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Synthesis of functionally diverse bicyclic sulfonamides as constrained proline analogues and application to the design of potential thrombin inhibitors

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Dedicated to Professor K. C. Nicolaou, chemist extraordinaire, and master molecule builder, wishing him the best in chemistry and in life

Abstract—Bicyclic sulfonamides were synthesized from 4-alkenyl *N*-alkenylsulfonyl L-prolines using a ring-closure metathesis reaction. Three types of bicyclic sulfonamides varying in the size of the second ring (5,5; 5,6; 5,7) were synthesized. A sulfonamide counterpart of an indolizidinone 2-carboxylic acid was synthesized and evaluated for its activity against the enzyme thrombin.

1. Introduction

The acyclic sulfonamide group has been extensively used as a surrogate for an amide function in the design of peptidomimetic structures.[1] Indeed, the sulfonamide group can be considered as a transition state isostere for proteases.[2,3] A large number of such replacements can be found in the synthesis of potential enzyme inhibitors and antagonists with widespread applications in pharmaceutical research.[4] Cyclic sulfonamides (sultams) can be considered to be the functional analogues of the corresponding lactam structures.[5] Their incorporation in peptidic motifs can lead to conformational restriction in that substructure similar to the corresponding lactams. Although cyclic sulfonamides, including aromatic variants, are not found in nature, a recently introduced drug for the treatment of glaucoma (brinzolamide, Azopt),[6] incorporates such a functionality as a bicyclic thiophene analogue. Cyclic sulfonamides have also found applications as agrochemicals,[7] and as potential chemotherapeutic agents.[8]

Monocyclic and polycyclic sultams can be prepared by a variety of methods relying on intramolecular cyclizations.[9] The advent of the ring-closure metathesis reaction[10] especially utilizing the Grubbs catalysts,[11] has considerably facilitated the synthesis of such sultams, and expanded the scope of their applications. A variety of monocyclic sulfonamides can be accessed in excellent yields with the first generation Grubbs catalyst (benzylidene-bis(tricyclohexylphosphine) dichlororuthenium).[12] To the best of our knowledge, bicyclic enantiopure and functionalized sulfonamides have not been reported utilizing a direct ring-closure metathesis reaction. A route to oligomeric bicyclic sulfonamides has been recently reported via a ring-opening metathesis reaction.[13] We describe herein the synthesis of diversely functionalized bicyclic sulfonamides as constrained proline analogues. We also report on a sulfonamide surrogate of an indolizidinone 2-carboxylic acid patterned after a low nanomolar prototypical thrombin inhibitor.[14,15]

2. Results and discussion

The known 4-*cis*-(2-propenyl)-*N*-Boc-L-proline benzyl ester[16] **3** was treated with trifluoroacetic acid, then with ethenesulfonyl chloride prepared from 2-chloroethylsulfonyl chloride and triethylamine,[17] to give **5** in excellent overall yield. Treatment of **5** under the conditions of ring-closure metathesis with the first generation Grubbs catalyst **A**[11] gave the bicyclic sulfonamide **6** albeit in 22% yield only. Hydrogenation afforded the corresponding carboxylic acid **7**. When the catalyst was changed to the more reactive second generation version **B**, and the cyclization conducted on the 2-TBDPS ether analogue **10**, the corresponding bicyclic sulfonamide **11** was obtained in 79% yield. Its structure was determined unambiguously by a single crystal X-ray analysis. Cleavage of the TBDPS group afforded the corresponding alcohol **12**.

The synthesis of the 6-membered homologue is shown in

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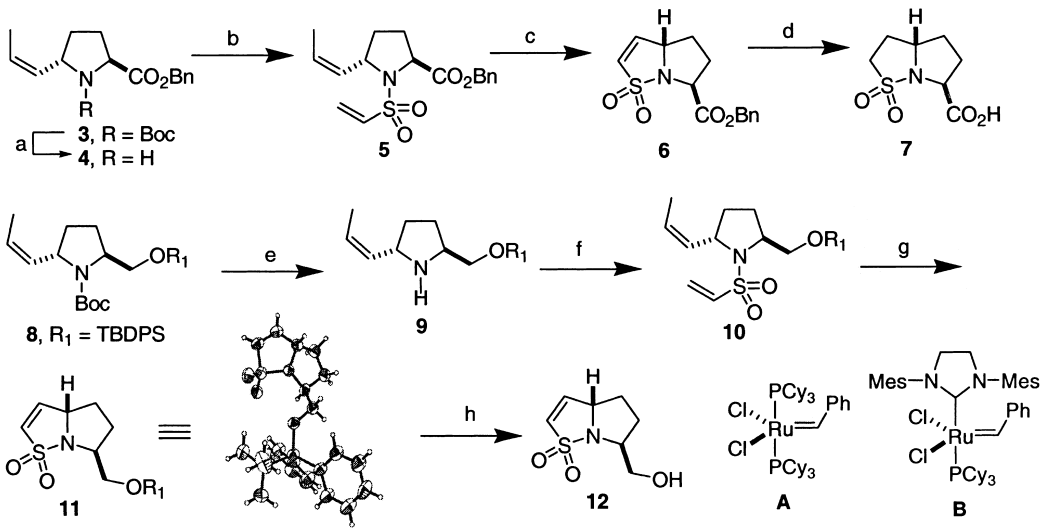
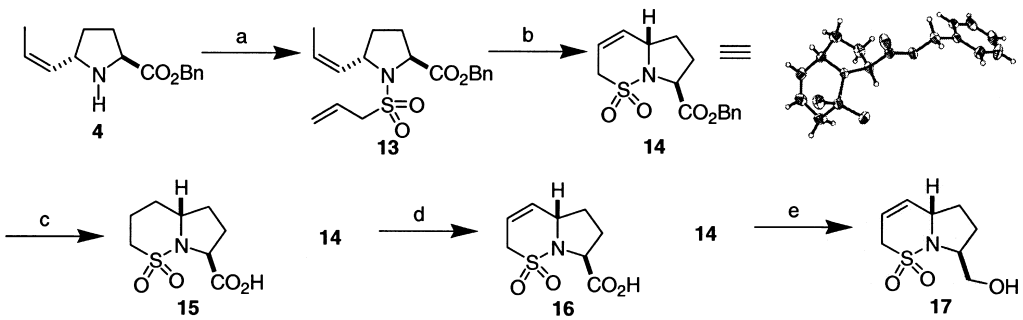


Scheme 1. *Reagents and conditions*: (a) TFA, CH_2Cl_2, 89%; (b) ethenesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C to rt, 81%; (c) **A**, 6 mol%, reflux, 48 h, 22%; (d) H_2, Pd/C, MeOH, 48 h, 74%; (e) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 94%; (f) ethenesulfonyl chloride, Et_3N, Ch_2Cl_2, 0°C to rt, 47%; (g) **B**, 5 mol%, toluene, reflux, 48 h, 79%; (h) TBAF, THF, 57%.

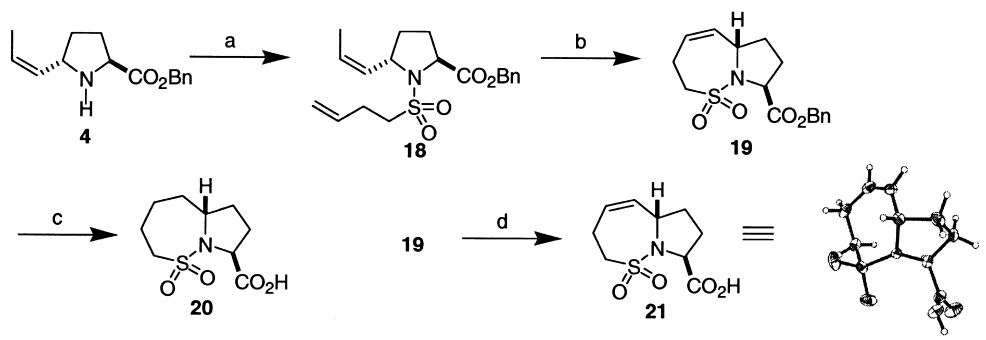
Scheme 2. Thus, *N*-sulfonylation of **4** afforded **13** which was subjected to ring-closure metathesis with reagent **A** to give **14** in quantitative yield. The structure and position of the double bond was unequivocally determined by single crystal X-ray analysis. Hydrogenation led to the carboxylic acid **15**. It was also possible to cleave the benzyl ester selectively using conditions of catalytic transfer hydrogenation to afford the acid **16**. Reduction of the benzyl ester group in **14** gave the alcohol **17**.

The 7-membered analogue of **16** was prepared using the same protocol as shown in Scheme 3. Thus, ring-closure metathesis of **18** afforded the bicyclic sulfonamide **19** in excellent yield, which upon hydrogenation gave the saturated acid **20**. Compound **19** could be converted to the corresponding free acid **21** by treatment with LiOH in this case without affecting the double bond, as confirmed by a single crystal X-ray structure.

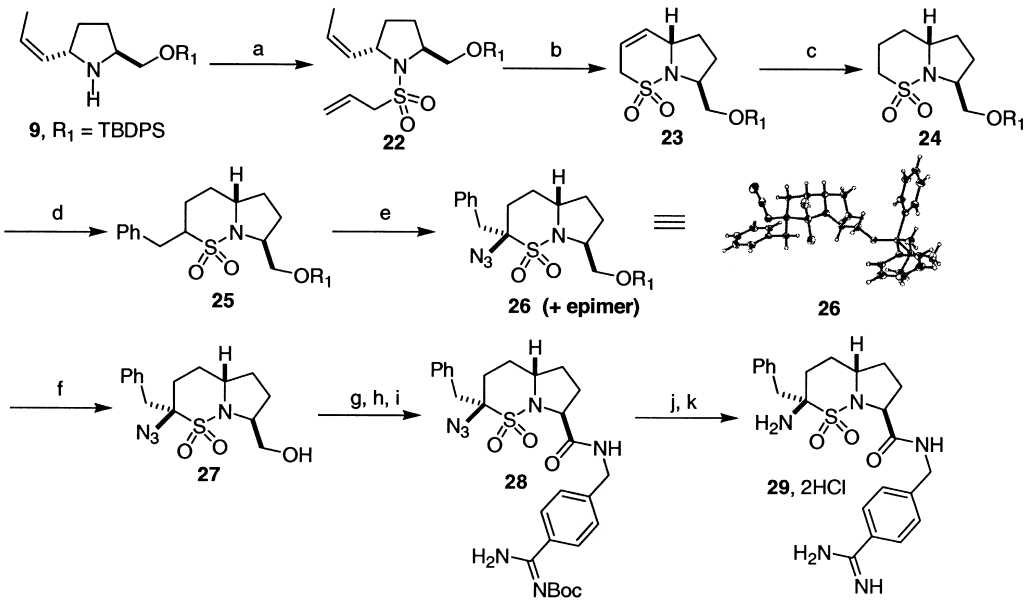
A noteworthy feature in the three bicyclic sulfonamide products obtained by ring-closure metathesis in Schemes 1–3 is the disposition of the double bond which does not migrate from its original position in the six and seven-membered ring systems. The X-ray crystal structures show



Scheme 2. *Reagents and conditions*: (a) prop-2-ene-1-sulfonyl chloride, Et_3N, CH_2Cl_2, 0°C, 63%; (b) **A**, 3 mol%, CH_2Cl_2, 3 h, 98%; (c) H_2, Pd/C, MeOH/EtOAc, 1 h, 99%; (d) cyclohexadiene, Pd/C, EtOAc, 6 h, 90%; (e) DiBAL-H, THF/toluene, −78°C to rt, 1.5 h, 85%.



Scheme 3. *Reagents and conditions*: (a) but-3-ene-1-sulfonyl chloride, Et_3N, CH_2Cl_2, 0°C, 1 h, 55%; (b) **A**, 6 mol%, CH_2Cl_2, 2 h, 81%; (c) H_2, Pd/C, MeOH, 1 h, 86%; (d) LiOH, H_2O/THF, 16 h, 85%.



Scheme 4. *Reagents and conditions*: (a) prop-2-ene-1-sulfonyl chloride, Et_3N, CH_2Cl_2, 0°C 63%; (b) **A**, 3 mol%, CH_2Cl_2, reflux, 15 h, 93%; (c) H_2, Pd/C, EtOAc, 99%; (d) *t*-BuLi, BnBr, THF, −78°C, 87%; (e) *t*-BuLi, trisyl-azide, THF, −78°C, **26** (40%), epimer (24%); (f) TBAF, THF, 86%; (g) Dess-Martin, CH_2Cl_2; (h) NaO_2Cl, NaH_2PO_4, 2-methyl-butene, *t*-BuOH/H_2O; (i) EDC, HOBt, *i*-Pr_2NEt, *N*-Boc aminomethylbenzamidine, DMF, 65%; (j) H_2, Pd/C, MeOH; (k) HCl (3N)/MeOH (1:1), 60%.

interesting conformational features in **14** and **21**, respectively. Clearly these exquisitely functionalized bicyclic sulfonamide analogues of constrained prolines can find many applications as turn mimetics,[18] lactam complements,[19] and scaffolds for further diversity.[20] In this context, we describe the stereocontrolled functionalization of the sultam related to an indolizidinone 2-carboxylic acid.[14,21,22] Thus, compound **9** was *N*-sulfonylated to **22**, then subjected to ring-closure metathesis to give **23** in 93% yield (Scheme 4). Hydrogenation to **24** followed by treatment with *t*-BuLi gave the α-sulfonyl carbanion, which was benzylated with benzyl bromide to give **25** as a mixture of epimers.[14] Formation of the corresponding α-sulfonyl carbanion[23] with *t*-BuLi, and treatment with trisyl azide[14b,24] afforded a 1.2:1 mixture of epimeric tertiary azides. The modestly prevalent isomer **26** was characterized by a single X-ray structure. It should be noted that the azide group adopts a pseudo equatorial orientation in the six-membered chair-like sultam subunit.

Cleavage of the TBDPS group from **26** afforded **27** which was oxidized to the carboxylic acid, and the latter converted to the *p*-*N*-Boc amidino benzylamide derivative **28**. Catalytic hydrogenation and treatment with acid gave the bicyclic sulfonamide **29** as the bis-hydrochloride salt.

We have previously reported on the synthesis of corresponding indolizidinone analogues **1** and **2** (Fig. 1) as inhibitors of thrombin[14a] and Factor VIIa,[14b] respectively. When tested against thrombin, compound **29** showed considerably weaker inhibition (IC_{50} 494 nM) compared to **1** (IC_{50} 20 nM) and **1a** (IC_{50} 4 nM),[25] inspite of the presence of a more favored amino group at C-3. It is not known whether the loss of antithrombin activity is due to poorer binding of the sulfone group to Gly 216,[15] compared to the lactam carbonyl analogues in **1** or **2**. Clearly more studies are needed to assess the H-bonding capacity of cyclic α-amino sulfonamides such as **29** compared to their lactam analogues.[2,19]

It is of interest to compare the azidation of the closely related indolizidinones **30**[14b] and **31**[25] under the same conditions (Scheme 5). In the case of **30**, the major product was the desired 3*R* 'up' azide **32**, probably due to the approach of the electrophile from the convex face of the bicyclic system, because the pseudoaxial 5-methoxy group

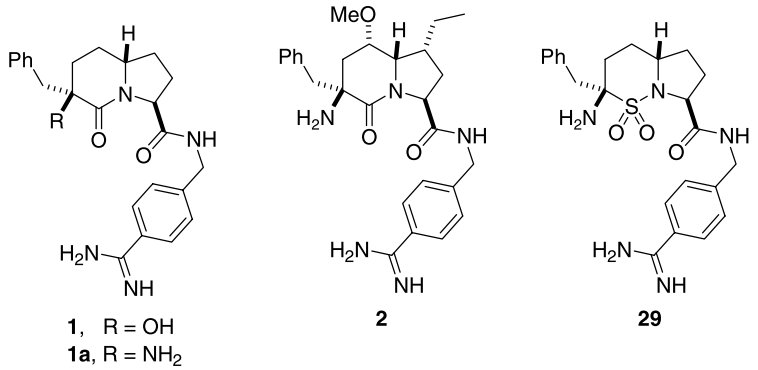
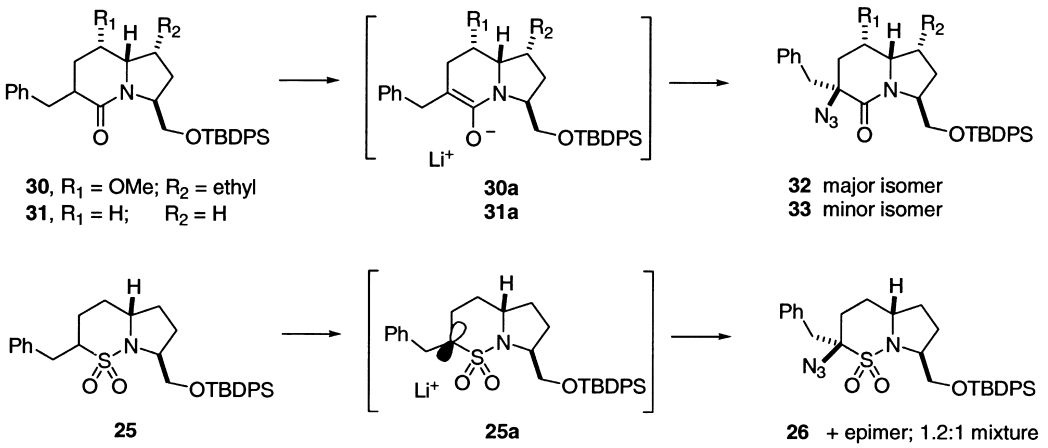


Figure 1. Constrained proline analogues as inhibitors of thrombin.



Scheme 5.

on the concave face exerts a steric influence towards the approach of the electrophile from that side. In the absence of such a substituent as in **31**, the azidation led to a 1:2 mixture of **33** (minor) and its epimer. Presumably the bulky TBDPS group has a more dominant influence in this case compared to the substituted counterpart **30**. Based on extensive studies on α-alkyl sulfonyl carbanions,[23,26] we can assume that the lithium anion **25a** is pyramidal, with the cation near the sulfonyl oxygens. Therefore the approach of the electrophile will be subject to two inherently opposing factors, namely the TBDPS group on the convex face and the topology of the concave side, probably bearing a pseudo-equatorially disposed benzylic substituent, resulting in a mixture of tertiary azides. More studies are needed to better understand the stereochemical preferences in the reaction with various carbon and hetero-atom based electrophiles of these constrained sulfonamide carbanions.

3. Conclusion

We have described practical syntheses of enantiopure bicyclic sulfonamides endowed with sites for functional diversity. These compounds can be functionalized next to the sulfonamide group via carbanion formation. The facile alkylation and azidation at this site are unprecedented examples within this class of bicyclic sulfonamides. It is hoped that such functionalized bicyclic sulfonamides containing two or more sites for diversification will find application in the design of prototypical bioactive molecules.

4. Experimental

4.1. General

Flash chromatography was performed on 230–240 mesh silica gel.[27] Thin-layer chromatography (TLC) was performed on glass plates coated with 0.02 mm layer of silica gel 60 F_{254}. All solvents were distilled freshly before use. 400-MHz ^{1}H NMR, 100-MHz ^{13}C NMR spectra were determined in $CDCl_3$ unless otherwise noted. Wherever necessary, ^{1}H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY). Low and high-resolution mass spectra were recorded on VG Micromass, Ael-MS902 or Kratos MS-50 spectrometers using fast atom bombardment (FAB) technique. Optical rotations were measured at 25°C at the sodium line.

4.1.1. (2*S*,5*S*)-5-*cis*-Propenyl-pyrrolidine-2-carboxylic acid benzyl ester (4). To a solution of **3** (1.14 g, 3.30 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (5 mL, 66.0 mmol). The reaction mixture was stirred at room temperature for 1 h then quenched with solid $NaHCO_3$ until no further effervescence was observed. The mixture was partitioned between water and CH_2Cl_2, the organic phases were dried over Na_2SO_4 and evaporated. The yellow residue was purified by column chromatography (50%, EtOAc/hexanes) to furnish the title compound **2** (720 mg, 89%) as a pale yellow oil: $[\alpha]_D=-46.2$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.52 (m, 1H), 1.66 (dd, *J*=1.2, 6.9 Hz, 3H), 1.87–1.98 (m, 2H), 2.25–2.32 (m, 1H), 2.36 (br, 1H), 3.94–4.05 (m, 1H), 4.07–4.11 (m, 1H), 5.17 (s, 2H), 5.33–5.38 (m, 1H), 5.47–5.54 (m, 1H), 7.32–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 29.5, 32.0, 54.4, 59.1, 66.6, 125.4, 128.1, 128.2, 126.5, 133.2, 135.7, 175.6; ν_{max}/cm^{-1} 3351, 2965, 1735, 1190; HRMS calcd for $C_{15}H_{20}NO_2$ (M+1) 246.14940; found 246.14860.

4.1.2. (2*S*,5*S*)-1-Ethenesulfonyl-5-*cis*-propenyl-pyrrolidine-2-carboxylic acid benzyl ester (5). To a solution of chloroethanesulfonylchloride[17a] (0.140 mL, 1.33 mmol) in CH_2Cl_2 (3 mL), was added Et_3N (0.185 mL, 1.33 mmol) at −78°C under argon. The reaction mixture was allowed to slowly warm to 0°C over 2 h then a solution of **4** (326 mg, 1.33 mmol) in CH_2Cl_2 (3 mL) and Et_3N (0.19 mL, 1.33 mmol) were added. The reaction mixture was allowed to warm to room temperature, stirred for a further 2 h, and then was partitioned between 10% HCl (aq.) and CH_2Cl_2. The organic phases were combined, washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (10%, EtOAc/hexanes) to yield the title compound **5** (360 mg, 81%) as a colorless oil: $[\alpha]_D=+26.9$ (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64–1.71 (m, 4H), 1.96–2.00 (m, 1H), 2.26–2.39 (m, 2H), 4.40–4.42 (m, 1H), 4.73–4.77 (m, 1H), 5.22 (m, *J*=11.1, 14 Hz, 2H), 5.37–5.43 (m, 1H), 5.53–5.61 (m, 1H), 5.86 (dd, *J*=1.3, 9.9 Hz, 1H), 6.18 (dd, *J*=1.3, 16.6 Hz, 1H), 6.59 (ddd, *J*=1.3, 9.9, 16.6 Hz, 1H), 7.34–7.38 (m, 5H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 12.9, 29.1, 31.7, 55.8, 61.0, 67.0, 126.3, 126.4, 128.1, 128.3, 128.5, 130.1, 135.4, 136.1, 172.5; ν_{max}/cm^{-1} 2957, 1746, 1345, 1148; HRMS calcd for $C_{17}H_{22}NO_4S$ (M+1) 336.12695; found 336.12590.

4.1.3. (6*S*)-1,1-Dioxo-3a,4,5,6-tetrahydro-1*H*-1λ⁶-pyrrolo[1,2-*b*]-isothiazole-6-carboxylic acid benzyl ester (6). To a de-gassed solution of **5** (174 mg, 0.52 mmol) in CH_2Cl_2 (52 mL), Grubbs' catalyst **A** (26 mg, 0.031 mmol) was added under argon. The solution was refluxed for 48 h then evaporated. The residue was purified by filtration through a pad of Florisil followed by column chromatography (50%, EtOAc/hexanes) to furnish the title compound **6** (33 mg, 22%): $[\alpha]_D=-21.8$ (*c* 1.14, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73–1.80 (m, 1H), 2.21–2.36 (m, 3H), 4.62 (t, *J*=6.7 Hz, 1H), 4.68–4.72 (m, 1H), 5.23 (ABq, *J*=12.4 Hz, sep. *J*=19.8 Hz, 2H), 6.68 (dd, *J*=2.3, 6.5 Hz, 1H), 6.79 (dd, *J*=2.0, 6.5 Hz, 1H), 7.31–7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0, 30.2, 60.8, 67.2, 67.3, 127.6, 128.1, 128.3, 128.6, 135.3, 139.3, 170.6; ν_{max}/cm^{-1} 1746, 1306, 1154; HRMS calcd for $C_{14}H_{16}NO_4S$ (M+1) 294.08002; found 294.07940.

4.1.4. (6*S*)-1,1-Dioxo-hexahydro-1λ⁶-pyrrolo[1,2-*b*]-isothiazole-6-carboxylic acid (7). A solution of **6** (13.4 mg, 0.046 mmol) in methanol (0.5 mL) was stirred under an atmosphere of hydrogen in the presence of a catalytic amount of 10% palladium-on-charcoal for 48 h. The suspension was then filtered through a Celite pad and the filtrate was evaporated to yield the title compound **7** (7 mg, 74%) as a white semi-solid: $[\alpha]_D=-70.8$ (*c* 0.36, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.67–1.77 (m, 1H), 2.01–2.11 (m, 1H), 2.16–2.25 (m, 2H), 2.36–2.44 (m, 1H), 2.51–2.60 (m, 1H), 3.02–3.10 (m, 1H), 3.23–3.29 (m, 1H), 4.09–4.15 (m, 1H), 4.37 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 27.0, 31.5, 32.6, 46.0, 63.4, 63.9, 175.6; ν_{max}/cm^{-1} 2927, 1728, 1317, 1151; HRMS calcd for $C_7H_{12}NO_4S$ (M+1) 206.04870; found 206.04450.

4.1.5. (2*S*,5*S*)-2-(*tert*-Butyl-diphenylsilanyloxymethyl)-5-*cis*-propenyl-pyrrolidine (9). TMSOTf (0.63 mL, 3.51 mmol) was added to a 0°C solution of **8** (1.40 g, 2.92 mmol) and *i*-Pr_2NEt (1.02 mL, 5.85 mmol) in CH_2Cl_2 (20 mL). The solution was stirred for 1.5 h, quenched with saturated aqueous $NaHCO_3$ (15 mL), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc/hexanes) to afford **9** (1.04 g, 94%) as a colorless oil: $[\alpha]_D=+12.1$ (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.64 (d, *J*=6.9 Hz, 3H), 1.68–1.82 (m, 2H), 2.10–2.15 (m, 2H), 3.64–3.68 (m, 1H), 3.77–3.90 (m, 2H), 4.33–4.39 (m, 1H), 5.47–5.52 (m, 1H), 5.61–5.66 (m, 1H), 7.36–7.45 (m, 6H), 7.61–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 19.0, 26.6, 26.8, 31.6, 55.7, 59.3, 64.3, 127.3, 127.7, 129.3, 129.8, 132.6, 132.7, 135.5, 135.6; ν_{max}/cm^{-1} 2959, 2860, 1683, 1429, 1202, 1135, 1114; HRMS calcd for $C_{24}H_{33}NOSi$ (M+) 379.233143; found 379.233444.

4.1.6. (2*S*,5*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-1-ethenesulfonyl-5-*cis*-propenyl-pyrrolidine (10). Dry Et_3N (0.40 mL, 2.90 mmol) was added to a −78°C solution of chloroethanesulfonylchloride (0.30 mL, 2.90 mmol) in dry CH_2Cl_2 (7.3 mL). The mixture was slowly warmed to 0°C over a period of 1.5 h and the amine **9** (1.04 g, 2.74 mmol) in CH_2Cl_2 (2.0 mL) and Et_3N (0.40 mL, 2.90 mmol) were added via canula. The mixture was stirred for 15 h, quenched with the addition of 1N HCl, and the resulting solution was extracted with CH_2Cl_2 and processed as usual. The resulting residue was purified by column chromatography (30–50% CH_2Cl_2/hexanes) to afford **10** (607 mg, 47%) as a colorless oil: $[\alpha]_D=+50.1$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.54–1.63 (m, 1H), 1.71–1.75 (m, 3H), 2.04–2.09 (m, 1H), 2.15–2.23 (m, 2H), 3.59–3.68 (m, 2H), 4.00–4.03 (m, 1H), 4.70 (t, *J*=6.9 Hz, 1H), 5.35 (t, *J*=10.5 Hz, 1H), 5.58–5.62 (m, 1H), 5.76 (dd, *J*=5.3, 9.9 Hz, 1H), 6.03 (dd, *J*=4.4, 16.6 Hz, 1H), 6.42 (dd, *J*=9.9, 16.6 Hz, 1H), 7.39–7.47 (m, 6H), 7.68–7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 19.7, 27.2, 27.4, 31.0, 57.3, 60.5, 66.0, 125.9, 127.4, 128.1, 130.0, 130.1, 133.9, 134.0, 136.0, 136.1, 136.5; ν_{max}/cm^{-1} 2933, 2858, 1473, 1428, 1348, 1151, 1113; HRMS calcd for $C_{26}H_{36}NO_3SSi$ (M+1) 470.21852; found 470.21640.

4.1.7. (6*S*)-6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3a,4,5,6-tetrahydro-pyrrolo[1,2-*b*]isothiazole 1,1-dioxide (11). Grubbs second generation's catalyst **B** (10 mg, 0.28 mmol) was added to a solution of diene **10** (100 mg, 0.21 mmol) in toluene (20 mL) and the mixture was heated at reflux 2 days. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography (20% EtOAc/hexanes) to afford **11** (72 mg, 79%) as a pale brown oil: $[\alpha]_D=-6.2$ (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.65 (m, 1H), 1.97 (m, 1H), 2.12 (m, 1H), 2.22 (m, 1H), 3.67 (dd, *J*=6.1, 10.3 Hz, 1H), 3.78 (dd, *J*=5.3, 10.3 Hz, 1H), 4.15 (m, 1H), 4.53 (t, *J*=7.7 Hz, 1H), 6.61 (dd, *J*=2.6, 6.5 Hz, 1H), 6.77 (dd, *J*=1.9, 6.4 Hz, 1H), 7.39–7.47 (m, 6H), 7.70–7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 27.2, 30.1, 30.9, 61.7, 67.0, 67.9, 127.9, 128.2, 133.6, 133.7, 136.0, 136.1, 139.2, 139.8; ν_{max}/cm^{-1} 2931, 2858, 1306, 1155, 1113; HRMS calcd for $C_{23}H_{30}NO_3SSi$ (M+1) 428.17157; found 428.17181.

4.1.8. (6*S*)-(1,1-Dioxo-3a,4,5,6-tetrahydro-1*H*-1λ⁶-pyrrolo[1,2-*b*]isothiazol-6-yl)-methanol (12). TBAF (1 M in THF, 0.70 mL, 0.70 mmol) was added dropwise to a solution of **11** (200 mg, 0.47 mmol) in THF (2.4 mL). After stirring for 1.5 h, a saturated solution of $NaHCO_3$ (10 mL) was added and extracted with EtOAc. The organic layer was processed as usual to yield a residue which was purified by column chromatography (75–100% EtOAc/hexanes) to give the title compound (**12**) (51 mg, 57%) as a clear, colorless oil; $[\alpha]_D=+24.8$ (*c* 1.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–1.70 (m, 1H), 1.96–2.06 (m, 1H), 2.12–2.19 (m, 1H), 2.23–2.30 (m, 1H), 2.49 (br, 1H), 3.59 (dd, *J*=5.7, 11.5 Hz, 1H), 3.75 (dd, *J*=5.7, 11.5 Hz, 1H), 4.04 (m, 1H), 4.57 (td, *J*=1.9, 6.8 Hz, 1H), 6.61 (dd, *J*=2.0, 6.4 Hz, 1H), 6.83 (dd, *J*=2.0, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 31.3, 62.2, 65.0, 68.1, 127.5, 140.1; ν_{max}/cm^{-1} 3509 (br), 2923, 1606, 1280, 1147; HRMS calcd for $C_7H_{12}NO_3S$ (M+1) 190.05379; found 190.05430.

4.1.9. (2*S*,5*S*)-1-(Prop-2-ene-1-sulfonyl)-5-*cis*-propenyl-pyrrolidine-2-carboxylic acid benzyl ester (13). To a

solution of **4** (336 mg, 1.37 mmol) in CH_2Cl_2 (10 mL) at 0°C were added Et_3N (0.191 mL, 1.37 mmol) and prop-2-ene-1-sulfonylchloride[17b] (192 mg, 1.37 mmol) under argon. After 1 h the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic phases were washed with 10% HCl then brine, dried over Na_2SO_4 and evaporated. Purification of the residue by column chromatography (10% EtOAc/hexanes) yielded the title compound **13** (301 mg, 63%) as a colorless oil: $[\alpha]_D=-42.5$ (*c* 2.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.64–1.67 (m, 1H), 1.77 (dd, *J*=1.7, 7.0 Hz, 3H), 1.94–1.99 (m, 1H), 2.23–2.42 (m, 2H), 3.77 (d, *J*=7.3 Hz, 2H), 4.40–4.42 (m, 1H), 4.92–4.97 (m, 1H), 5.19 (ABq, *J*=12.3 Hz, sep. *J*=14.5 Hz, 2H), 5.36–5.43 (m, 3H), 5.61–5.69 (m, 1H), 5.87–5.98 (m, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 29.4, 31.9, 56.0, 59.1, 59.3, 62.7, 62.9, 67.4, 77.5, 123.7, 127.7, 128.7, 129.0, 130.7, 136.0, 173.0; ν_{max}/cm^{-1} 2958, 1747, 1341, 1144; HRMS calcd for $C_{18}H_{23}NO_4S$ (M+1) 350.14261; found 350.14340.

4.1.10. (7*S*)-1,1-Dioxo-1,2,4a,5,6,7-hexahydro-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazine-7-carboxylic acid benzyl ester (14). To a de-gassed solution of **13** (100 mg, 0.29 mmol) in CH_2Cl_2 (29 mL) under argon was added Grubbs' catalyst **A** (7 mg, 0.0087 mmol). The mixture was stirred at room temperature for 3 h then evaporated. The residue was purified by filtration through a pad of Florisil followed by column chromatography (25% EtOAc/hexanes) to furnish the title compound **14** (87 mg, 98%) as a white solid: mp 139°C; $[\alpha]_D=-55.5$ (*c* 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83–1.89 (m, 1H), 2.01–2.08 (m, 1H), 2.17–2.34 (m, 2H), 3.54–3.70 (m, 2H), 4.29 (dd, *J*=3.0, 9.2 Hz, 1H), 4.72–4.74 (m, 1H), 5.20 (s, 2H), 5.68–5.79 (m, 2H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 30.6, 43.9, 61.1, 63.0, 67.1, 119.9, 128.0, 128.2, 128.5, 129.0, 135.4, 171.2; ν_{max}/cm^{-1} 2957, 1750, 1346, 1156; HRMS calcd for $C_{15}H_{18}NO_4S$ (M+1) 308.09564; found 308.09630.

4.1.11. (7*S*)-1,1-Dioxo-octahydro-1λ⁶-pyrrolo[1,2-*b*]-[1,2]thiazine-7-carboxylic acid (15). A solution of **14** (28 mg, 0.092 mmol) in methanol (1 mL) and ethyl acetate (1 mL) was stirred at room temperature under an atmosphere of hydrogen in the presence of a catalytic amount of 10% palladium-on-charcoal for 1 h. The reaction mixture was filtered through a pad of Celite and evaporated to yield the title compound **15** as a white solid (20 mg, 99%): mp>150°C decomp., $[\alpha]_D=-46.4$ (*c* 0.88, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.37–1.48 (m, 1H), 1.57–1.63 (m, 1H), 1.77 (dd, *J*=7.5, 12.5 Hz, 1H), 2.00–2.06 (m, 1H), 2.14–2.25 (m, 3H), 2.45–2.55 (m, 1H), 2.92–2.99 (m, 1H), 3.04–3.09 (m, 1H), 4.04–4.10 (m, 1H), 4.31 (dd, *J*=2.3, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 24.3, 28.2, 29.2, 31.7, 47.8, 61.4, 63.1, 176.3; ν_{max}/cm^{-1} 3236, 2920, 1763, 1323, 1129, 1113; HRMS calcd for $C_8H_{14}NO_4S$ (M+1) 220.06436; found 220.06480.

4.1.12. (7*S*)-1,1-Dioxo-1,2,4a,5,6,7-hexahydro-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazine-7-carboxylic acid (16). A suspension of 10% palladium-on-charcoal (200 mg) in ethyl acetate (7 mL) and 1,4-cyclohexadiene (5 mL) was stirred at room temperature for 15 min. A solution of **14** (124 mg, 0.40 mmol) in ethyl acetate (3 mL) was then added. The suspension was stirred at room temperature for 6 h then filtered through a Celite pad and evaporated to afford the title compound **16** (78 mg, 90%) as a white, crystalline solid: mp>180°C decomp., $[\alpha]_D=-58.6$ (*c* 0.63, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.92–1.98 (m, 1H), 2.05–2.13 (m, 1H), 2.25–2.40 (m, 2H), 3.57–3.64 (m, 1H), 3.87–3.93 (m, 1H), 4.30–4.35 (m, 1H), 4.67–4.70 (m, 1H), 5.75–5.80 (m, 1H), 5.83–5.88 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 29.6, 31.5, 44.4, 62.4, 64.9, 122.2, 129.7, 175.7; ν_{max}/cm^{-1} 1745, 1327, 1137; HRMS calcd for $C_8H_{12}NO_4S$ (M+1) 218.025230; found 218.026072.

4.1.13. (7*S*)-(1,1-Dioxo-1,2,4a,5,6,7-hexahydro-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazin-7-yl)-methanol (17). To a solution of **14** (27 mg, 0.087 mmol) in THF (2 mL) at −78°C under argon was slowly added diisobutylaluminium hydride (0.23 mL, 1.5 M solution in toluene, 0.35 mmol). The reaction mixture was allowed to warm to room temperature over 1.5 h, quenched with methanol (0.1 mL), then treated with a saturated aqueous solution of potassium sodium L-tartrate tetrahydrate (5 mL) for 1.5 h. Extraction with ethyl acetate and usual processing yielded the title compound **17** (15 mg, 85%) as a white solid after column chromatography (50% EtOAc/hexanes): mp 68°C; $[\alpha]_D=-43.3$ (*c* 0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.81–1.91 (m, 2H), 1.99–2.10 (m, 1H), 2.16–2.26 (m, 1H), 2.32 (br., 1H), 3.53–3.72 (m, 5H), 4.65–4.66 (m, 1H), 5.66–5.69 (m, 1H), 5.77–5.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 29.7, 42.3, 61.9, 63.8, 66.1, 119.9, 129.3; ν_{max}/cm^{-1} 3515, 1336, 1157; HRMS calcd for $C_8H_{14}NO_3S$ (M+1) 204.06944; found 204.07030.

4.1.14. (2*S*,5*S*)-1-(But-3-ene-1-sulfonyl)-5-*cis*-propenyl-pyrrolidine-2-carboxylic acid benzyl ester (18). To a solution of **4** (68 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) at 0°C under argon were added Et_3N (0.059 mL, 0.42 mmol) and but-3-ene-1-sulfonylchloride[17c] (65 mg, 0.42 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was then partitioned between CH_2Cl_2 and 10% HCl, and the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Purification of the residue by column chromatography (10% EtOAc/hexanes) yielded the title compound **18** (50 mg, 55%) as a colorless oil: $[\alpha]_D=-15.0$ (*c* 4.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.65–1.72 (m, 1H), 1.76 (dd, *J*=1.7, 7.0 Hz, 3H), 1.98–2.01 (m, 1H), 2.25–2.57 (m, 4H), 3.08–3.12 (m, 2H), 4.42–4.44 (m, 1H), 4.89–4.94 (m, 1H), 5.04–5.16 (m, 2H), 5.19 (ABq, *J*=12.3 Hz, sep. *J*=13.8 Hz, 2H), 5.37–5.43 (m, 1H), 5.58–5.66 (m, 1H), 5.73–5.83 (m, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 27.5, 29.0, 31.5, 53.3, 55.3, 61.9, 67.0, 116.6, 127.1, 128.1, 128.2, 128.5, 129.9, 134.4, 135.5, 172.5; ν_{max}/cm^{-1} 2957, 1746, 1341, 1143; HRMS calcd for $C_{19}H_{26}NO_4S$ (M+1) 364.15826; found 364.15910.

4.1.15. (8*S*)-1,1-Dioxo-2,3,5a,6,7,8-hexahydro-1*H*-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazepine-8-carboxylic acid benzyl ester (19). To a de-gassed solution of **18** (28 mg, 0.077 mmol) in CH_2Cl_2 (8 mL) under argon was added Grubbs' catalyst **A** (4 mg, 0.0046 mmol). The solution was stirred at room temperature for 2 h then evaporated. The residue was purified by filtration through a pad of Florisil followed by column chromatography (50% EtOAc/hexanes)

to furnish the title compound **19** (20 mg, 81%) as a colorless oil: $[\alpha]_D=-36.6$ (*c* 4.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.86 (m, 1H), 1.96–2.05 (m, 1H), 2.22–2.34 (m, 2H), 2.46–2.62 (m, 2H), 3.02–3.09 (m, 1H), 3.28–3.34 (m, 1H), 4.29 (d, *J*=7.8 Hz, 1H), 4.55 (br, 1H), 5.19 (s, 2H), 5.55–5.59 (m, 1H), 5.85–5.92 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 28.8, 31.7, 52.5, 56.7, 60.4, 66.9, 128.0, 128.1, 128.4, 130.3, 135.4, 136.0, 171.8; ν_{max}/cm^{-1} 2954, 1750, 1340, 1139; HRMS calcd for $C_{16}H_{20}NO_4S$ (M+1) 322.11130; found 322.10990.

4.1.16. (8*S*)-1,1-Dioxo-octahydro-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazepine-8-carboxylic acid (20). A solution of **19** (39.8 mg, 0.12 mmol) in methanol (5 mL) was stirred at room temperature under an atmosphere of hydrogen gas, in the presence of a catalytic amount of 10% palladium-on-charcoal for 1 h. The suspension was filtered through a Celite pad and the filtrate evaporated to yield the title compound **20** (24 mg, 86%) as a white crystalline solid: mp 147°C; $[\alpha]_D=-86.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.42–1.57 (m, 1H), 1.69–2.13 (m, 7H), 2.16–2.25 (m, 1H), 2.31–2.41 (m, 1H), 2.93–3.00 (m, 1H), 3.25–3.31 (m, 1H), 3.94–3.97 (m, 1H), 4.34–4.42 (m, 1H), 10.18–10.68 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 24.1, 28.7, 31.7, 32.3, 53.9, 57.8, 61.9, 178.2; ν_{max}/cm^{-1} 2938, 1716, 1335, 1307, 1142; HRMS calcd for $C_9H_{16}NO_4S$ (M+1) 234.08000; found 234.08080.

4.1.17. (8*S*)-1,1-Dioxo-2,3,5a,6,7,8-hexahydro-1*H*-1λ⁶-pyrrolo[1,2-*b*][1,2]thiazepine-8-carboxylic acid (21). A solution of **19** (41 mg, 0.13 mmol) in THF (1 mL) and water (1 mL) was treated with lithium hydroxide (8 mg, 0.19 mmol) at room temperature overnight. The solvent was removed and the residue partitioned between diethyl ether and water. The aqueous phase was treated dropwise with conc. HCl to pH 2 and extracted with ethyl acetate. The organic phases were dried over Na_2SO_4 and evaporated to yield the title compound **21** (25 mg, 85%) as a white, crystalline solid: mp 130°C; $[\alpha]_D=-54.0$ (*c* 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.88–1.90 (m, 1H), 2.14–2.23 (m, 1H), 2.28–2.41 (m, 2H), 2.48–2.65 (m, 2H), 3.05–3.12 (m, 1H), 3.32–3.38 (m, 1H), 4.27 (d, *J*=8.0 Hz, 1H), 4.57 (br, 1H), 5.57–5.61 (m, 1H), 5.87–5.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 29.0, 31.9, 52.6, 57.1, 60.3, 130.3, 136.0, 176.9; ν_{max}/cm^{-1} 1723, 1337, 1137; HRMS calcd for $C_9H_{14}NO_4S$ (M+1) 232.06436; found 232.06540.

4.1.18. (2*S*,5*S*)-1-(Prop-2-ene-1-sulfonyl)-2-(*tert*-butyl-diphenylsilanyloxymethyl)-5-*cis*-propenyl-pyrrolidine (22). To a solution of amine **9** (132 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) at 0°C under argon were added Et_3N (0.049 mL, 0.35 mmol) and prop-2-ene-1-sulfonyl-chloride[17b] (79 mg, 0.56 mmol) in CH_2Cl_2 (2 mL). After 2 h the reaction mixture was partitioned between CH_2Cl_2 and 10% HCl. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Purification of the residue by column chromatography (5% EtOAc/hexanes) yielded the title compound **22** (107 mg, 63%) as a colorless oil: $[\alpha]_D=-6.5$ (*c* 2.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.51–1.56 (m, 1H), 1.75 (dd, *J*=1.7, 6.9 Hz, 3H), 2.01–2.17 (m, 3H), 3.54–3.58 (m, 1H), 3.63–3.76 (m, 2H), 3.84–3.89 (m, 1H), 4.01 (dd, *J*=3.6, 10.0 Hz, 1H), 4.64–4.69 (m, 1H), 5.31–5.42 (m, 3H), 5.62–5.69 (m, 1H), 5.83–5.94 (m, 1H), 7.36–7.46 (m, 6H), 7.66–7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 19.2, 26.4, 26.9, 30.4, 56.1, 58.2, 61.6, 65.1, 122.7, 126.5, 127.5, 127.6, 129.4, 129.6, 133.4, 133.5, 135.5, 135.6; ν_{max}/cm^{-1} 2959, 1344, 1145, 1113; HRMS calcd for $C_{27}H_{38}NO_3SSi$ (M+1) 484.23416; found 484.23530.

4.1.19. (7*S*)-7-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-*b*][1,2]thiazine 1,1-dioxide (23). To a de-gassed solution of **22** (90 mg, 0.19 mmol) in CH_2Cl_2 (19 mL) under argon was added Grubbs' catalyst **A** (5 mg, 0.0056 mmol). The mixture was heated at reflux for 16 h then evaporated, the residue was purified by filtration through a pad of Florisil followed by column chromatography (20% EtOAc/hexanes) to furnish the title compound **23** (78 mg, 93%) as a colorless oil: $[\alpha]_D=-46.4$ (*c* 3.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.75–1.80 (m, 1H), 1.93–2.18 (m, 3H), 3.46–3.84 (m, 5H), 4.57–4.58 (m, 1H), 5.63–5.66 (m, 1H), 5.74–5.79 (m, 1H), 7.37–7.46 (m, 4H), 7.63–7.69 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.6, 26.8, 29.3, 42.3, 61.5, 63.2, 66.6, 120.2, 127.6, 129.4, 129.6, 133.8, 135.4; ν_{max}/cm^{-1} 2932, 2858, 1347, 1157, 1112; HRMS calcd for $C_{24}H_{32}NO_3SSi$ (M+1) 442.18723; found 442.188850.

4.1.20. (7*S*)-7-(*tert*-Butyl-diphenyl-silanyloxymethyl)-hexahydro-2*H*-pyrrolo[1,2-*b*][1,2]thiazine 1,1-dioxide (24). A solution of **23** (61 mg, 0.14 mmol) in methanol (10 mL) was stirred at room temperature under an atmosphere of hydrogen gas, in the presence of a catalytic amount of 10% Pd/C for 2 h. The suspension was then filtered through a Celite pad and evaporated to yield the title compound **24** (60 mg, 97%) as a colorless oil: $[\alpha]_D=-28.9$ (*c* 2.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.23–1.35 (m, 1H), 1.56–1.64 (m, 2H), 2.05–2.16 (m, 4H), 2.22–2.33 (m, 1H), 2.75 (td, *J*=3.9, 13.2 Hz, 1H), 3.07 (dt, *J*=3.4, 13.2 Hz, 1H), 3.54–3.59 (m, 1H), 3.84–3.88 (m, 2H), 3.94–3.99 (m, 1H), 7.36–7.44 (m, 6H), 7.65–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.1, 25.6, 26.8, 27.6, 30.2, 46.7, 60.9, 61.1, 66.9, 127.6, 129.6, 133.4, 133.5, 135.5, 135.6; ν_{max}/cm^{-1} 2933, 2858, 1333, 1146, 1113; HRMS calcd for $C_{24}H_{34}NO_3SSi$ (M+1) 444.20288; found 444.20360.

4.1.21. (7*S*)-2-Benzyl-7-(*tert*-butyl-diphenyl-silanyloxymethyl)-hexahydro-pyrrolo[1,2-*b*][1,2]thiazine 1,1-dioxide (25). The substrate **24** (279 mg, 0.63 mmol) was dissolved in THF (3.2 mL) and cooled to −78°C under argon atmosphere. *t*-BuLi (1.7 M in pentane, 0.41 mL, 0.69 mmol) was added dropwise and the resulting yellow mixture was stirred at −78°C for 45 min. Benzyl bromide (0.09 mL, 0.82 mmol) was slowly added at −78°C and stirring was continued for another hour at −78°C. Saturated aqueous $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by column chromatography (10% EtOAc/hexanes) to afford **25** (291 mg, 87%) as a colorless oil: $[\alpha]_D=-53.6$ (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.30 (m, 1H), 1.57 (m, 2H), 1.94 (m, 2H), 2.13 (m, 3H), 2.68 (t, *J*=13.0 Hz, 1H), 2.91 (m, 1H),

3.53 (dd, J=2.6, 13.4 Hz, 1H), 3.62 (t, J=8.1 Hz, 1H), 3.90–3.97 (m, 3H), 7.24 (m, 2H), 7.28 (m, 1H), 7.35 (m, 2H), 7.44 (m, 6H), 7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.4, 28.4, 29.6, 30.6, 34.4, 59.1, 61.4, 61.5, 67.4, 127.3, 128.2, 129.1, 129.9, 130.1, 133.8, 136.0, 136.1, 137.3; ν_{max}/cm^{-1} 2932, 1472, 1324, 1205, 1149, 1113, 1031, 760, 701; HRMS calcd for $C_{31}H_{39}NO_3SSi$ (M+) 533.24202; found 533.24179.

4.1.22. (2*S*,7*S*)-2-Azido-2-benzyl-7-(*tert*-butyl-diphenyl-silanyloxymethyl)-hexahydro-pyrrolo[1,2-*b*][1,2]thiazine 1,1-dioxide (26). The substrate **25** (500 mg, 0.94 mmol) was dissolved in THF (4.7 mL) and cooled to −78°C under argon atmosphere. *t*-BuLi (1.7 M in pentane, 0.72 mL, 1.22 mmol) was added dropwise and the resulting yellow mixture was stirred at −78°C for 55 min. Trizyl azide (436 mg, 1.41 mmol) in THF (0.5 mL) was slowly added and stirring was continued for 6 h at −78°C. Saturated aqueous $NaHCO_3$ (15 mL) was added and the aqueous phase was extracted with EtOAc, the organic phase was dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by column chromatography (40% hexanes/CH_2Cl_2) to afford **26** (217 mg, 40%) as a colorless oil which was crystallized from CH_2Cl_2: mp 144°C; $[\alpha]_D$=−4.5 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.26–1.33 (m, 1H), 1.59–1.71 (m, 2H), 1.84–1.90 (m, 2H), 2.17–2.35 (m, 3H), 2.91 (d, J=14.1 Hz, 1H), 3.22 (d, J=14.1 Hz, 1H), 3.61 (dd, J=7.6, 10.1 Hz, 1H), 3.83 (dd, J=3.7, 10.2 Hz, 1H), 4.03–4.08 (m, 2H), 7.27–7.47 (m, 6H), 7.68–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 26.3, 27.3, 28.4, 29.5, 30.6, 36.4, 60.3, 63.5, 67.0, 79.1, 128.1, 128.2, 129.0, 130.2, 130.9, 133.7, 134.0, 136.0, 136.1; ν_{max}/cm^{-1} 2955, 2858, 2107, 1428, 1333, 1154, 1112; HRMS calcd for $C_{31}H_{39}N_4O_3SSi$ (M+1) 575.24342; found 575.24304.

4.1.23. (2*S*,7*S*)-(2-Azido-2-benzyl-1,1-dioxo-octahydro-1λ^6-pyrrolo[1,2-*b*][1,2]thiazin-7-yl)-methanol (27). The substrate **26** (190 mg, 0.33 mmol) was dissolved in dry THF (3.5 mL) at room temperature and TBAF (1 M in THF, 0.66 mL, 0.66 mmol) was added dropwise. After stirring for 1.25 h, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The aqueous phase was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by column chromatography (70% EtOAc/hexanes) to afford **27** (96 mg, 86%) as a colorless oil: $[\alpha]_D$=+34.2 (*c* 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69–1.76 (m, 2H), 1.83–1.89 (m, 2H), 2.07–2.10 (m, 1H), 2.25–2.30 (m, 3H), 2.97 (d, J=14.1 Hz, 1H), 3.21 (d, J=14.1 Hz, 1H), 3.64–3.73 (m, 3H), 4.02–4.05 (m, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.3, 29.5, 31.2, 36.5, 60.9, 64.1, 66.4, 79.5, 128.1, 129.0, 130.8, 133.8; ν_{max}/cm^{-1} 2959, 2104, 1454, 1329, 1150, 699; HRMS calcd for $C_{15}H_{20}N_4O_3S$ (M+) 336.12565; found 336.12598.

4.1.24. (2*S*,7*S*)-[Amino-(4-{[(2-azido-2-benzyl-1,1-dioxo-octahydro-1λ^6-pyrrolo[1,2-*b*][1,2]thiazine-7-carbonyl)-amino]-methyl}-phenyl)-methylene]-carbamic acid *tert*-butyl ester (28). To a stirred solution of alcohol **27** (45 mg, 0.13 mmol) in dry CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (74 mg, 0.17 mmol). The resulting suspension was stirred 1 h, quenched with 1:1 mixture of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness to yield a crude aldehyde which was dissolved in *t*-BuOH (1.4 mL), cooled to 0°C and 2-methyl-2-butene (0.67 mL, 1.3 mmol) was added. A solution of NaH_2PO_4 (101 mg, 0.73 mmol) and NaO_2Cl (60 mg, 0.67 mmol) in H_2O (1.4 mL) was added dropwise. After stirring for 45 min, 1N HCl (2 mL) was added and the aqueous phase was extracted with EtOAc. The combined organic phases were dried, filtered and evaporated to yield a colorless foam. To a solution of crude acid in DMF (3.0 mL) were successively added EDC (30 mg, 0.16 mmol), HOBt (21 mg, 0.16 mmol) and *i*-Pr_2NEt (0.05 mL, 0.26 mmol). After stirring for 20 min, *N*-Boc aminomethyl benzamidine (39 mg, 0.16 mmol) was added, the resulting mixture was stirred overnight then evaporated to dryness. The residue was dissolved in saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (2% MeOH/EtOAc) afford **28** (49 mg, 65%) as a colorless oil: $[\alpha]_D$=+4.2 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.67–1.72 (m, 1H), 1.78–1.86 (m, 1H), 1.89–1.92 (m, 2H), 2.16–2.23 (m, 1H), 2.25–2.34 (m, 1H), 2.38–2.43 (m, 2H), 2.85 (d, J=14.1 Hz, 1H), 3.20 (d, J=14.0 Hz, 1H), 4.15–4.16 (m, 1H), 4.42–4.55 (m, 3H), 7.14 (t, J=5.9 Hz, 1H), 7.26–7.37 (m, 7H), 7.78 (d, J=8.1 Hz, 2H); ^{13}C NMR (100. MHz, $CDCl_3$) δ 27.3, 28.0, 28.1, 28.2, 28.7, 30.6, 35.8, 42.9, 60.3, 64.0, 79.0, 79.5, 127.0, 127.7, 128.5, 130.2, 132.7, 133.8, 141.9, 171.0; ν_{max}/cm^{-1} 2108, 1616, 1281, 1142; HRMS calcd for $C_{28}H_{36}N_7O_5S$ (M+1) 582.2499; found 582.2512.

4.1.25. (2*S*,7*S*)-2-Amino-2-benzyl-1,1-dioxo-octahydro-1λ^6-pyrrolo[1,2-*b*][1,2]thiazine-7-carboxylic acid 4-carbamimidoyl-benzylamide (29). The substrate **28** (6.3 mg, 0.01 mmol) was dissolved in MeOH (1 mL) and Pd/C (20 mg) was added. The suspension was hydrogenated overnight under 40 psi, after which it was filtered through a pad of Celite (MeOH rinse), and concentrated to give a colorless oil which was dissolved in MeOH (1 mL) and 6N HCl (1 mL) was added. The solution was stirred at room temperature overnight. The solvent was removed by high vacuum evaporation and gave the desired compound **29** (3.6 mg, 73%) as a hydrochloride salt: $[\alpha]_D$=−38.9 (*c* 0.18, CH_3OH); ^{1}H NMR (400 MHz, CD_3OH) δ 1.70–1.73 (m, 1H), 1.82–1.91 (m, 2H), 1.93–1.98 (m, 1H), 2.16–2.28 (m, 2H), 2.37–2.43 (m, 1H), 2.60 (s, 1H), 2.90–2.99 (m, 1H), 3.09 (dd, J=4.6, 13.6 Hz, 1H), 3.57–3.70 (m, 2H), 4.19–4.25 (m, 1H), 4.29–4.38 (m, 1H), 7.16–7.24 (m, 5H), 7.33 (d, J=8.0 Hz, 2H), 7.78 (d, J=8.1 Hz, 2H); ν_{max}/cm^{-1} 3059, 1680, 1560; HRMS calcd for $C_{23}H_{29}N_5O_3S$ (M+) 455.57313; found 455.57297.

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