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Synthesis of a small library of non-symmetric cyclic sulfamide HIV-1 protease inhibitors

Anna Ax [a], Advait A. Joshi [a], Kristina M. Orrling [a], Lotta Vrang [b], Bertil Samuelsson [b], Anders Hallberg [a], Anders Karlén [a], Mats Larhed [a,*]

[a] Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala University, BMC, Box 574, SE-751 23 Uppsala, Sweden
[b] Medivir AB, Lunastigen 7, SE-141 44 Huddinge, Sweden

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ABSTRACT

A set of 11 non-symmetric cyclic sulfamide HIV-1 protease inhibitors were synthesized and evaluated. The use of a key microwave-assisted silver(I) oxide mediated selective mono N-benzylation reaction enabled fast and straightforward synthesis. The K_i values of the new inhibitors ranged between 0.28 μM and >20 μM.

1. Introduction

HIV/AIDS has become a major challenge for mankind to deal with. The testimony to this fact is provided by the latest report by WHO/UNAIDS, which states that the number of people living with HIV has escalated to 33.4 million and 7400 people get infected everyday.[1] As an outcome of extensive research to arrest the pandemic, combination therapies using HIV-1 nucleoside reverse transcriptase inhibitors and HIV-1 protease inhibitors have been launched to ensure a decline in HIV/AIDS related mortality. However, gradual resistance towards the marketed HIV inhibitors is leading to a failure of antiretroviral therapy.[1] Hence, there is a constant need of novel HIV-1 inhibitors to combat the disease.

In the quest of discovering novel HIV-1 protease inhibitors, Lam and co-workers reported the potent urea-based cyclic compounds with four side-chains.[2] With an aim of introducing further structural diversity and improving potency, we modified the water mimicking urea group in Lam's compounds to a sulfamide group.[3] This enabled us to develop a series of moderately active (K_i values of 0.53–9.7 μM) symmetric cyclic sulfamide based HIV-1 protease inhibitors with biaryl side-chains designed to span from P2/P2′ to P1/P1′ (Fig. 1, **A**).[4] Furthermore, di-*ortho*-extension using a flexible three atom amide tether furnished a highly active inhibitor (Fig. 1, **B**) with a K_i value of 20 nM.[5] Molecular modelling suggested a difference in the occupation of the S1 and S1′ sub-sites and it was shown that non-symmetric inhibitors might exhibit good activity despite reduced molecular weight (Fig. 1, **C**).[5] Thus, we embarked upon a study of a class of P2/P2′ non-symmetric *ortho*-decorated

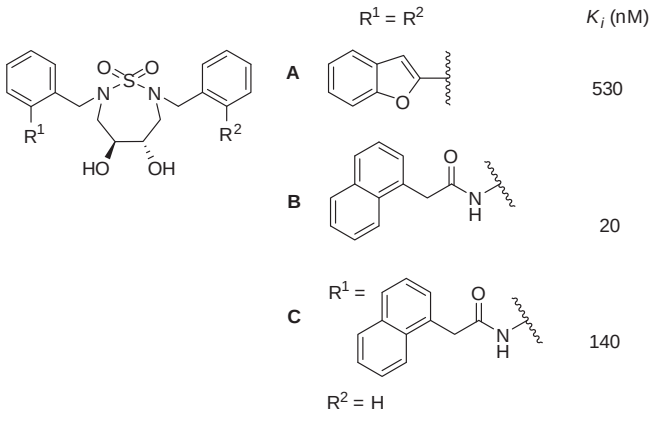

Figure 1. Symmetric and non-symmetric cyclic sulfamide based HIV-1 protease inhibitors.

* Corresponding author. Tel.: +46 18 471 4667; fax: +46 18 471 4474; e-mail address: mats.larhed@orgfarm.uu.se (M. Larhed).

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cyclic *N*-benzylsulfamide based HIV-1 protease inhibitors. To enable smooth compound production, a selective and fast route to three *N*-monobenzylated sulfamide key intermediates would be highly beneficial.

Controlled microwave (MW) heating using sequential single-mode reactors has had a profound impact on drug discovery chemistry.[6–8] Controlled MW radiation has proven to be a powerful tool for both speeding up chemical optimizations and for efficient preparation of new target compounds, enabling facile synthesis of small chemical libraries. Raising the reaction temperature well above that applied in conventional heating of a specific reaction may, however, lead to reduced selectivity between competing reaction routes.[9–11]

We herein report the use of a microwave-promoted silver(I) oxide mediated mono N-benzylation procedure as a key step for preparation of three seven-membered *N*-monobenzylated sulfamide core structures **2a**–**c** from the parent structure **1**. Based on this synthetic methodology, a small library of 11 non-symmetric novel cyclic HIV-1 protease inhibitors (**3a**–**k**) were synthesized and evaluated.

2. Results and discussion

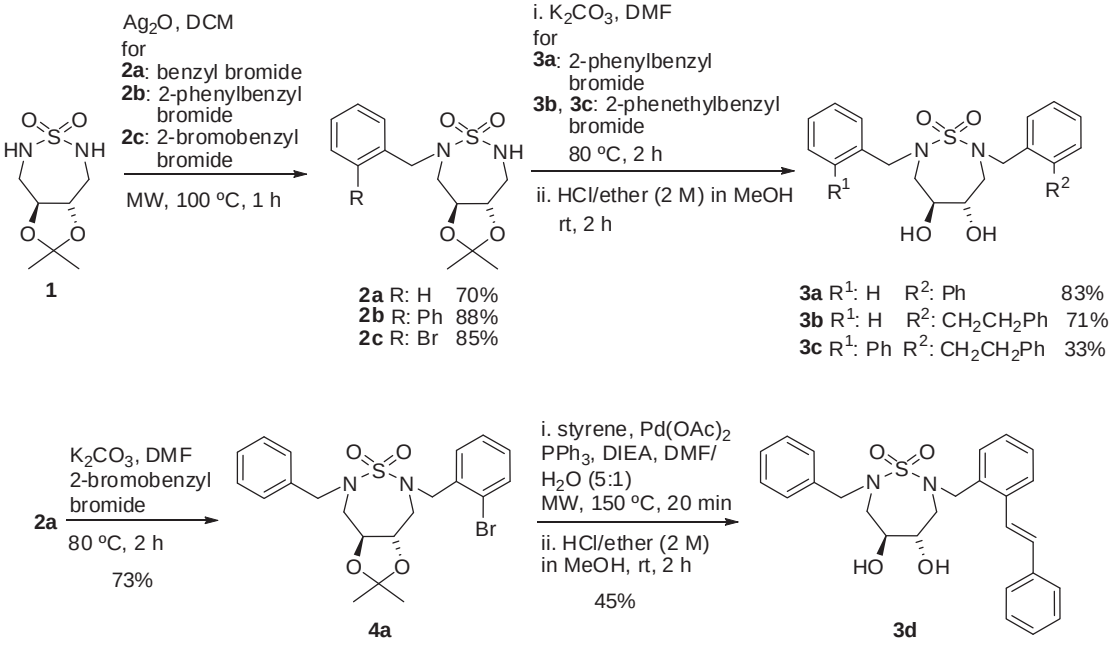
The seven-membered cyclic scaffold **1**, prepared as previously reported,[4] served as the starting point for the synthesis of compounds **3a**–**k**, as depicted in Schemes 1 and 2. The alkylating reactant 2-phenethylbenzyl bromide was synthesized from 2-phenethylbenzyl alcohol using phosphorus tribromide.[12] Selective mono N-alkylations of **1** to afford compounds **2a**,[5] **2b** and **2c** were performed using 1.5 equiv of silver(I) oxide and either benzyl bromide, 2-phenylbenzyl bromide or 2-bromobenzyl bromide (Scheme 1).

to deliver **3a** and **3b** in 83% and 71% yields, respectively. Intermediate **2b** was reacted with 2-phenethylbenzyl bromide and the product was deprotected using HCl/ether (2 M) to afford **3c** in 33% yield. The non-symmetrically alkylated sulfonamide **4a** was prepared by alkylating **2a** with 2-bromobenzyl bromide using potassium carbonate in DMF in 73% yield. Intermediate **4a** was *ortho*-substituted with styrene using a microwave-promoted palladium (0)-catalyzed Heck reaction[13] followed by deprotection to generate **3d** in 45% yield. Compound **2c** was *N*-benzylated in the same fashion as **2a** to give dialkylated **4b** and **4c** in 74% and 73% yields, respectively (Scheme 2).

The bromo derivatives **4b** and **4c** were subjected to microwave mediated Heck couplings[13] with styrene (150 °C, 20 min), followed by deprotection (2 M HCl/ether) to afford compounds **3e** and **3f** in 14% and 54% isolated yields, respectively. Compound **2d** was produced in 85% yield from **2c** via a Negishi-coupling[14] with benzylzinc bromide (oil bath, 80 °C, 64 h). Intermediate **2d** served as the precursor for the synthesis of **3g**, **3h** and **3i**, which were obtained via benzylation with the corresponding alkylating agent and subsequent deprotection to afford the final inhibitors in 49%, 72% and 26% yields, respectively (Scheme 2). Inhibitor **3j** was prepared in 20% yield from **2d**, through an alkylation with 2-bromobenzyl bromide followed by a microwave-assisted Heck coupling–deprotection sequence.

HIV-1 protease inhibitor **3k** was synthesized by alkylating **2c** with *N*-[2-(bromomethyl)phenyl]-2-(naphthalen-1-yl)acetamide **8** (44% yield) followed by deprotection with 2 M HCl/ether in MeOH (64% yield, Scheme 3).

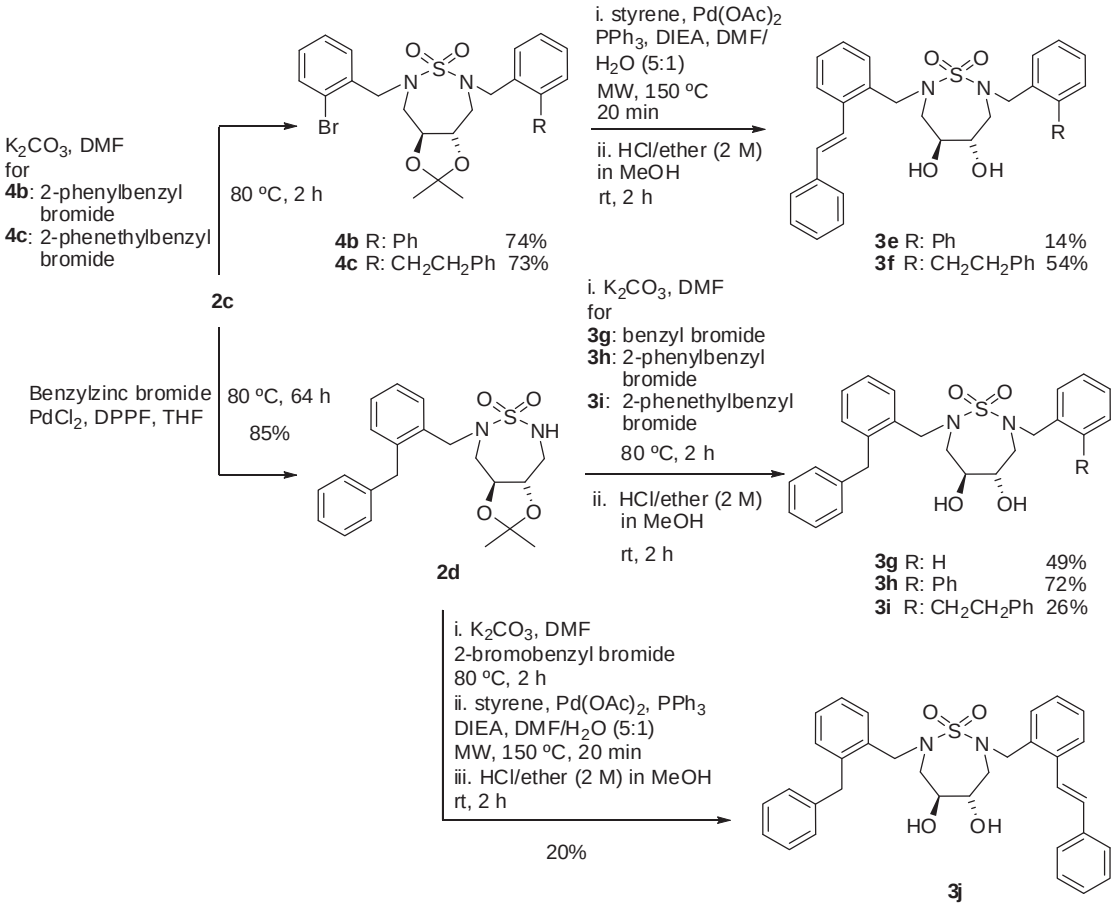
Building block **8** was prepared by coupling **6** (obtained by TBS protection of 2-aminobenzyl alcohol **5** in 91% isolated yield)[15] with 1-naphthaleneacetic acid in presence of EDCI, HOBt and *N*-methylmorpholine to provide amide **7** (83%), which was then depro-



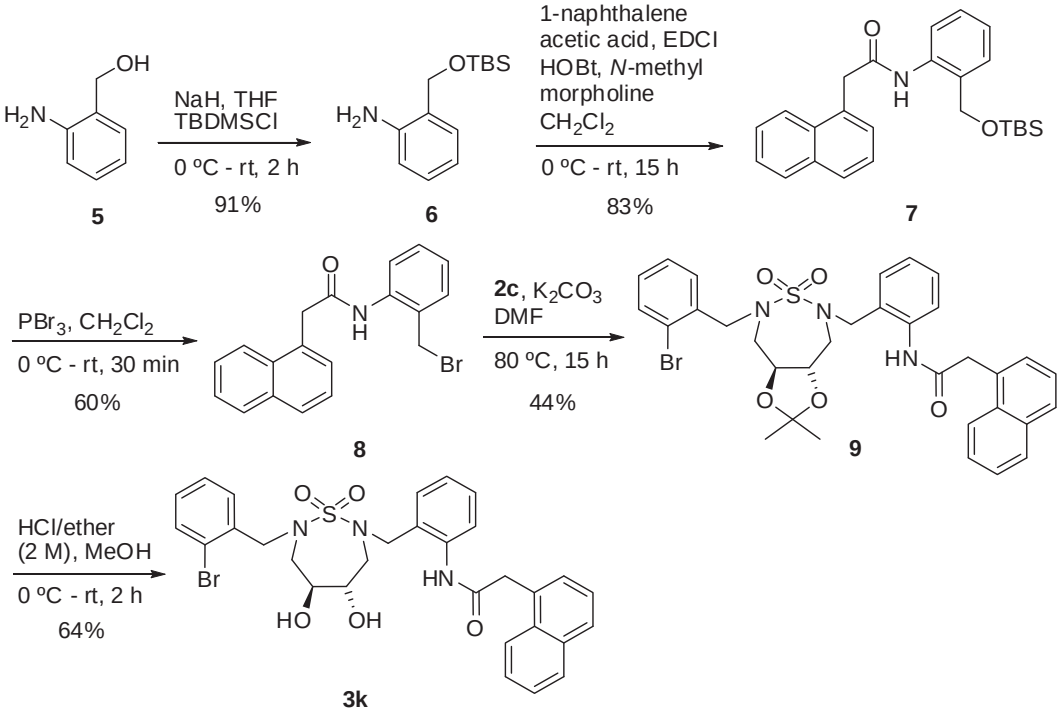
Scheme 1. Synthesis of HIV-1 protease inhibitors **3a**–**d**.

The reactions were heated by single-mode microwave irradiation in a sealed vessel to 100 °C for 1 h, yielding a ratio of mono-/dibenzylation of >95:5. Monofunctionalized **2a** was thereafter alkylated with either 2-phenylbenzyl bromide or 2-phenethylbenzyl bromide using potassium carbonate in DMF, and the resulting products were directly deprotected using HCl/ether (2 M)

tected and brominated in a one-pot fashion using phosphorous tribromide (yield: 60%). Buchwald amidation reaction using Pd $(OAc)_2$, Xantphos and caesium carbonate in THF to further decorate inhibitor **3k** did not succeed.[16,17] Moreover, Buchwald amidation using the aforementioned conditions proved to be unsuccessful on the protected intermediate **9** as well. Interestingly, the reaction

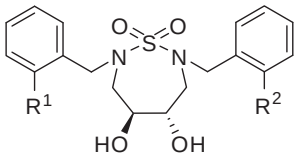


Scheme 2. Synthesis of HIV-1 protease inhibitors **3e**–**j**.



Scheme 3. Synthesis of HIV-1 protease inhibitor **3k**.

Table 1
Inhibitory potency of non-symmetric cyclic sulfamide based HIV-1 protease inhibitors **3a**–**k**



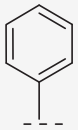
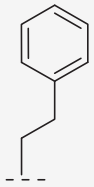
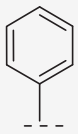
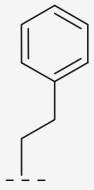
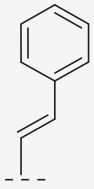
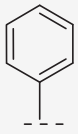
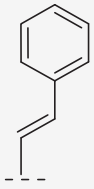
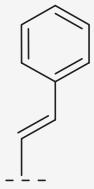
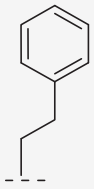
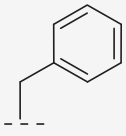
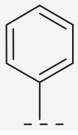
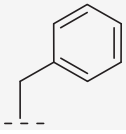
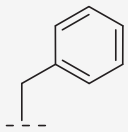
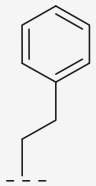
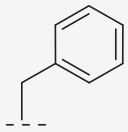
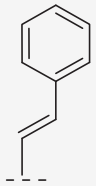
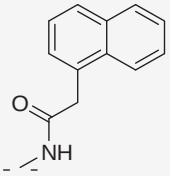
Inhibitor	R^1	R^2	K_i (μM)
3a			>20
3b			>20
3c			9.3
3d			>20
3e			4.9
3f			>20
3g			>20
3h			6.3

Table 1 (*continued*)

Inhibitor	R^1	R^2	K_i (μM)
3i			7.5
3j			1.8
3k	Br		0.28
Saquinavir	—	—	0.0002[18]

worked very well with full conversion when the same set of conditions was applied to model substrates (indole-3-acetamide and 2-bromotoluene). We speculate that the reason the amidation reaction failed in the case of **3k** and **9** might be attributable to trapping of the palladium catalyst by the substrate. The fact that the starting materials (**3k** and **9**) were recovered in more than 80% yield after the reaction supports this theory. The inhibitory activities of compounds **3a**–**k** and the approved inhibitor Saquinavir[18] are summarized in Table 1.

The four mono-substituted compounds (**3a**, **3b**, **3d**, **3g**) and compound **3f** were found to be inactive (K_i >20 μM). The remaining compounds showed moderate inhibitory activity with K_i values between 1.8 μM and 9.3 μM, except for the three atom *ortho*-elongated aryl bromide **3k**, which gave a K_i value of 0.28 μM. The best of the P2/P2′ group *ortho* substituent appeared to be the naphthyl acetamide group, as in **3k**. Taken together, all the non-symmetric compounds, except **3j** and **3k**, were less potent than the previously published symmetrically substituted compounds.[4] This indicated that incorporating non-symmetry around the cyclic sulfamide core **1** was not always beneficial for improving activity. However, careful selection of substituents to impart non-symmetry was equally important.

The mono N-benzylation of **1** was the key transformation to provide non-symmetric inhibitors **3a**–**k** (Scheme 1). The mono-/dibenzylation quotient was remarkably improved by addition of silver(I) oxide to the reaction mixture, yielding an impressive ratio of >95:5. Successful application of this reaction in the preparation of **2b** and **2c** suggests a more general scope of the methodology. Most likely, coordination of silver(I) to the sulfamide functionality of **1** results in the high chemoselectivity. Unfortunately, the selective mono N-benzylation reaction did not work with cyclic ureas because of competing O-benzylation (unpublished findings). Interestingly, silver(I) oxide has also been successfully applied for the selective monoprotection of symmetric diols.[19]

3. Conclusion

In summary, a series of non-symmetric cyclic sulfamide HIV-1 protease inhibitors with elongated *ortho*-P2/P2′ substituents were

synthesized by employing a selective microwave-assisted and silver mediated N-monobenzylation reaction and different palladium (0)-catalyzed coupling reactions. The ratio between mono- and dibenzylation in the selective N-alkylation was >95:5 after 100 °C microwave heating for 1 h. Out of 11 inhibitors, the most potent compound (**3k**) possessed a K_i value of 0.28 μM.

4. Experimental

4.1. General information

The microwave reactions were performed in an Emrys Synthesizer single-mode cavity producing controlled irradiation at 2450 MHz. The reaction temperature and pressure were determined using the built-in on-line sensors. Fourier transform infrared spectroscopy was performed by Varian 1000 FT-IR (Scimitar Series) apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 399.8 and 100.6 MHz, respectively. Chemical shifts are reported as δ values (ppm) indirectly referred to TMS by the solvent or the solvent residual signal. Elemental analyses were performed by Analytische Laboratorium Lindlar, Germany and were within ±0.4% of calculated values. Melting points were determined using Electrothermal melting point apparatus. All column chromatography purifications were performed with silica gel 60. Analytical RP-LC/MS was performed on a Gilson HPLC system with a Chromolith Performance RP-18e, 4.6×100 mm column, with an electrospray ionization quadropole mass spectrometer at a flow rate of 4 mL/min (H_2O/CH_3CN/0.05% HCOOH). A metal block was used for conventional heating.

4.2. HIV-1 protease inhibition

HIV-1 protease was cloned and heterologously expressed in *Escherichia coli* and purified as described previously.[20] The K_i values for the synthesized compounds were determined using a fluorometric assay.[20] In all assays, Saquinavir was used as a reference compound (K_i=0.0002 μM).[18]

4.3. General procedure for selective mono alkylation

Cyclic sulfamide scaffold **1** (0.225 mmol, 1 equiv), silver(I) oxide (78.2 mg, 0.337 mmol, 1.5 equiv) and benzyl bromide (41 μL, 0.225 mmol, 1 equiv) were added to a 2.0–5.0 mL microwave reaction vial and dissolved in 3 mL of dichloromethane. The reaction mixture was heated to 100 °C for 1 h using microwave irradiation. The reaction mixture was filtered using a centrifuge tube equipped with a filter and concentrated in vacuo. The crude product was purified by column chromatography. The selectivity for mono-/dibenzylation was >95:5 according to RP-LC/MS and ^{1}H NMR.

*4.3.1. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-4,5-O-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (**2a**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 3:7. Yield 49 mg (70%) as a pale coloured oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.40 (s, 3H), 3.07 (m, 2H), 3.47 (dd, J=13.6, 4.3 Hz, 1H), 3.59 (ddd, J=3.9, 4.7, 12.5 Hz, 1H), 4.14 (m, 2H), 4.28 (d, J=14.5 Hz, 1H), 4.40 (d, J=14.5 Hz, 1H), 4.69 (s, 1H), 7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9, 43.6, 48.1, 54.3, 77.4, 78.1, 109.6, 128.1, 128.3, 128.8, 135.7. Anal. Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.83; H, 6.45; N, 8.97. Found: C, 54.12; H, 6.36; N, 9.11.

*4.3.2. 3,4,5,6-Tetrahydro-(4S,5S)-2-[(2-phenyl)benzyl]-4,5-O-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (**2b**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 2:8. Yield 77 mg (88%) as a pale coloured oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.32 (s, 3H), 2.88 (m, 2H), 3.26 (dd, J=4.3, 13.4 Hz, 1H), 3.43 (m, 1H), 3.88 (m, 2H), 4.02 (m, 1H), 4.24 (d, J=14.7 Hz, 1H), 4.51 (d, J=14.7 Hz, 1H), 7.27 (m, 1H), 7.31 (m, 1H), 7.34–7.48 (m, 6H), 7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 26.9, 43.6, 47.4, 51.3, 77.4, 77.9, 109.5, 127.4, 127.9, 128.1, 128.4, 129.3, 129.4, 130.4, 132.9, 140.7, 142.0. Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21. Found: C, 62.02; H, 6.3; N, 7.33.

*4.3.3. 3,4,5,6-Tetrahydro-(4S,5S)-2-(2-bromobenzyl)- 4,5-O-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (**2c**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 3:7. Yield 75 mg (85%) as a white solid; mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (m, 3H), 1.37 (m, 3H), 3.08 (ddd, J=7.0, 9.5, 12.8 Hz, 1H), 3.15 (ddd, J=0.6, 9.4, 13.6 Hz, 1H), 3.50 (dd, J=4.2, 13.6 Hz, 1H), 3.59 (ddd, J=3.9, 4.7, 12.8 Hz, 1H), 4.22–4.32 (m, 2H), 4.46 (d, J=16.0 Hz, 1H), 4.51 (d, J=16.0 Hz, 1H), 6.72 (br m, 1H), 7.26 (ddd, J=1.7, 7.4, 8.0 Hz, 1H), 7.44 (ddd, J=1.2, 7.4, 7.8 Hz, 1H), 7.56 (dd, J=1.7, 7.8 Hz, 1H), 7.62 (dd, J=1.2, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 26.6, 43.5, 49.4, 54.0, 77.8, 78.7, 109.2, 128.2, 128.3, 129.6, 130.0, 132.9, 136.5. Anal. Calcd for $C_{14}H_{19}BrN_2O_4S$: C, 42.98; H, 4.89; N, 7.16. Found: C, 43.30; H, 5.04; N, 7.19.

4.4. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-4,5-*O*-isopropylidene-2-(2-phenylmethyl)benzyl-1,2,7-thiadiazepine 1,1-dioxide (2d)

In an oven-dried vial were placed **2c** (89 mg, 0.227 mmol), palladium chloride (2.8 mg, 0.0159 mmol), DPPF (3.8 mg, 6.81 μmol) and THF (2 mL), which was capped and then flushed with nitrogen gas. After a few minutes, benzylzinc bromide (2.27 mL, 1.133 mmol) was added to the reaction mixture and the vial was heated to 80 °C for 64 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate/*iso*-hexane 3:7) to yield 78 mg (85%) as a white solid; mp 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.29 (s, 3H), 2.78 (m, 2H), 3.16 (dd, J=4.2, 13.4 Hz, 1H), 3.45 (ddd, J=3.9, 5.4, 12.5 Hz, 1H), 3.72 (dm, J=3.9 Hz, 1H), 3.98 (m, 1H), 4.01 (d, J=16.0 Hz, 1H), 4.07 (s, 1H), 4.08 (d, J=16.0 Hz, 1H), 4.20 (d, J=14.0 Hz, 1H), 4.29 (d, J=14.0 Hz, 1H), 7.03 (m, 2H), 7.13 (m, 2H), 7.18–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 26.9, 38.3, 43.4, 47.4, 51.9, 76.9, 78.1, 109.6, 126.1, 127.0, 128.4, 128.5, 130.4, 131.7, 133.5, 139.1, 140.9. Anal. Calcd for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96. Found: C, 62.91; H, 6.61; N, 7.00.

4.5. General procedure for standard benzylation and subsequent deprotection

The sulfamide precursor (0.101 mmol, 1 equiv), substituted benzyl bromide (26.4 mg, 0.106 mmol, 1.05 equiv) and K_2CO_3 (141 mg, 1.01 mmol, 10 equiv) were added to a reaction vial and dissolved in 3 mL of DMF. Thereafter, the vial was capped and the reaction mixture was heated to 80 °C for 2 h. The reaction mixture was concentrated in vacuo, using toluene as a co-solvent. The residue was filtered through a short silica column using ethyl acetate and concentrated under reduced pressure. The resulting crude dialkylated product was dissolved in 5 mL of methanol and 1.5 mL of 2 M HCl/ether was added. The reaction mixture was stirred at room temperature for 2 h. After concentration in vacuo the crude product was purified by column chromatography.

*4.5.1. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-4,5-dihydroxy-7-[(2-phenyl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3a**).* Column chromatography was performed in methanol/dichloromethane 1:99. Yield 75 mg (83%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6 and D_2O): δ 2.94 (dd, J=3.1, 14.8 Hz, 1H), 3.03 (dd, J=3.4, 15.2 Hz, 1H), 3.18 (ddd, J=1.1, 10.0, 15.2 Hz, 1H), 3.28 (ddd, J=1.1, 10.0, 14.8 Hz, 1H), 3.35 (m, 1H), 3.50 (m, 1H), 4.42 (d, J=3.04 Hz, 1H), 4.47 (d, J=3.04 Hz, 1H), 4.62 (d, J=7.50 Hz, 1H), 4.67 (d, J=7.50 Hz, 1H), 7.18–7.48 (m, 13H), 7.64 (d, J=0.8, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 48.3,

48.6, 50.5, 52.8, 72.5, 72.7, 127.8, 128.1, 128.4, 128.5, 128.9, 129.1, 129.7, 130.5, 135.2, 138.2, 141.2, 142.4. Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.94; H, 6.14; N, 6.47.

*4.5.2. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-4,5-dihydroxy-7-[(2-phenethyl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3b**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 23.5 mg (71%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.84–3.08 (m, 8H), 3.14 (m, 2H), 3.32 (m, 2H), 3.63 (m, 2H), 4.55 (d, J=16.1 Hz, 2H), 4.59 (d, J=16.1 Hz, 2H), 4.70 (d, J=15.3 Hz, 2H), 4.72 (d, J=15.3 Hz, 2H), 7.18–7.20 (m, 1H), 7.25–7.31 (m, 8H), 7.34–7.41 (m, 2H), 7.45–7.47 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 35.0, 38.1, 48.5, 48.8, 50.5, 53.2, 73.0, 73.2, 126.7, 127.2, 128.3, 128.6, 128.9, 129.1, 129.4, 129.7, 130.7, 135.5, 138.5, 141.3, 142.6. Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.21; H, 6.36; N, 6.06.

*4.5.3. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-2-[(2-phenyl)benzyl]-7-[(2-phenethyl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3c**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 33.4 mg (33%) as a white solid; mp 44–46 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.84–3.10 (m, 6H), 3.23 (dd, J=9.5, 14.9 Hz, 1H), 3.29 (dd, J=9.8, 15.1 Hz, 1H), 3.44 (m, 1H), 3.55 (m, 1H), 4.20 (d, J=3.7 Hz, 1H), 4.24 (d, J=4.4 Hz, 1H), 4.52 (d, J=16.4 Hz, 1H), 4.58 (d, J=15.7 Hz, 1H), 4.70 (d, J=15.7 Hz, 1H), 4.72 (d, J=16.4 Hz, 1H), 7.18–7.30 (m, 9H), 7.34–7.42 (m, 4H), 7.43–7.50 (m, 4H), 7.71 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 35.0, 38.0, 48.3, 49.0, 50.4, 51.0, 72.9, 73.0, 126.7, 127.1, 128.1, 128.5, 128.6, 128.7, 129.1, 129.2, 129.4, 129.7, 130.0, 130.7, 130.8, 135.4, 135.5, 141.2, 141.5, 142.6, 142.7. Anal. Calcd for $C_{32}H_{34}N_2O_4S$: C, 70.82; H, 6.31; N, 5.16. Found: C, 70.59; H, 6.48; N, 5.28.

*4.5.4. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-7-[(2-bromo)benzyl]-4,5-O-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (**4a**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 3:7. Yield 35.7 mg (73%) as a pale coloured oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.27 (s, 3H), 3.02 (dd, J=9.2, 12.8 Hz, 1H), 3.11 (dd, J=9.1, 12.9 Hz, 1H), 3.46 (dd, J=4.5, 12.8 Hz, 1H), 3.50 (dd, J=4.5, 12.9 Hz, 1H), 4.24 (m, 2H), 4.36 (d, J=14.7 Hz, 1H), 4.49 (d, J=14.68 Hz, 1H), 4.50 (d, J=15.32 Hz, 1H), 4.59 (d, J=15.32 Hz, 1H), 7.18 (m, 1H), 7.29–7.39 (m, 6H), 7.54 (dd, J=1.7, 7.7 Hz, 1H) 7.57 (dd, J=1.3, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9 (corresponds to both methyl groups according to HSQC), 48.3, 49.0, 54.5, 55.2, 77.4, 77.6, 109.8, 123.5, 127.9, 128.1 128.4, 128.8, 129.4, 130.1, 132.9, 135.2, 135.9. Anal. Calcd for $C_{21}H_{25}BrN_2O_4S$: C, 52.39; H, 5.23; N, 5.82. Found: C, 52.52; H, 5.42; N, 5.79.

*4.5.5. 3,4,5,6-Tetrahydro-(4S,5S)-2-[(2-bromo)benzyl]-4,5-O-isopropylidene-2-(2-phenyl)benzyl-1,2,7-thiadiazepine 1,1-dioxide (**4b**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 3:7. Yield 35 mg (74%) as a pale coloured oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.29 (s, 3H), 2.78 (m, 1H), 3.16 (dd, J=4.2, 13.4 Hz, 1H), 3.45 (ddd, J=3.9, 5.4, 12.5 Hz, 1H), 3.72 (dm, J=3.9 Hz, 1H), 3.98 (m, 1H), 4.01 (d, J=16.0 Hz, 1H), 4.07 (s, 1H), 4.08 (d, J=16.0 Hz, 1H), 4.20 (d, J=14.0 Hz, 1H), 4.29 (d, J=14.0 Hz, 1H), 7.03 (m, 4H), 7.13 (m, 4H), 7.18–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 26.9, 38.3, 43.4, 47.4, 51.9, 76.9, 78.1, 109.6, 126.1, 127.4, 127.7, 127.8, 127.9, 128.4, 128.8, 129.2, 129.4, 130.1, 130.2, 132.9, 133.5, 139.1, 140.9. Anal. Calcd for $C_{27}H_{29}BrN_2O_4S$: C, 58.17; H, 5.24; N, 5.02. Found: C, 58.37; H, 5.32; N, 5.14.

*4.5.6. 3,4,5,6-Tetrahydro-(4S,5S)-2-[(2-bromo)benzyl]-7-[(2-phenethyl)benzyl]-4,5-O-isopropylidene-1,2,7-thiadiazepine 1,1-dioxide (**4c**).* Column chromatography was performed in ethyl acetate/*iso*-hexane 3:7. Yield 33.6 mg (73%) as a pale coloured oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.40 (s, 3H), 2.85–3.03 (m, 5H), 3.07 (dd, J=9.0, 12.6 Hz, 1H), 3.34 (dd, J=4.1, 13.2 Hz, 1H), 3.58 (dd, J=5.0, 12.6 Hz, 1H), 4.19–4.34 (m, 4H), 4.49 (d, J=15.3 Hz, 1H), 4.62 (d, J=15.3 Hz, 1H), 7.14–7.38 (m, 11H), 7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 26.9, 34.2, 37.6, 47.6, 49.2, 51.7, 55.1, 76.7, 76.9, 77.9, 109.8, 123.5, 126.0, 126.5, 127.9, 128.3, 128.6, 129.4, 129.7, 130.1, 130.2, 132.9, 133.0, 135.3, 140.8, 141.3. Anal. Calcd for $C_{29}H_{33}BrN_2O_4S$: C, 59.49; H, 5.68; N, 4.78. Found: C, 59.32; H, 5.84; N, 4.84.

*4.5.7. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-4,5-dihydroxy-7-[(2-phenylmethyl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3g**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 18.3 mg (49%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.09 (dd, J=3.1, 14.9 Hz, 1H), 3.15 (dd, J=3.3, 15.1 Hz, 1H), 3.30 (dd, J=3.1, 9.5 Hz, 1H), 3.34 (dd, J=3.3, 9.7 Hz, 1H), 3.54 (m, 1H), 3.62 (m, 1H), 4.16 (m, 3H), 4.25 (d, J=4.6 Hz, 1H), 4.53 (d, J=16.0 Hz, 1H), 4.58 (d, J=15.5 Hz, 1H), 4.68 (d, J=15.5 Hz, 1H), 4.69 (d, J=16.0 Hz, 1H), 7.20 (m, 4H), 7.30 (m, 5H), 7.38 (m, 2H), 7.44 (m, 2H), 7.54 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 38.7, 48.6, 48.7, 50.6, 53.2, 73.0, 73.2, 126.9, 127.5, 128.4, 128.6, 128.9, 129.3, 129.4, 129.6, 129.8, 131.5, 135.9, 138.5, 140.3, 141.4. Anal. Calcd for $C_{25}H_{28}N_2O_4S$: C, 66.35; H, 6.24; N, 6.19. Found: C, 66.13; H, 6.20; N, 6.13.

*4.5.8. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-2-[(2-phenyl)benzyl]-7-[(2-phenylmethyl)benzyl]-1,2,7-thiadiazepane 1,1-dioxide (**3h**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 15.2 mg (72%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.0 (m, 2H), 3.24 (m, 2H), 3.43 (m, 2H), 4.14 (s, 2H), 4.59 (d, J=16.6 Hz, 1H), 4.54 (d, J=15.8 Hz, 1H), 4.64 (d, J=15.8 Hz, 1H), 4.70 (d, J=16.6 Hz, 1H), 7.14–7.32 (m, 9H), 7.33–7.51 (m, 8H), 7.78 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 38.0, 47.7, 48.3, 49.9, 50.3, 72.1, 72.2, 126.2, 126.9, 127.4, 127.5, 127.9, 128.0, 128.1, 128.6, 129.0, 129.1, 129.3, 130.2, 130.8, 134.8, 135.2, 139.7, 140.7, 140.9, 142.1. Anal. Calcd for $C_{31}H_{32}N_2O_4S$: C, 70.43; H, 6.10; N, 5.30. Found: C, 70.69; H, 6.23; N, 5.42.

*4.5.9. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-2-[(2-phenethyl)-benzyl]-7-(2-phenylmethyl)]benzyl-1,2,7-thiadiazepane 1,1-dioxide (**3i**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 7.2 mg (26%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.8–3.0 (m, 2H), 3.05 (m, 2H), 3.12 (m, 2H), 3.33 (m, 2H), 3.62 (m, 2H), 4.17 (s, 2H), 4.24 (d, J=4.3 Hz, 1H), 4.31 (d, J=4.3 Hz, 1H), 4.59 (d, J=15.6 Hz, 1H), 4.60 (d, J=15.6 Hz, 1H), 4.69 (d, J=15.6 Hz, 1H), 4.47 (d, J=15.6 Hz, 1H), 7.16–7.33 (m, 16H), 7.48 (m, 1H), 7.54 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 35.0, 38.1, 38.7, 48.5, 48.6, 50.6, 50.7, 73.1, 73.2, 126.7, 126.9, 127.2, 127.5, 128.6, 129.1, 129.3, 129.5, 129.6, 129.7, 129.8, 130.7, 131.5, 135.4, 135.9, 140.4, 141.3, 141.4, 142.6. Anal. Calcd for $C_{33}H_{36}N_2O_4S$: C, 71.20; H, 6.52; N, 5.03. Found: C, 71.44; H, 6.54; N, 5.16.

4.6. General procedure for Heck coupling and subsequent deprotection

The sulfamide precursor (0.067 mmol, 1 equiv), styrene (76.9 μL, 0.671 mmol, 10 equiv), $Pd(OAc)_2$ (1.5 mg, 6.71 μmol, 0.1 equiv), PPh_3 (5.3 mg, 0.020 mmol, 0.3 equiv) and DIEA (71.9 μL, 0.403 mmol, 6 equiv) were added to a 0.5–2.0 mL microwave reaction vial and dissolved in 1 mL of DMF and 200 μL of water. The reaction mixture was heated to 150 °C for 20 min using microwave irradiation. The reaction mixture was filtered to remove palladium black and concentrated in vacuo, using toluene as a co-solvent. The crude product was filtered through a short silica column before proceeding with the deprotection.

*4.6.1. 3,4,5,6-Tetrahydro-(4S,5S)-2-benzyl-4,5-dihydroxy-7-[(2-styryl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3d**).* Column chromatography was performed in methanol/dichloromethane 2:98.

Yield 13.9 mg (45%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.01 (dd, J=3.78, 15.0 Hz, 1H), 3.12 (m, 1H), 3.29–3.42 (m, 3H), 3.56 (m, 1H), 4.17 (m, 2H), 4.50 (d, J=16.0 Hz, 1H), 4.60 (d, J=15.0 Hz, 1H), 4.74 (d, J=16.0 Hz, 1H), 4.92 (d, J=15.0 Hz, 1H), 7.21 (d, J=16.4 Hz, 1H), 7.23–7.53 (m, 11H), 7.72 (d, J=8.2 Hz, 2H), 7.80 (d, J=16.4 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 48.6, 48.7, 51.2, 52.9, 73.1, 73.3, 126.0, 126.5, 127.8, 128.4, 128.5, 128.6, 128.7, 129.3, 129.4, 129.5, 131.2, 131.7, 134.9, 137.9, 138.4, 138.5. Anal. Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.22; H, 6.07; N, 6.03. Found: C, 67.08; H, 5.84; N, 6.15.

*4.6.2. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-7-[(2-phenyl)benzyl]-2-[(2-styryl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3e**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 7.4 mg (14%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.82 (m, 2H), 3.05 (m, 1H), 3.27 (m, 4H), 4.10 (s, 2H), 4.43 (d, J=16.50 Hz, 1H), 4.54 (d, J=14.8 Hz, 1H), 4.74 (d, J=16.5 Hz, 1H), 4.90 (d, J=14.8 Hz, 1H), 7.18–7.50 (m, 13H), 7.68–7.85 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6): δ 47.9, 48.1, 50.0, 50.6, 72.2, 72.6, 125.4, 125.8, 127.2, 127.4, 127.5, 127.8, 127.9, 128.0, 128.5, 128.6, 128.8, 129.3, 130.2, 130.6, 131.0, 134.2, 134.7, 137.2, 137.8, 140.9, 142.1. Anal. Calcd for $C_{32}H_{32}N_2O_4S\cdot\frac{1}{2}H_2O$: C, 71.09; H, 5.97; N, 5.18. Found: 70.89; H, 6.13; N, 5.07.

*4.6.3. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-7-[(2-phenethyl)benzyl]-2-[(2-styryl)benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3f**).* Column chromatography was performed in methanol/dichloromethane 2:98. Yield 13.4 mg (54%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.84–3.20 (m, 6H), 3.36 (m, 3H), 3.62 (m, 1H), 4.18 (s, 1H), 4.19 (s, 1H), 4.57 (d, J=15.4 Hz, 1H), 4.61 (d, J=14.6 Hz, 1H), 4.79 (d, J=15.4 Hz, 1H), 4.94 (d, J=14.6 Hz, 1H), 7.16–7.55 (m, 13H), 7.72–7.86 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6): δ 34.4, 37.4, 47.8, 47.9, 49.8. 50.7, 72.3, 72.8, 125.4, 125.8, 126.1, 126.5, 127.2, 127.8, 127.9, 127.9, 128.4, 128.6, 128.8, 128.8, 128.9, 130.0, 130.6, 131.0, 134.2, 134.7, 137.3, 137.9 140.6, 142.0. Anal. Calcd for $C_{34}H_{36}N_2O_4S$: C, 71.80; H, 6.38; N, 4.93. Found: C, 71.59; H, 6.49; N, 4.68.

*4.6.4. 3,4,5,6-Tetrahydro-(4S,5S)-4,5-dihydroxy-2-[(2-phenylmethyl) benzyl]-7-[(2-styryl)-benzyl]-1,2,7-thiadiazepine 1,1-dioxide (**3j**).* Column chromatography was performed in methanol/dichloromethane 1:99. Yield 11 mg (20%) as a pale coloured oil; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.94 (dd, J=3.3, 14.9 Hz, 1H), 3.12 (m, 1H), 3.28–3.42 (m, 3H), 3.48 (m, 1H), 4.14 (m, 4H), 4.56 (d, J=16.2 Hz, 1H), 4.59 (d, J=14.7 Hz, 1H), 4.71 (d, J=16.2 Hz, 1H), 4.91 (d, J=14.7 Hz, 1H), 7.15–7.42 (m, 12H), 7.51 (m, 2H), 7.71–7.84 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6): δ 38.7, 48.5, 48.6, 50.5, 51.3, 72.9, 73.3, 126.1, 126.5, 126.9, 127.6, 127.9, 128.5, 128.6, 129.3, 129.5, 129.6, 131.2, 131.5, 131.7, 134.8, 135.9, 137.9, 138.5, 140.3, 141.3. Anal. Calcd for $C_{33}H_{34}N_2O_4S$: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.12; H, 5.98; N, 4.92.

4.7. 2-[(*tert*-Butyldimethylsilyloxy)methyl]aniline (6)

To a cooled (0 °C), stirred suspension of NaH (60% dispersion in mineral oil, 2.3 g, 58.1 mmol) in anhydrous THF (10 mL) was added dropwise a solution of 2-aminobenzyl alcohol **5** (6.5 g, 52.8 mmol) in anhydrous THF (15 mL) and the mixture was stirred at 0 °C for 15 min under nitrogen atmosphere. To this was added dropwise a solution of *tert*-butyldimethylsilyl chloride (9.5 g, 63.3 mmol) in anhydrous THF (15 mL) and the reaction mixture was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and crushed ice was carefully added to quench the reaction. This was extracted with EtOAc (3×20 mL) and the combined extracts were washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/*iso*-hexane 0:100 to 10:90) to yield the title compound (11 g, 91%) as a dark yellow, viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.83 (s, 9H), 4.07 (br s, 2H), 4.61 (s, 2H), 6.57–6.64 (m, 2H), 6.94–7.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 23.5, 31.1, 70.1, 120.9, 123.1, 130.5, 133.6, 133.9, 151.4; MS (ESI) m/z 238.2 $(M+1)^+$.

4.8. *N*-[2-{((*tert*-Butyldimethylsilyloxy)methyl)phenyl}]-(naphthalen-1-yl)acetamide (7)

To a cooled (0 °C) suspension of 1-naphthaleneacetic acid (3.5 g, 18.8 mmol), **6** (5.8 g, 24.4 mmol) and HOBt (2.9 g, 19.0 mmol) in anhydrous DCM (50 mL) was added *N*-methylmorpholine (4.8 g, 47.4 mmol) and stirred for 30 min under nitrogen atmosphere. To this was added EDCI (5 g, 26 mmol) at 0 °C and the reaction mixture was gradually warmed to room temperature and stirred for 15 h. The reaction mixture was successively washed with water (2×20 mL), brine (2×20 mL) and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/*iso*-hexane 5:95 to 20:80) to yield the title compound (6 g, 83%) as a light yellow solid; mp 84–86 °C; IR (film) ν 3048, 2873, 2853, 1649, 1588, 1539, 1456, 1392, 1347, 1289, 1253, 1112, 1070, 971, 937, 836, 671, 568, 530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.87 (s, 9H), 4.31 (s, 2H), 4.35 (s, 2H), 7.11–7.15 (m, 2H), 7.36–7.41 (m, 1H), 7.56–7.67 (m, 4H), 7.94–8.02 (m, 2H), 8.22 (d, J=8 Hz, 2H), 8.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 23.4, 31.0, 48.5, 69.5, 127.5, 129.1, 129.2, 130.9, 131.3, 131.9, 133.1, 133.4, 133.7, 133.8, 134.0, 135.2, 136.2, 137.4, 139.2, 142.3, 174. 6; MS (ESI) m/z 406.4 $(M+1)^+$. HRMS calcd for m/z $C_{25}H_{31}NO_2Si+H^+$: 406.2202, found: 406.2182. Anal. Calcd for $C_{25}H_{31}NO_2Si$: C, 74.03; H, 7.70; N, 3.45. Found: C, 74.32; H, 7.91; N, 3.34.

4.9. *N*-[2-(Bromomethyl)phenyl]-2-(naphthalen-1-yl)-acetamide (8)

To a cooled (0 °C) solution of **7** (5.8 g, 14.3 mmol) in anhydrous DCM (20 mL) was added dropwise phosphorous tribromide (7.7 g, 28.6 mmol) under nitrogen atmosphere and stirred for 10 min. The cooling source was removed and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and neutralized with saturated $NaHCO_3$ solution. The reaction mixture was successively washed with water (2×10 mL), brine (2×10 mL) and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was triturated with *iso*-hexane (3×15 mL) and dried under vacuum to yield the title compound as a light yellow solid (3 g, 60%); mp 130–132 °C; IR (film) ν 3251, 1659, 1586, 1524, 1452, 1343, 1191, 871, 703, 606, 528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 2H), 4.20 (s, 2H), 6.93–7.03 (m, 2H), 7.21–7.29 (m, 2H), 7.43–7.51 (m, 4H), 7.79–7.87 (m, 3H), 7.97–8.0 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 43.2, 123.8, 124.4, 125.5, 126.2, 126.6, 127.3, 128.5, 129.3, 129.4, 129.5, 129.9, 130.1, 130.4, 132.3, 134.6, 136.2, 169.6; MS (ESI) m/z 354.2 $(M)^+$, 356.2 $(M+2)^+$. HRMS calcd for m/z $C_{19}H_{16}BrNO+H^+$: 354.0484, found: 354.0483. Anal. Calcd for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55; N, 3.95. Found: C, 64.06; H, 4.67; N, 4.09.

4.10. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-(2-bromobenzyl)-7-[(2-naphthyl)-acetamidobenzyl]-4,5-*O*-isopropylidene-1,2,7-thiadiazepine-1,1-dioxide (9)

To a solution of **2c** (67 mg, 0.17 mmol) in anhydrous DMF (3 mL) was added anhydrous, powdered K_2CO_3 (36 mg, 0.26 mmol) and the resulting suspension was stirred at 50 °C for 20 min. To this was added **8** (73 mg, 0.21 mmol) and the reaction mixture was stirred at 80 °C for 15 h under nitrogen atmosphere. Water was added to the reaction mixture and it was extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/*iso*-hexane 10:40 to 50:50) to

yield the title compound (50 mg, 44%) as a white solid; mp 72–74 °C; IR (film) ν 3373, 2984, 1689, 1591, 1519, 1449, 1333, 1230, 1152, 1090, 910, 869, 779, 728, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, J=4.4 Hz, 6H), 2.92–3.03 (m, 2H), 3.28 (dd, J=4, 13.6 Hz, 1H), 3.52 (dd, J=4.8, 12.4 Hz, 1H), 4.14–4.23 (m, 6H), 4.46 (d, J=15.2 Hz, 1H), 4.59 (d, J=15.2 Hz, 1H), 6.99–7.54 (m, 10H), 7.70 (d, J=8 Hz, 1H), 7.77 (d, J=8 Hz, 1H), 7.95 (d, J=8 Hz, 1H), 8.13 (d, J=8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 42.4, 47.5, 49.6, 52.0, 55.6, 76.9, 110.2, 123.8, 123.9, 124.4, 124.7, 125.9, 126.1, 126.6, 128.2, 128.3, 128.5, 128.9, 129.8, 129.9, 130.4, 130.9, 131.6, 132.5, 133.4, 134.1, 135.1, 137.4, 170.1; MS (ESI) m/z 664.5 $(M)^+$, 666.5 $(M+2)^+$. HRMS calcd for m/z $C_{33}H_{34}BrN_3O_5S+H^+$: 664.1481, found: 664.1470. Anal. Calcd for $C_{33}H_{34}BrN_3O_5S$: C, 59.64; H, 5.16; N, 6.32. Found: C, 59.78; H, 5.42; N, 6.02.

4.11. 3,4,5,6-Tetrahydro-(4*S*,5*S*)-2-[2-{2-(2-naphthyl)-acetamido}-benzyl]-7-(2-bromobenzyl)-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (3k)

To a cooled (0 °C) solution of **9** in MeOH (1 mL) was added a solution of HCl (2 M in diethyl ether, 4 mL). The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were removed under reduced pressure and the residue was taken up in water, neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc (2×10 mL). The combined extracts were washed with brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (methanol/dichloromethane 5:95) yielded the title compound (30 mg, 64%) as a pale coloured oil; IR (film) ν 3331, 1662, 1591, 1513, 1441, 1332, 1296, 1233, 1153, 1100, 1023, 954, 903, 874, 785, 750, 628, 524 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 3.21–3.43 (m, 6H), 3.67–3.71 (m, 1H), 4.29 (s, 2H), 4.53 (d, J=15.6 Hz, 1H), 4.70 (d, J=16.8 Hz, 2H), 4.89 (d, J=16.8 Hz, 1H), 7.14–7.65 (m, 11H), 7.82–7.93 (m, 3H), 8.29 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 41.4, 48.4, 48.5, 49.6, 52.9, 71.9, 72.8, 122.8, 123.7, 123.9, 124.6, 124.9, 125.7, 125.9, 126.4, 127.8, 128.3, 128.7, 128.8, 129.4, 129.6, 130.2, 132.5, 132.8, 133.1, 134.2, 136.6, 137.3, 137.4, 169.5; MS (ESI) m/z 624.4 $(M)^+$, 626.4 $(M+2)^+$. Anal. Calcd for $C_{30}H_{30}BrN_3O_5S$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.44; H, 5.07; N, 6.51.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.023.

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