Stereospecific Synthesis of Substituted Sulfamidates as Privileged Morpholine Building Blocks

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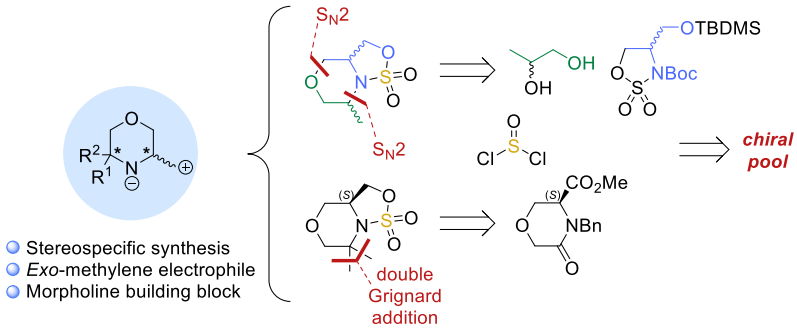

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Abstract Morpholine is a heterocyclic moiety widely used in medicinal chemistry as a building block. It has unique physicochemical properties, as it can improve both pharmacokinetic and pharmacodynamic properties of active pharmaceutical ingredients. However, the efficient synthesis of enantiomerically pure morpholine building blocks remains challenging. Herein, we report the synthesis of optically pure 3-hydroxymethylmorpholine building blocks, as well as their sulfamidates, exploiting a stereospecific strategy from chiral pool material.

Key words morpholines, sulfamidates, stereoselectivity, chiral building blocks, privileged scaffolds

Morpholine is a privileged structural component of bioactive molecules frequently exploited by medicinal chemists due to its favorable biochemical properties.[1,2] In the last decades, morpholine has been featured in several approved and experimental drugs, and synthetic strategies have been optimized to easily access libraries of morpholine-containing molecules.[2] Morpholine is a versatile heterocyclic system which has been exploited for the development of compounds with a wide range of biological activities, including antimicrobial, anti-inflammatory, antiemetic, antidiabetic and anticancer agents.[3-6] Morpholine is also the essential component of the pharmacophore for a variety of enzyme active-site inhibitors[7-11] and substituted morpholines have been successfully used to achieve selectivity especially in the field of kinases.[12, 13] As structural element of a drug, morpholine differs from other nitrogen-containing rings, such as piperidine and piperazine due to the electron-deficiency of the whole system resulting from the negative inductive effect of the oxygen atom in the ring and the lower basicity of the nitrogen atom.[4, 14] Furthermore, piperidine/morpholine bioisosteric replacement has been described to have a positive effect on metabolism, improve CYP3A4 profile, prolong bioavailability, and resulted in improved clearance.[1] The metabolism of morpholines typically is initiated by hydroxylation through CYP450 enzymes followed by the oxidation to a lactone or a lactam, which often undergo ring-opening to the corresponding amino- or hydroxy- carboxylic acids.[15, 16] In most cases, the metabolic fate of the morpholine scaffold leads to non-toxic metabolites. Chemical substitutions on the morpholine ring have been pointed out to influence CYP metabolism and have been exploited to optimize the metabolic stability of pre-clinical lead compounds.[17] Morpholine is included in the chemical space of Central Nervous System (CNS) scaffolds, and was successfully used to block overactivated target of rapamycin (TOR) signaling, and thus attenuated epileptic seizures.[18-21] Due to its balanced lipophilic-hydrophilic profile, the chair-like conformation, the moderate pKa value (8.7[14]) and basicity, morpholine building blocks represent useful tools for the development of drugs that can penetrate the blood-brain barrier and act on the CNS.[1] Beside their therapeutic potential, morpholine derivatives have found applications in the fields of stereoselective synthesis as chiral organocatalysts[22, 23] and

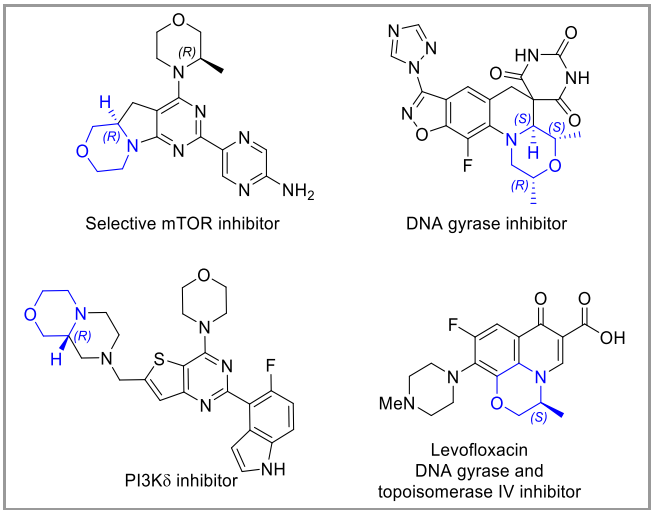


Figure 1. Selected morpholine moiety-containing bioactive compounds from Ref. 24-27.

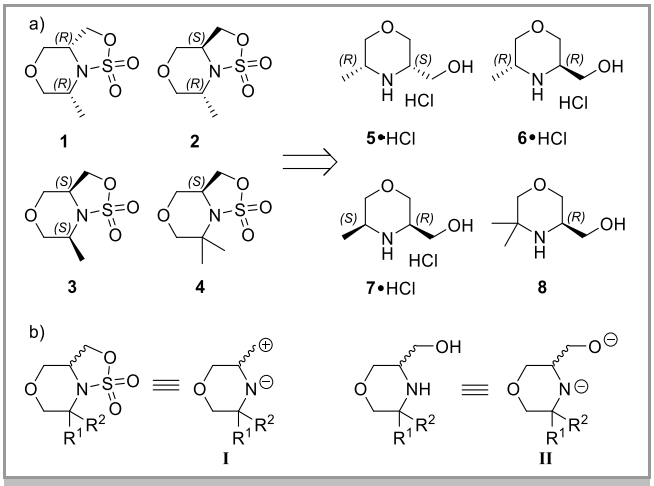


Figure 2. a) Retrosynthesis of sulfamidates from morpholinols; b) Sulfamidates and morpholinols as synthons.

ligands[28], as well as auxiliaries[29, 30]. Despite the relevance of morpholine moieties in both medicinal and synthetic organic chemistry, efficient synthetic methodologies for preparation of optically pure morpholine building blocks has remained underexplored. Morpholine fragments are mostly encountered in a simple *N*-substituted context, while their incorporation in an annulating fashion is less explored. Nevertheless, there are examples of biologically active compounds developed by both academia and industry that contain such morpholine residues (Figure 1).[24-27]

Herein, we report the stereospecific synthesis of optically pure sulfamidates **1-4** from 3-hydroxymethylmorpholines **5-8**, using a chiron approach (Figure 2a). Both 3-hydroxymethylmorpholines and their sulfamidates can be used to introduce privileged morpholine fragments on a variety of scaffolds. While 3-hydroxymethylmorpholines comprise two nucleophilic groups, sulfamidates can serve as retrosynthetic equivalents of synthon **I** (Figure 2b). Such sulfamidates are synthetic analogs of aziridines[31] and useful building blocks for the introduction of morpholines in a stereospecific[32-34] and even annulating[17, 24] fashion.

The retrosynthesis of 5-methylmorpholinols **5-7** is depicted in Figure 3. We propose a stereospecific strategy for the synthesis of compounds **5-7** *via* a stereospecific intramolecular nucleophilic aliphatic substitution reaction from **16a-c**, followed by the removal of protecting groups. Compounds **16a-c** were envisioned to be synthesized utilizing an intermolecular nucleophilic aliphatic substitution reaction from sulfamidates **9**-(*S*) and **9**-(*R*) and optically pure enantiomers of 1,2-propanediol **14**-(*S*) and **14**-(*R*), followed by the transformation of the secondary hydroxy group to a good leaving group such as tosylate. Sulfamidates **9**-(*S*) and **9**-(*R*) could be synthesized from a chiral pool accessible derivative of (*R*) and (*S*) serine **10**-(*R*) and **10**-(*S*), respectively. 5,5-Dimethylmorpholinol **8** was envisioned to be prepared *via* a different strategy, exploiting a double Grignard addition of methylmagnesium bromide to morpholinone **22** and deprotection, which could be obtained from compound **20**, that is either commercially available or accessible from **10**-(*S*), as previously reported.[24]

The synthesis of sulfamidates **9**-(*S*) and **9**-(*R*) is depicted in Scheme 1. Firstly, optically pure methyl-esters of *N*-Boc protected serines **10**-(*S*) and **10**-(*R*) were transformed to serinols **12**-(*R*) and **12**-(*S*), respectively, following a previously reported procedure.[35] Obtained serinols **12**-(*R*) and **12**-(*S*) were reacted with thionyl chloride and sulfimidates **13**-(*S*) and **13**-(*R*) were formed, respectively, which underwent a one-pot ruthenium-catalyzed oxidation to yield sulfamidates **9**-(*S*)[31] and **9**-(*R*) (Scheme 1). An optimization campaign of (*S*)-1,2-propanediol **14**-(*S*) alkylation to form compound **15a** was performed using sulfamidate **9**-(*S*) (Table 1). Caesium carbonate was identified as a suitable base with acetone as a solvent (entry 10), while the aqueous solution of citric acid was used to cleave sulfamate intermediate. In all the reactions containing carbonate as a base, the formation of the carbonate of 1,2-propanediol was observed.

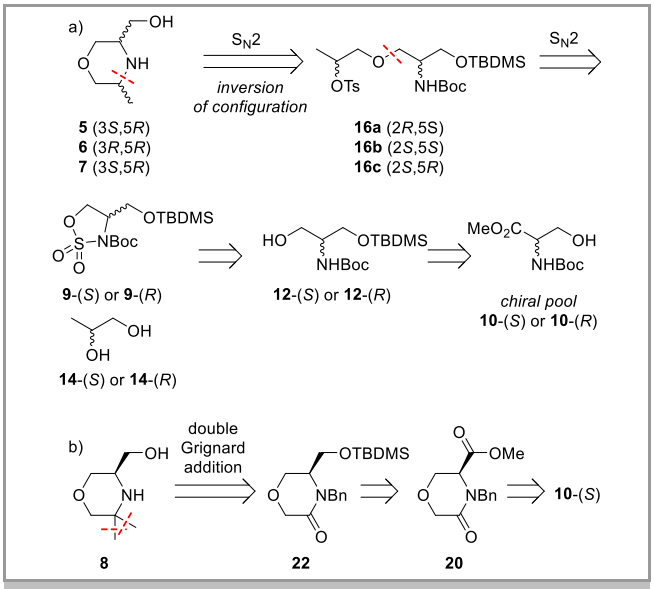
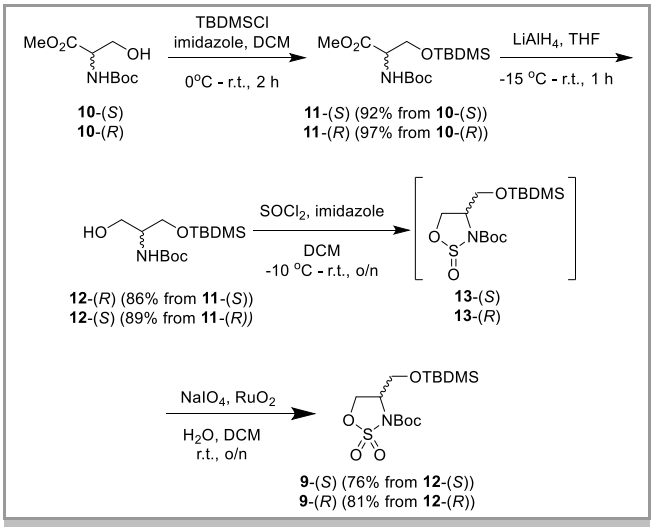


Figure 3. Retrosynthetic analysis of a) compounds **5**-**7**; b) compound **8**.

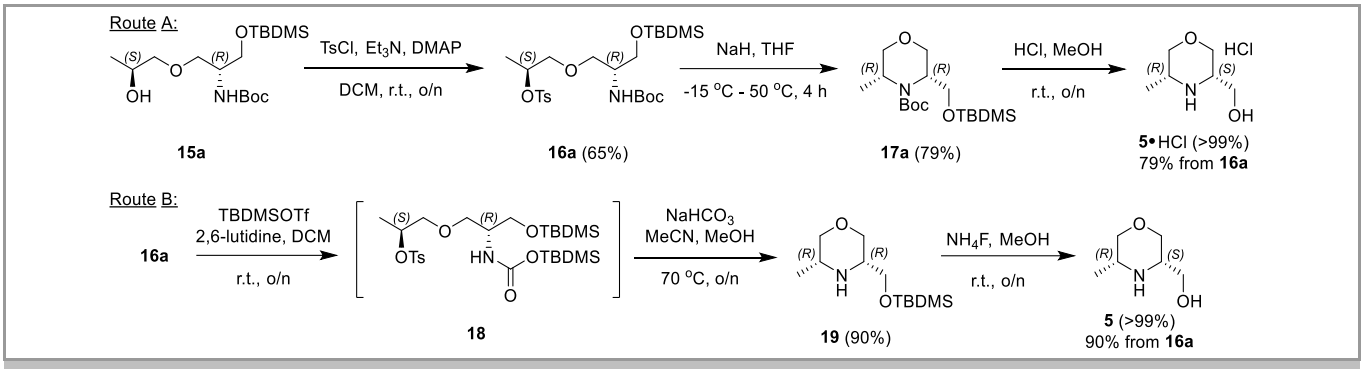


Scheme 1. Synthesis of sulfamidates **9**-(*S*) and **9**-(*R*). **9**-(*R*) was synthesized following the procedure previously reported for **9**-(*S*) in Ref. 31, 35.

A NaOH/DMF system was also investigated leading to a 21% yield. The selected caesium carbonate/acetone system (entry 10) was applied to synthesis of **15b** and **15c**, leading to a 32% and 36% yield, respectively (entries 13 and 14).

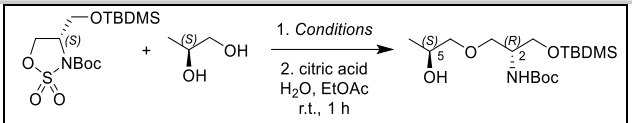
After identification of suitable alkylation conditions, tosylation of alcohol **15a** was performed to give tosylate **16a** (Scheme 2). Two S_N2 cyclization routes were tested. At first, **16a** was directly cyclized by deprotonating carbamate using sodium hydride to form *N*-Boc and *O*-TBDMS protected 3-hydroxymethyl-morpholine **17a** in a good yield (route A). Compound **17a** was then subjected to a one-step double deprotection with hydrochloric acid in methanol, yielding 3-hydroxymethylmorpholine **5**·HCl in quantitative yield.

Alternatively, carbamate was cleaved, yielding an amine that serves as a better nucleophile (route B). The selective Boc deprotection was achieved using TBDMSOTf and 2,6-lutidine in dichloromethane. Intermediate **18**, containing two TBDMS groups instead of a free amine, was directly cyclized using sodium bicarbonate in acetonitrile and methanol, where methanol was used to cleave the silyl carbamate, yielding compound **19** in excellent yield. Subsequently, the *O*-TBDMS group was removed using ammonium fluoride in methanol to give desired hydroxymethylmorpholine **5** in a quantitative yield.



Scheme 2. Synthesis of 3-hydroxymethylmorpholine **5**.

Table 1. Optimization of the alkylation reaction for the synthesis of **15a**.



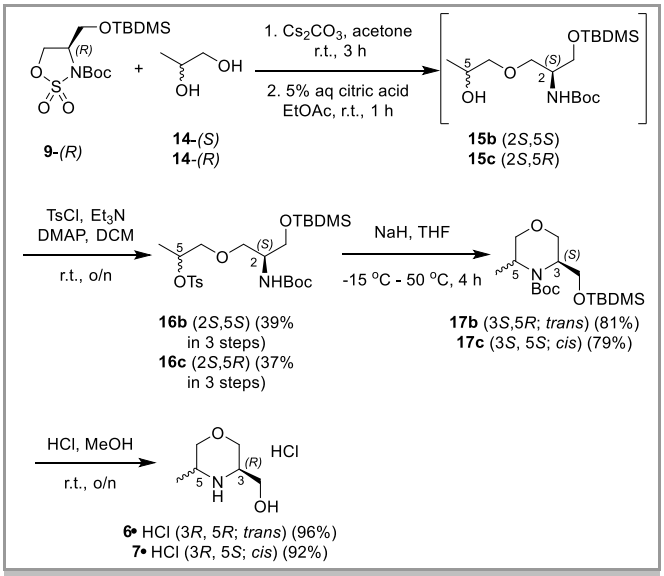
9-(*S*) **14**-(*S*) **15a** (2*R*,5*S*)

Entry	Base	Solvent	Yield (%)
1[a]	Na_2CO_3	DMF	0[c]
2[a]	K_2CO_3	DMF	<10
3[a]	Et_3N	DMF	0[d]
4[a]	NaH	THF	0[c]
5[a]	Cs_2CO_3	DMF	12
6[a]	Cs_2CO_3	THF	0[c]
7[a]	Cs_2CO_3	DCM	0[c]
8[a]	Cs_2CO_3	MeCN	18
9[a]	Cs_2CO_3	Acetone	26
10[b]	Cs_2CO_3	Acetone	42
11[b]	NaOH	DMF	21
12[b]	tBuOK	THF	0[c]
13[b,e]	Cs_2CO_3	Acetone	32
14[b,f]	Cs_2CO_3	Acetone	36

Reactions were performed on a 10 mmol scale at r.t. and the consumption of starting material was monitored by ^{1}H-NMR. The yield of isolated product **15** after column chromatography is depicted.
[a] **9**-(*S*), 1.2 eq of **14**-(*S*) and 1.2 eq of base to yield **15a** (2*R*,5*S*).
[b] 2.4 eq of **14**-(*S*) and 2.4 eq of base.
[c] Decomposition of staring material.
[d] No reaction.
[e] **9**-(*R*) and **14**-(*S*) to yield **15b** (2*S*,5*S*).
[f] **9**-(*R*) and **14**-(*R*) to yield **15c** (2*S*,5*R*).

Although route B allowed isolation of hydroxymethylmorpholine **5** in higher yield (90%), direct cyclization of the carbamate gave **5**·HCl in 79% yield, being the most efficient strategy as it required fewer steps, and Boc-protected morpholine **17a** was easier to purify, compared to the deprotected analogue **19**.

Stereoisomeric hydroxymethymorpholines **6**·HCl and **7**·HCl were synthesized from **14**-(*S*) and **14**-(*R*) respectively, and (*R*)-configured sulfamidate **9**-(*R*) employing an analog procedure (Scheme 3). After the alkylation of enantiomers of 1.2-propanediol **14**-(*S*) and **14**-(*R*) with **9**-(*R*), the tosylation was performed without prior isolation of the intermediate alcohols **15b** and **15c** to yield tosylates **16b** and **16c**,



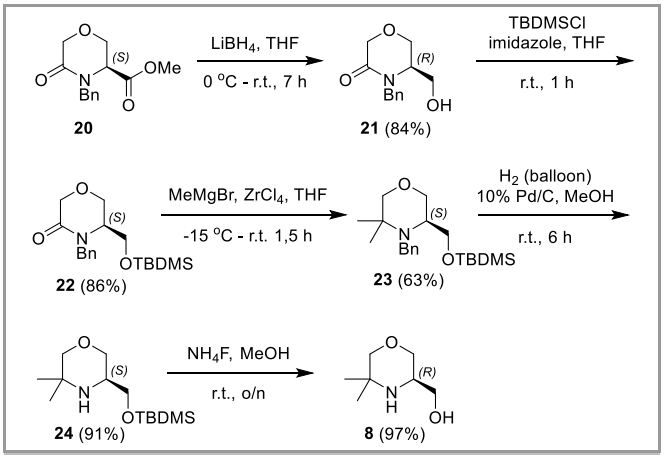
Scheme 3. Synthesis of methylmorpholines **6**·HCl and **7**·HCl.

respectively (Scheme 3). Performing the tosylations with crude alcohols allowed the isolation of compounds **16b** and **16c** in higher overall yields compared to the tosylation of a pure alcohol. Furthermore, using this approach, it was possible to bypass the chromatographic purification of a polar alcohol. Afterwards, the direct cyclization strategy was employed using sodium hydride to give compounds **17b** and **17c** in good yields, which were subjected to a one-step double deprotection with methanolic hydrochloric acid, yielding hydrochloride salts of hydroxymethyl-morpholines **6**·HCl and **7**·HCl in excellent yields. Following this approach, it was possible to isolate compounds **6**·HCl and **7**·HCl in 5 steps, utilizing two chromatographic purifications, both in a 30% overall yield from **9**-(*R*).

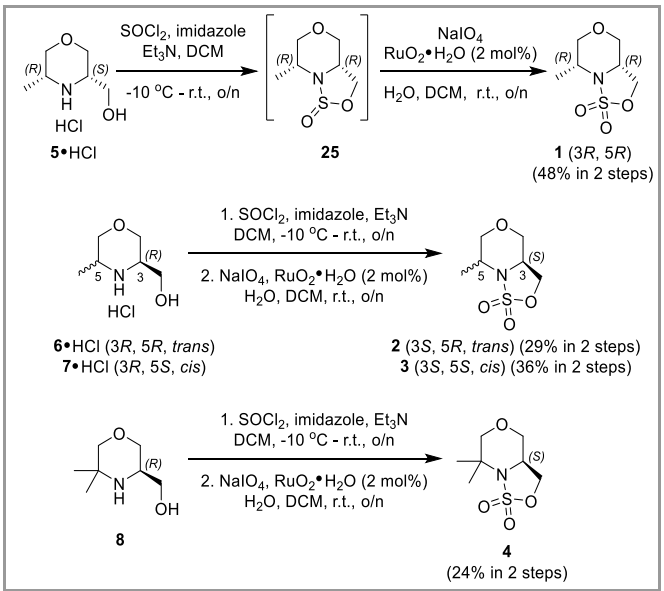
Dimethylmorpholinol **8** was synthesized using a chiron approach from optically pure benzyl-protected morpholinone **20** that is either accessible from **10**-(*S*)[24] or commercially available (Scheme 4). Morpholinone **20** was first reduced using lithium borohydride to give a benzyl-protected hydroxymethylmorpholinone **21** in an excellent yield, which was further transformed to a silyl ether, yielding compound **22**. Following the procedure developed by Denton & Wood[36] and exploited in the patent literature[37-39], morpholinone **22** was subjected to a double Grignard reaction with methylmagnesium bromide in presence of stoichiometric amounts of zirconium(IV) chloride, giving a benzyl-protected α,α-dimethylmorpholine **23** in a moderate yield (63%). The benzyl group was removed hydrogenolytically, followed by removal of the TBDMS protecting group using ammonium fluoride in methanol. Dimethylmorpholinol **8** was obtained as a free base in an overall yield of 40% over 5 steps.

With morpholinols **5**-**7** as hydrochloric salts and intermediate **8** as a free base, we proceeded with the synthesis of sulfamidates **1**-**4** (Scheme

5). For the synthesis of optically pure substituted sulfamidates, the same procedure reported for unsubstituted derivatives was exploited.[17, 24] However, the steric hindrance related to the presence of the methyl or dimethyl groups led to lower yields compared to unsubstituted analogs. As a first step, sulfimidate **25** was obtained in a reaction of hydroxymethylmorpholine hydrochloride **5**·HCl with thionyl chloride. Without prior isolation, sulfimidate **25** was then subjected to ruthenium-catalyzed oxidation in a biphasic water-DCM system, where hydrated ruthenium dioxide was used in a catalytic amount with sodium periodate as a stoichiometric oxidant. This catalytic system yields an active ruthenium tetroxide oxidant which partitions in both phases and performs oxidation in the organic phase, leading to the formation of sulfamidate **1** in a modest yield (Scheme 5). The analogous method was used for the synthesis of stereoisomeric sulfamidates **2** and **3** from respective hydrochloric salts, while sulfamidate **4** was synthesized from the corresponding hydroxymethylmorpholine **8**.



Scheme 4. Synthesis of dimethylhydroxymethylmorpholine **8.**



Scheme 5. Synthesis of sulfamidates **1-4**.

In conclusion, we report the stereospecific synthesis of stereoisomeric 3-hydroxymethyl-5-methylmorpholines **5-7** from sulfamidates **9**-(*S*) and **9**-(*R*), which were obtained from chiral pool-accessible derivatives of (*S*) and (*R*) serines **10**-(*S*) and **10**-(*R*). Furthermore, we disclose the synthesis of 3-hydroxymethyl-5,5-dimethylmorpholine **8** from a commercially available morpholinone **20**. Additionally, hydroxymethylmorpholines **5-8** were transformed to sulfamidates **1-4** using a one-pot sulfimidation and ruthenium tetroxide-mediated oxidation sequence. Sulfamidates **1**, **2** and **3** were synthesized in seven steps, in 10%, 9% and 10% overall yields, respectively, with three chromatographic purifications during the sequence. Sulfamidate **4** was synthesized in 7 steps *via* a different strategy in a 10% overall yield, utilizing four chromatographic purifications in total. Both hydroxymethylmorpholines **5-8** and sulfamidates **1-4** could be used as building blocks for the introduction of privileged morpholine subunits in the development of novel bioactive molecules.

Reagents were purchased at the highest commercial quality from Acros Organics, Sigma Aldrich, Fluorochem, Atomax Chemicals Co. Ltd or Apollo Scientific, and were used without further purification, if not otherwise noted. Solvents were purchased from Acros Organics in AcroSeal® bottles over molecular sieves. All reactions were carried out under nitrogen atmosphere in absolute solvents and glassware was heat-dried prior to use. Flash chromatographic purifications were performed on Isco CombiFlash Companion systems using prepacked silica gel columns (40-60 µm particle size RediSep) and Merck KGaA silica gel (pore size 60 Å, 230-400 mesh particle size). Thin layer chromatography (TLC) plates were obtained from Merck KGaA (Polygram SIL/UV254, 0.2 mm silica with fluorescence indicator). Potassium permanganate and p-anisaldehyde were used to visualize the respective compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 100 spectrometer on 400 MHz and 101 MHz, respectively. NMR spectra were obtained in deuterated chloroform ($CDCl_3$) with tetramethylsilane as an internal standard and deuterated methanol (CD_3OD). Chemical shifts are reported in ppm and corrected to the signal of deuterated solvent signal, namely 7.26 ppm ($CDCl_3$) and 3.34 ppm (CD_3OD) for ^{1}H NMR spectra, and 77.16 ppm ($CDCl_3$) and 49.86 ppm (CD_3OD) for ^{13}C NMR spectra. Coupling constants (J) are reported in Hertz (Hz). Multiplicities are reported as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dddd (doublet of doublet of doublet of doublet), t (triplet), m (multiplet) and brs (broad singlet). For high resolution mass spectra (HR-MS), a HR-ESI-QToF-MS measurement on a maXisTM 4G instrument from Bruker was used. High-resolution mass are given in m/z. MALDI-ToF mass spectra were obtained on a Voyager-DeTM Pro, while ESI-ITMS mass spectra were obtained from an AmaZon SL, both measured in m/z. Specific rotations ($[\alpha]_D^T$) were calculated based on the optical rotation measurements on a Perkin Elmer Polarimeter 341 and JASCO P-2000 polarimeter in a cuvette (l = 1 dm) at 589 nm, in chloroform and methanol as solvents, while the concentrations of the samples were given in mg/mL.

Methyl-(*S*)-2-(tert-butoxycarbonylamino)-3-(tert-butyldimethyl-silyloxy)propanoate (11-(*S*)):

Imidazole (171 mg, 2.51 mmol, 1.1 eq.) and tert-butylchloro-dimethylsilane (TBDMSCl, 447 mg, 2.97 mmol, 1.3 eq.) were added to a solution of **10**-(*S*) (500 mg, 2.28 mmol, 1.0 eq.) in DCM (10 mL) at 0°C. The reaction mixture was allowed to warm up to room temperature (r.t.) and stirred for 2h. After reaction completion, water (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Crude product was purified using column chromatography (SiO_2, CyH/EtOAc 95:5), to give compound **11**-(*S*) (700 mg, 2.10 mmol, 92%) as a yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.33 (d, J = 8.9 Hz, 1H), 4.35 (dt, J = 8.7 Hz, J = 3.0 Hz, 1H), 4.05 (dd, J = 10 Hz, J = 2.8 Hz, 1H), 3.82 (dd, J = 10.1 Hz, J= 3.1 Hz, 1H), 1.46 (s, 9H), 0.86 (s,9H), 0.03 (d, J = 5.4 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.4, 155.5, 80.0, 63.9, 55.7, 52.3, 28.4, 25.8, 18.3, -5.6.

NMR data agreed with previously reported data.[35]

Methyl-(*R*)-2-(tert-butoxycarbonylamino)-3-(tert-butyldimethyl-silyloxy)propanoate (11-(*R*)):

11-(*R*) was prepared starting from **10**-(*R*) (5.00 g, 22.8 mmol, 1.0 eq.) using Imidazole (1.71 g, 25.1 mmol, 1.1 eq.), TBDMSCl (4.47 g, 29.7 mmol, 1.3 eq.) in DCM (100 mL), following the same procedure described for **11**-(*S*). Crude product was purified using column chromatography (SiO_2,

CyH/EtOAc 8:2), to give **11**-(*R*) (7.30 g, 22.1 mmol, 97%) as a yellowish oil. The spectroscopic data are in agreement with those reported for **11**-(*S*).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{31}NNaO_5Si$: 356.1868; found: 356.1864.

Tert-butyl-(*S*)-(1-((tert-butyldimethylsilyl)oxy)-3-hydroxypropan-2-yl)carbamate (12-(*S*)):

To a solution of **11**-(*R*) (6.53 g, 19.6 mmol, 1.0 eq.) in dry THF (220 mL), $LiAlH_4$ (743 mg, 19.6 mmol, 1.0 eq.) was added portion-wise at -15°C. The reaction mixture was warmed to r.t. and stirred for 1h. After reaction completion, the reaction was quenched by slow addition of EtOAc (50 mL) and water (30 mL) at -15°C. The obtained mixture was filtered through a pad of Celite, and the solid was washed with EtOAc (3 x 30 mL). Layers were separated in a separatory funnel and the organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Crude product was purified using column chromatography (SiO_2, CyH/EtOAc 9:1) to give **12**-(*S*) (5.32 g, 17.4 mmol, 89%) as a yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.13 (s, 1H), 3.80 (m, 3H), 3.72–3.56 (m, 2H), 2.78 (s, 1H), 1.44 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.1, 79.7, 63.8, 60.5, 52.8, 28.5, 25.9, 18.3, -5.5.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{31}NNaO_4Si$: 328.1917; found: 328.1915.

Tert-butyl-(*R*)-(1-((tert-butyldimethylsilyl)oxy)-3-hydroxypropan-2-yl)carbamate (12-(*R*)):

12-(*R*) was prepared starting from **11**-(*R*) (586 mg, 1.76 mmol, 1.0 eq.) using $LiAlH_4$ (66.8 mg, 1.76 mmol, 1.0 eq.) in THF (25 mL), following the same procedure described for **12**-(*S*). Crude product was purified using column chromatography (SiO_2, CyH/EtOAc 9:1) to **12**-(*R*) (462 mg, 1.51 mmol, 86%) as a yellowish oil. The spectroscopic data are in agreement with those reported for **12**-(*S*).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H_{31}NNaO_4Si$: 328.1915; found: 328.1918.

NMR data agreed with previously reported data.[35]

Tert-butyl-(*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (9-(*S*)):

Step 1: Imidazole (21.0 g, 310 mmol, 6.3 eq.) was dissolved in DCM (90 mL) and the solution was cooled to –10°C. Thionyl chloride (6.84 mL, 94.3 mmol, 1.9 eq.) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 1h. The mixture mixture was cooled to – 10°C and a solution of **12**-(*R*) (15.0 g, 49.1 mmol, 1.0 eq.) in DCM (30 mL) was added dropwise. The reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by the addition of deionized water (10 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were concentrated under reduced pressure to give crude **13**-(*S*).

Step 2: Crude **13**-(*S*) was dissolved in DCM (150 mL) and the solution was cooled to 0°C. Water (150 mL), sodium periodate (27.1 g, 128 mmol, 2.6 eq.) and (RuO_2·xH_2O) (131 mg, 0.98 mmol, 0.02 eq.) were added. The mixture was stirred at r.t. overnight. The layers were separated, the aqueous layer was extracted with DCM (3 x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, DCM, 100%) to yield compound **9**-(*S*) (13.7 g, 37.3 mmol, 76%) as a white crystalline solid.

$[\alpha]_D^{21}$ = + 25.4 (*c* 2.31, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.65-4.56 (m, 2H), 4.26 (dddd, J = 8.2 Hz, J = 5.4 Hz, J = 4.1 Hz, J = 2.8 Hz, 1H), 3.86 (dd, J = 10.1, J = 4.0, 1H), 3.78 (dd, J = 10.1, J = 8.3 Hz, 1H), 1.55 (s, 9H), 0.89 (s, 9H), 0.08 (d, J = 2.7 Hz, 6H).

1HNMR is in agreement with the spectroscopic data published in Ref. [31].

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 148.8, 85.7, 67.6, 60.8, 57.7, 28.1, 25.9, 18.3, -5.4, -5.4.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{14}H_{29}NNaO_6SSi$: 390.1377; found: 390.1381.

Tert-butyl-(*R*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (9-(*R*)):

9-(*R*) was prepared starting from **12**-(*S*) (3.05 g, 10.0 mmol, 1.0 eq.) using imidazole (4.29 g, 63 mmol, 6.3 eq.), thionyl chloride (1.40 mL, 19.0 mmol, 1.9 eq.) in DCM (20 mL) for Step 1. Then, **13**-(*R*) (crude Step 1) using sodium periodate (5.56 g, 26.0 mmol, 26 eq.), (RuO_2·xH_2O) (27 mg, 0.2 mmol, 0.02 eq.), in DCM (30 mL) and water (30 mL) for Step 2, all following the same procedure described for **9**-(*S*). The crude product was purified by column chromatography (SiO_2, DCM, 100%) to yield compound **9**-(*R*) (2.98 g, 8.11 mmol, 81%) as a white crystalline solid.

$[\alpha]_D^{21}$ = – 25.5 (*c* 3.23, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.65-4.57 (m, 2H), 4.26 (dddd, J = 8.2 Hz, J = 5.4 Hz, J = 4.0 Hz, J = 2.8 Hz, 1H), 3.86 (ddd, J = 10.1, J = 4.1, J = 0.8 Hz, 1H), 3.78 (dd, J = 10.1, J = 8.3 Hz, 1H), 1.55 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 148.8, 85.7, 67.6, 60.8, 57.7, 28.1, 25.8, 18.3, -5.3, -5.4.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{14}H_{29}NNaO_6SSi$: 390.1377; found: 390.1380.

Tert-butyl-((*R*)-1-((tert-butyldimethylsilyl)oxy)-3-((*S*)-2-hydroxypropoxy)propan-2-yl)carbamate (15a):

To a suspension of dried Cs_2CO_3 (320 mg, 0.98 mmol, 2.4 eq.) and 3 Å molecular sieves in dry acetone (4 mL), (*S*)-sulfamidate **9**-(*S*) (150 mg, 0.41 mmol, 1.0 eq.) and (*S*)-propane-1,2-diol **14**-(*S*) (72 µL, 0.98 mmol, 2.4 eq.) were added. The resulting mixture was stirred at room temperature. After 4h, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (5 mL) and a 5% aq. citric acid solution was added until reaching pH = 4. The resulting mixture was stirred at r.t. for 1h. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The crude from product was purified by column chromatography (SiO_2, CyH/EtOAc/NEt_3 89:10:1) to yield **15a** (62 mg, 0.17 mmol, 42%) as a yellow oil.

$[\alpha]_D^{23}$ = + 15.8 (*c* 6.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.86 (d, J = 6.9 Hz, 1H), 3.99-3.91 (m, 1H), 3.85 3.76 (m, 1H), 3.72 (dd, J = 9.9 Hz, J = 3.6 Hz, 1H), 3.64-3.59 (m, 2H), 3.48 (dd, J = 9.5 Hz, J = 5.9 Hz, 1H), 3.44 (dd, J = 9.6 Hz, J = 3.2 Hz, 1H), 3.28 (dd, J = 9.6 Hz, J = 8.0 Hz, 1H), 2.51 (brs, 1H), 1.45 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.7, 79.6, 76.9, 69.8, 66.4, 61.8, 51.2, 28.5, 26.0, 18.8, 18.4, -5.3, -5.4.

MS (ESI): *m/z* = 386.1 [M+Na]$^+$.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{17}H_{37}NNaO_7Si$: 386.2333; found: 386.2340.

Tert-butyl-((*S*)-1-((tert-butyldimethylsilyl)oxy)-3-((*S*)-2-hydroxypropoxy)propan-2-yl)carbamate (15b):

15b was prepared starting from **9**-(*R*) (3.68 g, 10 mmol, 1.0 eq.) using (*S*)-propane-1,2-diol **14**-(*S*) (2.5 eq.), Cs_2CO_3 (8.15 g, 25.0 mmol, 2.5 eq.) in acetone (90 mL), following the same procedure described for **15a**. The crude product was used in a next step without further purification.

Tert-butyl-((*S*)-1-((tert-butyldimethylsilyl)oxy)-3-((*R*)-2-hydroxy-propoxy)propan-2-yl)carbamate (15c):

15c was prepared starting from **9**-(*R*) (6.25 g, 17 mmol, 1.0 eq.) using (*R*)-propane-1,2-diol **14**-(*R*) (3.12 mL, 42.5 mmol, 2.5 eq.), Cs_2CO_3 (13.9 g, 42.5 mmol, 2.5 eq.) in acetone (90 mL), following the same procedure described for **15a**. The crude product was used in a next step without further purification.

Tosylates 16a-c; general procedure:

To a solution of alcohol **15a-c** (1.0 eq.) in DCM, triethylamine (3.3 eq.) and 4-dimethylaminopyridine (DMAP, 0.6 eq.) were added. The mixture was stirred at r.t. for 10 min and *p*-toluenesulfonyl chloride (TsCl, 2.0 eq.) was added. The reaction mixture was stirred at r.t. overnight. After completion, water (10 mL) was added and the layers were separated. Aqueous layer was washed with DCM (3 x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Crude product was purified by column chromatography to obtain the desired compound **16a-c**.

(*S*)-1-((*R*)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyl-dimethyl-silyl)oxy)propoxy)propan-2-yl 4-methylbenzenesulfonate (16a):

16a was prepared starting from **15a** (1.10 g, 3.03 mmol, 1.0 eq.) using triethylamine (1.3 mL, 9.90 mmol, 3.3 eq.), DMAP (202 mg, 1.65 mmol, 0.6 eq.), TsCl (1.26 g, 6.60 mmol, 2.0 eq.) in DCM (20 mL). Flash chromatography (SiO_2, CyH/EtOAc 85:15) yielded the tosylate **16a** (1.01 g, 1.96 mmol, 65%) as a yellow oil.

$[\alpha]_D^{23}$ = + 0.38 (*c* 0.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 4.76 (d, J = 8.8 Hz, 1H), 4.68 (m, 1H), 3.72-3.58 (m, 1H), 3.55 (dd, J = 9.7 Hz, J = 3.8 Hz, 1H), 3.49-3.44 (m, 2H), 3.44-3.34 (m, 2H), 3.31 (dd, J = 9.2 Hz, J = 5.9 Hz, 1H), 2.42 (s, 3H), 1.44 (s, 9H), 1.27 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.5, 144.6, 134.4, 129.8, 127.9, 79.4, 78.0, 73.4, 69.5, 61.4, 51.1, 28.5, 26.0, 21.7, 18.3, 17.8, -5.3, -5.4.

MS (ESI): *m*/*z* = 540.1 $[M+Na]^+$.

HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{24}H_{43}NNaO_7SSi$: 540.2422; found: 540.2427.

(*S*)-1-((*S*)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethyl-silyl)oxy)propoxy)propan-2-yl 4-methylbenzenesulfonate (16b):

16b was prepared starting from **15b** (crude from **14**-(*S*) reaction) using triethylamine (4.46 mL, 33.0 mmol, 3.3 eq.), DMAP (1.25 g, 10.2 mmol, 0.6 eq.), TsCl (3.81 g, 20.0 mmol, 2.0 eq.) in DCM (100 mL). Flash chromatography (SiO_2, CyH/EtOAc 85:15) yielded the tosylate **16b** (2.00 g, 3.86 mmol, 39% after two steps) as a yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.84-7.77 (m, 2H), 7.37-7.30 (m, 2H), 4.75 (d, J = 8.1 Hz, 1H), 4.71-4.62 (m, 1H), 3.67-3.61 (m, 1H), 3.56 (dd, J = 9.7 Hz, J = 3.7 Hz, 1H), 3.53-3.30 (m, 5H) 2.44 (s, 3H) 1.45 (s, 9H), 1.28 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.3, 144.7, 134.4, 130.0, 129.8, 128.1, 128.0, 78.0, 73.4, 69.4, 61.4, 28.6, 26.0, 21.8, 18.4, 17.8, -5.4, -5.3.

MS (ESI): *m*/*z* = 518.1 $[M+H]^+$.

***(R)*-1-((*S*)-2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethyl-silyl)oxy)propoxy)propan-2-yl 4-methylbenzenesulfonate (16c):**

16c was prepared starting from **15c** (crude from **14**-(*S*) reaction) using triethylamine (7.57 mL, 56.1 mmol, 3.3 eq.), DMAP (1.15 g, 10.2 mmol, 0.6 eq.), TsCl (6.48 g, 34.0 mmol, 2.0 eq.) in DCM (120 mL). Flash chromatography (SiO_2, CyH/EtOAc 85:15) yielded tosylate **16c** (3.03 g, 5.85 mmol, 37% after two steps) as a yellowish oil.

$[\alpha]_D^{23}$ = + 2.29 (*c* 0.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86-7.72 (m, 2H), 7.41-7.21 (m, 2H), 4.76 (d, J = 8.8 Hz, 1H), 4.74-4.62 (m, 1H), 3.71-3.58 (m, 1H), 3.55 (dd, J = 9.7 Hz, J = 3.8 Hz, 1H), 3.50-3.34 (m, 4H), 3.31 (dd, J = 9.2 Hz, J = 5.8 Hz, 1H), 2.42 (s, 3H), 1.43 (s, 9H), 1.27 (d, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.5, 144.6, 134.4, 129.8, 127.9, 79.4, 78.0, 73.3, 69.5, 61.3, 51.1, 28.5, 25.9, 21.7, 18.3, 17.8, -5.4, -5.4.

MS (ESI): *m*/*z* = 518.1 $[M+H]^+$.

***N*-Boc and *O*-TBS protected 3-hydroxymethylmorpholine; general procedure:**

To a solution of compound **16a-c** (1.0 eq.) in THF, 60% sodium hydride oil dispersion (4.0 eq.) was added portion wise at -10°C. The suspension was stirred at -10°C for 30 min, allowed to warm to 50˚C and stirred overnight. Afterwards, the reaction mixture was cooled to 0°C and quenched by dropwise addition of MeOH. The organic solvents were removed under reduced pressure and DCM was added, the solids were filtered and washed with DCM. The filtrate was dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. The crude product was purified by column chromatography to yield the morpholine **17a-c**.

Tert-butyl (3*R*,5*R*)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-methylmorpholine-4-carboxylate (17a):

17a was prepared starting from **16a** (1.67 g, 3.23 mmol, 1.0 eq.) using 60% NaH (517 mg, 12.9 mmol, 4.0 eq.) in THF (20 mL). Flash chromatography (SiO_2, DCM 100%) yielded morpholine **17a** (887 mg, 2.57 mmol, 79%) as a colorless oil.

$[\alpha]_D^{21}$ = + 19.6 (*c* 8.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.08 (dd, J = 18.3 Hz, J = 11.8 Hz, 1H), 3.97-3.86 (m, 1H), 3.86-3.70 (m, 2H), 3.66 (d, J = 11 Hz, 1H), 3.55 (dd, J = 11.4 Hz, J = 3.6 Hz, 1H), 3.50-3.44 (m, 1H), 3.42-3.36 (m, 1H), 1.47 (s, 9H), 1.18 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 154.7, 79.8, 71.1, 65.7, 61.5, 52.2, 45.6, 28.4, 25.9, 19.6, 18.2, -5.31, -5.40.

MS (ESI): *m*/*z* = 368.1 $[M+Na]^+$.

HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{35}NNaO_4Si$: 368.2228; found: 338.2228.

Tert-butyl (3*S*,5*R*)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-methylmorpholine-4-carboxylate (17b):

17b was prepared starting from **16b** (1.20 g, 2.32 mmol, 1.0 eq.) using 60% NaH (371 mg, 9.28 mmol, 4.0 eq.) in THF (15 mL). Flash chromatography (SiO_2, DCM 100%) yielded morpholine **17b** (648 mg, 1.88 mmol, 81%) as a colorless oil.

$[\alpha]_D^{21}$ = -35.8 (*c* 8.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.99 (dd, J = 11.4 Hz, J = 1.9 Hz, 1H), 3.86-3.76 (m, 2H), 3.76 3.63 (m, 4H), 3.40 (dd, J = 11.3 Hz, J = 5.6 Hz, 1H), 1.46 (s, 9H), 1.31 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 155.6, 80.0, 70.6, 64.5, 61.4, 53.8, 47.8, 28.6, 26.0, 19.0, 18.4, -5.2, -5.3.

MS (ESI): *m*/*z* = 368.1 $[M+Na]^+$.

Tert-butyl (3*S*,5*S*)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-methylmorpholine-4-carboxylate (17c):

17c was prepared starting from **16c** (2.68 g, 5.18 mmol, 1.0 eq.) using 60% NaH (829 mg, 20.7 mmol, 4.0 eq.) in THF (15 mL). Flash chromatography (SiO_2, DCM 100%) to yield the morpholine **17c** (1.41 g, 4.09 mmol, 79%) as a colorless oil.

$[\alpha]_D^{21}$ = - 19.4 (*c* 3.62, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.10 (d, J = 12.2 Hz, 1H), 3.96-3.87 (m, 1H), 3.82-3.74 (m, 2H), 3.66 (d, J = 11.5 Hz, 1H), 3.54 (dd, J = 11.1, J = 4.2 Hz, 1H), 3.47 (ddd, J = 8.1 Hz, J = 3.3 Hz, J = 1.4 Hz, 1H), 3.40 (ddd, J = 11.6 Hz, J = 3.5 Hz, J = 1.4 Hz, 1H), 1.47 (s, 9H), 1.18 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (d, J = 3.5 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 154.8, 80.0, 71.2, 65.8, 61.6, 52.4, 45.7, 28.6, 26.0, 19.7, 18.4, -5.2, -5.3.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{36}NO_4Si$: 346.2408; found: 346.2402; *m/z* [M+Na]$^+$ calcd for $C_{17}H_{35}NNaO_4Si$: 368.2228; found: 368.2227.

3-hydroxymethylmorpholine 5·HCl-7·HCl; general procedure:

To a 1.6 M solution of hydrochloric acid in methanol (10 eq.) was added morpholine **17a-c** (1.0 eq.). The reaction mixture was stirred at r.t overnight. The solvents were removed under reduced pressure and co-evaporated with toluene. The crude solid was washed with cyclohexane to yield the HCl salt of the unprotected morpholines **5**·HCl**, 6**·HCl and **7**·HCl.

(3*S*,5*R*)-5-methyl-3-hydroxymethylmorpholine hydrochloride (5·HCl):

5·HCl was prepared starting from **17a** (798 mg, 2.31 mmol, 1.0 eq.) in a 1.6 M HCl solution in methanol (14.4 mL, 23.1 mmol, 10 eq.). Morpholinol **5·HCl** was obtained as a colorless solid and use without further purification (quantitative, yield).

$[\alpha]_D^{23} = -10.2$ (*c* 6.8, MeOH).

^{1}H NMR (MeOD, 400 MHz): δ = 4.02 (dd, J = 12.5 Hz, J = 3.3 Hz, 1H), 4.00-3.95 (m, 1H), 3.76 (dd, J = 11.9 Hz, J = 4.3 Hz, 1H), 3.64 (dd, J = 11.9 Hz, J = 6.0 Hz, 1H), 3.57-3.54 (m, 1H), 3.48-3.37 (m, 3H), 1.29 (d, J = 5.7 Hz, 3H).

^{13}C NMR (MeOD, 101 MHz): δ = 70.2, 66.5, 59.5, 58.5, 53.1, 14.1.

MS (ESI): *m/z* = 132.1 [M+Na]$^+$.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_6H_{14}NO_2$: 132.1019; found: 132.1020.

(3*R*,5*R*)-5-methyl-3-hydroxymethylmorpholine hydrochloride (6·HCl):

6·HCl was prepared starting from **17b** (401 mg, 1.16 mmol, 1.0 eq.) in a 1.6 M HCl solution in methanol (7.25 mL, 11.6 mmol, 10 eq.). Morpholinol **6·HCl** was obtained as a colorless solid and use without further purification (186 mg, 1.11 mmol, 96%).

$[\alpha]_D^{20} = -4.4$ (*c* 0.92, MeOH).

^{1}H NMR (MeOD, 400 MHz): δ = 3.94 3.85 (m, 2H), 3.81 (dd, J = 12.3 Hz, J = 6.4 Hz, 1H), 3.79 3.72 (m, 2H), 3.64 3.53 (m, 2H), 3.54 3.46 (m, 1H), 1.37 (d, J = 6.3 Hz, 3H).

^{13}C NMR (MeOD, 101 MHz): δ = 70.0, 66.0, 58.4, 53.5, 48.2, 14.1.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_6H_{14}NO_2$: 132.1020; found: 132.1019.

(3*R*,5*S*)-5-methyl-3-hydroxymethylmorpholine hydrochloride (7·HCl):

7·HCl was prepared starting from **17c** (1.10 g, 3.19 mmol, 1.0 eq.) in a 1.6 M HCl solution in methanol (19.9 mL, 31.9 mmol, 10 eq.). Morpholinol **7·HCl** was obtained as a colorless solid and use without further purification (491 mg, 2.93 mmol, 92%).

$[\alpha]_D^{21} = +10.9$ (*c* 1.8, MeOH).

^{1}H NMR (MeOD, 400 MHz): δ = 4.07-3.97 (m, 2H), 3.77 (dd, J = 12.3 Hz, J = 6.4 Hz, 1H), 3.67-3.61 (dd, J = 11.9 Hz, J = 6.0 Hz, 1H), 3.61-3.53 (dd, J = 11.9 Hz, J = 6.0 Hz, 1H), 3.50-3.37 (m, 3H), 1.37 (d, J = 6.3 Hz, 3H).

^{13}C NMR (MeOD, 101 MHz): δ = 70.3, 66.5, 59.5, 58.6, 53.1, 14.1

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_6H_{14}NO_2$: 132.1021; found: 132.1019.

Sulfamidates 1-3; general procedure:

Step 1: To a solution of imidazole (6.0 eq.) in DCM, thionyl chloride (2.0 eq.) was added dropwise at -10°C and the resulting mixture was stirred at 0°C for 2h. **5**·HCl-**7**·HCl (1.0 eq.) and Et_3N (2.0 eq.) were added at -10°C and the mixture was stirred at r.t. overnight. After reaction completion, deionized water was added to quench the reaction and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers were washed with brine and concentrated under reduced pressure to give crude sulfimidate (not isolated).

Step 2: The crude intermediate was dissolved in DCM and deionized water, sodium periodate (3.0 eq.) and (RuO_2·xH_2O) (0.02 eq.) were added. The mixture was stirred at r.t. overnight. The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_3 and concentrated under reduced pressure. The crude product was purified by column chromatography to obtain the respective sulfamidate **1-3**.

(3a*R*,7*R*)-7-methyltetrahydro-3*H*-[1,2,3]oxathiazolo[4,3-*c*][1,4]oxazine 1,1-dioxide (1):

1 was prepared starting from **5**·HCl (250 mg, 1.49 mmol, 1.0 eq.) using imidazole (609 mg, 8.95 mmol, 6.0 eq.), thionyl chloride (0.22 mL, 2.98 mmol, 2.0 eq.), triethylamine (0.40 mL, 2.98 mmol, 2.0 eq.) in DCM (6 mL) for Step 1. Then, sodium periodate (919 mg, 4.30 mmol, 3.0 eq.), (RuO_2·xH_2O) (2.0 mg, 0.015 mmol, 0.01 eq.) in DCM (10 mL) and water (10 mL) for Step 2. Flash chromatography (SiO_2, DCM 100%) yielded compound **1** (139 mg, 0.72 mmol, 48%) as a colorless solid.

$[\alpha]_D^{23} = -76.7$ (*c* 7.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.54 (dd, J = 7.8 Hz, J = 6.0 Hz, 1H), 4.15 (dd, J = 10.5 Hz, J = 7.8 Hz, 1H), 4.02 (dd, J = 11.0 Hz, J = 3.0 Hz, 1H), 3.83 (dd, J = 10.7 Hz, J = 2.4 Hz, 1H), 3.73-3.66 (m, 1H), 3.41 (dd, J = 11.0 Hz, J = 10.0 Hz, 1H), 3.31-3.14 (m, 2H), 1.34 (d, J = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 71.3, 69.5, 67.8, 56.6, 52.7, 13.7.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_6H_{11}NNaO_4S$: 216.0301; found: 216.0304.

(3a*S*,7*R*)-7-methyltetrahydro-3*H*-[1,2,3]oxathiazolo[4,3-*c*][1,4]oxazine 1,1-dioxide (2):

2 was prepared starting from **6**·HCl (90 mg, 0.53 mmol, 1.0 eq.) using imidazole (217 mg, 3.18 mmol, 6.0 eq.), thionyl chloride (80 µL, 1.06 mmol, 2.0 eq.), triethylamine (0.15 mL, 1.06 mmol, 2.0 eq.) in DCM (2 mL) for Step 1. Then, sodium periodate (340 mg, 1.59 mmol, 3.0 eq.), (RuO_2·xH_2O) (1.1 mg, 0.008 mmol, 0.01 eq.) in DCM (5 mL) and water (5 mL) for Step 2. Flash chromatography (SiO_2, DCM 100%) yielded compound **2** (29 mg, 0.15 mmol, 29%).

$[\alpha]_D^{23} = +2.97$ (*c* 12.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.54 (dd, J = 7.8 Hz, J = 6.0 Hz, 1H), 4.15 (dd, J = 10.5 Hz, J = 7.8 Hz, 1H), 4.02 (dd, J = 11.0 Hz, J = 3.0 Hz, 1H), 3.83 (dd, J = 10.7 Hz, J = 2.4 Hz, 1H), 3.73-3.66 (m, 1H), 3.41 (dd, J = 11.0 Hz, J = 10.0 Hz, 1H), 3.31-3.14 (m, 2H, H-3), 1.34 (d, J = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 71.3, 69.5, 67.8, 56.6, 52.7, 13.7.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_6H_{12}NO_4S$: 194.0480; found: 194.0482; *m/z* [M+Na]$^+$ calcd for $C_6H_{11}NNaO_4S$: 216.0301; found: 216.0300.

(3a*S*,7*S*)-7-methyltetrahydro-3*H*-[1,2,3]oxathiazolo[4,3-*c*][1,4]oxazine 1,1-dioxide (3):

3 was prepared starting from **7**·HCl (506 mg, 1.20 mmol, 1.0 eq.), using imidazole (490 mg, 7.20 mmol, 6.0 eq.), thionyl chloride (468 mL, 2.40 mmol, 2.0 eq.), triethylamine (0.18 mL, 2.40 mmol, 2.0 eq.) in DCM (8 mL) for Step 1. Then, sodium periodate (616 mg, 2.88 mmol, 3.0 eq.), (RuO_2·xH_2O) (2.7 mg, 0.02 mmol, 0.02 eq.) in DCM (12 mL) and water (10 mL) for Step 2. Flash chromatography (SiO_2, DCM 100%) yielded compound **3** (82 mg, 0.43 mmol, 36%) as a colorless solid.

$[\alpha]_D^{21}$ = + 105.6 (*c* 1.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.54 (dd, J = 7.8 Hz, J = 6.0 Hz, 1H), 4.15 (dd, J = 10.5 Hz, J = 7.8 Hz, 1H), 4.02 (dd, J = 11.0 Hz, J = 3.0 Hz, 1H), 3.83 (dd, J = 10.7 Hz, J = 2.4 Hz, 1H), 3.73-3.66 (m, 1H), 3.41 (dd, J = 11.0 Hz, J = 10.0 Hz, 1H), 3.31-3.14 (m, 2H, H-3), 1.34 (d, J = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 71.3, 69.5, 67.8, 56.6, 52.7, 13.7.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_6H_{12}NO_4S$: 194.0482; found: 194.0483; *m/z* $[M+Na]^+$ calcd for $C_6H_{11}NNaO_4S$: 216.0301; found: 216.0301.

(*R*)-4-benzyl-5-(hydroxymethyl)morpholin-3-one (21):

To a solution of the ester **20** (4.99 g, 20.0 mmol, 1.0 eq.) in THF (70 mL) was added dropwise a solution of $LiBH_4$ (1.74 g, 80.0 mmol, 4.0 eq.) in (50 mL) at 0°C. The mixture was stirred at r.t during 7h. The solution was diluted with EtOAc (100 mL) and quenched by the addition of EtOH (10 mL), MeOH (10 mL), deionized water (20 mL) and finally saturated aqueous solution of ammonium chloride (80 mL). The layers were separated and the aqueous layers were extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CyH/EtOAc 4:6) to yield the alcohol **21** (3.74 g, 16.9 mmol, 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39-7.21 (m, 5H), 5.30 (d, J = 15.0 Hz, 1H), 4.30 (d, J = 16.8 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H, 4.14-4.06 (m, 2H, H 3), 3.85 (dd, J = 11.1 Hz, J = 7.2 Hz, 1H), 3.76 (dd, J = 11.1 Hz, J = 3.8 Hz, 1H), 3.68 (dd, J = 12.0 Hz, J = 3.1 Hz, 1H), 3.30-3.21 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 167.6, 136.6, 129.0, 128.1, 127.9, 68.1, 65.8, 61.0, 55.4, 47.8.

MS (MALDI): *m/z* = 222.2 $[M+H]^+$.

(*S*)-4-benzyl-5-(((tert-butyldimethylsilyl)oxy)methyl)morpholin-3-one (22):

To a solution of alcohol **21** (3.60 g, 16.3 mmol, 1.0 eq.) in THF (40 mL) was added imidazole (3.32 g, 48.8 mmol, 3.0 eq.). A solution of tert-butylchlorodimethylsilane (TBDMSCl, 2.94 g, 19.52 mmol, 1.2 eq.) in THF (20 mL) was added dropwise and the mixture was stirred at r.t. for 1h. The mixture was quenched by addition of saturated aqueous solution of ammonium chloride (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvents were evaporated. The crude product was purified by column chromatography (SiO_2, CyH/EtOAc 8:2) to yield the TBS protected alcohol **22** (4.67 g, 13.93 mmol, 86%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41-7.20 (m, 5H), 5.33 (d, J = 14.9 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 14.9 Hz, 1H), 4.06-4.01 (m, 1H), 3.83-3.69 (m, 2H), 3.59 (dd, J = 11.8 Hz, J = 3.0 Hz, 1H), 3.27-3.19 (m, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 167.4, 136.9, 128.9, 128.2, 127.8, 68.1, 64.8, 61.1, 56.0, 48.0, 26.0, 18.3, -5.4, -5.3.

MS (MALDI): *m/z* = 336.4 $[M+H]^+$.

(*S*)-4-benzyl-5-(((tert-butyldimethylsilyl)oxy)methyl)-3,3-dimethylmorpholine (23):

To a solution of compound **22** (4.50 g, 13.4 mmol, 1.0 eq.) in THF (50 mL), at -15°C was added zirconium(IV) chloride (3.12 g, 13.4 mmol, 1.0 eq.) and the resulting mixture was stirred for 30 min. Then, 3 M solution of methylmagnesium bromide in Et_2O (13.4 mL, 40.2 mmol, 3.0 eq.) was added at -10°C dropwise and the mixture was stirred at r.t. for 1.5h. After completion, saturated aqueous solution of ammonium chloride was added dropwise at 0°C, Layers were separated and aqueous layer was washed with DCM (3 x 15 mL). Combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, CyH/EtOAc 9:1) to yield compound **23** (2.95 g, 8.43 mmol, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40-7.32 (m, 2H), 7.31-7.22 (m, 2H), 7.22-7.11 (m, 1H), 4.01 (dd, J = 11.3 Hz, J = 3.3 Hz, 1H), 3.96 (d, J = 16.7 Hz, 1H), 3.50-3.38 (m, 4H), 3.35 (dd, J = 10.0 Hz, J = 8.0 Hz, 1H), 3.00 (dd, J = 10.1, J = 8.7 Hz, 1H), 2.88-2.80 (m, 1H), 1.14 (s, 3H), 0.99 (s, 3H), 0.77 (s, 9H), -0.13 (s, 3H), -0.14 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 143.3, 128.2, 126.9, 126.4, 78.4, 71.9, 63.8, 59.1, 54.0, 52.4, 26.0, 24.7, 18.3, 17.3, -5.45, -5.51.

MS (MALDI): *m/z* = 350.3 $[M+H]^+$.

(*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3,3-dimethylmorpholine (24):

To a solution of the **23** (622 mg, 1.78 mmol, 1.0 eq.) in MeOH (50 mL), palladium on charcoal (62.2 mg, 10 mass%.) was added and the mixture was stirred at r.t. under hydrogen atmosphere (balloon) overnight. The mixture was filtered through Celite, washed with MeOH (3 x 10 mL) and the filtrate was evaporated to dryness under reduced pressure to yield the compound **24** (420 mg, 1.62 mmol, 91%) as a colorless oil. The crude was used in the next step without any further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.84 (dd, J = 9.8 Hz, J = 2.2 Hz, 1H), 3.57-3.40 (m, 3H), 3.20-3.05 (m, 3H), 1.25 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 76.9, 70.2, 64.4, 51.1, 49.3, 27.5, 26.0, 23.4, 18.4, -5.3, -5.3.

MS (MALDI): *m/z* = 260.2 $[M+H]^+$.

(*R*)-5,5-dimethyl-3-hydroxymethylmorpholine (8):

To a solution of compound **24** (352 mg, 1.36 mmol, 1.0 eq.) in MeOH (10 mL), ammonium fluoride (101 mg, 2.72 mmol, 2.0 eq.) was added and the mixture was stirred at r.t. overnight. The solvent was evaporated, the residue was suspended in acetonitrile (10 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness under reduced pressure to yield compound **8** (191 mg, 1.31 mmol, 97%) as a colorless oil. The crude was used in the next step without any further purification.

$[\alpha]_D^{21}$ = -1.82 (*c* 2.31, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.02 (dd, J = 11.3 Hz, J = 2.7 Hz, 1H), 3.69-3.53 (m, 3H), 3.53-3.36 (m, 3H), 1.43 (s, 3H), 1.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 74.6, 67.8, 60.5, 54.6, 53.2, 23.8, 20.9.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_{16}NO_2$: 146.1176; found: 146.1175.

(*R*)-7,7-dimethyltetrahydro-3*H*[1,2,3]oxathiazolo[4,3*c*][1,4]oxazine 1,1-dioxide (4):

Step 1: Imidazole (670 mg, 9.84 mmol, 6.0 eq.) was dissolved in DCM (5 mL) and the solution was cooled to -10°C. Thionyl chloride (0.25 mL, 3.34 mmol, 2.1 eq.) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 1h. The mixture was cooled to – 10°C and a solution of **8** (230 mg, 1.59 mmol, 1.0 eq.) and NEt_3 (0.42 mL, 3.16 mmol, 2.0 eq.) in DCM (2 mL) was added dropwise. The reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by the addition of deionized water (10 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine and concentrated under reduced pressure to give crude intermediate sulfimidate (not isolated).

Step 2: The crude sulfimidate was dissolved in DCM (10 mL) and the solution was cooled to 0°C and a suspension of sodium periodate (2.64 g, 12.34 mmol, 2.6 eq.) and (RuO_2·xH_2O) (2.67 mg, 0.02 mmol, 0.01 eq.) in deionized water (10 mL) was added. The mixture was stirred at r.t. overnight. The layers were separated, the aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude was purified by column chromatography (SiO_2, DCM 100%) to yield the desired sulfamidate **4** (79 mg, 0.38 mmol, 24%) as a colorless oil.

$[\alpha]_D^{21}$ = + 28.3 (*c* 3.69, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.53-4.51 (m, 1H), 4.11-3.99 (m, 3H), 3.46 (d, J = 11.3 Hz, 1H), 3.42-3.34 (m, 1H), 3.32 (d, J = 11.3 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 76.4, 68.8, 68.5, 56.3, 51.5, 22.7, 19.3.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_7H_{13}NNaO_4S$: 230.0458; found: 230.0457.

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Supporting Information

Supporting information for this article is available online at

Conflict of Interest

The authors declare no conflict of interest.

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