 (**A** *or* **B**), 21.11 (**A** *or* **B**) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{45}H_{59}N_2O_{10}^+$ 787.4164; Found 787.4173.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-(2-(cyclobut-1-en-1-yl)-2-(3,4,5-trimethoxyphenyl)acetyl)piperidine-2-carboxylate (11)

The reaction was carried out as described for **1**, using **51** (80 mg, 0.27 mmol). Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **11** as a slightly yellow oil (50 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.24) and diastereoisomers (1:0.8, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 7.27 – 7.23 (m, 1H, **A**), 7.21 – 7.15 (m, 1H, **B**), 6.94 – 6.89 (m, 1H, **A**), 6.89 – 6.74 (m, 6H, **A** + **B**) 6.76

– 6.73 (m, 1H, **B**), 6.70 – 6.61 (m, 4H, **A** + **B**), 6.50 (s, 2H, **A**), 6.43 (s, 2H, **B**), 5.86 – 5.82 (m, 1H, **A**), 5.78 – 5.74 (m, 2H, **A** + **B**), 5.64 (dd, *J* = 8.1, 5.6 Hz, 1H, **B**), 5.50 (br d, *J* = 5.2 Hz, 1H, **A**), 5.47 (br d, *J* = 5.7 Hz, 1H, **B**), 4.50 (s, 2H, **A** + **B**), 4.16 – 4.09 (m, 4H, **A** + **B**), 3.86 (s, 3H, **A** *or* **B**), 3.85 (s, 3H, **A** *or* **B**), 3.848 (s, 3H, **A** *or* **B**), 3.846 (s, 3H, **A** *or* **B**), 3.84 – 3.83 (m, 9H, **A** + **B**), 3.84 – 3.80 (m, 2H, **A** + **B**), 3.81 (s, 3H, **B**), 3.77 – 3.73 (m, 8H, **A** + **B**), 3.72 (s, 6H, **B**), 3.21 (td, *J* = 13.3, 2.9 Hz, 1H, **A**), 3.02 (td, *J* = 13.1, 3.0 Hz, 1H, **B**), 2.86 – 2.78 (m, 4H, **A** + **B**), 2.66 – 2.48 (m, 16H, **A** + **B**), 2.42 – 2.29 (m, 8H, **A** + **B**), 2.28 – 1.96 (m, 4H, **A** + **B**), 1.78 – 1.50 (m, 6H, **A** + **B**), 1.38 – 1.27 (m, 2H, **A** + **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.24) and diastereoisomers (1:0.8, **A**:**B**). Only major rotamer for both diastereomers are reported here): δ 170.83 (**B**), 170.71 (**A**), 170.64 (**B**), 170.61 (**A**), 158.93 (**A** + **B**), 153.35 (**A**), 153.29 (**B**), 149.04 (**A** + **B**), 147.52 (**A** + **B**), 147.01 (**B**), 146.14 (**A**), 141.91 (**B**), 141.73(**A**), 137.16 (**A**), 136.93 (**B**), 133.66 (**A**), 133.62 (**B**), 132.92 (**A**), 132.22 (**B**), 131.77 (**A**), 131.33 (**B**), 129.79 (**A**), 129.72 (**B**), 120.29 (**A** + **B**), 119.20 (**A**), 118.92 (**B**), 114.06 (**A**), 113.98 (**B**), 113.28 (**A**), 112.96 (**B**), 111.88 (**A**), 111.86 (**B**), 111.46 (**A**), 111.45 (**B**), 105.88 (**A**), 105.80 (**B**), 76.38 (**A**), 76.30 (**B**), 67.01 (**A** + **B**), 65.84 (**A** + **B**), 61.00 (**A**), 60.92 (**B**), 57.79 (**A** + **B**), 56.35 (**A** + **B**), 56.16 (**A** + **B**), 56.08 (**A** + **B**), 56.01 (**A** + **B**), 54.20 (**A** + **B**), 52.40 (**A**), 52.21 (**B**), 51.88 (**A**), 51.64 (**B**), 44.05 (**A**), 43.91 (**B**), 38.34 (**B**), 38.26 (**A**), 31.50 (**B**), 31.45 (**A**), 31.17 (**A** + **B**), 27.06 (**B**), 27.01 (**A**), 26.92 (**A** + **B**), 25.42 (**B**), 25.31 (**A**), 21.21 (**A**), 21.09 (**B**) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{57}N_2O_{10}^+$ 773.40077; Found 773.39995.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl (*S*)-1-((*E*)-4-methyl-2-(3,4,5-trimethoxyphenyl)pent-2-enoyl)piperidine-2-carboxylate (12)

The reaction was carried out as described for **1**, using **54** (115 mg, 0.41 mmol). Purification was performed by flash column chromatography (30% acetone in toluene + 1% Et_3N) yielding **12** as a

slightly yellow oil (76 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers (1:0.17). Only major rotamere is reported here): δ 7.21 (t, J = 7.8 Hz, 1H), 6.85 – 6.76 (m, 4H), 6.69 – 6.62 (m, 2H), 6.55 (s, 2H), 5.73 – 5.66 (m, 1H), 5.59 (d, J = 10.3 Hz, 1H), 5.47 (d, J = 5.5 Hz, 1H), 4.11 (t, J = 5.9 Hz, 2H), 3.90 – 3.87 (m, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 3.83 (s, 3H), 3.79 (s, 6H), 3.74 (t, J = 4.7 Hz, 4H), 3.11 (td, J = 13.2, 3.1 Hz, 1H), 2.84 – 2.73 (m, 3H), 2.66 – 2.47 (m, 6H), 2.36 – 2.30 (m, 1H), 2.25 – 2.13 (m, 1H), 2.07 – 1.97 (m, 1H), 1.75 – 1.59 (m, 2H), 1.56 (d, J = 12.4 Hz, 1H), 1.40 – 1.22 (m, 2H), 1.07 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers (1:0.17). Only major rotamer is reported here): δ 171.47, 170.53, 158.84, 153.16, 149.01, 147.48, 141.73, 139.38, 137.68, 134.20, 133.60, 131.11, 129.76, 120.27, 118.99, 114.00, 113.18, 111.87, 111.43, 105.93, 76.37, 66.84, 65.66, 60.96, 57.71, 56.23, 56.05, 55.97, 54.13, 52.00, 45.21, 38.22, 31.39, 27.77, 26.84, 25.37, 22.91, 22.88, 21.33. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{59}N_2O_{10}^+$ 775.4164; Found 775.4157.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-(piperidin-1-yl)ethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (13)

To a solution of **63** (50.0 mg, 125 μmol), **56** (64 mg, 0.18 mmol) and 4-(dimethylamino) pyridine (41 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (42 mg, 0.20 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (30% acetone in toluene + 1% Et_3N) to yield **13** as a colorless oil (65 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.17 – 7.11 (m, 1H), 6.93 – 6.84 (m, 1H), 6.78 – 6.74 (m, 2H), 6.65 – 6.62 (m, 2H), 6.57 (br d, J = 7.7 Hz, 1H), 6.41 (s, 2H), 5.60 (dd, J = 8.0, 5.8 Hz, 1H), 5.46 (br d, J = 5.0 Hz, 1H), 4.07 (t, J = 6.2 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 – 3.79 (m,

1H), 3.78 (s, 3H), 3.69 (s, 6H), 3.59 – 3.55 (m, 1H), 2.81 (td, *J* = 13.4, 2.9 Hz, 1H), 2.74 (t, *J* = 6.2 Hz, 2H), 2.63 – 2.39 (m, 6H), 2.30 (br d, *J* = 13.6 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.97 – 1.86 (m, 1H), 1.73 – 1.63 (m, 3H), 1.61 – 1.56 (m, 5H), 1.47 – 1.39 (m, 3H), 1.30 – 1.20 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.63, 170.63, 158.91, 153.28, 148.95, 147.40, 141.83, 136.74, 135.44, 133.63, 129.60, 120.28, 118.45, 113.84, 113.03, 111.82, 111.38, 105.08, 76.04, 66.00, 60.85, 58.07, 56.09, 56.01, 55.92, 55.18, 52.11, 50.87, 43.50, 38.26, 31.34, 28.47, 26.97, 26.05, 25.47, 24.30, 21.07, 12.67. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{43}H_{59}N_2O_9^+$ 747.4215; Found 747.4211.

(*R*)-1-(3-(2-aminoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (14)

To a solution of **27** (9.4 mg, 12 μmol) in anhydrous CH_2Cl_2 (0.5 mL) was added trifluoroacetic acid (50 μL, 0.66 mmol) and the reaction mixture was left stirring for 3 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue subjected to flash column chromatography (10% MeOH in CH_2Cl_2 + 1% Et_3N) to afford **14** as a colorless oil (6.5 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 7.15 (t, *J* = 7.9 Hz, 1H), 6.79 – 6.75 (m, 2H), 6.71 – 6.70 (m, 1H), 6.67 – 6.63 (m, 2H), 6.62 (dt, *J* = 7.9, 1.3 Hz, 1H), 6.41 (s, 2H), 5.62 (dd, *J* = 8.0, 5.6 Hz, 1H), 5.49 – 5.45 (m, 1H), 4.02 – 3.98 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 – 3.80 (m, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.57 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.11 (dd, *J* = 5.9, 4.4 Hz, 2H), 2.78 (td, *J* = 13.3, 3.0 Hz, 1H), 2.55 (ddd, *J* = 14.7, 10.1, 5.5 Hz, 1H), 2.46 (ddd, *J* = 13.9, 9.4, 6.7 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.13 – 2.03 (m, 2H), 1.97 – 1.89 (m, 1H), 1.75 – 1.63 (m, 3H), 1.59 (br d, *J* = 13.6 Hz, 1H), 1.47 – 1.38 (m, 1H), 1.32 – 1.26 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 172.69, 170.76, 158.96, 153.32, 149.01, 147.47, 141.99, 136.79, 135.53, 133.64, 129.67, 120.35, 118.98, 113.81, 112.89, 111.89, 111.43, 105.19, 76.05,

69.56, 60.93, 56.17, 56.07, 55.98, 52.18, 50.94, 43.58, 41.45, 38.23, 31.43, 28.51, 26.96, 25.49, 21.06, 12.69. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{38}H_{51}N_2O_9^+$ 679.3589; Found 679.3575.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(pyridin-4-ylmethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (15)

To a solution of **66** (27 mg, 71 μmol), **56** (33 mg, 90 μmol) and 4-(dimethylamino) pyridine (75 mg, 0.61 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (19 mg, 92 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (EtOAc + 1% Et_3N) to yield **15** as a colorless oil (35 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 8.57 – 8.51 (m, 2H), 7.32 – 7.28 (m, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.81 – 6.80 (m, 1H), 6.75 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.61 – 6.56 (m, 3H), 6.31 (s, 2H), 5.55 (dd, *J* = 8.3, 5.3 Hz, 1H), 5.41 – 5.37 (m, 1H), 5.06 (d (*AB system*), *J* = 13.4 Hz, 1H), 5.03 (d (*AB system*), *J* = 13.4 Hz, 1H), 3.780 (s, 3H), 3.777 (s, 3H), 3.75 – 3.72 (m, 1H), 3.71 (s, 3H), 3.58 (s, 6H), 3.51 (dd, *J* = 7.9, 6.2 Hz, 1H), 2.76 (td, *J* = 13.3, 3.0 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.45 – 2.37 (m, 1H), 2.25 – 2.19 (m, 1H), 2.08 – 1.96 (m, 2H), 1.88 (dddd, *J* = 13.9, 9.6, 6.7, 5.4 Hz, 1H), 1.67 – 1.60 (m, 3H), 1.53 (br d, *J* = 14.1 Hz, 1H), 1.36 (qt, *J* = 12.9, 3.8 Hz, 1H), 1.26 – 1.17 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 172.74, 170.74, 158.29, 153.21, 150.00, 148.91, 147.38, 146.21, 142.23, 136.65, 135.32, 133.44, 129.67, 121.55, 120.21, 119.08, 114.11, 112.65, 111.74, 111.32, 104.94, 75.75, 68.14, 60.77, 55.94, 55.87, 52.07, 50.86, 43.43, 38.22, 31.28, 28.44,

26.85, 25.32, 20.86, 12.61 ppm (1 Signal missing from OMe, Overlaying with similar OMe signal). HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{42}H_{51}N_2O_9^+$ 727.3589; Found 727.3584.

(*R*)-1-(3-(4-aminophenethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (16)

To a solution of **26** (19.5 mg, 22.8 μmol) in anhydrous CH_2Cl_2 (1 mL) was added trifluoroacetic acid (80 μL, 1.1 mmol) and the reaction mixture was left stirring for 3 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue subjected to flash column chromatography (70% EtOAc in toluene + 1% Et_3N) to afford **16** as a colorless oil (16 mg, 93%). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 7.13 (t, *J* = 7.9 Hz, 1H), 7.07 (d (*AX system*), *J* = 8.2 Hz, 2H), 6.80 – 6.73 (m, 3H), 6.67 – 6.61 (m, 4H), 6.57 (d, *J* = 7.5 Hz, 1H), 6.42 (s, 2H), 5.60 (dd, *J* = 7.8, 5.9 Hz, 1H), 5.47 (br d, *J* = 4.7 Hz, 1H), 4.08 (t, *J* = 7.2 Hz, 2H), 3.843 (s, 3H), 3.841 (s, 3H), 3.82 – 3.80 (m, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.63 – 3.55 (m, 3H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.81 (td, *J* = 13.4, 2.8 Hz, 1H), 2.58 – 2.49 (m, 1H), 2.47 – 2.40 (m, 1H), 2.30 (br d, *J* = 12.1 Hz, 1H), 2.14 – 2.03 (m, 2H), 1.98 – 1.86 (m, 1H), 1.75 – 1.64 (m, 3H), 1.61 – 1.55 (m, 1H), 1.42 (qt, *J* = 12.8, 3.8 Hz, 1H), 1.34 – 1.22 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 172.65, 170.67, 158.98, 153.33, 148.99, 147.44, 145.04, 141.85, 136.79, 135.49, 133.67, 129.96, 129.65, 128.36, 120.33, 118.44, 115.42, 113.90, 113.01, 111.86, 111.42, 105.14, 76.12, 69.19, 60.90, 56.13, 56.06, 55.96, 52.15, 50.91, 43.55, 38.27, 35.09, 31.38, 28.51, 27.01, 25.52, 21.11, 12.72. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{44}H_{54}N_2O_9^{\bullet+}$ 754.3824; Found 754.3801.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(phosphonooxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (17)

To a solution of **25** (62 mg, 80 μmol) in anhydrous CH_2Cl_2 (5 mL) at -40 ºC was added trimethylsilyl iodide (23 μL, 0.16 mmol) and the reaction mixture was kept at this temperature for 1 hour and then allowed to heat to ambient temperature over the next 3 hours. The contents of the reaction vessel were concentrated *in vacuo* and the residue redissolved in THF (4 mL) and added water (1 mL). The resulting solution was left stirring for 1.5 hours before it was concentrated *in vacuo* and dried on high vacuum for several days to afford **17** as a dark yellow solid (61 mg, quantitative yield). ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 7.25 – 7.21 (m, 1H), 7.15 – 7.02 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.77 – 6.73 (m, 2H), 6.64 (dd, J = 8.2, 1.7 Hz, 1H), 6.55 (s, 2H), 5.56 – 5.49 (m, 1H), 5.28 (br d, J = 4.8 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.90 – 3.85 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.61 (s, 6H), 3.57 (s, 3H), 2.70 – 2.61 (m, 1H), 2.48 – 2.41 (m, 1H), 2.41 – 2.31 (m, 1H), 2.21 – 2.13 (m, 1H), 1.97 – 1.84 (m, 3H), 1.68 – 1.49 (m, 4H), 1.43 – 1.35 (m, 1H), 1.19 – 1.10 (m, 1H), 0.81 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 172.16, 170.27, 152.65, 151.36 (d, J = 6.2 Hz), 148.66, 147.07, 141.96, 136.24, 135.53, 133.05, 129.50, 121.19, 120.00, 119.38 (d, J = 4.3 Hz), 117.97 (d, J = 5.0 Hz), 112.17, 111.90, 105.11, 74.71, 59.82, 55.56, 55.48, 55.34, 51.53, 48.72, 42.88, 37.64, 30.48, 27.98, 26.36, 24.87, 20.55, 12.29 ppm. ^{31}P NMR (202 MHz, DMSO-d_6, mixture of rotamers 1:0.3, **A**:**B**) δ -5.08 (**B**), -5.15 (**A**). HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{36}H_{46}NO_{12}PNa^+$ 738.2650; Found 738.2638.

2-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl) piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid (18)

To a solution of **22** (113 mg, 151 μmol) in anhydrous CH_2Cl_2 (7 mL) was added trifluoroacetic acid (0.4 mL, 5.2 mmol) and the solution was left stirring at ambient temperature for 2.5 hours. The contents of the reaction vessel were concentrated *in vacuo*, followed by addition of toluene (7 mL). The resulting solution was concentrated *in vacuo* and the crude residue was purified by flash

column chromatography (40% EtOAc in toluene + 1% formic acid) to yield **18** as a colorless oil (85 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.05. Only major rotamer is reported here) δ 8.58 (br s, 1H), 7.19 – 7.16 (m, 1H), 6.85 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.76 – 6.73 (m, 1H), 6.72 (dd, J = 2.5, 1.5 Hz, 1H), 6.69 – 6.66 (m, 2H), 6.25 (s, 2H), 5.52 – 5.47 (m, 2H), 4.70 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.76 – 3.71 (m, 1H), 3.58 – 3.56 (m, 1H), 3.55 (s, 6H), 2.88 (td, J = 13.4, 3.1 Hz, 1H), 2.67 (ddd, J = 14.2, 9.7, 5.2 Hz, 1H), 2.55 (ddd, J = 14.2, 9.2, 6.7 Hz, 1H), 2.34 – 2.31 (m, 1H), 2.22 – 2.11 (m, 1H), 2.09 – 1.95 (m, 2H), 1.82 – 1.60 (m, 4H), 1.49 – 1.38 (m, 1H), 1.33 – 1.22 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.05. Only major rotamer is reported here) δ 173.77, 171.25, 170.17, 158.21, 153.28, 149.09, 147.56, 142.74, 136.65, 134.67, 133.44, 129.62, 120.34, 119.57, 115.82, 111.78, 111.47, 109.04, 104.95, 76.78, 65.67, 60.89, 56.06, 56.01, 56.00, 52.45, 51.22, 43.57, 38.51, 31.68, 28.30, 27.33, 25.30, 20.93, 12.61. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{38}H_{48}NO_{11}^+$ 694.3222; Found 694.3216.

4-(3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl) piperidine-2-carbonyl)oxy)phenoxy)butanoic acid (19)

62 (0.134 g, 0.172 mmol) were dissolved in 4 mL DCM and trifluoroacetic acid (0.15 mL, 1.8 mmol) were added and the solution was stirred for 6 hours before 1 drop of water was added because TLC analysis showed that not all starting material was consumed. The reaction mixture was then stirred overnight and additionally trifluoroacetic acid was added (0.2 mL, 2.4 mmol) and the reaction was stirred for another 24 hours before it was concentrated *in vacuo* and purified by flash column chromatography (70:30:1 of toluene, EtOAc and formic acid) to yield **19** (66 mg, 53 %). ^{1}H-NMR (500 MHz, $CDCl_3$, mixture of rotamers, major rotamer reported, rotamer ratio 1.0:0.17): δ 7.16 (s, 1H), 6.94 (d, J=9.0 Hz, 1H), 6.86 (t, J=2.1 Hz, 2H), 6.77 (d, J=8.0 Hz, 1H), 6.65 (q, J=2.0 Hz, 2H), 6.30 (s, 2H), 5.57 (dd, J=8.7, 4.6 Hz, 1H), 5.52 (d, J=6.2 Hz, 1H), 4.12 (m,

1H), 4.03 (m, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.91 (td, *J*=13.3, 3.2 Hz, 2H), 2.60 (m, 3H), 2.53 (m, 3H), 2.48 (m, 2H), 2.13 (m, 4H), 1.72 (m, 4H), 0.90 (m, 3H) ppm (Acid H not seen). ^{13}C-NMR (126 MHz, $CDCl_3$, mixture of rotamers, major rotamer reported): δ 173.93, 170.62, 159.19, 153.27, 149.08, 147.53, 142.50, 134.74, 133.70, 129.39, 120.33, 118.49, 113.92, 112.62, 111.82, 111.47, 105.08, 89.91, 76.08, 67.02, 60.91, 56.09, 56.02, 55.99, 52.38, 51.29, 38.49, 31.57, 31.37, 29.85, 28.36, 27.13, 25.28, 25.00, 24.81, 20.85, 12.53 ppm. HR-MS (MALDI, FT-ICR, dithranol): *m/z* 722.35204 [M+H$^+$], calculated mass for ($C_{40}H_{52}NO_{11}^+$) 722.35349.

(*R*)-1-(3-((1H-tetrazol-5-yl)methoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (20)

To a suspension of **23** (13 mg, 19 μmol) and $ZnCl_2$ (2.7 mg, 20 μmol) in *i*-PrOH (1.5 mL) was added sodium azide (1.5 mg, 23 μmol) and the reaction mixture was heated to 80 ºC for 3 hours. TLC analysis indicated complete conversion of **23** and the contents of the reaction vessel were partitioned between 1M HCl (10 mL) and EtOAc (10 mL) and the phases were separated. The aquous phase was extracted once more with EtOAc (10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **20** as a colorless oil (12.4 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.04. Only major rotamer is reported here) δ 7.19 (t, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.70 – 6.66 (m, 2H), 6.50 – 6.46 (m, 1H), 6.44 (s, 2H), 5.79 (d (*AB system*), *J* = 15.1 Hz, 1H), 5.68 (dd, *J* = 8.1, 5.6 Hz, 1H), 5.64 (d (*AB system*), *J* = 15.1 Hz, 1H), 5.57 (d, *J* = 4.7 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.68 (t, *J* = 7.3 Hz, 1H), 3.59 (s, 6H), 2.78 – 2.71 (m, 1H), 2.59 (ddd, *J* = 14.5, 9.4, 5.5 Hz, 1H), 2.50 (ddd, *J* = 14.3, 9.2, 6.7 Hz, 1H), 2.34 (br d, *J* = 13.5 Hz, 1H), 2.18 – 2.06 (m, 2H), 1.98 – 1.89 (m, 1H), 1.88 – 1.81 (m, 1H), 1.79 – 1.68 (m, 2H), 1.65 (br d, *J* = 13.5 Hz, 1H), 1.52 – 1.41 (m, 1H), 1.24 –

1.19 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.04. Only major rotamer is reported here) δ 174.31, 170.48, 157.37, 154.76, 153.17, 149.00, 147.47, 142.25, 136.08, 135.35, 133.44, 129.93, 121.71, 120.48, 113.44, 113.13, 111.98, 111.45, 105.30, 75.96, 61.26, 60.42, 56.24, 56.09, 56.03, 53.12, 50.86, 44.33, 37.69, 31.52, 27.61, 26.61, 25.18, 20.63, 12.41. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{38}H_{47}N_5O_9Na^+$ 740.3266; Found 740.3256.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-hydroxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (21)

To a solution of **24** (20 mg, 27 μmol) and acetic acid (4 μL, 70 μmol) in anhydrous THF (0.5 mL) at 0 ºC was added tributylammonium fluoride (on silica gel, 1.5 mmol fluoride/g resin, 42 mg, 64 μmol) and the reaction mixture was left stirring for 1.5 hour. The contents of the reaction vessel were concentrated *in vacuo* and crude residue purified by flash column chromatography (40% EtOAc in toluene) to yield **21** as a colorless oil (11 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 7.09 (t, J = 7.9 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.74 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 6.70 – 6.68 (m, 1H), 6.67 – 6.63 (m, 2H), 6.60 (br d, J = 7.5 Hz, 1H), 6.46 – 6.42 (m, 3H), 5.62 (dd, J = 7.8, 5.9 Hz, 1H), 5.47 (br d, J = 4.7 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 – 3.81 (m, 1H), 3.80 (s, 3H), 3.66 (s, 6H), 3.59 (t, J = 7.2 Hz, 1H), 2.71 (td, J = 13.3, 3.0 Hz, 1H), 2.52 (ddd, J = 14.8, 9.8, 5.5 Hz, 1H), 2.43 (ddd, J = 14.0, 9.4, 6.7 Hz, 1H), 2.28 (br d, J = 12.8 Hz, 1H), 2.13 – 2.06 (m, 1H), 2.04 – 2.00 (m, 1H), 1.92 – 1.84 (m, 1H), 1.79 – 1.73 (m, 1H), 1.71 – 1.63 (m, 2H), 1.61 – 1.55 (m, 1H), 1.42 (qt, J = 13.0, 3.6 Hz, 1H), 1.31 – 1.20 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 172.89, 170.89, 156.62, 153.31, 148.99, 147.44, 141.57, 136.91, 135.43, 133.66, 129.71, 120.35, 118.89, 115.44, 112.54, 111.90, 111.41, 105.69,

75.98, 60.97, 56.36, 56.07, 55.96, 52.26, 50.81, 43.73, 37.76, 31.41, 28.17, 26.85, 25.42, 20.79, 12.60. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{36}H_{46}NO_9^+$ 636.3167; Found 636.3154.

(*R*)-1-(3-(2-(tert-butoxy)-2-oxoethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (22)

To a solution of **57** (154 mg, 383 μmol), **56** (140 mg, 383 μmol) and 4-(dimethylamino) pyridine (111 mg, 909 μmol) in CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexyl carbodiimide (89 mg, 431 μmol). The resulting solution was allowed to heat to ambient temperature and left stirring overnight, before it was filtered and the filtrate concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the crude filtrate was purified by flash column chromatography (30% EtOAc in toluene) to afford **22** (230 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.15 (t, J = 7.9 Hz, 1H), 6.79 – 6.73 (m, 3H), 6.66 – 6.60 (m, 3H), 6.41 (s, 2H), 5.61 (dd, J = 7.9, 5.7 Hz, 1H), 5.45 (br d, J = 4.6 Hz, 1H), 4.51 (s, 2H), 3.844 (s, 3H), 3.838 (s, 3H), 3.81 – 3.79 (m, 1H), 3.78 (s, 3H), 3.69 (s, 6H), 3.59 – 3.56 (m, 1H), 2.80 (td, J = 13.4, 3.0 Hz, 1H), 2.59 – 2.48 (m, 1H), 2.47 – 2.39 (m, 1H), 2.32 – 2.26 (m, 1H), 2.12 – 2.02 (m, 2H), 1.95 – 1.87 (m, 1H), 1.75 – 1.65 (m, 3H), 1.62 – 1.56 (m, 2H), 1.47 (s, 9H), 1.31 – 1.23 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.69, 170.69, 168.07, 158.03, 153.32, 148.98, 147.43, 142.00, 136.77, 135.44, 133.59, 129.69, 120.29, 119.35, 113.96, 113.14, 111.82, 111.40, 105.08, 82.38, 75.86, 65.86, 60.87, 56.09, 56.03, 55.94, 52.16, 50.90, 43.56, 38.28, 31.30, 28.49, 28.15, 26.93, 25.47, 21.03, 12.69. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{42}H_{55}NO_{11}Na^+$ 772.3667; Found 772.3652.

(*R*)-1-(3-(cyanomethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (23)

To a solution of **58** (23 mg, 70 μmol), **56**(28 mg, 77 μmol) and 4-(dimethylamino) pyridine (29 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (16 mg, 78 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (40% EtOAc in toluene) to yield **23** as a colorless oil (33 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 7.22 – 7.18 (m, 1H), 6.87 – 6.84 (m, 1H), 6.84 – 6.80 (m, 1H), 6.79 – 6.74 (m, 2H), 6.69 – 6.64 (m, 2H), 6.37 (s, 2H), 5.63 (dd, *J* = 8.3, 5.3 Hz, 1H), 5.43 (br d, *J* = 4.4 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 – 3.79 (m, 1H), 3.78 (s, 3H), 3.64 (s, 6H), 3.61 – 3.54 (m, 1H), 2.80 (td, *J* = 13.3, 3.0 Hz, 1H), 2.62 – 2.45 (m, 2H), 2.30 – 2.24 (m, 1H), 2.15 – 2.01 (m, 2H), 1.99 – 1.90 (m, 1H), 1.79 – 1.66 (m, 3H), 1.65 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.32 – 1.22 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.99, 171.04, 156.89, 153.35, 149.06, 147.52, 142.78, 136.81, 135.41, 133.46, 129.98, 120.88, 120.37, 115.46, 114.82, 112.20, 111.85, 111.45, 105.09, 75.56, 60.91, 56.08, 56.07, 56.00, 53.69, 52.29, 51.01, 43.66, 38.36, 31.37, 28.58, 26.84, 25.33, 20.82, 12.69. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{38}H_{47}N_2O_9^+$ 675.3276; Found 675.3270.

(*R*)-1-(3-((tert-butyldimethylsilyl)oxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (24)

To a solution of **59** (39 mg, 97 μmol), **56** (38 mg, 0.10 mmol) and 4-(dimethylamino) pyridine (32 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (25 mg, 0.12 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring for 1.5 hours. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was

performed and the filtrate subjected to flash column chromatography (5% EtOAc in CH_2Cl_2) to yield **24** as a colorless oil (45 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 7.09 (t, J = 7.9 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.71 (ddd, J = 8.0, 2.4, 1.0 Hz, 1H), 6.70 – 6.68 (m, 1H), 6.66 – 6.62 (m, 2H), 6.57 (dt, J = 7.6, 1.2 Hz, 1H), 6.45 (s, 2H), 5.61 (dd, J = 7.5, 6.1 Hz, 1H), 5.49 – 5.46 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 – 3.80 (m, 1H), 3.80 (s, 3H), 3.73 (s, 6H), 3.58 (br t, J = 7.2 Hz, 1H), 2.80 (td, J = 13.4, 2.9 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.41 (ddd, J = 13.9, 9.5, 6.4 Hz, 1H), 2.34 – 2.29 (m, 1H), 2.13 – 2.02 (m, 2H), 1.91 (ddt, J = 12.6, 9.9, 6.3 Hz, 1H), 1.76 – 1.63 (m, 3H), 1.61 – 1.54 (m, 1H), 1.42 (qt, J = 13.0, 3.8 Hz, 1H), 1.32 – 1.20 (m, 1H), 0.97 (s, 9H), 0.90 (t, J = 7.3 Hz, 3H), 0.18 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.57, 170.57, 155.66, 153.34, 149.00, 147.44, 141.70, 136.82, 135.55, 133.70, 129.64, 120.32, 119.58, 119.20, 118.63, 111.84, 111.41, 105.18, 75.98, 60.91, 56.18, 56.06, 55.96, 52.17, 50.88, 43.58, 38.22, 31.32, 28.48, 27.02, 25.81, 25.57, 21.18, 18.32, 12.69, -4.26. ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{42}H_{60}NO_9Si^+$ 750.4032; Found 750.4021.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-((methylthio)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (25)

To a solution of **60** (211 mg, 0.50 mmol), **56** (191 mg, 0.52 mmol) and 4-(dimethylamino) pyridine (150 mg, 1.23 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 ºC was added N,N′-dicyclohexyl-carbodiimide (121 mg, 0.59 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (70% EtOAc in toluene) to yield **25** as a slightly yellow oil (224 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.21 (t, J = 7.9 Hz, 1H), 7.13 (ddt, J = 8.2, 2.3, 1.1 Hz, 1H), 7.07 – 7.05 (m, 1H), 6.80 – 6.78 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.67 – 6.61 (m,

2H), 6.44 (s, 2H), 5.64 (dd, *J* = 8.0, 5.6 Hz, 1H), 5.49 – 5.44 (m, 1H), 4.24 – 4.16 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 – 3.80 (m, 1H), 3.79 (s, 3H), 3.72 (s, 6H), 3.59 (dd, *J* = 7.5, 6.8 Hz, 1H), 2.79 (td, *J* = 13.4, 3.0 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.43 (ddd, *J* = 14.0, 9.4, 6.6 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.13 – 2.01 (m, 2H), 1.91 (dddd, *J* = 13.8, 9.7, 6.6, 5.6 Hz, 1H), 1.77 – 1.64 (m, 3H), 1.62 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.36 – 1.31 (m, 6H), 1.29 – 1.23 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.67, 170.58, 153.35, 150.80 (d, *J* = 6.7 Hz), 149.03, 147.50, 142.35, 136.82, 135.51, 133.44, 130.01, 122.75, 120.33, 119.47 (d, *J* = 4.4 Hz), 118.39 (d, *J* = 5.5 Hz), 111.84, 111.44, 105.15, 75.49, 64.77 (d, *J* = 5.6 Hz), 60.90, 56.15, 56.06, 55.98, 52.16, 50.85, 43.62, 38.25, 31.29, 28.48, 26.96, 25.51, 21.14, 16.23 (d, *J* = 6.6 Hz), 12.68. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{55}NO_{12}P^+$ 772.3456; Found 772.3446.

(*R*)-1-(3-(4-((tert-butoxycarbonyl)amino)phenethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (26)

To a solution of **64** (50 mg, 99 μmol), **56** (47 mg, 0.13 mmol) and 4-(dimethylamino) pyridine (36 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (33 mg, 0.16 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (20% EtOAc in toluene) to yield **26** as a colorless oil (66 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.32 – 7.27 (m, 2H), 7.21 – 7.17 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.72 (m, 3H), 6.66 – 6.61 (m, 2H), 6.57 (br dt, *J* = 7.9, 1.2 Hz, 1H), 6.42 (s, 2H), 5.59 (dd, *J* = 7.9, 5.7 Hz, 1H), 5.48 – 5.45 (m, 1H), 4.14 – 4.09 (m, 2H), 3.840 (s, 3H), 3.838 (s, 3H), 3.81 – 3.80 (m, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.60 – 3.56 (m, 1H), 3.02 (t, *J* = 7.1 Hz, 2H), 2.81 (td, *J* = 13.4, 2.9 Hz, 1H), 2.58 – 2.49 (m, 1H), 2.44 (ddd, *J* = 14.1, 9.4, 6.7 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.13 – 2.03

(m, 2H), 1.97 – 1.86 (m, 1H), 1.75 – 1.66 (m, 3H), 1.61 – 1.56 (m, 1H), 1.51 (s, 9H), 1.47 – 1.37 (m, 1H), 1.31 – 1.21 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.66, 170.67, 158.90, 153.32, 152.95, 148.98, 147.43, 141.88, 136.93, 136.79, 135.49, 133.65, 133.00, 129.63, 129.61, 120.32, 118.90, 118.54, 113.90, 112.96, 111.85, 111.41, 105.13, 80.52, 76.08, 68.81, 60.89, 56.12, 56.05, 55.95, 52.15, 50.89, 43.54, 38.25, 35.23, 31.38, 28.51, 28.47, 27.00, 25.51, 21.10, 12.71 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{49}H_{62}N_2O_{11}Na^+$ 877.4246; Found 877.4231.

(*R*)-1-(3-(2-((*tert*-butoxycarbonyl)amino)ethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (27)

A solution of **65** (40 mg, 93 μmol), **56** (38 mg, 95 μmol) and 4-(dimethylamino)pyridine (25 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1 mL) was cooled to 0 ºC before N,N´-dicyclohexyl carbodiimide (21 mg, 0.10 mmol) was added. The resulting solution was allowed to heat to ambient temperature and left stirring overnight, before it was filtered and the filtrate concentrated (to approximately 0.5 mL). A second filtration was performed and the filtrate was purified by flash column chromatography (5% MeOH in CH_2Cl_2) to afford **27** as a colorless oil (40 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 7.18 – 7.13 (m, 1H), 6.79 – 6.74 (m, 2H), 6.70 – 6.68 (m, 1H), 6.67 – 6.63 (m, 2H), 6.61 (d, J = 7.6 Hz, 1H), 6.42 (s, 2H), 5.61 (dd, J = 8.0, 5.7 Hz, 1H), 5.47 (d, J = 4.6 Hz, 1H), 5.20 (br s, 1H), 4.05 – 3.96 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 – 3.79 (m, 1H), 3.79 (s, 3H), 3.68 (s, 6H), 3.57 (t, J = 7.1 Hz, 1H), 3.55 – 3.47 (m, 2H), 2.79 (td, J = 13.3, 2.9 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.46 (ddd, J = 14.0, 9.3, 6.7 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.14 – 2.02 (m, 2H), 1.98 – 1.87 (m, 1H), 1.76 – 1.67 (m, 3H), 1.62 – 1.56 (m, 1H), 1.44 (s, 10H), 1.32 – 1.23 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 172.69,

170.74, 158.76, 156.10, 153.34, 149.00, 147.46, 142.05, 136.86, 135.45, 133.59, 129.68, 120.33, 119.00, 113.75, 112.73, 111.86, 111.42, 105.20, 79.54, 75.98, 67.31, 60.89, 56.15, 56.05, 55.96, 52.15, 50.94, 43.56, 40.19, 38.27, 31.41, 28.53, 28.28, 26.94, 25.48, 21.04, 12.68. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{43}H_{58}N_2O_{11}Na^+$ 801.3933; Found 801.3923.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-oxo-2-phenylethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (28)

To a solution of **67** (15 mg, 37 μmol), **56** (15 mg, 41 μmol) and 4-(dimethylamino) pyridine (15 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N′*-dicyclohexylcarbodiimide (9 mg, 44 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (30% EtOAc in toluene) to yield **28** as a colorless oil (21 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 8.06 – 8.02 (m, 2H), 7.64 – 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 7.17 – 7.13 (m, 1H), 7.00 – 6.92 (m, 1H), 6.87 – 6.85 (m, 1H), 6.83 (ddd, J = 8.2, 2.6, 0.7 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.66 – 6.63 (m, 2H), 6.37 (s, 2H), 5.60 (dd, J = 8.2, 5.4 Hz, 1H), 5.45 (dd, J = 5.8, 1.6 Hz, 1H), 5.36 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 – 3.78 (m, 1H), 3.78 (s, 3H), 3.64 (s, 6H), 3.59 – 3.55 (m, 1H), 2.83 (td, J = 13.3, 2.9 Hz, 1H), 2.59 – 2.43 (m, 2H), 2.31 – 2.23 (m, 1H), 2.14 – 2.01 (m, 2H), 1.98 – 1.90 (m, 1H), 1.75 – 1.63 (m, 3H), 1.63 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.32 – 1.25 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 194.55, 172.95, 170.91, 158.26, 153.33, 149.03, 147.47, 142.28, 136.76, 135.38, 134.79, 133.92, 133.61, 129.75, 128.95, 128.31, 120.35, 119.34, 114.55, 112.41, 111.84, 111.42, 105.01, 75.89, 70.88, 60.89, 56.06, 56.04, 55.98, 52.19, 50.98, 43.58,

38.38, 31.36, 28.55, 26.95, 25.43, 20.92, 12.77. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{52}NO_{10}^+$ 754.3586; Found 754.3577.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-oxopropoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (29)

To a solution of **68** (24 mg, 70 μmol), **56** (39 mg, 0.11 mmol) and 4-(dimethylamino) pyridine (31 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (16 mg, 78 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (30% EtOAc in toluene) to yield **29** as a colorless oil (16 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 7.19 – 7.14 (m, 1H), 6.79 – 6.73 (m, 3H), 6.68 – 6.62 (m, 3H), 6.38 (s, 2H), 5.61 (dd, J = 8.3, 5.3 Hz, 1H), 5.48 – 5.42 (m, 1H), 4.59 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 – 3.78 (m, 1H), 3.78 (s, 3H), 3.66 (s, 6H), 3.58 (dd, J = 7.9, 6.3 Hz, 1H), 2.81 (td, J = 13.3, 3.1 Hz, 1H), 2.55 (ddd, J = 14.2, 9.7, 5.4 Hz, 1H), 2.47 (ddd, J = 14.2, 9.4, 6.7 Hz, 1H), 2.31 – 2.29 (m, 1H), 2.27 (s, 3H), 2.14 – 2.03 (m, 2H), 1.96 – 1.89 (m, 1H), 1.73 – 1.65 (m, 3H), 1.62 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.31 – 1.24 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.2. Only major rotamer is reported here) δ 205.47, 172.86, 170.83, 157.95, 153.32, 149.02, 147.49, 142.40, 136.76, 135.41, 133.54, 129.84, 120.33, 119.49, 114.10, 112.54, 111.84, 111.43, 105.06, 75.80, 73.17, 60.88, 56.06, 56.05, 55.97, 52.19, 50.96, 43.56, 38.35, 31.39, 28.55, 26.94, 26.72, 25.42, 20.96, 12.70 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{39}H_{49}NO_{10}Na^+$ 714.3249; Found 714.3245.

3-((*R*)-3-(3,4-dimethoxyphenyl)-1-(((*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carbonyl)oxy)propyl)phenyl morpholine-4-carboxylate (30)

To a solution of **70** (35 mg, 87 μmol), **56** (47 mg, 0.13 mmol) and 4-(dimethylamino) pyridine (61 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (38 mg, 0.18 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (80% EtOAc in toluene) to yield **30** as a colorless oil (59 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 7.25 – 7.23 (m, 1H), 7.01 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.98 (t, J = 2.0 Hz, 1H), 6.84 (dt, J = 7.8, 1.4 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.66 – 6.62 (m, 2H), 6.42 (s, 2H), 5.65 (dd, J = 8.2, 5.4 Hz, 1H), 5.49 – 5.45 (m, 1H), 3.848 (s, 3H), 3.845 (s, 3H), 3.82 – 3.80 (m, 1H), 3.79 (s, 3H), 3.76 – 3.73 (m, 4H), 3.70 (s, 6H), 3.68 – 3.65 (m, 2H), 3.60 – 3.53 (m, 3H), 2.80 (td, J = 13.4, 3.1 Hz, 1H), 2.55 (ddd, J = 14.5, 9.4, 5.5 Hz, 1H), 2.47 (ddd, J = 13.9, 9.4, 6.7 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.14 – 2.03 (m, 2H), 1.99 – 1.93 (m, 1H), 1.75 – 1.65 (m, 3H), 1.63 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.31 – 1.23 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.3. Only major rotamer is reported here) δ 172.69, 170.67, 153.61, 153.34, 151.26, 149.01, 147.47, 141.85, 136.80, 135.50, 133.51, 129.57, 123.12, 121.28, 120.35, 120.02, 111.88, 111.43, 105.15, 75.58, 66.75, 66.66, 60.91, 56.15, 56.06, 55.97, 52.15, 50.91, 45.02, 44.25, 43.56, 38.23, 31.36, 28.49, 27.00, 25.50, 21.10, 12.71 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{41}H_{53}N_2O_{11}^+$ 749.3644; Found 749.3640.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (31)

To a solution of **69** (116 mg, 355 μmol), **56** (148 mg, 0.405 mmol) and 4-(dimethylamino) pyridine (101 mg, 0.827 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (82 mg, 397 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (30% EtOAc in toluene) to yield **31** as a colorless oil (215 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.20 – 7.14 (m, 1H), 6.86 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.67 – 6.63 (m, 3H), 6.41 (s, 2H), 5.62 (dd, J = 8.0, 5.6 Hz, 1H), 5.51 – 5.43 (m, 1H), 4.69 (d, J = 2.4 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 – 3.77 (m, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.58 (dd, J = 7.9, 6.5 Hz, 1H), 2.81 (td, J = 13.3, 3.1 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.53 (t, J = 2.4 Hz, 1H), 2.46 (ddd, J = 14.0, 9.4, 6.6 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.13 – 2.04 (m, 2H), 1.98 – 1.89 (m, 1H), 1.75 – 1.65 (m, 3H), 1.63 – 1.55 (m, 1H), 1.47 – 1.38 (m, 1H), 1.31 – 1.24 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.69, 170.70, 157.66, 153.32, 149.00, 147.45, 142.04, 136.78, 135.44, 133.60, 129.67, 120.31, 119.41, 114.25, 113.21, 111.84, 111.41, 105.09, 78.65, 75.92, 75.75, 60.88, 56.10, 56.04, 55.95, 55.92, 52.15, 50.90, 43.55, 38.29, 31.33, 28.50, 26.96, 25.48, 21.05, 12.68. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{39}H_{48}NO_9^+$ 674.3324; Found 674.3318.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-(morpholine-4-carboxamido)ethoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (32)

To a solution of **72** (16 mg, 36 μmol), **56** (23 mg, 63 μmol) and 4-(dimethylamino) pyridine (19 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (17 mg, 82 μmol). The reaction mixture was allowed to heat to ambient temperature and left stirring

overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (EtOAc + 2% MeOH) to yield **32** as a colorless oil (20 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.16 (t, J = 7.9 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.69 – 6.62 (m, 4H), 6.40 (s, 2H), 5.60 (dd, J = 8.1, 5.4 Hz, 1H), 5.46 (br d, J = 4.3 Hz, 1H), 5.18 (t, J = 5.6 Hz, 1H), 4.08 – 4.02 (m, 2H), 3.852 (s, 3H), 3.849 (s, 3H), 3.82 – 3.78 (m, 1H), 3.78 (s, 3H), 3.70 – 3.65 (m, 12H), 3.59 – 3.56 (m, 1H), 3.37 (t, J = 4.9 Hz, 4H), 2.80 (td, J = 13.4, 3.0 Hz, 1H), 2.56 (ddd, J = 14.5, 9.5, 5.6 Hz, 1H), 2.46 (ddd, J = 14.0, 9.5, 6.7 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.13 – 2.04 (m, 2H), 1.97 – 1.89 (m, 1H), 1.75 – 1.65 (m, 3H), 1.61 – 1.54 (m, 1H), 1.43 (qt, J = 13.1, 3.8 Hz, 1H), 1.33 – 1.25 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.76, 170.76, 158.83, 157.94, 153.31, 149.03, 147.51, 142.18, 136.84, 135.41, 133.56, 129.73, 120.35, 119.07, 113.75, 112.73, 111.88, 111.44, 105.19, 76.04, 67.53, 66.66, 60.87, 56.14, 56.08, 55.99, 52.17, 50.94, 44.11, 43.59, 40.54, 38.36, 31.47, 28.50, 26.96, 25.48, 21.04, 12.70. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{43}H_{58}N_3O_{11}^+$ 792.4066; Found 792.4056.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-((methylthio)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (33)

To a solution of **71** (30 mg, 86 μmol), **56** (41 mg, 0.11 mmol) and 4-(dimethylamino) pyridine (27 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added *N*,*N*′-dicyclohexylcarbodiimide (25 mg, 0.12 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (20% EtOAc in toluene) to yield **33** as a colorless oil (31.5 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is

reported here) δ 7.17 (t, J = 7.9 Hz, 1H), 6.83 (ddd, J = 8.1, 2.6, 0.9 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.67 – 6.63 (m, 3H), 6.42 (s, 2H), 5.62 (dd, J = 8.0, 5.6 Hz, 1H), 5.49 – 5.43 (m, 1H), 5.14 (d (*AB system*), J = 11.5 Hz, 1H), 5.13 (d (*AB system*), J = 11.5 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.81 – 3.79 (m, 1H), 3.79 (s, 3H), 3.69 (s, 6H), 3.58 (dd, J = 7.8, 6.4 Hz, 1H), 2.81 (td, J = 13.3, 3.1 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.46 (ddd, J = 14.0, 9.6, 6.7 Hz, 1H), 2.32 – 2.28 (m, 1H), 2.24 (s, 3H), 2.14 – 2.03 (m, 2H), 1.93 (dddd, J = 13.8, 9.8, 6.7, 5.6 Hz, 1H), 1.76 – 1.64 (m, 3H), 1.60 – 1.53 (m, 1H), 1.43 (qt, J = 12.9, 4.1 Hz, 1H), 1.32 – 1.23 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.70, 170.75, 157.24, 153.34, 149.01, 147.46, 142.04, 136.81, 135.48, 133.61, 129.64, 120.34, 119.56, 115.30, 114.11, 111.85, 111.42, 105.13, 75.90, 72.52, 60.90, 56.13, 56.06, 55.97, 52.18, 50.94, 43.59, 38.32, 31.35, 28.53, 26.97, 25.49, 21.06, 14.77, 12.70. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{38}H_{49}NO_9SNa^+$ 718.3020; Found 718.3010.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-((methylsulfonyl)methoxy)phenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (34)

To a solution of **33** (17 mg, 24 μmol) in anhydrous CH_2Cl_2 (1 mL) at 0 ºC was added *meta*-chloroperbenzoic acid (19 mg, 85 μmol) and the resulting solution was stirred for 2 hours before it was subjected to flash column chromatography (40% EtOAc in toluene) to afford **34** as a colorless oil (9 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 7.21 (t, J = 7.9 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.81 – 6.73 (m, 2H), 6.69 – 6.61 (m, 2H), 6.36 (s, 2H), 5.62 (dd, J = 8.3, 5.1 Hz, 1H), 5.42 (br d, J = 5.9 Hz, 1H), 5.07 (d (*AB system*), J = 12.0 Hz, 1H), 5.04 (d (*AB system*), J = 12.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 – 3.78 (m, 1H), 3.78 (s, 3H), 3.64 (s, 6H), 3.60 – 3.55 (m, 1H), 3.00 (s, 3H), 2.82 (td, J = 13.2, 2.8 Hz, 1H), 2.58 (ddd, J = 14.5, 9.4, 5.3 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.30 – 2.24 (m, 1H), 2.16 – 2.05 (m, 2H), 2.00 – 1.91 (m, 1H), 1.77 – 1.65 (m, 3H), 1.65 – 1.58 (m, 1H), 1.49 – 1.39 (m, 1H), 1.33 –

1.27 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 173.07, 170.99, 157.37, 153.34, 149.08, 147.55, 142.90, 136.80, 135.44, 133.44, 130.00, 121.21, 120.36, 115.51, 113.17, 111.86, 111.46, 105.09, 82.07, 75.54, 60.91, 56.09, 56.08, 56.01, 52.33, 51.03, 43.62, 38.67, 38.40, 31.40, 28.60, 26.87, 25.34, 20.87, 12.73. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{38}H_{49}NO_{11}SNa^+$ 750.2919; Found 750.2903.

3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (35)

To a solution of 3-(3,4-dimethoxyphenyl)-1-propanol (42.5 mg, 153 μmol), **56** (80 mg, 0.18 mmol) and 4-(dimethylamino) pyridine (145 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 ºC was added N,N´-dicyclohexylcarbodiimide (54 mg, 0.17 mmol). The reaction mixture was allowed to heat to ambient temperature and left stirring overnight. The resulting suspension was filtered and the filtrate was concentrated (to approximately 0.5 mL) by passing a stream of nitrogen over the surface. A second filtration was performed and the filtrate subjected to flash column chromatography (30% EtOAc in toluene) to yield **35** as a colorless oil (65 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 6.78 – 6.74 (m, 1H), 6.67 – 6.63 (m, 2H), 6.46 (s, 2H), 5.39 – 5.36 (m, 1H), 4.08 (dt, J = 10.8, 6.6 Hz, 1H), 4.02 (dt, J = 10.8, 6.6 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 6H), 3.80 (s, 3H), 3.81 – 3.75 (m, 1H), 3.59 (dd, J = 7.9, 6.4 Hz, 1H), 2.89 (td, J = 13.3, 3.1 Hz, 1H), 2.53 (t, J = 7.6 Hz, 2H), 2.29 – 2.20 (m, 1H), 2.16 – 2.04 (m, 1H), 1.88 – 1.78 (m, 2H), 1.76 – 1.58 (m, 4H), 1.43 (qt, J = 12.9, 3.8 Hz, 1H), 1.31 – 1.22 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.87, 171.26, 153.28, 149.00, 147.44, 136.76, 135.48, 133.68, 120.32, 111.83, 111.39, 105.16, 64.19, 60.88, 56.23, 56.04, 55.94, 52.30, 51.02, 43.57, 31.68, 30.45, 28.40, 26.96, 25.45, 21.12, 12.70. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{42}NO_8^+$ 544.2905; Found 544.2900.

(*S*)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)piperidine-2-carboxylic acid (37)[23]

To a solution of **36** (2.02 g, 7.24 mmol) in water (15 mL) was slowly added $NaHCO_3$ (8.1 g, 96 mmol). After gas evolution had ceased acetone (40 mL) was added followed by 9-fluorenylmethoxycarbonyl chloride (3.94 g, 15.2 mmol) and the solution was left stirring for 18 hours at ambient temperature. The reaction mixture was concentrated *in vacuo* removing acetone and the resulting aqueous suspension was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2 + 1% formic acid) to yield **37** as a pale yellow solid (2.1 g, 83%). $[\alpha]_D^{25}$ −34.5 (*c* = 1.1, $CHCl_3$). Mp 155 – 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.7, **A**:**B**): δ 10.77 (br s, 1.7H, **A** + **B**), 7.79 (d, *J* = 7.4 Hz, 2H, **A**), 7.77 – 7.73 (m, 1.4H, **B**), 7.64 (t, *J* = 7.3 Hz, 2H, **A**), 7.57 (t, *J* = 7.6 Hz, 1.4H, **B**), 7.45 – 7.29 (m, 6.8H, **A** + **B**), 5.09 (d, *J* = 4.9 Hz, 1H, **A**), 4.79 (d, *J* = 4.9 Hz, 0.7H, **B**), 4.57 – 4.40 (m, 3.4H, **A** + **B**), 4.32 (t, *J* = 7.0 Hz, 1H, **A**), 4.25 (t, *J* = 6.4 Hz, 0.7H, **B**), 4.16 (d, *J* = 12.8 Hz, 0.7H, **B**), 4.09 (d, *J* = 12.5 Hz, 1H, **A**), 3.22 – 3.15 (m, 1H, **A**), 3.08 – 3.01 (m, 0.7H, **B**), 2.34 (d, *J* = 12.9 Hz, 1H, **A**), 2.26 (d, *J* = 13.2 Hz, 0.7H, **B**), 1.80 – 1.67 (m, 5.1H, **A + B**), 1.51 – 1.31 (m, 3.4H, **A** + **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.7, **A**:**B**): δ 177.21 (**A**), 177.13 (**B**), 156.70 (**A**), 156.01 (**B**), 143.87 (**B**), 143.85 (**A**), 141.31 (**A**), 141.26 (**B**), 127.70 (**A**), 127.67 (**B**), 127.08 (**A**), 127.03 (**B**), 125.10 (**A**), 125.09 (**A**), 124.94 (**B**), 124.84 (**B**), 120.10 (**B**), 119.97 (**A**), 67.91 (**A**), 67.72 (**B**), 54.34 (**B**), 54.24 (**A**), 47.20 (**A + B**), 41.95 (**A**), 41.72 (**B**), 26.74 (**B**), 26.57 (**A**), 24.69 (**A**), 24.46 (**B**), 20.73 (**A**), 20.59 (**B**) ppm (1 extra peak (**A** + **B**) Fmoc group not completely symmetrical). HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_4Na^+$ 374.1363; Found 374.1372.

1-((9H-fluoren-9-yl)methyl) 2-((*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-morpholinoethoxy)phenyl)propyl) (*S*)-piperidine-1,2-dicarboxylate (39)[24]

To a solution of **37** (402 mg, 1.14 mmol), **38** (418 mg, 1.04 mmol), 4-(dimethylamino)pyridine (12 mg, 0.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 ºC was added N,N´-dicyclohexylcarbodiimide (236 mg, 1.14 mmol). The reaction mixture was allowed to heat to ambient temperature and was stirred at this temperature overnight. The resulting suspension was filtered and the filtrate was concentrated (to a total volume of approximately 3 mL) by passing a stream of nitrogen over the surface. A second filtration was performed before the filtrate was subjected to flash column chromatography (40% acetone in toluene + 1% Et_3N) to yield **39** as a colorless oil (508 mg, 94%).. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers 1:0.7, **A**:**B**): δ 7.77 (dd, J = 7.2, 2.3 Hz, 2H, **A**), 7.72 (d, J = 7.4 Hz, 1.4H, **B**), 7.59 (t, J = 8.4 Hz, 2H, **A**), 7.49 (d, J = 7.4 Hz, 0.7H), 7.45 – 7.14 (m, 9.2H, **A** + **B**), 6.92 (d, J = 7.4 Hz, 1.7H, **A** + **B**), 6.88 (s, 2H, **A** + **B**), 6.83 (d, J = 8.2 Hz, 1H, **A**), 6.78 (d, J = 7.6 Hz, 0.7H, **B**), 6.75 (s, 0.7H, **B**), 6.74 (s, 1H, **A**), 6.67 – 6.58 (m, 3.4H, **A** + **B**), 5.80 – 5.72 (m, 1.7H, **A** + **B**), 5.04 (d, J = 4.4 Hz, 1H, **A**), 4.90 (d, J = 4.2 Hz, 0.7H, **B**), 4.49 – 4.32 (m, 3.4H, **A** + **B**), 4.28 (t, J = 7.1 Hz, 1H, **A**), 4.17 – 4.06 (m, 4.4H, **A** + **B**), 3.99 (t, J = 5.4 Hz, 1.4H, **B**), 3.84 (s, 5.1H, **A** + **B**), 3.82 (s, 3H, **A**), 3.80 (s, 2.1H, **B**), 3.73 – 3.68 (m, 6.8H, **A** + **B**), 3.16 (td, J = 12.8, 2.2 Hz, 0.7H, **B**), 3.00 (td, J = 13.3, 2.4 Hz, 0.7H, **B**), 2.77 (t, J = 5.7 Hz, 2H, **A**), 2.69 (t, J = 5.6 Hz, 1.4H, **B**), 2.59 – 2.49 (m, 10.2H, **A** + **B**), 2.33 – 2.29 (m, 1.7H, **A** + **B**), 2.26 – 2.16 (m, 1.7H, **A** + **B**), 2.07 – 1.98 (m, 1.7H, **A** + **B**), 1.79 – 1.66 (m, 5.1H, **A** + **B**), 1.52 – 1.42 (m, 1.7H, **A** + **B**), 1.33 – 1.22 (m, 1.7H, **A** + **B**) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers 1:0.7, **A**:**B**): δ 171.07 (**A** + **B**), 158.98 (**A** + **B**), 156.50 (**A**), 156.04 (**B**), 148.99 (**B**), 148.98 (**A**), 147.47 (**B**), 147.42 (**A**), 144.22 (**A**), 144.16 (**B**), 143.99 (**A**), 143.93 (**B**), 141.80 (**A**), 141.62 (**B**), 141.42 (**A**), 141.40 (**A**), 141.33 (**B**), 141.30 (**B**), 133.63 (**A**), 133.50 (**B**), 129.75 (**A** + **B**), 127.81 (**A**), 127.78 (**B**), 127.17 (**A** + **B**), 125.20 (**A**), 125.09 (**B**), 120.22 (**A**), 120.20 (**B**), 120.11 (**B**), 120.09 (**A**), 120.06 (**A**), 120.04 (**B**), 119.16 (**B**), 119.01 (**A**), 114.05 (**A** + **B**), 113.20 (**B**), 113.18 (**A**), 111.82 (**A**), 111.73 (**B**), 111.42 (**A** + **B**), 76.67 (**B**), 76.41 (**A**), 67.99 (**B**), 67.89 (**A**), 67.03 (**A** + **B**), 65.86

(**A**), 65.82 (**B**), 57.77 (**A**), 57.69 (**B**), 56.03 (**A** + **B**), 55.92 (**A** + **B**), 55.02 (**B**), 54.64 (**A**), 54.21 (**A**), 54.19 (**B**), 47.33 (**A** + **B**), 42.12 (**A**), 41.99 (**B**), 38.22 (**A**), 38.19 (**B**), 31.35 (**B**), 31.32 (**A**), 27.17 (**B**), 26.96 (**A**), 24.93 (**A**), 24.68 (**B**), 20.94 (**A**), 20.81 (**B**) ppm (3 extra peaks (3**A** + 3**B**) Fmoc group not completely symmetrical). HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{51}N_2O_8^+$ 735.3640; Found 735.3631.

(*S*)-2-(naphthalen-2-yl)butanoic acid (40)

To a solution of 2-(naphthalen-2-yl)acetic acid (230 mg, 1.24 mmol) and Koga's base (571 mg, 127 mmol) in anhydrous THF (4 mL) at 0 ºC was added dropwise *n*-BuLi (2.15 mL, 2.3 M solution in hexanes, 4.94 mmol). After addition the reaction mixture was left stirring 15 min, then cooled to -78 ºC and left at this temperature for 5 min before adding ethyl iodide (0.4 mL, 5.0 mmol). The reaction was left stirring 5 min before adding MeOH (1 mL) and letting the solution heat to ambient temperature. The reaction mixture was partitioned between 1 M aqueous HCl (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was extracted 4 times with EtOAc (20 mL). The combined organic phases were washed with water (30 mL) followed by brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (15% EtOAc in heptane + 1% formic acid) to yield **40** as a white solid (190 mg, 54%). $[\alpha]_D^{25}$ +79.6 (*c* = 0.36, $CHCl_3$) (lit.[25]: $[\alpha]_D^{25}$ +93.3 (*c* = 1, $CHCl_3$) – 96% ee). Ee: 82% based on optical rotation. Mp 103 – 105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.79 (m, 3H), 7.78 – 7.74 (m, 1H), 7.50 – 7.42 (m, 3H), 3.64 (t, *J* = 7.4 Hz, 3H), 2.20 (dp, *J* = 13.6, 7.4 Hz, 1H), 1.93 (dp, *J* = 13.6, 7.4 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 180.04, 135.89, 133.54, 132.89, 128.52, 127.96, 127.76, 127.26, 126.32, 126.05, 126.05, 53.51, 26.37, 12.27 ppm. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{15}O_2^+$ 215.1067; Found 215.1073.

(±)-2-(3,4,5-fluorophenyl)butanoic acid (41)

The reaction was carried out as described for compound **40**, using 3,4,5-trifluorophenylacetic acid (250 mg, 1.31 mmol), Koga's base (608 mg, 1.35 mmol), *n*-BuLi (2.3 mL, 2.3 M in hexanes, 5.29 mmol) and ethyl iodide (0.45 mL, 5.63 mmol). The reaction was quenched with MeOH 15 min after complete addition of ethyl iodide. Purification was performed by flash column chromatography (10% EtOAc in toluene + 1% formic acid) yielding **41** (170 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (dd, J = 8.3, 6.5 Hz, 2H), 3.40 (t, J = 7.7 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.86 – 1.69 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.84, 151.32 (ddd, J = 250.4, 10.0, 4.0 Hz), 139.31 (dt, J = 251.5, 15.2 Hz), 134.63 – 134.20 (m), 112.49 (dd, J = 16.5, 5.2 Hz), 52.51, 26.52, 12.01 ppm. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}F_3O_2^+$ 219.0627; Found 219.0635.

(*S*)-2-(4-bromophenyl)butanoic acid (42)

The reaction was carried out as described for compound **40**, using 2-(4-bromophenyl)acetic acid (770 mg, 3.58 mmol), Koga's base (1.65 g, 3.69 mmol), *n*-BuLi (5.8 mL, 2.5 M in hexanes, 14.5 mmol) and ethyl iodide (1.2 mL, 15 mmol). The reaction was quenched with MeOH 15 min after complete addition of ethyl iodide. Purification was performed by flash column chromatography (15% EtOAc in toluene + 1% formic acid) yielding **42** (526 mg, 52%). $[\alpha]_D^{25}$ +46.6 (c = 1.0, $CHCl_3$) (litt.**Error! Bookmark not defined.**: $[\alpha]_D^{25}$ +49.5 (c = 1, $CHCl_3$) – 93% ee). Ee: 88% based on optical rotation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.43 (m, 2H), 7.21 – 7.17 (m, 2H), 3.42 (t, J = 7.7 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.84 – 1.73 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.55, 137.41, 131.92, 129.98, 121.62, 52.79, 26.39, 12.13 ppm. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{12}BrO_2^+$ 243.0015; Found 243.0017.

(*S*)-2-(4-ethoxy-3,5-dimethoxyphenyl)butanoic acid (44).

Ethyl iodide (0.50 mL, 6.25 mmol) was added to a suspension of (4-hydroxy-3,5-dimethoxyphenyl)acetic acid (**43**, 0.500 g, 2.35 mmol) and potassium carbonate (1.07 g, 7.75 mmol) in 13.0 mL DMSO. The reaction was heated to 60 ºC for 5 h, after which additional ethyl iodide (0.25 mL, 3.13 mmol) was added to the reaction. After a total of 7 h TLC showed the reaction was complete, and the suspension was cooled to room temperature and diluted with 1 M aqueous HCl. The aqueous phase was extracted with EtOAc 3 x 25 mL and the combined organic phases were washed with brine, dried with $NaSO_4$, filtered and concentrated *in vacuo* to a red/brown oil. The oil was purified by flash column chromatography (30% EtOAc in heptane, + 1% formic acid) to yield the 4-ethoxy ethyl ester as a red/brown oil (0.392 g, 62 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.50 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.84 (s, 6H), 3.54 (s 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 153.6, 136.2, 129.6, 106.5, 69.0, 61.0, 56.3, 41.8, 15.7, 14.4 ppm.

Water (10 mL) was added to this ethyl ester (0.392 g, 1.46 mmol) in MeOH (5.0 mL). After a short while, lithium hydroxide monohydrate (0.323 g, 7.52 mmol) was added, and the solution was stirred overnight. It was then quenched with HCl (25 mL, 1 M). The aqueous solution was extracted with diethyl ether (3 x 25 mL) and the combined organic phases was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (40% EtOAc in toluene +1% formic acid) to yield the 4-ethoxy acid as a pale yellow oil (0.327 g, 91 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.49 (s, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.82 (s, 6H), 3.57 (s, 2H), 1.34 (t, J = 7.1, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$) δ 177.8, 153.7, 136.3, 128.7, 106.6, 69.0, 56.2, 41.5, 15.6 ppm.

To a solution of this compound (0.192 g, 0.799 mmol) and Koga's base (0.876 mmol) in 10 mL THF at 0 ºC was added dropwise *n*-BuLi (3 mL, 1.6 M in hexane, 4.8 mmol) over one hour. During

the time of addition, the color of the solution changed from clear to pale yellow. After complete addition, the reaction mixture was stirred at additional 15 min. at 0 ºC and the cooled to -78 ºC. EtI (0.4 mL, 4.8 mmol) was added over 10 min. After 2.5 h TLC showed that the reaction was completed and was quenched with 1 mL methanol and diluted with 1 M aqueous HCl until it was acidic. The reaction turned orange. The mixture was extracted with EtOAc (3 x 45 mL), then the combined organic phase was washed twice with brine, dried with $MgSO_4$, filtered and concentrated. The crude residue was purified with column chromatography (25% EtOAc in toluene + 1% formic acid) to yield **44** as a red/brown solid (0.167 g, 78 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.53 (s, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.84 (s, 6H), 3.39 (t, J = 7.7 Hz, 1H), 2.09 (dq, J = 13.6, 7.5 Hz, 1H), 1.80 (dq, J = 13.6, 7.4 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 177.89, 153.71, 136.47, 133.93, 105.19, 69.03, 56.29, 53.32, 26.67, 15.69, 12.29 ppm. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{14}H_{20}O_5^+$ 268,13053; Found 268,13046.

(*S*)-2-(3,5-methoxy-4-propoxyphenyl) butanoic acid (45)

1-Iodopropane (0.6 mL, 6.15 mmol) was added to a suspension of (4-hydroxy-3,5-dimethoxyphenyl)acetic acid (**43**, 0.5077 g, 2.36 mmol) and $CsCO_3$ (2.46 g, 12.8 mmol) at 65 ºC and left overnight. TLC indicated complete reaction and was quenched and diluted with 1 M aqueous HCl and the aqueous phase was extracted with EtOAc (3 x 45 mL) and the combined organic phase was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified with flash column chromatography (25% EtOAc in heptane, + 1% formic acid) to yield the 4-propoxy propylester as a pale oil (0.323 g, 46 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.50 (s, 2H), 4.06 (t, J = 6.7 Hz, 2H), 3.90 (t, J = 7.0 Hz, 2H), 3.83 (2 x s, 6H), 3.54 (s, 2H), 1.76 (h, J = 7.3 Hz, 2H), 1.65 (h, J = 7.4, 2H), 0.99 (t, J = 7.4, 3H), 0.92 (t, J = 7.4, 3H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.8, 153.6, 136.6, 129.5, 106.6, 75.3, 66.6, 56.3, 41.8, 23.5, 22.1, 10.5, 10.4 ppm.

To a solution of this propyl ester (0.323 g, 1.09 mmol), 7.5 mL methanol and 4 mL water, lithium hydroxide monohydrate was added (0.250 g, 5.84 mmol). The reaction was stirred overnight and quenched with 30 mL 1 M aqueous HCl. The aqueous phase was extracted with 3 x 25 mL EtOAc and the combined organic phase was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified with column chromatography (40% EtOAc in heptane + 1% formic acid) to yield the 4-propoxy acid as a slightly yellow oil (0.141 g, 41 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.49 (s, 2H), 3.91 (t, J = 6.9 Hz, 2H), 3.83 (s, 6H), 3.58 (s, 2H), 1.76 (h, J = 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 177.3, 153.7, 136.8, 128.5, 106.8, 75.3, 56.3, 41.4, 23.4, 10.5 ppm.

To a solution of the acid (0.141 g, 0.55 mmol), Koga's base (0.256 g, 0.56 mmol) and dry THF, *n*-BuLi (1.5 mL, 1.6 M in hexane, 2.4 mmol) was added at 0 ºC over 1 hour. During the time of addition, the reaction turned from clear to pale yellow. After the addition was complete, the reaction was stirred for additional 15 min. and then cooled to -78 ºC. Iodoethane (2 mL, 2.50 mmol) was added over 10 min. After 2.5 h, the reaction was quenched with 1 mL ethanol and 1 mL water. The mixture was diluted with 1 M aqueous HCl (35 mL). The aqueous phase was extracted with 3 x 25 mL EtOAc, and the combined organic phase was washed with saturated aqueous $Na_2S_2O_3$. It was then washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified with flash column chromatography (40% EtOAc in heptane +1% formic acid) to yield **45** (66.3 mg, 42 %) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.52 (s, 2H), 3.91 (t, J = 6.9 Hz, 2H), 3.39 (t, J = 7.7, 1H), 2.08 (m, 1H), 1.78 (m, 3H), 0.99 (t, J = 7.4, 3 H), 0.96 (t, J = 7.4, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$) δ 177.7, 153.5, 136.7, 133.7, 105.2, 75.1, 56.2, 53.1, 26.5, 23.3, 12.1,

10.3 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{23}O_5^+$ 283.15400; Found 283.15409.

(*S*)-2-(3,5-dimethoxy-4-octyloxyphenyl) butanoic acid (46)

To a suspension of (3,5-dimethoxy-4-hydroxyphenyl)acetic acid (**43**, 0.510 g, 2.36 mmol) and K_2CO_3 (1.32 g, 9.56 mmol) in 5 mL of dry DMF at 60 ºC, 1-bromooctane (1.7 mL, 2.02 g, 10.5 mmol) was added. The suspension was stirred for 27 hours until the TLC showed the reaction was complete. The yellow suspension was then diluted with 1 M aqueous HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed twice with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The oil was purified with column chromatography (30% EtOAc in heptane +1% formic acid) to yield the 4-octyloxy octyl ester as a light brown oil (0.50 g, 48 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.50 (s, 2H), 4.09 (t, J = 6.8 Hz, 2H), 3.93 (t, J = 6.8 Hz, 2H), 3.83 (2 x s, 6H), 3.54 (s, 2H), 1.74 (dt, J = 14.8, 6.9 Hz, 2H), 1.62 (dt, J = 14.3, 6.7 Hz, 2H) 1.47 – 1.38 (m, 2H), 1.36 – 1.23 (m, 18H), 0.88 (m, 6H) ppm. ^{13}C (126 MHz, $CDCl_3$): δ 171.84, 153.59, 136.61, 129.36, 105.58, 73.67, 65.23, 56.26, 41.87, 32.01, 31.92, 30.24, 29.56, 29.46, 29.34, 29.33, 28.75, 26.05, 26.01, 25.82, 22.78, 14.25, 14.22 ppm.

To a solution of this compound (0.50 g) in 10 mL of water, 5 mL of MeOH and lithium hydroxide monohydrate (0.561 g, 13.3 mmol) was added. The solution was stirred for 17 hours and quenched with 50 mL of 1 M aqueous HCl. The aqueous phase was extracted with EtOAc (3 x 30 mL), and then the organic phase was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (40% EtOAc in heptane +1% formic acid) to yield the 4-octyl carboxylic acid as a clear oil (0.364 g, 99 %). ^{1}HNMR (500 MHz, $CDCl_3$): δ 6.49 (s, 2H), 3.93 (t, J = 6.9 Hz, 2H), 3.83 (2 x s, 6H), 3.58 (s, 2H), 1.74 (dt, J = 14.7, 7.0 Hz, 2H), 1.47 – 1.38 (m, 2H), 1.35 – 1-22 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H) ppm. ^{13}C-NMR (126

MHz, $CDCl_3$): δ 176.53, 153.69, 136.87, 128.53, 106.69, 73.70, 56.43, 56.17, 41.38, 41.20, 32.00, 30.23, 25.99, 22.82, 14.23 ppm.

To a solution of the acid (0.356 g, 1.10 mmol) and Koga's base (0.556 g, 1.2 mmol) in dry THF (10 mL), n-BuLi (2.9 mL, 1.6 M in hexane, 4.64 mmol) was added dropwise at 0 ºC over an hour. During the time of the addition the color of the solution turned from pale white to purple, then blue, green, brown and red respectively. The reaction mixture was agitated for additional 15 min. after the addition was complete. The reaction mixture was then cooled to -78 ºC. Iodoethane (0.4 mL, 4.98 mmol) was added over 10 min. and the reaction color turned green. After 5 hours, the reaction was complete and was quenched with 1 mL of methanol followed by 1 mL of water. The reaction mixture was diluted with aqueous HCl (1M, 30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine, saturated aqueous $Na_2S_2O_3$, dried with $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (30% EtOAc in heptane + 1% formic acid) to yield **46** as a clear oil (0.132 g, 34 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.52 (s, 2H), 3.93 (t, J = 6.9 Hz, 2H), 3.83 (s, 6H), 3.38 (t, J = 7.7 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.84 – 1.71 (m, 4H), 1.45 – 1.40 (m, 3H), 1.31 – 1.27 (m, 6H), 0.94 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 178.37, 153.66, 136.94, 133.76, 105.33, 73.67, 56.32, 53.37, 32.01, 30.24, 29.56, 29.46, 26.66, 26.46, 26.00, 22.82, 14.26, 12.28 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{32}O_5Na^+$ 375.2140; Found 375.2137.

(*S*)-2-(4-isobutoxy-3,5-dimethoxyphenyl)butyric acid (47)

To a suspension of (3,5-dimethoxy-4-hydroxyphenyl)acetic acid (**43**, 0.509 g, 2.79 mmol) and K_2CO_3 (2.61 g, 18.9 mmol) in 7 mL of dry DMF at 60 ºC, isobutyl bromide (1.1 mL, 1.39 g, 10 mmol) was added and the mixture stirred for 23 hours after which the TLC indicated that the reaction was complete. The reaction mixture was then diluted with 50 mL 1 M aqueous HCl and

extracted with EtOAc (3 x 25 mL). The combined organic phase was then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (15%EtOAc in heptane + 1% formic acid) to yield the isobutoxy isobutyl ester as a yellow oil (0.448 g, 55 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.50 (s, 2H), 3.88 (d, J = 6.6 Hz, 2H), 3.82 (s, 6H), 3.70 (d, J = 6.8, 2H), 3.54 (s, 2H), 2.04 (n, J = 6.8 Hz, 1H), 1.92 (n, J = 6.8 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H), 0.90 (d, J = 6.7 Hz, 6H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.79, 153.51, 137.03, 129.43, 106.81, 80.28, 71.10, 56.33, 41.90, 29.17, 27.88, 19.44, 19.18 ppm.

To a solution of this ester in methanol (8 mL) and water (8 mL), lithium hydroxide monohydrate was added (0.273 g, 6.51 mmol). The suspension was stirred overnight and quenched with aqueous HCl (1 M, 50 mL) and extracted with 3 x 25 mL EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc in heptane + 1% formic acid) to yield the 4-isobutoxy carboxylic acid as a white solid (0.265 g, 71 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.49 (s, 2H), 3.82 (s, 6H), 3.70 (d, J = 6.7 Hz, 2H), 3.57 (s, 2H), 2.04 (n, J = 6.7, 1H), 1,01 (d, J = 6.7 Hz, 6H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 177.30, 153.60, 137.29, 128.38, 106.93, 80.30, 56.36, 41.38, 29.16, 19.42 ppm.

To a solution of the acid (0.265 g, 0.986 mmol) and Koga's base (0.535 g, 0.119 mmol) in dry THF (10 mL) at 0 ºC, *n*-BuLi (1.58 mL, 2.5 M in hexane, 3.95 mmol) was added dropwise over an hour. After complete addition, the reaction mixture was stirred for additional 15 min before it was cooled to -78 ºC. To the cold solution, EtI (0.32 mL, 3,96 mmol) was added over 10 min. The reaction was stirred for additional 3 hours and quenched with methanol (1 mL) and water (1 mL). The solution was then diluted with 25 mL of aqueous HCl (1 M, 25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phase was then washed with brine, dried over $MgSO_4$, filtered

and concentrated *in vacuo.* The crude residue was purified by column chromatography (30% EtOAc in heptane +1% formic acid) to yield **47** as a white solid (0.153 g, 46 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.52(s, 2H), 3.82 (2 x s, 6H), 3.70 (d, J = 6.8 Hz, 2H), 3.38 (t, J = 7.6 Hz, 1H), 2.13-2.08 (m, 2H), 1.87-1.73 (m, 1H), 1.00 (d, J=6.8 Hz, 6H), 0.92 (t, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 177.83, 153.61, 137.36, 133.67, 105.55, 80.26, 56.40, 53.26, 29.17, 26.66, 19.43, 12.27 ppm. HRMS (ESI/FTICR) *m/z:* $[M+H]^+$ Calcd for $C_{16}H_{25}O_5^+$ 297.16965; Found 297.16973.

3-Hydroxy-3-methyl-2-(3,4,5-trimethoxyphenyl)butanoic acid (48)

The reaction was carried out as described for compound **40**, using 3,4,5-trimethoxyphenyl acetic acid (300 mg, 1.33 mmol), Koga's base (613 mg, 1.37 mmol), *n*-BuLi (3.3 mL, 1.6 M in hexanes, 5.3 mmol) and anhydrous acetone (0.4 mL, 5.5 mmol). The reaction was quenched with MeOH 30 min after addition of acetone. Purification was performed by flash column chromatography (10-50% EtOAc in toluene + 1% formic acid) yielding **48** (297 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 2H), 3.84 (s, 6H), 3.84 (s, 3H), 3.55 (s, 1H), 1.40 (s, 3H), 1.15 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.08, 153.16, 137.97, 130.43, 107.03, 72.16, 61.00, 60.55, 56.32, 29.65, 27.04 ppm. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{21}O_6^+$ 285.1333; Found 285.1339.

2-(1-hydroxycyclohexyl)-2-(3,4,5-trimethoxyphenyl)acetic acid (49)

The reaction was carried out as described for compound **40**, using 3,4,5-trimethoxyphenylacetic acid (300 mg, 1.33 mmol), Koga's base (613 mg, 1.37 mmol), *n*-BuLi (3.3 mL, 1.6 M in hexanes, 5.3 mmol) and cyclohexanone (0.55 mL, 5.3 mmol). The reaction was quenched with MeOH 30 min after addition of cyclohexanone. Purification was performed by flash column chromatography (30% EtOAc in toluene + 1% formic acid) yielding **49** (310 mg, 72%). Mp 63 – 65 °C . ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H), 3.57 (s, 1H), 1.82 – 1.75 (m, 1H), 1.75 – 1.64 (m, 1H), 1.63 – 1.50 (m, 4H), 1.49 – 1.37 (m, 2H), 1.29 – 1.17 (m, 2H) ppm. ^{13}C NMR (126

MHz, $CDCl_3$): δ 177.49, 153.11, 137.92, 129.74, 107.11, 77.41, 77.16, 76.90, 72.84, 60.98, 59.91, 56.30, 37.58, 34.86, 25.60, 22.04, 21.68 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{24}O_6Na^+$ 347.14651; Found 347.14655.

2-(1-hydroxycyclopentyl)-2-(3,4,5-trimethoxyphenyl)acetic acid (50)

The reaction was carried out as described for compound **40**, using 3,4,5-trimethoxyphenylacetic acid (300 mg, 1.33 mmol), Koga's base (613 mg, 1.37 mmol), *n*-BuLi (3.3 mL, 1.6 M in hexanes, 5.3 mmol) and cyclopentanone (0.47 mL, 5.3 mmol). The reaction was quenched with MeOH 30 min after addition of cyclopentanone. Purification was performed by flash column chromatography (30% EtOAc in toluene + 1% formic acid) yielding **50** (228 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H), 3.58 (s, 1H), 1.93 – 1.83 (m, 2H), 1.81 – 1.70 (m, 2H), 1.70 – 1.65 (m, 1H), 1.65 – 1.56 (m, 1H), 1.55 – 1.44 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.99, 153.13, 137.85, 131.07, 106.76, 83.04, 60.97, 59.20, 56.29, 40.41, 37.79, 23.85, 23.46 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{22}O_6Na^+$ 333.1309; Found 333.1312.

2-(1-hydroxycyclobutyl)-2-(3,4,5-trimethoxyphenyl)acetic acid (51)

The reaction was carried out as described for compound **40**, using 3,4,5-trimethoxyphenylacetic acid (300 mg, 1.33 mmol), Koga's base (613 mg, 1.37 mmol), *n*-BuLi (3.3 mL, 1.6 M in hexanes, 5.3 mmol) and cyclobutanone (0.40 mL, 5.3 mmol). The reaction was quenched with MeOH 3 hours after addition of cyclobutanone. Purification was performed by flash column chromatography (30% EtOAc in toluene + 1% formic acid) yielding **51** (150 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 2H), 3.82 (s, 6H), 3.82 (s, 3H), 3.78 (s, 1H), 2.24 – 2.17 (m, 2H), 2.08 – 2.01 (m, 1H), 2.00 – 1.92 (m, 1H), 1.92 – 1.83 (m, 1H), 1.67 – 1.55 (m, 1H) ppm. ^{13}C NMR (126 MHz,

$CDCl_3$): δ 177.46, 153.09, 137.76, 130.03, 106.84, 76.02, 60.91, 57.57, 56.25, 36.13, 32.57, 12.63 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{21}O_6^+$ 297.13326; Found 297.13337.

3-hydroxy-4-methyl-2-(3,4,5-trimethoxyphenyl)pentanoic acid (52)

To a solution of 3,4,5-trimethoxyphenylacetic acid (2.0 g, 8.8 mmol) in anhydrous THF (15 mL) at 0 ºC was added dropwise *n*-BuLi (7.4 mL, 2.5 M solution in hexanes, 18 mmol). The mixture was left stirring at 0 ºC for 30 min before adding isobutyraldehyde (3.3 mL, 36 mmol). After 3 hours the reaction was allowed to warm to ambient temperature and then partitioned between 1 M aqueous HCl (100 mL) and EtOAc (100 mL). The phases were separated and the aqueous phase was extracted 3 times with EtOAc (100 mL). The combined organic phases were washed with water (200 mL) followed by brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (40% EtOAc in toluene + 1% formic acid) to yield **52** (1.0 g, 39%). Mp 133 – 135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 (s, 2H), 4.04 (dd, *J* = 9.5, 2.8 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 3.65 (d, *J* = 9.5 Hz, 1H), 1.52 (dh, *J* = 9.5, 6.8, 2.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.11, 153.57, 137.84, 131.14, 105.62, 77.42, 60.98, 56.34, 56.07, 29.20, 20.40, 14.58 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{22}O_6Na^+$ 321.1309; Found 321.1303.

Ethyl 4-methyl-3-((methylsulfonyl)oxy)-2-(3,4,5-trimethoxyphenyl)pentanoate (53)

To a solution of **52** (1.0 g, 3.4 mmol) in absolute EtOH (50 mL) over 3Å Molecular Sieves was added AcCl (10 mL, 141 mmol) and the reaction was cautiously stirred overnight. TLC analysis indicated complete reaction and the suspension were filtered through a pad of Celite and the filtrate concentrated *in vacuo*. To the solid residue was added toluene (30 mL) and the resulting suspension was concentrated *in vacuo* to remove remaining EtOH. To the crude solid was added pyridine (20 mL), mesyl chloride (4 mL, 52 mmol) and DMAP (1.0 g, 8.2 mmol) and the reaction was left

stirring overnight. TLC analysis indicated formation of product but also unreacted starting material, so additional pyridine (20 mL), mesyl chloride (4 mL, 52 mmol) and DMAP (1.0 g, 8.2 mmol) was added together with CH_2Cl_2 (20 mL). The reaction was stirred overnight and TLC analysis indicated complete reaction. The contents of the reaction vessel was concentrated *in vacuo* and the crude solid purified by flash column chromatography (20% EtOAc in toluene) to yield **53** (713 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 2H), 5.29 (dd, J = 11.0, 1.8 Hz, 1H), 4.19 (dq, J = 10.9, 7.1 Hz, 1H), 4.10 (dq, J = 10.9, 7.1 Hz, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 3.03 (s, 3H), 1.69 (dh, J = 6.9, 1.8 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.90, 153.73, 138.18, 129.83, 105.62, 88.54, 61.64, 61.00, 56.41, 54.80, 39.10, 29.20, 20.09, 15.14, 14.20 ppm. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{18}H_{28}O_8S^+$ 404.1499; Found 404.1494.

(*E*)-4-methyl-2-(3,4,5-trimethoxyphenyl)pent-2-enoic acid (54)

To a solution of **53** (713 mg, 1.8 mmol) in $CHCl_3$ was added DBU (0.55 mL, 3.7 mmol). After 7 hours TLC analysis indicate complete reaction and the reaction mixture was concentrated *in vacuo*. The solid residue was dissolved in MeOH (10 mL) and water was added (10 mL) together with LiOH (monohydrate, 415 mg, 9.9 mmol) and the resulting solution was stirred overnight. The reaction mixture was partitioned between 1 M aqueous HCl (30 mL) and EtOAc (30 mL). The phases were separated and the aqueous phase was extracted 3 times with EtOAc (30 mL). The combined organic phases were washed with water (100 mL) followed by brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc in toluene + 1% formic acid) to yield **54** (265 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (d, J = 10.6 Hz, 1H), 6.39 (s, 2H), 3.87 (s, 3H), 3.84 (s, 6H), 2.48 (dh, J = 10.6, 6.6 Hz, 1H), 1.02 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.78, 154.35,

153.06, 137.62, 130.94, 130.51, 106.88, 60.99, 56.24, 29.01, 22.27 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{20}O_5Na^+$ 303.1208; Found 303.1211.

***Tert*-butyl (*R*)-2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (57)**

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 423 mg, 1.47 mmol) and *tert*-butyl-2-bromoacetate (0.24 mL, 1.6 mmol) in DMF (5 mL) was added K_2CO_3 (624 mg, 4.52 mmol). The resulting suspension was left stirring for 2.5 hours before it was concentrated *in vacuo* and purified by flash column chromatography (30% EtOAc in toluene) to afford **57** (586 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 1H), 6.96 (br d, J = 7.7 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.82 – 6.77 (m, 2H), 6.75 – 6.70 (m, 2H), 4.66 (ddd, J = 8.2, 5.1, 3.5 Hz, 1H), 4.52 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.73 – 2.58 (m, 2H), 2.13 – 2.04 (m, 1H), 2.03 – 1.95 (m, 1H), 1.87 (d, J = 3.5 Hz, 1H), 1.48 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.13, 158.29, 149.00, 147.35, 146.59, 134.46, 129.73, 120.33, 119.23, 113.75, 112.35, 111.90, 111.41, 82.52, 73.86, 65.80, 56.07, 55.97, 40.72, 31.74, 28.19 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{30}O_6Na^+$ 425.1935; Found 425.1931.

(*R*)-2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetonitrile (58)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 48 mg, 0.17 mmol) and 2-chloroacetonitrile (15 μL, 0.24 mmol) in DMF (2mL) was added K_2CO_3 (96 mg, 0.69 mmol) and the resulting suspension was left stirring for 2 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (40% EtOAc in toluene) to afford **58** as a colorless oil (42 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 8.1 Hz, 1H), 7.07 – 7.04 (m, 1H), 7.01 – 6.99 (m, 1H), 6.89 (ddd, J = 8.1, 2.7, 0.8 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.73 (dd, J = 8.1, 1.9 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 4.77 (s, 2H), 4.69 (dd, J = 8.0, 5.1 Hz, 1H), 3.855 (s, 3H), 3.849 (s, 3H), 2.74 – 2.59 (m, 2H), 2.13 – 1.95 (m, 3H) ppm. ^{13}C

NMR (126 MHz, $CDCl_3$) δ 156.85, 149.00, 147.37, 147.18, 134.26, 130.06, 120.75, 120.33, 115.22, 114.04, 112.61, 111.89, 111.43, 73.53, 56.05, 55.96, 53.69, 40.81, 31.68 ppm. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{19}H_{21}NO_4^{\bullet+}$ 327.1465; Found 327.1463.

(*R*)-1-(3-((tert-butyldimethylsilyl)oxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (59)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl) phenol (**55**, 101 mg, 0.350 mmol), 4-(dimethylamino) pyridine (28 mg, 0.23 mmol) and Et_3N (0.4 mL, 3 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added *tert*-butyldimethylsilyl chloride (69 mg, 0.46 mmol) and the resulting solution was left stirring for 30 min. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue was purified by flash column chromatography (5% EtOAc in CH_2Cl_2) to afford **59** as a colorless oil (98 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 7.8 Hz, 1H), 6.94 – 6.92 (m, 1H), 6.85 (t, J = 2.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.76 (ddd, J = 8.0, 2.4, 0.9 Hz, 1H), 6.74 – 6.70 (m, 2H), 4.63 (dd, J = 7.6, 5.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.73 – 2.56 (m, 2H), 2.15 – 1.94 (m, 2H), 1.87 (br s, 1H), 0.99 (s, 9H), 0.20 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.97, 148.96, 147.30, 146.42, 134.54, 129.56, 120.31, 119.34, 118.99, 117.75, 111.87, 111.38, 73.83, 56.04, 55.92, 40.72, 31.74, 25.74, 18.32, -4.26. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{23}H_{34}O_4Si^{\bullet+}$ 402.22209; Found 402.22205.

(*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenyl diethyl phosphate (60)

To a suspension of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 150 mg, 0.520 mmol) and K_2CO_3 (410 mg, 2.97 mmol) in anhydrous DMF (2 mL) was added diethyl chlorophosphate (0.1 mL, 0.7 mmol) and the resulting suspension was left stirring for 48 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (80% EtOAc in toluene) to afford **60** as a colorless oil (162 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.9 Hz, 1H), 7.22 – 7.20 (m, 1H), 7.15 – 7.13 (m, 1H), 7.13

– 7.09 (m, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.73 – 6.70 (m, 2H), 4.69 – 4.65 (m, 1H), 4.24 – 4.15 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 2.73 – 2.58 (m, 2H), 2.39 (br s, 1H), 2.12 – 1.93 (m, 2H), 1.34 (td, *J* = 7.1, 1.0 Hz, 3H), 1.33 (td, *J* = 7.1, 1.0 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.97 (d, *J* = 6.8 Hz), 148.98, 147.33, 147.17, 134.39, 129.82, 122.57, 120.32, 119.02 (d, *J* = 4.6 Hz), 117.69 (d, *J* = 5.1 Hz), 111.89, 111.40, 73.31, 64.72 (d, *J* = 6.1 Hz), 56.04, 55.94, 40.84, 31.69, 16.21 (d, *J* = 6.6 Hz) ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{29}O_7PNa^+$ 447.1543; Found 447.1540.

***Tert*-butyl (*R*)-4-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)butanoate (61)**

To a suspension of **55** (0.222 g, 0.770 mmol) and K_2CO_3 (0.634 g, 4.59 mmol) in 10 mL DMF at 90 ^oC, a solution of *t*-butyl 4-bromobutanoic acid ester (0.250 g, 1.12 mmol) in 6 mL THF added. The suspension was stirred for 19 hours before it was diluted with 1 M aq. HCl and extracted with 3 x 50 mL EtOAc. The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The remanence was purified by flash column chromatography (4:1 of toluene and EtOAc) to yield **61** (0.1380 g, 0.320 mmol, 42 %) as a clear oil. ^{1}H-NMR (500 MHz, CDCl3): *δ* 7.25 (t, *J*=8.1 Hz, 1H), 6.91 (m, 2H), 6.80 (m, 2H), 6.73 (dd, *J*=13.3, 2.0 Hz, 1H), 6.72 (d, *J*=2.0 Hz, 1H), 4.66 (dd, *J*=7.9, 5.2, 1H), 4.00 (t, *J*=6.2, 2H), 2.70 (ddd, *J*=13.8, 9.7, 5.7, 1H), 2.62 (ddd, *J*=14.0, 9.5, 6.5 Hz, 1H), 2.42 (t, *J*=7.3 Hz, 2H), 2.05 (m, 4 H), 1.45 (s, 9H) ppm. ^{13}C-NMR (126 MHz, CDCl3): *δ* 172.69, 159.29, 148.98, 147.33, 146.48, 134.51, 129.67, 120.34, 118.38, 113.67, 112.25, 111.91, 111.40, 80.52, 73.96, 67.00, 56.07, 55.06, 40.71, 32.17, 31.80, 28.26, 24.93 ppm.

(*R*)-1-(3-(4-(*tert*-butoxy)-4-oxobutoxy)phenyl)-3-(3,4-dimethoxyphenyl)propyl (*S*)-1-((*S*)-2-(3,4,5-trimethoxyphenyl)butanoyl)piperidine-2-carboxylate (62)

To a solution of **61** (0.138 g, 0.321 mmol) and **56** (0.131 g, 0.359 mmol) in DCM (5 mL) at 0^o C, 4-

dimethylaminopyridine (0.078 g, 0.64 mmol) was added and the solution was stirred for 10 minuttes. *N*,*N* '-diisopropylcarbodiimide (55 µL, 354 mmol) was added and the reaction mixture was slowly heated to room temperature over 1 hour and then stirred at this temperature for 6 hours before it was diluted with 25 mL DCM and washed with 5 x 25 mL of water, washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The remanence was purified by flash column chromatography (4:1 of toluene and EtOAc) to yield **62** (0.1054, 42 %) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$, mixture of rotamers and distereomers, major rotamer reported when possible, rotamer ratio: 1.0:0.46): δ 7.17 (s, 1H), 7.11 (t, 1H), 6.78 (m, 2H), 6.58 (dd, *J*=13.4, 2.0 Hz, 2H and s, 1H), 6.35 (s, 2H), 5.54 (dd, *J*=8.1, 5.6 Hz, 1H), 5.40 (d, *J*=5.0 Hz, 1H), 3.90 (m, 1H), 3.79 (s, 6H), 3.77 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 2.75 (dt, *J*=13.2, 2.8 Hz, 1H), 2.48 (m, 3H), 2.35 (m, 4H), 2.20 (m, 4H), 2.00 (m, 4H), 1.63 (m, 4H), 1.38 (s, 9H), 0.83 (d, *J*=2.3 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$, mixture of rotamers and distereomers, major rotamer reported): δ 172.66, 170.69, 159.01, 153.33, 148.99, 147.45, 141.90, 136.80, 135.49, 133.66, 129.67, 120.33, 118.50, 113.76, 112.98, 111.86, 111.42, 105.14, 80.47, 76.07, 66.98, 60.90, 56.13, 56.06, 52.16, 50.92, 43.56, 39.76, 38.28, 32.19, 28.51, 28.25, 26.99, 25.52, 24.93, 21.10, 12.70 ppm. HR-MS (MALDI, FT-ICR, dithranol): *m/z* 778.41479 [M+H$^+$], calculated mass for ($C_{44}H_{60}NO_{11}$+) 778.41609.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-ol (63)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl) phenol (**55**, 258 mg, 0.694 mmol) and 1-(2-bromoethyl) piperidine hydrobromide (280 mg, 1.03 mmol) in anhydrous DMF (2 mL) was added K_2CO_3 (482 mg, 3.49 mmol) and the resulting suspension was left stirring at 90 ºC overnight. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (30% acetone in toluene + 1% Et_3N) to afford **63** as a colorless oil (94 mg, 26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.1 Hz, 1H), 6.92 – 6.89 (m,

2H), 6.82 – 6.77 (m, 2H), 6.74 – 6.70 (m, 2H), 4.64 (dd, J = 7.7, 5.2 Hz, 1H), 4.08 (t, J = 6.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.74 (t, J = 6.1 Hz, 2H), 2.72 – 2.57 (m, 2H), 2.50 (br s, 4H), 2.23 (br s, 1H), 2.13 – 1.94 (m, 2H), 1.60 (p, J = 5.7 Hz, 4H), 1.47 – 1.41 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.18, 148.96, 147.31, 146.56, 134.55, 129.60, 120.32, 118.41, 113.75, 112.27, 111.90, 111.39, 73.87, 66.01, 58.07, 56.06, 55.95, 55.19, 40.72, 31.80, 26.00, 24.30 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{34}NO_4^+$ 400.2482; Found 400.2484.

Tert-Butyl (R)-(4-(2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)ethyl)phenyl) carbamate (64)

To a suspension of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl) phenol (**55**, 230 mg, 0.798 mmol) and K_2CO_3 (700 mg, 5.06 mmol) in anhydrous DMF (2 mL) was added *tert*-butyl (4-(2-bromoethyl)phenyl)carbamate (366 mg, 1.22 mmol) and the resulting suspension was left stirring at 90 ºC overnight. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (20% EtOAc in toluene) to afford **64** as a colorless oil (106 mg, 26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (br d, J = 8.1 Hz, 2H), 7.26 – 7.15 (m, 3H), 6.92 – 6.88 (m, 2H), 6.82 – 6.77 (m, 2H), 6.75 – 6.70 (m, 2H), 6.46 (br s, 1H), 4.64 (dd, J = 7.9, 5.2 Hz, 1H), 4.13 (t, J = 7.1 Hz, 2H), 3.85 (s, 6H), 3.04 (t, J = 7.1 Hz, 2H), 2.73 – 2.58 (m, 2H), 2.14 – 1.95 (m, 2H), 1.92 (br s, 1H), 1.51 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.17, 152.95, 148.96, 147.31, 146.45, 136.92, 134.51, 133.00, 129.65, 129.63, 120.33, 118.93, 118.39, 113.74, 112.25, 111.90, 111.39, 80.60, 73.94, 68.87, 56.05, 55.94, 40.68, 35.27, 31.77, 28.47 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{37}NO_6Na^+$ 530.2513; Found 530.2508.

Tert-butyl (_R_)-(2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)ethyl)carbamate (65)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 100 mg, 0.347 mmol) and *tert*-butyl (2-bromoethyl)carbamate (260 mg, 1.16 mmol) in DMF (2 mL) was added

K_2CO_3 (280 mg, 2.03 mmol) and the resulting suspension was heated to 60 ºC 6 h before it was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in toluene + 1% Et_3N) to afford **65** as a colorless oil (84 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 6.94 – 6.89 (m, 2H), 6.81 – 6.77 (m, 2H), 6.74 – 6.70 (m, 2H), 5.03 (br s, 1H), 4.68 – 4.63 (m, 1H), 4.00 (t, *J* = 5.0 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.51 (br q, *J* = 5.0 Hz, 2H), 2.74 – 2.58 (m, 2H), 2.15 (d, *J* = 2.8 Hz, 1H), 2.12 – 2.04 (m, 1H), 2.04 – 1.93 (m, 1H), 1.44 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.87, 156.01, 148.94, 147.30, 146.66, 134.46, 129.84, 120.30, 118.73, 113.52, 112.15, 111.89, 111.38, 79.66, 73.77, 67.22, 56.03, 55.92, 40.74, 40.21, 31.75, 28.49. HRMS (MALDI/FTICR) *m/z*: $[M + K]^+$ Calcd for $C_{24}H_{33}KNO_6^+$ 470.1940; Found 470.1938.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(pyridin-4-ylmethoxy)phenyl)propan-1-ol (66)

To a suspension of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl) phenol (**55**, 120 mg, 0.416 mmol) and K_2CO_3 (115 mg, 0.832 mmol) in anhydrous DMF (2 mL) was added 4-(bromomethyl) pyridine hydrobromide (126 mg, 0.498 mmol) and the resulting suspension was left stirring overnight. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (EtOAc + 1% Et_3N) to afford **66** as a colorless oil (27 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.60 (m, 2H), 7.38 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.02 – 6.98 (m, 1H), 6.99 – 6.96 (m, 1H), 6.87 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.74 – 6.71 (m, 2H), 5.10 (s, 2H), 4.68 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.860 (s, 3H), 3.855 (s, 3H), 2.74 – 2.59 (m, 2H), 2.14 – 1.95 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.56, 150.07, 149.02, 147.40, 146.82, 146.44, 134.40, 129.86, 121.67, 120.34, 119.20, 113.92, 112.48, 111.93, 111.43, 73.81, 68.25, 56.09, 55.99, 40.79, 31.78 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{26}NO_4^+$ 380.18563; Found 380.18558.

***tert*-butyl (*R*)-2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)acetate (67)**

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 43 mg, 0.15 mmol) and bromomethyl phenylketone (44 mg, 0.22 mmol) in DMF (2 mL) was added K_2CO_3 (96 mg, 0.69 mmol) and the resulting suspension was left stirring for 1 hour. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (30% EtOAc in toluene) to afford **67** as a white solid (50 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.98 (m, 2H), 7.62 (tt, J = 7.0, 1.1 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.26 (t, J = 7.7 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.85 (dd, J = 8.1, 2.4 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.74 – 6.70 (m, 2H), 5.28 (s, 2H), 4.66 (dd, J = 7.8, 5.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.74 – 2.57 (m, 2H), 2.13 – 1.95 (m, 2H), 1.87 (br s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.50, 158.37, 148.98, 147.33, 146.70, 134.69, 134.44, 134.04, 129.79, 128.99, 128.24, 120.33, 119.34, 113.89, 112.60, 111.89, 111.39, 73.80, 70.85, 56.06, 55.96, 40.68, 31.73 ppm. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{26}O_5Na^+$ 429.1672; Found 429.1669.

(*R*)-1-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)propan-2-one (68)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 75 mg, 0.26 mmol) and chloroacetone (40 µL, 0.50 mmol) in DMF (2mL) was added K_2CO_3 (145 mg, 1.05 mmol) and the resulting suspension was left stirring for 3 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (30% EtOAc in toluene) to afford **68** as a colorless oil (68 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.9 Hz, 1H), 6.97 – 6.95 (m, 1H), 6.92 – 6.91 (m, 1H), 6.79 – 6.75 (m, 2H), 6.73 – 6.70 (m, 2H), 4.66 (dd, J = 8.0, 5.1 Hz, 1H), 4.53 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.71 – 2.58 (m, 2H), 2.26 (s, 3H), 2.14 – 1.93 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.68, 158.03, 148.95, 147.31, 146.86, 134.37, 129.83, 120.30, 119.39, 113.50, 112.29, 111.88, 111.39, 73.67, 73.07, 56.02, 55.92,

40.75, 31.71, 26.71 ppm. HRMS (MALDI/FTICR) *m/z*: [M - e]$^+$ Calcd for $C_{20}H_{24}O_5^{\bullet+}$ 344.1618; Found 344.1615.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(prop-2-yn-1-yloxy)phenyl)propan-1-ol (69)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 195 mg, 0.676 mmol) and propargyl bromide (1 mL, 80% in toluene, 9 mmol) in DMF (10 mL) was added K_2CO_3 (409 mg, 2.96 mmol) and the resulting suspension was left stirring for 2.5 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (30% EtOAc in toluene) to afford **69** as a colorless oil (183 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.9 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.89 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.74 – 6.70 (m, 2H), 4.68 (d, J = 2.5 Hz, 2H), 4.65 (dd, J = 7.7, 5.4 Hz, 1H), 3.844 (s, 3H), 3.839 (s, 3H), 2.73 – 2.57 (m, 2H), 2.51 (t, J = 2.5 Hz, 1H), 2.13 – 1.95 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.79, 148.90, 147.26, 146.55, 134.42, 129.61, 120.27, 119.21, 113.90, 112.63, 111.86, 111.36, 78.64, 75.65, 73.71, 55.99, 55.89, 55.84, 40.63, 31.65 ppm. HRMS (MALDI/FTICR) *m/z*: [M + Na]$^+$ Calcd for $C_{20}H_{22}O_4Na^+$ 349.1410; Found 349.1409.

(*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenyl morpholine-4-carboxylate (70)

To a suspension of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl) phenol (**55**, 100 mg, 0.347 mmol) and K_2CO_3 (334 mg, 2.42 mmol) in anhydrous DMF (2 mL) was added morpholine-4-carbonyl chloride (0.13 mL, 1.1 mmol) and the resulting suspension was left stirring overnight. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (80% EtOAc in toluene) to afford **70** as a colorless oil (83 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.9 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.13 – 7.11 (m, 1H), 7.02 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.74 – 6.70 (m, 2H), 4.71 – 4.64 (m, 1H), 3.852 (s, 3H), 3.847 (s, 3H), 3.75 – 3.72 (m, 4H), 3.66 (br s, 2H), 3.55 (br s, 2H), 2.74 – 2.59

(m, 2H), 2.19 (d, J = 3.3 Hz, 1H), 2.13 – 1.95 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.82, 151.48, 148.96, 147.32, 146.59, 134.41, 129.48, 123.08, 120.86, 120.33, 119.35, 111.93, 111.39, 73.40, 66.74, 66.61, 56.05, 55.94, 44.99, 44.22, 40.72, 31.69 ppm. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{22}H_{27}NO_6^{\bullet+}$ 401.18329; Found 401.18332.

(*R*)-3-(3,4-dimethoxyphenyl)-1-(3-((methylthio)methoxy)phenyl)propan-1-ol (71)

To a solution of (*R*)-3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenol (**55**, 214 mg, 0.742 mmol) and chloromethyl methyl sulfide (70 µL, 0.84 mmol) in DMF (4 mL) was added K_2CO_3 (410 mg, 2.97 mmol) and the resulting suspension was left stirring for 48 hours. The contents of the reaction vessel were concentrated *in vacuo* and the crude residue purified by flash column chromatography (20% EtOAc in toluene) to afford **71** as a colorless oil (86 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 8.1 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.89 – 6.85 (m, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.75 – 6.71 (m, 2H), 5.15 (s, 2H), 4.67 (dd, J = 7.9, 5.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.75 – 2.58 (m, 2H), 2.25 (s, 3H), 2.16 – 1.90 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.37, 148.98, 147.34, 146.55, 134.45, 129.67, 120.33, 119.42, 115.10, 113.64, 111.89, 111.40, 73.83, 72.50, 56.06, 55.95, 40.71, 31.75, 14.76 ppm. HRMS (MALDI/FTICR) *m/z*: $[M - e]^+$ Calcd for $C_{19}H_{24}O_4S^{\bullet+}$ 348.1390; Found 348.1388.

(*R*)-*N*-(2-(3-(3-(3,4-dimethoxyphenyl)-1-hydroxypropyl)phenoxy)ethyl)morpholine-4-carboxamide (72)

To a solution of **65** (40 mg, 93 µmol) in anhydrous CH_2Cl_2 (1.5 mL) was added trifluoroacetic acid (0.20 mL, 2.6 mmol). After 1 hour TLC analysis indicated fully deprotection of Boc and the slightly yellow solution was concentrated *in vacuo*. The residue was dissolved in anhydrous DMF (2 mL) and Et_3N (13 µL, 93 µmol) and morpholine-4-carbonyl chloride (15 µL, 0.13 mmol) was added. The reaction mixture was left stirring for 2 hours before it was concentrated *in vacuo* and the crude

residue purified by flash column chromatography (2% MeOH in EtOAc + 1% Et_3N) to yield **72** as a colorless oil (33 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 8.0 Hz, 1H), 6.94 – 6.91 (m, 2H), 6.82 – 6.77 (m, 2H), 6.74 – 6.70 (m, 2H), 4.94 (t, J = 5.6 Hz, 1H), 4.66 (dd, J = 8.0, 5.0 Hz, 1H), 4.05 (t, J = 5.1 Hz, 2H), 3.853 (s, 3H), 3.848 (s, 3H), 3.68 – 3.62 (m, 6H), 3.36 – 3.30 (m, 4H), 2.71 (ddd, J = 14.1, 9.7, 5.6 Hz, 1H), 2.62 (ddd, J = 14.1, 9.4, 6.6 Hz, 1H), 2.14 (br s, 1H), 2.13 – 1.94 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.96, 157.79, 148.99, 147.36, 146.76, 134.43, 129.74, 120.32, 118.82, 113.58, 112.13, 111.92, 111.41, 73.78, 67.43, 66.56, 56.06, 55.97, 44.06, 40.81, 40.55, 31.79. HRMS (MALDI/FTICR) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{32}N_2O_6Na^+$ 467.2153; Found 467.2151.

Fluorescein Shield (73)

To a solution of **27** (12.2 mg, 15.7 μmol) in anhydrous CH_2Cl_2 (1 mL) was added trifluoroacetic acid (50 μL, 0.65 mmol). After 2 h TLC analysis indicated fully deprotection of the Boc group and the slightly yellow solution was concentrated *in vacuo*. The residue was dissolved in toluene (2 mL) and concentrated *in vacuo*, before DMF (2 mL), DIPEA (20 μL, 0.11 mmol) and **FluoresceinNHS** (10.2 mg, 21.6 μmol) was added. The dark yellow solution was left stirring for 1.5 h before it was concentrated *in vacuo* and the crude product purified by flash column chromatography (5% MeOH in CH_2Cl_2 + 1% formic acid) to yield **73** as a yellow solid (12.8 mg, 79%). ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 10.15 (s, 2H), 8.91 (br t, J = 5.5 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.91 – 6.73 (m, 3H), 6.69 (d, J = 1.9 Hz, 2H), 6.63 – 6.50 (m, 9H), 5.49 (dd, J = 8.3, 5.3 Hz, 1H), 5.25 (br d, J = 3.9 Hz, 1H), 4.05 (t, J = 5.8 Hz, 2H), 3.98 (br d, J = 13.1 Hz, 1H), 3.84 (t, J = 7.1 Hz, 1H), 3.70 (s, 6H), 3.58 – 3.55 (m, 11H), 2.67 – 2.61 (m, 1H), 2.47 – 2.41 (m, 1H), 2.38 – 2.30 (m, 1H), 2.17 – 2.11 (m, 1H), 1.96 – 1.84 (m, 3H), 1.64 – 1.50 (m, 4H), 1.40 – 1.31 (m,

1H), 1.16 – 1.07 (m, 1H), 0.78 (t, J = 7.3 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, DMSO-d_6, mixture of rotamers 1:0.25. Only major rotamer is reported here) δ 172.12, 170.31, 170.02, 168.01, 164.84, 159.62, 158.17, 152.83, 152.62, 151.84, 148.62, 147.04, 141.99, 140.41, 136.20, 135.95, 135.51, 133.13, 129.42, 129.23, 128.30, 124.89, 122.33, 119.96, 118.13, 113.76, 112.73, 112.17, 111.87, 109.13, 105.09, 102.24, 83.30, 75.07, 65.65, 59.81, 55.50, 55.32, 55.31, 51.50, 48.78, 42.82, 37.50, 30.55, 28.02, 26.33, 24.83, 20.47, 12.27 ppm (1 signal hidden under DMSO signal. Confirmed by NMR in $CDCl_3$). HRMS (MALDI/FTICR) *m/z*: $[M + 2H]^+$ Calcd for $C_{59}H_{61}N_2O_{15}^+$ 1038.41395; Found 1038.3626.

Fluorescence polarization assay for the measurement of the dissociation constant

The saturation binding measurement were performed in black, flat bottom 384-well NBS microplates (No.: 3820, Corning Life Science) on a Safire2 plate-reader (Tecan, Mannedorf, Switzerland). The Fluorescein probe **72** was measured at excitation/emission values of 485/535 nm (bandwidth = 20 and 25 nm, respectively). The fluorescent probe **72** was diluted from a DMSO stock in a HEPES buffer (20 mM HEPES, 0.01% Triton-X, pH 8), at double the final concentration required for the final assay. A 1:1 serial dilution of the His-MBP-DD was performed in HEPES buffer and each protein dilution was mixed with the diluted Fluorescein labeled probe (giving a final DMSO conc. of 1%) and transferred to the 384-well plate. After 30 minutes of incubation at ambient temperature, the fluorescence anisotropy was measured. The binding curves were analyzed using Prism 7.0 (GraphPad, La Jolla, CA, USA) and the data were fitted to a four parameter logistic curve to deduce the EC50. The error bars represent the standard deviation of experiments performed in three repetitions. The dissociation constant was determined using equation:

$$K_d = [EC_{50}] - \frac{[L_T]}{2}$$

where [EC_{50}] is the total concentration of His-MBP-DD, where equal amounts of free ligand of free and bound ligand is present, and [L_T] is the total concentration of fluorescent probe.

Fluorescence polarization competitive binding assay

The fluorescein labeled probe **72** and the competitive ligand was in parallel diluted from a DMSO stock solution in HEPES buffer (20 mM HEPES, 0.01% Triton-X, pH 8) to give a 20% final DMSO concentration at 40 times the final concentration (a fixed concentration of 3.6 nM for the fluorescent probe). A 1:1 serial dilution of the competitive ligand was then performed in the solution containing the probe **72**. Every sample was then diluted by a factor of 10 in HEPES buffer and the mixture of fluorescent probe and competitive inhibitor was then mixed with an equal volume of the protein, which had been diluted in HEPES buffer to give two times the concentration required for the final assay (34 nM). The samples were then transferred to a black, flat bottom 384-well NBS microplates (No.: 3820, Corning Life Science) and the fluorescence anisotropy was after 30 min of incubation measured on a Safire2 plate-reader (Tecan, Mannedorf, Switzerland). The data was afterwards processed to determining the fraction bound probe (F_{SB}) using the equation below, with A_{OBS} being the observed anisotropy, and A_F and A_B is the anisotropies of the free and bound probe respectively.

$$F_{SB} = \frac{A_{OBS} - A_F}{(A_B - A_{OBS}) + A_{OBS} - A_F}$$

The competitive binding curves were analyzed using Prism 7.0 (GraphPad, La Jolla, CA, USA) and the data were fitted to a four parameter logistic curve to deduce the IC_{50}. The error bars represent the standard deviation of experiments performed in triplicates. The K_i values were determined using the equation below, with f_0 being the fraction of bound probe over the fully bound species.

$$K_i = \frac{IC_{50}}{1 + \frac{[L_T](f_0 + 2)}{2K_d(f_0 + 1)} + f_o} + K_d \frac{f_0}{f_0 + 2}$$

Induced accumulation of DD-GFP in transgenic plants by Shld and derivatives

Shld and derivatives were diluted in H_20 with 0.05% silwett to a final concentration of 10µM, sprayed on 28-day old *Arabidopsis thaliana* plants expressing the RDDKeGFP protein. After 4 hours, 5 medium leaf disks were isolated and flash frozen in liquid nitrogen. Protein was extracted in 120µL LDS buffer (Novex NuPage) and boiled for 5 min. Total protein was separated by SDS-PAGE and electro-blotted. Immunoblots were blocked for 1 hour in TBS-Tween (0.1% v/v) and 5% BSA. GFP was detected by incubation with primary anti-GFP antibody (1/5000; Torrey Pines Biolabs), followed by incubation with anti-rabbit-IgG-HRP (1/5000; Promega). The horseradish peroxidase-conjugated antibody was visualized with ECL substrate (2mM 41BPA, 500 µM luminol, 100mM Tris pH 8,8 and $1{,}7 \cdot 10^{-2}$ H_2O_2) and pictures taken with a Sony A7S camera.

Ancillary information

Supporting information is available containing replacement curves of fluorescent probe **73** from His-MBP-DD-FKBP12 as measured by fluorescence polarization, NMR spectra of compounds **1-73**, LC-MS traces & spectra for compounds **1-35** and molecular formula strings and the associated biodata. The 3D models shown in Figure 5 was based on the PDB structure 1BL4. Authors will release the atomic coordinates upon article publication. Corresponding author is M. Bols (bols@chem.ku.dk). Non-standard abbreviation used: FKBP = FK binding protein, pK_a = minus logarithm of the acidity constant, DD = destabilizing domain, MBP = maltose-binding protein, HEPES = (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)

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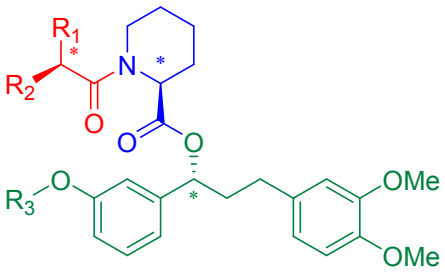
Graphical abstract (TOC)



ShId: R_1 = 3,4,5-$(MeO)_3$Ph; R_2 = Et
R_3 = 2-(N-morpholino)ethyl

1-12: R_1 = various aryl; R_2 = various alkyl; R_3 = 2-(N-morpholino)ethyl

13-35: R_1 = 3,4,5-$(MeO)_3$Ph; R_2 = Et; R_3 = various acidic, basic & neutral groups