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Synthesis of chiral 1,4-oxazepane-5-carboxylic acids from polymer-supported homoserine†

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The preparation of novel 1,4-oxazepane-5-carboxylic acids bearing two stereocenters is reported in this article. Fmoc-HSe(TBDMS)-OH immobilized on Wang resin was reacted with different nitrobenzenesulfonyl chlorides and alkylated with 2-bromoacetophenones to yield *N*-phenacyl nitrobenzenesulfonamides. Their cleavage from the polymer support using trifluoroacetic acid (TFA) led to the removal of the silyl protective group followed by spontaneous lactonization. In contrast, TFA/triethylsilane (Et₃SiH)-mediated cleavage yielded 1,4-oxazepane derivatives as a mixture of inseparable diastereomers. The regioselectivity/stereoselectivity depended on the substitution of the starting 2-bromoacetophenones and was studied in detail. Catalytic hydrogenation of the nitro group improved the separability of the resulting diastereomeric anilines, which allowed us to isolate and fully characterize the major isomers.

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Introduction

Chiral seven-membered heterocycles bearing one or more heteroatoms in their skeleton are an interesting group of compounds with unique physico-chemical and biological properties. The prominent heterocyclic scaffold within this group is represented by 1,4-oxazepanes, which occur in both synthetic compounds and natural products (Fig. 1).^{1–6}

Compounds bearing 1,4-oxazepane scaffolds have been reported as potent anticonvulsants⁷ and antifungal agents^{5,8} or agents to treat inflammatory bowel disease,⁹ lupus nephritis¹⁰ and respiratory diseases, including asthma and bronchiectasis.^{11,12} Over the past decade, synthetic chemists have struggled to develop different strategies to access 1,4-oxazepanes from various starting materials.

The most robust synthetic approaches reported to date are based on intramolecular cyclization of alkenols,^{13,14} alkynols^{15,16} or hydroxyketones,¹⁶ typically using Brønsted or Lewis acids; however, some alternative methods of limited applicability have also been described recently.^{17–25}

Although the synthetic availability of chiral 1,4-oxazepanes has already been determined, the decoration of the scaffold with reactive functional groups amenable to further diversification remains a challenging task due to the limited

applicability of previously developed procedures for functionalizing starting materials. In our previous contribution, we reported the simple synthesis of chiral morpholines starting from resin-bound serine.²⁶ Using either TFA- or TFA/Et₃SiH-induced cleavage of the corresponding polymer-supported intermediates (Fig. 2), we synthesized either dihydrooxazine-3-carboxylic acids or morpholine-3-carboxylic acids with full control of the newly formed stereocenter. Later, we extended this method to the simple synthesis of fused [6 + 7]^{27,28} or [6 + 6]^{29,30} morpholines. To eventually synthesize the corresponding homological compounds, we decided to use polymer-supported homoserine to access the 1,4-oxazepane-5-carboxylic acids suitable for further modification. In this article, we report on the applicability, regioselectivity and stereoselectivity of the proposed method.

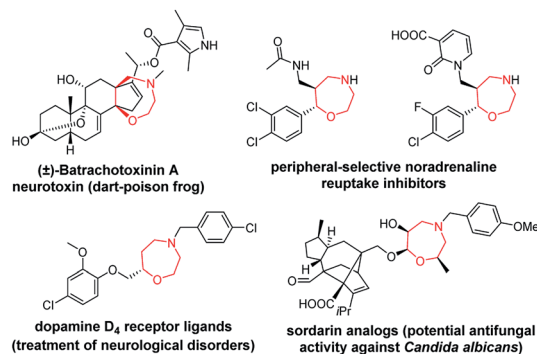


Fig. 1 Selected pharmacologically relevant compounds bearing a 1,4-oxazepane scaffold.^{1–6}

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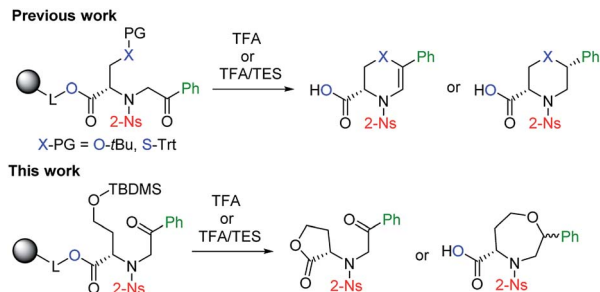


Fig. 2 Previously reported stereoselective synthesis of chiral (thio) morpholines and the application of the method to homologous starting material.

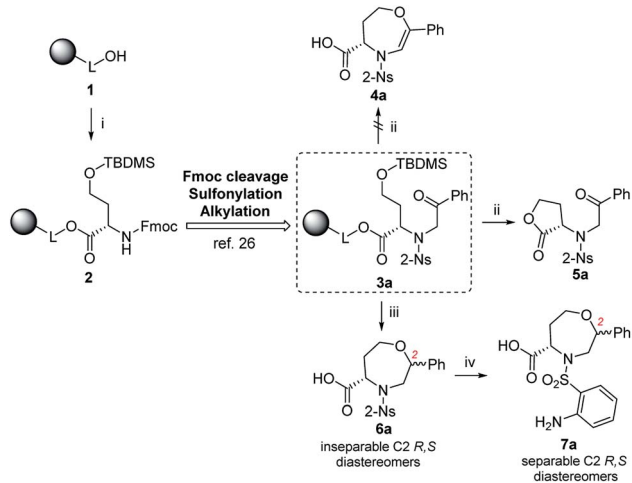
Results and discussion

Fmoc-HSe(TBDMS)-OH was prepared from homoserine in two steps^{31,32} and immobilized on Wang resin using the 1-hydroxybenzotriazole (HOBT)/diisopropylcarbodiimide (DIC) technique to suppress racemization. The key intermediate **3a** was synthesized according to our previous protocols²⁶ consisting of Fmoc-protective group cleavage, reaction with 2-nitrobenzenesulfonyl chloride (2-Ns-Cl) and alkylation using 2-bromoacetophenone (Scheme 1). Inspired by the smooth cyclization of serine-based analogs to 3,4-dihydro-1,4-oxazine-3-carboxylic acids,²⁶ we hypothesized that exposure of resin **3a** to TFA could yield the corresponding homologous product, *i.e.*, 4,5,6,7-tetrahydro-1,4-oxazepine-5-carboxylic acid **4a**. The reaction yielded a single product with 87% crude purity (calculated from HPLC-UV traces at 205–400 nm) and 74% overall yield (calculated from the ¹H NMR spectrum of the purified product). Although HRMS analysis corresponded to the molecular mass

of suggested product **4a**, NMR analysis (see ESI for details[†]) revealed preferential lactonization, which yielded compound **5a**. Interestingly, when Et₃SiH was added to the cleavage cocktail, a different course of reaction was observed. We received two chromatographically inseparable compounds with identical molecular masses (as indicated by HPLC-UV-MS analysis, the combined crude purity was 85%). To eventually improve the separability, we performed catalytic hydrogenation using palladium on carbon (Pd/C) in 2-isopropanol (IPA),²⁸ which again afforded a mixture of two isomers (the combined crude purity was 91%, and the ratio was 56 : 44, as calculated from HPLC-UV traces at 205–400 nm); however, in this case, reverse-phase chromatography (RP-HPLC) indicated possible separation. Consequently, the major isomer was successfully isolated using semipreparative RP-HPLC at 34% overall yield (calculated from the ¹H NMR spectrum of the purified product) and subjected to detailed NMR investigation.

We recorded and analyzed ¹H, ¹³C{¹H}, APT, ¹H–¹H COSY, ¹H–¹H NOESY, ¹H–¹³C HMQC, ¹H–¹³C HMBC and ¹H–¹⁵N HMBC NMR data to determine the constitution. Complete assignment of the ¹H, ¹³C and ¹⁵N signals was possible and is shown in the ESI (Fig. S17–S19 and Table S2[†]). In brief, by means of the homonuclear and heteronuclear correlation data, we identified the 1,4-oxazepane-5-carboxylic acid, phenyl and 2-aminobenzenesulfonyl moieties indicating the structure of **7a**. The connectivity between the oxazepane and phenyl rings was confirmed by three long-range ¹H–¹³C correlations (see ESI, Fig. S18[†]). Finally, the planar structure was established by the ¹H–¹H NOESY spectrum, which gave the key correlations between oxazepane protons and aminobenzenesulfonyl proton H¹⁹ and correlations between oxazepane protons and phenyl protons H^{9,13} (Fig. 3 and S19[†]). All the 1D and 2D NMR spectra can be found in the ESI (Fig. S20–S27[†]).

To determine the conformation and relative configuration of **7a**, we analyzed the ¹H–¹H coupling constants on the oxazepane ring and the NOE correlations in detail. Despite the spatial flexibility of seven membered rings leading to multiple possible conformational states, the analysis of vicinal ¹H–¹H couplings indicated that the scaffold existed in the most energetically favourable chair conformation (Fig. 3). Since the configuration of the C5 stereocenter was defined by the configuration of the starting material (*S*), the configuration of the newly formed C2 stereocenter was assigned as *R*.



Scheme 1 The reactivity of resin-bound intermediate **3a** under different reaction conditions. Reagents and conditions: (i) 1-hydroxybenzotriazole (HOBT), 4-(dimethylamino)pyridine (DMAP), diisopropylcarbodiimide (DIC), *N,N*-dimethylformamide (DMF), CH₂Cl₂, 24 h, rt; (ii) 50% trifluoroacetic acid (TFA)/CH₂Cl₂, 1 h, rt; (iii) TFA/triethylsilane (Et₃SiH)/CH₂Cl₂ (10 : 1 : 9), 30 min, rt; (iv) H₂, 10% palladium on carbon (Pd/C) or platinum(IV) oxide (PtO₂), 2-isopropanol (IPA), 24 h, rt.

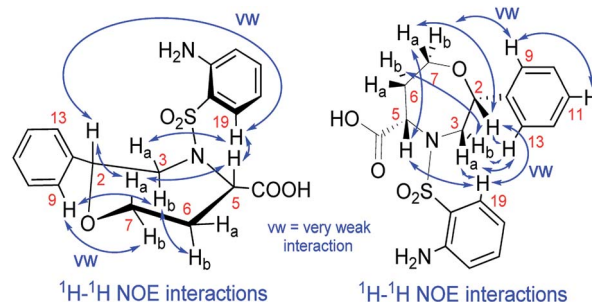
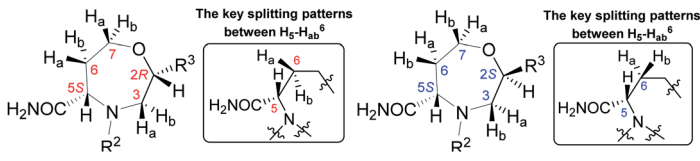


Fig. 3 The NOE correlations prove the constitution and configuration of oxazepane derivative **7a**.



Table 1 Comparison of ^1H chemical shifts, splitting patterns, and 2J and 3J homonuclear couplings for derivatives 7b^{2R} and 7b^{2S}


Position	C2 <i>R</i> isomer			C2 <i>S</i> isomer		
	^1H NMR δ_{H} [ppm]	Splitting pattern	J [Hz]	^1H NMR δ_{H} [ppm]	Splitting pattern	J [Hz]
H ²	4.28	dd	9.3, 1.2	4.64	dd	8.7, 1.6
H _a ³	3.82	ddd	16.2, 1.2, 1.2	3.63	dd	14.2, 1.6
H _b ³	3.53	dd	16.2, 9.6	3.43	dd	14.2, 8.7
H ⁵	4.49	ddd	10.8, 7.1, 1.0	4.59	dd	4.5, 4.5
H _a ⁶	2.46	dddd	15.7, 7.1, 6.3, 1.0	2.30	dddd	15.8, 4.5, 4.5, 1.6
H _b ⁶	2.21	dddd	15.7, 10.8, 9.3, 1.5	2.10	dddd	15.8, 11.0, 4.5, 3.0
H _a ⁷	3.67	ddd	12.9, 9.3, 1.0	3.78	ddd	12.8, 11.0, 1.6
H _b ⁷	4.05	ddd	12.9, 6.3, 1.5	4.02	ddd	12.8, 4.5, 3.0

Although we did not isolate and analyze the minor isomer of **7a**, in the case of **7b**, RP-HPLC purification enabled the separation and isolation of both isomers. Thorough NMR structural analysis indicated the formation of C2 *R,S* diastereomers 7b^{2R} and 7b^{2S} (Table 1). The ^1H NMR spectrum of 7b^{2R} was fairly similar to the spectrum of **7a**; hence, we concluded that this compound had the same configuration as **7a**. Compound 7b^{2S} was analyzed by 1D and 2D NMR spectroscopy (see ESI, Fig. S34–S41 and Table S3†) to verify the planar structure, assign all the ^1H and ^{13}C signals and determine the relative configuration. Finally, we confirmed the configuration of 7b^{2S} by analyzing the vicinal ^1H – ^1H couplings on the oxazepane ring and NOE correlations (Fig. 4).

Table 1 summarizes the ^1H chemical shifts, splitting patterns, and 2J and 3J homonuclear couplings observed in 7b^{2R} and 7b^{2S} . While the chemical shifts differ rather insignificantly between the two diastereomers, the splitting pattern of signal H⁵ and $^3J(\text{H}^5\text{--H}_a^6)$ and $^3J(\text{H}^5\text{--H}_b^6)$ can be used to differentiate between 7b^{2R} and 7b^{2S} . In the C2 *R* isomer 7b^{2R} , two relatively large couplings and one very small long-range coupling leading to a doublet of doublet of doublets are observed. However, in

the case of the C2 *S* isomer 7b^{2S} , the vicinal coupling constants are smaller and equal or nearly equal, and hence, the signal takes the shape of a pseudotriplet (dd). The same trend was observed in all derivatives 6–7.

After proving the structure and formation of the two diastereomers, we tried to improve the stereoselectivity by using a lower reaction temperature (0 °C or –20 °C); however, a nearly equal ratio of isomers was obtained. Furthermore, we tested the use of TMSOTf/Et₃SiH as reported earlier for an analogical starting material,¹⁷ but a complex mixture of unknown compounds was obtained.

To explain the different reaction outcomes depending on the composition of the cleavage cocktail, we suggested a reaction mechanism (Scheme 2). The protonation of intermediate **3a** cleaved from the resin can be followed by intramolecular attack of ketone or carboxylic acid with the hydroxy group as the internal nucleophile. With respect to the higher electrophilicity of the ketone, we presume that the formation of intermediate **B** over **E** is preferred. Intermediate **B** can be further stabilized by the formation of intermediates **C** and **D**; however, due to their limited stability, all the reactions in pathway **A–D** are reversible, which can lead to regeneration of starting material **A**. The same is true for the formation of **E** from **A**. In contrast, the conversion of **E** to **5a** is irreversible, as lactone does not undergo hydrolysis under the conditions used. In the presence of Et₃SiH, the preferential formation of **B** is considered again; however, the subsequently formed intermediates **C** and **D** are attacked by triethylsilane as the external nucleophile, which leads to the formation of stable compound **6a**. Consequently, the formation of lactone **5a** was not observed in this case.

After the determination of the reaction outcome, we used different starting materials to evaluate the limitations and scope of the methodology and to reveal the structure–regioselectivity and structure–stereoselectivity relationships. For this purpose, Wang resin was replaced with Rink amide resin,

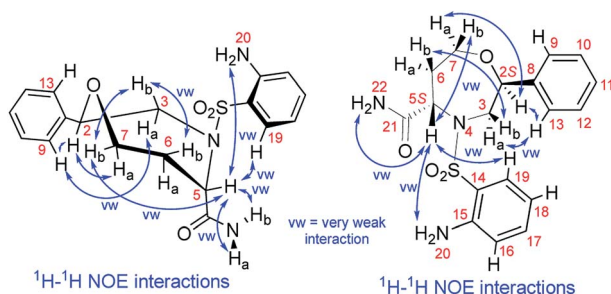
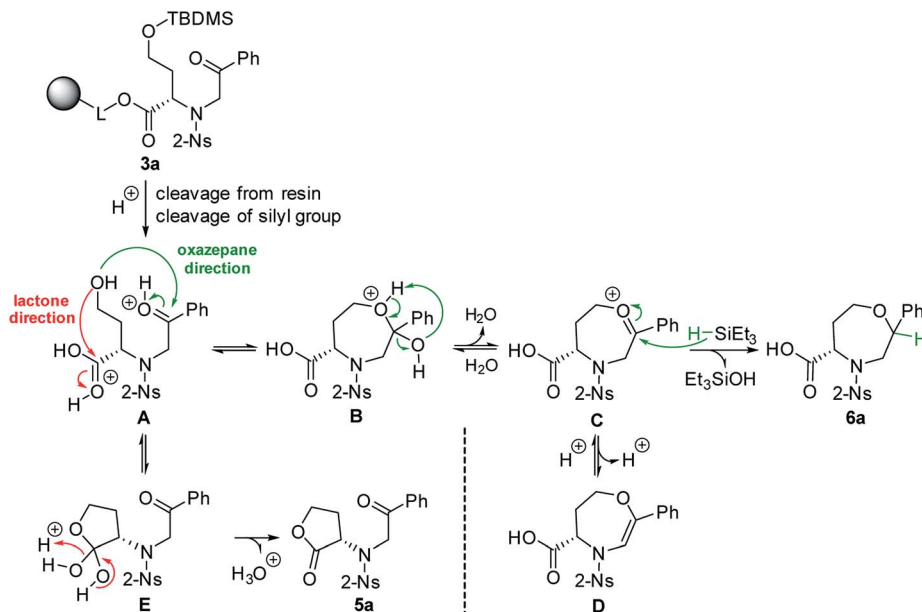


Fig. 4 The NOE correlations proving the configuration of oxazepane derivative 7b^{2S} .





Scheme 2 The hypothetical mechanism explaining the different reactivity of intermediate 3a.

Wang-piperazine resin and BAL resin with immobilized propylamine²⁶ to alter the carboxylic group to carboxamides. Furthermore, variously substituted sulfonyl chlorides and fourteen 2-bromoacetophenones bearing electron-donating or electron-withdrawing groups were selected, including one heterocyclic derivative (thienyl) and another aliphatic derivative (Me; Fig. 5).

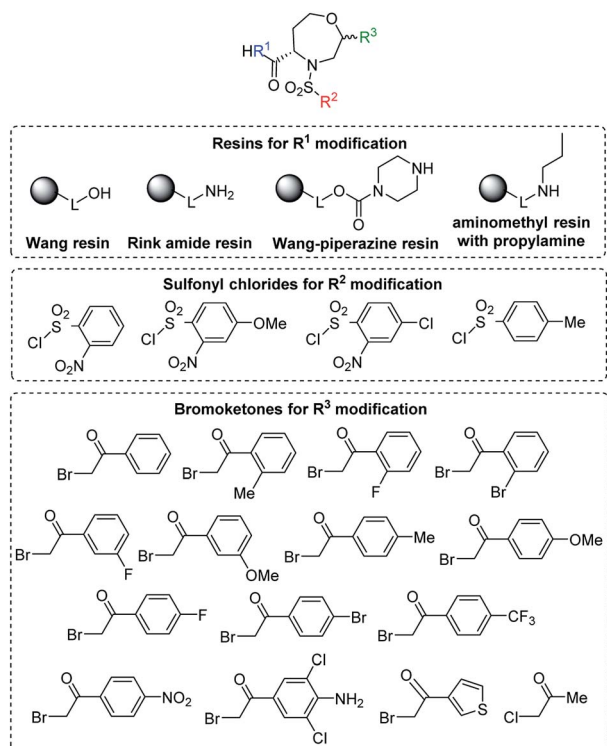
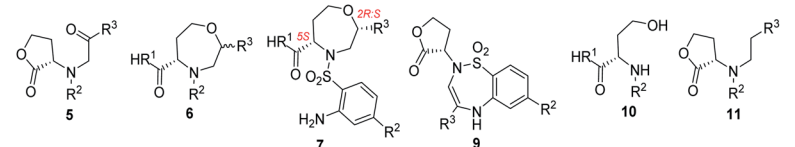


Fig. 5 General structure of target compounds and the list of the tested starting synthons (see Table 2 for the list of target compounds).

First, we tested the combination of 2-Ns-Cl and 2-bromoacetophenone with different resins. The use of Rink amide resin ($R^1 = \text{NH}_2$) required repetition of the alkylation step and yielded the final aniline **7b** in 89% crude purity as a mixture of C2 *R,S* diastereomers in a ratio of 45 : 55. Its RP-HPLC enabled the separation of both isomers in 9% (C2 *R* isomer) and 4% overall yields (C2 *S* isomer, Table 2). In the case of the Wang-piperazine resin ($R^1 = \text{piperazin-1-yl}$), the TFA/ Et_3SiH -mediated cleavage of the corresponding sulfonamide from the resin unexpectedly caused the cleavage of the piperazine moiety, and oxazepane-5-carboxylic acid derivative **7a** was obtained as a mixture of C2 *R,S* isomers in a ratio of 72 : 28. The major diastereomer was isolated in 10% overall yield. The use of BAL resin-immobilized propylamine failed in the alkylation step stage, which is in accordance with our previous results.²⁶

After that, various sulfonylating agents (Fig. 5) were tested, starting from intermediate **2** and using 2-bromoacetophenone as the alkylating agent. In the case of sulfonamides **3e** and **3g** bearing 4-methoxy-2-nitrobenzenesulfonyl group or tosyl group as R^2 , the alkylation required a longer reaction time (2 and 6 days, respectively) to completion. The TFA/ Et_3SiH cleavage of tosyl intermediate **3g** yielded the desired oxazepane in 73% crude purity as a partially separable mixture of C2 *R,S* isomers in a ratio of 62 : 38. Its RP-HPLC purification yielded the major isomer C2 *R* in 18% overall yield. In the case of **3e** and **3f** bearing 4-methoxy and 4-chloro-2-nitrobenzenesulfonyl as R^2 substituents, the nitro-oxazepane derivatives **6e** and **6f** were obtained as inseparable mixtures of C2 *R,S* diastereoisomers in 81–90% crude purities. Similar to previously reported results,²⁸ the hydrogenation of **6f** led to undesired hydrogenolysis of the C–Cl bond (Scheme 3). For this reason, Pd/C was replaced with PtO_2 , which yielded aniline **7f** in 86% crude purity as a mixture of C2 *R,S* diastereomers in a ratio of 70 : 30. In this case, the isolation of the major isomer from the diastereomeric mixture was



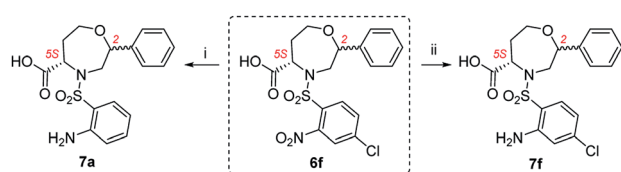
Table 2 The list of synthesized and fully characterized compounds^{a,b,c,d,e,f}


Cmpd	R ¹	R ²	R ³	Crude diastereomeric ratio of C2 <i>R</i> : <i>S</i> stereoisomers ^a [%]	Crude combined purity ^b [%]	Final purity of major purified isomer ^{c,d} [%]	Overall yield of major isomer ^e [%]
5a	—	2-Ns	Ph	—	87	99 ^c	74
6g	O	4-Me-Ph	Ph	62 : 38	73	97 ^d	18
7a	O	H	Ph	56 : 44	91	98 ^d	34
7a ^f	O	H	Ph	72 : 28	76	98 ^d	10
7b ^{2R}	NH	H	Ph	45 : 55	89	100 ^d	9
7b ^{2S}						100 ^d	4
7e	O	MeO	Ph	69 : 31	91	100 ^d	21
7f ^{2RS}	O	Cl	Ph	70 : 30	86	78 ^d	20
7i ^{2R}	O	H	2-F-Ph	29 : 71	69	100 ^d	4
7i ^{2S}						93 ^d	10
7k	O	H	3-F-Ph	64 : 36	70	100 ^d	10
7m	O	H	4-Me-Ph	77 : 23	90	100 ^d	19
7o	O	H	4-F-Ph	67 : 33	77	94 ^d	10
7q	O	H	4-CF ₃ -Ph	61 : 39	33	96 ^d	8
7t	O	H	3-Thienyl	93 : 7	89	98 ^d	22
9h	—	H	2-Me-Ph	—	50	99 ^c	19
9j	—	H	2-Br-Ph	—	49	99 ^c	13
10r	O	2-Ns	—	—	82	99 ^c	50
11n	—	2-Ns	4-MeO-Ph	—	77	99 ^c	33

^a Ratio of diastereomers prior to RP HPLC purification calculated from HPLC-UV traces at 205–400 nm. ^b Combined crude purity of diastereomers after the entire reaction sequence calculated from HPLC-UV traces at 205–400 nm. ^c Calculated from HPLC-UV traces at 205–400 nm after RP-HPLC purification. ^d Ratio of C2 *R,S* diastereomers calculated from ¹H NMR of the purified product. ^e Calculated from the ¹H NMR spectrum of the purified product. ^f Product prepared from Wang-piperazine resin.

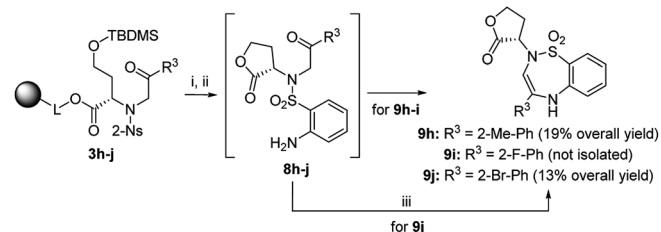
problematic and furnished the product C2 *R* in only 78% diastereomeric purity. In the case of **6e** bearing a 4-methoxy group, hydrogenation using PtO₂ suppressed the previously reported demethylation,²⁸ and the final compound **7e** was obtained in 91% crude purity as a mixture of C2 *R,S* diastereomers in a ratio of 69 : 31. RP-HPLC purification enabled the separation of the major C2 *R* isomer in 21% overall yield.

Finally, we tested various 2-haloketones bearing electron-donating and electron-withdrawing groups in the *o*-, *m*- and *p*-



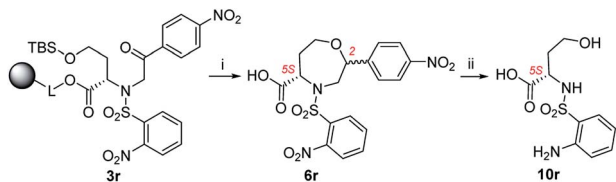
Scheme 3 Dehalogenation of oxazepane derivative **6f** during hydrogenation. Reagents and conditions: (i) H₂, Pd/C, IPA, 24 h, rt; (ii) H₂, PtO₂, IPA, 24 h, rt.

positions, and one heterocyclic and aliphatic derivative was included. All these building blocks were tested in combination with intermediate **2** and 2-Ns-Cl. In the case of **7j** and **7p** bearing 2-Br-Ph or 4-Br-Ph as R³, PtO₂ had to be used to avoid undesired debromination. The preferential formation of oxazepane was



Scheme 4 Preferential lactonization and formation of benzothiadiazepine 1,1-dioxide **9**. Reagents and conditions: (i) TFA/Et₃SiH/CH₂Cl₂ (10 : 1 : 9), 30 min, rt; (ii) H₂, 10% Pd/C (for derivatives **9h–i**) or PtO₂ (for derivative **9j**), IPA, 24 h, rt; (iii) 5% TFA/CH₂Cl₂, 24 h, rt.

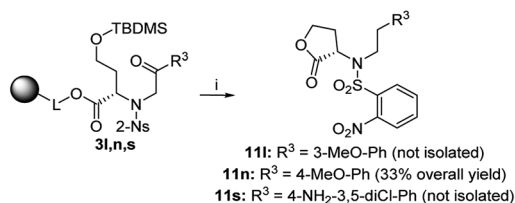




Scheme 5 Cleavage of oxazepane derivative **6r** during hydrogenation. Reagents and conditions: (i) TFA/Et₃SiH/CH₂Cl₂ (10 : 1 : 9), 30 min, rt; (ii) H₂, Pd/C, IPA, 24 h, rt.

observed in each case. In the case of **7p**, inseparable *C2 R,S* diastereomers were isolated in 14% overall yield as diastereomeric anilines in a ratio of 42 : 58. In the case of **3i** bearing 2-F-Ph as R³, the regioselectivity was compromised, and the TFA/Et₃SiH reaction yielded 1,4-oxazepane **6i** accompanied by lactone **5i** (26% according to HPLC). The following hydrogenation of the reaction mixture yielded the corresponding diastereomeric aniline **7i** (69% combined crude purity) and amino lactone **8i**, which spontaneously cyclized to benzothiadiazepine 1,1-dioxide **9i** (26% according to HPLC-UV-MS analysis) (Scheme 4).³³ In this case, RP-HPLC purification enabled the separation of both diastereomers. Intermediates **3h** (R³ = 2-Me-Ph) and **3j** (R³ = 2-Br-Ph) yielded lactones **5h** and **5j** as the major products (72% and 64% crude purities). Their hydrogenation yielded the corresponding anilines **8h** and **8j**, which were cyclized to benzothiadiazepine 1,1-dioxides **9h** and **9j**.³³ Derivatives **9h** and **9j** were isolated using semipreparative RP-HPLC at 19% overall yield and fully characterized. Interestingly, in contrast to previously reported results,³³ compounds **9** were fully stable and did not undergo ring contraction to benzothiadiazine 1,1-dioxides.

In the case of **3k** (3-F-Ph as R³), the TFA/Et₃SiH reaction and the subsequent hydrogenation yielded diastereomeric aniline **7k** in a ratio of 64 : 36 and 70% combined crude purity, and the major isomer was isolated and fully characterized. On the other hand, intermediate **3l** (3-MeO-Ph as R³) yielded a mixture of oxazepane derivative **6l** and lactone **11l** in a ratio of approximately 1 : 1, and for this reason, the products were not isolated (Scheme 6). Intermediates **3m**, **3o–q**, **t** were synthesized from *p*-substituted 2-bromoacetophenones (4-Me-Ph, 4-F-Ph, 4-Br-Ph and 4-CF₃-Ph as R³) and 3-thienyl derivative yielded oxazepanes **7m**, **7o–q**, **t** as separable *C2 R,S* diastereomers in variable ratios (Table 2) with combined crude purities in a range of 33–91%. In the case of oxazepane derivative **6r** (4-NO₂-Ph as R³),



Scheme 6 Preferential lactonization followed by ketone reduction to products **11**. Reagents and conditions: (i) TFA/Et₃SiH/CH₂Cl₂ (10 : 1 : 9), 24 h, rt.

hydrogenation using either Pd/C or PtO₂ led to cleavage of the heterocyclic scaffold, and compound **10r** was isolated (Scheme 5) in 82% crude purity and 50% overall yield (Table 2).

In the cases of **3n** (4-MeO-Ph as R³) and **3s** (4-NH₂-3,5-diCl-Ph as R³), we observed reversed regioselectivity, and after TFA/Et₃SiH cleavage, lactone derivatives **11n** and **11s** were formed exclusively; however, **11s** was accompanied with oxazepane **6s** as the minor product (30% crude purity). Due to the excess triethylsilane in the reaction mixture, the abovementioned derivatives were obtained as phenylethyl derivatives **11** (Scheme 6). The exposure to TFA/Et₃SiH had to be prolonged to make the reduction quantitative. In combination with the outcome obtained from intermediate **3l** (3-MeO-Ph as R³), we can state that electron-donating R³ groups in the *m*- or *p*-positions contribute to the formation of lactones, as they probably diminish the reactivity of adjacent ketones toward nucleophilic addition, which suppresses the formation of intermediate **C** (Scheme 2).

Similar to previously reported results,³⁴ the alkylation step with 2-chloroacetone provided the corresponding oxazepane **6u** in only 50% conversion. For this reason, the product was not isolated.

Conclusions

To conclude, we developed a simple methodology to prepare 2-phenyl-substituted-1,4-oxazepane-5-carboxylic acid derivatives. Although the formation of the oxazepane scaffold was non-stereoselective, as in the case of serine-based analogs leading to chiral morpholines,²⁶ the separation and full characterization of major diastereomers was feasible. The developed strategy provided rather minor limitations, *e.g.*, competitive lactonization in the cases of *m*- and *p*-electron-donating groups as R³ substituents. Importantly, the developed protocols and corresponding intermediates can be applied for the synthesis of differently fused 1,4-oxazepanes based on previously reported approaches targeted to fused morpholines.^{27–30}

Experimental section

General information

Solvents and chemicals were purchased from Sigma-Aldrich (Milwaukee, WI, <http://www.sigmaaldrich.com>), Acros Organic (Geel, Belgium, <http://www.acros.com>) and Fluorochem (Haddington, United Kingdom, <http://www.fluorochem.co.uk>). Wang resin (100–200 mesh, 1% DVB, 1.4 mmol g⁻¹), Rink resin (100–200 mesh, 1% DVB, 0.4 mmol g⁻¹) and aminomethyl resin (100–200 mesh, 1% DVB, 0.98 mmol g⁻¹) were obtained from AAPPTec (Louisville, KY, <http://www.aapptec.com>). Solid-phase synthesis was carried out in plastic reaction vessels (syringes, each equipped with a porous disk) using a manually operated synthesizer (Torviq, Niles, MI, <http://www.torviq.com>). All reactions were carried out at ambient temperature (23 °C) unless stated otherwise. The synthesis of Fmoc-HSe(TBDMS)-OH,^{31,32} immobilization of Fmoc-HSe(TBDMS)-OH on the resin²⁶ and *N*-phenacyl sulfonamides **3a–u**²⁶ was performed according to these reported protocols. The LC-MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph



Acquity with photodiode array detector and single quadrupole mass spectrometer (Waters), using X-Select C18 column with the mobile phase consisting of 10 mM ammonium acetate (AmAc) in H₂O and MeCN. The ESI source operated at discharge current of 5 μ A, vaporizer temperature of 350 °C and capillary temperature of 200 °C. For the LC/MS analysis, a sample of resin (~5 mg) was treated with TFA in CH₂Cl₂, the cleavage cocktail was evaporated under a stream of nitrogen, and cleaved compounds extracted into MeCN/H₂O (20% or 50%; 1 mL). Purification was carried out on C18 semipreparative RP-HPLC with the gradient of 10 mM aqueous AmAc and MeCN, flow rate 15 mL min⁻¹ or by normal phase by silica gel chromatography. Residual solvents (H₂O and AmAc buffer) were lyophilized by the ScanVac Coolsafe 110-4 working at -110 °C. All 1D and 2D NMR experiments were performed with using ECX500 spectrometer (JEOL RESONANCE, Tokyo, Japan) at magnetic field strength of 11.75 T corresponding to ¹H and ¹³C resonance frequencies of 500.16 MHz and 125.77 MHz at 27 °C. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). The signals of MeCN-*d*₃ were set at 1.94 ppm in ¹H NMR spectra and at 118.26 ppm in ¹³C NMR spectra. ¹⁵N chemical shifts were referenced to external 90% formamide in DMSO-*d*₆ at 112.00 ppm.³⁵ The assignment of ¹H, ¹³C{¹H} and ¹⁵N signals was done by APT, ¹H-¹H COSY, ¹H-¹H NOESY, ¹H-¹³C HMQC, ¹H-¹³C HMBC and ¹H-¹⁵N HMBC. Abbreviations in NMR spectra: br. s - broad singlet, br. d - broad doublet, s - singlet, d - doublet, dd - doublet of doublets, ddd - doublet of doublets of doublets, dddd - doublet of doublets of doublets of doublets, m - multiplet. Acetate salt (residual agent from the semipreparative HPLC purification) exhibited a singlet at 2.09–2.53 ppm in ¹H NMR spectra and two resonances at 41.00 ppm and 171.00 ppm in ¹³C NMR spectra. HRMS analysis was performed using LC-MS (Dionex Ultimate 3000, Thermo Fischer Scientific, MA, USA) with Exactive Plus Orbitrap high-resolution mass spectrometer (Thermo Exactive Plus, Thermo Fischer Scientific, MA, USA) operating at positive or negative full scan mode (120 000 FWHM) in the range of 100–1000 *m/z* with electrospray ionization working at 150 °C and the source voltage of 3.6 kV. Chromatographic separation was performed on column Phenomenex Gemini (C18, 50 × 2 mm, 3 μ m particle) with isocratic elution and mobile phase (MP) containing MeCN/10 mM AmAc (80 : 20; v/v). The samples were dissolved in the initial MP. The acquired data were internally calibrated with phthalate as a contaminant in MeOH (*m/z* 297.15909). IR spectra were measured by DRIFT (Diffuse Reflectance Infrared Fourier Transform) on a Thermo Nicolet AVATAR 370 FTIR spectrometer. Absorbance peaks (wavenumbers) are reported in reciprocal centimeters (cm⁻¹) and transmittances (T) are reported in percentages (%). Specific optical rotations were measured on Automatic Compact Polarimeter POL-1/2 (ATAGO, Japan) with LED Light Source and 589 nm interference filter at 24 °C. The length of cuvette was 2 cm and specific optical rotations are reported as follows: $[\alpha]_D^{25}$, concentration (g mL⁻¹) and solvent.

General method for calculation of yields using ¹H NMR. ¹H NMR spectra of external standard at three different

concentration levels were measured. In each spectrum, the solvent signal was integrated followed by the integration of selected H^{Ar} signal of external standard. Ratios of solvent/standard signal areas along with known quantity of standard were used to construct a calibration curve. Then, ¹H NMR spectra of studied sample were measured and the ratio of solvent/sample (selected H^{Ar} signal) areas was determined. Using the calibration curve, the quantity of compound in the sample was calculated.

General procedure for cleavage the TBDMS protecting group and lactonization 3a–u. The polymer-supported intermediate 3a–u (500 mg) was cleaved in the mixture of TFA/CH₂Cl₂ (5 mL, 50%) for 1 h at room temperature. Then the resin was washed three times with fresh cleavage cocktail (5 mL) and the combined fractions were evaporated using a stream of nitrogen, lyophilized overnight and purified by semipreparative RP HPLC.

(-)-(S)-2-Nitro-N-(2-oxo-2-phenethyl)-N-(2-oxotetrahydrofuran-3-yl)benzenesulfonamide 5a. Cleaved from 742 mg of resin 3a (0.528 mmol g⁻¹, 0.342 mmol of substrate). White amorphous solid (117.4 mg, 0.291 mmol, 74%). HPLC purity 99%. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 8.26 (dd, J = 7.7, 1.6 Hz, 1H, HC9), 7.94–7.96 (m, 2H, HC^{18,22}), 7.74–7.83 (m, 3H, HC^{10–12}), 7.63–7.67 (m, 1H, HC²⁰), 7.50–7.54 (m, 2H, HC^{19,21}), 5.25 (d, J = 19.2 Hz, 1H, H_aC¹⁵), 5.05 (dd, J = 12.4, 8.7 Hz, 1H, HC³), 4.60 (d, J = 19.2 Hz, 1H, H_bC¹⁵), 4.31 (ddd, J = 9.0, 9.0, 1.0 Hz, 1H, H_bC⁵), 4.24 (ddd, J = 11.2, 9.0, 5.8 Hz, 1H, H_aC⁵), 2.57 (dddd, J = 12.7, 8.7, 5.8, 1.0 Hz, 1H, H_bC⁴), 2.29 (dddd, J = 12.5, 12.5, 11.2, 9.0 Hz, 1H, H_aC⁴). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 194.7 (C16), 174.4 (C2), 148.9 (C13), 135.5 (C17), 135.4 (C9), 134.9 (C20), 133.8 (C8), 133.21 (C10), 131.6 (C12), 129.8 (C19,21), 128.9 (C18,22), 125.1 (C11), 66.7 (C5), 58.6 (C3), 53.2 (C15), 28.4 (C4). ¹⁵N NMR (51 MHz, MeCN-*d*₃): δ = 90.0 (N6), 372.9 (N14). HRMS (ESI, pos.): *m/z* calcd for C₁₈H₁₇N₂O₇S [M + H]⁺ 405.0751 found 405.0750. IR (DRIFT): $\bar{\nu}$ = 3101, 3953, 2930, 2918, 1780, 1595, 1544, 1378, 1340, 1301, 1206, 1157, 1080, 1063, 760, 742, 700 cm⁻¹. $[\alpha]_D^{25}$ = -21.0° (c = 0.00067 g mL⁻¹ in MeCN).

General procedure for cyclization to 1,4-oxazepanes 6a–u. The polymer-supported intermediate 3a–u (500 mg) was cleaved in TFA/Et₃SiH/CH₂Cl₂ (5 mL, 10 : 1 : 9) for 30 min (except for 3n and 3s) or 24 h (for derivatives 3n and 3s) at room temperature. Then the resin was washed three times with fresh cleavage cocktail (5 mL) and the combined fractions were evaporated using a stream of nitrogen and lyophilized overnight. The crude products were purified using RP-HPLC.

(-)-Ammonium (2R,5S)-2-phenyl-4-tosyl-1,4-oxazepane-5-carboxylate 6g. Cleaved from 860 mg of resin 3g (0.273 mmol g⁻¹, 0.235 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 62 : 38, the isolation of major C2 *R* epimer was performed. White amorphous solid (16.1 mg, 0.043 mmol, 18%). HPLC purity 97%. NMR: mixture with 3% of C2 *S* isomer. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.75 (d, J = 8.3 Hz, 2H), 7.23–7.37 (m, 7H), 4.81 (br. s, 5H, residual water), 4.55 (dd, J = 10.6, 7.1 Hz, 1H), 4.32 (d, J = 9.1 Hz, 1H), 4.02 (ddd, J = 12.7, 6.3, 1.5 Hz, 1H), 3.78 (ddd, J = 15.9, 1.0, 1.0 Hz, 1H), 3.47–3.55 (m, 1H), 3.49 (ddd, J = 12.7, 9.5, 1.2 Hz, 1H), 2.47–2.54 (m, 1H), 2.39 (s, 3H), 2.13 (dddd, J = 15.9, 10.6, 9.1, 1.6 Hz, 1H).



$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 175.7, 144.8, 141.0, 138.9, 130.7, 129.3, 128.7, 128.2, 127.0, 83.2, 67.7, 59.5, 54.4, 35.7, 21.5$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 393.1479 found 393.1482. IR (DRIFT): $\bar{\nu} = 3062, 3029, 2950, 2862, 11\ 917, 1723, 1596, 1450, 1334, 1306, 1171, 1152, 761, 746, 699\ \text{cm}^{-1}$. $[\alpha]_{\text{D}}^{24} = -36.2^\circ$ ($c = 0.00062\ \text{g mL}^{-1}$, MeCN).

(-)-(S)-N-(4-Methoxyphenethyl)-2-nitro-N-(2-oxotetrahydrofuran-3-yl)benzenesulfonamide **11n**. Cleaved from 577 mg of resin **3n** (0.225 mmol g^{-1} , 0.130 mmol of substrate) for 24 h at room temperature. Pale yellow amorphous solid (17.8 mg, 0.042 mmol, 33%). HPLC purity 99%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 8.13$ (dd, $J = 7.7, 1.5\ \text{Hz}$, 1H), 7.72–7.82 (m, 3H), 7.11 (d, $J = 8.5\ \text{Hz}$, 2H), 6.83 (d, $J = 8.5\ \text{Hz}$, 2H), 4.90 (dd, $J = 11.7, 9.0\ \text{Hz}$, 1H), 4.36–4.42 (m, 1H), 4.25 (ddd, $J = 10.7, 9.0, 6.3\ \text{Hz}$, 1H), 3.75 (s, 3H), 3.45–3.54 (m, 1H), 3.26–3.36 (m, 1H), 2.83–2.90 (m, 2H), 2.48 (dddd, $J = 12.5, 9.0, 6.3, 1.5\ \text{Hz}$, 1H), 2.33–2.44 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.7, 159.5, 149.3, 135.5, 133.3, 133.3, 131.4, 131.1, 130.9, 125.1, 114.9, 66.6, 58.5, 55.8, 49.9, 36.1, 27.9$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_7\text{S} [\text{M} + \text{H}]^+$ 421.1064 found 421.1066. IR (DRIFT): $\bar{\nu} = 2932, 2836, 1783, 1542, 1512, 1367, 1342, 1250, 1241, 1159, 785, 752, 708\ \text{cm}^{-1}$. $[\alpha]_{\text{D}}^{24} = -76.9^\circ$ ($c = 0.00029\ \text{g mL}^{-1}$, MeCN).

General procedure for catalytical hydrogenation of nitro group 7a–f, h–m, o–r, t, including 8j, 9h, and 10r. The synthesis of anilines **7a–f, h–m, o–r, t** and amino-lactones **8j, 9h** was performed according to the reported protocol²⁸ using 10% Pd/C or PtO₂ (for derivatives **6l, 6p, 6r, 6t, 5j**) for 24 h at room temperature. The crude evaporators were purified by silica gel chromatography in CH₂Cl₂/methanol (MeOH) (9/1; v/v, for derivatives **7a–f, h–m, o–r, t**) or ethyl acetate (EA)/*n*-hexane (Hex; 4/6 or 1/1; v/v; for derivatives **8j, 9h**, respectively) to remove residual catalyst after hydrogenation, and then subjected to RP-HPLC.

(-)-(2R,5S)-4-((2-Aminophenyl)sulfonyl)-2-phenyl-1,4-oxazepa-ne-5-carboxylic acid **7a**

Prepared from Wang resin. Cleaved from 785 mg of resin **3a** (0.140 mmol g^{-1} , 0.110 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 56 : 44, the isolation of the major C2 *R* epimer was performed. White amorphous solid (14.2 mg, 0.038 mmol, 34%). HPLC purity 97%. NMR: mixture with 2% of C2 *S* isomer. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.66$ (dd, $J = 8.1, 1.5\ \text{Hz}$, 1H, HC¹⁹), 7.34 (ddd, $J = 8.3, 7.2, 1.5\ \text{Hz}$, 1H, HC¹⁷), 7.23–7.30 (m, 3H, HC^{10–12}), 7.15 (m, 2H, HC^{9,13}), 6.84 (dd, $J = 8.3, 1.0\ \text{Hz}$, 1H, HC¹⁶), 6.75 (ddd, $J = 8.1, 7.2, 1.0\ \text{Hz}$, 1H, HC¹⁸), 4.66 (dd, $J = 10.4, 7.1\ \text{Hz}$, 1H, HC⁵), 4.16 (d, $J = 9.5\ \text{Hz}$, 1H, HC²), 4.02 (ddd, $J = 12.7, 6.3, 1.1\ \text{Hz}$, 1H, H_bC⁷), 3.70 (d, $J = 16.1\ \text{Hz}$, 1H, H_aC³), 3.65 (dd, $J = 12.7, 8.9\ \text{Hz}$, 1H, H_aC⁷), 3.50 (dd, $J = 16.1, 9.5\ \text{Hz}$, 1H, H_bC³), 2.54 (ddd, $J = 15.4, 7.1, 6.3\ \text{Hz}$, 1H, H_aC⁶), 2.16 (dddd, $J = 15.4, 10.4, 8.9, 1.1\ \text{Hz}$, 1H, H_bC⁶). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.8$ (C21), 147.5 (C15), 141.0 (C8), 135.4 (C17), 131.0 (C19), 129.3 (C10,12), 128.7 (C11), 127.1 (C9,13), 121.9 (C14), 118.6 (C16), 117.7 (C18), 82.7 (C2), 67.5 (C7), 59.1 (C5), 54.1 (C3), 35.6 (C6). ^{15}N NMR (51 MHz, MeCN- d_3): $\delta = 99.9$ (N4), 63.0 (N20). HRMS (ESI, pos.): m/z calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 377.1166 found 377.1167. IR (DRIFT): $\bar{\nu} = 2950, 2864, 1719, 1617, 1483, 1452,$

1317, 1169, 1140, 751, 698 cm^{-1} . $[\alpha]_{\text{D}}^{24} = -64.1^\circ$ ($c = 0.00020\ \text{g mL}^{-1}$, MeCN).

Prepared from Wang-piperazine resin. Cleaved from 669 mg of resin **3a** (0.601 mmol g^{-1} , 0.402 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 72 : 28, the isolation only of the major C2 *R* epimer was performed. White amorphous solid (14.5 mg, 0.039 mmol, 10%). HPLC purity 99%. NMR: mixture with 2% of C2 *S* isomer. The analytical data (^1H and ^{13}C NMR, HRMS, IR (DRIFT) and $[\alpha]_{\text{D}}^{24}$) corresponded with **7a** prepared from Wang resin.

(-)-(2R,5S)-4-((2-Aminophenyl)sulfonyl)-2-phenyl-1,4-oxazepane-5-carboxamide **7b**^{2R}. Cleaved from 1000 mg of resin **3b** (0.225 mmol g^{-1} , 0.225 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 45 : 55, the isolation of C2 *R* epimer was performed. White amorphous solid (7.2 mg, 0.019 mmol, 9%). HPLC purity 99%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.70$ (dd, $J = 8.2, 1.5\ \text{Hz}$, 1H), 7.39 (ddd, $J = 8.4, 7.1, 1.5\ \text{Hz}$, 1H), 7.26–7.33 (m, 3H), 7.20–7.21 (m, 2H), 6.89 (dd, $J = 8.4, 1.1\ \text{Hz}$, 1H), 6.80 (ddd, $J = 8.2, 7.1, 1.1\ \text{Hz}$, 1H), 6.34 (br. s, 1H), 5.68 (br. s, 1H), 5.38 (br. s, 2H), 4.49 (ddd, $J = 10.8, 7.1, 1.0\ \text{Hz}$, 1H), 4.28 (dd, $J = 9.3, 1.2\ \text{Hz}$, 1H), 4.05 (ddd, $J = 12.9, 6.3, 1.5\ \text{Hz}$, 1H), 3.82 (ddd, $J = 16.2, 1.2\ \text{Hz}$, 1.2, 1H), 3.67 (ddd, $J = 12.9, 9.3, 1.0\ \text{Hz}$, 1H), 3.53 (dd, $J = 16.2, 9.6\ \text{Hz}$, 1H), 2.46 (dddd, $J = 15.7, 7.1, 6.3, 1.0\ \text{Hz}$, 1H), 2.21 (dddd, $J = 15.7, 10.8, 9.3, 1.5\ \text{Hz}$, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.2, 147.4, 140.9, 135.7, 131.1, 129.3, 128.7, 127.1, 121.7, 118.8, 118.1, 82.7, 67.4, 59.3, 54.7, 35.6$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 376.1326 found 376.1326. IR (DRIFT): $\bar{\nu} = 3447, 3352, 3205, 3062, 3030, 2952, 2864, 1675, 1616, 1483, 1452, 1318, 1301, 1140, 748, 698\ \text{cm}^{-1}$. $[\alpha]_{\text{D}}^{24} = -62.5^\circ$ ($c = 0.00024\ \text{g mL}^{-1}$, MeCN).

(+)-(2S,5S)-4-((2-Aminophenyl)sulfonyl)-2-phenyl-1,4-oxazepa-ne-5-carboxamide **7b**^{2S}. Cleaved from 1000 mg of resin **3b** (0.225 mmol g^{-1} , 0.225 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 45 : 55, the isolation of C2 *S* epimer was performed. White amorphous solid (3.2 mg, 0.009 mmol, 4%). HPLC purity 99%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.58$ (dd, $J = 8.1, 1.6\ \text{Hz}$, 1H, HC¹⁹), 7.35 (ddd, $J = 8.5, 7.2, 1.6\ \text{Hz}$, 1H, HC¹⁷), 7.28–7.32 (m, 2H, HC^{10,12}), 7.24–7.28 (m, 1H, HC¹¹), 7.17–7.20 (m, 2H, HC^{9,13}), 6.85 (dd, $J = 8.5, 1.1\ \text{Hz}$, 1H, HC¹⁶), 6.75 (br. s, 1H, H_bN22), 6.70 (ddd, $J = 8.2, 7.2, 1.1\ \text{Hz}$, 1H, HC¹⁸), 5.99 (br. s, 1H, H_aN22), 5.62 (br. s, 2H, HN²⁰), 4.64 (dd, $J = 8.7, 1.6\ \text{Hz}$, 1H, HC²), 4.59 (dd, $J = 4.5, 4.5\ \text{Hz}$, 1H, HC⁵), 3.94 (ddd, $J = 12.8, 4.5, 3.0\ \text{Hz}$, 1H, H_bC⁷), 3.78 (ddd, $J = 12.8, 11.0, 1.6\ \text{Hz}$, 1H, H_aC⁷), 3.63 (dd, $J = 14.2, 1.6\ \text{Hz}$, 1H, H_aC³), 3.43 (dd, $J = 14.2, 8.7\ \text{Hz}$, 1H, H_bC³), 2.30 (dddd, $J = 15.8, 4.5, 4.5, 1.6\ \text{Hz}$, 1H, H_aC⁶), 2.10 (dddd, $J = 15.8, 11.0, 4.5, 3.0\ \text{Hz}$, 1H, overlap with water, H_bC⁶). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.4$ (C21), 148.0 (C15), 141.9 (C8), 135.7 (C17), 131.3 (C19), 129.3 (C10,12), 128.6 (C11), 126.6 (C9,13), 119.1 (C14), 118.7 (C16), 117.5 (C18), 81.4 (C2), 67.0 (C7), 59.4 (C5), 56.8 (C3), 33.0 (C6). HRMS (ESI, pos.): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 376.1326 found 376.1325. IR (DRIFT): $\bar{\nu} = 3448, 3350, 3216, 3061, 3029, 2969, 2954, 2920, 1676, 1616, 1483, 1452, 1318, 1303, 1142, 752, 699\ \text{cm}^{-1}$. $[\alpha]_{\text{D}}^{24} = +271.4^\circ$ ($c = 0.00007\ \text{g mL}^{-1}$, MeCN).



(-)-(2*R*,5*S*)-4-((2-Amino-4-methoxyphenyl)sulfonyl)-2-phenyl-1,4-oxazepane-5-carboxylic acid **7e**. Cleaved from 606 mg of resin **3e** (0.381 mmol g⁻¹, 0.230 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 69 : 31, the isolation of major C2 *R* epimer was performed. White amorphous solid (20.1 mg, 0.050 mmol, 21%). HPLC purity 99%. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.58 (d, *J* = 8.9 Hz, 1H), 7.22–7.30 (m, 3H), 7.15–7.16 (m, 2H), 6.31–6.35 (m, 2H), 5.02 (br. s, 2H), 4.61 (dd, *J* = 10.9, 7.1 Hz, 1H), 4.20 (d, *J* = 9.5 Hz, 1H), 4.02 (ddd, *J* = 12.7, 6.4, 1.2 Hz, 1H), 3.76 (s, 3H), 3.58–3.39 (m, 2H), 3.50 (dd, *J* = 16.1, 9.5 Hz, 1H), 2.46–2.54 (m, 1H), 2.16 (dddd, *J* = 15.4, 10.9, 9.2, 1.2 Hz, 1H). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 175.8, 165.5, 149.5, 141.1, 133.1, 129.3, 128.6, 127.0, 114.3, 105.4, 101.5, 82.7, 67.6, 59.5, 56.1, 54.1, 35.7. HRMS (ESI, pos.): *m/z* calcd for C₁₉H₂₃N₂O₆S [M + H]⁺ 407.1271 found 407.1269. IR (DRIFT): $\bar{\nu}$ = 3469, 3370, 3228, 3029, 2939, 2864, 1736, 1725, 1605, 1450, 1303, 1133, 752, 699, 689 cm⁻¹. [α]_D²⁴ = -16.8° (*c* = 0.00030 g mL⁻¹, MeCN).

(-)-(2*R*,5*S*)-4-((2-Amino-4-chlorophenyl)sulfonyl)-2-phenyl-1,4-oxazepane-5-carboxylic acid **7f**^{2RS}. Cleaved from 658 mg of resin **3f** (0.381 mmol g⁻¹, 0.251 mmol of substrate). The inseparable mixture of C2 *R* : *S* diastereomers in a ratio of 70 : 30, the interpretation of major C2 *R* epimer was performed. White amorphous solid (21.0 mg, 0.051 mmol, 20%). HPLC purity 78%. NMR: mixture with 22% of C2 *S* isomer. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.71 (d, *J* = 8.5 Hz, 1H), 7.39 (s, 1H), 7.29–7.30 (m, 2H), 7.20–7.26 (m, 3H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.01 (br. s, 2H), 4.66 (dd, *J* = 10.3, 7.2 Hz, 1H), 4.41 (d, *J* = 9.6 Hz, 1H), 4.06 (ddd, *J* = 12.6, 6.3, 1.5 Hz, 1H), 3.71 (ddd, *J* = 12.6, 8.9, 1.0 Hz, 1H), 3.65 (d, *J* = 16.0 Hz, 1H), 3.46 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.51–2.60 (m, 1H), 2.19 (dddd, *J* = 15.6, 10.5, 8.9, 1.5 Hz, 1H). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 175.7, 151.0, 148.6, 141.0, 132.6, 129.3, 128.7, 127.0, 121.4, 119.8, 114.7, 82.9, 67.6, 59.4, 54.5, 35.7. HRMS (ESI, pos.): *m/z* calcd for C₁₈H₂₀ClN₂O₅S [M + H]⁺ 411.0776 found 411.0777. IR (DRIFT): $\bar{\nu}$ = 3303, 3064, 3029, 2970, 2950, 2868, 1736, 1727, 1587, 1450, 1317, 1292, 1163, 758, 699 cm⁻¹. [α]_D²⁴ = -17.3° (*c* = 0.00098 g mL⁻¹, MeCN).

(-)-(2*R*,5*S*)-4-((2-Aminophenyl)sulfonyl)-2-(2-fluorophenyl)-1,4-oxazepane-5-carboxylic acid **7i**^{2R}. Cleaved from 386 mg of resin **3i** (0.273 mmol g⁻¹, 0.105 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 29 : 71, the isolation of major C2 *R* epimer was performed. White amorphous solid (1.6 mg, 0.004 mmol, 4%). HPLC purity 94%. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.64 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.28–7.37 (m, 3H), 7.14 (ddd, *J* = 8.6, 7.5, 1.1 Hz, 1H), 7.06 (ddd, *J* = 10.6, 8.3, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.72 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.69 (dd, *J* = 10.1, 7.2 Hz, 1H), 4.64 (dd, *J* = 9.7, 0.9 Hz, 1H), 4.03 (ddd, *J* = 12.7, 6.4, 1.9 Hz, 1H), 3.85 (ddd, *J* = 15.8, 0.9, 0.9 Hz, 1H), 3.68 (ddd, *J* = 12.7, 8.9, 1.4 Hz, 1H), 3.55 (ddd, *J* = 15.8, 9.7 Hz, 1H), 2.54 (dddd, *J* = 15.6, 7.2, 6.4, 1.4 Hz, 1H, overlap with water), 2.19 (dddd, *J* = 15.6, 10.1, 8.9, 1.9 Hz, 1H). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 175.5, 160.4 (d, *J* = 243.2 Hz), 147.4, 135.3, 130.9, 130.6 (d, *J* = 9.1 Hz), 129.2, 129.2, 127.7 (d, *J* = 13.1 Hz), 125.3 (d, *J* = 3.0 Hz), 121.8, 117.7, 116.8 (d, *J* = 26.2 Hz), 76.9, 67.4, 58.4, 52.6, 35.4. HRMS

(ESI, pos.): *m/z* calcd for C₁₈H₂₀FN₂O₅S [M + H]⁺ 395.1071 found 395.1072. IR (DRIFT): $\bar{\nu}$ = 3462, 3372, 3214, 2926, 2867, 1724, 1617, 1567, 1483, 1453, 1317, 1142, 753 cm⁻¹. [α]_D²⁴ = -68.2° (*c* = 0.00011 g mL⁻¹, MeCN).

(-)-(2*S*,5*S*)-4-((2-Aminophenyl)sulfonyl)-2-(2-fluorophenyl)-1,4-oxazepane-5-carboxylic acid **7i**^{2S}. Cleaved from 386 mg of resin **3i** (0.273 mmol g⁻¹, 0.105 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 29 : 71, the isolation of C2 *R* epimer was performed. White amorphous solid (4.1 mg, 0.010 mmol, 10%). HPLC purity 93%. NMR: mixture with 7% of C2 *R* isomer. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H), 7.26–7.31 (m, 2H), 7.14 (ddd, *J* = 8.6, 7.5, 1.1 Hz, 1H), 7.02 (ddd, *J* = 10.6, 8.2, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.65 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.93 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.78 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.02 (ddd, *J* = 13.0, 3.8, 3.8 Hz, 1H), 3.78 (ddd, *J* = 13.0, 11.2, 2.0 Hz, 1H), 3.61 (dd, *J* = 13.8, 2.0 Hz, 1H), 3.43 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.37 (dddd, *J* = 15.6, 4.8, 3.8, 2.0 Hz, 1H), 2.24 (dddd, *J* = 15.6, 11.2, 4.8, 3.8 Hz, 1H). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 174.3, 159.9 (d, *J* = 244.2 Hz), 148.0, 135.3, 131.1, 130.5 (d, *J* = 8.1 Hz), 128.8, 128.7, 128.6 (d, *J* = 4.0 Hz), 125.4 (d, *J* = 3.0 Hz), 119.7, 117.1, 116.0 (d, *J* = 21.2 Hz), 76.0, 68.0, 59.9, 54.7, 33.8. HRMS (ESI, pos.): *m/z* calcd for C₁₈H₂₀FN₂O₅S [M + H]⁺ 395.1071 found 395.1072. IR (DRIFT): $\bar{\nu}$ = 3463, 3370, 2920, 2863, 1719, 1618, 1566, 1484, 1453, 1318, 1141, 753 cm⁻¹. [α]_D²⁴ = -93.0° (*c* = 0.00050 g mL⁻¹, MeCN).

(-)-(2*R*,5*S*)-4-((2-Aminophenyl)sulfonyl)-2-(3-fluorophenyl)-1,4-oxazepane-5-carboxylic acid **7k**. Cleaved from 600 mg of resin **3k** (0.353 mmol g⁻¹, 0.212 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 64 : 36, the isolation of major C2 *R* epimer was performed. White amorphous solid (8.5 mg, 0.022 mmol, 10%). HPLC purity 99%. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.68 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.29 (ddd, *J* = 7.9, 7.9, 6.0 Hz, 1H), 6.87–6.99 (m, 3H), 6.85 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.75 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 4.62 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.19 (d, *J* = 9.2 Hz, 1H), 4.02 (ddd, *J* = 12.6, 6.3, 1.1 Hz, 1H), 3.70 (ddd, *J* = 15.8, 1.1, 1.1 Hz, 1H), 3.65 (ddd, *J* = 12.6, 9.2, 0.7 Hz, 1H), 3.50 (dd, *J* = 16.2, 9.6 Hz, 1H), 2.45–2.56 (m, 1H), 2.15 (dddd, *J* = 15.8, 10.8, 9.2, 1.2 Hz, 1H). ¹³C{¹H} NMR (126 MHz, MeCN-*d*₃): δ = 175.4, 163.6 (d, *J* = 243.2 Hz), 147.5, 143.7 (d, *J* = 7.1 Hz), 135.4, 131.1 (d, *J* = 9.1 Hz), 131.0, 123.0 (d, *J* = 2.0 Hz), 121.8, 118.6, 117.6, 115.3 (d, *J* = 21.2 Hz), 113.8 (d, *J* = 23.2 Hz), 82.0, 67.6, 59.4, 54.0, 36.0. HRMS (ESI, pos.): *m/z* calcd for C₁₈H₂₀FN₂O₅S [M + H]⁺ 395.1071 found 395.1073. IR (DRIFT): $\bar{\nu}$ = 3469, 3371, 2932, 2867, 1719, 1616, 1566, 1482, 1450, 1318, 1137, 89, 785, 748, 688 cm⁻¹. [α]_D²⁴ = -25.7° (*c* = 0.00070 g mL⁻¹, MeCN).

(+)-(2*R*,5*S*)-4-((2-Aminophenyl)sulfonyl)-2-(*p*-tolyl)-1,4-oxazepane-5-carboxylic acid **7m**. Cleaved from 615 mg of resin **3m** (0.173 mmol g⁻¹, 0.168 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 77 : 23, the isolation of major C2 *R* epimer was performed. White amorphous solid (8.0 mg, 0.021 mmol, 19%). HPLC purity 99%. ¹H NMR (500 MHz, MeCN-*d*₃): δ = 7.66 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.85 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.75 (ddd, *J* =



8.1, 7.1, 1.0 Hz, 1H), 4.67 (dd, $J = 10.8, 7.1$ Hz, 1H), 4.14 (d, $J = 9.0$ Hz, 1H), 4.01 (ddd, $J = 12.7, 6.3, 1.5$ Hz, 1H), 3.69 (ddd, $J = 16.2, 1.0, 1.0$ Hz, 1H), 3.64 (ddd, $J = 12.7, 9.0, 1.0$ Hz, 1H), 3.49 (dd, $J = 16.2, 9.6$ Hz, 1H), 2.46–2.56 (m, 1H), 2.29 (s, 3H), 2.16 (dddd, $J = 15.6, 10.8, 9.0, 1.5$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.6, 147.5, 138.4, 138.1, 135.4, 131.0, 129.9, 127.0, 122.0, 118.6, 117.6, 82.6, 67.4, 59.1, 54.1, 35.6, 21.1$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 391.1322 found 391.1324. IR (DRIFT): $\bar{\nu} = 3460, 3368, 3211, 2950, 2865, 1719, 1617, 1599, 1483, 1452, 1317, 1169, 814, 748, 690$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = +34.8^\circ$ ($c = 0.00023$ g mL^{-1} , MeCN).

(+)-(2R,5S)-4-((2-Aminophenyl)sulfonyl)-2-(4-fluorophenyl)-1,4-oxazepane-5-carboxylic acid 7o. Cleaved from 618 mg of resin **3o** (0.261 mmol g^{-1} , 0.161 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 67 : 33, the isolation of major C2 *R* epimer was performed. Pale yellow amorphous solid (6.3 mg, 0.016 mmol, 10%). HPLC purity 99%. NMR: mixture with 6% of C2 *S* isomer ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.66$ (dd, $J = 8.1, 1.6$ Hz, 1H), 7.33 (ddd, $J = 8.4, 7.2, 1.6$ Hz, 1H), 7.14 (br. d, $J = 8.6$ Hz, 2H), 6.99 (br. d, $J = 8.9$ Hz, 2H), 6.84 (dd, $J = 8.2, 1.0$ Hz, 1H), 6.74 (ddd, $J = 8.1, 7.1, 1.0$ Hz, 1H), 4.58 (dd, $J = 10.8, 7.0$ Hz, 1H), 4.15 (d, $J = 9.3$ Hz, 1H), 3.99 (ddd, $J = 12.6, 6.3, 1.3$ Hz, 1H), 3.60–3.67 (m, 2H), 3.50 (dd, $J = 16.2, 9.6$ Hz, 1H), 2.44–2.55 (m, 1H), 2.14 (dddd, $J = 15.6, 10.8, 9.2, 1.3$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 176.2, 163.0$ (d, $J = 244.2$ Hz), 147.5, 137.2 (d, $J = 3.0$ Hz), 135.4, 131.0, 129.0 (d, $J = 9.1$ Hz), 121.9, 118.6, 117.5, 115.9 (d, $J = 21.2$ Hz), 81.9, 67.7, 59.9, 54.0, 35.7. HRMS (ESI, pos.): m/z calcd for $\text{C}_{18}\text{H}_{20}\text{FN}_2\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 395.1071 found 395.1073. IR (DRIFT): $\bar{\nu} = 3460, 3368, 3210, 2929, 2863, 1717, 1601, 1566, 1509, 1483, 1453, 1317, 1300, 1140, 834, 802, 748, 689$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = +35.3^\circ$ ($c = 0.00017$ g mL^{-1} , MeCN).

(-)-(2R,5S)-4-((2-Aminophenyl)sulfonyl)-2-(4-(trifluoromethyl)phenyl)-1,4-oxazepane-5-carboxylic acid 7q. Cleaved from 510 mg of resin **3q** (0.657 mmol g^{-1} , 0.335 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 61 : 39, the isolation of major C2 *R* epimer was performed. Yellow amorphous solid (8.3 mg, 0.017 mmol, 8%). HPLC purity 97%. NMR: mixture with 4% of C2 *S* isomer. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.77$ (dd, $J = 7.9, 1.3$ Hz, 1H), 7.63 (br. d, $J = 8.2$ Hz, 2H), 7.50–7.58 (m, 1H), 7.42 (d, $J = 8.2$ Hz, 1H), 7.39 (br. d, $J = 8.2$ Hz, 2H), 6.94–7.02 (m, 1H), 4.71 (dd, $J = 9.1, 7.2$ Hz, 1H), 4.41 (d, $J = 9.4$ Hz, 1H), 4.08 (ddd, $J = 12.6, 6.1, 0.9$ Hz, 1H), 3.76 (dd, $J = 16.2$ Hz, 1H), 3.74 (dd, $J = 12.6, 9.1$ Hz, 1H), 3.47 (dd, $J = 16.0, 9.4$ Hz, 1H), 2.51–2.63 (m, 1H), 2.13–2.25 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 174.3, 149.9, 145.2, 135.6, 130.7, 130.1$ (q, $J = 32.1$ Hz), 127.7, 126.2 (q, $J = 3.9$ Hz), 125.4 (q, $J = 272.0$ Hz), 123.2, 120.4, 115.3, 82.3, 67.5, 58.9, 54.1, 41.2, 35.5. HRMS (ESI, pos.): m/z calcd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_5\text{S} [\text{M} + \text{H}]^+$ 445.1040 found 445.1042. IR (DRIFT): $\bar{\nu} = 3320, 2937, 2871, 1731, 1597, 1459, 1323, 1164, 1149, 835, 758$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = -73.1^\circ$ ($c = 0.00039$ g mL^{-1} , MeCN).

(-)-(2R,5S)-4-((2-Aminophenyl)sulfonyl)-2-(thiophen-3-yl)-1,4-oxazepane-5-carboxylic acid 7t. Cleaved from 570 mg of resin **3t** (0.213 mmol g^{-1} , 0.121 mmol of substrate). The separable mixture of C2 *R* : *S* diastereomers in a ratio of 93 : 7, the isolation of major C2 *R* epimer was performed. White

amorphous solid (10.8 mg, 0.028 mmol, 22%). HPLC purity 98%. NMR: mixture with 2% of C2 *S* isomer. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.76$ (dd, $J = 7.8, 0.9$ Hz, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 8.3$ Hz, 1H), 7.32 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.15–7.18 (m, 1H), 6.94 (dd, $J = 5.0, 1.3$ Hz, 2H), 4.64 (dd, $J = 10.0, 7.3$ Hz, 1H), 4.46 (d, $J = 9.5$ Hz, 1H), 4.02 (ddd, $J = 12.7, 6.4, 1.5$ Hz, 1H), 3.74 (d, $J = 16.0$ Hz, 1H), 3.69 (ddd, $J = 12.7, 9.0, 1.0$ Hz, 1H), 3.49 (dd, $J = 16.0, 9.5$ Hz, 1H), 2.47–2.56 (m, 1H), 2.15 (dddd, $J = 15.6, 10.4, 9.0, 1.5$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 175.2, 150.0, 142.1, 135.5, 130.7, 127.0, 126.9, 123.0, 122.3, 120.2, 115.2, 79.3, 67.5, 59.3, 53.5, 35.7$. HRMS (ESI, neg.): m/z calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_5\text{S}_2 [\text{M} - \text{H}]^-$ 381.0573 found 381.0581. IR (DRIFT): $\bar{\nu} = 3297, 3102, 2950, 2864, 1720, 1596, 1458, 1317, 1293, 1216, 1147, 1030, 955, 758$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = -221.9^\circ$ ($c = 0.00029$ g mL^{-1} , MeCN).

(-)-(S)-3-(1,1-Dioxo-4-(*o*-tolyl)benzo[*f*][1,2,5]thiadiazepin-2(5*H*)-yl)dihydrofuran-2(3*H*)-one 9h. Cleaved from 592 mg of resin **3h** (0.521 mmol g^{-1} , 0.308 mmol of substrate). Pale yellow amorphous solid (21.6 mg, 0.058 mmol, 19%). HPLC purity 99%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.77$ (dd, $J = 8.0, 1.6$ Hz, 1H), 7.40 (ddd, $J = 8.3, 7.3, 1.6$ Hz, 1H), 7.34 (ddd, $J = 8.9, 7.3, 1.6$ Hz, 1H), 7.26–7.31 (m, 2H), 7.21–7.25 (m, 1H), 6.99 (dd, $J = 8.3, 0.9$ Hz, 1H), 6.91–6.97 (m, 2H), 4.94 (d, $J = 1.2$ Hz, 1H), 4.89 (dd, $J = 11.3, 8.8$ Hz, 1H), 4.35 (ddd, $J = 9.0, 9.0, 1.6$ Hz, 1H), 4.16 (ddd, $J = 10.8, 9.0, 6.1$ Hz, 1H), 2.39–2.48 (m, 1H), 2.38 (s, 3H), 2.05–2.12 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 173.9, 143.4, 140.3, 138.5, 136.6, 134.8, 131.3, 131.1, 130.5, 130.3, 128.3, 126.7, 120.9, 120.4, 101.4, 66.7, 58.6, 26.3, 19.5$. HRMS (ESI, neg.): m/z calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_4\text{S} [\text{M} - \text{H}]^-$ 369.0904 found 369.0909. IR (DRIFT): $\bar{\nu} = 3345, 3066, 3016, 2920, 1775, 1663, 1474, 1335, 1159, 750$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = -42.1^\circ$ ($c = 0.00063$ g mL^{-1} , MeCN).

(+)-(S)-((2-Aminophenyl)sulfonyl)-L-homoserine 10r. Cleaved from 503 mg of resin **3r** (0.657 mmol g^{-1} , 0.330 mmol of substrate). Pale yellow amorphous solid (45.6 mg, 0.166 mmol, 50%). HPLC purity 99%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.63$ (dd, $J = 8.0, 1.4$ Hz, 1H), 7.34 (ddd, $J = 8.3, 7.2, 1.4$ Hz, 1H), 6.85 (dd, $J = 8.23, 1.1$ Hz, 1H), 6.75 (ddd, $J = 8.0, 7.2, 1.1$ Hz, 1H), 6.09 (br. s, 1H), 5.27 (br. s, 2H), 4.23–4.30 (m, 1H), 4.05–4.14 (m, 2H), 2.27 (dddd, $J = 12.5, 8.6, 5.9, 1.2$ Hz, 1H), 1.96–2.05 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 175.2, 147.1, 135.4, 130.2, 121.6, 118.3, 117.6, 66.6, 52.5, 30.7$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_5\text{S} [\text{M} - \text{H}]^-$ 273.0540 found 273.0546. IR (DRIFT): $\bar{\nu} = 3476, 3375, 3261, 1770, 1619, 1482, 1453, 1318, 754$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = +5.8^\circ$ ($c = 0.00119$ g mL^{-1} , MeCN).

Cyclization to benzothiadiazepine 1,1-dioxide 9j. The crude residue **8j** was dissolved in CH_2Cl_2 (3.8 mL) and TFA (200 μL , 5%) was added. The reaction mixture was shaken for 24 h at room temperature. Then it was evaporated to dryness using a stream of nitrogen. The product was purified by semi-preparative RP-HPLC.

(-)-(S)-3-(4-(2-Bromophenyl)-1,1-dioxobenzof[1,2,5]thiadiazepin-2(5*H*)-yl)dihydrofuran-2(3*H*)-one 9j. Cleaved from 589 mg of resin **3j** (0.521 mmol g^{-1} , 0.307 mmol of substrate). Pale yellow amorphous solid (16.8 mg, 0.039 mmol, 13%). HPLC purity 98%. ^1H NMR (500 MHz, MeCN- d_3): $\delta = 7.78$ (dd, $J = 8.0, 1.6$ Hz, 1H), 7.68 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.48 (dd, $J = 7.6,$



1.9 Hz, 1H), 7.40–7.45 (m, 2H), 7.35 (ddd, $J = 8.0, 7.4, 1.9$ Hz, 1H), 7.02 (br. s, 1H), 7.00 (dd, $J = 8.3, 0.9$ Hz, 1H), 6.97 (ddd, $J = 8.0, 7.4, 0.9$ Hz, 1H), 5.00 (d, $J = 1.2$ Hz, 1H), 4.91 (dd, $J = 11.5, 9.0$ Hz, 1H), 4.35 (ddd, $J = 10.4, 9.0, 1.4$ Hz, 1H), 4.15 (ddd, $J = 10.9, 9.0, 6.1$ Hz, 1H), 2.47–2.58 (m, 1H), 2.06 (dddd, $J = 12.4, 8.8, 6.1, 1.4$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, MeCN- d_3): $\delta = 173.7, 142.4, 140.2, 137.5, 134.9, 134.0, 132.8, 132.1, 131.2, 128.7, 128.5, 124.1, 120.9, 120.8, 102.7, 66.7, 58.7, 26.2$. HRMS (ESI, pos.): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{BrN}_2\text{O}_4\text{S} [\text{M} + \text{H}]^+$ 435.0009 found 435.0011. IR (DRIFT): $\bar{\nu} = 3349, 2921, 2851, 1776, 1662, 1594, 1475, 1338, 1162, 751$ cm^{-1} . $[\alpha]_{\text{D}}^{24} = -51.7^\circ$ ($c = 0.00029$ g mL^{-1} , MeCN).

Conflicts of interest

There are no conflicts to declare.

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