Supporting Information

Disubstituted bis-THF moieties as new P2 ligands in non-peptidal HIV-1 Protease Inhibitors

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1 Table of HPLC retention times and purity data

Compound	System A		System B	
	R _t (min)	Purity (%)	R _t (min)	Purity (%)
3a	-	-	0.97	88
3b	8.20	100	1.14	99
3c	9.40	100	1.26	98
3d	9.28	93	1.25	96
3e	-	-	1.16	99
3j	-	-	1.13	99
4a	-	-	1.04	97
4b	8.83	100	1.20	99
4c	-	-	1.26	96
4d	9.73	100	1.30	100
4e	9.43	100	1.22	99
4f	8.18	100	1.07	97
4g	8.36	96	1.09	94
4h	-	-	1.19	99
4i	-	-	1.23	78
4j	-	-	1.19	92
4k	-	-	1.11	95
5a	8.90	100	1.17	99
5e	-	-	1.27	99
5f	-	-	1.13	96
5g	-	-	1.16	98

System A (LC/MS):

HPLC: mobile phase: A: 0.1 % formic acid in 95 % H₂O and 5 % MeOH; B: pure MeOH.

Column: X Terra MS C18, 3.5 µm, 4.6 x 100 mm, 40 °C. Flow: 1.5 ml/min.

Gradient Timetable: 0 min (100 % A), 12.0 min (5 % A, 95 % B), 13.0 min (100 % A).

MS: Ion mode: ES+/ES-; Mass: 100 – 1500 m/z

System B (UPLC/MS):

UPLC: mobile phase: A: pure MeOH; B: 10 mM NH₄OAc in 90 % H₂O and 10 % MeCN.

Column: Aquity UPLC BEH C18, 1.7 µm, 2.1 x 50 mm, 70 °C. Flow: 0.7 ml/min.

Gradient Timetable: 0 min (5 % A, 95 % B), 1.3–1.5 min (95 % A, 5 % B), 1.7–2.0 min (5 % A, 95 % B)

MS: Ion mode: ES+/ES-; Mass: 160 – 1000 m/z

2 Crystallographic data

2.1 X-RAY STRUCTURE DETERMINATION DETAILS

Production of the protease material and co-crystallization of the PI with the protease was performed at +4 °C by hanging drop procedure according to the procedures described earlier.¹ Crystals belonged to the space group P21212.

X-ray data were recorded on MarResearch CCD-detectors on the synchrotron beam lines at I911-2 and I911-3 at MAX IV Laboratory in Lund, Sweden. Data processing and scaling was performed with MOSFLM² and SCALA from the CCP4 program suite.³ The structure was built in COOT⁴ and refined with the CCP4 programs. Figures were made in Swiss-PdbViewer⁵ and rendered in MOV-ray.⁶

¹ Andersson, H. O.; Fridborg, K.; Lowgren, S.; Alterman, M.; Muhlman, A.; Bjorsne, M.; Garg, N.; Kvarnstrom, I.; Schaal, W.; Classon, B.; Karlen, A.; Danielsson, U. H.; Ahlsen, G.; Nillroth, U.; Vrang, L.; Oberg, B.; Samuelsson, B.; Hallberg, A.; Unge, T. Optimization of P1-P3 groups in symmetric and asymmetric HIV-1 protease inhibitors. *Eur. J. Biochem.* **2003**, 270 (8), 1746-1758.

² Leslie, A. G. W. Integration of macromolecular diffraction data. *Acta Crystallogr. D* **1999**, 55, 1696-1702.

³ Bailey, S. The CCP4 Suite - Programs for Protein Crystallography. *Acta Crystallogr. D* **1994**, 50, 760-763.

⁴ Emsley, P.; Cowtan, K. Coot: model-building tools for molecular graphics. *Acta Crystallogr. D* **2004**, 60, 2126-2132.

⁵ Guex, N.; Peitsch, M. C. SWISS-MODEL and the Swiss-PdbViewer: An environment for comparative protein modeling. *Electrophoresis* **1997**, 18 (15), 2714-2723.

⁶ Persistence of Vision Pty. Ltd. (2004); Persistence of Vision Raytracer (Version 3.6). Retrieved from <http://www.povray.org/download/>

PI-Protease complex (Space group P2 ₁ 2 ₁ 2)								
PI:	3b	3j	4b	4f	4h	4i	4j	5f
PDB ID:	5AH9	5AH7	5AHA	5AHB	5AGZ	5AH8	5AH6	5AHC
Data collection								
Wavelength (Å)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cell axes lengths (Å)	a=58.38 b=85.64 c=46.02	a=58.39 b=85.89 c=46.28	a=58.38 b=85.96 c=46.44	a=58.49 b=85.93 c=46.36	a=58.41 b=85.96 c=46.44	a=58.45 b=85.72 c=46.35	a=58.29 b=86.18 c=46.40	a=58.49 b=86.09 c=46.20
Resolution range (Å)	25.6- 2.2	24.3- 1.0	48.3- 1.35	24.4- 1.50	48.3-1.20	20.9- 1.40	24.4-1.55	25.8- 1.50
No. of unique reflections	12 225	38 007	52 438	38 129	74183	45781	34 655	38 090
Multiplicity	7.2	4.7	6.2	5.6	4.5	4.5	3.7	4.8
Completeness (%)	99.9	98.1	100.0	87.3	99.2	98.4	99.7	99.7
R _{merge} (%)	8.9	8.3	8.2	10.1	8.6	8.7	10.0	12.4
R _{p.i.m.} (%)	4.4	3.7	2.8	4.1	3.0	5.3	5.1	5.7
<I>/s(<I>)	6.5	6.1	5.8	5.7	4.4	7.0	2.7	2.6
Refinement								
% free reflections(R _{free})	5.1	5.1	5.0	5.00	5.0	4.96	5.1	5.04
R _{conv.} (%)	19.3	19.9	20.9	19.5	21.5	20.6	21.34	20.5
R _{free.} (%)	21.5	22.5	22.5	21.8	23.3	22.1	23.8	22.8
R.m.s. bond length	0.006	0.007	0.008	0.006	0.039	0.071	0.006	0.004
R.m.s. angles	1.1	1.05	1.2	1.0	2.5	1.2	0.94	1.0
No.of atom positions (no solvent)	1600	1598	1608	1608	1624	1614	1610	1602
No.of solvent atom positions	290	290	290	290	290	290	290	290

3 Additional experimental procedures and spectroscopic data

3.1 General experimental Methods

All chemical reagents were obtained from commercial sources and used without further purification. THF was distilled from Na/benzophenone immediately prior use. CH₂Cl₂ and Et₃N were dried over CaH₂. Extra dry DMF and DMSO (H₂O < 50 ppm) were purchased from commercial sources. All glassware was flame-dried under vacuum and cooled under N₂ prior to use. Water or air sensitive reactions were performed under inert atmosphere, using dry solvents.

Reactions were monitored by TLC (MERCK Kieselgel 60 F₂₅₄, aluminium sheet). Detection was carried out by UV or by using one of the following dying reagents. *Anisaldehyde-reagent*: A solution of 5.1 mL *p*-anisaldehyde, 2.1 mL AcOH and 6.9 mL H₂SO₄ in 186 mL EtOH gives a reagent that will show coloured spots on the TLC after treatment with the heat gun. *KMnO₄-reagent*: A solution of 3 g KMnO₄, 20 g K₂CO₃ and 5 mL NaOH (aq., 5 w%) in 300 mL H₂O gives a reagent that will show yellow spots on the TLC after development with the heat gun.

Flash column chromatography was performed on silica gel (Merck silica gel 60, particle size 40–63 µm). All reported solvent mixtures are volume measures.

NMR spectra were recorded on a BRUKER AV300 [300.13 MHz (¹H NMR) and 75.47 MHz (¹³C NMR)] or a BRUKER DPX400 [400.13 MHz (¹H NMR) and 100.61 MHz (¹³C NMR)], respectively. The chemical shift (δ) is given in ppm using the residual solvent peak as an internal standard. The coupling constants (*J*) are given in Hertz (Hz). The splitting of the ¹H NMR signals was designated as follows: s... singlet, d... doublet, dd... doublet of doublets, ddd... doublet of doublets of doublets, t... triplet, dt... doublet of triplets, td... triplet of doublets, q... quartet, m... multiplet and br... broad

IR spectra were recorded on a Nicolet 380 FT-IR as a film. Absorption peaks are given in cm⁻¹ and the intensities were designated as follows: w... weak, m... medium, s... strong, vs... very strong and br... broad.

Optical rotation was measured on an OPTICAL ACTIVITY POLAAR 2001 at 589 nm. Melting points were measured on a GALLENKAMP melting point apparatus and are uncorrected. Low resolution electrospray mass spectra were recorded with a WATERS ZMD single quadrupol system. HRMS were measured on a BRUKER APEX III FT-ICR-MS system.

3.2 GENERAL PROCEDURES

General Procedure A: Parikh-Döring oxidation⁷

To a solution of Et₃N (3.7 equiv) in CH₂Cl₂/DMSO (5 mL/mmol, v/v 1:1) at 0 °C is added SO₃·pyridine (3 equiv) and the resulting mixture is stirred at 0 °C for 15 min. This mixture is then added dropwise over a period of 2–10 min via cannula to a solution of the corresponding alcohol (1 equiv) in CH₂Cl₂/DMSO (10 mL/mmol, v/v 2:1) at –10 °C. The reaction is stirred at –20 to 0 °C for 4 to 6 h and monitored by TLC. After completion, the mixture is poured into sat. aq. NH₄Cl/H₂O/petroleum ether (10 mL/mmol, v/v 1:1:2). The layers are separated and the aqueous phase is extracted with petroleum ether (3 × 5 mL/mmol). The combined organic layers are dried over anhydrous Na₂SO₄, filtered and the solvent is removed in vacuo to afford the desired ketone/aldehyde after purification by column chromatography.

⁷ Parikh, J. R.; Doering, W. v. E. Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. *J. Am. Chem. Soc.* **1967**, 89, 5505–5507.

General Procedure B: DDQ Oxidation⁸

To a solution of the PMB-ether in CH₂Cl₂/H₂O (10 mL/mmol, 18:1, v/v) is added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1.10 equiv) and the resulting mixture is stirred at rt for 4-6 h. After completion CH₂Cl₂ (10 mL/mmol) and sat. aq. NaHCO₃ (5 mL/mmol) are added. The phases are separated and the aqueous layer is extracted with CH₂Cl₂ (3 × 10 mL/mmol). The combined organic phases are washed again with sat. aq. NaHCO₃ (5 mL/mmol) and brine (5 mL/mmol), dried over anhydrous Na₂SO₄, filtered and the solvent is removed in vacuo. The crude product is then purified by column chromatography.

General procedure C: Acetamide formation

To a solution of the desired amine or amine hydrochloride (3.0 equiv), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI, 1.5 equiv) and Et₃N (3 equiv) in CH₂Cl₂ (15 mL/mmol) at 0 °C is added hydroxybenzotriazole (HOBt, 1.4 equiv) and a solution of the corresponding acid in CH₂Cl₂ (5 mL/mmol). The cooling is removed and the resulting mixture is stirred at rt for 15 h. After completion, the reaction mixture is poured into aq. sat. NaHCO₃ (10 mL/mmol), the phases are separated and the aqueous phase is extracted with CH₂Cl₂ (2 × 10 mL/mmol). The combined organic phases are washed with aq. HCl (10 mL/mmol, 1 M), dried over anhydrous Na₂SO₄, filtered and the solvent is removed in vacuo. The crude product is purified by column chromatography.

General Procedure D: Activation with DSC^{9,10} or ClCO₂PNP

To a solution of the alcohol and Et₃N (2.0 equiv) in CH₂Cl₂ (15 mL/mmol) is added *N,N'*-disuccinimidyl carbonate (DSC, 1.5 equiv) or *p*-nitrophenyl chloroformate (PNPOCOCl, 1.5 equiv) and the resulting mixture is stirred at rt for 18–24 h. After completion the reaction is diluted with CH₂Cl₂ (15 mL/mmol) and sat. aq. NaHCO₃ (7 mL/mmol). The phases are separated and the aqueous phase is extracted with CH₂Cl₂ (3 × 10 mL/mmol). The combined organic phases are dried over anhydrous Na₂SO₄, filtered and the solvent is removed in vacuo. The crude product is then purified by column chromatography.

General Procedure E: PI formation

To a solution of the mixed carbonate (1.15 equiv) and Et₃N (2.0 equiv) in CH₂Cl₂ (10 mL/mmol) is added amine **7a-d** (1 equiv) and the resulting mixture is stirred at rt for 1–3 d. After completion CH₂Cl₂ (10 mL/mmol) and sat. aq. NaHCO₃ (5 mL/mmol) are added. The phases are separated and the aqueous layer is extracted with CH₂Cl₂ (3 × 10 mL/mmol). The combined organic phases are dried over anhydrous Na₂SO₄, filtered and the solvent is removed in vacuo. The crude product is purified by column chromatography and HPLC.

⁸ Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. Specific removal of *o*-methoxybenzyl protection by DDQ oxidation. *Tetrahedron Lett.* **1982**, 23, 885-888.

⁹ Takeda, K.; Akagi, Y.; Saiki, A.; Tsukahara, T.; Ogura, H. Convenient Methods for Syntheses of Active Carbamates, Ureas and Nitrosoureas Using *N,N'*-disuccinimido Carbonate (DSC). *Tetrahedron Lett.* **1983**, 24, 4569-4572.

¹⁰ Ogura, H.; Kobayashi, T.; Shimizu, K.; Kawabe, K.; Takeda, K. Novel active ester synthesis reagent (*N,N'*-disuccinimidyl carbonate). *Tetrahedron Lett.* **1979**, 20, 4745-4746.

3.3 Synthesis of amine 14 from alcohol 8

(1S,5S,6R)-6-(4-Methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octan-4-one (11)

Following General Procedure A (2.2), oxidation of alcohol **8** (1.42 g, 5.3 mmol) with SO_3 -pyridine (2.58 g, 15.9 mmol) afforded after purification by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) the *title compound* **11** as a colourless oil (1.30 g, 93%). Traces of mixed acetal **S1** could be isolated pure after reduction of **11**. **Formula** $\text{C}_{14}\text{H}_{16}\text{O}_5$; **Mw** 264.27; **R_f** 0.23 (petroleum ether/acetone 80:20); **[α]_D** -55.0 (c 0.75, CHCl_3 , 25 °C); **IR** (film) 2937 (w), 2838 (w), 1760 (s), 1612 (m), 1514 (s), 1248 (s), 1179 (m), 1110 (m), 1031 (s), 954 (m), 824 (m) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.26 (2 H, d, J = 8.7 Hz), 6.89 (2 H, d, J = 8.7 Hz), 5.99 (1 H, d, J = 5.1 Hz), 4.72 (1 H, d, J = 11.2 Hz), 4.44 (1 H, d, J = 11.2 Hz), 4.42 (1 H, dt, J = 9.3, 6.8 Hz), 4.29 (1 H, d, J = 16.7 Hz), 4.11 (1 H, dd, J = 9.5, 6.4 Hz), 4.09 (1 H, d, J = 16.7 Hz), 3.91 (1 H, dd, J = 9.5, 7.3 Hz), 3.91 (3 H, s), 3.19 (1 H, dd, J = 9.3, 5.1 Hz) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl_3) δ 209.8 (C), 159.5 (C_{ar}), 129.7 ($2 \times \text{CH}_{\text{ar}}$), 129.1 (C_{ar}), 113.9 ($2 \times \text{CH}_{\text{ar}}$), 108.1 (CH), 78.9 (CH), 73.5 (CH_2), 72.6 (CH_2), 71.2 (CH_2), 55.3 (CH_3), 52.3 (CH) ppm; **HRMS** (ESI^+) for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$)⁺ calcd 287.0890, found 287.0893.

Byproduct: (1S,4R,5R,6R)-6-(4-Methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octane-4-methylsulfanylmethoxy-bicyclo-[3.3.0]-octane (**S1**): **Formula** $\text{C}_{16}\text{H}_{22}\text{O}_5\text{S}$; **Mw** 326.41; **R_f** 0.46 (petroleum ether/acetone 80:20); **[α]_D** $+21.6$ (c 0.73, CHCl_3 , 24 °C); **IR** (film) 2921 (m, br), 1760 (s), 1612 (w), 1513 (m), 1246 (s), 1020 (vs) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.30 (2 H, d, J = 8.7 Hz), 6.91 (2 H, d, J = 8.7 Hz), 5.81 (1 H, d, J = 5.1 Hz), 4.75 (1 H, m), 4.65 (1 H, d, J = 11.7 Hz), 4.61 (1 H, d, J = 11.7 Hz), 4.59 (1 H, d, J = 11.2 Hz), 4.48 (1 H, d, J = 11.2 Hz), 4.24 (1 H, td, J = 8.5, 6.8 Hz), 4.05 (1 H, m), 4.01 (1 H, dd, J = 10.3, 3.5 Hz), 3.98 (1 H, dd, J = 9.2, 6.7 Hz), 3.82 (3 H, s), 3.81 (1 H, app. t, J = 8.5 Hz), 2.96 (1 H, m), 2.17 (3 H, s) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl_3) δ 159.5 (C_{ar}), 129.5 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 113.9 ($2 \times \text{CH}_{\text{ar}}$), 108.9 (CH), 76.7 (CH), 76.6 (CH), 74.3 (CH_2), 73.4 (CH_2), 72.4 (CH_2), 70.9 (CH_2), 55.3 (CH_3), 51.8 (CH), 14.0 (CH_3) ppm; **HRMS** (ESI^+) for $\text{C}_{16}\text{H}_{22}\text{O}_5\text{NaS}$ ($\text{M} + \text{Na}$)⁺ calcd 349.1080, found 349.1078.

(1S,4S,5S,6R)-6-(4-Methoxybenzyloxy)-4-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (12)

To a solution of ketone **11** (1.01 g, 4.1 mmol) in EtOH/THF (15 mL, v/v 2:1) at 0 °C was added sodium borohydride (170 mg, 4.5 mmol). The resulting mixture was stirred at 0 °C for 2 h. After completion, the reaction was quenched with citric acid (10 w% in water, 10 mL) and concentrated under reduced pressure. The residue was then partitioned between Et₂O and brine (20 mL each), and the aqueous phase was extracted with Et₂O (2 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20) afforded the *title compound* **12** as a colourless oil (1.07 g, 97%). **Formula** C₁₄H₁₈O₅; **Mw** 266.29; **R_f** 0.25 (petroleum ether/acetone 75:25); [**α**]_D +19.1 (*c* 0.72, CHCl₃, 24 °C); **IR** (film) 3478 (br, w), 2955 (br, w), 2860 (w), 1612 (m), 1514 (s), 1250 (s) cm⁻¹; **¹H NMR** (300 MHz, acetone-d₆) δ 7.34 (2 H, d, *J* = 8.8 Hz), 6.94 (2 H, d, *J* = 8.8 Hz), 5.49 (1 H, d, *J* = 5.6 Hz), 4.64 (1 H, d, *J* = 11.2 Hz), 4.58 (1 H, d, *J* = 11.2 Hz), 4.49 (1 H, ddd, *J* = 8.2, 6.9, 6.0 Hz), 4.38 (1 H, m, simplifies to dt, *J* = 7.3, 5.7 Hz after D₂O-exchange), 4.16 (1 H, d, *J* = 6.0 Hz, OH, disappears after D₂O-exchange), 3.99 (1 H, dd, *J* = 8.8, 6.9 Hz), 3.88 (1 H, dd, *J* = 8.8, 6.0 Hz), 3.80 (1 H, dd, *J* = 8.7, 5.7 Hz), 3.80 (3 H, s), 3.77 (1 H, dd, *J* = 8.7, 5.7 Hz), 2.92 (1 H, ddd, *J* = 8.2, 7.3, 5.6 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.8 (C_{ar}), 129.7 (2 × CH_{ar}), 128.5 (C_{ar}), 114.2 (2 × CH_{ar}), 108.8 (CH), 80.6 (CH), 74.5 (CH₂), 73.8 (CH), 72.9 (CH₂), 71.3 (CH₂), 55.3 (CH₃), 46.6 (CH) ppm; **HRMS** (ESI⁺) for C₁₄H₁₈O₅Na (M + Na)⁺ calcd. 289.1046, found 289.1044.

Methanesulfonic acid (1S,4S,5R,6R)-6-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octane-4-yl ester (13)

To a solution of alcohol **12** (1.62 g, 6.1 mmol) and Et₃N (2.50 mL, 18.2 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added dropwise methanesulfonyl chloride (720 μL, 9.1 mmol) and the resulting mixture was stirred at rt for 44 h. After completion, the reaction was diluted with CH₂Cl₂ (25 mL) and consecutively washed with water, sat. aq. NaHCO₃ and brine (15 mL each). The organic phase was dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:10 to 70:30) afforded the *title compound* **13** as a white solid (1.47 g, 70%). **Formula** C₁₅H₂₀O₇S; **Mw** 344.38; **R_f** 0.20 (petroleum ether/acetone 70:30); **Mp** 85 °C; [**α**]_D –31.4 (*c* 1.31, CHCl₃, 26 °C); **IR** (film) 2937 (w), 2904 (w), 1612 (m), 1514 (m), 1351 (s), 1247 (s), 1173 (vs), 1030 (s), 968 (s), 912 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.30 (2 H, d, *J* = 8.8 Hz), 6.89 (2 H, d, *J* = 8.7 Hz), 5.65 (1 H, d, *J* = 5.4 Hz), 5.25 (1 H, ddd, *J* = 7.1, 4.8, 4.0 Hz), 4.56 (1 H, d, *J* = 11.2 Hz), 4.51 (1 H, d, *J* = 11.2 Hz), 4.35 (1 H, dd, *J* = 9.9, 4.0 Hz), 4.34 (1 H, td, *J* = 7.6, 6.3 Hz), 4.05 (1 H, dd, *J* = 8.4, 7.7 Hz), 4.00 (1 H, dd, *J* = 9.9, 4.8 Hz), 3.95 (1 H, dd, *J* = 8.5, 6.4 Hz), 3.82 (3 H, s), 2.98 (1 H, td, *J* = 7.3, 5.4 Hz), 2.90 (3 H, s) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.5 (C_{ar}), 129.7 (2 × CH_{ar}), 129.4 (C_{ar}), 113.9 (2 × CH_{ar}), 108.0 (CH), 78.3 (CH), 77.9 (CH), 73.5 (CH₂), 73.0 (CH₂), 71.7 (CH₂), 55.3 (CH₃), 47.7 (CH), 38.2 (CH₃) ppm; **HRMS** (ESI⁺) for C₁₅H₂₀O₇SNa (M + Na)⁺ calcd 367.0822, found 367.0823.

(1R,4R,5S,6R)-4-Azido-6-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octane (S2)

To a solution of mesylate **13** (605 mg, 1.75 mmol) in THF (7 mL) was added trimethylsilyl azide (347 μL , 2.6 mmol) and TBAF (2.6 mL, 2.6 mmol, 1 M in THF).¹¹ The resulting mixture was heated to 70 $^\circ\text{C}$ and stirred for 20 h. After completion the solvent was removed under reduced pressure and the crude product was directly applied to column chromatography (petroleum ether/EtOAc 80:20 to 60:40) afforded the *title compound* **S2** as a colourless oil (398 mg, 78%). **Formula** $\text{C}_{14}\text{H}_{17}\text{O}_4\text{N}_3$; **Mw** 291.30; **R_f** 0.28 (petroleum ether/acetone 85:15); **[α]_D** +46.5 (c 1.44, CHCl_3 , 24 $^\circ\text{C}$); **IR** (film) 2954 (w), 2881 (w), 2094 (s), 1612 (m), 1513 (s), 1246 (vs), 1107 (s), 1025 (vs) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.26 (2 H, d, $J = 8.7$ Hz), 6.91 (2 H, d, $J = 8.7$ Hz), 5.79 (1 H, d, $J = 5.1$ Hz), 4.53 (1 H, d, $J = 11.3$ Hz), 4.49 (1 H, d, $J = 11.3$ Hz), 4.36 (1 H, dt, $J = 4.4, 1.6$ Hz), 4.25 (1 H, ddd, $J = 8.8, 7.9, 6.7$ Hz), 4.09 (1 H, dd, $J = 10.2, 4.5$ Hz), 4.00 (1 H, m), 3.97 (1 H, dd, $J = 9.3, 6.7$ Hz), 3.83 (3 H, s), 3.62 (1 H, dd, $J = 9.3, 7.8$ Hz), 2.93 (1 H, ddt, $J = 8.8, 5.1, 1.3$ Hz) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl_3) δ 159.6 (C_{ar}), 129.4 (CH_{ar}), 129.2 (C_{ar}), 114.0 (CH_{ar}), 108.6 (CH), 76.4 (CH), 74.0 (CH_2), 72.5 (CH_2), 70.9 (CH_2), 61.3 (CH), 55.3 (CH_3), 51.9 (CH) ppm; **HRMS** (ESI^+) for $\text{C}_{14}\text{H}_{17}\text{O}_4\text{N}_3\text{Na}$ ($\text{M} + \text{Na}$)⁺ calcd 314.1111, found 314.1108.

(1R,4R,5S,6R)-4-Amino-6-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octane (14)

To a solution of azide **S2** (393 mg, 1.35 mmol) in dry EtOH (7 mL) under N_2 was added Pd/C (40 mg, 10 w%, 10% Pd). The flask was then put under H_2 -atmosphere and the reaction was stirred at rt for 20 h. After completion the reaction mixture was filtered over celite and the filtercake was washed with EtOH. The solvent was removed in vacuo to afford the *title compound* **14** as a colourless oil (355 mg, 99%). **Formula** $\text{C}_{14}\text{H}_{19}\text{NO}_4$; **Mw** 265.31; **R_f** 0.15 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90:10); **[α]_D** +3.6 (c 0.79, CH_2Cl_2 , 23 $^\circ\text{C}$); **IR** (film) 3330 (br. w), 2954 (br. m), 2877 (m), 1612 (m), 1514 (vs), 1247 (vs), 1111 (s), 1030 (vs) 820 (m) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.27 (2 H, d, $J = 8.7$ Hz), 6.90 (2 H, d, $J = 8.7$ Hz), 5.78 (1 H, d, $J = 5.1$ Hz), 4.54 (1 H, d, $J = 11.4$ Hz), 4.50 (1 H, d, $J = 11.4$ Hz), 4.21 (1 H, td, $J = 8.4, 6.9$ Hz), 4.07 (1 H, dd, $J = 9.2, 4.7$ Hz), 3.96 (1 H, dd, $J = 9.0, 6.8$ Hz), 3.86 (1 H, dt, $J = 4.4, 1.9$ Hz), 3.82 (3 H, s), 3.69 (1 H, dd, $J = 9.1, 2.1$ Hz), 3.61 (1 H, dd, $J = 9.0, 8.7$ Hz), 2.63 (1 H, ddt, $J = 8.4, 5.1, 1.5$ Hz), 1.41 (2 H, br. s, NH_2) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl_3) δ 159.5 (C_{ar}), 129.8 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 114.0 ($2 \times \text{CH}_{\text{ar}}$), 108.9 (CH), 77.8 (CH_2), 77.2 (CH), 72.4 (CH_2), 70.8 (CH_2), 55.3 (CH_3), 55.2 (CH), 52.1 (CH) ppm; **HRMS** (ESI^+) for $\text{C}_{14}\text{H}_{20}\text{NO}_4$ ($\text{M} + \text{H}$)⁺ calcd 266.1387, found 266.1387.

¹¹ Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. Azide and Cyanide Displacements via Hypervalent Silicate Intermediates†. *J. Org. Chem.* **1999**, 64, 3171-3177.

3.4 Synthesis of ligands 6c-k

N-(1*R*,4*R*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl carbamic acid benzyloxy ester (**S3**)

To a solution of amine **14** (172 mg, 0.65 mmol), DMAP (20 mg, 0.16 mmol) and pyridine (158 μ L, 1.95 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise benzyl chloroformate (138 μ L, 0.98 mmol) and the resulting mixture was stirred at rt for 2 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and sat. aq. NaHCO_3 (10 mL each). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with 2M HCl and brine (5 mL each), dried over anhydrous Na_2SO_4 , filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 75:25) afforded the *title compound* **S3** as a colourless oil (232 mg, 90%). **Formula** $\text{C}_{22}\text{H}_{25}\text{NO}_6$; **Mw** 399.44; **R_f** 0.25 (petroleum ether/acetone 80:20); **[α]_D** +30.5 (*c* 0.51, CHCl_3 , 22 °C); **IR** (film) 3323 (br. w), 2953 (w), 2886 (w), 1715 (s), 1612 (m), 1514 (s), 1246 (vs), 1084 (m), 1027 (s) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.40–7.29 (7 H, m), 6.90 (2 H, d, J = 8.3 Hz), 5.76 (1 H, d, J = 5.1 Hz), 5.22–5.04 (3 H, m), 4.72 (1 H, d, J = 11.0 Hz), 4.63 (1 H, dd, J = 7.5, 4.5 Hz), 4.49 (1 H, d, J = 11.2 Hz), 4.24 (1 H, dt, J = 8.0, 7.8 Hz), 4.06 (1 H, dd, J = 9.8, 4.4 Hz), 3.97 (1 H, dd, J = 9.3, 6.9 Hz), 3.86 (1 H, m, J = 10.5 Hz can be observed), 3.81 (3 H, s), 3.58 (1 H, t, J = 8.7 Hz), 2.83 (1 H, dd, J = 8.1, 5.6 Hz) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl_3) δ 159.5 (C_{ar}), 155.6 (C), 136.2 (C_{ar}), 129.6 ($2 \times \text{CH}_{\text{ar}}$), 129.5 (C_{ar}), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 128.3 (CH_{ar}), 128.1 ($2 \times \text{CH}_{\text{ar}}$), 114.0 ($2 \times \text{CH}_{\text{ar}}$), 108.7 (CH), 76.6 (CH), 75.1 (CH_2), 72.3 (CH_2), 71.4 (CH_2), 66.9 (CH_2), 55.3 (CH_3), 52.90 (CH), 52.88 (CH) ppm; **HRMS** (ESI^+) for $\text{C}_{22}\text{H}_{25}\text{NO}_6\text{Na}$ ($\text{M} + \text{Na}$)⁺ calcd 422.1571, found 422.1570.

N-(1*R*,4*R*,5*S*,6*R*)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl carbamic acid benzyloxy ester (**6c**)

Following General Procedure **B** (2.2), deprotection of ether **S3** (195 mg, 0.49 mmol) with DDQ (140 mg, 0.61 mmol) afforded after purification of by column chromatography (petroleum ether/acetone 75:25 to 65:35) the *title compound* **6c** as a colourless oil (123 mg, 88%). **Formula** $\text{C}_{14}\text{H}_{17}\text{NO}_5$; **Mw** 279.29; **R_f** 0.25 (petroleum ether/acetone 70:30); **[α]_D** +16.7 (*c* 0.62, CHCl_3 , 22 °C); **IR** (film) 3960 (br. m) 3312 (br. m), 1690 (vs), 1534 (s), 1256 (s), 1104 (br. s), 1008 (s) cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.42–7.30 (5 H, m), 5.75 (1 H, d, J = 5.3 Hz), 5.16 (1 H, d, J = 6.5 Hz), 5.13 (1 H, d, J = 12.3 Hz), 5.09 (1 H, d, J = 12.3 Hz), 4.60–4.51 (2 H, m), 4.18 (1 H, dd, J = 9.8, 5.7 Hz), 4.05 (1 H, dd, J = 9.2, 6.8 Hz), 3.77 (1 H, dd, J = 9.9, 2.8 Hz), 3.66–3.60 (2 H, m), 2.83 (1H, ddd, J = 7.8, 5.5, 1.9 Hz) ppm; **^{13}C NMR**

+ **DEPT** (100 MHz, CDCl₃) δ 156.3 (C), 136.0 (C_{ar}), 128.6 (2 $\times$ CH_{ar}), 128.4 (CH_{ar}), 128.1 (2 $\times$ CH_{ar}), 109.1 (CH), 73.6 (CH₂), 72.9 (CH₂), 70.0 (CH), 67.2 (CH₂), 55.3 (CH), 51.5 (CH) ppm; **HRMS** (ESI⁺) for C₁₄H₁₇NO₅Na (M + Na)⁺ calcd 302.0999, found 302.1002.

Benzyl carbamic acid (1*S*,4*R*,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (S4)

To a solution of alcohol **8** (475 mg, 1.78 mmol) and Et₃N (745 μ L, 5.36 mmol) in CH₂Cl₂ (10 mL) was then added *N,N'*-disuccinimidyl carbonate (685 mg, 2.68 mmol) and the resulting mixture was stirred at rt for 5 h. When the TLC revealed the absence of starting material, benzylamine (585 μ L, 5.36 mmol) was added dropwise and the resulting mixture was stirred at rt for further 24 h. After completion CH₂Cl₂ (20 mL) and sat. aq. NaHCO₃ (5 mL) were added, and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic phases were washed with sat. aq. NH₄Cl (5 mL) and brine (5 mL), dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20 to 75:25) afforded the *title compound* **S4** as a yellow oil (605 mg, 85%). **Formula** C₂₂H₂₅NO₆; **Mw** 399.44; **R_f** 0.38 (petroleum ether/acetone 75:25); [α]_D +26.4 (*c* 0.63, CHCl₃, 27 °C); **IR** (film) 3333 (br. w), 2953 (w), 2880 (w), 1717 (s), 1612 (m), 1514 (s), 1247 (vs), 1128 (m), 1107 (m), 1028 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.39–7.28 (7 H, m), 6.89 (2 H, d, *J* = 8.7 Hz), 5.81 (1 H, d, *J* = 5.3 Hz), 5.54 (1 H, d, *J* = 2.6 Hz), 5.05 (1 H, m), 4.71 (1 H, d, *J* = 11.2 Hz), 4.51 (1 H, d, *J* = 11.2 Hz), 4.41 (1 H, part of AB-system), 4.39 (1 H, part of AB-system), 4.26 (1 H, dt, *J* = 8.3, 7.6 Hz), 4.12–4.06 (2 H, m), 3.97 (1 H, dd, *J* = 9.3, 6.7 Hz), 3.81 (3 H, s), 3.64 (1 H, dd, *J* = 9.3, 7.9 Hz), 2.99 (1 H, dd, *J* = 8.8, 5.5 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.4 (C_{ar}), 155.7 (C), 138.1 (C_{ar}), 129.6 (2 $\times$ CH_{ar}, C_{ar}), 128.7 (2 $\times$ CH_{ar}), 127.6 (2 $\times$ CH_{ar}), 127.5 (CH_{ar}), 113.9 (2 $\times$ CH_{ar}), 108.9 (CH), 76.3 (CH), 76.1 (CH), 75.1 (CH₂), 72.4 (CH₂), 71.1 (CH₂), 55.3 (CH₃), 51.7 (CH), 45.1 (CH₂) ppm; **LRMS** (ESI⁺) *m/z* 422.1 (M + Na)⁺.

Benzyl carbamic acid (1*S*,4*R*,5*R*,6*R*)-6-hydroxy-2,8-dioxabicyclo[3.3.0]octane-4-yl ester (6d)

Following general procedure **B** (2.2), the reaction of ether **S4** (523 mg, 1.37 mmol) with DDQ (358 mg, 1.58 mmol) afforded after purification by column chromatography (petroleum ether/acetone 70:30 to 60:40) the *title compound* **6d** as an off-white solid (366 mg, 74%). **Formula** C₁₄H₁₇NO₅; **Mw** 279.29; **R_f** 0.34 (hexane/acetone 60:40); [α]_D +61.9 (*c* 0.51, acetone, 23 °C); **IR** (film) 3398 (m), 3330 (br. m), 2979 (w), 2937 (w), 2882 (w), 1695 (vs), 1533 (m), 1249 (s), 1114 (s), 1104 (m), 970 (m), 700 (m) cm⁻¹; **¹H NMR** (400 MHz, acetone-*d*₆) δ 7.34–7.21 (5 H, m), 6.82 (1 H, br. s, *NH*), 5.67 (1 H, d, *J* = 5.3 Hz), 5.47 (1 H, d, *J* = 3.7 Hz), 4.58 (1 H, d, *J* = 4.3 Hz, *OH*), 4.52 (1 H, dtd, *J* = 8.8, 6.6, 4.3 Hz), 4.33 (2 H, d, *J* = 6.2 Hz), 4.01 (1 H, dd, *J* = 10.5, 3.8 Hz), 3.90 (1 H, dt, *J* = 10.4, 1.0 Hz), 3.89 (1 H, dd, *J* = 9.1, 6.4 Hz), 3.48 (1 H, dd, *J* = 9.1, 7.1 Hz), 2.85 (1 H, dd, *J* = 8.7, 5.2 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, acetone-*d*₆) δ 157.2 (C), 140.8 (C_{ar}), 129.3 (2 $\times$ CH_{ar}), 128.2 (2 $\times$ CH_{ar}), 127.9 (CH_{ar}), 110.1 (CH), 76.3 (CH), 75.6 (CH₂), 73.9 (CH₂), 70.1 (CH), 54.1 (CH), 45.2 (CH₂) ppm; **HRMS** (ESI⁺) for C₁₄H₁₇NO₅Na (*M* + Na)⁺ calcd. 302.0999; found 302.0999.

2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octane-4-yloxy)-*N*-benzyl acetamide (S5)

Following general procedure **C** (2.2), the reaction of acid **15** (517 mg, 1.40 mmol) and benzyl amine (460 μ L, 4.20 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) the *title compound* **S5** as a colourless oil (527 mg; 91%). **Formula** C₂₃H₂₇NO₆; **Mw** 413.46; **R_f** 0.23 (hexane/acetone 65:35); [α]_D +25.2 (*c* 1.01, CHCl₃, 25 °C); **IR** (film) 3349 (w), 2934 (w), 1666 (s), 1513 (vs), 1247 (s), 1118 (s), 1028 (vs) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.38–7.27 (5 H, m), 7.23 (2 H, d, *J* = 8.7 Hz), 6.90 (2 H, d, *J* = 8.7 Hz), 6.82 (1 H, br. s, *NHBn*), 5.75 (1 H, d, *J* = 5.1 Hz), 4.54–4.43 (4 H, m), 4.41 (1 H, d, *J* = 3.5 Hz), 4.22 (1 H, ddd, *J* = 9.0, 7.9, 6.7 Hz), 4.03 (1 H, d, *J* = 10.5 Hz), 4.02 (1 H, d, *J* = 15.2 Hz), 3.97 (1 H, d, *J* = 15.2 Hz), 3.97 (1 H, dd, *J* = 10.5, 3.5 Hz), 3.94 (1 H, dd, *J* = 9.2, 6.5 Hz), 3.82 (3 H, s), 3.57 (1 H, dd, *J* = 9.2, 7.9 Hz), 2.89 (1 H, dd, *J* = 8.9, 5.1 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 170.0 (C), 170.0 (C_{ar}), 137.9 (C_{ar}), 129.4 (2 $\times$ CH_{ar}), 129.3 (C_{ar}), 128.7 (2 $\times$ CH_{ar}), 127.8 (2 $\times$ CH_{ar}), 127.6 (CH_{ar}), 114.0 (2 $\times$ CH_{ar}), 108.6 (CH), 80.7 (CH), 76.3 (CH), 73.8 (CH₂), 72.5 (CH₂), 71.0 (CH₂), 68.4 (CH₂), 55.3 (CH₃), 51.7 (CH), 42.9 (CH₂) ppm; **HRMS** (ESI⁺) for C₂₃H₂₇NO₆Na (*M* + Na)⁺ calcd 436.1731, found 436.1734.

2-((1*S*,4*R*,5*R*,6*R*)-6-hydroxy-2,8-dioxabicyclo[3.3.0]octane-4-yloxy) *N*-benzyl acetamide (6e)

Following general procedure **B** (2.2), the deprotection of PMB-ether **S5** (345 mg, 0.83 mmol) with DDQ (210 mg, 0.92 mmol) afforded after purification by column chromatography (petroleum ether/acetone 75:25 to 50:50) the *title compound* **6e** as a white solid (179 mg, 73%). **Formula** C₁₅H₁₉NO₅; **Mw** 292.32; **R_f** 0.38 (petroleum ether/ acetone 50:50); **Mp** 132–134 °C; [α]_D +34.0 (c 0.79, CHCl₃, 29 °C); **IR** (film) 3427 (m), 3336 (m), 2882 (w), 2360 (w), 1651 (vs), 1538 (s), 1116 (vs), 1056 (m), 1018 (vs), 1003 (s), 953 (m), 934 (m), 892 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.40–7.28 (5 H, m), 6.88 (1 H, br. s, NH), 5.76 (1 H, d, *J* = 5.1 Hz), 4.59–4.42 (4 H, m), 4.10–4.02 (4 H, m), 3.99 (1 H, dd, *J* = 9.3, 6.5 Hz), 3.57 (1 H, dd, *J* = 9.3, 7.4 Hz), 2.83 (1 H, dd, *J* = 8.6, 5.2 Hz), 2.79 (1 H, d, *J* = 4.6 Hz, OH) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 169.4 (C), 137.7 (C_{ar}), 128.8 (2 $\times$ CH_{ar}), 127.8 (2 $\times$ CH_{ar}), 128.7 (CH_{ar}), 109.0 (CH), 80.3 (CH), 74.0 (CH₂), 73.1 (CH₂), 69.6 (CH), 68.4 (CH₂), 53.1 (CH), 42.9 (CH₂) ppm.; **HRMS** (ESI⁺) for C₁₅H₁₉NO₅Na (M + Na)⁺ calcd 316.1155, found 316.1154.

2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octane-4-yloxy) *N,N*-dimethyl acetamide (S6)

Following general procedure **C** (2.2), the reaction of acid **15** (540 mg, 1.66 mmol) and dimethylamine hydrochloride (407 mg, 5.00 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 97:3 to 95:5) the *title compound* **S6** as a colourless oil (449 mg, 77%). **Formula** C₁₈H₂₅NO₆; **Mw** 351.39; **R_f** 0.44 (CH₂Cl₂/MeOH 95:5); **IR** (film) 2936 (w), 2875 (w), 1650 (s), 1612 (m), 1513 (s), 1248 (s), 1113 (vs), 1026 (vs) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.27 (2 H, d, *J* = 8.7 Hz), 6.89 (2 H, d, *J* = 8.7 Hz), 5.80 (1 H, d, *J* = 5.3 Hz), 4.58 (1 H, d, *J* = 11.2 Hz), 4.47 (1 H, d, *J* = 11.2 Hz), 4.45 (1 H, dt, *J* = 3.9, 1.3 Hz), 4.24 (1 H, ddd, *J* = 9.0, 8.1, 6.7 Hz), 4.18 (1 H, d, *J* = 13.6 Hz), 4.10 (1 H, d, *J* = 13.6 Hz), 4.09 (1 H, dt, *J* = 10.4, 1.3 Hz), 3.99 (1 H, dd, *J* = 10.5, 3.9 Hz), 3.96 (1 H, dd, *J* = 9.1, 6.7 Hz), 3.82 (3 H, s), 3.58 (1 H, dd, *J* = 9.2, 8.0 Hz), 3.04 (1 H, ddt, *J* = 9.0, 5.2, 1.1 Hz), 2.97 (3 H, s), 2.94 (3 H, s) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 168.7 (C), 159.4 (C_{ar}), 129.6 (C_{ar}), 129.3 (2 $\times$ CH_{ar}), 113.9 (2 $\times$ CH_{ar}), 108.8 (CH), 80.2 (CH), 76.6 (CH), 73.9 (CH₂), 72.2 (CH₂), 70.8 (CH₂), 68.3 (CH₂), 55.3 (CH₃), 51.9 (CH), 36.4 (CH₃), 35.5 (CH₃) ppm; **LRMS** (ESI⁺) *m/z* 374.2 (M + Na)⁺.

2-((1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-2,8-dioxabicyclo[3.3.0]octane-4-yloxy) *N,N*-dimethyl acetamide (6g)

To a solution of ether **S6** (665 mg, 1.89 mmol) in MeOH (15 mL) under N₂ was added Pd/C (165 mg, 25 w%, 10% Pd). The flask was then put under H₂-atmosphere and the reaction was stirred at rt for 18 h. After completion the reaction mixture was filtered over celite and the filter cake was washed with MeOH. The solvent was removed in vacuo to afford the *title compound* **6g** as a colourless oil (477 mg, 98%) in sufficient purity. **Formula** C₁₀H₁₇NO₅; **Mw** 231.25; **R_f** 0.23 (CH₂Cl₂/MeOH 95:5); [α]_D +63.1 (c 1.13, CHCl₃, 26 °C); **IR** (film) 3384 (br. w), 2938 (w), 2878 (w), 1635 (s), 1111 (s), 1019 (s), 1003 (s), 930 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.77 (1 H, d, *J* = 5.3 Hz), 4.55 (1 H, td, *J* = 8.4, 6.8 Hz), 4.50 (1 H, dt, *J* = 4.8, 2.4 Hz), 4.28 (1 H, d, *J* = 14.2 Hz), 4.10 (1 H, d, *J* = 14.3 Hz), 4.09 (1 H, dd, *J* = 10.2, 4.9 Hz), 4.01 (1 H, dd, *J* = 9.0, 6.7 Hz), 3.96 (1 H, ddd, *J* = 10.0, 2.5, 0.9 Hz), 3.53 (1 H, t, *J* = 8.7 Hz), 3.01 (3 H, s), 2.97 (3 H, s), 2.93 (1 H, dd, *J* = 8.4, 5.5, 2.4 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 169.8 (C), 109.1 (CH), 79.5 (CH), 73.7 (CH₂), 72.5 (CH₂), 69.8 (CH), 68.3 (CH₂), 53.6 (CH), 36.4 (CH₃), 35.6 (CH₃) ppm; **HRMS** (ESI⁺) for C₁₀H₁₇NO₅Na (M + Na)⁺ calcd 254.0999, found 254.1001.

(1*R*,4*R*,5*S*,6*R*)-4-Allyloxy-6-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]octane (16)

To a stirred solution of alcohol **8** (1.05 g, 3.93 mmol) in THF (15 mL) at 0 °C was added NaH (314 mg, 7.86 mmol, 60% in mineral oil). After 10 min, allyl bromide (680 μ L, 7.86 mmol) and TBAI (291 mg, 0.79 mmol) were added and the resulting mixture was stirred at 0 °C for 20 min and at rt for further 16 h. The reaction was quenched carefully with H₂O (20 mL) and Et₂O (20 mL). The phases were separated and the aqueous layer was extracted with Et₂O (2 $\times$ 20 mL). The combined organic layers were washed with aq. sat. NaHCO₃, dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 95:5 to 85:15) afforded the *title compound* **16** as a colourless oil (950 mg, 79%). **Formula** C₁₇H₂₂O₅; **Mw** 306.35; **R_f** 0.25 (petroleum ether/acetone 85:15); [α]_D +15.4 (c 1.0, CHCl₃, 27 °C); **IR** (film) 2937 (m), 2874 (m), 1612 (m), 1514 (s), 1249 (s), 1120 (s), 1027 (vs), 821 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.26 (2 H, d, *J* = 8.7 Hz), 6.90 (2 H, d, *J* = 8.7 Hz), 5.92 (1 H, ddt, *J* = 17.2, 10.4, 5.6 Hz), 5.81 (1 H, d, *J* = 5.2 Hz), 5.30 (1 H, dq, *J* = 17.3, 1.6 Hz), 5.20 (1 H, d, *J* = 10.4, 1.4 Hz), 4.55 (1 H, d, *J* = 11.4 Hz), 4.48 (1 H, d, *J* = 11.4 Hz), 4.40 (1 H, dt, *J* = 3.9, 1.2 Hz), 4.24 (1 H, ddd, *J* = 8.9, 8.3, 6.7 Hz), 4.07 (1 H, dt, *J* = 10.1, 1.3 Hz), 4.03–3.93 (4 H, m), 3.82 (3 H, s), 3.59 (1 H, dd, *J* = 9.0, 8.3 Hz), 2.96 (1 H, ddt, *J* = 9.0, 5.2, 1.1 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.5 (C_{ar}), 134.5 (CH), 129.6 (C_{ar}), 129.3 (2 $\times$ CH_{ar}), 117.3 (CH₂), 113.9 (2 $\times$ CH_{ar}), 108.9 (CH), 78.9 (CH), 76.6 (CH), 74.2 (CH₂), 72.3 (CH₂), 70.8 (CH₂), 70.1 (CH₂), 55.3 (CH₃), 52.0 (CH) ppm; **LRMS** (ESI⁺) *m/z* 329.2 (M + Na)⁺.

(1*S*,4*R*,5*R*,6*R*)-4-(2-Fluoroallyloxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (18)

Fluoroalkene **18** was prepared in two steps, according to a literature procedure.¹² To a solution of allyl ether **16** (937 mg, 3.05 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added *N*-bromosuccinimide (600 mg, 3.36 mmol) and triethylamine tris(hydrofluoride) and stirred at this temperature for 15 min. The cooling was removed and the reaction was stirred at rt for further 16 h. The reaction was poured into ice water (50 mL), basified with aq. NH₃ (~ 1 mL, 35 w%) and the resulting mixture was extracted with CH₂Cl₂ (4 × 30 mL). The combined organic phases were washed with aq. HCl (10 mL, 0.1 N) and aq. NaHCO₃ (10 mL, 5 w%), dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude by column chromatography (petroleum ether/acetone 90:10 to 80:20) successively afforded allyl ether **16** (433 mg, 46%) and bromofluoro ether **17** as a colourless oil (532 mg, 43%, 1:1 mixture of two diastereoisomers, *R_f* 0.29 (petroleum ether/acetone 80:20); ¹⁹F NMR δ –183.62 (dtdd, *J* = 46.5, 20.4, 19.9, 15.8 Hz), –183.62 (ddt, *J* = 46.4, 38.0, 19.0 Hz) ppm).

To a solution of bromofluoro ether **17** (800 mg, 1.97 mmol) in dry THF (15 mL) was added potassium *tert*-butoxide (443 mg, 3.94 mmol) and the reaction was stirred at rt for 22 h. The reaction was diluted with H₂O (15 mL) and the resulting mixture was extracted with Et₂O (3 × 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 75:25) afforded the *title compound* **18** as a colourless oil (363 mg, 57%). **Formula** C₁₇H₂₁FO₅; **Mw** 324.34; *R_f* 0.35 (petroleum ether/acetone 80:20); [*α*]_D +15.1 (*c* 1.0, CHCl₃, 23 °C); **IR** (film) 2937 (w), 2875 (w), 1681 (m), 1514 (s), 1249 (s), 1119 (s), 1028 (vs), 931 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25 (2 H, d, *J* = 8.7 Hz), 6.90 (1 H, d, *J* = 8.7 Hz), 5.81 (1 H, d, *J* = 5.3 Hz), 4.76 (1 H, dd, *J* = 16.5, 3.0 Hz), 4.56 (1 H, ddt, *J* = 48.5, 3.0, 0.8 Hz), 4.54 (1 H, d, *J* = 11.4 Hz), 4.48 (1 H, d, *J* = 11.4 Hz), 4.46 (1 H, dt, *J* = 3.9, 1.2 Hz), 4.24 (1 H, ddd, *J* = 9.0, 8.2, 6.7 Hz), 4.06 (1 H, dt, *J* = 10.4, 1.3 Hz), 4.01–3.95 (4 H, m), 3.82 (3 H, s), 3.58 (1 H, dd, *J* = 9.1, 8.1 Hz), 2.96 (1 H, ddt, *J* = 8.9, 5.2, 1.1 Hz) ppm; ¹³C NMR + DEPT (100 MHz, CDCl₃) δ 161.9 (CF, d, *J* = 237.1 Hz), 159.5 (C_{ar}), 129.5 (C_{ar}), 129.3 (2 × CH_{ar}), 114.0 (2 × CH_{ar}), 108.8 (CH), 93.1 (CH₂, d, *J* = 17.2 Hz), 79.5 (CH), 76.5 (CH), 73.9 (CH₂), 72.4 (CH₂), 70.8 (CH₂), 66.5 (CH₂, d, *J* = 33.3 Hz), 55.3 (CH₃), 52.1 (CH) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ –105.6 (ddt, *J* = 48.5, 16.5, 13.2 Hz, F-14); **LRMS** (ESI⁺) *m/z* 388.2 (M + Na+MeCN)⁺.

¹² Michel, D.; Schlosser, M. Odor-Structure Relationships Using Fluorine as a Probe. *Tetrahedron* **2000**, 56, 4253–4260.

(1S,4R,5R,6R)-4-(2-Fluoroallyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (6h)

Following general procedure **B** (2.2), the deprotection of PMB-ether **18** (340 mg, 1.05 mmol) with DDQ (262 mg, 1.15 mmol) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **6h** as a colourless oil (123 mg, 57%). **Formula** C₉H₁₃FO₄; **Mw** 204.20; **R_f** 0.29 (petroleum ether/ acetone 70:30); [**α**]_D +50.6 (c 1.0, CHCl₃, 25 °C); **IR** (film) 3434 (br. m), 2942 (w), 2879 (w), 1680 (m), 1219 (m), 1107 (s), 999 (vs), 928 (s), 849 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.82 (1 H, d, *J* = 5.3 Hz), 4.77 (1 H, dd, *J* = 16.5, 3.0 Hz), 4.59 (1 H, ddt, *J* = 48.5, 3.0, 0.8 Hz), 4.57 (1 H, dtd, *J* = 8.6, 6.5, 5.1 Hz), 4.49 (1 H, dt, *J* = 4.0, 1.2 Hz), 4.08 (1 H, dt, *J* = 10.2, 1.3 Hz), 4.05–3.99 (4 H, m), 3.62 (1 H, dd, *J* = 9.5, 6.7 Hz), 2.90 (1 H, ddt, *J* = 8.6, 5.3, 1.2 Hz), 1.90 (1 H, d, *J* = 5.2 Hz, OH) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 162.1 (CF, d, *J* = 259.1 Hz), 109.1 (CH), 162.1 (CH₂, d, *J* = 16.8 Hz), 79.2 (CH), 74.1 (CH₂), 73.3 (CH₂), 70.0 (CH), 66.5 (CH₂, d, *J* = 33.3 Hz), 53.5 (CH) ppm.; **¹⁹F NMR** (282 MHz, CDCl₃) δ -105.5 (ddt, *J* = 48.5, 16.5, 13.2 Hz, F-8) ppm; **HRMS** (ESI⁺) for C₉H₁₃FO₄Na (M + Na)⁺ calcd 227.0690, found 227.0689.

(1S,4R,5R,6R)-4-(2,2-Diethoxy-ethoxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (19)

To a stirred solution of alcohol **8** (817 mg, 3.07 mmol) in dry DMF (15 mL) at 0 °C was added NaH (245 mg, 6.14 mmol, 60% in mineral oil). After 20 min, bromoacetaldehyde diethyl acetal (940 μL, 6.14 mmol) and TBAI (225 mg, 0.61 mmol) were added and the resulting mixture was stirred at 0 °C for 20 min and at rt for further 18 h. The reaction was quenched carefully with citric acid (5 mL, 10 %), diluted with H₂O (20 mL) and the mixture was extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 75:25) successively afforded the *title compound* **19** as a colourless oil (402 mg, 34%) and starting alcohol **8** (271 mg, 33%). **Formula** C₂₀H₃₀O₇; **Mw** 382.45; **R_f** 0.80 (petroleum ether/acetone 70:30); **IR** (film) 2974 (w), 2931 (w), 2874 (w), 1612 (w), 1514 (m), 1248 (m), 1119 (vs), 1124 (s), 1028 (vs), 821 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.26 (2 H, d, *J* = 8.5 Hz), 6.90 (1 H, d, *J* = 8.7 Hz), 5.79 (1 H, d, *J* = 5.3 Hz), 4.59 (1 H, t, *J* = 5.1 Hz), 4.55 (1 H, d, *J* = 11.2 Hz), 4.47 (1 H, d, *J* = 11.2 Hz), 4.42 (1 H, dt, *J* = 3.9, 1.2 Hz), 4.22 (1 H, ddd, *J* = 8.8, 8.0, 6.6 Hz), 4.07 (1 H, dt, *J* = 10.2, 1.3 Hz), 3.98 (1 H, dd, *J* = 10.1, 3.8 Hz), 3.95 (1 H, dd, *J* = 9.0, 6.5 Hz), 3.82 (3 H, s), 3.76–3.66 (2 H, m), 3.61–3.52 (3 H, m), 3.51 (1 H, dd, *J* = 10.5, 5.2 Hz), 3.48 (1 H, dd, *J* = 10.5, 5.4 Hz), 2.98 (1 H, ddt, *J* = 8.9, 5.2, 1.2 Hz), 1.22 (6 H, t, *J* = 7.1 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.5 (C_{ar}), 129.6 (C_{ar}), 129.3 (2 × CH_{ar}), 114.0 (2 × CH_{ar}), 109.0 (CH), 101.2 (CH), 80.2 (CH), 76.5 (CH), 74.3 (CH₂), 72.2 (CH₂), 70.9 (CH₂), 70.1 (CH₂), 62.6 (CH₂), 62.5 (CH₂), 55.3 (CH₃), 51.8 (CH), 15.4 (CH₃), 15.3 (CH₃) ppm; **LRMS** (ESI⁺) *m/z* 405.3 (M + Na)⁺.

(1*R*,4*R*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-4-(3,3,3-trifluoropropoxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (21)

To a solution of acetal **19** (400 mg, 1.05 mmol) in THF (15 mL) was added aq. HCl (1 mL, 4.00 mmol, 4 M) and the resulting mixture was stirred at rt and monitored by TLC. When the majority of starting material was consumed, the reaction was neutralised with aq. sat. NaHCO₃ (10 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo to afford the corresponding crude aldehyde (359 mg) as a pale yellow oil.

Following literature procedures,¹³ a solution of this crude aldehyde (359 mg, 1.0 mmol) in dry THF (15 mL) was treated with TMSCF₃ (1.0 mL, 2.00 mmol, 2 M in THF) and cat. TBAF (50 µL, 0.05 mmol, 1 M in THF) and the resulting mixture was stirred at rt. After 18 h, TBAF (2.0 mL, 2.00 mmol, 1 M in THF) was added and the reaction was stirred for further 3 h. The reaction was quenched with H₂O (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20 to 60:40) afforded the two diastereoisomers of trifluoromethyl alcohol **20** as a pale yellow oil (130 mg, 34 %; *R_f* 0.40 (petroleum ether/acetone 70:30), ¹⁹F NMR δ -77.77 (d, *J* = 6.4 Hz), -77.84 (d, *J* = 6.4 Hz) ppm).

Transformation to trifluoropropyl ether **21** was achieved in two steps via Barton-McCombie deoxygenation.¹¹³ To a solution of diastereomeric alcohol **20** (253 mg, 0.64 mmol) in dry THF (10 mL) at -78 °C was added *n*BuLi (300 µL, 0.74 mmol, 2.5 M in hexanes) and *O*-phenyl chlorothiono formate (1.35 µL, 1.00 mmol) and the reaction was stirred for 1 h at -78 °C and for further 2 h at rt. After completion, the reaction was quenched with aq. sat. NaHCO₃ (10 mL) and extracted with Et₂O (3 × 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) afforded the intermediate thionocarbonate as a colourless oil (257 mg, 73 %; *R_f* 0.19 (petroleum ether/EtOAc 80:20), ¹⁹F NMR δ -74.64 (d, *J* = 6.2 Hz), -74.62 (d, *J* = 6.2 Hz) ppm).

To a solution of this thionocarbonate (2.55 mg, 0.50 mmol) in toluene (5 mL) was added tributyltin hydride (202 µL, 0.75 mmol) and AIBN (17 mg, 0.1 mmol) and the reaction was heated to reflux for 2 h. After completion, all volatiles were removed on vacuo and the crude product was purified by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) to afford the *title compound* **21** as a colourless oil (132 mg, 73%). **Formula** C₁₇H₂₁F₃O₅; **Mw** 362.34; *R_f* 0.16 (petroleum ether/EtOAc 80:20); [*α*]_D +11.9 (c 0.45, CHCl₃, 23 °C); **IR** (film) 2956 (w), 2879 (w), 1612 (m), 1514 (m), 1249 (vs), 1145 (s), 1124 (s), 1026 (vs), 822 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.25 (2 H, d, *J* = 8.7 Hz), 6.91 (1 H, d, *J* = 8.7 Hz), 5.78 (1 H, d, *J* = 5.2 Hz), 4.53 (1 H, d, *J* = 11.4 Hz), 4.49 (1 H, d, *J* = 11.4 Hz), 4.35 (1 H, dt, *J* = 3.9, 1.2 Hz), 4.24 (1 H, ddd, *J* = 8.7, 8.2, 6.7 Hz), 4.03 (1 H, dt, *J* = 10.2, 1.1 Hz), 3.97 (1 H, dd, *J* = 10.4, 3.9 Hz), 3.97 (1 H, dd, *J* = 9.0, 6.8 Hz), 3.82 (3 H, s), 3.62 (2 H, ddt, *J* = 15.7, 9.7, 6.6 Hz), 3.58 (1 H, dd, *J* = 9.0, 8.3 Hz), 2.91 (1 H, ddt, *J* = 9.0, 5.2, 1.2 Hz), 2.39 (2 H, qtd, *J* = 10.6, 6.7, 0.6 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 159.5 (C_{ar}), 129.5

¹³ Ma, J.; Katz, E.; Kyle, D. E.; Ziffer, H. Syntheses and Antimalarial Activities of 10-Substituted Deoxoartemisinins. *J. Med. Chem.* **2000**, 43, 4228-4232.

(C_{ar}), 129.3 (2 × CH_{ar}), 126.0 (CF₃, q, *J* = 277.0 Hz), 114.0 (2 × CH_{ar}), 108.8 (CH), 79.9 (CH), 76.5 (CH), 73.8 (CH₂), 72.4 (CH₂), 70.9 (CH₂), 61.9 (CH₂, d, *J* = 3.7 Hz), 55.3 (CH₃), 51.9 (CH), 34.5 (CH₂, q, *J* = 28.8 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -65.0 (t, *J* = 10.5 Hz); LRMS (ESI⁺) *m/z* 385.2 (M + Na)⁺, 426.2 (M + Na + MeCN)⁺.

(1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-4-(3,3,3-trifluoropropoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (6i**)**

Following general procedure **B** (3.2), the deprotection of PMB-ether **21** (125 mg, 0.34 mmol) with DDQ (90 mg, 0.37 mmol) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **6i** as a colourless oil (60 mg, 73%). **Formula** C₉H₁₃F₃O₄; **Mw** 242.19; **R_f** 0.34 (petroleum ether/ acetone 70:30); [**α**]_D +30.8 (c 0.41, CHCl₃, 23 °C); **IR** (film) 3439 (br. w), 2953 (w), 2885 (w), 1383 (w), 1254 (s), 1146 (s), 1120 (s), 1006 (s), 962 (m), 933 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.80 (1 H, d, *J* = 5.3 Hz), 4.57 (1 H, m), 4.38 (1 H, dt, *J* = 3.8, 1.2 Hz), 4.06 (1 H, dt, *J* = 10.1, 1.2 Hz), 4.01 (1 H, dd, *J* = 10.1, 3.8 Hz), 4.01 (1 H, dd, *J* = 9.5, 6.5 Hz), 3.66 (2 H, td, *J* = 6.7, 1.7 Hz), 3.62 (1 H, dd, *J* = 9.5, 6.7 Hz), 2.86 (1 H, ddt, *J* = 8.6, 5.2, 1.1 Hz), 2.41 (2 H, qt, *J* = 10.7, 6.7 Hz), 1.91 (1 H, d, *J* = 5.1 Hz, OH) ppm; ¹³C NMR + DEPT (100 MHz, CDCl₃) δ 126.0 (CF₃, q, *J* = 275.2 Hz), 109.1 (CH), 79.5 (CH), 74.0 (CH₂), 73.4 (CH₂), 70.0 (CH), 61.9 (CH₂, d, *J* = 3.7 Hz), 53.2 (CH), 34.4 (CH₂, q, *J* = 28.9 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -65.0 (t, *J* = 10.5 Hz); HRMS (ESI⁺) for C₉H₁₃F₃O₄Na (M + Na)⁺ calcd 265.0658, found 265.0665.

(1*S*,4*R*,5*S*,6*R*)-4-Chloro-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (S7**)**

To a solution of *endo*-alcohol **12** (1.00 g, 3.76 mmol) in pyridine (7 mL) at 0 °C was added thionyl chloride (330 μL, 4.50 mmol) and the resulting mixture was heated to 100 °C for 2 h. After cooling to rt, the reaction was poured into ice water (20 mL) and extracted with Et₂O (2 × 20 mL). The combined organic phases were washed with water and brine (5 mL each), dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 80:20) afforded the *title compound* **S7** as a white solid (422 mg, 39%). **Formula** C₁₄H₁₇ClO₄; **Mw** 284.74; **R_f** 0.40 (petroleum ether/acetone 80:20); **Mp** 74–76 °C; **IR** (film) 2936 (w), 2875 (w), 2837 (w), 1612 (m), 1514 (s), 1248 (s), 1110 (s), 1027 (vs), 921 (m), 821 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (2 H, d, *J* = 8.7 Hz), 6.91 (2 H, d, *J* = 8.7 Hz), 5.90 (1 H, d, *J* = 5.1 Hz), 4.76 (1 H, dt, *J* = 4.2, 1.4 Hz), 4.55 (1 H, d, *J* = 11.2 Hz), 4.49 (1 H, d, *J* = 11.2 Hz), 4.26 (1 H, dd, *J* = 10.6, 4.2 Hz), 4.21 (1 H, ddd, *J* = 8.8, 7.8, 6.7 Hz), 4.09 (1 H, dt, *J* = 10.6, 1.4 Hz), 3.98 (1 H, dd, *J* = 9.3, 6.6 Hz), 3.83 (3 H, s), 3.62 (1 H, dd, *J* = 9.3, 7.8 Hz), 3.18 (1 H, ddt, *J* = 9.0, 5.1, 1.4 Hz) ppm; ¹³C NMR + DEPT (100 MHz, CDCl₃) δ 159.6 (C_{ar}), 129.4 (2 × CH_{ar}), 129.2 (C_{ar}), 114.0 (2 × CH_{ar}), 108.8 (CH), 77.6 (CH₂), 76.6 (CH), 72.4 (CH₂), 70.9 (CH₂), 57.3 (CH), 55.8 (CH), 55.3 (CH₃) ppm; LRMS (ESI⁺) *m/z* 348.1 (M + Na + MeCN)⁺, 350.1 (M + Na + MeCN)⁺.

(1S,4R,5S,6R)-4-Chloro-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (6j)

Following general procedure **B** (2.2), the deprotection of PMB-ether **S7** (539 mg, 1.90 mmol) with DDQ (473 mg, 2.10 mmol) afforded after purification by column chromatography (petroleum ether/acetone 90:10 to 70:30) the *title compound* **6j** as a pale yellow oil (174 mg, 56%). **Formula** C₆H₉ClO₃; **Mw** 164.59; **R_f** 0.26 (petroleum ether/ acetone 70:30); [α]_D +85.1 (c 0.68, CHCl₃, 26 °C); **IR** (film) 3430 (br. m), 2982 (w), 2941 (w), 2881 (w), 1309 (w), 1230 (m), 1107 (s), 1077 (m), 1016 (s), 946 (m), 919 (s), 886 (m), 578 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.91 (1 H, d, *J* = 5.2 Hz), 4.80 (1 H, dt, *J* = 4.1, 1.3 Hz), 4.56 (1 H, dtd, *J* = 8.8, 6.4, 4.5 Hz), 4.28 (1 H, dd, *J* = 10.5, 4.0 Hz), 4.12 (1 H, dt, *J* = 10.5, 1.2 Hz), 4.04 (1 H, dd, *J* = 9.7, 6.3 Hz), 3.64 (1 H, dd, *J* = 9.6, 6.6 Hz), 3.12 (1 H, ddt, *J* = 8.8, 5.2, 1.1 Hz), 2.13 (1 H, d, *J* = 4.7 Hz, OH) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 109.0 (CH), 77.8 (CH₂), 73.3 (CH), 70.0 (CH₂), 57.2 (CH), 57.1 (CH) ppm; **HRMS** (ESI⁺) for C₆H₉ClO₃Na (M+Na)⁺ calcd 187.0132, found 187.0132.

(1S,4R,5S,6R)-4-Fluoro-6-hydroxy-2,8-dioxa-bicyclo-[3.3.0]-octane (6k)

Diethylaminosulfur trifluoride (170 μ L, 1.30 mmol) was added dropwise to a solution of alcohol **12** (285 mg, 1.07 mmol) and DMAP (260 mg, 2.14 mmol) in CH₂Cl₂ (2.5 mL) at -10 °C. The reaction was allowed to warm to rt and was stirred for further 18 h. After completion, the reaction mixture was cooled to -20 °C, quenched with MeOH (2 mL) and partitioned between CH₂Cl₂ and sat. aq. NaHCO₃ (8 mL each). The aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 65:35) afforded the intermediate PMB-protected fluoride as a colourless oil (104 mg, 36%; **R_f** 0.38 (petroleum ether/acetone 80:20); **¹H NMR** (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 5.87 (d, *J* = 5.2 Hz, 1 H), 5.44 (dd, *J* = 53.2, 3.1 Hz, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.27 (ddd, *J* = 9.1, 7.6, 6.6 Hz, 1 H), 4.21 (ddd, *J* = 23.0, 11.4, 1.6 Hz, 1 H), 4.05 (ddd, *J* = 39.6, 11.3, 3.0 Hz, 1 H), 3.96 (ddd, *J* = 9.4, 6.4, 1.2 Hz, 1 H), 3.83 (s, 3 H), 3.61 (dd, *J* = 9.4, 7.5 Hz, 1 H), 3.13 (dddd, *J* = 26.0, 9.1, 5.1, 1.5 Hz, 1 H) ppm; **¹⁹F NMR** (282 MHz, CDCl₃) δ -179.7 ppm).

Treatment of this PMB-ether (285 mg, 1.07 mmol) with DDQ (270 mg, 1.20 mmol) according to general procedure **B** (3.2) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 60:40) the *title compound* **6k** as a colourless oil (37.2 mg, 23%). **Formula** C₆H₉FO₃; **Mw** 148.13; **R_f** 0.25 (hexane/acetone 70:30); [α]_D +21.2 (c 1.06, CHCl₃, 25 °C); **IR** (film) 3417 (br. m), 2982 (w), 2941 (w), 2883 (w), 1228 (m), 1110 (s), 1001 (s), 959 (vs), 926 (s), 856 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.87 (1 H, d, *J* = 5.1 Hz), 5.47 (1 H, dd, *J* = 53.0, 3.0 Hz), 4.61 (1 H, dtd, *J* = 8.8, 6.1, 4.8 Hz), 4.24 (1 H, ddd, *J* = 23.1, 11.3, 1.6 Hz), 4.08 (1 H, ddd, *J* = 39.7, 11.5, 2.9 Hz), 4.01 (1 H, ddd, *J* = 9.8, 6.0, 1.1 Hz), 3.63 (1 H, dd, *J* = 9.7, 6.1 Hz), 3.08 (1 H, dddd, *J* = 25.6, 8.8, 5.3, 1.8 Hz), 2.18 (1 H, d, *J* = 4.9 Hz, OH) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 109.1 (CH), 93.7 (CHF, d, *J* = 176.9 Hz), 75.4 (CH₂, d, *J* = 22.8 Hz), 73.6 (CH₂), 69.5 (CH, d, *J* = 9.7 Hz), 53.6 (CH, d,

$J = 22.1$ Hz) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -180.4 (dddd, $J = 53.0, 39.7, 25.6, 23.1$ Hz) ppm; **LRMS** (Cl^+) m/z (%) 44.1 (12), 68.0 (100), 69.0 (18), 110.9 (10), 128.9 (10), 148.9 ($[\text{M}+\text{H}]^+$, 5), 165.9 ($[\text{M}+\text{NH}_4]^+$, 14).

3.5 Synthesis of protease inhibitors 3, 4 and 5

Protease inhibitor 3c

Following general procedure **D** (2.2), the reaction of alcohol **6c** (118 mg, 0.42 mmol) with DSC (161 mg, 0.63 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2) the corresponding mixed carbonate **23c** as a white solid (140 mg, 0.33 mmol, 78%; **R_f** 0.28 (CH₂Cl₂/MeOH 98:2); **IR** (film) 3330 (br. w), 2947 (br. w), 1737 (s), 1716 (s), 1525 (m), 1224 (s), 1200 (s), 1078 (m), 907 (s), 724 (vs) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.38–7.28 (5 H, m), 5.78 (1 H, d, *J* = 5.1 Hz), 5.35–5.26 (2 H, m), 5.11 (3 H, d, *J* = 11.8 Hz), 5.08 (3 H, d, *J* = 11.8 Hz), 4.42 (1 H, m), 4.13 (1 H, dd, *J* = 9.8, 4.4 Hz), 4.14 (1 H, dd, *J* = 10.7, 5.7 Hz), 3.97 (1 H, dd, *J* = 10.7, 5.0 Hz), 3.90 (1 H, m), 3.08 (1 H, m), 2.80 (4 H, br. s) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 168.3 (2 × C), 155.4 (C), 150.9 (C), 136.2 (C_{ar}), 128.5 (2 × CH_{ar}), 128.2 (CH_{ar}), 128.1 (2 × CH_{ar}), 108.3 (CH), 78.6 (CH), 74.2 (CH₂), 70.6 (CH₂), 66.9 (CH₂), 52.5 (CH), 52.2 (CH), 25.4 (2 × CH₂) ppm; **LRMS** (ESI⁺) *m/z* 443.1 (M + Na)⁺.

Following general procedure **E** (2.2), the reaction of this carbonate (74 mg, 0.18 mmol) and amine **7a** (60 mg, 0.15 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) and HPLC (CH₂Cl₂/MeOH 97:3) the PI **3c** as a white solid (96 mg, 90%). **Formula** C₃₅H₄₄N₄O₉S; **Mw** 696.81; **R_f** 0.28 (CH₂Cl₂/MeOH 96:4), **Mp** 118–120 °C, [**α**]_D +42.9 (*c* 0.73, CHCl₃, 26 °C); **IR** (film) 3363 (br. m), 2960 (br. w), 1701 (vs), 1628 (w), 1598 (s), 1529 (m), 1313 (s), 1251 (s), 1147 (vs), 1090 (vs), 732 (vs) cm⁻¹; **¹H NMR** (400 MHz, DMSO-*d*₆, T = 373 K) δ 7.42 (2 H, d, *J* = 8.7 Hz), 7.38–7.08 (11 H, m), 6.78 (1 H, br. s), 6.65 (2 H, d, *J* = 8.7 Hz), 5.65 (1 H, d, *J* = 5.1 Hz), 5.64 (2 H, s), 5.07 (1 H, d, *J* = 12.6 Hz), 5.04 (1 H, d, *J* = 12.6 Hz), 4.98 (1 H, m), 4.53 (1 H, d, *J* = 5.8 Hz), 4.07 (1 H, dd, *J* = 6.1, 4.6 Hz), 3.96–3.81 (2 H, m), 3.79–3.61 (4 H, m), 3.32 (1 H, dd, *J* = 14.9, 3.4 Hz), 2.99 (1 H, dd, *J* = 14.0, 4.0 Hz), 2.95 (1 H, dd, *J* = 13.8, 7.8 Hz), 2.92–2.84 (2 H, m), 2.79 (1 H, dd, *J* = 13.8, 6.9 Hz), 2.63 (1 H, dd, *J* = 14.0, 9.5 Hz), 1.96 (1 H, m), 0.85 (3 H, d, *J* = 6.6 Hz), 0.82 (3 H, d, *J* = 6.7 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 155.4 (C), 155.2 (C), 150.7 (C_{ar}), 137.5 (C_{ar}), 136.2 (C_{ar}), 129.5 (4 × CH_{ar} and C_{ar}), 128.6 (4 × CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 126.6 (CH_{ar}), 114.1 (2 × CH_{ar}), 108.3 (CH), 74.6 (CH₂), 72.3 (CH), 72.2 (CH), 71.4 (CH₂), 66.9 (CH₂), 58.8 (CH₂), 55.2 (CH), 53.7 (CH₂), 52.7 (CH), 52.5 (CH), 35.4 (CH₂), 27.3 (CH), 20.2 (CH₃), 19.9 (CH₃) ppm, one quaternary carbon was not observed; **HRMS** (ESI⁺) for C₃₅H₄₄N₄O₉SNa (M + Na)⁺ calcd. 719.2721, found 719.2733.

Protease Inhibitor 4c

Following general procedure **D** (2.2), the reaction of alcohol **6c** (118 mg, 0.42 mmol) with DSC (161 mg, 0.63 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2) the corresponding mixed carbonate **23c** as a white solid (140 mg,

0.33 mmol, 78%). Following general procedure **E** (2.2), the reaction of this carbonate (115 mg, 0.27 mmol) and amine **7b** (111 mg, 0.25 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) and HPLC (CH₂Cl₂/MeOH 96:4) the PI **4c** as a white solid (115 mg, 61%). **Formula** C₃₇H₄₅N₅O₁₀S; **Mw** 751.85; **R_f** 0.25 (CH₂Cl₂/MeOH 95:5); **Mp** 106–108 °C; [α]_D +39.1 (c 1.03, CHCl₃, 27 °C); **IR** (film) 3326 (br. w), 2960 (w), 1702 (s), 1656 (vs), 1580 (m), 1533 (m), 1463 (m), 1325 (m), 1240 (s), 1144 (s), 910 (m), 730 (vs), 700 (s) cm⁻¹; **¹H NMR** (400 MHz, DMSO-*d*₆, T = 363 K) δ 7.95 (1 H, q, *J* = 4.5 Hz), 7.68 (1 H, d, *J* = 1.8 Hz), 7.57 (1 H, dd, *J* = 8.2, 1.8 Hz), 7.36–7.09 (12 H, m), 6.88 (1 H, br. s), 5.64 (1 H, d, *J* = 5.1 Hz), 5.06 (1 H, d, *J* = 12.9 Hz), 5.03 (1 H, d, *J* = 12.9 Hz), 4.98 (1 H, br. s), 4.66 (1 H, d, *J* = 6.1 Hz), 4.05 (1 H, dd, *J* = 5.9, 4.9 Hz), 3.95–3.82 (2 H, m), 3.77–3.58 (4 H, m), 3.37 (1 H, dd, *J* = 14.9, 2.5 Hz), 3.04 (1 H, dd, *J* = 13.9, 8.0 Hz), 2.97 (3 H, d, *J* = 4.7 Hz), 3.00–2.84 (4 H, m), 2.61 (1 H, dd, *J* = 13.3, 10.0 Hz), 1.99 (1 H, m), 0.85 (3 H, d, *J* = 6.6 Hz), 0.81 (3 H, d, *J* = 6.7 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 164.7 (C_{ar}), 155.4 (C), 155.2 (C), 148.1 (C_{ar}), 147.7 (C_{ar}), 137.5 (C_{ar}), 136.1 (C_{ar}), 129.7 (C_{ar}), 129.4 (2 × CH_{ar}), 128.5 (4 × CH_{ar}), 128.3 (2 × CH_{ar}), 128.1 (CH_{ar}), 126.6 (CH_{ar}), 124.2 (CH_{ar}), 116.0 (CH_{ar}), 108.4 (CH and CH_{ar}), 74.5 (CH₂), 72.3 (CH), 72.2 (CH), 71.4 (CH₂), 66.9 (CH₂), 58.8 (CH₂), 55.2 (CH), 53.7 (CH₂), 52.6 (CH), 52.5 (CH), 35.4 (CH₂), 29.5 (CH₃), 27.2 (CH), 20.1 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI⁺) for C₃₇H₄₆N₅O₁₀S (M + H)⁺ calcd. 752.2960, found 752.2958.

Protease Inhibitor **3d**

Following general procedure **D** (2.2), the reaction of alcohol **6d** (350 mg, 1.25 mmol) with DSC (480 mg, 1.88 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) the corresponding mixed carbonate **23d** as a white solid (451 mg, 1.07 mmol, 82%; **R_f** 0.28 (CH₂Cl₂/MeOH 96:4); **Mp** 82 °C; [α]_D +39.0 (c 0.73, CHCl₃, 26 °C); **IR** (film) 3348 (br. w), 2930 (w), 2885 (w), 1813 (m), 1789 (m), 1740 (vs), 1525 (m), 1247 (s), 1232 (s), 1080 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.38–7.27 (7 H, m), 5.85 (1 H, d, *J* = 5.0 Hz), 5.39 (1 H, br. s), 5.37 (1 H, dt, *J* = 8.5, 5.2 Hz), 5.12 (1 H, m), 4.39 (1 H, part of AB-system), 4.37 (1 H, part of AB-system), 4.21 (1 H, dd, *J* = 10.7, 3.8 Hz), 4.18–4.07 (2 H, m), 3.97 (1 H, dd, *J* = 10.5, 5.1 Hz), 3.17 (1 H, dd, *J* = 8.5, 5.2 Hz), 2.84 (4 H, br. s) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 168.2 (2 × C), 155.3 (C), 150.9 (C), 138.1 (C_{ar}), 128.7 (2 × CH_{ar}), 127.61 (2 × CH_{ar}), 127.55 (CH_{ar}), 108.5 (CH), 78.1 (CH), 74.9 (CH), 74.7 (CH₂), 70.6 (CH₂), 51.6 (CH), 45.1 (CH₂), 25.4 (2 × CH₂) ppm; **HRMS** (ESI⁺) for C₁₉H₂₀N₂O₉Na (M + Na)⁺ calcd. 443.1061, found 443.1066).

Following general procedure **E** (2.2), the reaction of this carbonate (210 mg, 0.50 mmol) and amine **7a** (168 mg, 0.43 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) and HPLC (CH₂Cl₂/MeOH 96:4) the PI **3d** as a white solid (180 mg, 60%). **Formula** C₃₅H₄₄N₄O₉S; **Mw** 696.81; **R_f** 0.33 (CH₂Cl₂/MeOH 96:4); **Mp** 99–102 °C; [α]_D +50.7 (c 0.69, CHCl₃, 26 °C); **IR** (film) 3364 (br. w), 2961 (w), 2875 (w), 1704 (s), 1628 (w), 1596 (m), 1520 (m), 1312 (m), 1225 (s), 1144 (s), 1089 (s), 1017 (m), 730 (vs), 700 (s) cm⁻¹; **¹H NMR** (400 MHz, DMSO-*d*₆, T = 373 K) δ 7.43 (1 H, d, *J* = 8.7 Hz), 7.39–7.08 (11 H), 6.82 (1 H, br. s), 6.66 (2 H, d, *J* = 8.7 Hz), 5.68 (1 H, d, *J* = 5.2 Hz), 5.62 (2 H, s), 5.10 (1 H, d, *J* = 3.4 Hz), 5.04 (1 H, dt, *J* = 8.3, 5.6 Hz), 4.53 (1 H, d, *J* = 5.3 Hz), 4.22 (2 H, d, *J* = 6.2 Hz), 4.07–3.82 (4 H, m), 3.78–3.62 (2 H, m), 3.33 (1 H, dd, *J* = 14.8, 3.3 Hz), 3.03–2.93 (3 H, m), 2.89 (1 H, dd, *J* = 14.8, 8.1 Hz), 2.80 (1 H, dd, *J* = 13.7, 6.9 Hz),

2.64 (1 H, dd, $J = 14.1, 10.0$ Hz), 1.97 (1 H, m), 0.85 (3 H, d, $J = 6.6$ Hz), 0.82 (3 H, d, $J = 6.7$ Hz) ppm; $^{13}\text{C NMR} + \text{DEPT}$ (100 MHz, CDCl_3) δ 155.4 (C), 155.1 (C), 150.7 (C_{ar}), 138.1 (C_{ar}), 137.5 (C_{ar}), 129.5 ($4 \times \text{CH}_{\text{ar}}$ and C_{ar}), 128.7 ($2 \times \text{CH}_{\text{ar}}$), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 127.6 ($2 \times \text{CH}_{\text{ar}}$), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 114.1 ($2 \times \text{CH}_{\text{ar}}$), 108.7 (CH), 75.4 (CH), 74.9 (CH_2), 72.3 (CH), 71.8 (CH), 71.6 (CH_2), 58.8 (CH_2), 55.2 (CH), 53.7 (CH_2), 51.6 (CH), 45.1 (CH_2), 35.3 (CH_2), 27.3 (CH), 20.2 (CH_3), 19.9 (CH_3) ppm; **HRMS** (ESI $^{+}$) for $\text{C}_{35}\text{H}_{44}\text{N}_4\text{O}_9\text{SNa}$ ($\text{M} + \text{Na}$) $^{+}$ calcd. 719.2721, found 719.2714.

Protease Inhibitor 4d

Following general procedure **D** (2.2), the reaction of alcohol **6d** (350 mg, 1.25 mmol) with DSC (480 mg, 1.88 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2 to 96:4) the corresponding mixed carbonate **23d** as a white solid (451 mg, 1.07 mmol, 82%). Following general procedure **E** (2.2), the reaction of this carbonate (210 mg, 0.50 mmol) and amine **7b** (192 mg, 0.43 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2 to 94:6) and HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4) the PI **4d** as a white solid (207 mg, 63%). **Formula** $\text{C}_{37}\text{H}_{45}\text{N}_5\text{O}_{10}\text{S}$; **Mw** 751.85; **R_f** 0.30 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4); **Mp** 109–111 °C; $[\alpha]_{\text{D}}^{25} +53.8$ (c 0.59, CHCl_3 , 26 °C); **IR** (film) 3342 (br. w), 2961 (w), 2876 (w), 1714 (s), 1660 (vs), 1581 (m), 1530 (m), 1462 (m), 1330 (m), 1237 (s), 1181 (m), 1141 (s), 1031 (m), 908 (m), 730 (vs), 701 (s) cm^{-1} ; $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$, $T = 353$ K) δ 7.95 (1 H, q, $J = 4.5$ Hz), 7.68 (1 H, d, $J = 1.8$ Hz), 7.57 (1 H, dd, $J = 8.3, 1.8$ Hz), 7.43 (1 H, br. s), 7.33 (1 H, d, $J = 8.2$ Hz), 7.33–7.08 (10 H, m), 6.92 (1 H, br. s), 5.67 (1 H, d, $J = 5.1$ Hz), 5.07 (1 H, d, $J = 3.4$ Hz), 5.02 (1 H, br. s), 4.66 (1 H, d, $J = 6.2$ Hz), 4.20 (2 H, d, $J = 6.2$ Hz), 4.02–3.83 (3 H, m), 3.72–3.57 (3 H, m), 3.37 (1 H, dd, $J = 14.6, 3.1$ Hz), 3.04 (1 H, dd, $J = 13.9, 8.0$ Hz), 2.97 (3 H, d, $J = 4.8$ Hz), 3.01–2.92 (3 H, m), 2.87 (1 H, dd, $J = 13.8, 6.9$ Hz), 2.61 (1 H, dd, $J = 13.8, 10.2$ Hz), 1.98 (1 H, m), 0.85 (3 H, d, $J = 6.7$ Hz), 0.81 (3 H, d, $J = 6.6$ Hz) ppm; $^{13}\text{C NMR} + \text{DEPT}$ (100 MHz, CDCl_3) δ 164.7 (C_{ar}), 155.4 (C), 155.2 (C), 148.1 (C_{ar}), 147.7 (C_{ar}), 138.1 (C_{ar}), 137.5 (C_{ar}), 129.7 (C_{ar}), 129.4 ($2 \times \text{CH}_{\text{ar}}$), 128.7 ($2 \times \text{CH}_{\text{ar}}$), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 127.6 ($2 \times \text{CH}_{\text{ar}}$), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 124.2 (CH_{ar}), 116.1 (CH_{ar}), 108.7 (CH), 108.4 (CH_{ar}), 75.4 (CH), 74.8 (CH_2), 72.3 (CH), 71.8 (CH), 71.6 (CH_2), 58.7 (CH_2), 55.3 (CH), 53.7 (CH_2), 51.6 (CH), 45.1 (CH_2), 35.4 (CH_2), 29.5 (CH_3), 27.2 (CH), 20.1 (CH_3), 19.9 (CH_3) ppm; **HRMS** (ESI $^{+}$) for $\text{C}_{37}\text{H}_{45}\text{N}_5\text{O}_{10}\text{SNa}$ ($\text{M} + \text{Na}$) $^{+}$ calcd. 774.2779, found 774.2771.

Protease Inhibitor 3e

Following general procedure **D** (2.2), the reaction of alcohol **6e** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2 to 94:6) the corresponding mixed carbonate **23e** as a pale yellow oil

(234 mg, 0.54 mmol, 86%). Following general procedure **E** (2.2), the reaction of this carbonate (220 mg, 0.51 mmol) with amine **7a** (189 mg, 0.48 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) and by HPLC (CH₂Cl₂/MeOH 96:4) the PI **3e** as a white solid (234 mg, 68%). **Formula** C₃₆H₄₆N₄O₉S; **Mw** 710.84; **R_f** 0.31 (CH₂Cl₂/MeOH 96:4); **Mp** 95–97 °C; [α]_D +21.6 (c 0.87, CHCl₃, 27 °C); **IR** (film) 3363 (m), 2960 (w), 1712 (m), 1661 (m), 1596 (s), 1534 (m), 1313 (m), 1146 (s), 1090 (s), 909 (m), 729 (vs), 701 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.55 (2 H, d, *J* = 8.7 Hz), 7.39–7.12 (10 H, m), 6.75 (1 H, t, *J* = 5.7 Hz), 6.69 (2 H, d, *J* = 8.7 Hz), 5.71 (1 H, d, *J* = 5.3 Hz), 5.18 (1 H, d, *J* = 5.3 Hz), 5.06 (1 H, dt, *J* = 8.5, 5.9 Hz), 4.51 (1 H, dd, *J* = 14.8, 5.9 Hz), 4.47 (1 H, dd, *J* = 14.8, 5.9 Hz), 4.20 (2 H, br. s), 3.96 (1 H, dd, *J* = 10.2, 6.1 Hz), 3.93–3.86 (4 H, m), 3.75 (1 H, dd, *J* = 10.5, 3.6 Hz), 3.72–3.64 (3 H, m), 3.47 (1 H, d, *J* = 3.0 Hz), 3.15 (1 H, dd, *J* = 15.2, 8.5 Hz), 3.05 (1 H, dd, *J* = 14.0, 4.2 Hz), 3.01–2.92 (2 H, m), 2.88 (1 H, dd, *J* = 8.3, 5.4 Hz), 2.80 (1 H, dd, *J* = 13.6, 6.8 Hz), 2.76 (1 H, dd, *J* = 14.3, 10.2 Hz), 1.83 (1 H, m), 0.94 (3 H, d, *J* = 6.5 Hz), 0.90 (3 H, d, *J* = 6.5 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 168.9 (C), 155.1 (C), 150.8 (C_{ar}), 137.9 (C_{ar}), 137.8 (C_{ar}), 129.5 (2 $\times$ CH_{ar}), 129.4 (2 $\times$ CH_{ar}), 128.8 (2 $\times$ CH_{ar}), 128.5 (2 $\times$ CH_{ar}), 127.8 (2 $\times$ CH_{ar}), 127.6 (CH_{ar}), 126.6 (CH_{ar}), 126.0 (C_{ar}), 114.1 (2 $\times$ CH_{ar}), 108.8 (CH), 80.6 (CH), 73.8 (CH₂), 72.9 (CH), 72.1 (CH), 71.0 (CH₂), 68.2 (CH₂), 58.9 (CH₂), 55.5 (CH), 53.7 (CH₂), 51.3 (CH), 42.9 (CH₂), 35.4 (CH₂), 27.3 (CH), 20.2 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI+) for C₃₆H₄₆N₄O₉S (M + Na)⁺ calcd. 733.2878, found 733.2873.

Protease Inhibitor **4e**

Following general procedure **D** (2.2), the reaction of alcohol **6e** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) the corresponding mixed carbonate **23e** as a pale yellow oil (234 mg, 0.54 mmol, 86%). Following general procedure **E** (2.2), the reaction of this carbonate (212 mg, 0.49 mmol) with amine **7b** (208 mg, 0.46 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 96:4 to 94:6) and by HPLC (CH₂Cl₂/MeOH 96:4) the PI **4e** as a white solid (248 mg, 70%). **Formula** C₃₈H₄₇N₅O₁₀S; **Mw** 795.87; **R_f** 0.29 (CH₂Cl₂/MeOH 95:5); **Mp** 101–103 °C; [α]_D +26.1 (c 0.52, CHCl₃, 26 °C); **IR** (film) 3338 (br. w), 2960 (w), 1712 (m), 1655 (vs), 1580 (m), 1534 (m), 1326 (m), 1271 (m), 1239 (m), 1121 (s), 909 (s), 728 (vs), 700 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.67 (1 H, d, *J* = 1.6 Hz), 7.61 (1 H, dd, *J* = 8.3, 1.8 Hz), 7.40 (1 H, d, *J* = 8.3 Hz), 7.37–7.11 (10 H, m), 6.80 (1 H, t, *J* = 5.6 Hz), 5.93 (1 H, br. s), 5.70 (1 H, d, *J* = 5.1 Hz), 5.44 (1 H, d, *J* = 5.0 Hz), 5.04 (1 H, dt, *J* = 8.7, 5.9 Hz), 4.51 (1 H, dd, *J* = 16.9, 5.8 Hz), 4.47 (1 H, dd, *J* = 16.9, 5.8 Hz), 4.00–3.84 (5 H, m), 3.80–3.73 (2 H, m), 3.69 (1 H, d, *J* = 15.3 Hz), 3.66 (1 H, dd, *J* = 10.0, 5.5 Hz), 3.50 (1 H, d, *J* = 2.5 Hz), 3.14 (3 H, d, *J* = 4.8 Hz), 3.11 (2 H, dd, *J* = 13.1, 4.1 Hz), 3.07 (1 H, dd, *J* = 13.7, 4.1 Hz), 2.98–2.83 (3 H, m), 2.74 (1 H, dd, *J* = 13.7, 10.4 Hz), 1.86 (1 H, m), 0.91 (3 H, d, *J* = 6.4 Hz), 0.89 (3 H, d, *J* = 6.4 Hz) ppm. **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 169.1 (C), 164.8 (C_{ar}), 55.2 (C), 148.1 (C_{ar}), 147.9 (C_{ar}), 137.9 (C_{ar}), 137.5 (C_{ar}), 129.5 (C_{ar}), 129.3 (2 $\times$ CH_{ar}), 128.7 (2 $\times$ CH_{ar}), 128.4 (2 $\times$ CH_{ar}), 127.7 (2 $\times$ CH_{ar}), 127.6 (CH_{ar}), 126.5 (CH_{ar}), 124.2 (CH_{ar}), 116.0 (CH_{ar}), 108.8 (CH), 108.4 (CH_{ar}), 80.5 (CH), 73.8 (CH₂), 72.9 (CH), 72.1 (CH), 71.0 (CH₂), 68.1 (CH₂), 58.8 (CH₂), 55.6 (CH),

53.6 (CH₂), 51.3 (CH), 42.8 (CH₃), 35.5 (CH₂), 29.4 (CH₃), 27.1 (CH), 20.1 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI⁺) for C₃₈H₄₇N₅O₁₀SNa (M + Na)⁺ calcd. 788.2936, found 788.2925.

Protease Inhibitor 5e

Following general procedure **D** (2.2), the reaction of alcohol **6e** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) the corresponding mixed carbonate **23e** as a pale yellow oil (234 mg, 0.54 mmol, 86%). Following general procedure **E** (2.2), this carbonate was then reacted with amine **7c** (200 mg, 0.49 mmol) to afford after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) and by HPLC (CH₂Cl₂/MeOH 97:3) the PI **5e** as a white solid (313 mg, 88%). **Formula** C₃₇H₄₇N₃O₁₀S; **Mw** 725.85; **R_f** 0.39 (CH₂Cl₂/MeOH 95:5); **Mp** 88–90 °C; [α]_D +18.6 (c 0.93, CHCl₃, 25 °C); **IR** (film) 3360 (w), 2961 (w), 2931 (w), 1715 (m), 1662 (m), 1532 (m), 1332 (m), 1258 (s), 1150 (s), 1091 (s), 1022 (m), 908 (m), 727 (vs), 700 (s), 558 (vs) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (2 H, d, *J* = 9.0 Hz), 7.37–7.12 (10 H, m), 6.99 (2 H, d, *J* = 9.0 Hz), 6.79 (1 H, t, *J* = 5.7 Hz), 5.70 (1 H, d, *J* = 5.2 Hz), 5.41 (1 H, d, *J* = 8.8 Hz), 5.05 (1 H, dt, *J* = 8.6, 5.8 Hz), 4.50 (1 H, dd, *J* = 14.8, 5.9 Hz), 4.45 (1 H, dd, *J* = 14.8, 5.9 Hz), 3.93 (1 H, dd, *J* = 10.0, 6.1 Hz), 3.92–3.82 (4 H, m), 3.87 (3 H, s), 3.78–3.72 (2 H, m), 3.67 (1 H, dd, *J* = 10.0, 5.7 Hz), 3.65 (1 H, d, *J* = 14.8 Hz), 3.45 (1 H, d, *J* = 3.2 Hz), 3.14 (1 H, dd, *J* = 15.3, 8.3 Hz), 3.10–3.01 (2 H, m), 2.95 (1 H, dd, *J* = 13.5, 8.1 Hz), 2.88 (1 H, dd, *J* = 8.8, 5.2 Hz), 2.84 (1 H, dd, *J* = 13.5, 6.9 Hz), 2.76 (1 H, dd, *J* = 14.0, 10.2 Hz), 1.87 (1 H, m), 0.91 (3 H, d, *J* = 6.6 Hz), 0.88 (3 H, d, *J* = 6.6 Hz) ppm; ¹³C NMR + DEPT (100 MHz, CDCl₃) δ 168.9 (C), 163.0 (C_{ar}), 155.1 (C), 137.9 (C_{ar}), 137.8 (C_{ar}), 129.6 (C_{ar}), 129.4 (2 × CH_{ar}), 129.3 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 128.4 (2 × CH_{ar}), 127.7 (2 × CH_{ar}), 127.5 (CH_{ar}), 126.5 (CH_{ar}), 114.3 (2 × CH_{ar}), 108.7 (CH), 80.5 (CH), 73.8 (CH₂), 72.9 (CH), 72.1 (CH), 71.0 (CH₂), 68.1 (CH₂), 58.7 (CH₂), 55.6 (CH₃, C-18), 55.5 (CH), 53.5 (CH₂), 51.3 (CH), 42.8 (CH₂), 35.4 (CH₂), 27.1 (CH), 20.1 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI⁺) for C₃₇H₄₇N₃O₁₀SNa (M + Na)⁺ calcd 748.2874, found 748.2894.

Protease Inhibitor 4f

Following general procedure **D** (2.2), the reaction of alcohol **6f** (174 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 94:6) the corresponding mixed carbonate **23f** as a pale yellow oil (183 mg, 0.51 mmol, 64%). Following general procedure **E** (2.2), reaction of this carbonate (149 mg, 0.42 mmol) with amine **7b** (178 mg, 0.40 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 96:4 to 93:7) and by HPLC (CH₂Cl₂/MeOH 95:5) the PI **4f** as a white solid (232 mg, 84%). **Formula** C₃₂H₄₃N₅O₁₀S; **Mw** 689.78; **R_f** 0.20 (CH₂Cl₂/MeOH 95:5); **Mp** 91–93 °C; [α]_D +22.1 (c 0.84, CHCl₃, 26 °C); **IR** (film) 3348 (br.

w), 2959 (w), 1716 (m), 1659 (vs), 1581 (m), 1327 (m), 1272 (m), 1240 (m), 1146 (m), 1123 (m), 733 (vs) cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67 (1 H, d, $J = 1.4$ Hz), 7.62 (1 H, dd, $J = 8.2, 1.7$ Hz), 7.42 (1 H, d, $J = 8.3$ Hz), 7.31–7.17 (5 H, m), 6.46 (1 H, br. s), 5.77 (1 H, d, $J = 5.1$ Hz), 5.74 (1 H, br. s), 5.30 (1 H, d, $J = 8.9$ Hz), 5.07 (1 H, dt, $J = 8.7, 5.8$ Hz), 3.99 (1 H, dd, $J = 9.7, 6.3$ Hz), 3.98–3.81 (4 H, m), 3.80 (1 H, dd, $J = 10.5, 3.6$ Hz), 3.71–3.63 (3 H, m), 3.54 (1 H, d, $J = 3.0$ Hz), 3.16 (3 H, d, $J = 4.9$ Hz), 3.13–3.01 (3 H, m), 2.99–2.83 (3 H, m), 2.86 (3 H, d, $J = 5.0$ Hz), 2.77 (1 H, dd, $J = 13.9, 10.4$ Hz), 1.86 (1 H, m), 0.92 (3 H, d, $J = 6.7$ Hz), 0.90 (3 H, d, $J = 6.7$ Hz) ppm; $^{13}\text{C NMR} + \text{DEPT}$ (100 MHz, CDCl_3) δ 169.7 (C), 164.8 (C_{ar}), 155.1 (C), 148.2 (C_{ar}), 147.9 (C_{ar}), 137.8 (C_{ar}), 129.6 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 128.5 ($2 \times \text{CH}_{\text{ar}}$), 126.6 (CH_{ar}), 124.2 (CH_{ar}), 116.1 (CH_{ar}), 108.8 (CH), 108.4 (CH_{ar}), 80.4 (CH), 73.8 (CH_2), 72.8 (CH), 72.2 (CH), 71.0 (CH_2), 68.2 (CH_2), 58.9 (CH_2), 55.5 (CH), 53.6 (CH_2), 51.4 (CH), 35.5 (CH_2), 29.5 (CH_3), 27.2 (CH), 25.6 (CH_3), 20.1 (CH_3), 19.9 (CH_3) ppm; **HRMS** (ESI^+) for $\text{C}_{32}\text{H}_{43}\text{N}_5\text{O}_{10}\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ calcd. 712.2623, found 712.2626.

Protease Inhibitor **4g**

Following general procedure **D** (2.2), the reaction of alcohol **6g** (200 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3 to 95:5) the corresponding mixed carbonate **23g** as a pale yellow oil (206 mg, 0.55 mmol, 69%). Following general procedure **E** (2.2), the reaction of this carbonate (112 mg, 0.30 mmol) with amine **7b** (130 mg, 0.29 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3 to 95:5) and by HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) the PI **4g** as a white solid (124 mg, 61%). **Formula** $\text{C}_{33}\text{H}_{45}\text{N}_5\text{O}_9\text{S}$; **Mw** 703.80; **R_f** 0.25 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5); **Mp** 85–87 °C; $[\alpha]_{\text{D}}^{25} +21.9$ (c 1.13, CHCl_3 , 26 °C); **IR** (film) 3307 (br. w), 2959 (w), 1716 (m), 1654 (vs), 1580 (m), 1463 (m), 1327 (m), 1271 (m), 1239 (m), 1121 (s), 730 (vs) cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (1 H, s), 7.59 (1 H, d, $J = 8.3$ Hz), 7.37 (1 H, d, $J = 8.3$ Hz), 7.29–7.14 (5 H, m), 5.78 (1 H, d, $J = 5.3$ Hz), 5.67 (1 H, d, $J = 8.5$ Hz), 5.57 (1 H, br. s), 5.03 (1 H, dt, $J = 8.4, 6.1$ Hz), 4.16–3.80 (8 H, m), 3.73 (1 H, br. s), 3.61 (1 H, dd, $J = 9.5, 6.4$ Hz), 3.13 (3 H, d, $J = 4.8$ Hz), 3.11–2.93 (4 H, m), 2.96 (3 H, s), 2.93 (3 H, s), 2.92–2.84 (2 H, m), 2.80 (1 H, dd, $J = 13.9, 9.5$ Hz), 1.86 (1 H, m), 0.88 (6 H, d, $J = 6.5$ Hz) ppm; $^{13}\text{C NMR} + \text{DEPT}$ (100 MHz, CDCl_3) δ 168.8 (C), 164.8 (C_{ar}), 155.4 (C), 148.0 (C_{ar}), 147.8 (C_{ar}), 137.9 (C_{ar}), 129.6 (C_{ar}), 129.4 ($2 \times \text{CH}_{\text{ar}}$), 128.4 ($2 \times \text{CH}_{\text{ar}}$), 126.5 (CH_{ar}), 124.1 (CH_{ar}), 115.9 (CH_{ar}), 108.7 (CH), 108.3 (CH_{ar}), 79.6 (CH), 73.7 (CH_2), 72.6 (CH), 72.1 (CH), 70.9 (CH_2), 68.0 (CH_2), 58.6 (CH_2), 55.5 (CH), 53.5 (CH_2), 51.7 (CH), 36.5 (CH_3), 35.7 (CH_2), 35.5 (CH_3), 29.4 (CH_3), 27.1 (CH), 20.1 (CH_3), 19.9 (CH_3) ppm; **HRMS** (ESI^+) for $\text{C}_{33}\text{H}_{45}\text{N}_5\text{O}_{10}\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ calcd. 726.2779, found 726.2778

Protease Inhibitor 5g

Following general procedure **D** (2.2), the reaction of alcohol **6g** (200 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 97:3 to 95:5) the corresponding mixed carbonate **23g** as a pale yellow oil (206 mg, 0.55 mmol, 69%). Following general procedure **E** (2.2), this carbonate was then reacted with amine **7c** (203 mg, 0.50 mmol) to afford after purification by column chromatography (CH₂Cl₂/MeOH 97:3 to 95:5) and by HPLC (CH₂Cl₂/MeOH 97:3) the PI **5g** as a white solid (273 mg, 83%). **Formula** C₃₂H₄₅N₃O₁₀S; **Mw** 663.78; **R_f** 0.35 (CH₂Cl₂/MeOH 95:5); **Mp** 89–90 °C; [α]_D +19.3 (*c* 1.09, CHCl₃, 24 °C); **IR** (film) 3341 (w), 2959 (w), 2872 (w), 1716 (m), 1647 (m), 1497 (m), 1333 (m), 1258 (s), 1151 (vs), 1092 (s), 1023 (s), 730 (vs), 560 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.71 (2 H, d, *J* = 8.6 Hz), 7.32–7.20 (5 H, m), 6.99 (2 H, d, *J* = 9.0 Hz), 5.77 (1 H, d, *J* = 5.2 Hz), 5.53 (1 H, d, *J* = 8.3 Hz), 5.07 (1 H, dt, *J* = 8.3, 6.6 Hz), 4.17–3.82 (8 H, m), 3.88 (3 H, s), 3.67 (1 H, d, *J* = 1.9 Hz), 3.63 (1 H, dd, *J* = 10.0, 6.3 Hz), 3.18–2.76 (7 H, m), 2.98 (3 H, s, H-9), 2.94 (3 H, s, H-9), 1.84 (1 H, m), 0.92 (3 H, d, *J* = 6.6 Hz), 0.88 (3 H, d, *J* = 6.4 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 168.8 (C), 163.0 (C_{ar}), 155.4 (C), 137.8 (C_{ar}), 129.8 (C_{ar}), 129.5 (2 $\times$ CH_{ar}), 129.4 (2 $\times$ CH_{ar}), 128.5 (2 $\times$ CH_{ar}), 126.6 (CH_{ar}), 114.3 (2 $\times$ CH_{ar}), 108.7 (CH), 79.6 (CH), 73.8 (CH₂), 72.7 (CH), 72.1 (CH), 70.8 (CH₂), 68.1 (CH₂), 58.7 (CH₂), 55.6 (CH₃), 55.4 (CH), 53.6 (CH₂), 51.8 (CH), 36.5 (CH₃), 35.6 (CH₃), 35.5 (CH₂), 27.2 (CH), 20.1 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI⁺) for C₃₂H₄₅N₃O₁₀SNa (M + Na)⁺ calcd 686.2718, found 686.2744.

Protease Inhibitor 4h

Following general procedure **D** (2.2), the reaction of alcohol **6h** (115 mg, 0.56 mmol) with DSC (215 mg, 0.84 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 99:1 to 97:3) the corresponding mixed carbonate **23h** as a pale yellow oil (136 mg, 0.39 mmol, 70%). Following general procedure **E** (2.2), this carbonate was then reacted with amine **7b** (156 mg, 0.35 mmol) to afford after purification by column chromatography (CH₂Cl₂/MeOH 95:5 to 90:10) and by HPLC (CH₂Cl₂/MeOH 96:4) the PI **4h** as a white solid (182 mg, 77%). **Formula** C₃₂H₄₁FN₄O₉S; **Mw** 676.75; **R_f** 0.30 (CH₂Cl₂/MeOH 95:5); **Mp** 116–118 °C; [α]_D +18.0 (*c* 1.03, CHCl₃, 26 °C); **IR** (film) 3339 (m), 2960 (w), 2874 (w), 1716 (m), 1660 (vs), 1581 (m), 1463 (m), 1327 (m), 1255 (s), 1146 (vs), 1021 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.66 (1 H, d, *J* = 1.4 Hz), 7.62 (1 H, dd, *J* = 8.3, 1.7 Hz), 7.43 (1 H, d, *J* = 8.2 Hz), 7.33–7.21 (5 H, m), 5.79 (1 H, d, *J* = 5.1 Hz), 5.29 (1 H, q, *J* = 5.1 Hz), 5.11 (1 H, dt, *J* = 8.7, 5.9 Hz), 5.00 (1 H, q, *J* = 8.8 Hz), 4.73 (1 H, dd, *J* = 16.7, 3.0 Hz), 4.53 (1 H, dd, *J* = 48.4, 2.8 Hz), 4.04–3.82 (5 H, m), 3.81–3.65 (4 H, m), 3.59 (1 H, br. s), 3.18 (3 H, d, *J* = 5.1 Hz), 3.16–3.05 (2 H, m), 3.04–2.92 (3 H, m), 2.88–2.79

(2 H, m), 1.92 (1 H, m), 0.94 (3 H, d, $J = 6.6$ Hz), 0.91 (3 H, d, $J = 6.6$ Hz) ppm; ^{13}C NMR + DEPT (100 MHz, CDCl_3) δ 164.7 (C_{ar}), 162.6 (CF , d, $J = 236.0$ Hz), 155.2 (C), 148.2 (C_{ar}), 147.9 (C_{ar}), 137.5 (C_{ar}), 129.7 (C_{ar}), 129.4 ($2 \times \text{CH}_{\text{ar}}$), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 126.8 (CH_{ar}), 124.2 (CH_{ar}), 116.3 (CH_{ar}), 109.0 (CH), 108.4 (CH_{ar}), 92.8 (CH_2 , d, $J = 16.8$ Hz), 79.7 (CH), 74.3 (CH_2), 72.8 (CH), 72.4 (CH), 71.0 (CH_2), 66.3 (CH_2 , d, $J = 34.0$ Hz), 59.0 (CH_2), 55.3 (CH), 53.9 (CH_2), 51.5 (CH), 35.6 (CH_2), 29.6 (CH_3), 27.3 (CH), 20.2 (CH_3), 19.9 (CH_3) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -105.6 (ddt, $J = 48.5, 16.5, 13.2$ Hz); HRMS (ESI^+) for $\text{C}_{32}\text{H}_{41}\text{FN}_4\text{O}_9\text{SK}$ ($\text{M}+\text{K}$) $^+$ calcd 715.2210, found 715.2207.

Protease Inhibitor **4i**

Following general procedure **D** (2.2), the reaction of alcohol **6i** (55 mg, 0.23 mmol) with DSC (88 mg, 0.35 mmol) afforded the corresponding mixed carbonate **23i** as a pale yellow oil (85 mg, 0.22 mmol, 93%). Following general procedure **E** (2.2), subsequent reaction with amine **7b** (100 mg, 0.22 mmol) afforded after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4 to 95:5) and by HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3) the PI **4i** as a white solid (110 mg, 70%). **Formula** $\text{C}_{32}\text{H}_{41}\text{F}_3\text{N}_4\text{O}_9\text{S}$; **Mw** 714.75; **Mp** 110–112 °C; **R_f** 0.30 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4); **[α]_D** +14.2 (c 0.61, CHCl_3 , 23 °C); **IR** (film) 3339 (m), 2960 (w), 2874 (w), 1716 (m), 1660 (vs), 1581 (m), 1463 (m), 1327 (m), 1255 (s), 1146 (vs), 1021 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (1 H, d, $J = 1.6$ Hz), 7.63 (1 H, dd, $J = 8.3, 1.8$ Hz), 7.43 (1 H, d, $J = 8.2$ Hz), 7.33–7.19 (5 H, m), 5.76 (1 H, d, $J = 5.3$ Hz), 5.29 (1 H, q, $J = 4.9$ Hz), 5.10 (1 H, dt, $J = 9.0, 5.8$ Hz), 5.02 (1 H, d, $J = 9.1$ Hz), 3.99 (1 H, dd, $J = 10.0, 5.9$ Hz), 3.96–3.84 (3 H, m), 3.79 (1 H, dd, $J = 10.2, 3.7$ Hz), 3.70 (1 H, dd, $J = 10.0, 5.7$ Hz), 3.59 (1 H, d, $J = 2.5$ Hz), 3.51–3.42 (2 H, m), 3.34 (1 H, m), 3.18 (3 H, d, $J = 5.2$ Hz), 3.16 (1 H, dd, $J = 15.2, 8.8$ Hz), 3.09 (1 H, dd, $J = 14.1, 4.0$ Hz), 3.01 (1 H, dd, $J = 15.2, 2.7$ Hz), 2.98 (1 H, dd, $J = 13.4, 8.0$ Hz), 2.90 (1 H, dd, $J = 9.0, 5.2$ Hz), 2.85 (1 H, dd, $J = 13.3, 6.9$ Hz), 2.79 (1 H, dd, $J = 14.1, 9.6$ Hz), 2.33 (2 H, qt, $J = 10.7, 6.7$ Hz), 1.86 (1 H, m), 0.94 (3 H, d, $J = 6.6$ Hz), 0.91 (3 H, d, $J = 6.6$ Hz) ppm; ^{13}C NMR + DEPT (100 MHz, CDCl_3) δ 164.7 (C_{ar}), 155.2 (C), 148.2 (C_{ar}), 147.9 (C_{ar}), 137.7 (C_{ar}), 129.7 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 128.5 ($2 \times \text{CH}_{\text{ar}}$), 126.7 (CH_{ar}), 124.2 (CH_{ar}), 116.3 (CH_{ar}), 109.0 (CH), 108.4 (CH_{ar}), 80.0 (CH), 74.2 (CH_2), 72.9 (CH), 72.4 (CH), 71.1 (CH_2), 61.7 (CH_2 , d, $J = 3.3$ Hz), 59.0 (CH_2), 55.5 (CH), 53.8 (CH_2), 51.4 (CH), 35.6 (CH_2), 34.4 (CH_2 , q, $J = 28.5$ Hz), 29.6 (CH_3), 27.3 (CH), 20.1 (CH_3), 19.9 (CH_3) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -64.88 (CF_3 , t, $J = 10.6$ Hz), HRMS (ESI^+) for $\text{C}_{32}\text{H}_{41}\text{F}_3\text{N}_4\text{O}_9\text{SK}$ ($\text{M}+\text{K}$) $^+$ calcd. 753.2178, found 753.2172.

Protease Inhibitor 3j

Following general procedure **D** (2.2), the reaction of alcohol **6j** (165 mg, 1.00 mmol) with DSC (384 mg, 1.50 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 99:1 to 95:5) the corresponding mixed carbonate **23j** as a pale yellow oil (221 mg, 0.72 mmol, 72%). Following general procedure **E** (2.2), this carbonate (110 mg, 0.36 mmol) was then reacted with amine **7a** (125 mg, 0.32 mmol) to afford after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) and by HPLC (CH₂Cl₂/MeOH 96:4) the PI **3j** as a white solid (119 mg, 64%). **Formula** C₂₇H₃₆ClN₃O₇S; **Mw** 582.11; **R_f** 0.26 (CH₂Cl₂/MeOH 97:3); **Mp** 101–103 °C; [α]_D +30.0 (*c* 0.82, CHCl₃, 26 °C); **IR** (film) 3472 (br. w), 3369 (br. w), 2961 (w), 2873 (w), 1712 (m), 1595 (m), 1311 (m), 1145 (s), 1090 (s), 1020 (m), 910 (m), 729 (vs), 551 (s) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.56 (2 H, d, *J* = 8.6 Hz), 7.36–7.20 (5 H), 6.70 (2 H, d, *J* = 8.8 Hz), 5.87 (1 H, d, *J* = 5.1 Hz), 5.09 (1 H, dt, *J* = 8.6, 5.9 Hz), 5.01 (1 H, d, *J* = 8.6 Hz), 4.17 (2 H, s), 4.02–3.88 (5 H, m), 3.83 (1 H, d, *J* = 2.9 Hz), 3.73–3.67 (2 H, m), 3.18 (1 H, dd, *J* = 15.2, 8.8 Hz), 3.12 (1 H, dd, *J* = 8.8, 5.1 Hz), 3.08 (1 H, dd, *J* = 14.1, 4.0 Hz), 3.01–2.93 (2 H, m), 2.84–2.76 (2 H, m), 1.84 (1 H, m), 0.95 (3 H, d, *J* = 6.7 Hz), 0.90 (3 H, d, *J* = 6.6 Hz) ppm; **¹³C NMR + DEPT** (100 MHz, CDCl₃) δ 154.8 (C), 150.8 (C_{ar}), 137.5 (C_{ar}), 129.5 (2 $\times$ CH_{ar}), 129.3 (2 $\times$ CH_{ar}), 128.6 (2 $\times$ CH_{ar}), 126.8 (CH_{ar}), 126.0 (C_{ar}), 114.1 (2 $\times$ CH_{ar}), 108.9 (CH), 77.3 (CH₂), 72.8 (CH), 72.1 (CH), 71.0 (CH₂), 59.0 (CH₂), 57.4 (CH), 55.7 (CH), 55.2 (CH), 53.7 (CH₂), 35.5 (CH₂), 27.4 (CH), 20.2 (CH₃), 19.9 (CH₃) ppm; **HRMS** (ESI⁺) for C₂₇H₃₆ClN₃O₇SNa (M + Na)⁺ calcd 604.1855, found 604.1869.

Protease Inhibitor 4j

Following general procedure **D** (2.2), the reaction of alcohol **6j** (165 mg, 1.00 mmol) with DSC (384 mg, 1.50 mmol) afforded after purification by column chromatography (CH₂Cl₂/MeOH 99:1 to 95:5) the corresponding mixed carbonate **23j** as a pale yellow oil (221 mg, 0.72 mmol, 72%). Following general procedure **E** (2.2), this carbonate (110 mg, 0.36 mmol) was then reacted with amine **7b** (142 mg, 0.32 mmol) to afford after purification by column chromatography (CH₂Cl₂/MeOH 98:2 to 96:4) and by HPLC (CH₂Cl₂/MeOH 96:4) the PI **4j** as a white solid (148 mg, 73%). **Formula** C₂₉H₃₇ClN₄O₈S; **Mw** 637.14; **R_f** 0.20 (CH₂Cl₂/MeOH 96:4); **Mp** 138–140 °C; [α]_D +30.3 (*c* 0.58, CHCl₃, 26 °C); **IR** (film) 3337 (m), 2961 (w), 2873 (w), 1710 (m), 1656 (s), 1580 (m), 1324 (m), 1271 (m), 1238 (m), 1143 (m), 909 (m), 727 (vs), 599 (m) cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 7.67 (1 H, d, *J* = 1.6 Hz), 7.63 (1 H, dd, *J* = 8.2, 1.6 Hz), 7.43 (1 H, d, *J* = 8.3 Hz), 7.36–7.20 (5 H, m), 5.87 (1 H, d, *J* = 5.1 Hz), 5.39 (1 H, q, *J* = 4.7 Hz), 5.11–5.04 (2 H, m), 4.03–3.91 (5 H, m), 3.86 (1 H, d, *J* = 3.0 Hz), 3.69 (1 H, dd, *J* = 10.0, 5.6 Hz), 3.62 (1 H, br. s), 3.18 (3 H, d, *J* = 5.1 Hz), 3.21–3.07 (3 H, m), 3.04–2.95 (2 H, m), 2.87–2.77 (2 H, m), 1.86 (1 H, m), 0.94

(3 H, d, $J = 6.6$ Hz), 0.91 (3 H, d, $J = 6.6$ Hz) ppm; ^{13}C NMR + DEPT (100 MHz, CDCl_3) δ 164.7 (C_{ar}), 154.9 (C), 148.2 (C_{ar}), 147.9 (C_{ar}), 137.4 (C_{ar}), 129.7 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 126.9 (CH_{ar}), 124.2 (CH_{ar}), 116.3 (CH_{ar}), 108.7 (CH), 108.4 (CH_{ar}), 77.3 (CH_2), 72.8 (CH), 72.2 (CH), 71.1 (CH_2), 59.0 (CH_2), 57.3 (CH), 55.7 (CH), 55.2 (CH), 53.8 (CH_2), 35.5 (CH_2), 29.6 (CH_3), 27.3 (CH), 20.1 (CH_3), 19.9 (CH_3) ppm; HRMS (ESI^+) for $\text{C}_{29}\text{H}_{37}\text{ClN}_4\text{O}_8\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ calcd 659.1927, found 659.1937.

Protease Inhibitor 4k

Following general procedure **D** (2.2), the reaction of alcohol **6k** (25 mg, 0.17 mmol) with DSC (65 mg, 0.25 mmol) afforded the crude mixed carbonate **23k** as a pale yellow oil, which was subsequently reacted with amine **7b** (90 mg, 0.20 mmol) to afford after purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2 to 96:4) and by HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3) alcohol **6k** (10.2 mg, 41%) and PI **4k** as a white solid (13.1 mg, 12%). **Formula** $\text{C}_{29}\text{H}_{37}\text{FN}_4\text{O}_8\text{S}$; **Mw** 620.69; **R_f** 0.23 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4); **Mp** 122–124 °C; $[\alpha]_{\text{D}}^{25} +11.3$ (c 0.87, CHCl_3 , 26 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.67 (1 H, d, $J = 1.6$ Hz), 7.62 (1 H, dd, $J = 8.2, 1.8$ Hz), 7.42 (1 H, d, $J = 8.3$ Hz), 7.35–7.20 (5 H, m), 5.83 (1 H, d, $J = 5.2$ Hz), 5.43 (1 H, q, $J = 4.9$ Hz), 5.15 (1 H, dt, $J = 8.9, 5.7$ Hz), 5.05 (1 H, d, $J = 9.0$ Hz), 4.55 (1 H, dd, $J = 51.4, 2.3$ Hz), 4.07 (1 H, ddd, $J = 22.4, 11.1, 1.0$ Hz), 3.97 (1 H, dd, $J = 10.0, 5.7$ Hz), 3.95–3.89 (2 H, m), 3.82 (1 H, ddd, $J = 39.8, 11.2, 2.8$ Hz), 3.67 (1 H, dd, $J = 10.0, 5.2$ Hz), 3.62 (1 H, d, $J = 2.1$ Hz), 3.17 (3 H, d, $J = 5.1$ Hz), 3.17 (1 H, dd, $J = 15.2, 8.7$ Hz), 3.13–3.02 (3 H, m), 2.98 (1 H, dd, $J = 13.4, 8.2$ Hz), 4.55 (1 H, dd, $J = 13.5, 6.9$ Hz), 2.80 (1 H, dd, $J = 13.9, 9.3$ Hz), 1.86 (1 H, m), 0.94 (3 H, d, $J = 6.6$ Hz), 0.90 (3 H, d, $J = 6.6$ Hz) ppm; ^{13}C NMR + DEPT (100 MHz, CDCl_3) δ 164.7 (C_{ar}), 154.9 (C), 148.2 (C_{ar}), 147.9 (C_{ar}), 137.4 (C_{ar}), 129.6 (C_{ar}), 129.3 ($2 \times \text{CH}_{\text{ar}}$), 128.6 ($2 \times \text{CH}_{\text{ar}}$), 126.8 (CH_{ar}), 124.2 (CH_{ar}), 116.3 (CH_{ar}), 108.8 (CH), 108.4 (CH_{ar}), 93.2 (CH, d, $J = 179.3$ Hz), 74.9 (CH_2 , d, $J = 22.7$ Hz), 72.8 (CH), 71.7 (CH, d, $J = 9.5$ Hz), 71.2 (CH_2), 59.0 (CH_2), 55.2 (CH), 53.8 (CH_2), 52.2 (CH, d, $J = 23.4$ Hz), 35.6 (CH_2), 29.6 (CH_3), 27.3 (CH), 20.1 (CH_3), 19.9 (CH_3) ppm; ^{19}F NMR (282 MHz, CDCl_3) δ -179.1 (ddt, $J = 51.4, 39.8, 23.0$ Hz) ppm; HRMS (ESI^+) for $\text{C}_{29}\text{H}_{37}\text{FN}_4\text{O}_8\text{SNa}$ ($\text{M} + \text{Na}$) $^+$ calcd 643.2208, found 643.2222.

4 ^1H and ^{13}C NMR spectra for compounds 3, 4 and 5

Compound **3c**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$, $T = 373\text{ K}$)

Compound **3c**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4c**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$, $T = 363\text{ K}$)

Compound **4c**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **3d**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$, $T = 373\text{ K}$)

Compound **3d**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4d**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$, $T = 353\text{ K}$)

Compound **4d**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **3e**: ^1H NMR (400 MHz, CDCl_3)

Compound **3e**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4c**: ^1H NMR (400 MHz, CDCl_3)

Compound **4e**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **5e**: ^1H NMR (400 MHz, CDCl_3)

Compound **5e**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4f**: ^1H NMR (400 MHz, CDCl_3)

Compound **4f**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **5f**: ^1H NMR (400 MHz, CDCl_3)

Compound **5f**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4g**: ^1H NMR (400 MHz, CDCl_3)

Compound **4g**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **5g**: ^1H NMR (400 MHz, CDCl_3)

Compound **5g**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4h**: ^1H NMR (400 MHz, CDCl_3)

Compound **4h**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4i**: ^1H NMR (400 MHz, CDCl_3)

Compound **4i**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **3j**: ^1H NMR (400 MHz, CDCl_3)

Compound **3j**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4j**: ^1H NMR (400 MHz, CDCl_3)

Compound **4j**: ^{13}C NMR (100 MHz, CDCl_3)

Compound **4k**: ^1H NMR (400 MHz, CDCl_3)

Compound **4k**: ^{13}C NMR (100 MHz, CDCl_3)