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Rhodium-Catalyzed Intramolecular Formation of *N*-Sulfamoyl 2,3-Aziridino-γ-lactones and Their Use for the Enantiospecific Synthesis of α,β-Diamino Acid Derivatives

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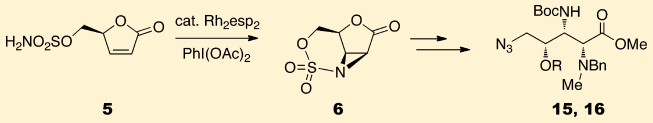
Supporting Information

ABSTRACT: 4-Hydroxymethylbutenolide **4** was transformed into its sulfamoyl derivative **5**, which upon treatment with iodosobenzene diacetate and magnesium oxide in the presence of a rhodium catalyst afforded the product of intramolecular aziridination **6**. Reaction of **6** with primary or secondary amines in DMA led to regioselective opening of the aziridine ring at C2 to give the corresponding bicyclic derivatives **7a**−**7g** in good to excellent yields. Methanolysis of the lactone ring of the *N*-benzyl-*N*-methyl derivative **7c** followed by protection of the resulting secondary hydroxy group and treatment of the product with Boc anhydride provided the activated cyclic sulfamates **13** and **14**. The latter then reacted with a second nucleophile (azide or thiophenol) to give the corresponding difunctionalized α,β-diamino methyl esters **15**−**18**, **20**.



5 **6** **15, 16**

INTRODUCTION

2,3-Aziridino-γ-lactones have been shown to be valuable starting materials for the preparation of α- and β-amino acids.[1−5] Unlike the well-documented aziridino-2-carboxylic esters, known to react with nucleophiles almost always at the C-3 position to give the corresponding α-amino acids,[6] 2,3-aziridino-γ-lactones show different reactivity depending on the type of nucleophile used. Thus, while hard nucleophiles (e.g., alcohols) also react exclusively at the C-3 position in S_N2 fashion to afford optically pure α-amino acids, soft nucleophiles (e.g., thiols, azide, indole, halides) attack only at the C-2 position, leading to the formation of α-substituted β-amino acids (Figure 1).

This particular reactivity of aziridino-γ-lactones has been successfully applied to the enantiospecific synthesis of the α-amino acids (2*S*,3*S*,4*S*)-dihydroxyglutamic acid (**1**)[7,8] and (−)-polyoxamic acid (**2**)[9] as well as to a protected form of APTO (**3**),[10] the β-amino acid component of the marine cyclic depsipeptide, microsclerodermin D (Figure 2).

Several methodologies have been developed that allow access to 2,3-aziridino-γ-lactones. All of these are multistep procedures starting from D-ribose (or D-lyxose)[1,2] or from a butenone derivative.[10,11] The synthesis of 2,3-aziridino-γ-lactones from β-lactams has also been described.[12]

The direct aziridination of olefins by nitrenes generated from metal-catalyzed formation of metallanitrenes from hypervalent iodine reagents such as arylsulfonyliminoiodanes PhI=NSO_2Ar is a subject of considerable current synthetic interest.[13] The initial premises of the reaction having been established by Mansuy and co-workers,[14] it was Evans[15] who conducted a thorough methodological study of the reaction, showing that copper(I) and (II) salts were the most efficient catalysts for generating the reactive nitrene species from the iminoiodanes and that the aziridination could be made stereoselective by including chiral ligands in the reaction mixture (Figure 3).

The advent of one-pot procedures whereby the arylsulfonyliminoiodanes are generated in situ by reaction of the arylsulfonamide and iodosylbenzene PhI=O or iodosophenyl diacetate $PhI(OAc)_2$ circumvented the necessity of preparing these sensitive reagents beforehand.[16] This procedure also allowed extension of the aziridination reaction to its intramolecular version starting from olefinic sulfonamides. Besides being more reactive, replacement of the sulfonamide by a sulfamate in these intramolecular reactions introduces another electrophilic center, which after nucleophilic aziridine opening and sulfamate activation, allows further chemical transformations of the substrate (Figure 4).[17] In this regard, we have recently described a copper-catalyzed stereocontrolled version of this intramolecular olefin aziridination starting from sulfamates[17b] as well as its application to the synthesis of neuroactive steroid analogues.[18]

In this paper then, we wish to report the adaptation of this procedure to the intramolecular aziridination of the sulfamate **5** derived from commercially available butenolide **4**, the reactivity of the product toward nucleophiles, and application of the procedure to the synthesis of α,β-diamino acids (Figure 5). Many examples of the latter are found in nature or as

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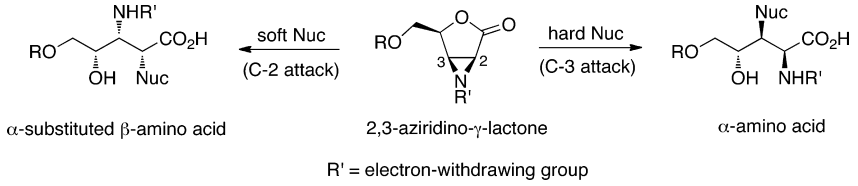

Figure 1. Reactivity of aziridino-γ-lactones.

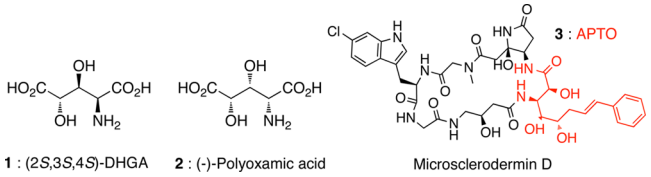

Figure 2. α- and β-amino acids prepared from 2,3-aziridino-γ-lactones.

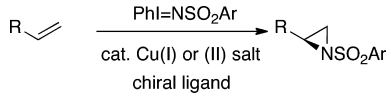

Figure 3. Copper-catalyzed iminoiodane-mediated aziridination of olefins.

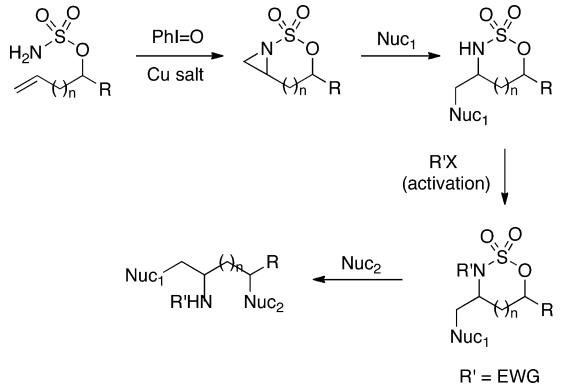

Figure 4. Intramolecular aziridination of olefinic sulfamates and reaction with nucleophiles.

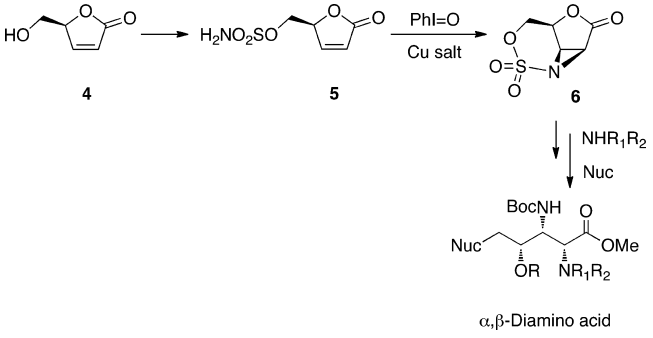

Figure 5. Proposed synthesis of aziridino-γ-lactones via intramolecular aziridination by a sulfamate and use for preparation of α,β-diamino acids.

components of natural products. Moreover, α,β-diamino acids form the core structure of a wide variety of therapeutically useful drugs.[19]

RESULTS AND DISCUSSION

Butenolide **4** was first treated with chlorosulfonylisocyanate and formic acid in DMA to give the corresponding 5-*O*-sulfamate **5** in 62% yield.[17] Surprisingly, attempted aziridination of sulfamate **6** using the standard conditions shown to be successful for intramolecular aziridination of olefinic sulfamates (10 mol % $Cu(CH_3CN)_4PF_6$, 1.2 equiv of PhI=O, molecular sieves in CH_3CN)[17] resulted only in complete recovery of starting material despite prolonged reaction times. The use of different copper salts and solvents had no visible effects on this outcome. We thus decided to resort to rhodium catalysts to effect this reaction. The use of rhodium complexes for aziridination of olefins by sulfonamides and sulfamates (usually in the presence of $PhI(OAc)_2$) has been well described.[20] However, in contrast to copper catalysis, rhodium catalysts tend to favor C−H insertion at allylic or benzylic carbons if this possibility exists on the substrate rather than aziridination.[13a,21] This is indeed the case with butenolide **5**, the allylic C-4 position being in principle susceptible to C−H amination by the sulfamate. Du Bois and co-workers have described a highly effective rhodium complex, $Rh_2(esp)_2$ (esp = $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionic acid), useful for the aziridination of olefins.[22] We thus decided to apply Du Bois' reaction conditions (5 mol % $Rh_2(esp)_2$, 1.2 equiv of $PhI(OAc)_2$ and MgO in CH_3CN at rt for 4 h) to substrate **5**, and we were pleased to obtain the desired aziridine-lactone **6** in 50% yield with no trace by NMR of the competing product of C−H allylic amination (Scheme 1).

The structure of compound **6** was confirmed by X-ray crystallography (see the Supporting Information).[23]

We then proceeded to study the reactivity of cyclic sulfonamide **6** toward various amines. Compound **6** being quite poorly soluble in apolar organic solvents, the first experiments using benzylamine as nucleophile were run in DMF at room temperature. As shown in Table 1 (entry 1), the only product isolated after 24 h from the complicated reaction mixture was compound **8a**, obtained in only 22% yield, the result of lactone opening by the amine to give the benzylamide followed by attack at the C-3 position. The structure of compound **8a** was unambiguously determined by an X-ray crystallographic study (see the Supporting Information).[24] Similarly, the more reactive *o,p*-dimethoxybenzylamine provided **8b**, obtained in only 23% yield (Table 1, entry 3). More satisfactory results were obtained when DMA was used as the solvent. Thus, both benzylamine and *o,p*-dimethoxybenzylamine now provided only the products of C-2 attack of aziridine **6**, that is, compounds **7a** and **7b**, in 70 and 58% yields, respectively, after only 1−1.5 h reaction times (Table 1, entries 2 and 4). Using DMA as solvent, secondary amines also gave the products of type **7**, though reaction times increased and yields decreased as the steric bulk of the nucleophile increased. *N*-Methyl-, *N*-ethyl-, and *N*-benzyl-benzylamine thus furnished products **7c**, **7d**, and **7e** in 80, 55, and 35% yields after 1, 48, and 120 h reaction times, respectively (Table 1, entries 5−7).

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Scheme 1

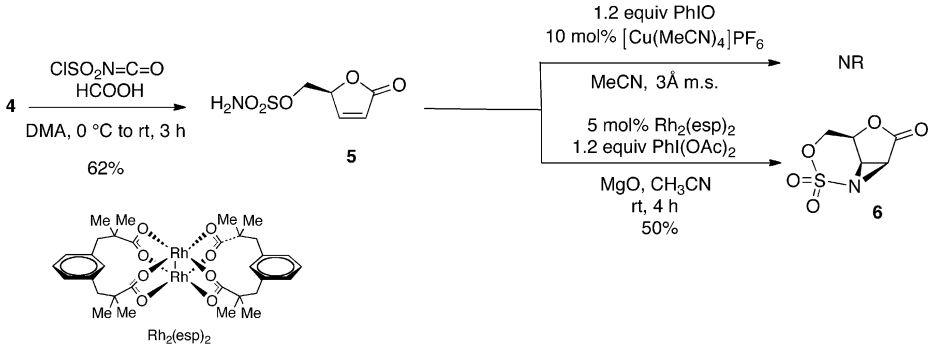
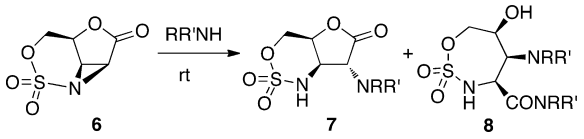


Table 1. Reaction of Cyclic Sulfonamide 6 with Various Amines



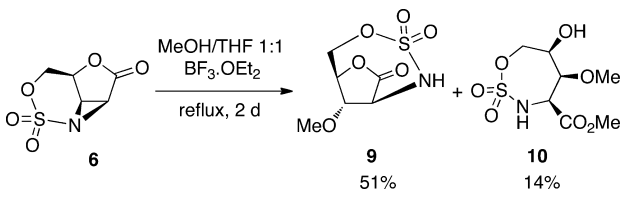
entry	R	R′	solvent	time (h)	cpd no.	yield (%)	cpd no.	yield[a] (%)
1	Bn	H	DMF	24	**7a**		**8a**	22
2	Bn	H	DMA	1	**7a**	70	**8a**	
3	*o,p*-$(MeO)_2$Bn	H	DMF	24	**7b**		**8b**	23
4	*o,p*-$(MeO)_2$Bn	H	DMA	1.5	**7b**	58	**8b**	
5	Bn	Me	DMA	1	**7c**	80	**8c**	
6	Bn	Et	DMA	48	**7d**	55	**8d**	
7	Bn	Bn	DMA	120	**7e**	35	**8e**	
8	Ph	Me	DMA	48	**7f**	60	**8f**	
9	Et	Et	DMA	1	**7g**	20	**8g**	

[a]Yields reported are after purification by column chromatography.

N-Phenyl-*N*-methylamine also provided a satisfactory yield of C-2 ring-opened product **7f** (60%; Table 1, entry 8), while diethylamine gave product **7g** in only 20% yield (Table 1, entry 9).

Opening of the aziridine ring of compound **6** by a hard nucleophile, methanol, proved surprisingly difficult. After 2 days of reflux in a 1:1 mixture of methanol and THF (the latter added to ensure solubility) and in the presence of 1 equiv of boron trifluoride etherate, a 51% yield of the expected product of C-3 attack, compound **9**, was obtained, accompanied by 14% of the product corresponding to methanolysis of the lactone function of **9**, that is, compound **10** (Scheme 2).[25]

Scheme 2



Our primary objective being the preparation of *α,β*-diamino acids, we next studied the reactivity of the cyclic sulfamate after amine-promoted aziridine opening of **6**. For this model study, the *N*-benzyl-*N*-methyl derivative **7c** was chosen as starting material. Reaction of the latter with methanol at room temperature for 4 days provided the methyl ester **11** (Scheme 3). In order to avoid relactonization, the free hydroxy function of **11** was immediately acetylated using acetic anhydride in pyridine to give **12**. Transformation of the sulfamate **12** into its activated *N*-Boc derivative **13** was then accomplished by reaction with Boc anhydride and DMAP in DMF. The overall yield of **13** was 85% for the 3 steps.

Alternatively, the secondary OH group of compound **11** could be benzylated using benzyl trichloroacetimidate and TFA in CH_2Cl_2/cyclohexane to give, after treatment with Boc anhydride, compound **14** (Scheme 4). The overall yield for the three steps was in this case slightly lower (60%).

Reaction of the activated sulfamates with nucleophiles was then investigated. Gratifyingly, reaction of the *O*-acetyl derivative **13** with sodium azide in DMA provided the 5-azido *α,β*-diamino ester **15**, the product of sulfamate ring-opening followed by loss of SO_3. The *O*-benzyl derivative **14** provided, under the same reaction conditions, the analogous 5-azido product **16** in 65% yield. Similarly, phenylthiolate reacted with **13** to give the 5-thiophenyl analogue **17** in 77% yield (Scheme 5).

The advantage of the *O*-benzyl versus the *O*-acetyl protecting group in **16** and **15**, respectively, became apparent during initial attempts at deprotection of these compounds. Thus, treatment of **15** with TFA in CH_2Cl_2 effectively removed the Boc group, but this was accompanied by *O*- to *N*-migration of the acetyl group, affording **18** in 66% yield accompanied by **19**, the product of lactonization, isolated in 25% yield (Scheme 6). On the other hand, similar treatment of the *O*-Bn derivative **16** with TFA allowed smooth conversion to the free *β*-amino compound **20** in 80% yield.

In conclusion, we have developed an efficient intramolecular rhodium-catalyzed, iminoiodane-mediated aziridination of 4-

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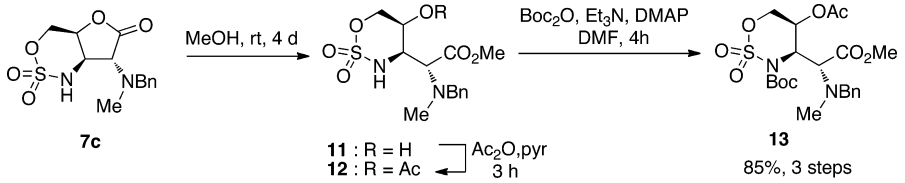
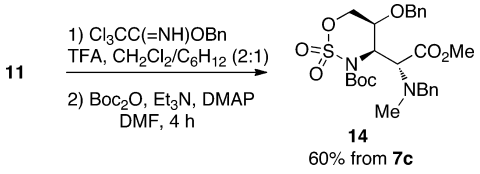
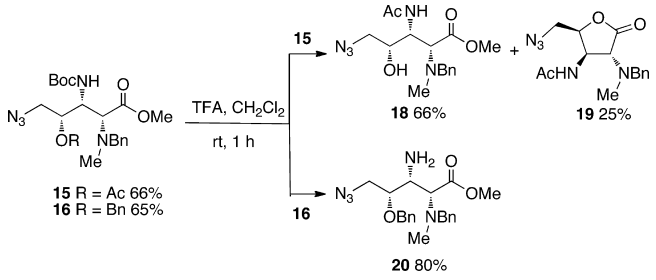
Scheme 3



Scheme 4



Scheme 6



sulfamoylmethylbutenolide to give the corresponding aziridino-γ-lactone. Regioselective opening of the aziridine ring with amines followed by cyclic sulfamate activation and nucleophilic opening then gives access to α,β-diamino acids. The procedure allows for the stereospecific preparation of highly substituted derivatives, which can be useful for the preparation of natural products or therapeutic agents. Studies in this direction are presently being pursued.

EXPERIMENTAL SECTION

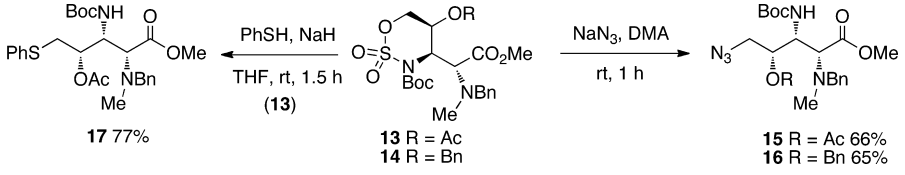
General Methods. Melting points, measured in capillary tubes, are uncorrected. IR spectra were recorded on an FT-IR spectrometer. Optical rotations were determined at 20 °C. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts (d) are reported in parts per million with reference to $CDCl_3$ (^{1}H, 7.27; ^{13}C, 77.00), CD_3OD (^{1}H, 3.31; ^{13}C, 49.00), D_2O (^{1}H, 4.79) or DMSO-d_6 (^{1}H, 2.50; ^{13}C, 39.51). The following abbreviations are used for the proton spectra multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintuplet; m, multiplet; br, broad. Coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained using electrospray ionization and a time of flight analyzer (ESI-MS) for high resolution mass spectra (HRMS). Thin-layer chromatography was performed on silica gel-coated aluminum plates and visualized under a UV lamp (254 nm) and with a solution of *p*-anisaldehyde (5%) in ethanol/H_2SO_4/AcOH (90/5/1) or a solution of ninhydrin (2% in ethanol). Flash chromatography was performed on silica gel at medium pressure (300 mbars). All solvents were freshly distilled when required. $Rh_2(esp)_2$ was purchased from Sigma-Aldrich.

(*S*)-(5-Oxo-2,5-dihydrofuran-2-yl)methyl Sulfamate (5). HCO_2H (331 mL, 8.76 mmol) was added dropwise to neat $OCNSO_2Cl$ (658 mL, 8.76 mmol) at 0 °C with vigorous stirring.[26] Gas evolved during addition. The resulting viscous suspension was stirred for 18 h at rt. The mixture was cooled to 0 °C, DMA (2 mL) was added, and the solution was stirred for 5 min. A solution of alcohol **4** (500 mg, 4.38 mmol) in DMA (2 mL) was added dropwise, the reaction was allowed to warm to rt, and stirring was continued until the reaction was complete (2−3 h) as determined by TLC. The reaction was quenched by the successive addition of EtOAc (30 mL) and saturated aqueous NaCl solution (15 mL). The mixture was poured into a mixture of EtOAc (40 mL) and H_2O (15 mL). The organic phase was collected, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, washed with saturated aqueous NaCl solution (2 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography on silica gel (EtOAc/heptane 9:1) afforded sulfamic ester **5** (521 mg, 2.7 mmol) in 62% yield as a white amorphous solid: R_f 0.2 (EtOAc/heptane 7:3); IR (film) 3354, 3204, 3098, 1737, 1726, 1567, 1365, 1276, 1163, 1092, 1051, 987, 928 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 4.31 (dd, J = 5.1 Hz, J = 11.3 Hz, 1H), 4.52 (dd, J = 11.3 Hz, J = 3.2 Hz, 1H), 5.44 (m, 1H), 6.26 (dd, J = 2.1 Hz, J = 11.3 Hz, 1H), 6.84 (br s, 2H), 7.74 (dd, J = 1.5 Hz, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 68.3, 81.4, 126.3, 154.1, 172.9; HREIMS m/z calcd for $[C_5H_7NO_5SNa]^+$ 215.9943, found 215.9946.

(1*R*,6*S*,9*S*)-2-Aza-4,7-dioxa-3-thiatricyclo[4.3.0.0]nonan-8-one (6). To a suspension of sulfamate **5** (585 mg, 3.03 mmol) in CH_3CN (15 mL) were added successively MgO (40.3 mg, 281 mmol), $PhI(OAc)_2$ (1.07 g, 3.33 mmol), and $Rh_2(esp)_2$ (46 mg, 0.06 mmol). The reaction mixture was refluxed during 2 h, cooled, and filtered through a pad of Celite, which was washed with acetone. The filtrate was concentrated under reduced pressure, and the crude product was taken up in methanol. A white precipitate formed, which was collected by filtration and washed with methanol affording aziridine **6** (274 mg, 1.56 mmol) in 52% yield: R_f 0.30 (EtOAc/heptane 7:3); $[\alpha]_D^{20}$ = −7.0 (c 1.71, acetone); mp 185 °C (decomp.); IR (film) 1785, 1379, 1076, 985, 774, 678 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.99 (d, J = 3.7 Hz), 4.59 (m, 1H), 4.65 (dd, J = 2.7 Hz, J = 12.4 Hz, 1H), 5.00 (dd, J = 0.6 Hz, J = 12.4 Hz), 5.17 (m, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 45, 51.8, 68.6, 74.3, 167.1; HRESMS m/z calcd for $[C_5H_4NO_5S]^-$ 189.9810, found 189.9808. The structure of compound **6** was confirmed by single-crystal X-ray crystallography (see the Supporting Information).

(4a*S*,7*R*,7a*R*)-7-(Benzylamino)tetrahydrofuro[3,2-*d*][1,2,3]-oxathiazin-6(1*H*)-one 2,2-Dioxide (7a). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added benzylamine (14 μL, 0.12 mmol, 1.2 equiv). The reaction mixture was stirred for 1 h and diluted with EtOAc (3 mL) and

Scheme 5



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saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish compound **7a** (20.1 mg, 0.07 mmol, 70% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, J = 2.0 Hz, 1H), 3.90 (s, 2H), 4.29 (dd, J = 1.9 Hz, J = 4.1 Hz, 1H), 4.65 (m, 1H), 4.82 (dd, J = 1.6 Hz, J = 13.6 Hz, 1H), 4.89 (dd, J = 2.5 Hz, J = 13.6 Hz, 1H), 7.24−7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 59.9, 62.3, 70.2, 71.2, 127.9, 128.3, 128.8, 137.9, 173.3; IR 3165, 3013, 2924, 2853, 2746, 1737, 1633, 1552, 1430, 1360, 1181, 1024, 941, 749 cm^{-1}; HRESMS m/z calcd for $[C_{12}H_{14}N_2O_5SNa]^+$ 321.0521, found 321.0532.

(4a*S*,7*R*,7a*R*)-7-[(2,4-Dimethoxybenzyl)amino]-tetrahydrofuro[3,2-*d*][1,2,3]oxathiazin-6(1*H*)-one 2,2-Dioxide (7b). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added 2,4-dimethoxybenzylamine (20 μL, 0.13 mmol, 1.3 equiv). The reaction mixture was stirred for 1.5 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish compound **7b** (20.7 mg, 0.058 mmol, 58% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85 (s, 2H), 4.47 (dd, J = 6.4 Hz, J = 3.6 Hz, 1H), 4.80 (m, 1H), 4.91 (dd, J = 13.9 Hz, J = 1.4 Hz, 1H), 4.98 (dd, J = 13.9 Hz, J = 2.1 Hz, 1H), 6.49 (dd, J = 8.3 Hz, J = 2.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 7.1 Hz, 1H), 7.22 (d, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.7, 55.6, 55.8, 60.7, 62.7, 71.1, 72.4, 99.2, 105.0, 119.8, 131.6, 159.7, 161.6, 174.1; IR (film, ν, cm^{-1}) 3211, 2939, 2839, 1784, 1515, 1368, 1261, 1204, 766 cm^{-1}; HRESMS m/z calcd for $[C_{14}H_{18}N_2O_7SNa]^+$ 381.0733, found 381.0698.

(4a*S*,7*R*,7a*R*)-7-[Benzyl(methyl)amino]tetrahydrofuro[3,2-*d*]-[1,2,3]oxathiazin-6(1*H*)-one 2,2-Dioxide (7c). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added *N*-methylbenzylamine (17 μL, 0.13 mmol, 1.3 equiv). The reaction mixture was stirred for 1 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish compound **7c** (24.1 mg, 0.08 mmol, 80% yield) as a white amorphous solid: $[\alpha]^{26}_D$ = +49.9 (*c* 1.0, $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.34 (s, 3H), 3.80 (d, 1H, J = 3.2 Hz), 3.82 (s, 2H), 4.71 (dd, 1H, $J_{7a\text{-}7}$ = 5.5 Hz, $J_{7a\text{-}4a}$= 3.4 Hz), 4.81−4.92 (m, 2H), 4.93−4.95 (m, 1H), 7.14 (br s, 1H), 7.23−7.39 (m, 5H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$), 75 MHz) δ 39.2, 57.5, 59.8, 68.2, 71.8, 72.5, 128.2, 129.2, 129.7, 139.1, 172.9; HRESMS m/z calcd for $[C_{13}H_{15}N_2O_5]^-$ 311.0702, found 311.0703.

(4a*S*,7*R*,7a*R*)-7-[Benzyl(ethyl)amino]tetrahydrofuro[3,2-*d*]-[1,2,3]oxathiazin-6(1*H*)-one 2,2-Dioxide (7d). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added *N*-ethylbenzylamine (14 μL, 0.13 mmol; 1.3 equiv). The reaction mixture was stirred for 48 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 6:4) to furnish compound **7d** (17.9 mg, 0.055 mmol, 55% yield) as a white amorphous solid: $[\alpha]^{23}_D$ = +51.6 (*c* 1.0. $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.08 (t, 3H, J = 7.1 Hz), 2.74 (q, 2H, J = 7.1 Hz), 3.81 (s, 2H), 4.06 (d, 1H, J = 4.5 Hz), 4.65 (m, 1H), 4.85 (m, 2H), 4.94 (m, 1H), 7.17 (d, 1H, J = 6.1 Hz), 7.22−7.41 (m, 5H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 13.0, 46.3, 55.6, 57.6, 64.9, 71.9, 72.5, 128.0, 129.2, 129.4, 139.9, 173.5. IR (film) 3204, 1771, 1449, 1362, 1188, 1060; HRESMS m/z calcd for $[C_{14}H_{18}N_2O_5SNa]^+$ 349.0834, found 349.0834.

(4a*S*,7*R*,7a*R*)-7-[Dibenzylamino]tetrahydrofuro[3,2-*d*][1,2,3]-oxathiazin-6(1*H*)-one 2,2-Dioxide (7e). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added *N*,*N*-dibenzylamine (28 μL, 0.18 mmol; 1.4 equiv). The reaction mixture was stirred for 5 days and diluted with EtOAc (1 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish compound **7e** (13.5 mg, 0.03 mmol, 35% yield) as a colorless oil: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.83 (s, 4H), 3.96 (d, 1H, J = 3.4 Hz), 4.75−4.80 (m, 2H), 4.87 (dd, 1H, J = 13.5 Hz, J = 2.8 Hz), 4.90 (m, 1H), 7.05 (d, 1H, J = 5.8 Hz), 7.23−7.43 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 55.8, 57.0, 64.7, 71.8, 72.2, 128.3, 129.3, 129.7, 139.1, 173.7; HRESMS m/z calcd for $[C_{19}H_{20}N_2O_5SNa]^+$ 411.0991, found 411.0987.

(4a*S*,7*R*,7a*R*)-7-[Phenyl(methyl)amino]tetrahydrofuro[3,2-*d*]-[1,2,3]oxathiazin-6(1*H*)-one 2,2-Dioxide (7f). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMA (1 mL) under argon at room temperature was added *N*,*N*-methylphenylamine (20 μL, 0.13 mmol, 1.3 equiv). The reaction mixture was stirred for 2 days and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 6:4) to furnish compound **7f** (17.8 mg, 0.06 mmol, 60% yield) as a white amorphous solid: $[\alpha]^{20}_D$ = +56.8 (*c* 1.0. $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.93 (s, 3H), 4.71 (m, 1H), 4.89 (m, 2H), 5..05−5.09 (m, 2H), 6.82 (m, 1H), 6.97 (m, 2H), 7.26 (m, 2H), 7.38 (br s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 35.6, 57.6, 64.4, 72.1, 72.5, 115.5, 120.0, 130.1, 150.0, 171.8; HRESMS m/z calcd for $[C_{12}H_{14}N_2O_5SNa]^+$ 321.0521, found 321.0535.

(4a*S*,7*R*,7a*R*)-7-[Diethylamino]tetrahydrofuro[3,2-*d*][1,2,3]-oxathiazin-6(1*H*)-one 2,2-Dioxide (7g). To a solution of aziridine **6** (30 mg, 0.15 mmol) in DMA (1 mL) under argon at room temperature was added *N*,*N*-diethylamine (19.6 μL, 0.18 mmol; 1.2 equiv). The reaction mixture was stirred for 1 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 1:1) to furnish compound **7g** (7.9 mg, 0.03 mmol, 20% yield) as a colorless oil: $[\alpha]^{21}_D$ = +47.4 (*c* 1.0, $(CH_3)_2CO$); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.05 (t, 6H, J = 7.1 Hz), 2.71 (q, 4H, J = 7.1 Hz), 3.90 (d, 1H, J = 3.9 Hz), 4.53 (m, 1H), 4.80−4.87 (m, 2H), 4.90 (m, 1H), 7.22 (br s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 13.2, 45.4, 57.9, 65.2, 71.7, 72.5, 173.4; HRESMS m/z calcd for $[C_9H_{16}N_2O_5SNa]^+$ 287.0678, found 287.0681.

(4*S*,5*S*,6*S*)-*N*-(2-Benzyl)-5-[(2-benzyl)amino]-6-hydroxy-1,2,3-oxathiazepane-4-carboxamide 2,2-Dioxide (8a). To a solution of aziridine **6** (40 mg, 0.21 mmol) in DMF (2 mL) under argon at room temperature was added benzylamine (34 μL, 0.31 mmol, 1.5 equiv). The reaction mixture was stirred for 24 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish compound **8a** (14 mg, 0.047 mmol, 22% yield) as an amorphous white solid: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.39, 3.48 (2× d, 2H, ^2J = 12.8 Hz), 3.88 (br s, 3H), 4.06 (ddd, 1H, J = 10.7 Hz, J = 3.7 Hz, J = 3.6 Hz), 4.22 (dd, 1H, J = 12.3 Hz, J = 10.7 Hz), 4.30 (m, 3H), 4.42 (2× d, 2H, J = 14.6 Hz), 7.06−7.25 (m, 11H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 43.9, 53.2, 56.4, 60.2, 67.7, 69.5, 127.8, 127.9, 128.7, 129.1, 129.2, 139.9, 169.3; HRESMS m/z calcd for

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$[C_{19}H_{23}N_3O_5SNa]^+$ 428.1256, found 428.1246. The structure of compound **8a** was confirmed by single-crystal X-ray crystallography (see the Supporting Information).

(4*S*,5*S*,6*S*)-*N*-(2,4-Dimethoxybenzyl)-5-[(2,4-dimethoxybenzyl)amino]-6-hydroxy-1,2,3-oxathiazepane-4-carboxamide 2,2-Dioxide (8b). To a solution of aziridine **6** (20 mg, 0.1 mmol) in DMF (2 mL) under argon at 0 °C was added 2,4-dimethoxybenzylamine (22.5 μL, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred for 24 h and diluted with EtOAc (3 mL) and saturated aqueous NaCl (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residue obtained was purified by chromatography on silica gel (EtOAc/heptane 7:3) to furnish **8b** (12 mg, 0.02 mmol, 23% yield) as a colorless oil: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.30 (d, 1H, ^2J = 12.5 Hz), 3.48 (d, 1H, ^2J = 12.5 Hz), 3.72, 3.78, 3.79, 3.81 (4x s, 12H), 3.84 (s, 1H), 3.86 (d, 1H,J = 3.7 Hz), 3.92 (ddd, 1H, ^2J = 12.2 Hz, J_{H7-H6} = 3.2 Hz, J_{H7-OH} = 0.8 Hz), 4.12 (ddd, 1H, $J_{H6-H7'}$ = 10.6 Hz, J_{H6-H7} = 3.5 Hz, J_{H6-H5} = 3.5 Hz), 4.28 (dd, 1H, ^2J = 12.0 Hz, $J_{H6-H7'}$ = 10.7 Hz), 4.30 (dd, 1H, ^2J = 14.3 Hz, J = 5.2 Hz), 4.50 (dd, 1H, ^2J = 14.3 Hz, J = 6.3 Hz), 6.35−6.55 (m, 4H) 6.95 (d, 1H, J = 8.2 Hz), 7.19 (d, 1H, J = 8.2 Hz), 7.84 (b, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 39.3, 47.8, 55.6, 55.7, 55.9, 56.2, 59.1, 67.5, 69.6, 99.1, 99.2, 104.7, 105.1, 119.4, 121.0, 130.7, 131.6, 159.4, 159.8, 161.5, 169.1; HRESMS m/z calcd for $[C_{23}H_{31}N_3O_9SNa]^+$ 548.1679, found 548.1715.

(1*R*,6*S*,9*S*)-9-Methoxy-4,7-dioxa-3-thia-2-azabicyclo[4.2.1]-nonan-8-one 3,3-Dioxide (9) and Methyl (4*S*,5*R*,6*R*)-6-Hydroxy-5-methoxy-1,2,3-oxathiazepane-4-carboxylate 2,2-Dioxide (10). To a suspension of aziridine **6** (50 mg, 0.26 mmol) in MeOH (1.5 mL) was added $BF_3{\cdot}OEt_2$ (0.036 mL, 0.29 mmol) at rt. The reaction mixture was refluxed during 48 h, cooled, and washed successively with saturated aqueous solutions of $NaHCO_3$ (2 × 1 mL) and NaCl (2 × 1 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting oil was purified by flash chromatography on silica gel (EtOAc/heptane 7:3) to furnish compounds **9** (32.2 mg, 0.14 mmol) in 51% yield and **10** (10.6 mg, 0.04 mmol) in 14% yield. Data for **9**: R_f 0.40 (EtOAc/heptane 7:3); $[\alpha]^{20}_D$ = −8.07 (c 0.5, MeOH); IR (neat, cm^{-1}) 3281, 2997, 2922, 2850, 1785, 1430, 1369, 1259, 1171, 1075, 932, 744, 634; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.78 (s, 1H), 4.48 (dd, J = 2.7 Hz, J = 13.1 Hz), 4.56 (dd, J = 1.0 Hz, J = 13.1 Hz, 1H), 4.75 (s, 1H), 4.90 (m, 1H), 5.51 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1, 57.5, 70.4, 78.6, 82.3, 172.8; HRESMS m/z calcd for $[C_6H_8NO_6S]^-$ 222.0072, found 222.0067.

Data for **10**: R_f 0.45 (EtOAc/heptane 7:3); $[\alpha]^{20}_D$ = +28.97 (c 0.8, MeOH); IR (neat, cm^{-1}) 3491, 3269, 2955, 1741, 1633, 1434, 1360, 1179, 1092, 989, 967, 791, 622; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (d, J = 10.4 Hz, 1H), 3.50 (s, 3H), 3.85 (s, 3H), 4.05 (m, 2H), 4.12 (m, 1H), 4.15 (d, J = 3.5 Hz), 4.35 (dd, J = 1.7 Hz, J = 10.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.4, 55.0, 61.4, 66.6, 70.0, 80.6, 168.7; HRESMS m/z calcd for $[C_7H_{13}NO_7SNa]^+$ 278.0310, found 278.0307.

(2*R*)-Methyl 2-[(4*R*,5*S*)-(5-Acetyloxy-2,2-dioxide-1,2,3-oxathiazine-tetrahydro-4-yl)-2-benzyl(methyl)amino) Acetate (12) and (2*R*)-Methyl 2-[(4*R*,5*S*)-(5-Acetyloxy-3-*tert*-butoxycarbonylamino-2,2-dioxide-1,2,3-oxathiazine-tetrahydro-4-yl)-2-benzyl(methyl)amino) acetate (13). Compound **7c** (80 mg, 0.42 mmol) was dissolved in methanol (10 mL), and the solution was stirred for 96 h at rt. The solvent was then removed under vacuum to furnish a white residue (**11**, 85 mg, 0.25 mmol). The latter (66 mg, 0.19 mmol), unstable and used without further purification, was dissolved in pyridine (2 mL), and acetic anhydride (181 μL, 1.92 mmol, 10 equiv) was added. The solution was stirred for 4 h at rt, and the solvents were evaporated in vacuo affording **12** as a homogeneous white solid by TLC (73 mg, 0.19 mmol, 99% yield). This crude product was dissolved in DMF (1 mL) and Boc_2O (50 mg, 0.23 mmol, 1.2 equiv), and triethylamine (31.6 μL, 1.2 equiv) and DMAP (3 mg, 0.023 mmol, 0.12 equiv) were added. The reaction mixture was stirred for 4 h, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/heptane 1:1) to furnish compound **13** (80 mg, 0.16 mmol, 85% yield after 3 steps) as a colorless oil.

Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 3H), 2.21 (s, 3H), 3.23 (d, 1H, J = 10.6 Hz), 3.53, 3.70 (2× d, 2H, ^2J = 12.8 Hz), 3.71 (s, 3H), 4.22 (dd, 1H, J = 10.6 Hz, J = 3.9 Hz), 4.40 (dd, 1H, ^2J = 12.9 Hz, J_{H6-H5} = 1.7 Hz), 4.70 (dd, 1H, ^2J = 12.9 Hz, $J_{H6'-H5}$ = 1.5 Hz), 4.76 (dd, 1H, J_{H5-H4} = 3.2 Hz, $J_{H5-H6'}$ = 1.5 Hz), 4.84 (b, 1H), 7.16−7.29 (m, 5H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 37.8, 52.1, 55.5, 59.6, 62.1, 63.0, 74.1, 127.9, 128.8, 129.5, 137.7, 169.1, 170.1; HRESMS m/z calcd for $[C_{16}H_{22}N_2O_7SNa]^+$ 409.1045, found 409.1053.

Compound **13**: $[\alpha]^{20}_D$ = +17.5 (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1744, 1708, 1221, 1156, 749; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.46 (s, 9H), 1.93 (s, 3H), 2.05 (s, 3H), 3.69, 3.79 (2× d, 2H, ^2J = 12.5 Hz), 3.84 (s, 3H), 4.03 (d, 1H, $J_{H2'-H4}$ = 11.5 Hz), 4.67 (d, 1H, ^2J = 12.8 Hz), 4.96 (d, 1H, ^2J = 13.2 Hz), 5.45 (b, 1H), 5.72 (b, 1H), 7.22−7.54 (m, 5H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 20.6, 27.9, 37.0, 51.6, 56.5, 62.4, 67.2, 67.3, 74.8, 85.7, 128.0, 128.9, 130.2, 139.9, 151.4, 169.5, 169.9; HRESMS m/z calcd for $[C_{21}H_{30}N_2O_9SNa]^+$ 509.1570, found 509.1580.

(2*R*)-Methyl 2-[(4*R*,5*S*)-(5-Benzyloxy-3-*tert*-butoxycarbonylamino-2,2-dioxide-1,2,3-oxathiazine-tetrahydro-4-yl)-2-benzyl-(methyl)amino) Acetate (14). Crude compound **11** (66 mg, 0.192 mmol) was dissolved in CH_2Cl_2/cyclohexane 2:1 (6 mL), and benzyl 2,2,2-trichloroacetimidate (215 μL, 1.14 mmol) and trifluoromethanosulfonic acid (33 μL, 0.38 mmol) were added. After 4 h of stirring, the solvents were evaporated under vacuum, and the resulting solid was dissolved in ethyl acetate. Celite was added, and the suspension was transferred to a silica gel chromatography column, which was eluted with CH_2Cl_2/heptane/CH_3OH (1:1:0.2). The product obtained was immediately dissolved in DMF (1 mL) and treated with Boc_2O (34.8 mg, 0.16 mmol, 1.2 equiv), triethylamine (11.6 μL, 0.16 mmol, 1.2 equiv), and DMAP (2 mg, 0.1 equiv). The reaction mixture was stirred for 4 h at rt, saturated aqueous $NaHCO_3$ was added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 3 mL), and the organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The oil obtained was purified by flash chromatography on silica gel (EtOAc/heptane 1:1) to furnish compound **14** (60.9 mg, 0.11 mmol, 60% yield) as a colorless oil: $[\alpha]^{22}_D$ = +23.1 (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) 2927, 2359, 1808, 1731, 1259, 1146, 778; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.43 (s, 9H), 1.93 (s, 3H), 3.45 (s, 3H) 3.64 (d, 1H, ^2J = 12.6 Hz), 3.74 (d, 1H, ^2J = 12.6 Hz), 3.98 (d, 1H, $J_{H2'-H4}$ = 11.5 Hz), 4.50 (d, 1H, ^2J = 11.3 Hz), 4.54 (ddd, 1H, J_{H5-H4} = 7.8 Hz, J_{H5-H6} = 4.6 Hz, $J_{H5-H6'}$ = 3.2 Hz), 4.64 (d, 1H, ^2J = 11.3 Hz), 4.74 (dd, 1H, $J_{H6-H6'}$ = 12.5 Hz, J_{H6-H5} = 3.2 Hz), 4.82 (dd, 1H, ^2J = 12.5 Hz, $^2J_{H6'-H5}$ = 4.6 Hz), 5.53 (dd, 1H, J_{H4-H7} = 11.5 Hz, J_{H4-H5} = 7.8 Hz), 7.21−7.49 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 28.0, 37.2, 51.1, 57.2, 62.5, 67.0, 73.2, 73.8, 74.4, 85.4, 127.9, 128.7, 128.9, 129.2, 130.2, 138.6, 140.2, 151.7, 169.3; HRESMS m/z calcd for $[C_{26}H_{34}N_2O_8SNa]^+$ 557.1934, found 557.1952.

(2*R*,3*R*,4*R*)-Methyl 4-Acetoxy-5-azido-2-(benzyl(methyl)-amino)-3-(*tert*-butoxycarbonylamino)pentanoate (15). To a solution of **13** (32 mg, 0.048 mmol) in DMA (0.6 mL) was added NaN_3 (4.3 mg, 0.048 mmol). The reaction mixture was stirred for 1 h and then partitioned between EtOAc (2 mL) and saturated aqueous NaCl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 2 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum, affording compound **15** (14 mg, 0.03 mmol, 66% yield) as a colorless oil: $[\alpha]^{24}_D$ = +40.5 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.45 (s, 9H), 2.00 (s, 3H), 2.09 (s, 3H), 3.42 (d, 1H, J_{H2-H3} = 11.3 Hz), 3.50 (dd, 1H, ^2J = 15.7 Hz, J_{H-H4} = 8.1 Hz), 3.54 (dd, 1H, ^2J = 15.7 Hz, J_{H-H4} = 7.0 Hz), 3.55, 3.75 (2× d, 2H, ^2J = 13.5 Hz), 4.34 (m, 1H), 5.09 (ddd, 1H, J_{H4-H} = 8.1 Hz, J = 5.1 Hz, J = 1.5 Hz), 5.90 (d, 1H, J = 9.6 Hz), 7.20−7.37 (m, 5H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 20.7, 28.6, 37.8, 51.1, 51.5, 52.7, 60.1, 67.2, 72.2, 79.5, 127.9, 129.0, 129.5, 140.4, 157.2, 170.7; FTIR (film, ν cm^{-1}) 2975, 2098, 1729, 1713, 1496, 1218, 1047, 699; HRESMS m/z calcd for $[C_{21}H_{31}N_5O_6Na]^+$ 472.2172, found 472.2177.

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(2*R*,3*R*,4*R*)-Methyl 5-Azido-2-(benzyl(methyl)amino)-4-(benzyloxy)-3-(*tert*-butoxycarbonylamino)pentanoate (16). To a solution of **14** (35 mg, 0.065 mmol) in DMA (0.6 mL) was added NaN_3 (10 mg, 0.154 mmol). The reaction mixture was stirred for 1 h and then partitioned between EtOAc (2 mL) and saturated aqueous NaCl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 2 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum affording compound **16** (21 mg, 0.04 mmol, 65% yield) as a colorless oil: $[\alpha]^{25}_D$ = +41.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.43 (s, 9H), 2.16 (s, 3H), 3.42−3.66 (m, 5H), 3.69 (s, 3H), 3.79 (d, 1H, *J* = 12.2 Hz), 4.30 (m, 1H) 4.48, 4.68 (2× d, 2H, ^2J = 11.2 Hz), 5.55 (d, *J* = 8.2 Hz), 7.19−7.39 (m, 10H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 28.7, 38.4, 51.4, 52.8, 59.7, 66.8, 73.8, 78.4, 79.3, 127.9, 128.5, 129.1, 129.7, 138.9, 140.4, 157.0, 170.9; FTIR (film, ν cm^{-1}) 2928, 2099, 1727, 1713, 1495, 1164, 697; HRESMS *m*/*z* calcd for $[C_{26}H_{35}N_5O_5Na]^+$ 520.2536, found 520.2528.

(2*R*,3*R*,4*S*)-Methyl 4-Acetoxy-2-(benzyl(methyl)amino)-3-(*tert*-butoxycarbonylamino)-5-(phenylthio)pentanoate (17). To a solution of thiophenol (11.8 μL, 0.11 mmol, 1.3 equiv) in THF (1 mL) was added a suspension of NaH in mineral oil (5 mg, 0.12 mmol, 1.4 equiv). A solution of compound **13** (43 mg, 0.088 mmol) in THF (0.4 mL) was added, and the reaction mixture was stirred for 1.5 h at rt. The mixture was then partitioned between EtOAc (2 mL) and saturated aqueous NaCl (2 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 2 mL). The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum, affording compound **17** (43.7 mg, 0.08 mmol, 77%) as a colorless oil: $[\alpha]^{26}_D$ = +52.8 (*c* 1.0. $CHCl_3$); IR (neat, cm^{-1}) 2952, 2927, 1730, 1497, 1221, 1023, 738; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 1.46 (s, 9H), 1.90 (s, 3H), 2.11 (s, 3H), 3.15−3.18 (m, 2H), 3.39 (d, 1H, J_{H2-H3} = 11.3 Hz), 3.54, 3.76 (2× d, 2H, ^2J = 13.3 Hz), 3.65 (s, 3H), 4.53 (m, 1H), 5.06 (m, 1H), 5.83 (d, 1H, J_{NH-H3} = 9.4 Hz), 7.18−7.44 (m, 10H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 20.6, 28.7, 35.9, 38.0, 51.4, 51.8, 60.1, 67.6, 72.5, 79.4, 127.0, 127.8, 129.0, 129.6, 129.8, 130.1, 137.0, 140.5, 157.3, 170.5, 170.6; HRESMS *m*/*z* calcd for $[C_{27}H_{36}N_2O_6SNa]^+$ 539.2192, found 539.2202.

(2*R*,3*R*,4*R*)-Methyl 3-Acetamido-5-azido-2-(benzyl(methyl)-amino)-4-hydroxypentanoate (18) and Compound 19. To a solution of compound **15** (29 mg, 0.064 mmol) in CH_2Cl_2 (2 mL) was added TFA (99 μL, 0.128 mmol, 2 equiv). The reaction mixture was stirred for 1 h and then evaporated to dryness under vacuum. The crude product was taken up in EtOAc (1 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 1 mL). The combined aqueous layers were extracted with EtOAc (1 mL), and the organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness under vacuum. The residual oil was purified by preparative chromatography on silica gel (EtOAc/heptane 1:1) furnishing compounds **18** (14.7 mg, 0.04 mmol) and **19** (5 mg, 0.016 mmol) in 66 and 25% yield, respectively.

Compound 18. Colorless oil: $[\alpha]^{25}_D$ = +45.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.24 (s, 3H), 3.30 (d, 1H, *J* = 3.6 Hz), 3.32 (s, 1H), 3.57 (d, 1H, ^2J = 13.4 Hz), 3.66 (d, 1H, J_{H2-H3} = 9.9 Hz), 3.72 (d, 1H, J_{HD-HC} = 13.4 Hz), 3.74 (m, 1H), 3.77 (s, 3H), 4.29 (m, 1H), 5.75 (d, 1H, *J* = 8.5 Hz), 7.21−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 38.7, 50.3, 51.7, 55.0, 65.4, 70.3, 127.6, 128.6, 128.8, 138.8, 170.5, 171.2. FTIR (film, cm^{-1}) 3289, 2926, 2098, 1778, 1726, 1649, 1260, 740; HRESMS *m*/*z* calcd for $[C_{16}H_{23}N_5O_4Na]^+$ 372.1648, found 372.1636.

Compound 19. Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.44 (s, 3H), 3.41, 3.64 (2× d, 2H, *J* = 13.3 Hz), 3.77 (d, 1H, *J* = 10.2 Hz), 3.83, 3.89 (2× d, 2H, ^2J = 13.0 Hz), 4.70−4.81 (m, 2H), 5.52 (sl, 1H), 7.26−7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 37.8, 49.5, 51.5, 59.0, 64.0, 75.9, 127.9, 128.7, 129.1, 138.6, 171.1, 171.8. FTIR (film, cm^{-1}) 3282, 2928, 2111, 1777, 1658, 1538, 1453, 1290, 742; HRESMS *m*/*z* calcd for $[C_{15}H_{19}N_5O_3Na]^+$ 340.1386, found 340.1370.

(2*R*,3*R*,4*R*)-Methyl 3-Amino-5-azido-2-(benzyl(methyl)-amino)-4-(benzyloxy)pentanoate (20). To a solution of compound **16** (13.5 mg, 0.027 mmol) in CH_2Cl_2 (40 μL) was added TFA (4.2 μL, 0.054 mmol, 2 equiv). The reaction mixture was stirred for 1 h and then evaporated to dryness under vacuum. The resulting residue was taken up in EtOAc (2 mL) and washed with saturated aqueous NaCl (2 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL), and the organic phases were combined and dried over $MgSO_4$. Removal of the solvent under vacuum provided compound **20** (8.5 mg 0.02 mmol, 80% yield) as a yellow pale oil: $[\alpha]^{27}_D$ = +38.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.13, 3.26 (2× d, 2H, *J* = 10.3 Hz), 3.47 (m, 1H), 3.51−3.66 (m, 3H), 3.68 (s, 3H), 3.76 (d, 1H, *J* = 13.3 Hz), 4.35, 4.61 (2× d, 2H, *J* = 10.9 Hz), (d,1H, *J* = 10.9 Hz), 7.14−7.33 (m, 10H). FTIR (film, cm^{-1}) 2946, 2097, 1724, 1433, 741; HRESMS *m*/*z* calcd for $[C_{21}H_{27}N_5O_3Na]^+$ 420.2012, found 420.2001.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **5**, **6**, **7a**−**7g**, **8a**, **8b**, **9**, **10**, **12**−**19** and ^{1}H NMR spectrum of compound **20**. ORTEP drawings of compounds **6** and **8a** and X-ray data of **6** and **8a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) X-ray crystallographic data for compound **6** have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, U.K. (deposition number CCDC 837575).
(24) X-ray crystallographic data for compound **8a** have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, U.K. (deposition number CCDC 837577).
(25) We previously explained the C-2 vs C-3 selectivity of opening of *N*-acetylaziridine-γ-lactones by soft and hard nucleophiles, respectively, using MNDO calculations (see refs 1 and 2). While we have not repeated these calculations on the tricyclic *N*-sulfamoylaziridine-γ-lactone **6** in order to corroborate the regioselectivity of aziridine opening by the amines at C-2 and of methanol at C-3, a reviewer has pointed out that our results can be rationalized by NBO analysis. In this case, attack of the amines at C-2 would correspond to simple nucleophilic addition at this more electrophilic center compared to C-3, while for methanol, the situation is reversed because of the coordination of boron trifluoride etherate (modeled as a protonated *N*-sulfamoyl function). We thank the reviewer for this insight.
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