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Design and synthesis of MMP inhibitors using *N*-arylsulfonylaziridine hydroxamic acids as constrained scaffolds

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Abstract—The synthesis of *cis*- and *trans*-aziridine hydroxamic acid derivatives as MMP inhibitors is described using enantio- and diastereoselective methods for the formation of trisubstituted aziridines. Their preliminary inhibitory activity is reported and discussed in the context of modeling studies.

1. Introduction

The matrix metalloproteinases (MMPs) are zinc-proteinases that belong to three subfamilies comprising the collagenases, stromelysins and gelatinases. They play a critical role in the degradation and remodeling of extracellular matrix.[1] The overproduction of MMPs, as a result of certain pathological conditions, can lead to serious or even fatal disorders such as tumor metastasis, arthritis or multiple sclerosis. Their crucial implication in such pathologies prompted chemists to develop inhibitors such as Batimastat (**1**),[2] CGS 27023A (**2**)[3] or AG3340 (**4**)[4] (Fig. 1). Concurrently, X-ray crystallography and NMR conformational studies provided insights into the mode of action of existing inhibitors. For instance, tertiary structures of MMPs co-crystallized or in solution with a wide range of inhibitors

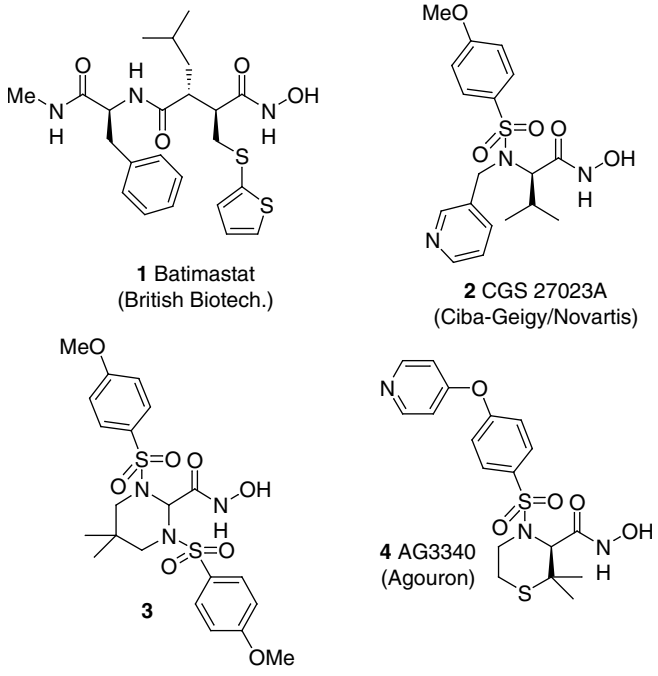

Figure 1. Selected inhibitors of MMPs.

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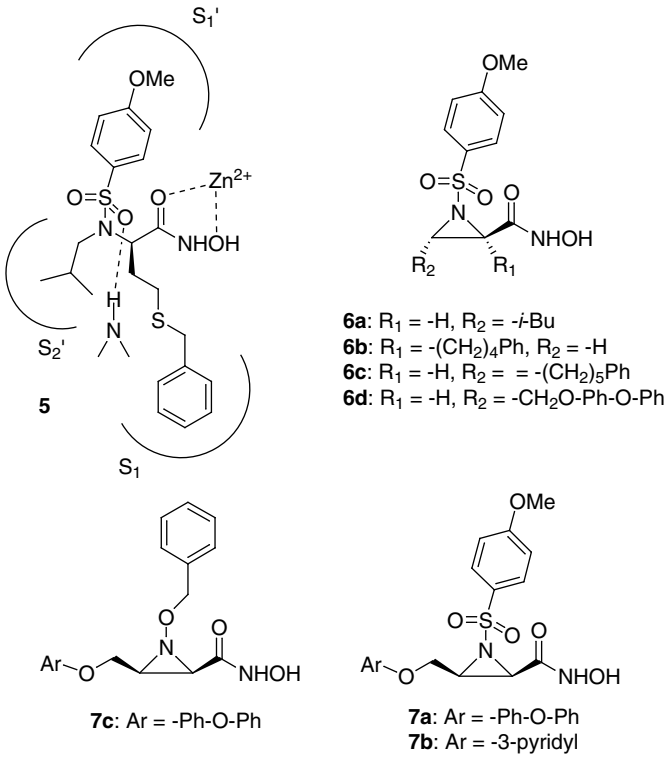


Figure 2. Proposed binding mode of **5** in MMP-3 and designed aziridine-based inhibitors.

such as **1**,[5] **2**,[6] or **3**[7] have been elucidated with good resolution.

Rigidifying acyclic active compounds into motifs that closely resemble their bioactive conformation often provides compounds with enhanced biological potency.[8] Combining our experience in asymmetric methodology[9,10] and our recent interest in MMP inhibitors[11] led us to the preparation of constrained analogs with cyclopropane[12,13] and tetrahydrofuran rings.[14] These were found to be inactive or weakly active inhibitors. We next turned our attention to a more rational design and the exploitation of the aziridine[15] moiety which has only been seldom exploited as a peptidomimetic.[16] Despite the lack of precedents, we considered *N*-arylsulfonyl aziridines as potential constrained MMP inhibitors. However, before embarking on a synthetic program, we chose to conduct molecular modeling studies in order to assess the structural requirements of these enzymes for optimal binding.[14] Since access to enantiomerically pure or enriched fully-substituted aziridines is poorly precedented, we limited our approach to the synthesis of tri-substituted aziridines, and their evaluation as inhibitors of MMPs in vitro (Fig. 2).

2. Results and discussion

2.1. Docking study and design

We have recently disclosed potent acyclic MMP inhibitors, such as **5**,[11] and proposed a binding mode to MMP-3 in analogy to previously reported inhibitors using GRID[17] (Fig. 2). More recently, we found that AutoDock, a fully automated docking program,[18] nicely predicts the same binding mode of **5** to MMP-3 (Fig. 3a). The crucial interactions involving hydrophobic (in S_1 and S_1' pockets), electrostatic (chelation of the zinc dication by the hydroxamic acid), and hydrogen-bonding (the sulfonamide with the protein backbone) are clearly shown pictorially. AutoDock considers the zinc atom as a spherical atom, and the geometries of coordination cannot be predicted. We considered that the electrostatic treatment of the zinc–ligand interaction would be adequate for this study.

As a first generation, we sought to constrain structure **5** as the corresponding *N*-arylsulfonyl *trans*-aziridine **6a**, and the gem disubstituted compound **6b** (Fig. 2). In order to test the design principle, the proposed analogs were docked inside the catalytic site of MMP-3 using AutoDock program suite.[18] The proposed model for **6a** agreed with the expected binding mode as can be seen in Fig. 3b. The modeling of the analog **6b** showed that the ring strain distorted the molecule. This resulted in an unfavorable conformation where the hydroxamic acid did not chelate the zinc atom and the overall orientation was reversed compared to **5**. Consequently, **6b** was not considered as a good candidate and was not synthesized. However the alternative substitution pattern in **6c** was nicely fitted by AutoDock into the required S_1 site (Fig. 3c). Thus, **6a** and **6c** were chosen as first targets for synthesis.

Although a single conformation was found for **6a**, two binding modes within the same energy range were proposed for **6c** where the long hydrophobic side chain fitted in the S_1 or the S_2' pockets (Fig. 3c). This last observation led us to design compounds with less flexible side chains. We

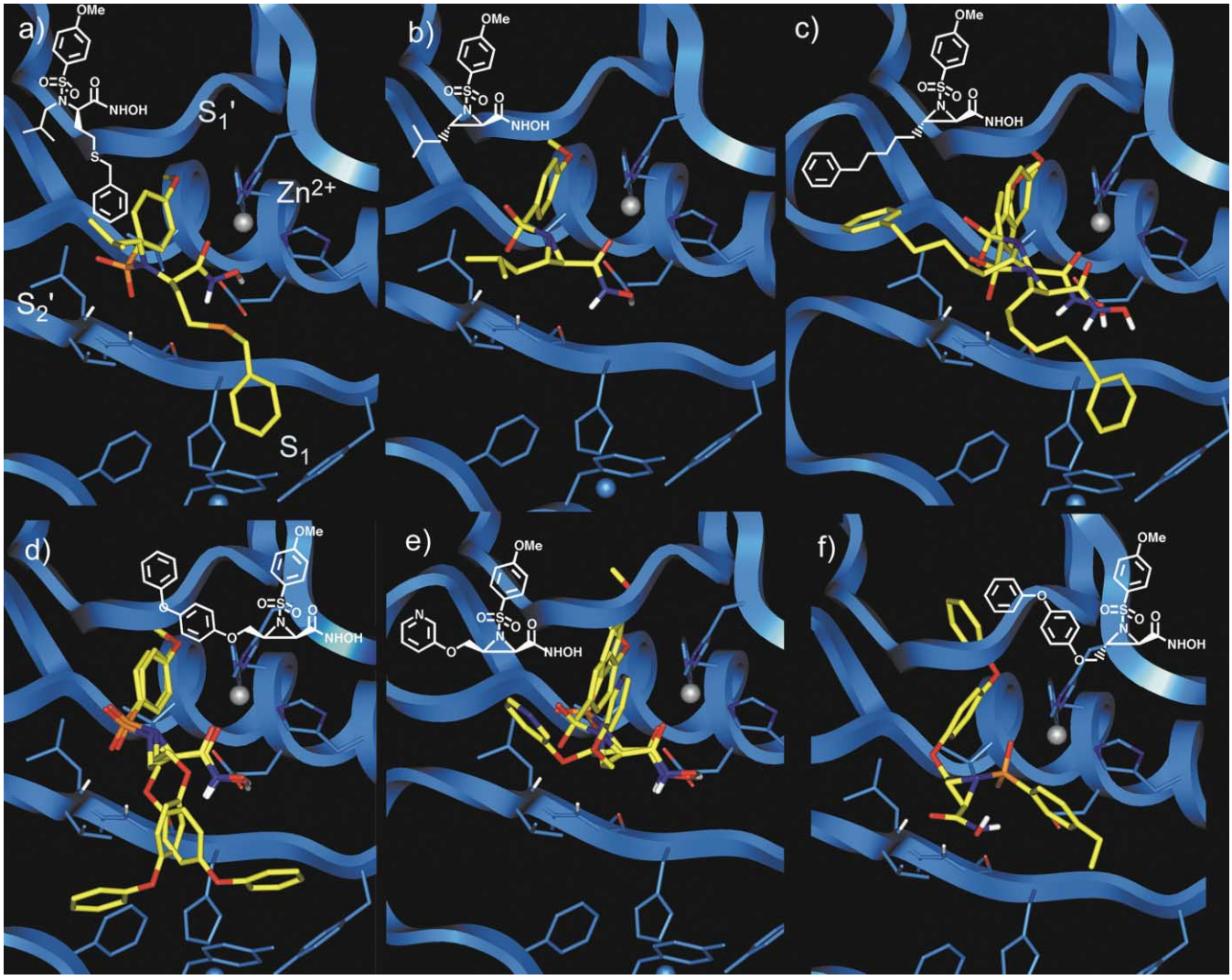


Figure 3. Proposed binding modes of **5** (a), **6a** (b), and **7b** (e), reverse mode for **6d** (f) and two binding modes for **6c** (c), and **7a** (d) in MMP-3 catalytic site from AutoDock docking studies. The zinc atom is represented by the gray circle. See text for details.

chose phenoxyphenyl and 3-pyridyl substituents as appropriate appendages while keeping the *p*-methoxyphenyl sulfonyl group constant.

The *cis*-aziridine analog **7a**, lacking the P_1 side chain, was proposed to adopt the expected conformation and orientation as **5**, **6a** and **6c**, with the phenoxy moiety fitting in the S_1 pocket or a slightly different binding mode. AutoDock suggested two orientations for the phenoxy moiety in **7a** (Fig. 3d). The program predicted the expected conformation and orientation for **7b** (Fig. 3e). Surprinsingly, the *trans*-aziridine analog **6d** bound in a reverse mode with the phenoxyphenyl side-chain fitting into the S_1' pocket while the sulfonamide was chelated to the zinc atom (Fig. 3f). Reverse modes of binding have been observed in docking studies and in crystal structures. For example, the pyridine and the methoxy phenyl rings of CGS 27023A were observed to change positions while docked in HFC.[6] Batimastat co-crystallized in atrolysin C did not chelate the zinc atom with the hydroxamic acid but with the terminal methyl amide.[19] This result prompted us to also consider **7c** as a target structure, in order to assess the strength of the reverse binding mode and the role of the sulfonamide and phenoxyphenyl groups.

2.2. Synthesis

Two methods were used to synthesize the intended aziridines (Fig. 4). The *trans*-aziridine analogs were prepared exploiting a modified version (vide infra) of the procedure developed by Cardillo et al. (Fig. 4a).[20] This auxiliary-based method involves the conjugate addition of *O*-benzyl hydroxylamine to α,β-unsaturated amide followed by intramolecular electrophilic amination to form the aziridine with concomitant expulsion of the benzyloxy group.

Access to the *cis*-aziridine analogs was made possible by a recently disclosed method using the C_2 symmetrical chiral chloroallylic phosphonamide depicted in Fig. 4b.[10] Previous reports from this laboratory had shown that a chloroallyl phosphonamide anion readily added to α,β-unsaturated esters, ketones, lactones and lactams to afford the corresponding trisubstituted cyclopropanes with high diastereoselectivity.[9]

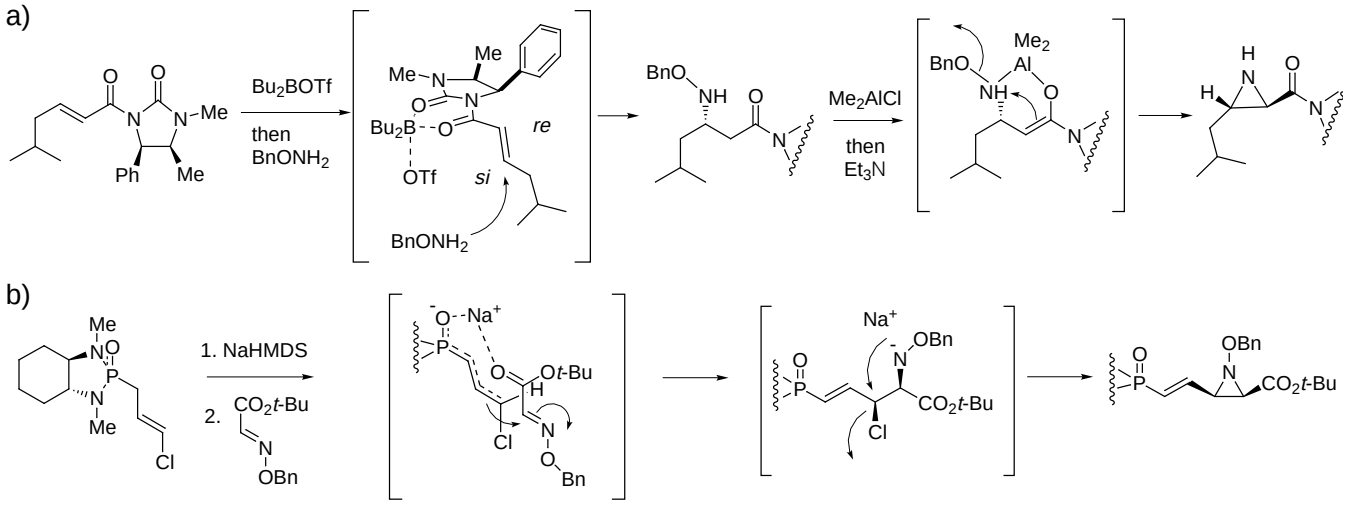


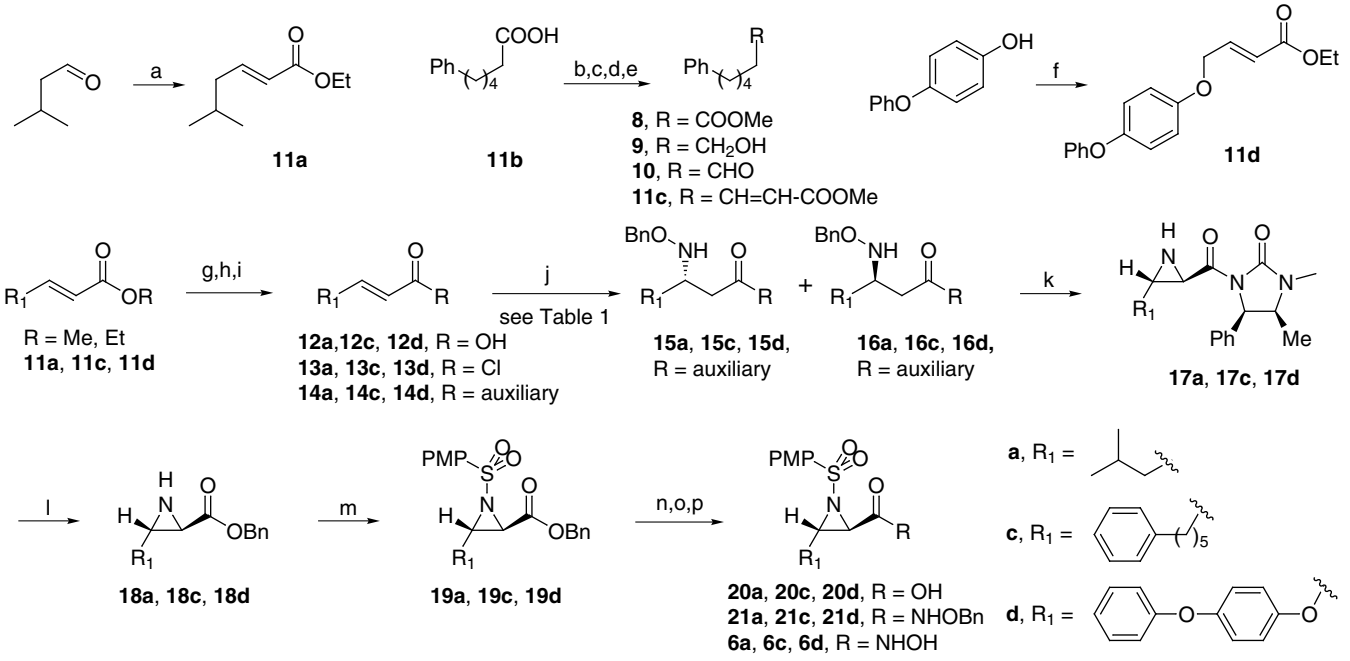
Figure 4. Aziridination methodologies.

2.3. Synthesis of the *trans*-aziridine analogs

The substrates for the key transformations were prepared from isovaleraldehyde, 6-phenylhexanoic acid and *p*-phenoxyphenol using standard methodologies[21] to give the intermediates **11a**, **11c** and **11d**, respectively (Scheme 1). The chiral auxiliary was then introduced to provide the desired α,β-unsaturated amides **14a**, **14c** and **14d**.

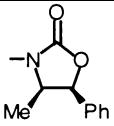
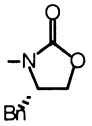
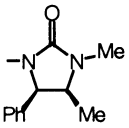
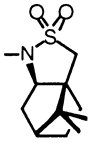
In order to optimize the stereoselectivity of the key conjugate addition of *O*-benzyl-hydroxylamine, different Lewis acids and auxiliaries were surveyed (Table 1). Using $SnCl_4$ and $TiCl_4$ and a variety of auxiliaries led to good to excellent yields with variable selectivities. In all but one case (no reaction using the camphor sultam auxiliary, entry 10), the diastereoisomers **15a** and **16a** were inseparable. Using the oxazolidinone derived from ephedrine afforded the mixture of the desired products as a crystalline solid. A further optimization with different Lewis acids secured a practical method since **15a** was obtained as a single isomer (entry 8).

When the conjugate addition was performed using dimethylaluminium chloride Me_2AlCl as Lewis acid, as proposed by Cardillo and co-workers,[20b] a fairly disappointing diastereoisomeric ratio was obtained (entry 7). The observed reversal of selectivity (entries 5 and 7) of this chelation-controlled conjugate addition was rationalized by the



Scheme 1. (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 90%; (b) TMSCl, MeOH, quant.; (c) DIBAL-H, THF, −78°C then 0°C, 76%; (d) SO_3.Pyridine, CH_2Cl_2, DMSO, quant.; (e) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 92%; (f) (*E*)-$BrCH_2CH{=}CHCO_2Et$, K_2CO_3, 18-crown-6, acetone, 74%; (g) LiOH, H_2O/THF, 91-96-59%; (h) $(COCl)_2$, DMF, CH_2Cl_2; (i) auxiliary, BuLi, −78°C then **13**, 95-68-78% (over 2 steps); (j) Bu_2BOTf, CH_2Cl_2 then $BnONH_2$, −78°C, 88-93-91%; (k) Me_2AlCl, CH_2Cl_2, 0°C then Et_3N, rt, 92-94-96%; (l) BnOLi, THF, 92-93-73%; (m) $PMPSO_2Cl$, Et_3N, CH_2Cl_2, 71–79% (for **19a** and **19c**); or i: $PMPSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, 30°C, 63%; ii: NaHMDS, THF, −78°C to rt, 90% (for **19d**); (n) H_2, Pd/C, EtOH, 91–86% (for **20a**, **20c**); (o) $BnONH_2$, EDC, HOBt, NMM, THF, 70–69% (for **21a**, **21c**), 35% (over 2 steps, for **21d**) (p) H_2, $Pd/BaSO_4$, EtOH, 76-83-90%.

Table 1.

Entry	X	Lewis acid	**15a/16a**[a]	Yield (%)[b]
1		$TiCl_4$	45:55[c]	85
2		$SnCl_4$	13:87[c]	66
3		$TiCl_4$	30:70[c]	79
4		$SnCl_4$	59:41[c]	71
5		$TiCl_4$	28:72	77
6		$SnCl_4$	30:70	99
7		Me_2AlCl	73:27	47 (50)[d]
8		Bu_2BOTf	>97:<3[e]	88
9		Bu_2BOTf (1.4 equiv.)	97:3	35
10		$TiCl_4$	–	0 (99)[d]

[a] Determined by ^1H NMR of the crude mixture.
[b] Isolated yield.
[c] Major isomer not determined.
[d] Yield of recovered starting material.
[e] A single isomer observed by ^1H NMR.

authors on the basis of NMR studies.[20a] They concluded that bulky Lewis acids such as $TiCl_4$ favor a distorted chelated intermediate, with titanium retaining its four chloride ligands while bischelating the dicarbonyl substrate. Consequently, the acyl chain is forced above the plane exposing the *re* face to the nucleophilic attack (Fig. 4a). On the other hand, Me_2AlCl loses its chloride during the process forming a fully planar complex opening the *si* face to the attack.[20b] From this rationalization we envisioned that dibutylboron triflate (Bu_2BOTf), known to efficiently promote asymmetric auxiliary-based aldol reactions via planar complexes,[22] would catalyze more efficiently the present reaction. Gratifyingly, the use of Bu_2BOTf as a Lewis acid provided the expected product **15a** as a single isomer, according to ^1H NMR spectral data (entry 8). Similarly, reacting **14c** and **14d** under the same conditions afforded the adducts as a 95:5 mixture and a single isomer, respectively.

Closure of the aziridine ring in **15a**, **15c** and **15d** was achieved by treatment with Me_2AlCl to provide **17a**, **17c** and **17d**, respectively (Scheme 1). The auxiliary was removed upon treatment with lithium benzyloxide to give the corresponding benzyl esters. The free aziridines **18a** and **18c** reacted with the suitable sulfonyl chloride to afford **19a** and **19c**, respectively. However, using similar conditions, **18d** led to a mixture of starting material, **19d** and a product resulting from the opening of the now activated aziridine with chloride anion released by the reagent. Since our attempts to suppress this nucleophilic ring opening were not successful, we opted to convert all our material to the ring-opened intermediate. Closure of the ring could subsequently be achieved using NaHMDS to provide **19a**. With **19a**, **19c** and **19d** in hand, hydrogenolysis of the benzyl esters, coupling with *O*-benzylhydroxylamine and final deprotection under optimized conditions afforded the hydroxamic acids **6a**, **6c** and **6d**.[23]

Single crystal X-ray analysis of **19a** and **17c** ascertained their relative as well as their absolute configuration (Fig. 5). Unfortunately, none of the intermediates in the synthesis of **6d** provided suitable crystals for X-ray diffraction.

2.4. Synthesis of the *cis*-aziridine analogs

Addition of the anion of **22**[9] to *tert*-butylglyoxylate *O*-benzylimine **23** led to aziridine **24** as a single isomer (Scheme 2).[10] Ozonolysis followed by a reductive workup provided us with alcohol **25**.

Introduction of the side chains was performed using the Mitsunobu reaction with the appropriate phenols.[24] After extensive optimization, it was found that performing the reaction in CH_2Cl_2 gave the best yields.

According to the previously reported study,[10] hydrogenolysis of the N–O bond was done after the reduction of the ester. Thus, **26a** and **26b** were transformed into the corresponding silyl ethers **28a** and **28b**, respectively, by

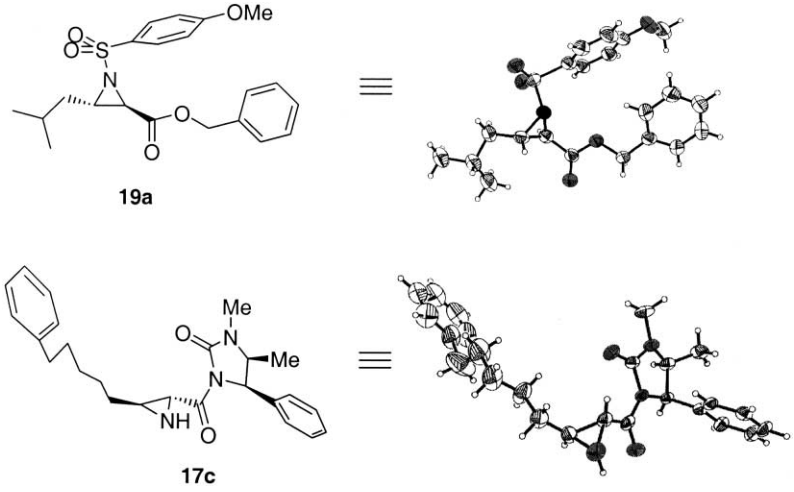
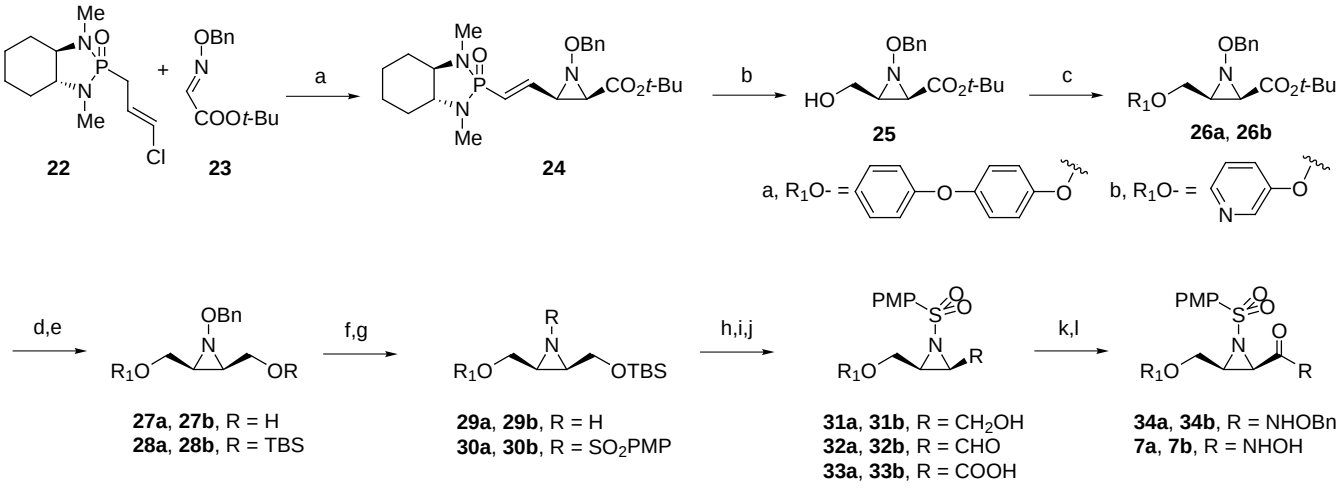
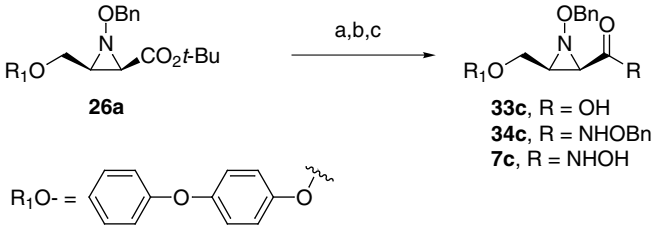


Figure 5. ORTEP diagrams of **19a** and **17c**.



Scheme 2. (a) NaHMDS, THF, −78°C, 78%; (b) i: O_3, CH_2Cl_2, EtOH, −78°C; ii: $NaBH_4$, −78°C to 0°C, 94%; (c) R_1OH, DEAD, PPh_3, CH_2Cl_2, 92–52%; (d) DIBAL-H, CH_2Cl_2, −78°C to 0°C, 93–77%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 97–87%; (f) H_2, $Pd/BaSO_4$, EtOH, 89–97%; (g) $PMPSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 67–97%; (h) TBAF, THF, 0°C, 84–81%; (i) Dess-Martin periodinane, CH_2Cl_2, 85–92%; (j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/*t*-BuOH, CH_2Cl_2, 0°C, 95% (for **33a**); (k) EDC, HOBt, $BnONH_2$.HCl, DIPEA, THF, 71–52% (over 2 steps, for **34b**); (l) H_2, $Pd/BaSO_4$, EtOH, 51–43%.



Scheme 3. (a) TFA, CH_2Cl_2, 0°C to rt; (b) EDC, HOBt, $BnONH_2$.HCl, DIPEA, THF, 81% (2 steps); (c) H_2, $Pd/BaSO_4$, EtOH, 52%.

reduction with DIBAL-H, followed by treatment with TBSOTf. Hydrogenolysis of **28a** and **28b** using $Pd/BaSO_4$ produced the free aziridines, which were converted to the corresponding sulfonamides **30a** and **30b** by reaction with *p*-methoxyphenyl sulfonyl chloride at 0°C, to avoid the opening of the now activated aziridine by the released chloride anion.

With the appropriate functionality introduced at C-3 and on the nitrogen, we were left with the oxidation of the primary alcohol to the corresponding acid in the presence of an activated *N*-arylsulfonyl aziridine derivative before transformation to the desired hydroxamic acid. Deprotection of **30a** and **30b** with TBAF gave the corresponding alcohols, which were first oxidized to aldehydes using the Dess–Martin periodinane reagent,[25] and then to acids **33a** and **33b** using $NaClO_2$.[26] During the last oxidation step, the temperature of the reaction had to be maintained at 0°C to avoid decomposition. Hydroxamic acids **7a** and **7b** were then obtained by coupling with $BnONH_2$ in presence of EDC and HOBT, followed by hydrogenolysis under optimized conditions (Scheme 2).[23] The synthesis of **7c** was achieved by starting from **26a**, by conversion of the *tert*-butyl ester into the desired hydroxamic acid (Scheme 3).

2.5. Biological evaluation and discussion

The inhibitory activity on MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 are reported in Table 2. The potency of **6a**, **6c** and **7b** relative to **5** was substantially decreased, while compounds **6d**, **7a** and **7c** were virtually inactive. The lack of either P_1 or P_2' side-chain may be responsible for the loss of activity compared to **5** as can be seen in the docking studies (Fig. 3). As expected, the pyridyl group, known to be a highly efficient P_2 side-chain[3] as in **7b**, provided a

Table 2.

Compound	IC_{50} (nM)				
	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13
5	104	0.7	0.7	2.5	12
6a	>10 000	617	213	184	380
6c	26 400	259	595	203	231
6d	>100 000	15 000	10 000	4770	8775
7a	50 000	3600	2000	500	>100 000
7b	15 000	237	164	83	300
7c	56 000	98 000	>100 000	>100 000	>100 000

Average values based on two determinations; for details see Ref. 11.

beneficial effect on the MMP inhibition compared to the other aziridine analogs (Table 2). Also, the *cis*-aziridine analog **7a** was relatively more active than the *trans*-isomer **6d**, which exhibited a reverse binding mode according to AutoDock (Fig. 3d and f).

3. Conclusions

As part of our studies on conformationally constrained MMP inhibitors, we used *cis*- and *trans*-aziridines as scaffolds to construct a series of analogs. The syntheses were carried out exploiting two different and highly stereocontrolled aziridination methodologies affording the intended targets. Docking studies indicated unfavorable interactions with MMP-3 as a prototypical MMP for some analogs, but the validation of its utility as a predictive tool for bioactivity was limited by the absence of a P_1 side-chain in the compounds. The incorporation of such functionality may lead to more active MMP inhibitors in this series.

4. Experimental

4.1. Docking

The molecular modeling was performed on Silicon Graphics Indigo2 and Octane2 workstations running IRIX (version 6.2). The X-ray structure of MMP-3 was retrieved form the Protein Data Bank, and the designed molecules were built up and energy-minimized using Insight II® version 95.0 program and Discover® package.[27,28] Atomic partial charges of the inhibitors were calculated using the semi-empirical MNDO method implemented in the MOPAC program. The atomic partial charges of the enzyme were calculated using the AMBER force field. The macromolecules and the ligands were prepared for AutoDock following the original paper[18] and the dockings were performed using the Lamarckian Genetic Algorithm.[18] PDB ID codes for MMP-3/inhibitor structures, 1CAQ, 1BQO, 1B3D, 1HF5.

4.2. Chemistry

Solvents were distilled under positive pressure of dry nitrogen before use and dried by standard methods; THF and ether, from K/benzophenone; and CH_2Cl_2 and toluene, from $CaCl_2$. All commercially available reagents were used without further purification. 4 Å molecular sieves were dried at 140°C prior to use. All reactions were performed under nitrogen atmosphere. NMR (^1H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers in $CDCl_3$ or CD_3OD with residual $CHCl_3$ and CH_3OH as the internal standard. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902 or Kratos MS-50 spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by UV or by development using $KMnO_4$ or $FeCl_3$ solutions. Flash column chromatography was performed using (40–60 μm) silica gel at increased pressure. Melting points recorded were uncorrected.

4.2.1. 6-Phenyl-hexanoic acid methyl ester (8). To 6-phenyl-hexanoic acid **11b** (2.7 g, 14.0 mmol) in MeOH (70 mL) was added TMSCl (7.1 mL, 56 mmol) at 0°C. The resulting mixture was stirred overnight, quenched with water (10 mL), concentrated in vacuo, dissolved in CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 1:0 then 9:1) to afford **8** (2.88 g, quant., colorless oil); R_f=0.60 (hexanes/EtOAc, 9:1); IR (neat/NaCl) 1740.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.21–7.18 (m, 3H), 3.69 (s, 3H), 2.64 (t, 2H, J=7.8 Hz), 2.33 (t, 2H, J=7.5 Hz), 1.73–1.62 (m, 4H), 1.43–1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 142.4, 128.3, 128.2, 125.6, 51.4, 35.7, 33.9, 31.0, 28.7, 24.7; LRMS (TOF EI+, *m/z*, %): 206 (32) (M^+), 174 (100); HRMS calcd for $C_{13}H_{18}O_2$ ($M+H^+$) 206.13068; found 206.13153.

4.2.2. 6-Phenyl-hexanol (9). To a solution of **8** (1.5 g, 7.28 mmol) in THF (150 mL) was added DIBAL-H (10.6 mL, 1.5 M in toluene, 15.9 mmol) at −78°C. The resulting mixture was stirred at 0°C for 2 h, quenched with water, filtered over Celite, concentrated in vacuo, dissolved in CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1 then 4:1) to afford **9** (980 mg, 76%, colorless oil); R_f=0.48 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 3339.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 7.23–7.21 (m, 3H), 3.66 (t, 2H, J=6.6 Hz), 2.66 (t, 2H, J=7.9 Hz), 1.80 (br. m, 1H), 1.68 (m, 2H), 1.60 (m, 2H), 1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 128.2, 128.1, 125.5, 62.6, 35.7, 32.5, 31.3, 28.9, 25.5; LRMS (TOF EI+, *m/z*, %): 178 (100) (M^+), 160 (95); HRMS calcd for $C_{12}H_{18}O$ (M^+) 178.13576; found 178.13531.

4.2.3. 6-Phenyl-hexanal (10). To a solution of **9** (968 mg, 5.5 mmol) in CH_2Cl_2 (15 mL) and DMSO (30 mL) was added SO_3·pyridine complex (3.5 g, 22.0 mmol) at 0°C. The resulting mixture was stirred at 0°C for 1.5 h, diluted with Et_2O, washed with H_2O, 1N $NaHSO_4$, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford **10** (955 mg, quant., yellowish oil); R_f=0.41 (hexanes/EtOAc, 9:1); IR (neat/NaCl) 1725.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (d, 1H, J=1.6 Hz), 7.32–7.27 (m, 2H), 7.22–7.18 (m, 3H), 2.64 (t, 2H, J=7.7 Hz), 2.66 (dt, 2H, J=1.6, 7.4 Hz), 1.73–1.63 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 142.3, 128.3, 128.2, 125.6, 43.7, 35.6, 31.1, 28.6, 21.8; LRMS (TOF EI+, *m/z*, %): 192 (100) ($M+H_2O^+$), 174 (25), 130 (37); HRMS calcd for $C_{12}H_{16}O$ (M^+) 176.12011; found 176.12071.

4.2.4. (*E*)-8-Phenyl-oct-2-enoic acid methyl ester (11c). To a solution of **10** (950 mg, 5.5 mmol) in CH_2Cl_2 (40 mL) was added methyl (triphenylphosphoranylidene)–acetate (2.8 g, 8.2 mmol). After stirring for 15 min, the mixture was diluted with hexanes, the white solid was filtered and the organic phase was concentrated in vacuo. The residue was purified by flash chromatography (hexanes/

EtOAc, 1:0 then 9:1) to afford **11c** (1160 mg, 92%, colorless oil); R_f=0.48 (hexanes/EtOAc, 9:1); IR (neat/NaCl) 1725.6, 1658.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.22–7.18 (m, 3H), 6.99 (dt, 1H, J=7.0, 14.6 Hz), 5.84 (d, 2H, J=14.6 Hz), 3.75 (s, 3H), 2.63 (t, 2H, J=7.8 Hz), 2.22 (dt, 2H, J=7.0, 7.0 Hz), 1.65 (m, 2H), 1.51 (m, 2H), 1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 149.6, 142.5, 128.3, 128.2, 125.6, 120.8, 51.3, 35.7, 32.0, 31.2, 28.7, 27.8; LRMS (TOF EI+, *m/z*, %): 232 (100) ($M+H^+$), 176 (57), 172 (77); HRMS calcd for $C_{15}H_{20}O_2$ (M^+) 232.14633; found 232.14565.

4.2.5. (*E*)-4-(4-Phenoxy-phenoxy)-but-2-enoic acid ethyl ester (11d). To a solution of 4-phenoxyphenol (1.60 g, 8.6 mmol), K_2CO_3 (2.0 g, 14.6 mmol) and 18-crown-6 (113 mg, 0.43 mmol) in acetone (60 mL) was added ethyl bromocrotonate (1.18 mL, 8.6 mmol). After stirring for 16 h, the solution was filtered and the residue purified by flash chromatography to provide **11d** (1.89 g, 74% white oil); R_f=0.48 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 1721.7, 1589.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H), 7.14–6.88 (m, 3H), 6.22 (dt, 1H, J= 2.1, 15.8 Hz), 4.70 (dd, 2H, J=2.1, 4.0 Hz), 4.23 (q, 2H, J=7.1 Hz), 1.32 (t, 1H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 158.1, 154.1, 150.5, 142.2, 129.4, 122.4, 121.8, 120.5, 117.5, 115.5, 66.7, 60.3, 14.0; LRMS (TOF EI+, *m/z*, %): 298 (100) (M^+); HRMS calcd for $C_{18}H_{18}O_4$ 298.12051; found 298.12089.

4.2.6. (*E*)-5-Methyl-hex-2-enoic acid (12a). The acid was prepared from **11a** as previously reported.[21]

4.2.7. (*E*)-8-Phenyl-oct-2-enoic acid (12c). To a solution of **11c** (1.10 g, 4.7 mmol) in THF (60 mL) was added a solution of LiOH (794 mg, 19.0 mmol) in water (7 mL). After stirring for 48 h at 45°C, the reaction was quenched with diluted HCl to pH ~3 then extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 4:1 then 2:1) afforded **12c** (995 g, 96%, colorless oil); R_f=0.10–0.33 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 3027.1, 1696.4, 1651.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.23–7.20 (m, 3H), 7.12 (dt, 1H, J=6.7, 14.6 Hz), 5.85 (d, 2H, J=14.6 Hz), 2.64 (t, 2H, J= 7.8 Hz), 2.20 (dt, 2H, J=7.0, 7.0 Hz), 1.67 (m, 2H), 1.54 (m, 2H), 1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 152.2, 142.4, 128.3, 128.2, 125.6, 120.7, 35.7, 32.1, 31.1, 28.7, 27.6; LRMS (TOF EI+, *m/z*, %): 218 (100) (M^+), 172 (73), 158 (67); HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.13068; found 218.13172.

4.2.8. (*E*)-4-(4-Phenoxy-phenoxy)-but-2-enoic acid (12d). As described above for **12c**, **11d** (1.95 g, 6.54 mmol) in THF (40 mL) and a solution of LiOH (960 mg, 22.9 mmol) in water (10 mL) at rt afforded, after flash chromatography (hexanes/EtOAc, 4:1 then 1:1), **12d** (1.04 g, 59%, white powder); R_f=0.30 (hexanes/EtOAc, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 3H), 7.12–6.87 (m, 6H), 6.25 (dt, 1H, J=2.1, 15.7 Hz), 4.72 (dd, 2H, J=2.1, 4.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.2, 154.1, 150.9, 145.3, 129.6, 122.6, 121.1, 120.7, 117.8, 115.7, 66.8; LRMS (TOF EI+, *m/z*, %): 270 (100) (M^+); HRMS calcd for $C_{16}H_{14}O_4$ 270.08921; found 270.08974.

4.2.9. (*E*)-1,5-(*S*)-Dimethyl-3-(5-methyl-hex-2-enoyl)-4-(*R*)-phenyl-imidazolidin-2-one (14a). To **12a** (507 mg, 4.0 mmol) in CH_2Cl_2 (7 mL), dissolved in DMF (30 μL), was added oxalyl chloride (0.52 mL, 5.9 mmol) at 0°C. The solution was stirred for 30 min at 0°C then 3 h at rt. The resulting mixture was concentrated and co-evaporated with dry THF (2×20 mL) to afford crude **13a** which was used in the following step. To a solution of 1,5-dimethyl-4-phenyl-imidazolidin-2-one (570 mg, 3.0 mmol) in THF (50 mL), was added *n*-BuLi (1.2 mL, 2.5 M solution, 3.0 mmol) at −78°C. After stirring for 45 min, **13a** was added and the resulting mixture stirred at −78°C for 1 h. After quenching with satd NH_4Cl, the solution was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 7:3) afforded **14a** (850 mg, 95%). Further recrystallization (CH_2Cl_2/MeOH, H_2O) afforded **14a** (775 mg, white needles) with high purity; R_f=0.51 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−87.0 (*c* 0.7, $CHCl_3$); mp 154°C; IR (neat/NaCl) 1716.5, 1670.5, 1633.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dt, 1H, J=1.4, 15.0 Hz), 7.39–7.25 (m, 3H), 7.25–7.15 (m, 2H), 7.00 (ddd, 1H, J=7.2, 7.2, 15.0 Hz), 6.20–5.70 (br. s, 1H), 5.36 (d, 1H, J=8.4 Hz), 3.92 (ddd, 1H, J=6.4, 8.4, 13.0 Hz), 2.84 (s, 3H), 2.12 (2dd, 2H, J=7.2, 7.2 Hz), 1.75 (m, 1H), 0.91 (d, 6H, J=6.4 Hz), 0.82 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 164.8, 155.9, 148.3, 136.7, 128.4, 128.0, 126.9, 122.6, 59.4, 53.9, 41.7, 28.1, 27.9, 22.4, 22.3, 14.9; LRMS: (TOF EI+, *m/z*, %): 300 (100) (M^+), 283 (30); HRMS calcd for $C_{18}H_{24}O_2N_2$ (M^+) 300.18378; found 300.18410.

4.2.10. (*E*)-1,5-(*S*)-Dimethyl-4-(*R*)-phenyl-3-(9-phenyl-oct-2-enoyl)-imidazolidin-2-one (14c). Following the same procedure above, **12c** (993 mg, 4.55 mmol) in DMF (35 μL), oxalyl chloride (0.48 mL, 5.46 mmol) then 1,5-dimethyl-4-phenyl-imidazolidin-2-one (1.30 g, 6.82 mmol) and *n*-BuLi (2.0 mL, 2.5 M solution, 5.0 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1 then 7:3), **14c** (1.40 g, 68%, colorless oil); R_f=0.15 (hexanes/EtOAc, 4:1); IR (neat/NaCl) 1727.7, 1673.5, 1634.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, 1H, J=1.4, 15.4 Hz), 7.36–7.27 (m, 5H), 7.20–7.18 (m, 5H), 7.12 (dt, 1H, J=7.0, 15.4 Hz), 5.37 (d, 1H, J=8.6 Hz), 3.92 (m, 1H), 2.86 (s, 3H), 2.61 (t, 2H, J=7.9 Hz), 2.25 (m, 2H), 1.64 (m, 2H), 1.52 (m, 2H), 1.38 (m, 2H), 0.83 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 155.8, 149.1, 142.5, 136.6, 128.3, 128.2, 128.1, 127.8, 126.8, 125.4, 121.5, 59.3, 53.7, 35.6, 32.3, 31.1, 28.7, 28.0, 27.9, 14.8; LRMS (TOF EI+, *m/z*, %): 390 (100) (M^+); HRMS calcd for $C_{25}H_{30}O_2N_2$ (M^+) 390.23073; found 390.23111.

4.2.11. (*E*)-1,5-(*S*)-Dimethyl-3-[4-(4-phenoxy-phenoxy)-but-2-enoyl]-4-(*R*)-phenyl-imidazolidin-2-one (14d). Following the same procedure **12d** (560 mg, 2.07 mmol) in DMF (16 μL), oxalyl chloride (0.22 mL, 2.48 mmol) then 1,5-dimethyl-4-phenyl-imidazolidin-2-one (591 mg, 3.11 mmol) and *n*-BuLi (0.91 mL, 2.5 M solution, 2.28 mmol) afforded, after flash chromatography (hexanes/EtOAc/CH_2Cl_2, 7:3:0 then 7:2:1), **14d** (717 mg, 78%, white crystals); R_f=0.38 (hexanes/EtOAc, 3:2); $[\alpha]_D$= −41.6 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dt, 1H, J=2.0, 15.6 Hz), 7.38–6.90 (m, 15H), 5.38 (d, 1H, J=8.4 Hz), 4.70 (dd, 2H, J=2.0, 4.5 Hz) 3.92 (ddd, 1H,

J=6.6, 8.4, 13.0 Hz), 2.86 (s, 3H), 0.82 (d, 3H, J= 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 158.3, 155.6, 154.5, 150.4, 142.0, 136.4, 129.5, 128.5, 128.0, 126.9, 122.6, 122.4, 120.7, 117.6, 115.9, 67.6, 59.4, 53.8, 28.1, 14.9; LRMS (FAB, NBA, *m/z*, %): 443 (44) ($M+H^+$), 257 (48); HRMS calcd for $C_{27}H_{27}O_4N_2$ 443.19708; found 443.19810.

4.2.12. 1-(3-(*S*)-Benzyloxyamino-5-methyl-hexanoyl)-3,4-(*S*)-dimethyl-5-(*R*)-phenyl-imidazolidin-2-one (15a). To a solution of **14a** (270 mg, 0.90 mmol) in CH_2Cl_2 (30 mL) was added dropwise Bu_2BOTf (0.99 mL, 1 M solution in CH_2Cl_2, 0.99 mmol) at −78°C, After stirring for 15 min, $BnONH_2$ (390 mg, 3.2 mmol) in CH_2Cl_2 (9 mL) was added, and the solution was stirred for 1 h. After quenching with a mixture of MeOH/10% aq. NaOH, the product was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 7:3) afforded **15a** (335 mg, 88%, white powder) as a single isomer; R_f=0.25 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−34.1 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3268.9, 1731.5, 1683.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 8H), 7.20–7.10 (m, 2H), 5.26 (d, 1H, J=8.3 Hz), 4.61 (AB, 2H, J=11.0 Hz), 3.83 (ddd, 1H, J=6.4, 8.3, 13.0 Hz), 3.44–3.32 (m, 2H), 3.10 (m, 1H), 2.80 (s, 3H), 1.70 (m, 1H), 1.47 (m, 1H), 1.39–1.17 (m, 2H), 0.88 (d, 6H, J=6.4 Hz), 0.78 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 171.6, 155.8, 138.1, 136.5, 128.4, 128.1, 127.9, 127.4, 126.8, 76.1, 59.2, 55.4, 53.8, 41.1, 37.9, 28.1, 24.7, 22.7, 22.6, 14.8; LRMS: (FAB, NBA, *m/z*, %): 556 (22), 424 (65) ($M+H^+$), 285 (67); HRMS calcd for $C_{25}H_{34}O_3N_3$ ($M+H^+$) 424.26001; found 424.25950.

4.2.13. 1-(3-(*S*)-Benzyloxyamino-8-phenyl-octanoyl)-3,4-(*S*)-dimethyl-5-phenyl-(*R*)-imidazolidin-2-one (15c). Following the same procedure as above, **14c** (683 mg, 1.75 mmol), Bu_2BOTf (1.92 mL, 1 M solution in CH_2Cl_2, 1.92 mmol) and $BnONH_2$ (645 mg, 5.2 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1 then 3:2), **15c** (831 mg, 93%, colorless oil); R_f=0.29 (hexanes/EtOAc, 7:3); IR (neat/NaCl) 3446.1, 1731.5, 1680.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 7.21–7.14 (m, 5H), 6.30–5.50 (br. s, 1H), 5.28 (d, 1H, J=8.6 Hz), 4.63 (s, 2H), 3.85 (m, 1H), 3.30 (m, 2H), 3.13 (br. d, 1H, J= 11.7 Hz), 2.84 (s, 3H), 2.60 (t, 2H, J=7.7 Hz), 1.61 (m, 2H), 1.45–1.27 (m, 6H), 0.80 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.7, 142.7, 138.1, 136.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.4, 126.8, 125.4, 76.2, 59.1, 57.3, 53.7, 37.7, 35.8, 31.9, 31.3, 29.2, 28.0, 25.7, 14.8; LRMS (FAB, *m/z*, %): 514 (100) ($M+H^+$), 406 (25); HRMS calcd for $C_{32}H_{40}O_3N_3$ ($M+H^+$) 514.30695; found 514.30810.

4.2.14. 1-[3-(*R*)-Benzyloxyamino-4-(4-phenoxy-phenoxy)-butyryl]-3,4-(*S*)-dimethyl-5-(*R*)-phenyl-imidazolidin-2-one (15d). Following the same procedure above, **14d** (550 mg, 1.24 mmol), Bu_2BOTf (1.37 mL, 1 M solution in CH_2Cl_2, 1.37 mmol) and $BnONH_2$ (457 mg, 3.72 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1), **15d** (638 mg, 91%, colorless oil); R_f=0.38 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−23.7 (*c* 2.1, $CHCl_3$); IR (neat/NaCl) 3268.8, 1731.6, 1681.7, 1588.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 10H), 7.21–7.14 (m, 2H), 7.05 (m, 1H), 6.99–6.92 (m, 4H), 6.90–6.83 (m, 2H), 6.22 (d, 1H, J=5.5 Hz), 5.29 (d, 1H, J=8.4 Hz), 4.68 (s, 2H), 4.13 (m, 2H), 3.88 (ddd, 1H, J=6.5, 8.4, 13.0 Hz), 3.79 (m, 1H), 3.45 (dd, 1H, J=7.0, 17.8 Hz), 3.33 (dd, 1H, J=6.0, 17.8 Hz), 2.84 (s, 3H), 0.80 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 158.5, 155.7, 155.0, 150.1, 137.8, 136.4, 129.5, 128.5, 128.4, 128.3, 128.1, 127.7, 126.9, 122.3, 120.7, 117.5, 115.6, 76.4, 67.4, 59.3, 56.6, 53.9, 35.2, 28.1, 14.9; LRMS: (FAB, NBA, *m/z*, %): 566 (52) ($M+H^+$), 366 (25); HRMS calcd for $C_{34}H_{36}O_5N_3$ ($M+H^+$) 566.26550; found 566.26710.

4.2.15. 1-(3-(*S*)-Isobutyl-aziridine-2-(*R*)-carbonyl)-3,4-(*S*)-dimethyl-5-(*R*)-phenyl-imidazolidin-2-one (17a). To a solution of **15a** (421 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added Me_2AlCl (3 mL, 1 M solution in CH_2Cl_2, 3.0 mmol) at 0°C, After stirring for 20 min, Et_3N (0.56 mL, 4 mmol) was added. After stirring for 1 h at rt, water was added and the solution was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1 then 7:3) to afford **17a** (290 mg, 92%, white crystals) as a single isomer; R_f=0.51 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−72.1 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3275.9, 1727.9, 1664.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (m, 3H), 7.21–7.08 (m, 2H), 5.32 (d, 1H, J=8.8 Hz), 3.95 (ddd, 1H, J=6.5, 8.8, 13.0 Hz), 3.81 (d, 1H, J=2.8 Hz), 2.88 (s, 3H), 2.15 (m, 1H), 1.82 (m, 2H), 1.50 (ddd, 1H, J=5.1, 8.3, 14.0 Hz), 1.31 (ddd, 1H, J=7.0, 7.0, 14.0 Hz), 0.95 (d, 6H, J= 6.7 Hz), 0.82 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 171.5, 155.5, 136.1, 128.6, 128.3, 126.9, 59.4, 54.1, 41.9, 39.9, 35.6, 28.2, 27.0, 22.7, 22.4, 15.1; LRMS: (FAB, NBA, *m/z*, %): 316 (100) ($M+H^+$); HRMS calcd for $C_{18}H_{26}O_2N_3$ ($M+H^+$) 316.20251; found 316.20160.

4.2.16. 1,5-(*S*)-Dimethyl-4-(*R*)-phenyl-3-[3-(*S*)-(5-phenyl-pentyl)-aziridine-2-(*R*)-carbonyl]-imidazolidin-2-one (17c). Following the procedure described above, **15c** (795 mg, 1.54 mmol) was treated with Me_2AlCl (3.9 mL, 1 M solution in CH_2Cl_2, 3.9 mmol) then Et_3N (0.72 mL, 5.2 mmol) to afford, after flash chromatography (hexanes/EtOAc, 4:1), **17c** (586 mg, 94%, white needles); R_f=0.22 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−90.3 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3272.6, 1728.0, 1662.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 7.21–7.18 (m, 5H), 5.33 (d, 1H, J=8.9 Hz), 3.96 (m, 1H), 3.84 (br. s, 1H), 2.88 (s, 3H), 2.63 (t, 2H, J=7.7 Hz), 2.12 (m, 1H), 1.76–1.35 (m, 9H), 0.84 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.4, 142.6, 136.0, 128.4, 128.2, 128.1, 128.0, 126.8, 125.4, 59.2, 53.9, 41.0, 35.7, 35.6, 32.7, 31.2, 28.9, 28.1, 26.7, 14.9; LRMS (FAB, *m/z*, %): 406 (100) ($M+H^+$); HRMS calcd for $C_{25}H_{32}O_2N_3$ ($M+H^+$) 406.24945; found 406.24910.

4.2.17. 1,5-(*S*)-Dimethyl-3-[3-(*R*)-(4-phenoxy-phenoxy-methyl)-aziridine-2-(*R*)-carbonyl]-4-(*R*)-phenyl-imidazolidin-2-one (17d). Following the procedure described above, **15d** (423 mg, 0.75 mmol) was treated with Me_2AlCl (2.25 mL, 1 M solution in CH_2Cl_2, 2.25 mmol) then Et_3N (0.42 mL, 3.0 mmol) to afford, after flash chromatography (hexanes/EtOAc, 4:1), **17d** (328 mg, 96%, colorless oil); R_f=0.28 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−84.3 (*c* 1.0,

$CHCl_3$); IR (neat/NaCl) 3278.5, 1731.7, 1673.5, 1589.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 7.22–7.18 (m, 2H), 7.05 (m, 1H), 7.00–6.89 (m, 6H), 5.35 (d, 1H, J=8.6 Hz), 4.18 (dd, 1H, J=4.0, 10.2 Hz), 4.10 (dd, 1H, J=2.2, 7.7 Hz), 3.98 (ddd, 1H, J=6.6, 8.6, 13.0 Hz), 3.96 (dd, 1H, J=6.7, 10.2 Hz), 2.90 (s, 3H), 2.61 (m, 1H), 1.90 (dd, 1H, J=7.7, 7.7 Hz), 0.83 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 170.3, 158.3, 155.4, 154.8, 150.3, 135.8, 129.5, 128.6, 128.3, 126.8, 122.3, 120.6, 117.5, 115.7, 70.0, 59.4, 54.1, 38.5, 33.7, 28.1, 15.0; LRMS: (FAB, NBA, *m/z*, %): 458 (50) ($M+H^+$); HRMS calcd for $C_{27}H_{28}O_4N_3$ ($M+H^+$) 458.20798; found 458.20660.

4.2.18. 3-(*S*)-Isobutyl-aziridine-2-(*R*)-carboxylic acid benzyl ester (18a). To a solution of benzyl alcohol (0.162 mL, 1.57 mmol) in THF (3 mL) was added dropwise *n*-BuLi (0.63 mL, 2.5 M solution, 1.57 mmol) at 0°C. After stirring for 20 min, **17a** (248 mg, 0.79 mmol) in THF (3 mL) was added. After stirring for 2 h at 0°C, water (2 mL) was added. The product was extracted with CH_2Cl_2, and the organic phase was washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford **18a** (169 mg, 92%, white oil); R_f=0.72 (hexanes/EtOAc, 3:2); $[\alpha]_D$=−28.9 (*c* 0.6, $CHCl_3$); IR (neat/NaCl) 3286.6, 1729.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 5.20 (AB, 2H, J=12.0 Hz), 2.36 (s, 1H), 2.29 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.45–1.25 (m, 2H), 0.96 (d, 6H, J=6.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 172.6, 135.2, 128.6, 128.2, 127.5, 67.2, 41.5, 38.5, 35.4, 27.0, 22.7, 22.2; LRMS: (TOF EI+, *m/z*, %): 234 (15) ($M+H^+$), 233 (20) (M^+),142 (100); HRMS calcd for $C_{14}H_{19}O_2N$ (M^+) 233.14158; found 233.14106.

4.2.19. 3-(*S*)-(5-Phenyl-pentyl)-aziridine-2-(*R*)-carboxylic acid benzyl ester (18c). Following the procedure described above, **17c** (880 mg, 2.18 mmol), benzyl alcohol (0.48 mL, 4.8 mmol) and *n*-BuLi (1.76 mL, 2.5 M solution in hexanes, 4.4 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1), **18c** (1:1.2 mixture with BnOH, 1115 mg, 93%, colorless oil); R_f=0.48 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−14.8 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3286.8, 1729.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.12 (m, 10H), 5.22 (d, 1H, J=12.3 Hz), 5.16 (d, 1H, J=12.3 Hz), 2.61 (t, 2H, J=7.8 Hz), 2.33 (m, 1H), 2.25 (m, 1H), 1.63 (m, 2H), 1.51–1.35 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 142.5, 141.2, 135.2, 128.6, 128.4, 128.32, 128.30, 128.26, 128.2, 127.3, 126.8, 125.6, 67.2, 64.7, 39.7, 35.7, 35.1, 32.3, 31.3, 28.8, 26.8; LRMS (TOF EI+, *m/z*, %): 323 (2) (M^+), 232 (56), 188 (100); HRMS calcd for $C_{21}H_{25}O_2N_1$ (M^+) 323.188529; found 323.18777.

4.2.20. 3-(*R*)-(4-Phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyl ester (18d). Following the procedure described above, **17d** (875 mg, 1.91 mmol), benzyl alcohol (0.40 mL, 3.83 mmol) and *n*-BuLi (1.53 mL, 2.5 M solution in hexanes, 3.83 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1), **18d** (525 mg, 73%, colorless oil); R_f=0.40 (hexanes/EtOAc, 1:1); $[\alpha]_D$=−42.4 (*c* 0.6, $CHCl_3$); IR (neat/NaCl) 3287.6, 1728.3, 1588.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.39 (m, 5H), 7.38–7.30 (m, 2H), 7.05 (m, 1H), 6.99–6.92 (m, 4H), 6.90–6.85 (m, 2H), 5.23 (AB, 2H, J=11.9 Hz), 3.98 (m, 2H), 2.79 (m, 1H), 2.63 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 158.2, 154.6, 150.6, 135.0, 129.6, 128.7, 128.6, 128.4, 122.5, 120.7, 117.7, 115.7, 69.4, 67.6, 37.4, 33.5; LRMS: (TOF EI+, *m/z*, %): 375 (100) (M^+), 313 (22), 186 (32); HRMS calcd for $C_{23}H_{21}O_4N$ (M^+) 375.14706; found 375.14740.

4.2.21. 3-(*S*)-Isobutyl-1-(4-methoxy-benzenesulfonyl)-aziridine-2-(*R*)-carboxylic acid benzyl ester (19a). To a solution of **18a** (105 mg, 0.45 mmol) in CH_2Cl_2 (15 mL) was added at 0°C a solution of Et_3N (0.17 mL, 1.23 mmol) and PMP–SO_2Cl (254 mg, 1.23 mmol). The resulting solution was stirred for 48 h at rt then extracted with CH_2Cl_2. The organic phase was washed with satd NH_4Cl and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to afford **19a** (129 mg, 71%, white crystals); R_f=0.37 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+1.8 (*c* 0.5, $CHCl_3$); IR (neat/NaCl) 1747.9, 1596.1, 1579.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 2H, J=8.9 Hz), 7.40–7.31 (m, 3H), 7.23–7.18 (m, 2H), 6.94 (d, 2H, J=8.9 Hz), 5.14 (s, 2H), 3.88 (s, 3H), 3.32 (d, 1H, J=4.3 Hz), 3.12 (m, 1H), 2.13 (ddd, 1H, J=5.0, 5.0, 13.4 Hz), 1.82 (m, 1H), 1.73 (ddd, 1H, J=8.5, 8.5, 13.4 Hz), 0.98 (d, 6H, J=6.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 166.9, 163.5, 135.0, 131.4, 129.7, 128.7, 128.5, 128.4, 128.0, 114.1, 67.3, 55.6, 48.2, 44.2, 36.4, 27.4, 22.8, 21.8; LRMS: (FAB, NBA, *m/z*, %): 404 (35) ($M+H^+$); HRMS calcd for $C_{21}H_{26}O_5NS$ ($M+H^+$) 404.15317; found 404.15160.

4.2.22. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(5-phenyl-pentyl)-aziridine-2-(*R*)-carboxylic acid benzyl ester (19c). Following the procedure described above, **18c** (1.2:1 mixture with BnOH, 630 mg, 1.17 mmol), Et_3N (0.65 mL, 4.67 mmol) and PMP–SO_2Cl (968 mg, 4.67 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1), **19c** (527 mg, 91%, colorless oil); R_f=0.46 (hexanes/EtOAc, 4:1); $[\alpha]_D$=−1.3 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 1747.7, 1596.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, 2H, J=8.9 Hz), 7.34–7.16 (m, 10H), 6.96 (d, 2H, J=8.9 Hz), 5.13 (s, 2H), 3.87 (s, 2H), 3.31 (d, 1H, J=4.0 Hz), 3.10 (m, 1H), 2.60 (t, 2H, J=7.7 Hz), 2.09 (m, 1H), 1.92 (m, 1H), 1.67–1.37 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.5, 142.4, 134.9, 131.3, 129.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 125.6, 114.1, 67.3, 55.6, 49.1, 43.8, 35.7, 31.9, 31.1, 29.6, 28.6, 28.4, 27.9, 27.5; LRMS (FAB, EI, *m/z*, %): 494 (62) ($M+H^+$), 278 (41); HRMS calcd for $C_{28}H_{32}O_5NS$ ($M+H^+$) 494.20013; found 494.19900.

4.2.23. 1-(4-Methoxy-benzenesulfonyl)-3-(*R*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyl ester (19d). To a solution of **18d** (255 mg, 0.68 mmol) in CH_2Cl_2 (5 mL) was added at 0°C, DMAP (15 mg), Et_3N (0.38 mL, 1.23 mmol) and PMP–SO_2Cl (563 mg, 2.72 mmol). The resulting solution was stirred for 72 h at 30°C then concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 9:1 then 4:1) afforded the ring-opened intermediate (249 mg, 63%, colorless oil); R_f=0.28 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+41.9 (*c* 1.0, $CHCl_3$); IR

(neat/NaCl) 3273.3, 1748.3, 1596.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 2H, J=8.9 Hz), 7.40–7.28 (m, 7H), 7.08 (m, 1H), 6.99–6.90 (m, 6H), 6.70 (d, 2H, J=8.9 Hz), 5.48 (d, 1H, J=8.8 Hz), 5.12 (AB, 2H, J=12.0 Hz), 4,60 (d, 2H, J=5.8 Hz), 4.22–4.14 (m, 2H), 3.90 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 163.1, 158.0, 153.6, 151.0, 134.5, 131.5, 129.6, 129.3, 128.6, 128.2, 122.7, 120.5, 117.8, 115.6, 114.2, 68.1, 66.5, 56.4, 55.6, 55.1; LRMS: (FAB, NBA, *m/z*, %): 581 (39) ($M+H^+$), 186 (80), 133 (100); HRMS calcd for $C_{30}H_{28}O_7SN^{35}Cl$ ($M+H^+$) 581.12750; found 581.12650.To a solution of this intermediate (317 mg, 0.54 mmol) was added NaHMDS (0.55 mL, 1 M solution, 0.55 mmol) at −78°C. The resulting solution was stirred at 0°C then at rt for 4 h. The solution was diluted with CH_2Cl_2, then washed with water, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 4:1) afforded **19d** (267 mg, 90%, colorless oil); R_f=0.40 (hexanes/EtOAc, 4:1); $[\alpha]_D$=+9.1 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 1747.3, 1595.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 2H, J=8.9 Hz), 7.40–7.29 (m, 7H), 7.08 (m, 1H), 6.99–6.92 (m, 6H), 6.89 (d, 2H, J=8.9 Hz), 5.19 (s, 2H), 4.52 (dd, 1H, J=5.2, 10.4 Hz), 4.39 (dd, 1H, J=5.2, 10.4 Hz), 3.88 (s, 3H), 3.59 (ddd, 1H, J=4.1, 5.2, 5.2 Hz), 3.57 (d, 1H, J=4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.7, 158.1, 154.0, 150.9, 134.7, 130.3, 130.0, 129.6, 128.52, 128.48, 128.2, 122.6, 120.6, 117.7, 115.9, 114.2, 67.7, 64.7, 55.6, 45.5, 41.9; LRMS: (FAB, NBA, *m/z*, %): 545 (62) (M^+), 171 (100); HRMS calcd for $C_{30}H_{27}O_7SN$ (M^+) 545.15082; found 545.15290.

4.2.24. 3-(*S*)-Isobutyl-1-(4-methoxy-benzenesulfonyl)-aziridine-2-(*R*)-carboxylic acid (20a). A solution of **19a** (79 mg, 0.196 mmol) in EtOH (10 mL) was stirred under H_2 (1 atm) in presence of 10% Pd/C for 16 h. The resulting solution was filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1 then 9:1) to afford **20a** (56 mg, 91%, colorless oil); R_f=0.33 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$=+3.3 (*c* 1.7, $CHCl_3$); IR (neat/NaCl) 3498.0, 3264.6, 1738.8, 1596.1, 1579.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (br. s, 1H), 7.88 (d, 2H, J=8.9 Hz), 6.95 (d, 2H, J=8.9 Hz), 3.88 (s, 3H), 3.22 (d, 1H, J=2.2 Hz), 3.06 (m, 1H), 1.98 (m, 1H), 1.55–1.27 (m, 2H), 0.93 (d, 6H, J=6.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 172.5, 163.5, 131.3, 129.7, 114.2, 55.6, 44.8, 48.4, 36.6, 27.2, 22.8, 21.7; LRMS: (TOF EI+, *m/z*, %): 313 (17) (M^+), 142 (100); HRMS calcd for $C_{14}H_{19}O_5NS$ (M^+) 313.09839; found 313.09832.

4.2.25. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(5-phenyl-pentyl)-aziridine-2-(*R*)-carboxylic acid (20c). Following the procedure described above, **19c** (504 mg, 1.02 mmol), was stirred under H_2 (1 atm) in presence of 10% Pd/C to afford, after flash chromatography (CH_2Cl_2/MeOH, 99:1 then 9:1), **20c** (355 mg, 86%, colorless oil); R_f=0.2–0.4 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$=−1.9 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 3350.0, 1724.3, 1596.7 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.88 (d, 2H, J=8.9 Hz), 7.26–7.12 (m, 5H), 7.09 (d, 2H, J=8.9 Hz), 3.88 (s, 3H), 3.24 (d, 1H, J=4.0 Hz), 3.00 (m, 1H), 2.60 (t, 2H, J=7.7 Hz), 2.03–1.85 (m, 2H), 1.69–1.33 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.5, 165.1, 143.6, 132.6, 130.7, 129.3, 129.2, 126.6, 115.3, 79.3, 56.2, 50.5, 45.1, 36.6, 32.4, 29.6, 29.0, 28.4.

4.2.26. 3-(*S*)-Isobutyl-1-(4-methoxy-benzenesulfonyl)-aziridine-2-(*R*)-carboxylic acid benzyloxy-amide (21a). To a solution of **20a** (68 mg, 0.22 mmol) in THF (8 mL) were successively added EDC (51 mg, 0.26 mmol), HOBt (35 mg, 0.26 mmol) and *N*-methyl morpholine (170 μL, 0.65 mmol). After stirring for 20 min, $BnONH_2$·HCl (104 mg, 0.65 mmol) was added, the resulting mixture was stirred overnight then diluted with ether, washed with 0.1N HCl, water, 0.5N $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 4:1) provided **21a** (64 mg, 70%, colorless oil); R_f=0.48 (hexanes/EtOAc, 3:2); $[\alpha]_D$=+22.4 (*c* 1.4, $CHCl_3$); IR (neat/NaCl) 3190.4, 1672.6, 1596.0, 1579.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.80 (d, 2H, J=8.9 Hz), 7.38–7.28 (m, 3H), 7.27–7.20 (m, 2H), 6.95 (d, 2H, J=8.9 Hz), 4.82 (d, 1H, J=10.7 Hz), 4.74 (d, 1H, J=10.7 Hz), 3.90 (s, 3H), 3.28 (d, 1H, J=4.0 Hz), 2.70 (ddd, 1H, J=4.0, 4.0, 8.8 Hz), 2.15 (ddd, 1H, J=4.0, 4.0, 13.3 Hz), 1.81 (m, 1H), 1.72 (ddd, 1H, J=8.8, 8.8, 13.3 Hz), 1.01 (d, 3H, J=6.7 Hz), 0.99 (d, 3H, J=6.7 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ, 164.0, 163.5, 134.5, 130.8, 129.6, 129.2, 129.0, 128.7, 128.6, 114.5, 78.3, 55.7, 50.2, 44.2, 36.0, 27.5, 22.8, 21.8; LRMS: (TOF EI+, *m/z*, %): 419 (40) ($M+H^+$), 418 (65) (M^+), 247 (100); HRMS calcd for $C_{21}H_{26}O_5N_2S$ (M^+) 418.15624; found 418.15610.

4.2.27. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(5-phenyl-pentyl)-aziridine-2-(*R*)-carboxylic acid benzyloxy-amide (21c). Following the procedure described above, **20c** (230 mg, 0.57 mmol), EDC (167 mg, 0.86 mmol), HOBt (116 mg, 0.86 mmol), *N*-methyl morpholine (310 μL, 2.85 mmol) and $BnONH_2$ (210 mg, 1.71 mmol) afforded, after flash chromatography (hexanes/EtOAc, 3:2), **21c** (201 mg, 69%, colorless oil); R_f=0.31 (hexanes/EtOAc, 3:2); $[\alpha]_D$=+14.0 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3193.9, 1670.6, 1596.4, 1579.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.80 (d, 2H, J=8.9 Hz), 7.38–7.17 (m, 10H), 6.96 (d, 2H, J=8.9 Hz), 4.81 (d, 2H, J=11.3 Hz), 4.73 (d, 2H, J=11.3 Hz), 3.89 (s, 3H), 3.26 (d, 1H, J=4.0 Hz), 2.71 (m, 1H), 2.62 (t, 2H, J=7.7 Hz), 2.11 (m, 1H), 1.94 (m, 1H), 1.67–1.37 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 163.4, 142.3, 134.4, 130.6, 129.6, 129.0, 128.8, 128.5, 128.3, 128.2, 125.6, 114.4, 78.3, 55.6, 50.8, 43.6, 35.6, 31.1, 28.5, 28.3, 27.5; LRMS (FAB EI, *m/z*, %): 509 (16) ($M+H^+$), 307 (20); HRMS calcd for $C_{28}H_{33}O_5N_2S$ ($M+H^+$) 509.21103; found 509.21010.

4.2.28. 1-(4-Methoxy-benzenesulfonyl)-3-(*R*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyloxy-amide (21d). Following the procedure described above, **19d** (91 mg, 0.167 mmol) was treated with H_2, in presence of 10% Pd/C (70 mg) to afford **20d**. Without further purification, **20d** was coupled following the same procedure as for **21a** with $BnONH_2$ (61 mg, 0.50 mmol) in presence of EDC (39 mg, 0.20 mmol), HOBt (27 mg, 0.20 mmol) and *N*-methyl morpholine (0.13 mL, 1.17 mmol) to afford, after flash chromatography (hexanes/EtOAc, 4:1), **21d** (35 mg, 35%, over 2 steps, colorless oil); R_f=0.32 (hexanes/EtOAc, 3:2); $[\alpha]_D$=+1.3 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3196.2, 1675.8, 1595.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.83 (d, 2H,

J=8.9 Hz), 7.40–7.24 (m, 7H), 7.08 (m, 1H), 6.99–6.92 (m, 6H), 6.84 (d, 2H, J=8.9 Hz), 4.85 (AB, 2H, J=10.9 Hz), 4.53 (dd, 1H, J=5.8, 10.5 Hz), 4.41 (dd, 1H, J=5.0, 10.5 Hz), 3.89 (s, 3H), 3.50 (d, 1H, J=3.8 Hz), 3.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.6, 158.1, 153.9, 151.1, 134.4, 130.2, 129.7, 129.3, 129.0, 128.7, 122.7, 120.7, 117.8, 115.9, 114.4, 78.5, 64.3, 55.7, 47.4, 41.0; LRMS: (FAB, NBA, *m/z*, %): 561 (14) ($M+H^+$).

4.2.29. 3-(*S*)-Isobutyl-1-(4-methoxy-benzenesulfonyl)-aziridine-2-(*R*)-carboxylic acid hydroxyamide (6a). To a solution of **21a** (64 mg, 0.15 mmol) in EtOH (20 mL) was added Pd/$BaSO_4$ (50 mg) and the resulting mixture was stirred overnight under H_2 (1 atm). The suspension was filtered and the filtrate was concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1) provided **6a** (38 mg, 76%, colorless oil); R_f=0.48 (CH_2Cl_2/MeOH, 19:1); $[\alpha]_D$=+20.6 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3298.4, 3200.1, 1672.1, 1595.9, 1579.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.88 (d, 2H, J=8.9 Hz), 7.02 (d, 2H, J=8.9 Hz), 3.91 (s, 3H), 3.32 (d, 1H, J=4.0 Hz), 2.85 (ddd, 1H, J=4.0, 4.2, 8.5 Hz), 2.12 (ddd, 1H, J=4.2, 4.2, 13.0 Hz), 1.80 (m, 1H), 1.72 (ddd, 1H, J=8.5, 8.5, 13.0 Hz), 1.00 (d, 3H, J=6.7 Hz), 0.97 (d, 3H, J=6.7 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 164.1, 163.9, 130.6, 129.7, 114.6, 55.7, 50.0, 43.6, 36.0, 27.4, 22.8, 21.8; LRMS: (TOF EI+, *m/z*, %): 328 (65) (M^+), 310 (100), 187 (45); HRMS calcd for $C_{14}H_{20}O_5N_2S$ (M^+) 328.10929; found 328.10952.

4.2.30. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(5-phenyl-pentyl)-aziridine-2-(*R*)-carboxylic acid hydroxyamide (6c). Following the procedure described above, **21c** (131 mg, 0.258 mmol), H_2 and Pd/$BaSO_4$ afforded, after flash chromatography (CH_2Cl_2/MeOH, 19:1), **6c** (90 mg, 83%, white oil); R_f=0.43 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$=+20.0 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 3293.9, 1670.3, 1596.4, 1579.6 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (d, 2H, J=8.9 Hz), 7.27–7.12 (m, 10H), 7.08 (d, 2H, J=8.9 Hz), 3.87 (s, 3H), 3.18 (d, 1H, J=4.0 Hz), 3.02 (m, 1H), 2.60 (t, 2H, J=7.7 Hz), 2.06 (m, 1H), 1.93 (m, 1H), 1.67–1.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.3, 142.9, 131.0, 130.2, 128.8, 128.7, 126.1, 114.9, 56.1, 50.7, 43.6, 36.1, 31.6, 29.1, 28.2, 27.9; LRMS (FAB EI, *m/z*, %): 419 (56) ($M+H^+$); HRMS calcd for $C_{21}H_{27}O_5N_2S$ ($M+H^+$) 419.16406; found 419.161280.

4.2.31. 1-(4-Methoxy-benzenesulfonyl)-3-(*R*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid hydroxy-amide (6d). Following the procedure described above, **21d** (20 mg, 0.036 mmol), H_2 and Pd/$BaSO_4$ afforded, after flash chromatography (CH_2Cl_2/MeOH, 19:1), **6d** (15 mg, 90%, white oil); R_f=0.42 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$=+13.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35–8.80 (br. s, 1H), 7.88 (d, 2H, J=8.9 Hz), 7.34–7.26 (m, 2H), 7.05 (m, 1H), 6.99–6.90 (m, 6H), 6.79 (d, 2H, J=8.9 Hz), 4.45 (dd, 1H, J=5.9, 10.4 Hz), 4.39 (dd, 1H, J=4.2, 10.4 Hz), 3.85 (s, 3H), 3.60 (m, 1H), 3.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 163.2, 158.1, 153.9, 151.0, 130.2, 129.7, 129.5, 122.7, 120.6, 117.8, 115.8, 114.4, 64.4, 55.7, 47.0, 40.5; LRMS: (FAB, NBA, *m/z*, %): 380 (10) ($M+H^+$).

4.2.32. (*E*)-1-Benzyloxy-3-(*R*)-[2-(1,3-dimethyl-2-oxo-4-(*R*)-5-(*R*)-[octahydro-2λ^5-benzo[1,3,2]diazaphosphol-2-yl)-vinyl]-aziridine-2-(*R*)-carboxylic acid *tert*-butyl ester (24). To a solution of NaHMDS (4.26 mL, 1 M solution in THF, 4.26 mmol) in THF (40 mL) at −78°C was added a solution of phosphonamide **22** (1.02 g, 3.88 mmol) in THF (60 mL) via canula. After 5 min, a solution of oxime **23** (1.09 g, 4.63 mmol) in THF (50 mL) was canulated. After 1 h, the red solution was poured into a 1:1 mixture of satd NH_4Cl and EtOAc. The product was extracted with EtOAc and the organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (100% EtOAc) to afford **24** (1.39 g, 78%, light yellow oil); $[\alpha]_D$=−48.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.21 (m, 5H), 6.27 (ddd, 1H, J=7.8, 17.0, 20.1 Hz), 5.83 (dd, 1H, J=17.1, 19.2 Hz), 4.78 (AB, 2H, J=11.3 Hz), 2.91 (t, 1H, J=9.0 Hz), 2.82 (d, 1H, J=9.2 Hz), 2.69–2.64 (m, 1H), 2.44 (d, 3H, J=11.5 Hz), 2.34 (d, 3H, J=11.3 Hz), 2.28–2.22 (m, 1H), 1.96–1.90 (m, 1H), 1.88–1.83 (m, 1H), 1.79–1.74 (m, 2H), 1.37 (s, 9H), 1.27–1.14 (m, 3H), 1.07–1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 141.6, 141.5, 136.1, 128.8, 128.3, 128.1, 125.6, 124.0, 82.0, 75.0, 64.0, 64.0, 63.5, 63.5, 49.9, 48.7, 48.6, 28.6, 28.5, 28.4, 28.3, 27.9, 27.7, 27.6, 24.1, 24.0; ^{31}P NMR (161 MHz, $CDCl_3$) δ 32.7; LRMS (FAB, NBA, *m/z*) 462 ($M+H^+$), 406 ($M-t$-Bu); HRMS calcd for $C_{24}H_{37}N_3O_4P$ ($M+H^+$) 462.25217; found 462.25310.

4.2.33. 1-Benzyloxy-3-(*S*)-hydroxymethyl-aziridine-2-(*R*)-carboxylic acid *tert*-butyl ester (25). Through a solution of **24** (1.39 g, 3.01 mmol) in a mixture of CH_2Cl_2 (80 mL) and EtOH (40 mL) cooled to −78°C, was passed ozone until a blue color persisted. Excess ozone was then removed by flowing nitrogen through the solution, which was followed by the addition of $NaBH_4$ (380 mg, 10.0 mmol). The solution was then warmed to 0°C, and stirred until disappearance of the ozonide/aldehyde by TLC. Acetone (10 mL) was then added, and the solvents were removed in vacuo at 0°C. The residue was then diluted with EtOAc, and successively washed with satd $NaHCO_3$ and brine. The organic phase was then dried, concentrated in vacuo, and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give **25** (788 mg, 94%, colorless oil); $[\alpha]_D$=+38.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.21–7.09 (m, 3H), 4.80 (s, 2H), 3.84 (dd, 1H, J=7.1, 12.0 Hz), 3.68 (dd, 1H, J=5.5, 12.0 Hz), 2.72 (d, 1H, J=9.2 Hz), 2.58 (ddd, 1H, J=5.5, 7.1, 9.2 Hz), 1.94–1.87 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 136.4, 128.8, 128.3, 128.1, 82.2, 75.0, 58.5, 49.8, 45.8, 27.8; LRMS (FAB, NBA, *m/z*) 280 ($M+H^+$), 224 ($M-t$-Bu); HRMS calcd for $C_{15}H_{22}NO_4$ ($M+H^+$) 280.15488; found 280.15570.

4.2.34. 1-Benzyloxy-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid *tert*-butyl ester (26a). To a solution of **25** (343 mg, 1.23 mmol), PPh_3 (487 mg, 1.85 mmol) and 4-phenoxyphenol (342 mg, 1.84 mmol) in CH_2Cl_2 (25 mL) was added DEAD (0.290 mL, 1.84 mmol) over 5 min. After stirring for five days, the solution was concentrated in vacuo and the residue purified by flash chromatography (hexanes/EtOAc, 19:1) to afford **26a** (504 mg, 92%, colorless oil); $[\alpha]_D$=+12.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 7H), 7.07–7.03 (m, 1H), 6.98–6.87 (m, 6H), 4.85 (AB, 2H, J=11.2 Hz), 4.24 (dd, 1H, J=6.9, 10.9 Hz), 4.04 (dd, 1H, J=5.8, 10.9 Hz), 2.92–2.86 (m, 1H), 2.77 (d, 1H, J=9.3 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 158.2, 154.5, 150.4, 136.3, 129.5, 128.8, 128.3, 128.1, 122.4, 120.6, 117.6, 115.7, 82.1, 74.9, 64.2, 47.1, 45.4, 27.9; LRMS (FAB, NBA, *m/z*): 447 (M^+), 392 (M−*t*-Bu); HRMS calcd for $C_{27}H_{29}NO_5$ (M^+) 447.20456; found 447.20490.

4.2.35. 1-Benzyloxy-3-(*S*)-(pyridin-3-yloxymethyl)-aziridine-2-(*R*)-carboxylic acid *tert*-butyl ester (26b). Following the same procedure described above, **25** (740 mg, 2.65 mmol), PPh_3 (1.05 g, 4.0 mmol), 3-hydroxypyridine (380 mg, 4.0 mmol) and DEAD (0.63 mL, 4.0 mmol) afforded, after flash chromatography (hexanes/EtOAc, 4:1 then 7:3), **26b** (492 mg, 52%, yellowish oil); $[\alpha]_D$=+8.4 (*c* 0.7, $CHCl_3$); R_f=0.33 (hexanes/EtOAc, 1:1); IR (neat/NaCl) 3338.0, 1730.6 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br. s, 1H), 8.22 (dd, 1H, J=2.2, 3.5 Hz), 7.38–7.30 (m, 5H), 7.20 (m, 2H), 4.84 (AB, 2H, J=11.5 Hz), 4.31 (dd, 1H, J=7.0, 10.8 Hz), 4.09 (dd, 1H, J=5.6, 10.8 Hz), 2.88 (ddd, 1H, J=5.6, 7.0, 9.3 Hz), 2.77 (d, 1H, J=9.3 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 142.3, 138.2, 136.2, 128.7, 128.3, 128.0, 123.7, 120.9, 82.2, 74.9, 63.9, 46.7, 45.2, 27.8; LRMS (FAB, NBA, *m/z*, %): 356 (70) (M^+), 326 (65), 300 (15) (M−*t*-Bu), 272 (32), 204 (96), 176 (100); HRMS calcd for $C_{20}H_{24}N_2O_4$ (M^+) 356.17361; found 356.17440.

4.2.36. [1-Benzyloxy-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridin-2-(*R*)-yl]-methanol (27a). To a solution of **26a** (470 mg, 1.05 mmol) in CH_2Cl_2 (45 mL) at −78°C was added DIBALH (2.8 mL, 4.20 mmol, 1.5 M solution in toluene). After stirring for 30 min at −78°C and 30 min at 0°C, 1 M HCl (30 mL) was slowly added and the solution extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 3:2) to afford **27a** (370 mg, 93%, colorless oil); $[\alpha]_D$=−28.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 7H), 7.09–7.05 (m, 1H), 7.01–6.95 (m, 4H), 6.91–6.87 (m, 2H), 4.82 (AB, 2H, J=11.5 Hz), 4.11 (dd, 1H, J=7.2, 10.8 Hz), 3.88 (dd, 1H, J=6.2, 10.8 Hz), 3.66 (dd, 1H, J=5.9, 12.2 Hz), 3.61 (dd, 1H, J=7.0, 12.2 Hz), 2.70 (ddd, 1H, J=6.3, 7.1, 9.1 Hz), 2.58 (ddd, 1H, J=5.9, 6.9, 9.1 Hz), 2.06–1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 154.3, 150.6, 136.9, 129.5, 128.6, 128.0, 122.5, 120.6, 117.6, 115,7, 74.6, 65.7, 59.5, 47.3, 45.0; LRMS (FAB, NBA, *m/z*): 400 (M+Na^+); HRMS calcd for $C_{23}H_{23}O_4NNa$ (M+Na^+) 400.15247; found 400.15400.

4.2.37. [1-Benzyloxy-3-(*S*)-(pyridin-3-yloxymethyl)-aziridin-2-(*R*)-yl]-methanol (27b). Following the same procedure described above, **26b** (360 mg, 1.0 mmol) and DIBAL–H (2.7 mL, 4.0 mmol, 1.5 M solution in toluene) afforded, after flash chromatography (hexanes/EtOAc, 1:1 then 1:0), **27b** (220 mg, 77%, colorless oil); $[\alpha]_D$=−18.1 (*c* 1.4, $CHCl_3$); R_f=0.21 (hexanes/EtOAc, 2:3); IR (neat/NaCl) 3381.1 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, 1H, J=1.3, 2.0 Hz), 8.23 (dd, 1H, J=2.5, 3.2 Hz), 7.38–7.33 (m, 5H), 7.22–7.19 (m, 2H), 4.82 (s, 2H), 4.08 (dd, 1H, J=7.1, 10.6 Hz), 3.99 (dd, 1H, J=5.5, 10.6 Hz), 3.69 (dd, 1H, J=5.1, 12.0 Hz), 3.60 (dd, 1H, J=7.0, 12.0 Hz), 2.68 (ddd, 1H, J=5.5, 7.1, 9.1 Hz), 2.58 (ddd, 1H, J=5.1, 7.0, 9.1 Hz), 2.49 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 142.3, 137.9, 136.8, 128.6, 128.4, 128.1, 123.9, 121.5, 74.6, 65.6, 59.3, 47.4, 44.9; LRMS (TOF EI+, *m/z*, %): 286 (100) (M^+), 256 (87); HRMS calcd for $C_{16}H_{18}O_3N_2$ (M^+) 286.13174; found 286.13146.

4.2.38. 1-Benzyloxy-2-(*R*)-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine (28a). To a solution of **27a** (370 mg, 0.981 mmol) in CH_2Cl_2 (35 mL) at 0°C, was added 2,6-lutidine (0.251 mL, 2.16 mmol) and TBSOTf (0.338 mL, 1.47 mmol). After stirring for 30 min, the mixture was diluted with CH_2Cl_2 (125 mL), successively washed with satd $NaHCO_3$ and satd NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 49:1) to afford **28a** (470 mg, 97%, yellowish oil); $[\alpha]_D$=+11.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.29 (m, 7H), 7.10–7.06 (m, 1H), 7.03–6.88 (m, 6H), 4.84 (s, 2H), 4.05–3.96 (m, 2H), 3.75 (dd, 1H, J=7.1, 11.5 Hz), 3.69 (dd, 1H, J=6.8, 11.5 Hz), 2.71–2.66 (m, 1H), 2.60–2.54 (m, 1H), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 154.7, 150.4, 137.0, 129.5, 128.5, 128.3, 127.8, 122.4, 120.6, 117.6, 115.7, 74.3, 65.7, 60.5, 47.7, 45.1, 25.8, 18.2, −5.4, −5.5; LRMS (FAB, NBA, *m/z*): 492 (M+H^+); HRMS calcd for $C_{29}H_{38}O_4NSi$ (M+H^+) 492.25702; found 492.25630.

4.2.39. 3-[1-Benzyloxy-3-(*R*)-(*tert*-butyl-dimethyl-silanyloxymethyl)-aziridin-2-(*S*)-ylmethoxy]-pyridine (28b). Following the same procedure described above, **27b** (220 mg, 0.77 mmol), 2,6-lutidine (0.197 mL, 1.69 mmol) and TBSOTf (0.264 mL, 1.15 mmol) afforded, after flash chromatography (EtOAc), **28b** (268 mg, 87%, colorless oil); $[\alpha]_D$=−7.5 (*c* 2.1, $CHCl_3$); R_f=0.29 (hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (br. m, 1H), 8.23 (br. m, 1H), 7.38–7.33 (m, 5H), 7.22–7.19 (m, 2H), 4.79 (s, 2H), 4.08 (dd, 1H, J=4.8, 10.8 Hz), 3.98 (dd, 1H, J=7.5, 10.8 Hz), 3.74 (dd, 1H, J=6.8, 10.6 Hz), 3.63 (dd, 1H, J=5.8, 10.6 Hz), 2.64 (ddd, 1H, J=4.8, 7.5, 9.0 Hz), 2.54 (ddd, 1H, J=5.8, 6.8, 9.0 Hz), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 142.3, 138.1, 136.9, 128.6, 128.3, 127.9, 123.8, 121.3, 74.5, 65.7, 60.5, 47.7, 44.9, 25.8, 18.2, −5.3, −5.4; LRMS (TOF EI+, *m/z*, %): 400 (1) (M^+), 343 (100), 313 (17); HRMS calcd for $C_{22}H_{32}O_3N_2Si$ (M^+) 400.21282; found 400.21973.

4.2.40. 2-(*R*)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine (29a). A mixture of **28a** (300 mg, 0.611 mmol) in EtOH (20 mL) was stirred in presence of Pd/$BaSO_4$ (300 mg, 5% w/w) under H_2 (1 atm) for 14 h. Filtration and flash chromatography (hexanes/EtOAc, 5:1) afforded **29a** (210 mg, 89%, colorless oil); $[\alpha]_D$=+5.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 4H), 7.06–7.04 (m, 1H), 7.03–6.88 (m, 4H), 4.05 (dd, 1H, J=5.3, 10.3 Hz), 3.99 (dd, 1H, J=6.8, 10.3 Hz), 3.83 (dd, 1H, J=5.8, 11.2 Hz), 3.66 (dd, 1H, J=6.1, 11.2 Hz), 2.58–2.54 (m, 1H), 2.46–2.41 (m, 1H), 1.92–1.80 (br. m, 1H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 154.8, 150.2,

141.0, 129.5, 128.4, 127.4, 126.8, 122.3, 120.6, 117.5, 115.5, 67.9, 65.0, 62.5, 35.2, 32.8, 25.8, 18.2, −5.3, −5.4; LRMS (FAB, NBA, *m/z*): 386 ($M+H^+$); HRMS calcd for $C_{22}H_{32}O_3NSi$ 386.21515; found 386.21670.

4.2.41. 3-[3-(*R*)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-aziridin-2-(*S*)-ylmethoxy]-pyridine (29b). Following the same procedure described above, **28b** (222 mg, 0.56 mmol) and $Pd/BaSO_4$ (200 mg, 5% w/w) afforded, after flash chromatography (hexanes/EtOAc, 1:4), **29b** (158 mg, 97%, colorless oil); $[\alpha]_D=+2.8$ (*c* 1.4, $CHCl_3$); $R_f=0.15$ (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (br. m, 1H), 8.23 (br. m, 1H), 7.22–7.19 (m, 2H), 4.14 (dd, 1H, *J*=4.8, 10.1 Hz), 4.04 (dd, 1H, *J*=6.8, 10.1 Hz), 3.86 (dd, 1H, *J*=5.8, 11.1 Hz), 3.63 (dd, 1H, *J*=6.1, 11.1 Hz), 2.58 (br. m, 1H), 2.48 (br. m, 1H), 2.05–1.55 (br. s, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 138.0, 123.8, 121.2, 68.1, 62.7, 35.2, 32.6, 25.9, 18.3, −5.2, −5.4; LRMS (TOF EI+, *m/z*, %): 295 (2) ($M+H^+$), 237 (100); HRMS calcd for $C_{15}H_{27}O_2N_2Si$ ($M+H^+$) 295.18418; found 295.18504.

4.2.42. 2-(*R*)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine (30a). To a solution of **29a** (125 mg, 0.323 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (82 μL, 0.583 mmol) and PMP–SO_2Cl (80 mg, 0.388 mmol) at 0°C. After stirring at 0°C for 12 h, the mixture was diluted with CH_2Cl_2 (40 mL), washed with satd NH_4Cl and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (hexanes/EtOAc, 9:1) afforded **30a** (121 mg, 67%, white oil); $[\alpha]_D=+13.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.33–7.28 (m, 2H), 7.10–7.03 (m, 1H), 6.99–6.89 (m, 6H), 6.75–6.71 (m, 2H), 4.10 (dd, 1H, *J*=5.0, 11.3 Hz), 4.04 (dd, 1H, *J*=6.8, 11.3 Hz), 3.87 (s, 3H), 3.85 (dd, 1H, *J*=5.8, 11.5 Hz), 3.75 (dd, 1H, *J*=5.6, 11.4 Hz), 3.25–3.20 (m, 1H), 3.16–3.12 (m, 1H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 158.1, 154.2, 153.5, 130.2, 129.5, 129.1, 122.5, 120.5, 117.6, 115.4, 114.1, 63.2, 60.2, 55.5, 43.6, 41.7, 25.7, 18.1, −5.5, −5.6; LRMS (FAB, NBA, *m/z*): 556 ($M+H^+$), 498 ($M-t$-Bu); HRMS calcd for $C_{29}H_{37}O_6NNaSiS$ ($M+Na^+$) 578.20087; found 578.20090.

4.2.43. 3-[3-(*R*)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-aziridin-2-(*S*)-ylmethoxy]-pyridine (30b). Following the same procedure as for **30a**, **29b** (158 mg, 0.54 mmol), Et_3N (150 μL, 1.07 mmol) and PMP–SO_2Cl (334 mg, 1.6 mmol) at 0°C for 90 min afforded, after flash chromatography (hexanes/EtOAc, 4:1 then 3:2), **30b** (241 mg, 97%, colorless oil); $[\alpha]_D=+9.1$ (*c* 0.9, $CHCl_3$); $R_f=0.26$ (hexanes/EtOAc, 1:1); IR (neat/NaCl) 3422.2, 1596.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, 1H, *J*=1.4, 4.4 Hz), 8.15 (dd, 1H, *J*=0.6, 2.4 Hz), 7.86 (d, 2H, *J*=8.9 Hz), 7.15 (ddd, 1H, *J*=0.6, 4.4, 8.4 Hz), 7.05 (ddd, 1H, *J*=1.4, 2.4, 8.4 Hz), 6.96 (d, 2H, *J*=8.9 Hz), 4.20 (dd, 1H, *J*=4.2, 10.9 Hz), 4.10 (dd, 1H, *J*=6.9, 10.9 Hz), 3.90 (dd, 1H, *J*=5.2, 11.4 Hz), 3.88 (s, 3H), 3.74 (dd, 1H, *J*=5.7, 11.4 Hz), 3.21 (ddd, 1H, *J*=4.2, 6.9, 13.0 Hz), 3.18 (ddd, 1H, *J*=5.2, 5.7, 13.0 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 154.3, 142.5, 138.0, 130.3, 128.9, 123.7, 120.8, 114.1, 65.1, 60.2, 55.6, 43.4, 41.7, 25.7, 18.2, −5.46, −5.52; LRMS (FAB, NBA, *m/z*, %): 929 (23) (2x$M+H^+$), 465 (38) ($M+H^+$); HRMS calcd for $C_{22}H_{33}O_5N_2SiS$ ($M+H^+$) 465.18796; found 465.18960.

4.2.44. [1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridin-2-(*R*)-yl]-methanol (31a). To a solution of **30a** (121 mg, 0.218 mmol) in THF (10 mL) at 0°C was added TBAF (0.24 mL, 0.240 mmol, 1 M solution in THF). After stirring for 15 min, the solution was poured into a mixture of satd $NaHCO_3$ (10 mL) and EtOAc (40 mL). The solution was extracted with EtOAc, the organic layer dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 3:2) to afford **31a** (81 mg, 84%, colorless oil); $[\alpha]_D=+5.7$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.33–7.28 (m, 2H), 7.08–7.03 (m, 1H), 7.01–6.89 (m, 6H), 6.75–6.71 (m, 2H), 4.12 (dd, 1H, *J*=6.5, 10.9 Hz), 4.08 (dd, 1H, *J*=5.2, 10.8 Hz), 3.88 (s, 3H), 3.83 (dd, 1H, *J*=5.0, 12.3 Hz), 3.77 (dd, 1H, *J*=5.8, 12.3 Hz), 3.26–3.18 (m, 2H), 2.12–1.98 (br. m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 158.0, 153,9, 150.8, 130.2, 129.5, 128.5, 122.5, 120.5, 117.6, 115.5, 114.2, 65.2, 59.2, 55.6, 43.3, 42.0; LRMS (FAB, NBA, *m/z*): 464 ($M+Na^+$); HRMS calcd for $C_{23}H_{23}O_6NNaS$ 464.11438 ($M+Na^+$); found 464.11420.

4.2.45. [1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(pyridin-3-yloxymethyl)-aziridin-2-(*R*)-yl]-methanol (31b). Following the same procedure described above, **30b** (233 mg, 0.50 mmol) and TBAF (0.5 mL, 0.5 mmol, 1 M solution in THF) afforded, after flash chromatography (hexanes/EtOAc, 1:1 then 1:2), **31b** (142 mg, 81%, colorless oil); $[\alpha]_D=-10.0$ (*c* 0.6, $CHCl_3$); $R_f=0.22$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.28–8.10 (br. m, 2H), 7.88 (d, 2H, *J*=8.9 Hz), 7.18 (br. m, 1H), 7.08 (br. d, 1H, *J*=8.2 Hz), 6.97 (d, 2H, *J*=8.9 Hz), 4.18 (m, 2H), 3.90 (m, 4H), 3.72 (dd, 1H, *J*=5.2, 10.9 Hz), 3.21 (m, 2H), 2.28 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 142.4, 137.7, 130.2, 129.0, 128.3, 123.7, 120.9, 114.2, 64.9, 59.0, 55.6, 43.1, 42.1, 29.5; LRMS (TOF EI+, *m/z*, %): 350 (100) (M^+), 187 (63); HRMS calcd for $C_{16}H_{18}O_5N_2S$ (M^+) 350.09364; found 350.09217.

4.2.46. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carbaldehyde (32a). To a solution of **31a** (81 mg, 0.184 mmol) in CH_2Cl_2 (10 mL) was added the Dess–Martin periodinane[25] (151 mg, 0.367 mmol). After stirring for 1 h, the solution was concentrated, and the residue was purified by flash chromatography (hexanes/EtOAc, 3:2) to afford **32a** (69 mg, 85%, yellowish oil); $[\alpha]_D=+28.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, 1H, *J*=4.0 Hz), 7.92–7.88 (m, 2H), 7.33–7.29 (m, 2H), 7.08–7.05 (m, 1H), 7.04–7.00 (m, 2H), 6.95–6.89 (m, 4H), 6.75–6.72 (m, 2H), 4.19 (d, 2H, *J*=4.4 Hz), 3.89 (s, 3H), 3.48–3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 164.2, 157.9, 153.6, 151.0, 130.4, 129.6, 127.7, 122.6, 120.5, 117.7, 115.6, 114.5, 64.1, 55.7, 45.4, 43.8; LRMS (FAB, NBA, *m/z*): 440 ($M+H^+$); HRMS calcd for $C_{23}H_{22}O_6NS$ ($M+H^+$) 440.11679; found 440.11820.

4.2.47. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(pyridin-3-yl-oxymethyl)-aziridine-2-(*R*)-carbaldehyde (32b). Following

the same procedure described above, **31b** (87 mg, 0.24 mmol) and the Dess–Martin periodinane[25] (425 mg, 0.98 mmol) afforded, after flash chromatography (hexanes/EtOAc, 1:2 then 1:4), **32b** (77 mg, 92%, colorless oil); $[\alpha]_D$=+10.3 (*c* 1.7, $CHCl_3$); R_f=0.27 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (d, 1H, *J*=3.5 Hz), 8.27–8.11 (m, 2H), 7.88 (d, 2H, *J*=8.9 Hz), 7.18 (br. d, 1H, *J*=8.4 Hz), 7.08 (br. d, 1H, *J*=8.4 Hz), 7.00 (d, 2H, *J*=8.9 Hz), 4.21 (m, 2H), 3.90 (s, 3H), 3.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 164.2, 153.8, 142.7, 137.6, 130.4, 127.4, 123.8, 121.2, 114.5, 63.9, 55.7, 45.1, 43.5.

4.2.48. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid (33a). To a solution of **32a** (73 mg, 0.16 mmol) in *t*-BuOH (5 mL) and CH_2Cl_2 (1 mL) was added a solution of NaH_2PO_4 (37 mg, 0.235 mmol) in water (1 mL). The solution was cooled to 0°C and 2-methyl-2-butene (0.4 mL) was added followed by $NaClO_2$ (42 mg, 0.465 mmol). After stirring for 5 h, the suspension was filtered, the filtrate was concentrated, and the residue purified by flash chromatography (EtOAc/MeOH, 6:1) to afford **33a** (67 mg, 95%, white oil); $[\alpha]_D$=+50.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.89–7.85 (m, 2H), 7.31–7.26 (m, 2H), 7.07–7.00 (m, 3H), 6.90–6.74 (m, 6H), 4.21–4.17 (m, 1H), 4.13–4.04 (m, 1H), 3.86 (s, 3H), 3.48–3.39 (m, 1H), 3.29–3.22 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.6, 164.9, 159.7, 155.9, 151.9, 131.6, 130.7, 129.7, 123.6, 121.5, 118.7, 116.7, 115.4, 66.2, 56.3, 43.8; LRMS (FAB, NBA, *m/z*): 478 ($M+Na^+$), 456 ($M+H^+$); HRMS calcd for $C_{23}H_{22}O_7NS$ ($M+H^+$) 456.11169; found 456.11020.

4.2.49. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyl-oxy-amide (34a). To a solution of **33a** (49 mg, 0.108 mmol) in THF (4 mL) were added HOBt (18 mg, 0.130 mmol) and EDC (26 mg, 0.130 mmol) at 0°C. After stirring for 30 min at rt, $BnONH_2$.HCl (21 mg, 0.130 mmol) and DIPEA (42 μL, 0.238 mmol) were added and the resulting solution stirred for a further 24 h, diluted with EtOAc (50 mL), washed with 0.1N HCl, 0.1 M $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc, 3:2) to afford **34a** (43 mg, 71%, white foam); $[\alpha]_D$=+12.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.83–7.80 (m, 1H), 7.34 (s, 5H), 7.32–7.27 (m, 3H), 7.08–7.04 (m, 1H), 6.99–6.85 (m, 6H), 6.64–6.61 (m, 2H), 4.88 (AB, 1H, *J*=11.3 Hz), 4.14 (dd, 1H, *J*=3.7, 11.1 Hz), 3.89 (s, 3H), 3.77 (dd, 1H, *J*=7.4, 11.2 Hz), 3.52 (d, 1H, *J*=7.6 Hz), 3.28–3.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.7, 158.0, 153.7, 150.7, 134.4, 130.4, 129.5, 129.0, 128.8, 128.5, 127.1, 122.5, 120.4, 117.6, 115.4, 114.4, 78.4, 64.4, 55.6, 42.8, 39.5; LRMS (FAB, NBA, *m/z*): 561 ($M+H^+$); HRMS calcd for $C_{30}H_{29}O_7N_2S$ 561.16956 ($M+H^+$); found 561.17040.

4.2.50. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(pyridin-3-yloxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyl-oxy-amide (34b). Following the same procedure described above, **32b** (60 mg, 0.17 mmol), NaH_2PO_4 (40 mg, 0.26 mmol), 2-methyl-2-butene (0.2 mL) and $NaClO_2$ (47 mg, 0.52 mmol) afforded the acid **33b**, which was used in the next step without further purification. Following the same procedure as for **34a**, reaction of **33b** with HOBt (35 mg, 0.26 mmol), EDC (50 mg, 0.26 mmol), $BnONH_2$ (63 mg, 0.52 mmol) and *N*-methyl morpholine (130 μL, 1.2 mmol) afforded, after flash chromatography (CH_2Cl_2/MeOH, 1:0 then 49:1), **34b** (42 mg, 52%, colorless oil); $[\alpha]_D$=+17.3 (*c* 1.5, $CHCl_3$); R_f=0.49 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (br. s, 1H), 8.19 (br. m, 1H), 8.06 (br. m, 1H), 7.80 (d, 2H, *J*=8.9 Hz), 7.32 (m, 5H), 7.18 (br. d, 1H, *J*=8.5 Hz), 7.01 (br. d, 1H, *J*=8.5 Hz), 6.94 (d, 2H, *J*=8.9 Hz), 4.92 (d, 1H, *J*=11.4 Hz), 4.86 (d, 1H, *J*=11.4 Hz), 4.21 (dd, 1H, *J*=3.7, 11.4 Hz), 3.89 (s, 3H), 3.88 (m, 1H), 3.53 (d, 1H, *J*=7.5 Hz), 3.25 (ddd, 1H, *J*=3.5, 7.5, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.7, 153.9, 142.3, 137.8, 134.6, 130.5, 129.1, 128.8, 128.6, 127.1, 123.8, 120.9, 114.4, 78.4, 64.3, 55.7, 42.6, 39.3; LRMS (FAB, NBA, *m/z*, %): 470 (16) ($M+H^+$); HRMS calcd for $C_{23}H_{24}O_6N_3S$ 470.13858 ($M+H^+$); found 470.13640.

4.2.51. 1-Benzyloxy-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid benzyloxy-amide (34c). To a solution of **26a** (28 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) at 0°C. After stirring for 2 h at rt, the solution was concentrated. The residue was purified by flash chromatography (neat EtOAc) to afford **33c** used in the next step. As described for **34a**, **33c**, HOBt (11 mg, 0.078 mmol), EDC (15 mg, 0.078 mmol), $BnONH_2$.HCl (31 mg, 0.195 mmol) and DIPEA (80 μL, 0.455 mmol) afforded, after flash chromatography (hexanes/EtOAc, 2:1), **34c** (25 mg, 81%, colorless oil); $[\alpha]_D$=+27.1 (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br. s, 1H), 7.39–7.22 (m, 12H), 7.09–7.04 (m, 1H), 6.99–6.93 (m, 4H), 6.87–6.80 (m, 2H), 4.73 (AB, 2H, *J*=11.3 Hz), 4.76 (s, 2H), 4.07–4.03 (m, 1H), 3.74 (m, 1H), 2.91–2.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 156.1, 154.2, 150.6, 136.4, 134.7, 129.5, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 122.4, 120.1, 117.5, 115.7, 78.2, 74.8, 64.7, 46.6, 44.4; LRMS (FAB, NBA, *m/z*): 497 ($M+H^+$).

4.2.52. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid hydroxy-amide (7a). A mixture of **34a** (32 mg, 0.057 mmol) and Pd/$BaSO_4$ (32 mg, 5%) in EtOH (5 mL) were stirred under H_2 (1 atm) for 6 h (monitored by TLC). After filtration and flash chromatography (EtOAc/hexanes, 4:1), **7a** (17 mg, 51%, white solid) was obtained; $[\alpha]_D$=+29.5 (*c* 0.8, $CHCl_3$); mp 74–77°C (CH_2Cl_2/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65–9.10 (br. s, 1H), 7.87–7.85 (m, 2H), 7.30–7.25 (m, 2H), 7.06–6.83 (m, 7H), 6.65–6.62 (m, 2H), 4.25–4.16 (m, 1H), 3.90–3.82 (m, 1H), 3.86 (s, 3H), 3.65–3.62 (d, 1H, *J*=7.4 Hz), 3.56–3.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 162.3, 158.0, 153.7, 150.6, 130.5, 129.5, 127.0, 122.5, 120.4, 117.6, 115, 3, 114.4, 64.2, 55.6, 43.1; LRMS (FAB, NBA, *m/z*): 471 ($M+H^+$), 470 (M^+); HRMS calcd for $C_{23}H_{22}O_7N_2S$ (M^+) 470.11478; found 470.11610.

4.2.53. 1-(4-Methoxy-benzenesulfonyl)-3-(*S*)-(pyridin-3-yloxymethyl)-aziridine-2-(*R*)-carboxylic acid hydroxy-amide (7b). Following the same procedure as for **7a**, **34b** (31 mg, 0.066 mmol) and Pd/$BaSO_4$ (30 mg, 5%) afforded, after flash chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1),

7b (11 mg, 43%, colorless oil); $[\alpha]_D$=+10.1 (*c* 0.2, $CHCl_3$); R_f=0.19 (CH_2Cl_2/MeOH, 9:1); ^1H NMR (300 MHz, CD_3OD) δ 8.17–8.02 (m, 2H), 7.83 (d, 2H, *J*=8.9 Hz), 7.37–7.28 (m, 2H), 7.02 (d, 2H, *J*=8.9 Hz), 4.36–4.24 (m, 2H), 3.89 (s, 3H), 3.45 (d, 1H, *J*=7.5 Hz), 3.25 (ddd, 1H, *J*=3.5, 3.5, 7.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.9, 163.8, 141.9, 137.9, 131.8, 129.0, 126.0, 123.8, 115.6, 65.6, 56.4, 43.8, 39.7; LRMS (FAB, NBA, *m/z*): 379 ($M+H^+$).

4.2.54. 1-Benzyloxy-3-(*S*)-(4-phenoxy-phenoxymethyl)-aziridine-2-(*R*)-carboxylic acid hydroxyamide (7c). As described above, **20c** (24 mg, 0.048 mmol) and Pd/$BaSO_4$ (5%, 20 mg) in EtOH (4 mL) afforded **7c** (10 mg, 52%, white oil); $[\alpha]_D$=+61.8 (*c* 0.5, CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ 7.36–7.24 (m, 7H), 7.05–6.99 (m, 1H), 6.95–6.86 (m, 6H), 4.79 (s, 2H), 4.08 (dd, 1H, *J*=6.8, 11.2 Hz), 4.04 (dd, 1H, *J*=5.3, 11.2 Hz), 2.89 (ddd, 1H, *J*=5.2, 6.8, 9.3 Hz), 2.78 (d, 1H, *J*=9.3 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.9, 159.8, 156.2, 152.0, 138.2, 129.8, 129.4, 129.1, 123.6, 121.6, 118.7, 117.0, 75.8, 65.7, 48.1, 45.0; LRMS (FAB, NBA, *m/z*): 407 ($M+H^+$); HRMS calcd for $C_{23}H_{23}N_2O_5$ 407.16071; found 407.15970.

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