Chemical tools to modulate endocannabinoid biosynthesis

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Chiral disubstituted piperidinyl ureas: a class of dual diacylglycerol lipase-α and ABHD6 inhibitors

Based on
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Introduction

Diacylglycerol lipase α and diacylglycerol lipase β (DAGLα and DAGLβ) are intracellular, multi-domain, transmembrane serine hydrolases that employ a Ser-His-Asp catalytic triad to specifically hydrolyse arachidonate-containing diglycerides to form the endocannabinoid 2-arachidonoylglycerol (2-AG) in the brain and peripheral tissues.[1,2] Endocannabinoid signalling is involved in various neurophysiological functions, such as learning, memory, pain sensation, adult neurogenesis and regulation of the energy balance.[3-5] 2-AG is hydrolysed by monoacylglycerol lipase into arachidonic acid, which is a precursor for pro-inflammatory prostaglandins.[6-8] Consequently, the development of DAGL inhibitors that perturb 2-AG production is an emerging strategy for potential therapeutic intervention in various human diseases, including metabolic syndrome related diseases and neuroinflammation.[9,10]

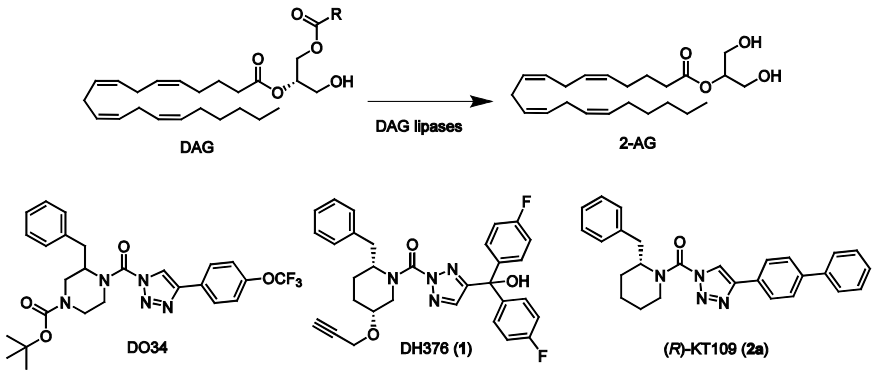


Figure 1. Conversion of DAG into 2-AG by DAG lipases and chemical structures of their inhibitors DO34, DH376 and (*R*)-KT109.

Previously, the discoveries of α-ketoheterocycles,[11-13] glycinesulfonamides[14] and triazole ureas (e.g. DO34 and DH376 (**1**))[15] were reported as selective DAGL inhibitors (Figure. 1). DH376 and DO34 are brain active DAGL inhibitors that reduce 2-AG levels in a time- and dose-dependent manner in mouse brain. They also reduce lipopolysaccharide-induced pro-inflammatory prostaglandin and cytokine levels in mouse brain, as well as anapyrexia and refeeding in fasted mice.[15] Of note, most DAGL inhibitors cross-react with α,β-hydrolase domain containing protein 6 (ABHD6), which has a minor role in the hydrolysis of 2-AG,[16] degrades bis(monoacylglycero)phosphate,[17] and acts as a lysophosphatidyl hydrolase.[18] Inhibition of ABHD6 produces neuroprotective, anti-obesity and anti-inflammatory effects in preclinical disease models.[19,20] Thus, dual inhibition of DAGLs and ABHD6 may actually be advantageous from a therapeutic point of view.

The design of DH376 and DO34 was inspired by (*R*)-KT109 (**2a**),[21,22] the first *in vivo* active DAGLα inhibitor. Both compounds are covalent irreversible inhibitors that feature a 2-benzylpiperidine moiety that confers selectivity and activity towards DAGLs and ABHD6. Previously, an enantioselective synthesis route for DH376 was described (Chapter 2) based on the experience with the synthesis of chiral piperidines from easily available starting materials following a strategy that encompasses enzyme-catalysed cyanohydrin synthesis followed by a transamination-reduction -ring-closing metathesis series of events.[23-25]

The strategy, as demonstrated earlier in the synthesis of polyhydroxylated piperidines (termed iminosugars), is especially suited for the construction of chiral, enantiopure 2-alkylpiperidines bearing one or more hydroxyl substituents. Therefore, in this way, piperidinylureas bearing multiple substituents, amongst which solubilizing hydroxyl groups, would be easy to accomplish. To demonstrate the validity of this reasoning, and to extend the panel of putative

serine hydrolase inactivators, a small library of chiral, disubstituted piperidinylureas **3**, **4a**-**7a**, **4b**-**7b, 6c**, **8** and **9**-**18** were made and the results are described in this chapter.

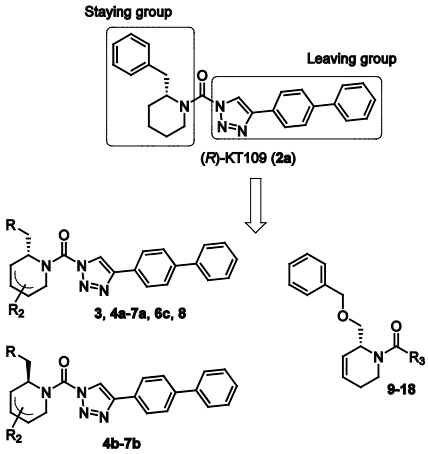
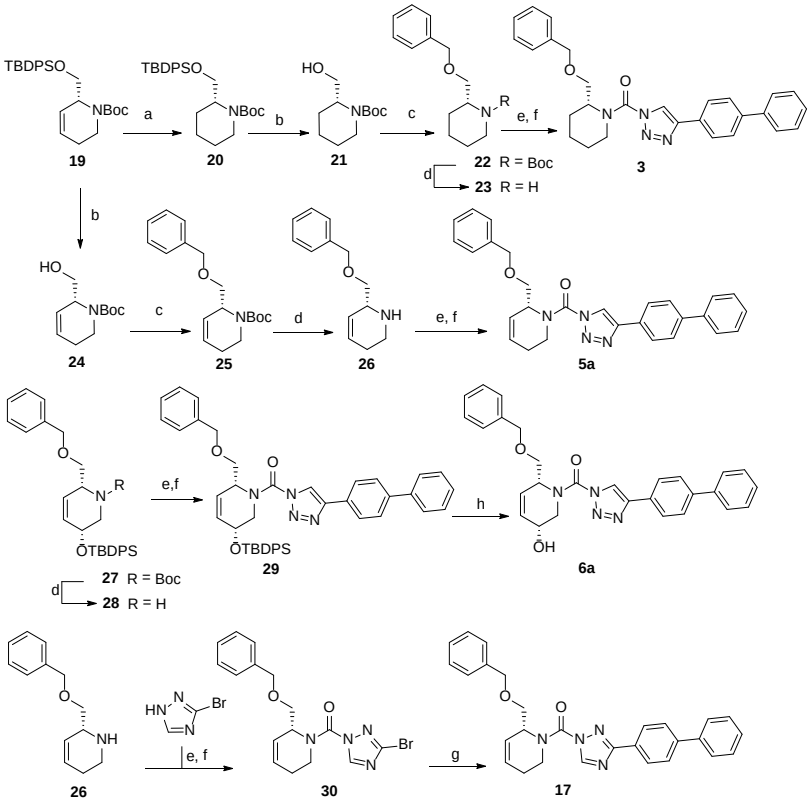


Figure 2. Design of compounds **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18** based on lead **2a**.

Results and discussion

Chemistry

To systematically investigate the structure-activity relationship of the covalent irreversible inhibitors, the attention was focused first on the modification of staying group, resulting 1,2,3-triazole ureas **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** (Figure 2, Table 1 and 2). Next, the influence of electrophilicity of the leaving group (i.e. triazole scaffold) was explored by synthesizing compounds **9**-**18**. The synthesis started with compound **3**, as a close homologue of lead compound **2a** with a methyloxy moiety inserted into the benzylic position. The synthesis route commenced with *O*-TBDPS-protected intermediate **19** that was prepared according to the previously established procedure.[26] Treatment of **19** with 10% Pd/C in MeOH gave hydrogenated intermediate **20**, and ensuing desilylation and benzylation of the primary alcohol yielded Boc-protected intermediate **22** (Scheme 1). Removal of the Boc group using 25% (v/v) TFA in DCM gave amine **23** in near quantitative yield. Finally, triphosgene-mediated condensation of **23** with 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3 -triazole and isolation of the 1,4-regioisomer by silica gel chromatography provided compound **3** in >95% ee as determined by chiral HPLC.

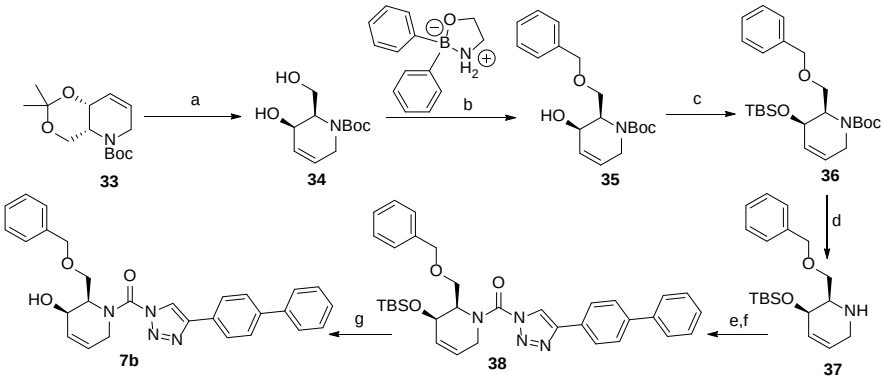


Scheme 1. Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, 95%; (b) TBAF, THF, r.t., 98% (**21**), 92% (**24**); (c) BnBr, TBAI, NaH, DMF, 90% (**22**), 90% (**25**); (d) 25% TFA, DCM, 84% (**26**), 85% (**28**); (e) DIPEA, triphosgene, THF, 0 ^{o}C; (f) DIPEA, DMAP, 1,2,3-triazole, THF, 60 ^{o}C, 25% (**3**), 30% (**5a**), 40% (**30**) over 2 steps; (g) 1,4-dioxane: H_2O (2:1), biphenyl boronic acid, $PdCl_2$(dppf), 80 ^{o}C, 75%; (h) HF-pyridine, THF : pyridine = 1:1 (v/v), 20% over 3 steps (based on **28**).

Following a related sequence of events, but using TBAF for the desilylation step, compound **5a** was obtained (Scheme 1). Compound **5b** (the enantiomer of **5a**) was synthesized in the same fashion as described for **5a** (see experimental section, Scheme 3). For the synthesis of compound **6a**, key intermediate **27** was prepared by employing a previously reported method.[15,24] Subsequently, removal of the Boc group using 25% (v/v) TFA in DCM generated amine **28** that was directly coupled with 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole. After silica gel chromatography, 1,4-regioisomer **29** was isolated and ensuing desilylation with HF-pyridine yielded target compound **6a** (Scheme 1). In a similar manner, compounds **4a**, **4b, 6b, 6c** and **8** with different stereochemistry and substitution pattern on the piperidine ring were prepared (see experimental

section). The synthesis of compound **7b** started with piperidene **33** that was previously prepared according to the reported method.[27,28] Deprotection of **33** with catalytic amount of *p*-TsOH yielded diol intermediate **34** that was then regioselectively benzylated using boronic amide as catalyst.[29] After *O*-silylation and *N*-Boc deprotection, free amine **37** was obtained via triphosgene coupling with triazole. Finally, desylilation (HF-pyridine) gave target compound **7b** (Scheme 2). Compound **7a** (being a diastereoisomer of **7b**) was obtained in the same fashion (see experimental section).

Compounds **9**-**17** were prepared by triphosgene-mediated condensation of free amine **26** with the appropriate heterocycle. As an example, heterocycle **17** (Scheme 1) synthesized by coupling of **26** with 3-bromo-*1H*-1,2,4-triazole followed by Suzuki coupling with 4-biphenylboronic acid (Scheme 1). Finally, the *para*-nitrophenyl carbamate derivative **18** was prepared following a strategy as followed for triazole derivative **5a** with 4-nitrophenol instead of 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (see experimental section).



Scheme 2. Reagents and conditions: (a) cat. *p*-TsOH, MeOH, 86%; (b) BnBr, K_2CO_3, KI, MeCN, 60 °C, 89%; (c) TBS-Cl, imidazole, DMF, 95%; (d) 10% TFA, DCM, 0 °C, 69%. (e) DIPEA, triphosgene, THF, 0 °C; (f) DIPEA, DMAP, 1,2,3-triazole, THF, 60 °C; (g) HF-pyridine, THF : pyridine = 1:1 (v/v), 15% over 3 steps.

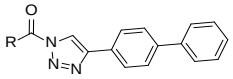
Biological evaluation

The potency of of **3**, **4a-7a**, **4b-7b**, **6c**, **8** and **9**-**18**, as DAGLα inhibitors was established in a colorimetric assay using *para*-nitrophenylbutyrate as a surrogate substrate and membrane fractions from HEK293T cells overexpressing recombinant human DAGLα. As a reference, the biochemical data of (*R*)-KT109 (**2a**) was shown. (*R*)-KT109 (**2a**) is more potent than its enantiomer, (*S*)-KT109 (**2b**), as described in Chapter 2. The same stereochemistry at the C-2 position was preferred for the compounds tested

(e.g. compare compounds **4a**-**6a** vs **4b**-**6b**). A 30-100-fold drop in potency of benzyloxy-containing compounds (**3** and **5**a was found. This may suggest that a lipophilic pocket in DAGLα, which accommodates the 2-benzylpiperidine moiety, is restricted in size or, alternatively, that a polar, flexible linker is less preferred. Introduction of polar hydroxyl groups at other positions in the unsaturated piperidines (e.g. **4a** vs **8**) also reduced the activity over 20-fold. Of note, introduction of a chiral hydroxyl group at the C-3 position of an unsaturated piperidine ring (compounds **7a** and **7b**) abolished the activity against DAGLα ($pIC_{50} < 5$), whereas a hydroxyl at the C-5 position (compounds **6a** and **6c**) was allowed. This suggests that the position of the chiral hydroxyl group plays an important role in the binding site of DAGLα. However, a change in conformation of the piperidine ring induced by the double bond can also not be excluded to be responsible for the decrease in potency. Of note, the stereochemistry of the chiral hydroxyl at the C-5 position in the ring (**6a** vs **6c**) is not important for DAGL activity, which may suggest that this functional group does not make any significant interaction in the binding pocket and may protrude into a solvent exposed region. Compounds **10**-**12** were equally potent as compound **5a**, but **9** showed ~10-fold less activity. The pyrazoles (**13** and **15**), imidazoles (**14** and **16**), 1,2,4-triazole (**17**) and carbamate (**18**) were inactive. This is in line with a reduced electrophilicity of their warhead imparted by the heterocycle.

To screen derivatives **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18** for ABHD6 inhibitory activity, a real-time, fluorescence-based natural substrate assay was employed with membranes from HEK293T cells expressing recombinant human ABHD6. In general, the inhibitory potency of the compounds followed the same trend as observed for DAGLα inhibition (Table 1 and 2). To compare the DAGLα and ABHD6 activities of the compounds, their pIC_{50} values against both targets was plotted (Figure 3). Most of the compounds were dual DAGLα /ABHD6 inhibitors and a linear relationship (r^2 =0.85) for the potency was observed. Compounds **6b**, **7a** and **7b** were inactive against DAGLα, but still showed inhibition against ABHD6 ($pIC_{50} > 6$). Therefore, these compounds could be interesting starting points for the discovery of selective ABHD6 inhibitors.

Table 1. Structure-activity relationship (SAR) of triazole ureas **3, 4a**-**7a, 4b**-**7b, 6c,** and **8**. Inhibition of recombinant human DAGLα or ABHD6 was measured by indicated assays. Data represent average values ± SEM; n = 4 per group.



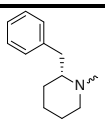
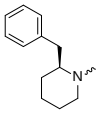
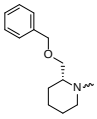
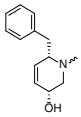
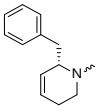
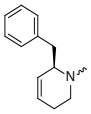
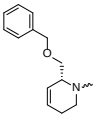
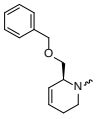
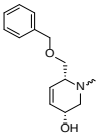
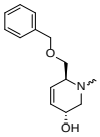
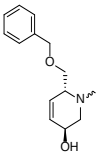
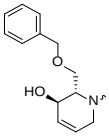
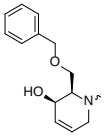
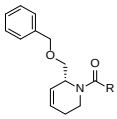
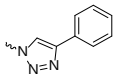
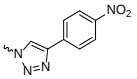
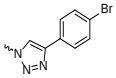
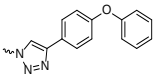
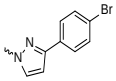
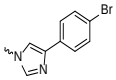
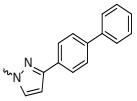
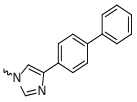
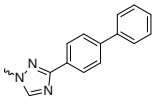
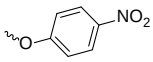
Entry	R	pIC_5 (DAGLα)	pIC_{50} (ABHD6)	Entry	R	pIC_{50} (DAGLα)	pIC_{50} (ABHD6)
2a		9.1±0.1	8.6±0.1	**2b**		7.4±0.1	6.2±0.1
3		7.1±0.1	8.5±0.1	**8**		7.8±0.1	8.5±0.2
4a		9.1±0.1	8.6±0.1	**4b**		7.1±0.1	7.6±0.1
5a		7.6±0.1	7.9±0.1	**5b**		5.9±0.2	7.0±0.1
6a		7.6±0.1	8.3±0.1	**6b**		<5	6.5±0.1
6c		7.5±0.2	8.0±0.1				
7a		<5	6.1±0.1	**7b**		<5	6.6±0.1

Table 2. Structure-activity relationship (SAR) of compounds **9-18**. Inhibition of recombinant human DAGLα or ABHD6 was measured by indicated assays. Data represent average values ± SEM; n = 4 per group.



Entry	R	pIC_{50} (DAGLα)	pIC_{50} (ABHD6)
9		6.8±0.1	6.8±0.1
10		7.8±0.1	7.5±0.1
11		7.8±0.1	7.8±0.1
12		7.6±0.1	8.2±0.1
13		<5	<5
14		<5	<5
15		<5	<5
16		<5	<5
17		<5	<5
18		<5	<5

Finally, to evaluate the selectivity of compounds (**3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18**) across a broad panel of serine hydrolases, activity-based protein profiling (ABPP) was applied using mouse brain membrane proteome. Fluorophosphonate (FP)-based probes are routinely used in competitive ABPP experiments to determine the selectivity of serine hydrolase inhibitors.[30,31] However, FP-based probes do not label DAGLα. MB064, a Bodipy-tagged tetrahydrolipstatin based β-lactone probe, was therefore previously developed, to detect endogenous DAGLα in brain proteomes[31]. Thus, both TAMRA-FP and MB064 were applied to assess the activity and selectivity of the dual DAGLα and ABHD6 inhibitors. In brief, inhibitors **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18** at 10 µM were incubated for 30 min with mouse brain membrane homogenates and performed a gel-based ABPP assay using MB064 (0.25 µM, 20 min) or TAMRA-FP (0.5 µM, 20 min). Almost complete blockade of DAGLα and ABHD6 was observed by compounds **3**, **4a**-**6a**, **4b**, **6c** and **8**-**12**, which is consistent with the results of the biochemical assay (Figure 4a and Table 3). Most compounds showed excellent selectivity over the other serine hydrolases (Figure 4). Compounds **3**, **5a**, **6c** and **9**-**12** did, however, reduce the labeling of DDHD2 (Figure 4a), while compounds **6c**, **9** and **10** were non-selective and prevented the labelling of several unknown off-targets (Figure 4a and 4b).

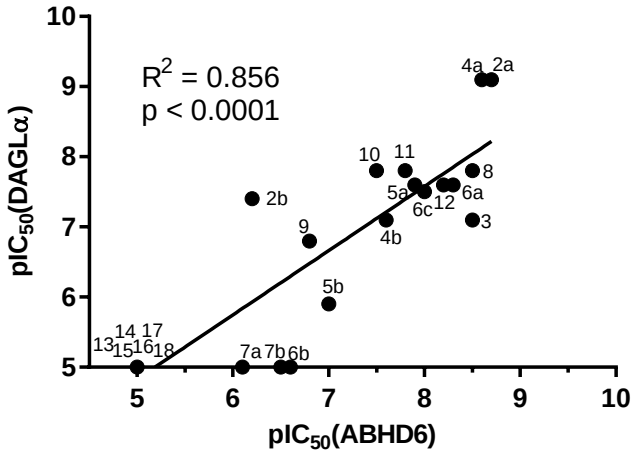


Figure 3. Graphical representation of DAGLα versus ABHD6 inhibition (pIC_{50}) compounds **2a**, **2b**, **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18**.

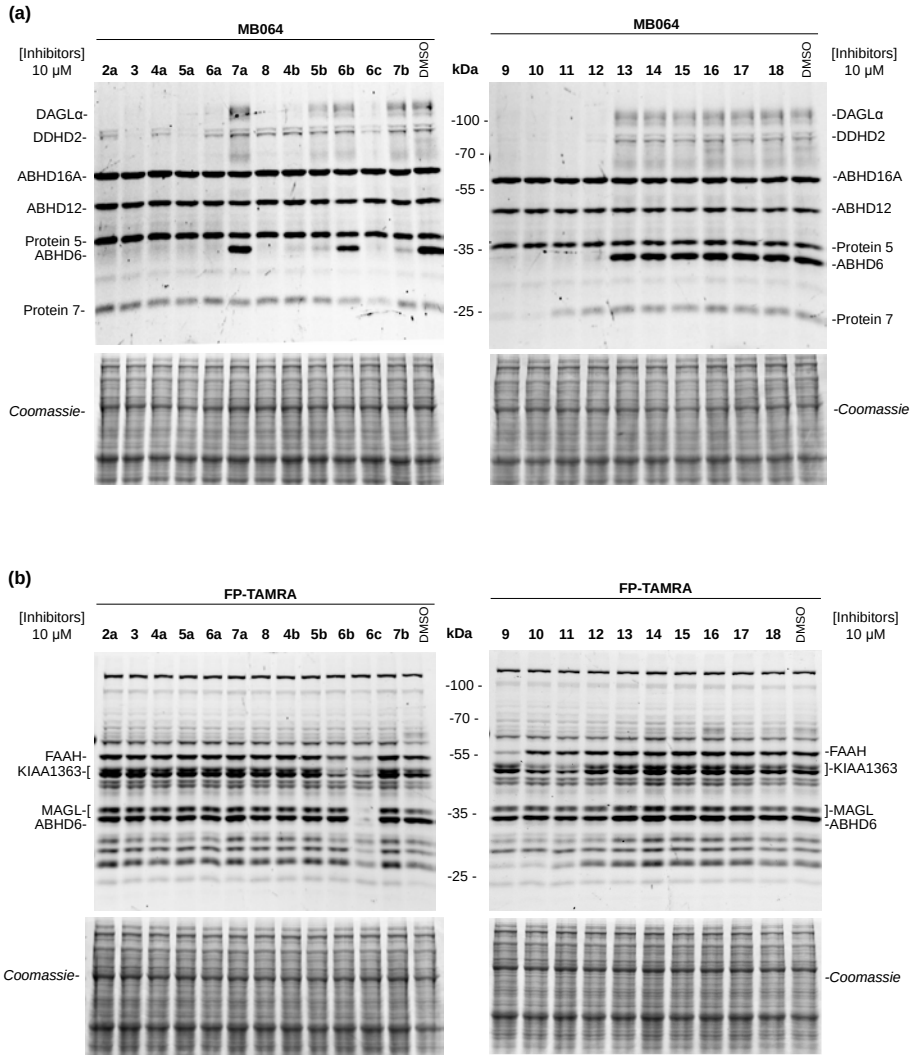


Figure 4. Selectivity profile of compounds **2a**, **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18** (10 µM, 30 min) across mouse brain membrane serine hydrolases as determined by competitive ABPP using two broad-spectrum probes MB064 (0.25 µM, 20 min) (a) and FP-TAMRA (0.5 µM, 20 min) (b). Coomassie staining gel were used as a loading control.

Table 3 . Inhibitory values for compounds **2a**, **3**, **4a**-**7a**, **4b**-**7b**, **6c**, **8** and **9**-**18** (10 µM, 30 min) against native DAGLα and ABHD6 using competitive activity–based protein profiling (ABPP) with probe MB064 (0.25 µM, 20 min). Data represent Means±SEM, n=3. Values are corrected for protein loading per lane as determined by coomassie staining.

Entry	Inhibition (%)		Entry	Inhibition (%)	
	DAGLα	ABHD6		DAGLα	ABHD6
2a	99±0	95±1	**7b**	18±11	83±2
3	96±1	96±0	**9**	89±5	89±2
4a	99±0	96±1	**10**	95±2	93±1
5a	94±2	96±0	**11**	93±3	94±1
6a	87±5	95±2	**12**	93±3	86±2
7a	6±13	18±9	**13**	-3±5	-3±4
8	92±2	96±2	**14**	-9±15	-15±15
4b	83±5	90±3	**15**	-14±18	-3±19
5b	30±12	84±5	**16**	-13±14	-28±15
6b	5±14	50±7	**17**	0±12	-16±9
6c	85±2	95±2	**18**	-11±12	-12±9

Conclusions

In summary, the enantioselective synthesis and structure–activity relationship studies of chiral, disubstituted piperidinylureas as dual inhibitors of DAGLα and ABHD6 were investigated in this chapter. The SAR studies revealed the stereochemistry of the C-2 substitution on the piperidine ring plays an important role. Incorporation of a hydroxyl group at the C-5 position on piperidine ring maintained the activity against DAGLα and ABHD6, whereas a hydroxyl at the C-3 position completely abolished all DAGLα activity. Competitive activity-based protein profiling confirmed the activity of the inhibitors against endogenous DAGLα and ABHD6 and revealed differences in the selectivity profile against other serine hydrolases.

Experimental section

Biological assays

Cloning Procedures

DAGLα and ABHD6 constructs were obtained as reported previously.[30] Plasmids were isolated from transformed XL-10 Z-competent cells (Maxi Prep,

Qiagen) and verified by Sanger sequencing (BaseClear). The sequences were confirmed by sequence analysis at the Leiden Genome Technology Centre.

Cell culture and membrane preparation

Cell culture was performed as previously reported.[30] In brief, HEK293T cells were grown in DMEM with stable glutamine and phenolred (PAA or Sigma) with 10% New Born Calf serum, penicillin and streptomycin. Cells were passaged every 2-3 days by resuspending in medium and seeding them to appropriate confluence. Membranes were prepared from transiently transfected HEK293T cells. One day prior to transfection 10^7 cells were seeded in a 15 cm petri dish. Cells were transfected by the addition of a 3:1 mixture of polyethyleneimine (60µg) and plasmid DNA (20µg) in 2 mL serum free medium. The medium was refreshed after 24 hours, and after 72 h the cells were harvested by suspending them in 20 mL medium. The suspension was centrifuged for 10 min at 1000 rpm, and the supernatant was removed. The cell pellet was stored at -80 ^{o}C until use.

Cell pellets were thawed on ice and suspended in lysis buffer A (20 mM Hepes, 2 mM DTT, 0.25 M sucrose, 1 mM $MgCl_2$, 25 U/mL Benzonase). The suspension was homogenized by polytrone (3 × 7 sec) and incubated for 30 min on ice. The suspension was subjected to ultracentrifugation (93.000 × g, 30 min, 4 ^{o}C, Beckman Coulter, Type Ti70 rotor) to yield the cytosolic fraction in the supernatant and the membrane fraction as a pellet. The pellet was resuspended in lysis buffer B (20 mM Hepes, 2 mM DTT). The protein concentration was determined with Quick Start Bradford reagent (BioRad) or Qubit™ fluorometric quantitation (Life Technologies). The protein fractions were diluted to a total protein concentration of 1 mg/mL and stored in small aliquots at -80 ^{o}C until use.

Biochemical DAGL activity assay

The biochemical hDAGLα assay was performed as reported previously.[30] In brief, the biochemical hDAGLα activity assay is based on the hydrolysis of para-nitrophenylbutyrate (PNP-butyrate) by membrane preparations from HEK293T cells transiently transfected with hDAGLα. Reactions were performed in 50 mM pH 7.2 HEPES buffer with 0.05 µg/µL final protein concentration hDAGLα transfected protein.

Natural substrate based fluorescence assay (ABHD6)

The natural substrate assay was performed as reported previously.[14,32] Standard assay conditions: 25 µM 2-AG, 0.2 U/mL glycerol kinase (GK), glycerol-3-phosphate oxidase (GPO) and horseradish peroxidase (HRP), 0.125 mM ATP, 10 µM Amplifu™Red, 5% DMSO and 0.5% acetonitrile in a total volume of 200 µL. The final protein (ABHD6) concentration is 40 µg/mL.

Preparation of mouse brain membrane proteome

Mouse brain membrane proteome preparation was performed as previously reported.[15,30] In brief, mouse brains were isolated according to guidelines approved by the ethical committee of Leiden University (DEC#10095). Mouse brains were Dounce homogenized in pH 7.2 lysis buffer A (20 mM HEPES pH 7.2, 2 mM DTT, 1 mM $MgCl_2$, 25 U/mL Benzonase) and incubated for 5 min on ice, followed by low speed spin (2,500 × g, 3 min, 4 ^{o}C) to remove debris. The supernatant was subjected to ultracentrifugation (100,000 × g, 45 min, 4 ^{o}C, Beckman Coulter, Type Ti70 rotor) to yield the cytosolic fraction in the supernatant and the membrane fraction as a pellet. The pellet was resuspended in storage buffer B (20 mM HEPES pH 7.2, 2 mM DTT). The total protein concentration was determined with Quick Start Bradford reagent (Bio-Rad) or QubitTM fluorometric quantitation (Life Technologies). Membranes and supernatant were flash frozen in liquid nitrogen and stored in aliquots at -80 ^{o}C until use.

Activity based protein profiling in mouse brain

Mouse brain proteome (2 mg/mL, 19.5 µL) was incubated with DMSO or inhibitor in 0.5 µL DMSO for 30 min at r.t. and subsequently incubated with 500 nM (final concentration) ABP FP-TAMRA for 20 min at r.t. before the reaction was quenched with standard 3x Laemmli sample buffer. The gels were scanned using a ChemiDoc MP system and analyzed using Image Lab 4.1.

Chemistry

General Synthetic Methods

Reagents were purchased from Sigma Aldrich, Acros or Merck and used without further purification unless noted otherwise. Some reactions were performed using oven or flame-dried glassware and dry solvents. All moisture sensitive reactions were performed under an argon atmosphere. Traces of water were removed from starting compounds by co-evaporation with toluene. ^{1}H-and ^{13}C-NMR spectra were recorded on a Bruker AV 400 MHz spectrometer at 400 (^{1}H) and 101 (^{13}C) MHz, or on a Bruker DMX-600 spectrometer 600 (^{1}H) and 150 (^{13}C) MHz using $CDCl_3$, or CD_3OD as solvent, unless stated otherwise. Chemical shift values are reported in ppm with tetramethylsilane or solvent resonance as the internal standard ($CDCl_3$, δ 7.26 for ^{1}H, δ 77.16 for ^{13}C; CD_3OD, δ 3.31 for ^{1}H, δ 49.00 for ^{13}C; $(CD_3)_2SO$, δ 2.50 for ^{1}H, δ 39.52 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants *J* (Hz), and integration. High-resolution mass spectra (HRMS) were recorded by direct injection (2 µL of a 2 µM solution in

water/acetonitrile 50/50 (v/v) and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 ^{o}C) with resolution R = 60,000 at m/z 400 (mass range m/z = 150-2,000) and dioctylphthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). LC-MS analysis was performed on a Finnigan Surveyor HPLC system with a Gemmi C_{18} 50x4.60 mm column (detection at 200-600 nm), coupled to a Finnigan LCQ Adantage Max mass spectrometer with ESI. The applied buffers were H_2O, MeCN and 1.0% TFA in H_2O (0.1% TFA end concentration). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). Flash chromatography was performed using SiliCycle silica gel type SilicaFlash P60 (230 – 400 mesh). TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H_2O (500 mL) and H_2SO_4 (25 mL)) or a $KMnO_4$ stain (K_2CO_3 (40 g), $KMnO_4$ (6 g), H_2O (600 mL) and 10% NaOH (5 mL)). All final compounds were determined to be above 90% pure by LC-MS analysis.

(*R*)-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-((benzyloxy)methyl)piperidin-1-yl)methanone (3). A solution of (*R*)-2-((benzyloxy)methyl)piperidine (50.0 mg, 0.244 mmol) in THF was treated with DIPEA (0.128 mL, 0.731 mmol) and bis(trichloromethyl) carbonate (36.1 mg, 0.122 mmol) and the reaction mixture was stirred for 30 min at 0 ^{o}C. After that the reaction mixture was poured into water and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.128 mL, 0.731 mmol), DMAP (29.8 mg, 0.244 mmol) and 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (48.5 mg, 0.219 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^{o}C and poured into saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), washed with water, brine, dried over $MgSO_4$ and filtered. The solvents are removed under reduced pressure to yield the crude triazole urea as a mixture of N1- and N2-carbamoylated regioisomers (2 to 1 ratio). The N1-carbamoyl triazole was isolated by silica gel chromatography (pentane/EtOAc 100:1 → 5:1) to afford compound **3** (27.6 mg, 0.061 mmol, 25% yield). $[\alpha]_D^{22}$ = +58.7 (*c* = 0.3, $CHCl_3$). HRMS calculated for $C_{28}H_{28}N_4O_2$ $[M+H]^+$ 453.2285, found: 453.2286. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.69 – 7.59 (m, 4H), 7.49 – 7.43 (m, 2H), 7.41 – 7.23 (m, 6H), 4.83 (br, 1H), 4.46 (br, 2H), 4.25 (d, *J* = 6.0 Hz, 1H), 3.86 (t, *J* = 9.6 Hz, 1H), 3.44 (br, 1H), 3.15 (br, 1H), 1.98 – 1.53 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.44, 146.48, 141.36, 140.63, 137.93, 128.98, 128.84, 128.59, 127.95, 127.86, 127.68, 127.65, 127.14, 126.37, 121.21, 73.30, 68.05, 53.34, 41.93, 25.67, 25.22, 19.58.

(*S*)-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(6-benzyl-3,6-dihydropyridin-1(2*H*)-yl)methanone (4a). The title compound was synthesized from (*S*)-6-benzyl-1,2,3,6-tetrahydropyridine (43.0 mg, 0.248 mmol) according to the

procedure described for compound **3**. This furnished compound **4a** (34.8 mg, 0.083 mmol, 33% yield). $[\alpha]_D^{22}$ = +59.6 (*c* = 0.4, $CHCl_3$). HRMS calculated for $C_{27}H_{25}N_4O$ $[M+H]^+$ 421.2023, found: 421.2021. ^{1}H NMR ($CDCl_3$, 600 MHz, mixture of two rotamers ratio A/B = 53/47) Major rotamer: δ 8.36 (br, 0.5H), 7.95 – 7.87 (m, 2H), 7.77 (br, 0.5H) 7.69 (d, *J* = 5.2 Hz, 2H), 7.64 (d, *J* = 4.8 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.38 – 7.28 (m, 3H), 7.25 – 7.12 (m, 3H), 5.97 – 5.93 (m, 1H), 5.69 – 5.63 (m, 1H), 5.37 (br, 0.5H), 4.93 (br, 0.5H), 4.54 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.29 – 3.26 (m, 1H), 3.23 – 3.18 (m, 1H), 3.05 – 2.90 (m, 1H), 2.65 – 2.51 (m, 1H), 2.23 – 2.11 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) Major rotamer: δ 151.36, 148.86, 146.60, 141.58, 140.59, 137.18, 129.74, 129.01, 128.82, 128.66, 127.77, 127.69, 127.14, 126.94, 126.40, 125.75, 120.93, 57.43, 41.94, 40.95, 25.82.

(*R*)-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)methanone (5a). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (50.0 mg, 0.246 mmol) according to the procedure described for compound **3**. This furnished compound **5a** (33.2 mg, 0.074 mmol, 30% yield). $[\alpha]_D^{22}$ = +146.5 (*c* = 0.4, $CHCl_3$). The enantiomeric purity was determined on a Daicel Chiralcel OD-H column (4.5 X 250 mm, 20:80 IPA/Hex, flow rate of 1 mL/min): 23.2 min, e.e.>96%. HRMS calculated for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451.2129, found: 451.2130. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.87 (br, 2H), 7.87 – 7.62 (m, 4H), 7.48 – 7.44 (m, 2H), 7.40 – 7.34 (m, 1H), 7.34 – 7.24 (m, 5H), 6.05 (br, 1H), 5.71 (br, 1H), 5.34 (br, 0.5H), 4.96 (br, 0.5H), 4.51 (br, 3H), 3.86 – 3.32 (m, 3H), 2.59 (br, 1H), 2.16 (br, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.76, 146.42, 141.45, 140.58, 137.83, 128.98, 128.68, 128.56, 127.88, 127.79, 127.68, 127.61, 127.35, 127.13, 126.40, 124.90, 121.31, 73.39, 71.00, 55.65, 39.06, 25.77.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(*(3R,6R)*-6-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (6a). A solution of (*3R*,*6R*)-6-((benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,6-tetrahydropyridine **37** (200 mg, 0.437 mmol) in THF was treated with DIPEA (0.229 mL, 1.31 mmol) and bis(trichloromethyl) carbonate (64.8 mg, 0.218 mmol) and the reaction mixture was stirred for 30 min at 0 ^{o}C. The mixture was poured into water and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water, brine dried over $MgSO_4$, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.229 mL, 1.31 mmol), DMAP (53.4 mg, 0.437 mmol) and 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (106 mg, 0.481 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^{o}C and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The N1-carbamoyl triazole urea **29** was isolated by silica gel chromatography (1-10% ethyl acetate/pentane) as top TLC spot. HF-pyridine (0.235 mL, 2.61 mmol) was subsequently added to a solution of N1-carbamoyl triazole urea in THF and pyridine (1:1; 2 mL) with ice cooling, and the reaction mixture was stirred over night at room temperature. The mixture was diluted with ethyl acetate (40 mL), and then washed with $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated under reduced pressure.

Purification by flash chromatography to furnish compound **6a** (40 mg, 0.086 mmol, 20% yield). $[\alpha]_D^{22}$ = +7.2 (*c* = 1.4, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$ 467.2078, found: 467.2078. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (br, 1H), 7.88 (d, *J* = 4.8 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.59 (m, 2H), 7.48 – 7.43 (m, 2H), 7.39 – 7.34 (m, 1H), 7.34 – 7.23 (m, 5H), 6.04 (d, *J* = 10.4 Hz, 1H), 5.81 (br, 1H), 4.65 (d, *J* = 8.3 Hz, 2H), 4.51 (br, 2H), 3.76 (br, 2H), 3.24 (br, 1H), 2.51 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.61, 146.51, 141.53, 140.41, 137.57, 132.51, 128.89, 128.50, 128.32, 127.88, 127.75, 127.65, 127.62, 127.03, 126.34, 125.55, 121.18, 73.40, 70.02, 63.86, 51.29, 36.61.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(*(2S,3R)*-2-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (7a). The title compound was synthesized from (*2S,3R*)-2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (30.0 mg, 0.09 mmol) and 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (20.0 mg, 0.09 mmol), according to the procedure described for compound **6a**. This furnished compound **7a** (6.2 mg, 0.013 mmol, 15% yield). $[\alpha]_D^{22}$ = +8.13 (*c* = 0.2, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$ 467.2078, found: 467.2077. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.42 – 7.37 (m, 1H), 7.34 – 7.28 (m, 5H), 6.07 – 6.01 (m, 1H), 5.95 (br, 1H), 4.82 (br, 1H), 4.56 – 4.38 (m, 3H), 4.12 (br, 1H), 3.81 (br, 1H), 3.56 (br, 1H), 3.42 (br, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.24, 149.41, 142.62, 140.33, 137.56, 133.90, 129.05, 128.62, 128.02, 127.93, 127.89, 127.82, 127.65, 127.20, 127.11, 126.32, 126.27, 73.26, 67.00, 63.89, 59.94, 42.01.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(*(3R,6S)*-6-benzyl-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (8). The title compound was synthesized from (*3R,6S*)-6-benzyl-1,2,3,6-tetrahydropyridin-3-ol (80.0 mg, 0.187 mmol) and 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (41.4 mg, 0.187 mmol) according to the procedure described for compound **6a**. This furnished compound **8** (13.0 mg, 0.030 mmol, 16% yield). $[\alpha]_D^{20}$ = 3.70 (*c* = 1.0, $CHCl_3$). HRMS calculated for $C_{27}H_{24}N_4O_2$ $[M+H]^+$ 437.1972, found: 437.1971. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br, 1H), 7.90 (br, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.41 – 7.14 (m, 6H), 5.93 (d, *J* = 11.7 Hz, 1H), 5.72 (dd, *J* = 10.4, 3.7 Hz, 1H), 5.41 (br, 0.4H), 4.86 (br, 0.6H), 4.70 (dd, *J* = 12.9, 5.1 Hz, 2H), 3.25 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.12 – 2.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.05, 146.48, 141.68, 140.52, 136.85, 131.10, 130.89, 129.58, 129.01, 128.85, 128.41, 127.81, 127.75, 127.16, 127.03, 126.43, 121.01, 64.19, 56.74, 47.83, 46.24.

(*R*)-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(6-benzyl-3,6-dihydropyridin-1(2*H*)-yl)methanone (4b). The title compound was synthesized from (*R*)-6-benzyl-1,2,3,6-tetrahydropyridine (75.0 mg, 0.433 mmol) according to the procedure described for compound **3**. This furnished compound **4b** (58.3 mg, 0.139 mmol, 32% yield). $[\alpha]_D^{22}$ = -75.20 (*c* = 0.5, $CHCl_3$). HRMS calculated for $C_{27}H_{24}N_4O$ $[M+H]^+$ 421.2023, found: 421.2021. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of two

rotamers ratio A/B = 56/44) Major rotamer: δ 8.36 (br, 0.5H), 7.97 – 7.87 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 4.0 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.38 – 7.28 (m, 3H), 7.25 – 7.11 (m, 3H), 5.95 – 5.92 (m, 1H), 5.66 – 5.63 (m, 1H), 5.37 (br, 0.5H), 4.93 (br, 0.5H), 4.54 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.30 – 3.26 (m, 1H), 3.23 – 3.18 (m, 1H), 3.06 – 2.98 (m, 1H), 2.61 – 2.49 (m, 1H), 2.22 – 2.11 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) Major rotamer: δ 151.55, 148.86, 146.59, 141. 63, 140.57, 137.21, 129.72, 128.98, 128.81, 128.64, 127.74, 127.68, 127.13, 126.67, 126.36, 125.73, 120.92, 57.39, 41.95, 39.73, 25.79.

(*S*)-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)methanone (5b). The title compound was synthesized from (*S*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (50.0 mg, 0.251 mmol) according to the procedures described for compound **3**. This furnished compound **5b** (31.1 mg, 0.069 mmol, 28% yield). $[\alpha]_D^{22}$ = -154.0 (*c* = 0.8, $CHCl_3$). The enantiomeric purity was determined on a Daicel Chiralcel OD-H column (4.6 X 250 mm, 20:80 IPA/Hex, flow rate of 1 mL/min): 15.6 min, e.e.>95%. HRMS calculated for $C_{28}H_{26}N_4O_2$ $[M+H]^+$ 451.2129, found: 451.2128. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (br, 1H), 7.87 (br, 2H), 7.69 – 7.63 (m, 4H), 7.48 – 7.44 (m, 2H), 7.40 – 7.32 (m, 1H), 7.32 – 7.15 (m, 5H), 6.11 – 5.97 (m, 1H), 5.71 (br, 1H), 5.32 (br, 0.5H), 4.96 (br, 0.5H), 4.49 (br, 3H), 3.73 (br, 2H), 3.32 (br, 1H), 2.56 (br, 1H), 2.15 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.07, 146.41, 141.42, 140.55, 137.88, 128.96, 128.67, 128.53, 127.85, 127.77, 127.65, 127.56, 127.33, 127.11, 126.38, 124.88, 121.23, 73.37, 70.84, 55.16, 38.82, 24.95.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)((*3R,6S*)-6-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (**6b**). The title compound was synthesized from (*3R,6S*)-6-((benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,6-tetrahydropyridine (100 mg, 0.221 mmol) according to the procedure described for compound **6a**. This furnished compound **6b** (16.3 mg, 0.035 mmol, 16% yield). $[\alpha]_D^{22}$ = -144.2 (*c* = 0.7, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$ 467.2078, found: 467.2077. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br, 0.5H), 8.05 (br, 0.5H), 7.85 (br, 2H), 7.71 – 7.56 (m, 4H), 7.50 – 7.44 (m, 2H), 7.41 – 7.15 (m, 6H), 6.23 – 6.16 (m, 1H), 5.90 (br, 1H), 5.41 (br, 0.4H), 5.07 (br, 0.6H), 4.70 – 4.35 (m, 3H), 4.26 (d, *J* = 5.4 Hz, 1H), 3.86 – 3.49 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.99, 146.77, 141.67, 140.49, 137.70, 134.90, 129.03, 128.99, 128.61, 128.40, 127.98, 127.89, 127.71, 127.17, 127.12, 126.38, 121.31, 73.48, 69.80, 62.49, 54.20, 49.40.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)((*3S,6R*)-6-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (6c). The title compound was synthesized from (*3S,6R*)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (82.0 mg, 0.246 mmol) according to the procedure described for compound **6a**. This furnished compound **6c** (19.6 mg, 0.042 mmol, 17% yield). $[\alpha]_D^{22}$ = -142.7 (*c* = 0.2, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$ 467.2078, found: 467.2079. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (br, 1H), 7.94 – 7.78 (m, 2H), 7.71 – 7.60 (m, 4H), 7.48

– 7.42 (m, 2H), 7.41 – 7.23 (m, 6H), 6.25 – 6.16 (m, 1H), 5.90 (br, 1H), 5.41 (br, 0.4H), 5.05 (br, 0.6H), 4.62 (br, 2H), 4.40 (br, 1H), 4.27 (d, *J* = 5.4 Hz, 1H), 3.91 – 3.48 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.91, 146.74, 141.64, 140.51, 137.69, 135.37, 133.11, 128.99, 128.62, 128.43, 128.35, 128.00, 127.79, 127.72, 127.13, 126.41, 121.35, 73.50, 69.80, 62.59, 54.33, 49.93.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)((*2R,3R*)-2-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridin-1(2*H*)-yl)methanone (7b). The title compound was synthesized from (*2R,3R*)-2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine **37** (30.0 mg, 0.090 mmol) according to the procedure described for compound **6a**. This furnished compound **7b** (6.6 mg, 0.014 mmol, 15% yield). $[\alpha]_D^{22}$ = -17.4 (*c* = 0.4, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$ 467.2077, found: 467.2078. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.35 (m, 1H), 7.34 – 7.27 (m, 5H), 5.84 (d, *J* = 10.4 Hz, 1H), 5.74 (br, 1H), 5.10 – 4.85 (m, 2H), 4.52 (br, 2H), 4.29 (br, 1H), 3.90 – 3.76 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.36, 149.33, 142.49, 140.36, 137.59, 133.79, 129.05, 128.96, 128.61, 127.98, 127.94, 127.91, 127.83, 127.82, 127.20, 127.10, 123.48, 73.46, 65.95, 65.83, 56.73, 42.07.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(4-phenyl-1*H*-1,2,3-triazol-1-yl)methanone (9). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)-1,2,3,6 -tetrahydropyridine (70.0 mg, 0.344 mmol) and 4-phenyl-1*H*-1,2,3-triazole (55.0 mg, 0.379 mmol) according to the procedure described for compound **3**. This furnished compound **9** (45.1 mg, 0.121 mmol, 35% yield). $[\alpha]_D^{20}$ = 125.1 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{22}H_{22}N_4O_2$ $[M+H]^+$ 375.1816, found: 375.1815. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br, 1H), 7.80 (br, 2H), 7.46 – 7.40 (m, 2H), 7.35 – 7.17 (m, 6H), 6.03 (s, 1H), 5.68 (br, 1H), 5.30 (br, 0.5H), 4.96 (br, 0.5H), 4.67 – 4.30 (m, 3H), 3.85 – 3.20 (m, 3H), 2.53 (br, 1H), 2.16 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.66, 137.81, 129.70, 128.98, 128.67, 128.49, 127.82, 127.74, 127.53, 125.96, 125.63, 124.86, 121.23, 73.33, 70.55, 55.37, 42.72, 24.87.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)methanone (10). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)- 1,2,3,6-tetrahydropyridine (70.0 mg, 0.344 mmol) and 4-(4-nitrophenyl)-1*H*-1,2,3-triazole (72.0 mg, 0.379 mmol) according to the procedure described for compound **3**. This furnished compound **10** (54.9 mg, 0.13 mmol, 38% yield). $[\alpha]_D^{22}$ = +123 (*c* = 0.9, $CHCl_3$). HRMS calculated for $C_{22}H_{21}N_5O_4$ $[M+H]^+$. 420.1666, found: 420.1666. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.21 (m, 2H), 8.18 – 7.81 (m, 3H), 7.36 - 7.21 (m, 5H), 6.08 – 6.04 (m, 1H), 5.67 (br, 1H), 5.28 (br, 0.5H), 4.97 (br, 0.5H), 4.71 – 4.32 (m, 3H), 3.85 – 3.20 (m, 3H), 2.54 (br, 1H), 2.22 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.63, 144.67, 137.61, 135.98, 135.55, 128.54, 127.92, 127.66, 127.14, 126.51, 124.43, 124.38, 122.96, 73.44, 70.71, 55.84, 41.11, 24.42.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methanone (11). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (50.0 mg, 0.246 mmol) according to the procedure described for compound **3**. This furnished compound **11** (35.7 mg, 0.079 mmol, 32% yield). $[\alpha]_D^{22}$ = +136.3 (*c* = 2.5, $CHCl_3$). The enantiomeric purity was determined on a Daicel Chiralcel OD-H column (4.6 X 250 mm, 20:80 IPA/Hex, flow rate of 1 mL/min): 17.4 min, e.e.>93%. HRMS calculated for $C_{22}H_{21}BrN_4O_2$ $[M+H]^+$. 453.0921, found: 453.0920. ^{1}H NMR ($(CD_3)_2SO$, 400 MHz, 100 ^oC): δ 8.82 (s, 1H), 7.85 (d, *J* = 6.8 Hz, 2H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.31-7.26 (m, 5H), 6.05 - 6.01 (m, 1H), 5.80 – 5.76 (m, 1H), 4.92 (s, 1H), 4.50 (s, 2H), 4.12 (dd, *J* = 5.6 Hz, 13.2 Hz, 1H), 3.75-3.67 (m, 2H), 3.38 (t, *J* = 13.2 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.18 – 2.16 (m, 1H). ^{13}C NMR ($CDCl_3$, 400MHz) δ 145.54, 137.70, 132.06, 129.60, 128.62, 128.44, 127.79, 127.71, 127.52, 127.40, 122.52, 121.39, 73.27, 70.71, 55.56, 38.87, 24.83.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(4-(4-phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methanone (12). The title compound was synthesized from ((*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (70.0 mg, 0.344 mmol) and 4-(4-phenoxyphenyl)-1*H*-1,2,3-triazole (90.0 mg, 0.443 mmol) according to the procedure described for compound **3**. This furnished compound **12** (52.0 mg, 0.112 mmol, 32% yield). $[\alpha]_D^{20}$ = 112.5 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_3$ $[M+H]^+$. 467.2078, found: 467.2077. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br, 1H), 7.76 (br, 2H), 7.39 – 7.27 (m, 7H), 7.17 – 7.10 (m, 1H), 7.08 – 7.04 (m, 4H), 6.09 – 5.96 (m, 1H), 5.70 (br s, 1H), 5.31 (br, 0.5H), 4.95 (br, 0.5H), 4.48 (br, 3H), 3.90 – 3.21 (m, 3H), 2.55 (br, 1H), 2.16 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.85, 156.84, 149.76, 146.23, 137.78, 129.95, 128.51, 127.83, 127.75, 127.55, 127.51, 126.15, 124.74, 123.74, 120.73, 119.30, 119.07, 73.34, 70.70, 55.57, 38.83, 24.83.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(3-(4-bromophenyl)-1*H*-pyrazol-1-yl)methanone (13). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (63.0 mg, 0.310 mmol) and 3-(4-bromophenyl)-1H-pyrazole (76.0 mg, 0.341 mmol) according to the procedures described for compound **3**. This furnished compound **13** (119 mg, 0.263 mmol, 85% yield). $[\alpha]_D^{20}$ = 93.8 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{23}H_{22}BrN_3O_2$ $[M+H]^+$. 452.0968, found: 452.0969. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.8 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.20 (m, 5H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.05 – 5.96 (m, 1H), 5.82 – 5.74 (m, 1H), 5.35 (br, 1H), 4.55 (br, 3H), 3.85 (br, 1H), 3.79 – 3.75 (m, 1H), 3.32 (br, 1H), 2.55 (br, 1H), 2.10 (dt, *J* = 17.4, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.18, 138.12, 133.54, 131.88, 131.46, 128.40, 127.67, 127.62, 127.52, 127.10, 125.48, 122.66, 114.16, 104.49, 73.30, 71.24, 54.98, 41.93, 25.14.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(4-(4-bromophenyl)-1*H*-imidazol-1-yl)methanone (14). The title compound was synthesized from (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (68.0 mg, 0.335 mmol) and 4-(4-bromophenyl)-1*H*-imidazole (82.0 mg, 0.368 mmol) according to the procedure

described for compound **3**. This furnished compound **14** (129 mg, 0.284 mmol, 85% yield). $[\alpha]_D^{20}$ = 80.8 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{23}H_{22}BrN_3O_2$ $[M+H]^+$. 452.0968, found: 452.0965. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.67 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.27 (m, 5H), 5.98 – 5.95 (m, 1H), 5.59 (d, *J* = 8.4 Hz, 1H), 4.66 (br, 1H), 4.54 (s, 2H), 4.17 – 4.05 (m, 1H), 3.67 – 3.61 (m, 2H), 3.29 – 3.19 (m, 1H), 2.53 – 2.36 (m, 1H), 2.10 (dt, *J* = 16.0, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.50, 140.97, 137.57, 137.38, 132.18, 131.67, 128.59, 128.06, 127.92, 126.70, 126.66, 123.97, 121.01, 114.11, 73.48, 69.66, 55.31, 38.52, 24.66.

(*R*)-(3-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazol-1-yl)(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)methanone (15). A solution of (*R*)-(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl) (3-(4-bromophenyl)-1*H*-pyrazol-1-yl)methanone (40.0 mg, 0.088 mmol) in dioxane and water (2:1; 6 mL) was treated with phenylboronic acid (21.6 mg, 0.177 mmol), K_2CO_3 (36.7 mg, 0.265 mmol), $PdCl_2$(dppf) (9.71 mg, 0.013 mmol) and the reaction mixture was stirred for 6h at 80 ^{o}C under Ar. The mixture was poured into water and extracted with ethyl acetate (3 x 20 mL), the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to furnish compound **15** (30.6 mg, 0.068 mmol, 77% yield). $[\alpha]_D^{20}$ = 52.9 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{29}H_{27}N_3O_2$ $[M+H]^+$. 450.2176, found: 450.2173. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.7 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.62 (m, 4H), 7.49 – 7.43 (m, 2H), 7.39 – 7.25 (m, 6H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.08 – 5.98 (m, 1H), 5.81 (d, *J* = 8.2 Hz, 1H), 5.42 (br, 1H), 4.58 (s, 3H), 3.89 (br, 1H), 3.82 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.35 (br s, 1H), 2.65 – 2.53 (m, 1H), 2.13 (dt, *J* = 17.4, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.01, 141.46, 140.72, 138.27, 134.16, 133.47, 131.55, 128.97, 128.49, 127.72, 127.62, 127.53, 127.24, 127.13, 126.78, 126.58, 125.67, 104.73, 73.38, 71.73, 54.41, 41.64, 25.18.

(*R*)-(3-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazol-1-yl)(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)methanone (16). The title compound was synthesized from compound **14** (40.0 mg, 0.088 mmol) according to the procedure described for compound **15**. This furnished compound **16** (27.8 mg, 0.062 mmol, 70% yield). $[\alpha]_D^{20}$ = 82.0 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{29}H_{27}N_3O_2$ $[M+H]^+$. 450.2176, found: 450.2166. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.70 (s, 1H), 7.68 – 7.60 (m, 4H), 7.46 – 7.42 (m, 2H), 7.39 – 7.31 (m, 6H), 6.01 – 5.97 (m, 1H), 5.61 (d, *J* = 8.0 Hz, 1H), 4.71 (br, 1H), 4.57 (d, *J* = 12.0 Hz, 2H), 4.18 – 4.03 (m, 1H), 3.69 – 3.60 (m, 2H), 3.28 (br, 1H), 2.46 (br, 1H), 2.11 (dt, *J* = 17.5, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.76, 141.86, 140.88, 140.13, 137.62, 137.54, 132.27, 128.88, 128.70, 128.14, 128.00, 127.88, 127.41, 127.35, 127.03, 125.60, 124.21, 113.91, 73.58, 69.82, 55.37, 39.91, 24.85.

(*R*)-(3-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,4-triazol-1-yl)(6-((benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)methanone (17). A solution of (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (60.0 mg, 0.295 mmol) in THF

was treated with DIPEA (0.155 mL, 0.885 mmol) and bis(trichloromethyl) carbonate (43.8 mg, 0.148 mmol) and the reaction mixture was stirred for 30 min at 0 ^{o}C. After that the reaction mixture was poured into water and extracted with ethyl acetate (3 x 10 mL).The organic layer was washed with water, brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.155 mL, 0.885 mmol), DMAP (36.1 mg, 0.295 mmol) and 3-bromo-1*H*-1,2,4-triazole (48.0 mg, 0.325 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^{o}C and poured into saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), washed with water, brine, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure to yield the crude 1,2,4-triazole urea, which was purified by silica gel chromatography (1-10% ethyl acetate/pentane). The purified 1,2,4-triazole urea (40.0 mg, 0.106 mmol) was subsequently reacted with [1,1'-biphenyl]-4-ylboronic acid (46.2 mg, 0.233 mmol) according to the same procedure described for compound **15**. This furnished compound **17** (35.8 mg, 0.080 mmol, 27% yield overall). $[\alpha]_D^{22}$ = +109.3 (*c* = 0.6, $CHCl_3$). HRMS calculated for $C_{28}H_{26}N_4O_2$ $[M+H]^+$. 451.2129, found: 451.2128. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.39 – 7.25 (m, 6H), 6.08 – 6.01 (m, 1H), 5.76 (d, *J* = 8.1 Hz, 1H), 5.48 (br, 1H), 4.54 (br, 3H), 3.81 – 3.69 (m, 2H), 3.34 (br, 1H), 2.55 (br, 1H), 2.15 (dt, *J* = 16.0, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.33, 147.48, 142.84, 140.56, 137.96, 129.06, 128.99, 128.94, 128.55, 127.88, 127.81, 127.67, 127.50, 127.36, 127.21, 124.84, 114.20, 73.41, 71.32, 55.34, 42.71, 25.68.

4-Nitrophenyl (*R*)-6-((benzyloxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (18). To a stirred solution of 4-nitrophenol (38.3 mg, 0.275 mmol), pyridine (0.032 mL, 0.394 mmol) in dichloromethane, triphosgene (29.2 mg, 0.098 mmol) was added. After stirring at room temperature for 1h, TLC was used to confirm that reaction was complete. (*R*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (40.0 mg, 0.197 mmol) and pyridine were then added to the mixture, and the reaction mixture was stirred for 12h at room temperature. Dichloromethane was removed *in vacuo* and the residual was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water, brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (2-20% ethyl acetate/pentane) to afford compound **18** (56.5 mg, 0.153 mmol, 78% yield). $[\alpha]_D^{20}$ = 87.2 (c = 1.0, $CHCl_3$). HRMS [ESI+] m/z: calculated for $C_{20}H_{20}N_2O_5$ $[M+H]^+$. 369.3914, found: 369.3915. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 12 Hz, 1H), 7.37 – 7.27 (m, 6H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.02 (br, 1H), 5.74 (t, *J* = 12.7 Hz, 1H), 4.77 (br, 1H), 4.64 – 4.52 (m, 2H), 4.27 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.71 – 3.58 (m, 2H), 3.31 (t, *J* = 11.0 Hz, 0.4H), 3.10 (td, *J* = 12.7, 3.4 Hz, 0.6H), 2.39 – 2.30 (m, 1H), 2.10 (d, *J* = 17.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.50, 152.99, 144.84, 137.90, 128.60, 128.00, 127.76, 125.50, 125.09, 124.41, 122.42, 73.49, 70.93, 52.97, 37.91, 24.85.

***tert*-Butyl (*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)piperidine-1-carboxylate (20)**. Compound **19** was prepared according to the reported method.[26] Obtained

tert-Butyl (*R*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **19** (800 mg, 1.77 mmol) was dissolved in MeOH (40 mL) and Pd/C (188 mg, 0.177 mmol) were added subsequently. The reaction was stirred overnight under a hydrogen atmosphere. After filtering over Celite and evaporation of the solvents the crude target compound was obtained. The residue was purified by flash chromatography (pentane/EtOAc = 99 : 1 → 90 : 10) to furnish the title compound (763 mg, 1.68 mmol, 95% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.0 Hz, 4H), 7.43 – 7.37 (m, 6H), 4.36 (br, 1H), 3.95 (d, *J* = 11.2 Hz, 1H), 3.72-3.65 (m, 2H), 2.63 (t, *J* = 12.1 Hz, 1H), 1.92 (d, *J* = 12.0 Hz, 1H), 1.55 (d, *J* = 8.0 Hz, 3H), 1.43 (app. s, 11H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.08, 135.56, 133.54, 129.66, 127.70, 79.10, 61.55, 51.84, 40.10, 28.47, 26.84, 25.31, 25.01, 19.20. LC-MS m/z: calculated for $C_{27}H_{39}NO_3Si$ $[M+H]^+$ 454.27, found: 454.06.

***tert*-Butyl (*R*)-2-(hydroxymethyl)piperidine-1-carboxylate (21)**. A solution of TBAF (3.17 mL, 3.17 mmol) was added to a solution of *tert*-butyl (*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl) piperidine-1-carboxylate **20** (960 mg, 2.12 mmol) in THF (30 mL) with ice cooling and the mixture was stirred at R.T. for 18h. After being diluted with water, the mixture was extracted with ethyl acetate (3 x 30 mL), the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc = 10 : 1 → 3 : 1) to furnish title compound (446 mg, 2.07 mmol, 98% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.17 (m, 1H), 3.90 (d, *J* = 12.2 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.57 (dd, *J* = 11.0, 6.4 Hz, 1H), 2.81 (t, *J* = 12.2 Hz, 1H), 2.70 (br, 1H), 1.67 (d, *J* = 11.2 Hz, 1H), 1.62 – 1.50 (m, 3H), 1.41 (app. s, 11H). ^{13}C NMR (101MHz, $CDCl_3$) δ 155.23, 79.81, 61.25, 52.40, 39.93, 28.34, 25.31, 25.15, 19.56. LC-MS m/z: calculated for $C_{11}H_{21}NO_3$ $[M+H]^+$ 216.15, found: 216.52.

***tert*-Butyl (*R*)-2-((benzyloxy)methyl)piperidine-1-carboxylate (22)**. To a solution of **21** (217 mg, 1.01 mmol), BnBr (345 mg, 2.02 mmol), TBAI (14.9 mg, 0.040 mmol) in dry DMF 5 mL, was added NaH (81.0 mg, 2.02 mmol, 60% in mineral oil) with ice cooling. The reaction mixture was stirred overnight and quenched with saturated aqueous ammonium chloride. The mixture was diluted with DCM and washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/EtOAc = 10 : 1 → 3 : 1) to furnish title compound (277 mg, 0.907 mmol, 90% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.28 – 7.25 (m, 1H), 4.53 (d, *J* = 12.0 Hz, 2H), 4.44 (br, 1H), 3.97 (d, *J* = 12.9 Hz, 1H), 3.53 (d, *J* = 7.3 Hz, 2H), 2.72 (t, *J* = 12.6 Hz, 1H), 1.86 (d, *J* = 12.0 Hz, 1H), 1.67 – 1.49 (m, 3H), 1.44 (app. s, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.22, 138.44, 128.32, 127.51, 79.25, 72.77, 67.87, 49.29, 40.01, 28.45, 25.32, 25.22, 19.24. LC-MS m/z: calculated for $C_{18}H_{27}NO_3$ $[M+H]^+$ 306.20, found: 306.01.

(*R*)-2-((Benzyloxy)methyl)piperidine (23). Compound **22** (264 mg, 0.864 mmol) was dissolved in a mixture of 25% TFA in DCM (5 mL). The reaction mixture was stirred at r.t. for 2.5h until TLC analysis showed the reaction was completely converted. The

mixture was co-evaporated with toluene (3 x 20 mL), the residue diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product that was used without further purification (151 mg, 0.735 mmol, 85% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 4.50 (d, *J* = 12.0 Hz, 2H), 3.44 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.31 (t, *J* = 8.8 Hz, 1H), 3.06 (d, *J* = 11.6 Hz, 1H), 3.00 (br, 1H), 2.80 – 2.74 (m, 1H), 2.61 (td, *J* = 11.7, 2.8 Hz, 1H), 1.78 (d, *J* = 11.8 Hz, 1H), 1.59 (d, *J* = 13.1 Hz, 1H), 1.52 (d, *J* = 13.0 Hz, 1H), 1.49 – 1.26 (m, 2H), 1.21 – 1.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.27, 128.36, 127.73, 127.60, 75.16, 73.37, 56.27, 46.41, 28.63, 26.18, 24.37. LC-MS m/z: calculated for $C_{13}H_{19}NO$ $[M+H]^+$ 206.15, found: 206.43.

***tert*-Butyl (*R*)-6-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (24)**. The title compound was synthesized from **19** (596 mg, 1.32 mmol) and TBAF (1.59 mL, 1.59 mmol) according to the procedures described for compound **21**. This furnished title compound (196 mg, 0.920 mmol, 92% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 5.86 (br, 1H), 5.58 (dt, *J* = 10.2, 2.8 Hz, 1H), 4.43 (br, 1H), 3.99 (br, 1H), 3.57 (d, *J* = 6.6 Hz, 2H), 3.29 (br, 1H), 2.86 (br, 1H), 2.10 (br, 1H), 1.88 (dt, *J* = 17.2, 4.2 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz,) δ 154.48, 127.35, 124.97, 79.97, 64.71, 54.01, 38.22, 28.37, 24.80. LC-MS m/z: calculated for $C_{11}H_{19}NO_3$ $[M+H]^+$ 214.28, found: 214.72.

***tert*-Butyl (*R*)-6-((benzyloxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (25)**. The title compound was synthesized from compound **24** (520 mg, 2.44 mmol) according to the procedures described for compound **22**. This furnished title compound (666 mg, 2.19 mmol, 90% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.23 (m, 5H), 5.88 – 5.84 (m, 1H), 5.58 (dt, *J* =12.0, 4.0 Hz, 1H), 4.52 (s, 2H), 4.28 (br, 1H), 4.05 (br, 1H), 3.56 (br, 1H), 3.51 (br, 1H), 2.93 (br, 1H), 2.29 (br, 1H), 1.97 (d, *J* = 8.7 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 101MHz) δ 154.53, 138.32, 128.31, 128.25, 127.66, 127.53, 127.37, 79.40, 72.03, 71.26, 51.90, 37.06, 28.40, 25.00. LC-MS m/z: calculated for $C_{18}H_{25}NO_3$ $[M+H]^+$ 304.40, found: 303.99.

(*R*)-6-((Benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (26). The title compound was synthesized from compound **25** (303 mg, 0.999 mmol) according to the procedures described for compound **23**. This furnished title compound (181 mg, 0.890 mmol, 89% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.29 – 7.24 (m, 1H), 5.86 – 5.83 (m, 1H), 5.53 (dt, *J* = 10.2, 1.9 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 2H), 3.62 – 3.54 (m, 1H), 3.56 – 3.46 (m, 1H), 3.46 – 3.37 (m, 1H), 3.09 – 3.03 (m, 1H), 2.87 – 2.81 (m, 1H), 2.24 – 2.13 (m, 2H), 2.04 – 1.97 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.26, 128.43, 127.78, 127.68, 126.81, 73.61, 73.38, 53.82, 41.32, 25.98. LC-MS m/z: calculated for $C_{13}H_{17}NO$ $[M+H]^+$ 204.29, found: 204.68.

(*R*)-(6-((Benzyloxy)methyl)-3,6-dihydropyridin-1(2*H*)-yl)(3-bromo-1*H*-1,2,4-triazol -1-yl)methanone (30). A solution of **26** (60.0 mg, 0.295 mmol) in THF was treated with DIPEA (0.155 mL, 0.885 mmol) and bis(trichloromethyl) carbonate (43.8 mg,

0.148 mmol) and the reaction mixture was stirred for 30 min at 0 ^{o}C. After that the reaction mixture was poured into water and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.155 mL, 0.885 mmol), DMAP (36.1 mg, 0.295 mmol) and 4-(4-bromophenyl)-1*H*-1,2,3-triazole (48.0 mg, 0.325 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^{o}C and poured into saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), washed with water, brine, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure to yield the crude product. Purification by silica gel chromatography (pentane/EtOAc 100:1 → 5:1) afforded title compound (45.0 mg, 0.119 mmol, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.54 – 7.02 (m, 5H), 6.01 (dd, *J* = 10.3, 6.0 Hz, 1H), 5.69 (s, 1H), 5.51 – 4.79 (m, 1H), 4.70 – 4.21 (m, 3H), 3.65 (s, 2H), 3.26 (s, 1H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.22 – 2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.54, 147.91, 141.23, 137.74, 128.56, 127.94, 127.69, 127.42, 124.86, 73.32, 70.52, 54.66, 29.80, 25.04. LC-MS m/z: calculated for $C_{16}H_{17}BrN_4O_2$ $[M+H]^+$ 378.24, found: 378.59.

(*3R,6R*)-6-((Benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,6-tetrahydro pyridine (28). The Boc-protected compound *tert*-butyl (*3R,6R*)-6-((benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate **27** was prepared according the route reported.[23,24] The title compound was synthesized from **27** (500 mg, 0.896 mmol) according to the procedures described for compound **23** and furnished the free amine compound (347 mg, 0.758 mmol, 85% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 4H), 7.39 – 7.22 (m, 11H), 5.71 (s, 2H), 4.54 (s, 2H), 4.0 – 4.06 (m, 1H), 3.55 – 3.51 (m, 1H), 3.49 – 3.45 (m, 1H), 3.39 – 3.35(m, 1H), 2.98 (dd, *J* = 13.8, 4.2Hz, 1H), 2.77 (dd, *J* = 12.2, 4.0 Hz, 1H), 2.56 (br s, 1H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.19, 135.80, 135.69, 134.15, 134.01, 130.67, 130.39, 129.65, 129.58, 128.33, 127.62, 127.54, 127.52, 127.51, 73.18, 71.82, 64.24, 53.71, 48.88, 26.96, 19.15.

(*3R,6S*)-6-((Benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,6-tetrahydro pyridine (31). The Boc-protected *tert*-butyl (*3R,6S*)-6-((benzyloxy)methyl)-3-((*tert*-butyldiphenylsilyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate was prepared according the route reported.[23,24] The target compound was synthesized from Boc-protected compound (500 mg, 0.896 mmol) according to the procedure described for compound **23**. This furnished title compound (357 mg, 0.781 mmol, 87% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.69 – 7.63 (m, 4H), 7.43 – 7.34 (m, 6H), 7.32 – 7.23(m, 5H), 5.77 (d, *J* = 12.2 Hz, 1H), 5.57 (d, *J* = 11.8 Hz, 1H), 4.47 (s, 2H), 4.33 (s, 1H), 3.67 – 3.65(m, 1H), 3.50 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.37 – 3.33 (m, 1H), 3.18 (dd, *J* = 12.3, 4.1 Hz, 1H), 2.81 – 2.79 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.84, 135.93, 135.86, 135.80, 133.89, 133.77, 131.95, 129.88, 129.83, 128.46, 127.82, 127.79, 127.74, 127.48, 73.41, 71.89, 65.16, 53.34, 48.61, 27.01, 19.23.

(*3S,6R*)-6-((Benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydropyridine (32). The Boc-protected *tert*-butyl (*3S,6R*)-6-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate was prepared according the reported route.[23,24] To a solution of Boc-protected compound (210 mg, 0.480 mmol) was added 10% TFA in DCM (5 mL) with ice cooling, the reaction mixture was stirred at r.t. for 0.5h and subsequently co-evaporated with toluene (3x20 mL), the residue was diluted with ethyl acetate, washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure, which afforded the crude product (97.0 mg, 0.291 mmol, 54% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 5.82 – 5.68 (m, 1H), 5.60 (dt, *J* = 10.3, 1.8 Hz, 1H), 4.60 – 4.45 (m, 2H), 4.35 – 4.29 (m, 1H), 3.62 – 3.54 (m, 1H), 3.50 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.37 – 3.28 (m, 1H), 3.22 (dd, *J* = 12.1, 5.7 Hz, 1H), 2.64 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.25 (br, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.14, 132.52, 128.49, 128.28, 127.84, 127.78, 73.83, 73.51, 65.84, 54.06, 50.44, 25.98, 18.31, -4.51, -4.62.

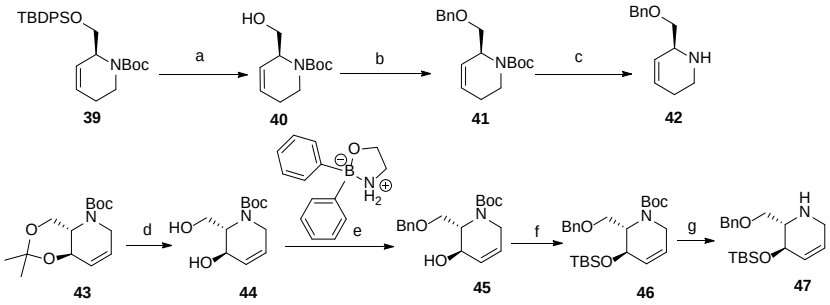
***tert*-Butyl (2*R*,3*R*)-3-hydroxy-2-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (34).** Compound **33** was prepared according to the reported methods.[28] To a solution of compound **33** (790 mg, 2.92 mmol) in MeOH (25 mL) was added catalytic amount of *p*-TsOH (27.8 mg, 0.146 mmol). The reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. The reaction mixture was evaporated under reduced pressure and the residue was purified by flash chromatography to furnish title compound *tert*-butyl (*2R,3R*)-3-hydroxy-2-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (576 mg, 2.51 mmol, 86% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (br, *J* = 12.0 Hz, 1H), 5.69 (d, *J* = 12.0 Hz, 1H), 4.68 – 4.57 (m, 2H), 4.16 – 4.04 (m, 1H), 4.00 – 3.98 (m, 1H), 3.61 (dd, *J* = 11.3, 6.7 Hz, 1H), 3.51 (d, *J* = 16.5 Hz, 1H), 3.02 (br, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.03, 128.19, 124.16, 80.79, 66.91, 60.43, 53.37, 40.94, 28.50. LC-MS m/z: calculated for $C_{11}H_{19}NO_4$ $[M+H]^+$ 230.28, found: 230.86.

***tert*-Butyl (*2R,3R*)-2-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate (35)**. 2-Aminoethylborinate (10mol%), compound **34** (250 mg, 1.09 mmol), KI (217 mg, 1.31 mmol) and K_2CO_3 (181 mg, 1.31 mmol) were transferred to a 2-dram vial containing a magnetic stir bar. The vial was then sealed with a septum and purged with argon. Anhydrous acetonitrile was added to the flask, followed by benzyl bromide (0.233 mL, 1.96 mmol). The resulting mixture was stirred at 60 ^{o}C for 24h. The mixture was then transferred to a separation funnel containing water and ethyl acetate, the organic layer was separated, and the aqueous layer was extracted two more times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The resulting crude material was purified by silica gel chromatography (pentane/EtOAc 10:1 → 2:1) to furnish title compound (310 mg, 0.972 mmol, 89% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 5.73 (d, *J* = 10.4 Hz, 1H), 5.65 (br, 1H), 4.91 (br, 1H), 4.59 – 4.49 (m, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.08 (br, 1H), 3.85 – 3.73 (m, 1H), 3.72

– 3.33 (m, 3H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.11, 137.89, 128.68, 128.41, 127.73, 127.63, 123.92, 80.32, 73.08, 66.21, 65.93, 50.01, 40.73, 28.46. LC-MS m/z: calculated for $C_{18}H_{25}NO_4$ $[M+H]^+$ 320.40, found: 320.76.

***tert*-Butyl (*2R,3R*)-2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)- 3,6-dihydropyridine-1(2*H*)-carboxylate (36).** Imidazole (243 mg, 3.57 mmol) and TBS-Cl (484 mg, 3.21 mmol) were added to a stirred solution of *tert*-butyl (*2S,3R*)-2-((benzyloxy)methyl)- 3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate **35** (570 mg, 1.79 mmol) in DMF with ice cooling, and stirred at room temperature for 2h. The reaction mixture was quenched with water, and extracted with EtOAc (3 x 50 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (pentane/EtOAc 100:1 →10:1) to furnish the title compound (735 mg, 1.70 mmol, 95% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.70 – 5.57 (m, 2H), 5.03 – 4.84 (m, 1H), 4.79 – 4.41 (m, 3H), 4.32 – 4.22 (m, 0.5H), 4.12 – 4.03 (m, 0.5H), 3.77 – 3.70 (m, 1H), 3.64 – 3.52 (m, 1H), 3.53 – 3.41 (m, 1H), 1.53 (s, 9H), 0.94 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.34, 138.63, 129.08, 128.34, 127.73, 127.52, 124.54, 79.86, 72.60, 66.18, 65.12, 53.81, 40.48, 28.47, 25.85, 18.11, -4.69, -4.84. LC-MS m/z: calculated for $C_{24}H_{39}NO_4$ Si $[M+H]^+$ 434.66, found: 434.12.

(*2R,3R*)-2-((Benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydro pyridine (37). To a solution of compound **36** (540 mg, 1.25 mmol) was added 10% TFA in DCM (5mL) in DCM with ice cooling. The reaction mixture was stirred at r.t. for 0.5h. The reaction mixture was co-evaporated with toluene (3 x 20 mL), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$. Concentration under reduced pressure afforded the crude product (290 mg, 0.871 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 4H), 7.30 – 7.28 (m, 1H), 5.88 – 5.79 (m, 2H), 4.53 (s, 2H), 4.14 – 4.07 (m, 1H), 3.54 – 3.51 (m, 2H), 3.38 – 3.34 (m, 1H), 3.32 (d, *J* = 4.0 Hz, 1H), 2.99 (dt, *J* = 4.0 Hz, 8.0 Hz, 1H), 2.94 – 2.87 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.39, 130.42, 128.48, 128.18, 128.01, 127.74, 73.58, 70.37, 63.46, 57.38, 44.90, 26.01, 18.21, -3.89, -4.72. LC-MS m/z: calculated for $C_{19}H_{31}NO_2Si$ $[M+H]^+$ 334.55, found: 334.92.



Scheme 3. Synthesis of key intermediates **42** and **47**. Reagents and conditions: (a) TBAF, THF, r.t. 92%; (b) BnBr, TBAI, NaH, DMF, 87%; (c) 25% TFA (v/v), DCM, r.t., 82%; (d) cat. *p*-TsOH, MeOH, 84%; (e) BnBr, KI, MeCN, 60 °C, 90%; (f) TBSCl, imidazole, DMF, 95%; (g) 10% TFA, DCM, 0 °C, 71%.

***tert*-Butyl (*S*)-6-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (40)**. The title compound was synthesized from compound **39** (596 mg, 1.32 mmol) according to the procedures described for compound **21**. This furnished title compound (196 mg, 0.920 mmol, 92% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.89 – 5.77 (m, 1H), 5.57 (dt, *J* = 10.2, 2.8 Hz, 1H), 4.39 (br s, 1H), 3.96 (br s, 1H), 3.54 (d, *J* = 6.4 Hz, 2H), 3.33 (br s, 1H), 2.84 (br s, 1H), 2.08 (br s, 1H) 1.86 (dt, *J* = 16.0 Hz, 4.0Hz, 1H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.67, 127.20, 125.01, 79.87, 64.33, 53.93, 38.13, 28.32, 24.75. LC-MS m/z: calculated for $C_{11}H_{19}NO_3$ $[M+H]^+$ 214.28, found: 214.65.

***tert*-Butyl (*S*)-6-((benzyloxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (41)**. The title compound was synthesized from alcohol **40** (360 mg, 1.69 mmol) according to the procedures described for compound **22**. This furnished title compound (446 mg, 1.47 mmol, 87% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.21 (m, 5H), 5.93 (br, 1H), 5.74 (d, *J* = 12.0 Hz, 1H), 4.58 – 4.50 (m, 3H), 4.19 – 4.06 (m, 1H), 3.56 (br, 2H), 3.04 – 2.83 (m, 1H), 2.19 (br, 1H), 1.97 (d, *J* = 12.0 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz,) δ 154.74, 138.53, 128.43, 127.60, 127.55, 126.92, 125.99, 79.74, 73.14, 71.43, 51.96, 37.17, 28.56, 25.03. LC-MS m/z: calculated for $C_{18}H_{25}NO_3$ $[M+H]^+$ 304.40, found: 303.89.

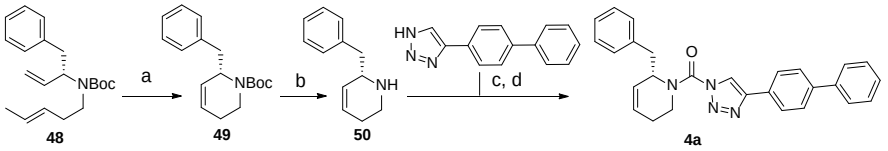
(*S*)-6-((Benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (42). The title compound was synthesized from **41** (500 mg, 1.65 mmol) according to the procedures described for compound **23**. This furnished (*S*)-6-((benzyloxy)methyl)-1,2,3,6-tetrahydropyridine (275 mg, 1.35 mmol, 82% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 4H), 7.19 – 7.23 (m, 1H), 5.86 - 5.81 (m, 1H), 5.54 – 5.50 (m, 1H), 4.52 (d, *J* = 8.0 Hz, 2H), 3.59 – 3.55 (m, 1H), 3.46 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.38 (app. t, *J* = 8.0 Hz, 1H), 3.07 – 3.01 (m, 1H), 2.86 – 2.79 (m, 1H), 2.36 (br s, 1H), 2.21 – 2.11(m, 1H), 2.06 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.10, 128.25, 127.59, 127.49, 127.47, 126.66, 73.42, 73.19, 53.64, 41.15, 25.81. LC-MS m/z: calculated for $C_{13}H_{17}NO$ $[M+H]^+$ 204.29, found: 204.88.

***tert*-Butyl (*2S,3R*)-3-hydroxy-2-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (44)**. Compound **43** was prepared according to the literature reported method.[28] The title compound was synthesized from **43** (280 mg, 1.1 mmol) and *p*-TsOH (28.0 mg, 0.15 mmol), according to the procedures described for compound **34**. This furnished title compound (200 mg, 0.87 mmol, 84% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.81 (m, 1H), 5.77 (br, 1H), 4.38 – 4.28 (m, 1H), 4.12 (br, 2H), 3.89 (br, 2H), 3.53 – 3.33 (m, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.28, 127.16, 124.51, 80.31, 62.76, 60.64, 57.79, 41.08, 28.33. LC-MS m/z: calculated for $C_{11}H_{19}NO_4$ $[M+H]^+$ 230.28, found: 230.59.

***tert*-Butyl (*2S,3R*)-2-((benzyloxy)methyl)-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate (45)**. Title compound was synthesized from compound **44** (280 mg, 1.22 mmol), benzyl bromide (0.140 mL, 1.18 mmol), KI (130 mg, 0.79 mmol) and K_2CO_3 (109 mg, 0.79 mmol), according to the procedures described for the preparation of compound **35**. This furnished title compound (188 mg, 0.590 mmol, 90% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.13 (m, 5H), 5.89 (br, 1H), 5.84 (br, 1H), 4.80 – 4.38 (m, 3H), 4.24 (br, 1H), 4.09 (br, 1H), 3.49 – 3.31 (m, 3H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.72, 138.10, 128.30, 127.93, 127.56, 127.49, 124.72, 80.09, 72.73, 67.80, 63.56, 56.46, 40.19, 28.36. LC-MS m/z: calculated for $C_{18}H_{25}NO_4$ $[M+H]^+$ 320.40, found: 320.08.

***tert*-Butyl (*2S,3R*)-2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-3,6-dihydro pyridine-1(2*H*)-carboxylate (46)**. The title compound was synthesized from compound **45** (570 mg, 1.78 mmol), and TBS-Cl (480 mg, 3.21 mmol), according to the procedures described for compound **36**. This furnished title compound (740 mg, 1.70 mmol, 95% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 5H), 5.79 (d, *J* = 11.4 Hz, 2H), 4.66 – 4.47 (m, 3H), 4.34 (br d, *J* = 20.0 Hz 1H), 4.19 (br, 1H), 3.37 (m, 3H), 1.46 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.40, 138.29, 128.32, 127.56, 127.38, 127.20, 124.66, 79.58, 72.72, 68.21, 64.35, 56.50, 39.94, 28.41, 25.91, 18.26, -4.36, -4.54. LC-MS m/z: calculated for $C_{24}H_{39}NO_4Si$ $[M+H]^+$ 434.66, found: 434.89.

(*2S,3R*)-2-((Benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6-tetrahydro pyridine (47). The title compound was synthesized from compound **46** (210 mg, 0.484 mmol) according to the procedures described for compound **37**. This furnished crude product (120 mg, 0.344 mmol, 71% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 4H), 7.38 – 7.32 (m, 1H), 5.85 – 5.80 (m, 1H), 5.71 (dd, *J* = 10.2, 2.1 Hz, 1H), 4.70 – 4.53 (m, 2H), 4.18 (d, *J* = 8.2 Hz, 1H), 3.80 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.60 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.53 – 3.45 (m, 1H), 3.37 – 3.31 (m, 1H), 2.85 – 2.81 (m, 1H), 2.61 (br, 1H), 0.95 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.17, 130.30, 128.44, 127.89, 127.84, 127.73, 73.47, 71.06, 66.61, 59.02, 44.66, 29.72, 25.87, -4.09, -4.76. LC-MS m/z: calculated for $C_{19}H_{31}NO_2Si$ $[M+H]^+$ 334.55, found: 334.68.



Scheme 4. Enantioselective synthesis of compound **4a**. Reagents and conditions: (a) Grubbs I cat. 4 mol %, DCM, reflux, 48h; (b) 25% TFA, DCM; (c) DIPEA, Triphosgene, THF, 0 °C; (d) DIPEA, DMAP, triazole , THF, 60 °C.

***tert*-Butyl (*S*)-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate (49)**. The title compound was prepared according to the literature reported method as depicted in S.Scheme 2. In brief, the diene **48** (425 mg, 1.35 mmol) was dissolved in DCM (10 mL) and purged with argon. After the addition of Grubb's 1st generation catalyst (42.0 mg, 0.050 mmol, 3.6 mol%) and refluxing overnight TLC analysis confirmed complete conversion. The solvent was evaporated and the crude product purified by silica gel column chromatography using pentane : EtOAc = 97 : 3 as the eluent to afford the title compound (252 mg, 0.920 mmol, 68% yield). $[\alpha]_D^{21}$ = +161 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.1802; found: 274.1802. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.28 – 7.21 (m, 2H), 7.20 – 7.14 (m, 3H), 5.79 (dd, *J* = 10.3, 6.1 Hz, 1H), 5.54 (dt, *J* = 10.3, 3.3 Hz, 1H), 4.54 (s, 1H), 4.11 (s, 1H), 2.89 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.15 (m, 1H), 1.88 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, 60 °C) δ 154.28, 138.23, 129.36, 128.10, 127.94, 126.06, 125.38, 79.17, 53.47, 40.20, 36.30, 28.29, 24.85.

(*S*)-6-Benzyl-1,2,3,6-tetrahydropyridine (50). Boc-protected compound **49** (100 mg, 0.366 mmol) was added 25% TFA in DCM (5 mL), the reaction mixture was stirred at r.t. for 0.5h. The reaction mixture was co-evaporated with toluene (3 x 20 mL). The residue was diluted with ethyl acetate, washed with 10% Na_2CO_3, water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **50** was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 5.85 – 5.74 (m, 1H), 5.70 – 5.54 (m, 1H), 3.56 – 3.53 (m, 1H), 3.07 – 3.03 (m, 1H), 2.85 – 2.73 (m, 2H), 2.71 – 2.65 (m, 1H), 2.27 – 2.13 (m, 1H), 2.03 (br, 1H), 1.99 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.99, 130.34, 129.30, 128.47, 126.32, 126.13, 55.46, 42.61, 42.15, 25.91.

***tert*-Butyl (*R*)-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate (51)**. The title compound was prepared as described for the preparation of **49**, and afforded compound **51** (491 mg, 1.80 mmol). $[\alpha]_D^{21}$ = -172 (c =1.0 $CHCl_3$). HRMS calculated for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.1802; found: 274.1803. IR 2974, 2926, 1690, 1454, 1416, 1391, 1364, 1337, 1279, 1250, 1171, 1107. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.08 (m, 5H), 5.81 (s, 1H), 5.63 – 5.48 (m, 1H), 4.68 – 4.42 (m, 1H), 4.33 – 3.94 (m, 1H), 2.99 – 2.82 (m, 1H), 2.84 – 2.67 (m, 2H), 2.19 (m, 1H), 2.02 – 1.83 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.34, 138.25, 129.40, 128.22, 127.70, 126.15, 125.63, 79.33, 53.84, 40.27, 35.87, 28.29, 24.85.

(*R*)-6-Benzyl-1,2,3,6-tetrahydropyridine (52). The title compound was prepared as described for **50** from *tert*-butyl (*R*)-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate (130 mg, 0.476 mmol). The crude product was obtained that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.25 – 7.15 (m, 3H), 5.81 – 5.76 (m, 1H), 5.65 – 5.61 (m, 1H), 3.56 – 3.50 (m, 1H), 3.06 - 3.01 (m, 1H), 2.85 – 2.72 (m, 2H), 2.72 – 2.49 (m, 1H), 2.28 – 2.07 (m, 1H), 1.99 – 1.90 (m, 1H), 1.88 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.95, 130.32, 129.22, 128.39, 126.24, 126.05, 55.40, 42.58, 42.10, 25.88.

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