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PAPER

Platinum catalyzed 7-*endo* cyclization of internal alkynyl amides and its application to synthesis of the caprazamycin core†‡

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The scope and limitations of the platinum catalyzed 7-*endo* cyclization of internal alkynyl amides were investigated. Substitution of the alkyne with an aryl group gave better results, presumably because it stabilized the transition state. Applying the reaction to a secondary amide, the caprazamycin core was successfully synthesized from commercially available material in eight steps.

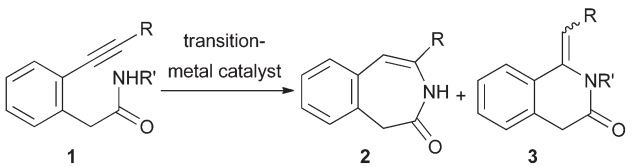
Introduction

Transition metal-catalyzed inter- and intramolecular hydroamidation is a powerful method for the synthesis of amides, which are fundamental structures in natural products and pharmaceutical compounds.[1] Coupling an amide with an alkyne is of particular interest, because this approach is atom economical and provides enamides under mild conditions. For example, Goossen and co-workers described the anti-Markovnikov addition of an amide to an alkyne.[2] The stereochemistry was controlled by a ruthenium catalyst, Lewis acid, and ligands. Takai and Kuninobu *et al.* reported rhenium-catalyzed intermolecular hydroamidation of unactivated terminal alkynes for synthesis of (*E*)-enamides.[3] Copper-catalyzed intermolecular amidation of alkynes was also reported by the Evano and Kundu groups.[4,5] Intramolecular hydroamidation of an alkyne was broadly investigated for formation of *N*-heterocycles using palladium,[6] copper,[7] gold,[8] and platinum catalysts.[9–12] Interestingly, a nitrogen-containing seven-membered ring could be constructed using these reactions. Mitchell *et al.* reported synthesis of benzoazepinone *via* palladium-catalyzed intramolecular hydroamidation of internal alkynes **1** substituted with one alkyl group and one aryl group (Scheme 1, R = alkyl).[6a] Liu and co-workers described a gold-catalyzed 7-*endo* cyclization of alkynyl amide substituted with two aryl groups (R = aryl).[8] However, these reaction conditions are not applicable to various substituted alkynyl amides. For example, Mitchell *et al.* found that palladium-catalyzed intramolecular hydroamidation of alkynes, substituted with two aryl groups (R = aryl) gave a six-membered product **3** rather than a seven-membered one.[6c] Thus, a reliable method is still required for preparing various cyclic enamides, and especially for controlling regiochemistry.

We recently reported intramolecular hydroamidation of terminal alkynes using $PtCl_2$ and $Bi(OTf)_3$ as catalysts.[9,13,14] Starting from the same alkynyl amide, the 7-*endo* cyclization using a platinum catalyst produced 1,4-diazepanone derivatives and the 6-*exo* cyclization using a bismuth catalyst produced piperazin-2-one derivatives. These reactions are useful because terminal alkynes can be used. The obtained structures are found in natural products and pharmaceutical compounds, such as caprazamycin A, which could be used to develop new drug candidates for tuberculosis (Fig. 1).[15] For further application, the substrate scope and limitations of the reaction conditions need to be determined. In this paper, we will report platinum-catalyzed hydroamidation of internal alkynes with various substrates, and synthetic studies of the caprazamycin core using the developed reaction.

Results and discussion

Initially, phenyl substituted alkynyl amide **7** was prepared from L-phenylalanine methyl ester hydrochloride **4** for platinum and bismuth-catalyzed cyclizations. Ammonolysis of methyl ester was followed by nosyl (Ns) protection[16] to give amide **5** (Scheme 2). After introduction of a propargyl group, the



Scheme 1 Transition metal-catalyzed hydroamidation.

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‡Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectral data and crystallographic data of compound **9** in CIF. CCDC 869849. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25111f

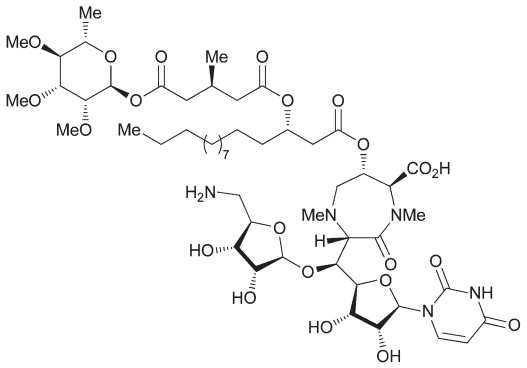
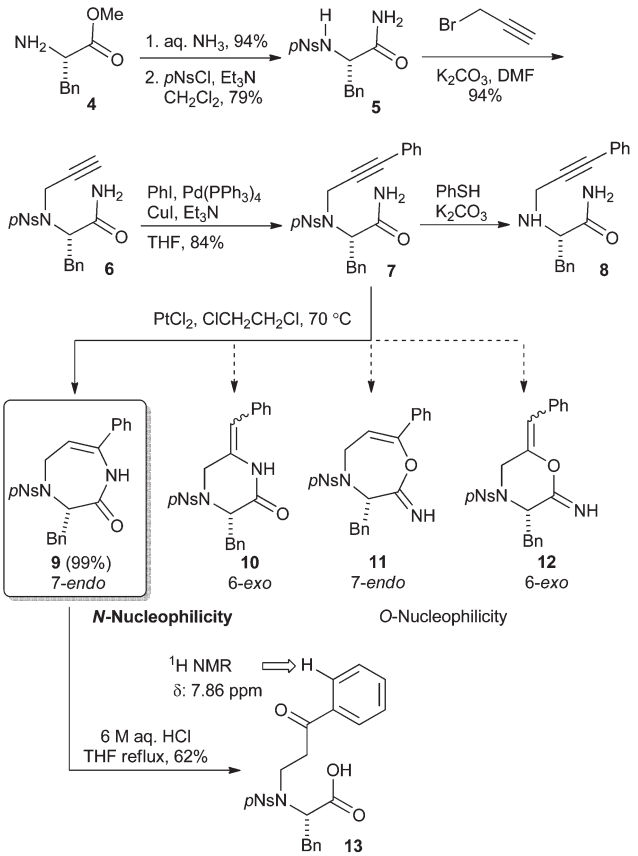


Fig. 1 Caprazamycin A.



Scheme 2 The synthesis of alkynyl amide **7** and its cyclization.

resultant terminal alkyne was treated with PhI, a catalytic amount of $Pd(PPh_3)_4$, and CuI to give the cyclization precursor **7**.[17] In the platinum and bismuth catalyzed reactions, the four isomers **9**, **10**, **11** and **12** might be produced by nucleophilic addition of the nitrogen or oxygen atom of the amide *via* 6-*exo* or 7-*endo* cyclization after activation of the alkyne by the metal catalyst. When the phenyl substituted alkynyl amide **7** was treated with $PtCl_2$ in dichloroethane at 70 °C, 7-*endo* cyclized product **9** was obtained as a single isomer. By contrast, bismuth-catalyzed cyclization of **7** did not proceed at all. Structural characterization of the 7-*endo* cyclized product **9** was confusing, although spectroscopic analysis, including NMR spectroscopy,

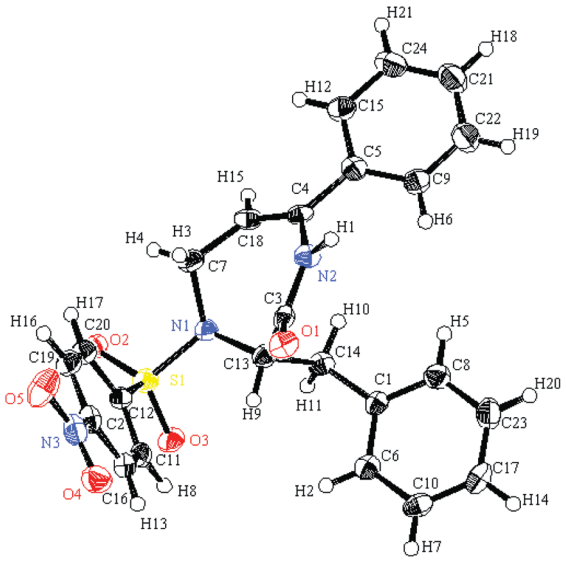


Fig. 2 The X-ray structure of compound **9**. Thermal ellipsoids are shown at the 50% probability level.

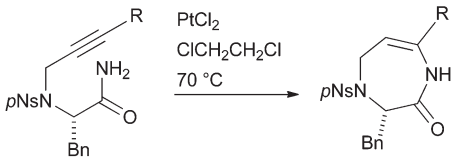
clearly showed that it contained an enamide moiety.[18] Thus, the cyclized product **9** was hydrolyzed under acidic conditions to ketocarboxylic acid **13**, whose structure was determined by NMR spectroscopy. These results indicated that the platinum catalyzed cyclization gave the 7-*endo* cyclized product **9**. The structure of compound **9** was also unambiguously secured by X-ray crystal structure analysis (Fig. 2).[19] Protection of the amine was essential for this reaction. Platinum-catalyzed cyclization of compound **8** prepared from **7** by deprotection of the Ns group resulted in recovery of the starting material **8**, because the platinum catalyst was probably inactivated by coordination of the secondary amine.

Scope and limitations of platinum catalyzed 7-*endo* cyclization

We then investigated the effect of substitution on the 7-*endo* cyclization. Aryl alkynyl amides **14a–d** with electron rich aromatic rings, such as 2,4-dimethoxyphenyl, *p*-methoxyphenyl, tolyl and naphthyl, were treated with $PtCl_2$ in dichloroethane at 70 °C. In these cases, the platinum catalyzed 7-*endo* cyclization proceeded to give the desired products **15a–d** in 70–97% yield (Table 1, entries 1–4). For diazepanone **15d**, the regioselectivity was confirmed again by hydrolysis under acidic conditions (Scheme 3). The obtained carboxylic acid **16** indicated that nucleophilic addition of nitrogen occurred at the sp carbon next to the naphthyl group. Interestingly, the 7-*endo* cyclization of aryl alkynyl amide **14g** with a nitrophenyl group did not proceed at all. The cyclizations of aryl alkynyl amides **14e** and **14f** with chlorine and trifluoromethyl groups on the aromatic ring, respectively, gave the cyclized products in excellent yields (entries 5–7). These results suggest that electron donating and weak electron withdrawing groups are tolerated on the aromatic ring, but strong electron withdrawing groups suppress the 7-*endo* cyclization.

Other substituents on the alkyne were also examined. With methyl alkynyl amides **14h** in the platinum catalyzed cyclization, the cyclized product **15h** was obtained in low yield along with a

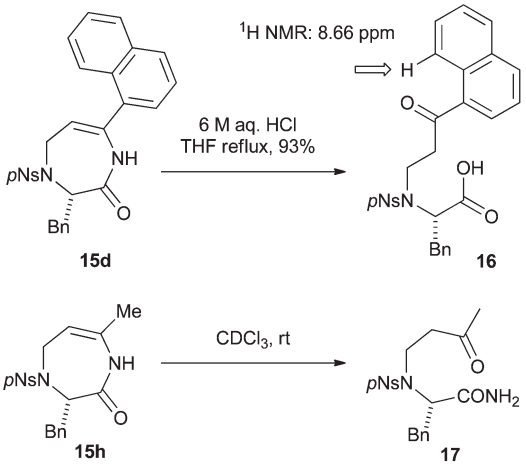
Table 1 7-*endo-dig* hydroamidation of aryl alkynyl amides **14a–i**



14a-i **15a-i**

Entry	Alkyne	R	Product	Yield[a] (%)
1	**14a**	2,4-$(MeO)_2C_6H_3$	**15a**	72
2	**14b**	*p*$MeOC_6H_4$	**15b**	82
3	**14c**	*p*MeC_6H_4	**15c**	70
4	**14d**	1-Naphthyl	**15d**	97
5	**14e**	*p*ClC_6H_4	**15e**	99
6	**14f**	*p*$CF_3C_6H_4$	**15f**	99
7	**14g**	*p*$NO_2C_6H_4$	**15g**	0
8	**14h**	Me	**15h**	33[b]
9	**14i**	TMS	**15i**	0[c]

[a] Isolated yield. [b] Methyl ketone **17** was obtained in 63% yield as by-product. [c] No reaction.

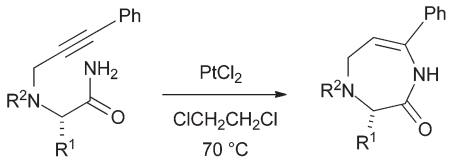


Scheme 3 The hydrolysis of cyclized products **15d** and **15h**.

large amount of ketone **17** (Table 1, entry 8). While the 7-*endo* cyclized products were generally stable under the reaction conditions, in $CDCl_3$ product **15h** was almost fully decomposed to by-product **17** within a few days (Scheme 3). Thus the by-product **17** would be produced *via* hydrolysis of compound **15h** because of its lability under the reaction conditions. The 7-*endo* cyclization of trimethylsilyl alkynyl amide **14i** was also attempted, but no reaction was observed, presumably because of steric hindrance of the silyl group (entry 9).

Next, substituents at the α-position of the amide were examined. We previously observed a substitution effect at this position in the reaction of terminal alkynyl amides.[9] As the R^1 group became bulkier, the yield increased. In sharp contrast, the platinum catalyzed cyclization of internal alkynyl amides **18a**, **b**, and **c** substituted with phenyl groups derived from leucine, valine, and alanine, respectively, proceeded smoothly to give diazepanones **19a–c** in 82–84% yield (Table 2, entries 1–3). Compared with the reactions for the corresponding terminal alkynes, the selectivity and reactivity increased with a phenyl substituent on

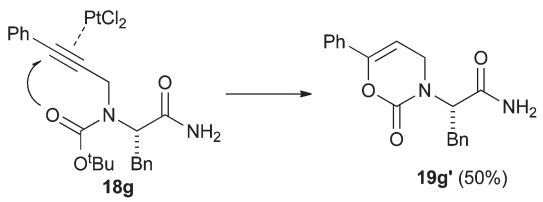
Table 2 Effect of substitution at the α-position and protecting group for the secondary amine of alkynyl amides in the 7-*endo-dig* hydroamidation



18a-g **19a-g**

Entry	Alkyne	R^1	R^2	Product	Yield[a] (%)
1	**18a**	^{i}Bu	*p*Ns	**19a**	84
2	**18b**	^{i}Pr	*p*Ns	**19b**	84
3	**18c**	Me	*p*Ns	**19c**	82
4	**18d**	Bn	Ts	**19d**	92
5	**18e**	Bn	$CO_2{}^i$Pr	**19e**	98
6	**18f**	Bn	Cbz	**19f**	72
7	**18g**	Bn	Boc	**19g**	29[b]

[a] Isolated yield. [b] Starting material (20%) was recovered and **19g′** was obtained in 50% yield.



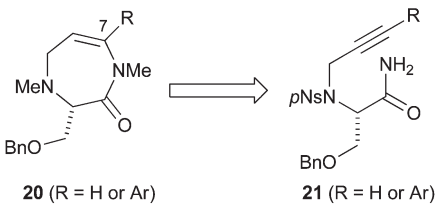
Scheme 4 The side reaction with a Boc protecting group.

alkyne (**18a–c**, R^1 = ^{i}Bu, ^{i}Pr and Me). Several protecting groups could be employed for the secondary amine instead of the Ns group. The reactions of **18d–f** protected with tosyl, $-CO_2{}^i$Pr, and Cbz groups proceeded smoothly to give the 7-*endo* cyclized products **19d–f** in 72–98% yields (entries 4–6). When the Boc protecting group was used, the reaction gave the desired product **19g** (29%) along with a large amount of a 6-*endo* cyclized product **19g′** (50%), which was produced *via* nucleophilic addition of the oxygen atom of Boc group following loss of a *tert*-butyl group (Table 2, entry 7 and Scheme 4).[20]

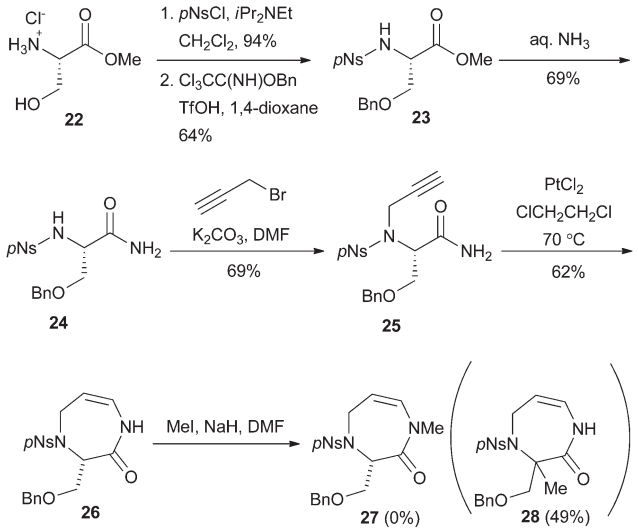
These investigations indicate the presence of an aromatic ring on the alkyne stabilizes the transition state of the 7-*endo* cyclization after activation of the alkyne by the platinum catalyst. Consequently, the reaction was accelerated and the yields were improved with an aromatic substituent compared with cyclization of a terminal alkyne. These results will be helpful in synthesis of substituted diazepanones, and we applied the reaction to synthesis of the caprazamycin core.

Application to synthesis of the caprazamycin core

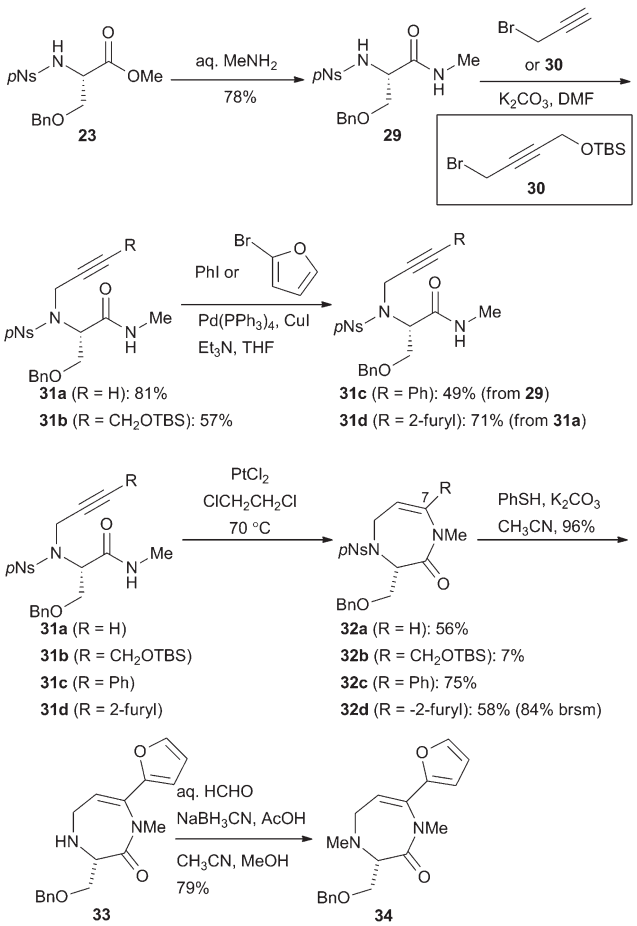
Caprazamycins were isolated from *Streptomyces* sp. MK730-62F2 by Igarashi *et al.* when screening drug seeds for tuberculosis (Fig. 1).[15] The structure was determined by extensive spectral analysis, including 2D NMR, derivatization, and X-ray crystallography. Caprazamycins are lipo-nucleoside antibiotics, which have a diazepanone core with amino sugar, uridine, and lipid



Scheme 5 The synthetic strategy for the caprazamycin core **20**.



Scheme 6 Hydroamidation of terminal alkynylamide **25** and attempted introduction of a methyl group.



Scheme 7 Hydroamidation of secondary alkynyl amides **31a–d** and synthesis of the core structure of caprazamycin **34**.

side chains. These compounds show antibacterial activity against *Mycobacterium tuberculosis*, including multi-drug resistant strains (*e.g.*, caprazamycin A: MIC = 3.3 μg mL^{-1}). They are thought to inhibit MraY for biosynthesis of peptidoglycan.[21] Because of their interesting biological activities and structures, lipo-nucleoside antibiotics, including caprazamycins, have attracted attention from synthetic chemists and pharmacists. Total synthesis of caprazole, which is a caprazamycin hemisphere, was achieved by Matsuda and Ichikawa *et al*.[22] Several attempts have been made to construct the diazepanone skeleton in these compounds, including reductive amination, intramolecular amidation, and amination *via* double epoxide ring opening.[23–30] Platinum catalyzed 7-*endo* cyclization could provide a concise route for synthesis of the caprazamycin core, and we designed compound **20** as a model compound for this strategy (Scheme 5).

The synthesis commenced with Ns protection of serine methyl ester hydrochloride **22** (Scheme 6). After benzylation of the hydroxyl group using benzyl trichloroacetimidate and a catalytic amount of TfOH,[31] the product **23** was converted to amide **24** by ammonolysis. Propargylation of amide **24** gave the precursor for the 7-*endo* cyclization. As expected, treatment of **25** with 20 mol% of $PtCl_2$ in dichloroethane at 70 °C gave diazepanone **26** in 62% yield with excellent regioselectivity. Unfortunately, methylation of enamide did not give the desired compound **27**. When compound **26** was treated with MeI and NaH in DMF, alkylation at the α-position of the amide proceeded to give compound **28**. *N*-Alkylation using MeI and potassium carbonate in acetone gave a complex mixture.

Thus, the synthetic route was revised, and the methyl group was introduced before construction of the diazepanone core. Because caprazamycins have a substituent at the C7 position, internal alkynyl amides were also required. The secondary alkynyl amide was investigated for the 7-*endo* cyclization. The reaction of **23** with aqueous methyl amine proceeded smoothly to give secondary amide **29**, which was coupled with propargyl bromide and ((4-bromobut-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane **30** for preparing alkynyl amides **31a** and **31b** (Scheme 7). Aryl substituted amides **31c** and **31d** were synthesized from terminal alkynyl amide **31a** by Sonogashira coupling.[15] The platinum catalyzed 7-*endo* cyclizations of these alkynyl amides were investigated. The reaction of compound **31a** under standard conditions gave diazepanone **32a** in 56% yield. While the cyclization of dialkynyl amide **31b** had a poor yield, the aryl alkynyl amide **31c** was easily converted to diazepanone **32c**. These results are consistent with our previous observations. The reaction of furyl substituted alkynyl amide **31d** gave the desired cyclized product **32d**. Because the furyl group could be converted to carboxylate under oxidizing conditions,[32] diazepanone **32d** was converted to the model compound **34** *via* deprotection of the Ns group by treatment with PhSH and potassium carbonate and introduction of the methyl group to the resultant amine **33** by reductive amination. The synthesis of model compound **34**

was accomplished from commercially available serine methyl ester hydrochloride **22** in eight steps.

Conclusions

In summary, we examined the platinum catalyzed 7-*endo* cyclization using various internal alkynyl amides substituted with aryl and alkyl groups. Compared with terminal alkynes, the 7-*endo* cyclization of alkynyl amides with aryl substituents proceeded smoothly, presumably because of stabilization of the transition state. The developed conditions were tolerant of several substituents, such as alkyl groups at the α-position and protecting groups for the amine. The reaction was successfully applied to the synthesis of the caprazamycin core using a secondary alkynyl amide. The model compound **34** was readily accessed from commercially available amino acid derivatives in eight steps. The developed method is a reliable and powerful method for construction of seven-membered diazepanones, and the synthesis of caprazamycin is currently under investigation.

Experimental

General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Analytical thin-layer chromatography was performed with silica gel 60 (Merck). Silica gel column chromatography was performed with Kanto silica gel 60 (particle size, 63–210 μm). All melting points were determined on YAMAMOTO micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-LA 500 at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00) in $CDCl_3$, solvent residual peak (δ 2.04) in acetone-d_6 and solvent residual peak (δ 2.49) in DMSO. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-LA 500 at 126 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO (δ 39.5). Infrared spectra were recorded on a FT/IR-4100 Fourier-transform infrared spectrometer ATR (attenuated total reflectance). Low and high resolution mass spectra were recorded on JEOL JMS-HX/HX 110A mass spectrometer. Optical rotations were determined with a JASCO P-2200KDT polarimeter and are the average of five measurements.

Material

Anhydrous CH_2Cl_2, DMF, CH_3CN and 1,2-dichloroethane (DCE) were purchased from KANTO Chemical Co. Aldrich and Wako chemicals. Materials were obtained from Tokyo Chemical Industry Co., Ltd Aldrich Inc., and other commercial suppliers and used without further purification.

Scheme 1: (*S*)-2-(4-nitro-*N*-(prop-2-ynyl)phenylsulfonamido)-3-phenylpropanamide 6. L-Phenylalanine methyl ester hydrochloride (5 g, 23.18 mmol) was dissolved in 28% aqueous ammonia (50 mL, 0.5 M). After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure to give (*S*)-2-amino-3-phenylpropanamide as a white solid (3 g, 79%).

At 0 °C, to a solution of the above amide (3.00 g, 18.32 mmol) in CH_2Cl_2 (60 mL, 0.3 M) was added Et_3N (5.1 mL, 36.64 mmol, 2 eq.) and subsequently *p*-NsCl (4.06 g, 18.32 mmol, 1 eq.). The reaction mixture was warmed to room temperature and stirred overnight. The precipitate was collected by filtration and washed with $CHCl_3$ (× 3). The resultant white solid corresponding to (*S*)-2-(4-nitrophenylsulfonamido)-3-phenylpropanamide **5** was used without further purification (6 g, 94%).

At 0 °C, to a solution of the above Ns-amide **5** (3.10 g, 8.87 mmol) in DMF (65 mL, 0.14 M) was added K_2CO_3 (2.45 g, 17.75 mmol, 2 eq.) and subsequently propargyl bromide (1.58 mL, 17.75 mmol, 2 eq.). The reaction mixture was warmed to room temperature and stirred for 10 h. After removal the precipitate by filtration, the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc, 1 : 1) afforded the corresponding alkynyl amide **6** as a beige solid (3.22 g, 94%): $[\alpha]_D^{25}$ −127.6 (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (t, 1H, *J* = 2.4 Hz), 2.89 (dd, 1H, *J* = 14.8, 6.2 Hz), 3.35 (dd, 1H, *J* = 14.8, 6.2 Hz), 4.22 (dd, 1H, *J* = 18.8, 2.4 Hz), 4.50 (dd, 1H, *J* = 18.8, 2.4 Hz), 4.61 (dd, 1H, *J* = 8.5, 6.1 Hz), 5.68 (br, 1H, NH_2), 6.30 (br, 1H, NH_2), 7.04–7.15 (m, 5H), 7.75 (d, 2H, *J* = 8.5 Hz), 8.11 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.0, 34.6, 62.4, 74.2, 78.2, 123.9 (2C), 126.9, 128.4 (2C), 128.6 (2C), 129.2 (2C), 136.7, 144.9, 149.9, 170.7; Mp: 129–130 °C; IR (ATR) *ν* 3480, 3370, 3285, 2100, 1670 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{18}N_3O_5S$ [(M + H)$^+$] 388.0967 found 388.0960.

(*S*)-2-(4-Nitro-*N*-(3-phenylprop-2-ynyl)phenylsulfonamido)-3-phenylpropanamide 7. A mixture of iodobenzene (0.22 mL, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) in Et_3N (14 mL, 0.3 M) was stirred for 30 min at room temperature under argon atmosphere. To this mixture was added **6** (774 mg, 2.0 mmol) in solution in THF (6 mL) and the resultant mixture was stirred for 5 h. After removal Et_3N under reduced pressure, the residue was dissolved in $CHCl_3$, washed by brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc, 2 : 1) afforded the corresponding phenylacetylene **7** as an orange oil (781 mg, 84%): $[\alpha]_D^{27}$ −107.8 (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.96 (dd, 1H, *J* = 14.5, 9.4 Hz), 3.42 (dd, 1H, *J* = 14.5, 5.7 Hz), 4.39 (d, 1H, *J* = 18.3 Hz), 4.71 (d, 1H, *J* = 18.3 Hz), 4.72 (m, 1H), 5.47 (br, 1H, NH_2), 6.35 (br, 1H, NH_2), 7.08–7.16 (m, 5H), 7.25 (m, 1H), 7.30–7.38 (m, 4H), 7.69 (d, 2H, *J* = 8.9 Hz), 7.99 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.5, 34.9, 62.7, 83.4, 86.0, 121.7, 123.8 (2C), 126.9, 128.4 (2C), 128.5 (2C), 128.6 (2C), 129.1, 129.3 (2C), 131.3 (2C), 137.0, 145.2, 149.7, 170.8; Mp: 152–153 °C; IR (ATR) *ν* 3474, 3334, 1664, 1602, 1529 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{22}N_3O_5S$ [(M + H)$^+$] 464.1280 found 464.1284.

(*S*,*Z*)-3-Benzyl-4-(4-nitrophenylsulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 9. A solution of alkynylamide **7** (93 mg, 0.20 mmol) and $PtCl_2$ (5.3 mg, 0.02 mmol) in $ClCH_2CH_2Cl$ (1.4 mL) was stirred at 70 °C for 20 h. After cooling, the reaction mixture was concentrated under reduced

pressure. Purification by silica gel chromatography (hexane–EtOAc = 1 : 1) afforded compound **9** (92 mg, 99%) as a pale yellow solid: $[\alpha]_D^{25}$ +25.5 (*c* 0.83, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 3.22 (dd, 1H, *J* = 14.6, 9.4 Hz), 3.32 (dd, 1H, *J* = 14.6, 6.5 Hz), 4.14 (dd, 1H, *J* = 17.7, 4.0 Hz), 4.34 (dd, 1H, *J* = 17.7, 5.4 Hz), 5.03 (dd, 1H, *J* = 9.4, 6.5 Hz), 5.38 (t, 1H, *J* = 5.5 Hz), 6.66 (br, 1H, NH), 7.18–7.20 (m, 3H), 7.26–7.28 (m, 2H), 7.37–7.39 (m, 5H), 7.88 (d, 2H, *J* = 8.5 Hz), 8.20 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 35.9, 43.1, 63.6, 107.7, 124.1 (2C), 126.0 (2C), 127.4, 128.5 (2C), 128.8 (4C), 129.1 (2C), 129.7, 135.1, 136.6, 137.1, 144.5, 150.0, 171.3; Mp: 205–206 °C; IR (ATR) *ν* 3299, 3028, 2922, 1672, 1653, 1528 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{21}N_3O_5S$ $[M^+]$ 463.1202 found 463.1198.

Hydrolysis of (*S*,*Z*)-3-benzyl-4-(4-nitrophenylsulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 9. To a solution of **9** (14.1 mg, 0.031 mmol) in THF/H_2O (3.0 mL/0.60 mL) was added conc. HCl (0.60 mL). The resultant mixture was stirred under reflux overnight and then diluted with water (5 mL) and extracted with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by GPC ($CHCl_3$) to give **13** (9.0 mg, 62%): ^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, 2H, *J* = 8.6 Hz), 7.87 (d, 2H, *J* = 8.0 Hz), 7.73 (d, 2H, *J* = 8.6 Hz), 7.58 (d, 1H, *J* = 7.5 Hz), 7.46 (d, 2H, *J* = 7.5 Hz), 7.25–7.22 (m, 3H), 7.20–7.17 (m, 3H), 4.96 (dd, 1H, *J* = 10.3, 5.2 Hz), 3.81 (ddd, 1H, *J* = 14.9, 9.1, 5.7 Hz), 3.62 (ddd, 1H, *J* = 17.8, 8.6, 5.7 Hz), 3.53 (ddd, 1H, *J* = 14.9, 8.6, 5.7 Hz), 3.41 (dd, 1H, *J* = 14.9, 5.2 Hz), 3.19 (ddd, 1H, *J* = 17.8, 9.1, 5.2 Hz), 3.14 (dd, 1H, *J* = 14.9, 10.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.3, 173.9, 149.9, 144.7, 136.2, 136.0, 133.6, 129.0, 128.9, 128.7, 128.5, 128.0, 127.3, 124.0, 61.7, 40.9, 39.4, 35.5; IR *ν* 2923, 2854, 1744, 1681, 1531, 1350 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{24}N_3O_6S$ $[(M - H)^-]$ 481.1070 found 481.1099.

Tables 1 and 2: general procedure for Sonogashira coupling

A mixture of iodobenzene (2.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), and CuI (0.2 mmol) in Et_3N (14 mL) was stirred for 30 min at room temperature under an argon atmosphere. To this mixture was added **6** (2.0 mmol) in solution in THF (6 mL) and the resultant mixture was stirred with TLC monitoring until the starting material disappeared. After removal of Et_3N under reduced pressure, the residue was dissolved in $CHCl_3$, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc) afforded the corresponding phenylacetylene **14a–g**.

(*S*)-2-(*N*-(3-(2,4-Dimethoxyphenyl)prop-2-yn-1-yl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14a. $[\alpha]_D^{24}$ −82.8 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, *J* = 9.2 Hz), 7.79 (d, 2H, *J* = 9.2 Hz), 7.14–7.06 (m, 6H), 6.44–6.41 (m, 3H), 5.56 (s, 1H), 4.73 (d, 1H, *J* = 18.9 Hz), 4.69 (dd, 1H, J = 8.6, 5.8 Hz), 4.38 (d, 1H, *J* = 18.9 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.44 (dd, 1H, *J* = 14.4, 5.8 Hz), 3.00 (dd, 1H, *J* = 14.4, 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 161.7, 161.5, 149.7, 145.3, 137.3, 134.1, 129.3, 128.6, 128.5, 126.7, 123.7, 105.0, 103.3, 98.5, 85.8, 83.0, 62.8, 55.6, 55.5, 35.5, 34.5; IR (ATR) *ν* 3650, 1690, 1606, 1529 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{26}N_3O_7S$ $[(M + H)^+]$ 524.1491, found 524.1477.

(*S*)-2-(*N*-(3-(4-Methoxyphenyl)prop-2-ynyl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14b. Yellow solid (86%); $[\alpha]_D^{26}$ −97.4 (*c* 0.79, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.96 (dd, 1H, *J* = 14.3, 9.1 Hz), 3.42 (dd, 1H, *J* = 14.3, 5.1 Hz), 3.83 (s, 3H), 4.36 (d, 1H, *J* = 18.5 Hz), 4.69 (d, 1H, *J* = 18.5 Hz), 4.72 (dd, 1H, *J* = 9.1, 5.1 Hz), 5.47 (br, 1H, NH_2), 6.36 (br, 1H, NH_2), 6.83 (d, 2H, *J* = 8.6 Hz), 7.07–7.26 (m, 7H), 7.68 (d, 2H, *J* = 9.1 Hz), 7.97 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.4, 35.0, 55.3, 62.7, 82.0, 88.1, 113.6, 114.2 (2C), 123.8 (2C), 126.8, 128.4 (2C), 128.6 (2C), 129.4 (2C), 132.8 (2C), 137.1, 145.2, 149.7, 160.1, 170.9; Mp: 155–156 °C; IR (ATR) *ν* 3464, 3367, 1683, 1605, 1527, 1508 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{24}N_3O_6S$ $[(M + H)^+]$ 494.1386 found 494.1380.

(*S*)-2-(4-Nitro-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)phenylsulfonamido)-3-phenylpropanamide 14c. $[\alpha]_D^{25}$ −91.4 (*c* 0.93, $CDCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, *J* = 8.3 Hz), 7.68 (d, 2H, *J* = 8.3 Hz), 7.17–7.07 (m, 9H), 6.37 (s, 1H), 5.64 (s, 1H), 4.74 (dd, 1H, *J* = 9.2, 3.8 Hz), 4.70 (d, 1H, *J* = 18.6 Hz), 4.37 (d, 1H, *J* = 18.6 Hz), 3.42 (dd, 1H, *J* = 14.6, 9.2 Hz), 2.96 (dd, 1H, *J* = 14.6, 5.2 Hz), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 149.7, 145.2, 139.4, 137.1, 131.2, 129.4, 129.3, 128.6, 128.4, 126.8, 123.8, 118.6, 86.2, 82.8, 62.7, 35.0, 34.5, 21.5. IR (ATR) *ν* 3458, 3362, 2922, 1734, 1685, 1528 cm^{-1}. HRMS (FAB) calcd for $C_{25}H_{24}N_3O_5S$ $[(M + H)^+]$ 478.1437, found 478.1427.

(*S*)-2-(*N*-(3-(Naphthalen-1-yl)prop-2-ynyl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14d. Beige oil (87%); $[\alpha]_D^{26}$ −99.7 (*c* 1.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 3.04 (dd, 1H, *J* = 14.5, 9.1 Hz), 3.46 (dd, 1H, *J* = 14.5, 5.7 Hz), 4.57 (d, 1H, *J* = 18.3 Hz), 4.79 (dd, 1H, *J* = 9.1, 5.7 Hz), 4.84 (d, 1H, *J* = 18.3 Hz), 5.87 (br, 1H, NH_2), 6.41 (br, 1H, NH_2), 7.08–7.16 (m, 5H), 7.38–7.52 (m, 4H), 7.69 (d, 2H, *J* = 9.1 Hz), 7.84–7.86 (m, 4H), 8.00 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.8, 35.1, 62.5, 84.2, 88.1, 119.3, 123.8 (2C), 125.1, 125.5, 126.6, 126.9, 127.0, 128.4 (2C), 128.5, 128.7 (2C), 129.3 (2C), 129.5, 130.6, 133.0, 133.1, 136.9, 145.2, 149.6, 170.9; Mp: 165–166 °C; IR (ATR) *ν* 3467, 3370, 1683, 1606, 1526 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{24}N_3O_5S$ $[(M + H)^+]$ 514.1437 found 514.1434.

(*S*)-2-(*N*-(3-(4-Chlorophenyl)prop-2-ynyl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14e. Beige solid (96%); $[\alpha]_D^{26}$ −83.1 (*c* 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.94 (dd, 1H, *J* = 14.5, 9.1 Hz), 3.40 (dd, 1H, *J* = 14.5, 5.7 Hz), 4.42 (d, 1H, *J* = 18.5 Hz), 4.67 (d, 1H, *J* = 18.5 Hz), 4.72 (dd, 1H, *J* = 9.1, 5.7 Hz), 5.71 (br, 1H, NH_2), 6.37 (br, 1H, NH_2), 7.07–7.09 (m, 4H), 7.17–7.19 (m, 3H), 7.26–7.31 (m, 2H, *J* = 8.5 Hz), 7.68 (d, 2H, *J* = 9.1 Hz), 8.00 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.5, 34.8, 62.4, 84.4, 84.7, 120.1, 123.9 (2C), 126.9, 128.4 (2C), 128.6 (2C), 128.9 (2C), 129.3 (2C), 132.5 (2C), 135.2, 136.9, 145.0, 149.8, 170.9; Mp: 154–155 °C; IR (ATR) *ν* 3463, 3350, 3108, 2975, 2919, 1684, 1589 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{21}ClN_3O_5S$ $[(M + H)^+]$ 498.0890 found 498.0878.

(*S*)-2-(4-Nitro-*N*-(3-(4-(trifluoromethyl)phenyl)prop-2-ynyl)-phenylsulfonamido)-3-phenylpropanamide 14f. Beige solid (95%); $[\alpha]_D^{25}$ −85.1 (*c* 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.96 (dd, 1H, *J* = 14.5, 9.1 Hz), 3.40 (dd, 1H, *J* = 14.5, 5.7 Hz), 4.47 (d, 1H, *J* = 18.5 Hz), 4.69 (d, 1H, *J* = 18.5 Hz), 4.72 (m, 1H), 5.64 (br, 1H, NH_2), 6.37 (br, 1H, NH_2), 7.08–7.11 (m, 5H), 7.37 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 8.02 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.6, 34.7, 62.3, 84.4, 85.9, 123.6 (q, *J* = 273. 4 Hz), 124.7 (2C), 125.5 (2C), 127.0, 128.4 (2C), 128.6 (2C), 129.2 (2C), 130.8 (q, *J* = 33.0 Hz), 131.6 (2C), 136.8 (2C), 145.0, 149.8, 170.9; Mp: 167–168 °C; IR (ATR) *v* 3475, 3340, 3197, 3117, 1667, 1605, 1530 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{21}F_3N_3O_5S$ [(M + H)$^+$] 532.1154 found 532.1160.

(*S*)-2-(4-Nitro-*N*-(3-(4-nitrophenyl)prop-2-yn-1-yl)phenyl-sulfonamido)-3-phenylpropanamide 14g. $[\alpha]_D^{25}$ −43.5 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, 2H, *J* = 8.0 Hz), 8,05 (d, 2H, *J* = 7.7 Hz), 7.70 (d, 2H, *J* = 7.5 Hz), 7.44 (d, 2H, *J* = 8.1 Hz), 7.19–7.05 (m, 5H), 6.34 (s, 1H), 5.50 (s, 1H), 4.72 (ddd, 1H, *J* = 9.2, 5.7, 1.4 Hz), 4.69 (d, 1H, *J* = 17.8 Hz), 4.53 (dd, 1H, *J* = 18.6, 1.2 Hz), 3.41 (dd, 1H, *J* = 14.9, 5.7 Hz), 2.96 (dd, 1H, *J* = 14.8, 9.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 149.9, 147.5, 144.8, 136.6, 132.2, 129.2, 128.7, 128.5, 128.3, 127.0, 124.0, 123.7, 88.6, 83.7, 62.1, 34.7, 34.65; IR (ATR) *v* 3853, 3734, 3628, 1770, 1685, 1521 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{21}N_4O_7S$ [(M + H)$^+$] 509.1131, found 509.1122.

Tables 1 and 2: general procedure for 7-*endo* cyclization using $PtCl_2$

A solution of alkynylamide (1 eq.) and $PtCl_2$ (10 mol%) in $ClCH_2CH_2Cl$ (0.15 M) was stirred at 70 °C with TLC monitoring. After the starting material disappeared, the reaction mixture was concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc) afforded the corresponding cyclic enamide.

(*S*,*Z*)-3-Benzyl-7-(2,4-dimethoxyphenyl)-4-((4-nitrophenyl)-sulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15a. $[\alpha]_D^{25}$ +20.9 (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, 2H, *J* = 8.9 Hz), 7.93 (d, 2H, *J* = 8.6 Hz), 7.30–7.18 (m, 5H), 7.07 (d, 1H, *J* = 8.6 Hz), 6.89 (s, 1H), 6.45 (dd, 1H, *J* = 8.3, 2.3 Hz), 6.42 (d, 1H, *J* = 2.3 Hz), 5.20 (t, 1H, *J* = 4.9, 4.0 Hz), 4.99 (t, 1H, *J* = 9.5, 6.9 Hz), 4.37 (dd, 1H, *J* = 18.3, 5.2 Hz), 4.10 (dd, 1H, *J* = 18.3, 4.0 Hz), 3.83 (s, 3H), 3.75 (s, 3H), 3.35 (dd, 1H, *J* = 14.3, 6.9 Hz), 3.24 (dd, 1H, *J* = 14.3, 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 161.8, 157.1, 150.0, 144.6, 135.2, 134.6, 130.5, 128.79, 128.75, 128.6, 127.3, 124.0, 118.7, 109.0, 104.7, 98.8, 63.5, 55.52, 55.49, 43.2, 35.5; IR (ATR) *v* 3365, 3105, 2933, 1664, 1607, 1528 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{26}N_3O_7S$ [(M + H)$^+$] 524.1491, found 524.1487.

(*S*,*Z*)-3-Benzyl-7-(4-methoxyphenyl)-4-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15b. Yellow oil (82%); $[\alpha]_D^{25}$ +28.5 (*c* 2.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.11 (dd, 1H, *J* = 14.3, 9.1 Hz), 3.18 (dd, 1H, *J* = 14.3, 7.4 Hz), 3.72 (s, 3H), 4.04 (dd, 1H, *J* = 16.9, 5.1 Hz), 4.09 (dd, 1H, *J* = 16.9, 5.1 Hz), 4.86 (t, 1H, *J* = 7.4 Hz), 5.29 (t, 1H, *J* = 5.1 Hz), 6.78 (d, 2H, *J* = 8.5 Hz), 6.95 (br, 1H, NH), 7.08–7.18 (m, 7H), 7.78 (d, 2H, *J* = 9.1 Hz), 8.08 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.6, 36.4, 43.1, 55.4, 64.0, 106.3, 114.3 (2C), 124.0 (2C), 127.3 (2C), 128.5 (2C), 128.7 (2C), 128.8 (2C), 128.9, 135.2, 136.9, 144.3, 150.0, 160.7, 171.1; IR (ATR) *v* 3210, 3106, 3032, 2919, 2849, 1667, 1606 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{23}N_3O_6S$ [M$^+$] 493.1308 found 493.1293.

(*S*,*Z*)-3-Benzyl-4-((4-nitrophenyl)sulfonyl)-7-(*p*-tolyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15c. $[\alpha]_D^{25}$ +31.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, 2H, *J* = 8.6 Hz), 7.89 (d, 2H, *J* = 8.6 Hz), 7.29–7.15 (m, 9H), 6.68 (s, 1H), 5.37 (t, 1H, *J* = 4.6 Hz), 5.01 (t, 1H, *J* = 7.5 Hz), 4.28 (dd, 1H, *J* = 17.5, 5.5 Hz), 4.13 (dd, 1H, *J* = 17.5, 4.3 Hz), 3.31 (dd, 1H, *J* = 14,6, 6.9 Hz), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 150.0, 144.4, 139.9, 136.7, 135.1, 134.0, 129.7, 128.79, 128.77, 128.5, 127.3, 125.8, 124.1, 107.0, 63.8, 43.1, 36.1, 21.2; IR (ATR) *v* 3734, 2981, 2917, 1770, 1670, 1530, 1350 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{24}N_3O_5S$ [(M + H)$^+$] 478.1437, found 478.1436.

(*S*,*Z*)-3-Benzyl-7-(naphthalen-1-yl)-4-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15d. Beige solid (87%); $[\alpha]_D^{25}$ +7.8 (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31 (dd, 1H, *J* = 14.8, 10.9 Hz), 3.42 (dd, 1H, *J* = 14.8, 5.1 Hz), 4.12 (dd, 1H, *J* = 19.7, 2.2 Hz), 4.57 (dd, 1H, *J* = 19.7, 5.1 Hz), 5.10 (dd, 1H, *J* = 10.9, 5.1 Hz), 5.16 (t, 1H, *J* = 2.2 Hz), 6.74 (br, 1H, NH), 7.20–7.27 (m, 6H), 7.41 (t, 1H, *J* = 6.9 Hz), 7.47–7.50 (m, 2H), 7.69 (br d, 1H), 7.83 (m, 4H), 8.19 (d, 2H, *J* = 9.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 34.4, 42.7, 62.7, 109.9, 124.1 (3C), 125.2, 126.4, 126.5, 127.0, 127.4, 128.4 (2C), 128.6 (2C), 128.7, 128.8 (2C), 129.7, 130.3, 133.6 (2C), 134.9, 135.6, 144.9, 149.9, 171.8; Mp: 197–198 °C; IR (ATR) *v* 3310, 2919, 1700, 1679, 1605, 1520 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{24}N_3O_5S$ [(M + H)$^+$] 514.1437 found 514.1442.

(*S*,*Z*)-3-Benzyl-7-(4-chlorophenyl)-4-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15e. Beige solid (99%); $[\alpha]_D^{26}$ +25.4 (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (dd, 1H, *J* = 14.9, 9.5 Hz), 3.27 (dd, 1H, *J* = 14.9, 6.8 Hz), 4.13 (dd, 1H, *J* = 17.7, 4.3 Hz), 4.30 (dd, 1H, *J* = 17.7, 5.7 Hz), 4.95 (dd, 1H, *J* = 9.5, 6.8 Hz), 5.39 (t, 1H, *J* = 4.5 Hz), 6.98 (br, 1H, NH), 7.14–7.16 (m, 2H), 7.23–7.26 (m, 5H), 7.33–7.35 (m, 2H), 7.83 (d, 2H, *J* = 9.1 Hz), 8.17 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 35.8, 43.0, 63.6, 108.3, 124.1 (2C), 127.3, 128.4 (6C), 128.6, 128.8 (2C), 129.3, 135.0, 135.3, 135.6, 135.8, 144.3, 150.0, 171.4; Mp: 197–198 °C; IR (ATR) *v* 3297, 3099, 3027, 2922, 1674, 1653, 1598, 1529 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{20}ClN_3O_5S$ [M$^+$] 497.0812 found 497.0822.

(*S*,*Z*)-3-Benzyl-4-(4-nitrophenylsulfonyl)-7-(4-(trifluoromethyl)-phenyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15f. Beige solid (99%); $[\alpha]_D^{26}$ +30.0 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (dd, 1H, *J* = 14.9, 9.7 Hz), 3.29 (dd, 1H, *J* = 14.9, 6.3 Hz), 4.15 (dd, 1H, *J* = 18.0, 4.0 Hz), 4.38 (dd, 1H, *J* = 18.0, 5.1 Hz), 4.97 (dd, 1H, *J* = 9.7, 6.3 Hz), 5.44 (t, 1H, *J* = 4.0 Hz), 7.04 (br, 1H, NH), 7.13–7.15 (m, 2H), 7.24–7.26 (m, 3H), 7.42–7.44 (m, 2H), 7.63–7.65 (m, 2H), 7.88 (d, 2H, *J* = 8.6 Hz), 8.20 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 35.5, 43.0, 63.6, 109.7, 123.9 (q, *J* = 271.0), 124.1 (2C), 126.0, 126.6 (2C), 127.4 (2C), 128.4 (2C), 128.7 (2C), 128.8 (2C), 131.6 (q,

J = 33.0), 134.9, 135.4, 140.6, 144.4, 150.0, 171.6; Mp: 202–203 °C; IR (ATR) ν 3292, 2921, 1676, 1654, 1529 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{20}F_3N_3O_5S$ $[M^+]$ 531.1076 found 531.1076.

Hydrolysis of (*S*,*Z*)-3-benzyl-7-(4-chlorophenyl)-4-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 15e. To a solution of **15e** (25.2 mg, 0.031 mmol) in THF/H_2O (1.0 mL/0.20 mL) was added conc. HCl (0.20 mL). The resultant mixture was stirred reflux overnight and then diluted with water (5 mL) and extracted with $CHCl_3$ (5 × 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by GPC ($CHCl_3$) to give **16** (24.3 mg, 93%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, 1H, J = 8.0 Hz), 8.08 (d, 2H, J = 8.6 Hz), 7.99 (d, 1H, J = 8.6 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.83 (d, 1H, J = 6.9 Hz), 7.67 (d, 2H, J = 8.6 Hz), 7.58 (ddd, 1H, J = 6.9, 6.9, 1.7 Hz), 7.53 (ddd, 1H, J = 6.9, 6.9, 1.2 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.24–7.17 (m, 5H), 4.93 (dd, 1H, J = 10.3, 5.6 Hz), 3.85 (m, 1H), 3.67–3.57 (m, 2H), 3.37 (dd, 1H, J = 14.9, 5.6 Hz), 3.25 (m, 1H), 3.14 (dd, 1H, J = 14.9, 10.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.7, 175.1, 149.9, 144.8, 136.2, 134.3, 134.0, 133.7, 130.2, 129.1, 129.0, 128.9, 127.1, 126.6, 125.6, 124.4, 42.4, 41.0, 35.5; IR ν 2917, 2849, 1713, 1678, 1530, 1349, 1165 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{25}N_2O_7S$ $[M - H]^-$ 531.1226 found 531.1229.

(*S*,*Z*)-3-Isobutyl-4-(4-nitrophenylsulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 19a. Orange oil (84%); $[\alpha]_D^{26}$ +8.9 (c 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (d, 3H, J = 6.3 Hz), 0.99 (d, 3H, J = 6.3 Hz), 1.70–1.74 (m, 2H), 1.82–1.86 (m, 1H), 4.08 (dd, 1H, J = 18.3, 3.5 Hz), 4.46 (dd, 1H, J = 18.3, 5.1 Hz), 4.77 (br dd, 1H), 5.22 (t, 1H, J = 5.1 Hz), 6.73 (br, 1H, NH), 7.12–7.15 (m, 2H), 7.27–7.35 (m, 3H), 8.04 (d, 2H, J = 9.2 Hz), 8.27 (d, 2H, J = 9.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.5, 22.6, 24.3, 38.3, 42.5, 60.7, 107.3, 124.0 (2C), 125.8 (2C), 128.7 (2C), 128.9 (2C), 129.5, 136.1, 137.1, 144.5, 150.0, 172.4; IR (ATR) ν 3106, 2959, 2932, 2870, 1661, 1528 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{24}N_3O_5S$ $[(M + H)^+]$ 430.1437 found 430.1418.

(*S*,*Z*)-3-Isopropyl-4-(4-nitrophenylsulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 19b. Yellow oil (84%); $[\alpha]_D^{25}$ −50.9 (c1.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (d, 3H, J = 1.4 Hz), 1.05 (d, 3H, J = 1.4 Hz), 2.17–2.22 (m, 1H), 4.11–4.14 (m, 2H), 4.22 (d, 1H, J = 11.4 Hz), 5.40 (t, 1H, J = 5.1 Hz), 7.04 (br, 1H, NH), 7.26–7.28 (m, 2H), 7.36–7.38 (m, 3H), 8.03 (d, 2H, J = 9.1 Hz), 8.26 (d, 2H, J = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.6 (2C), 27.5, 43.0, 69.7, 107.4, 124.0 (2C), 125.9 (2C), 128.9 (4C), 129.6, 136.3, 137.6, 143.9, 150.0, 170.8; IR (ATR) ν 3218, 3105, 2968, 2932, 2872, 1667, 1527 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{21}N_3O_5S$ $[M^+]$ 415.1202 found 415.1200.

(*S*,*Z*)-3-Methyl-4-(4-nitrophenylsulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 19c. Yellow oil (84%); $[\alpha]_D^{26}$ −19.8 (c 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (d, 3H, J = 7.4 Hz), 4.15 (dd, 1H, J = 17.7, 4.0 Hz), 4.40 (dd, 1H, J = 17.7, 5.2 Hz), 4.83 (q, 1H, J = 7.4 Hz), 5.29 (t, 1H, J = 5.2 Hz), 6.74 (br, 1H, NH), 7.17–7.19 (m, 2H), 7.32–7.36 (m, 3H), 8.03 (d, 2H, J = 9.1 Hz), 8.26 (d, 2H, J = 9.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.3, 42.8, 58.3, 107.5, 124.1 (2C), 125.9 (2C), 128.6 (2C), 129.0 (2C), 129.6, 136.6, 137.0, 144.5, 150.1, 172.3; IR (ATR) ν 3230, 3104, 2925, 1666, 1606, 1529 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{18}N_3O_5S$ $[(M + H)^+]$ 388.0967 found 388.0973.

(*S*)-3-Benzyl-7-phenyl-4-tosyl-4,5-dihydro-1*H*-1,4-diazepin-2-(3*H*)-one 19d. $[\alpha]_D^{25}$ +32.4 (c 0.94, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 8.3 Hz), 7.42–7.34 (m, 3H), 7.32–7.16 (m, 9H), 6.58 (s, 1H), 5.37 (t, 1H, J = 4.0 Hz), 5.03 (t, 1H, J = 8.1 Hz), 4.26 (dd, 1H, J = 17.8, 5.5 Hz), 4.05 (dd, 1H, J = 17.8, 4.3 Hz), 3.28 (dd, 1H, J = 14.6, 7.5 Hz), 3.18 (dd, J = 14.6, 9.2 Hz), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 143.7, 137.3, 136.3, 135.8, 135.4, 129.5, 129.4, 128.9, 128.8, 128.7, 127.5, 127.1, 126.0, 108.4, 63.3, 42.8, 36.2, 21.5; IR (ATR) ν 3750, 1770, 1670, 1245, 1162 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{25}N_2O_3S$ $[(M + H)^+]$ 433.1586, found 433.1555.

(*S*)-Isopropyl 2-benzyl-3-oxo-5-phenyl-2,3,4,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate 19e. $[\alpha]_D^{25}$ +5.2 (c 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.20 (m, 10H), 6.93 (s, 1H), 5.40 (s, 1H), 4.94 (m, 1H), 4.82 (br, 1H), 4.18 (br, 2H), 3.32 (s, 2H), 1.30–1.20 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 155.4, 138.1, 137.0, 135.8, 129.6, 129.1, 128.9, 128.5, 126.8, 126.2, 110.5, 69.8, 62.5, 44.3, 35.2, 22.05, 22.00; IR (ATR) ν 3244, 2979, 1686, 1414, 1373, 1246 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{25}N_2O_3$ $[(M + H)^+]$ 365.1865, found 365.1856.

(*S*)-Benzyl 2-benzyl-3-oxo-5-phenyl-2,3,4,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate 19f. $[\alpha]_D^{25}$ +10.8 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.09 (m, 15H), 6.93 (br, 1H), 5.41 (br, 1H), 5.15 (s, 2H), 4.95 (br, 1H), 4.23 (br, 2H), 3.29 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.5, 138.03, 136.6, 129.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 126.8, 126.2, 110.2, 67.8, 62.5, 44.0, 35.0; IR (ATR) ν 3255, 3061, 3029, 2956, 1697, 1419, 1244 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{25}N_2O_3$ $[(M + H)^+]$ 413.1865, found 413.1864.

(*S*)-*tert*-Butyl 2-benzyl-3-oxo-5-phenyl-2,3,4,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate 19g. $[\alpha]_D^{25}$ +0.40 (c 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.20 (m, 10H), 6.79 (s, 1H), 5.38 (s, 1H), 4.70 (br, 1H), 4.27 (br, 1H), 4.02 (br, 1H), 3.31 (br, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 154.9, 138.4, 137.4, 135.7, 129.1, 129.0, 128.95, 128.89, 128.5, 126.7, 126.2, 110.8, 62.9, 44.7, 35.3, 28.3; IR (ATR) ν 3256, 2981, 1770, 1697, 1367, 1247 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{27}N_2O_3$ $[(M + H)^+]$ 379.2022, found 379.2000.

(*S*)-2-(2-Oxo-6-phenyl-2*H*-1,3-oxazin-3(4*H*)-yl)-3-phenylpropanamide 19g′. $[\alpha]_D^{25}$ −48.9 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 7.5 Hz), 7.35–7.16 (m, 8H), 6.25 (s, 1H), 5.64 (s, 1H), 5,48 (s, 1H), 4.74 (t, 1H, J = 8.6, 7.5 Hz), 4.49 (dd, J = 14.3, 1.8 Hz), 3.32 (dd, 1H, J = 14.3, 7.5 Hz), 3.07 (dd, 1H, J = 14.3, 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 155.8, 141.6, 135.7, 133.1, 128.9, 128.7, 128.5, 128.2, 127.3, 127.0, 103.5, 57.1, 46.5, 34.8; IR (ATR) ν 3734, 2994, 1770, 1697, 1220 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{19}N_2O_3$ $[(M + H)^+]$ 323.1396, found 323.1384.

(*S*)-2-(*N*-(But-2-yn-1-yl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14h. At 0 °C, to a solution of Ns-amide **5** (429 mg, 1.23 mmol), 2-butyn-1-ol (0.09 mL, 1.23 mmol) and PPh_3 (322 mg, 1.23 mmol) in THF (10 mL) was added dropwise DIAD (248 mg, 1.23 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The resultant solution was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc, 1 : 1) afforded the corresponding alkynyl amide **14h** (192 mg, 39%) as a white solid: $[\alpha]_D^{25}$ −104.7 (*c* 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, 2H, J = 8.6 Hz), 7.70 (d, 2H, J = 8.6 Hz), 7.15 (t, 1H, J = 6.9 Hz), 7.10 (t, 2H, J = 6.9 Hz), 7.05 (d, 2H, J = 6.9 Hz), 6.35 (br, 1H), 5.51 (br, 1H), 4.41 (dq, 1H, J = 17.8, 2.3 Hz), 4.13 (dq, 1H, J = 17.8, 2.3 Hz), 3.38 (dd, 1H, J = 14.9, 5.7 Hz), 2.90 (dd, 1H, J = 14.9, 9.2 Hz), 1.73 (t, 3H, J = 2.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.0, 149.8, 145.2, 137.2, 129.3, 128.52, 128.45, 126.8, 123.7, 82.4, 73.6, 62.6, 34.7, 34.3, 3.4; IR (ATR): ν 3438, 2920, 2854, 1691, 1607, 1527, 1348, 1152 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{19}H_{20}N_3O_5S$ [(M + H)$^+$] 402.1124; found: 402.1148.

7-*endo* Cyclization of (*S*)-2-(*N*-(but-2-yn-1-yl)-4-nitrophenylsulfonamido)-3-phenylpropanamide 14h using $PtCl_2$. 15h: $[\alpha]_D^{25}$ +55.9 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, 2H, J = 9.0 Hz), 7.77 (d, 2H, J = 9.0 Hz), 7.24–7.21 (m, 3H), 7.14–7.12 (m, 2H), 6.18 (m, 1H), 4.94 (dd, 1H, J = 10.7, 5.6 Hz), 4.82 (m, 1H), 4.29 (m, 1H), 3.89 (m, 1H), 3.27 (dd, 1H, J = 14.6, 5.6 Hz), 3.10 (dd, 1H, J = 14.6, 10.7 Hz), 1.76 (d, 1H, J = 1.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 148.6, 144.9, 135.0, 128.8, 128.6, 128.4, 127.3, 123.9, 105.4, 62.8, 42.4, 34.8, 23.5; IR (ATR): ν 3103, 2976, 2919, 1666, 1529, 1348, 1236, 1165, 1091 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{19}H_{20}N_3O_5S$ [(M + H)$^+$] 402.1124; found: 402.1148.

17: $[\alpha]_D^{24}$ −20.2 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, 2H, J = 8.8 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.13–7.07 (m, 3H), 7.00–6.95 (m, 2H), 6.42 (br, 1H), 5.41 (br, 1H), 4.59 (dd, 1H, J = 9.3, 6.1 Hz), 3.74 (m, 1H), 3.62 (ddd, 1H, J = 15.1, 9.3, 5.8 Hz), 3.19 (dd, 1H, J = 14.9, 6.1 Hz), 3.08–2.92 (m, 2H), 2.80 (dd, 1H, J = 14.9, 9.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.4, 171.9, 149.8, 144.5, 136.3, 129.0, 128.7, 127.9, 126.9, 124.2, 61.2, 43.3, 39.7, 33.8, 30.1; IR (ATR): ν 3460, 3362, 2924, 2835, 1692, 1529, 1349, 1160 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{19}H_{22}N_3O_6S$ [(M + H)$^+$] 420.1229; found: 420.1221.

(*S*)-2-(4-Nitro-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)phenylsulfonamido)-3-phenylpropanamide 14i. At 0 °C, to a solution of Ns-amide **5** (349 mg, 1.00 mmol) in CH_3CN (10 mL) was added K_2CO_3 (829 mg, 6.0 mmol) and subsequently TMS-propargyl bromide (191 mg, 1.0 mmol). The reaction mixture was warmed to room temperature and stirred overnight. After removal of the precipitate by filtration, the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (hexane–EtOAc, 1 : 1) afforded the corresponding TMS-alkynyl amide **14i** (161 mg, 35%) as a beige solid: $[\alpha]_D^{25}$ −113.4 (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, 2H, J = 9.0 Hz), 7.71 (d, 2H, J = 9.0 Hz), 7.13 (m, 1H), 708–7.06 (m, 4H), 6.37 (br, 1H), 5.48 (br, 1H), 4.63 (dd, 1H, J = 9.5, 5.1 Hz), 4.55 (d, 1H, 18.8 Hz), 4.15 (d, 1H, J = 18.8 Hz), 3.35 (dd, 1H, J = 14.6, 5.1 Hz), 2.90 (dd, 1H, J = 14.6, 9.5 Hz), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 149.8, 145.1, 137.2, 129.3, 128.51, 128.46, 126.8, 123.8, 99.7, 91.3, 63.0, 35.0, 34.3, −0.4; IR (ATR): ν 3468, 3365, 2960, 2180, 1682, 1605, 1529, 1348, 1160, 846 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{21}H_{26}N_3O_5SSi$ [(M + H)$^+$]: 460.1362; found: 460.1371.

(*S*)-Methyl 3-(benzyloxy)-2-(4-nitrophenylsulfonamido)-propanoate 23. To a solution of **22** (15.4 g, 99.1 mmol) in CH_2Cl_2 (500 mL) was added diisopropylethylamine (38 mL, 218 mmol) and *p*NsCl (23.1 g, 104 mmol) successively at 0 °C, and the solution was stirred at the same temperature for 3.5 h. The reaction was quenched with saturated aq. NH_4Cl and concentrated. The residue was dissolved in H_2O and extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized from EtOAc–hexane to afford Ns amide (28.3 mg, 94%) as a colorless solid: $[\alpha]_D^{25}$ −4.2 (*c* 1.0, acetone); ^{1}H NMR (acetone-d_6, 500 MHz): δ 8.43 (d, 2H, J = 9.2 Hz), 8.15 (d, 2H, J = 9.2 Hz), 7.29 (d, 1H, J = 9.2 Hz), 4.24 (t, 1H, J = 5.7 Hz), 4.17 (ddd, 1H, J = 4.6, 4.6, 9.2 Hz), 3.86 (ddd, 1H, J = 5.2, 5.7, 10.9 Hz), 3.76 (ddd, 1H, J = 5.2, 5.7, 10.9 Hz), 3.49 (s, 3H); ^{13}C NMR (acetone-d_6, 126 MHz): δ 170.7, 150.9, 148.0, 129.3, 125.0 63.8, 59.3, 52.4; IR (ATR) ν 3546, 3261, 3107, 2959, 2894, 1741, 1606, 1526, 1446, 1433, 1349, 1313 cm^{-1}; HRMS (FAB$^+$) Calcd for $C_{10}H_{12}N_2O_7S$ [(M + H)$^+$]: 305.0443; found: 305.0440.

To a solution of the above Ns amide (4.25 g, 14.0 mmol) in 1,4-dioxane (75 mL) was added benzyl 2,2,2-trichloroacetimidate (3.37 mL, 18.1 m mol) and TfOH (0.185 mL, 2.10 mmol) at room temperature and stirred at the same temperature for 1.5 h. The resulting mixture was diluted with EtOAc, and washed with saturated aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. After purification by silica gel column chromatography (hexane–EtOAc = 2 : 1), the crude product was recrystallized from hexane–EtOAc to afford **23** (3.52 g, 64%) as a colorless solid: $[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): δ 8.28 (d, 2H, J = 8.6 Hz), 8.01 (d, 2H, J = 8.6 Hz), 7.36–7.26 (m, 3H), 7.22–7.17 (m, 2H), 5.66 (br s, 1H), 4.45 (q, 2H, J = 12.0 Hz), 4.24 (ddd, 1H, J = 9.2, 3.4, 3.4 Hz), 3.81 (dd, 1H, J = 9.2, 3.4 Hz), 3.66 (dd, 1H, J = 9.2, 3.4 Hz), 3.61 (s, 3H); ^{13}C NMR (126 MHz, $CHCl_3$): δ 169.5, 150.0, 146.2, 136.9, 128.5, 128.3, 128.1, 127.7, 124.2, 73.4, 70.2, 56.3, 52.9; IR (ATR): ν 3279, 3106, 2955, 2871, 1745, 1348, 1312, 1167, 1138, 1092 cm^{-1} HRMS (FAB$^+$): Calcd for $C_{17}H_{18}N_2O_7S$ [(M + H)$^+$]: 395.0913; found: 395.0913.

(*S*)-3-(Benzyloxy)-2-(4-nitrophenylsulfonamido)propanamide 24. To a solution of **23** (2.79 g, 7.08 mmol) in 1,4-dioxane (18 mL) was added 28% aq. NH_3 (18 mL) at room temperature, and stirred at the same temperature for 20 h. After additional 28% aq. NH_3 (9.0 mL) was added, and then the solution was stirred for 7 h. The solution was added H_2O (18 mL), and stirred for an additional 25 h. The resulting solution was concentrated, and the resulting residue was recrystallized from MeOH–toluene–hexane to afford **24** (1.86 g, 69%) as a colorless solid: $[\alpha]_D^{26}$ +37.4 (*c* 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.59 (d, 1H, J = 8.6 Hz), 8.34 (dt, 2H, J = 8.6, 1.7 Hz), 8.08

(dt, 2H, J = 8.6, 1.7 Hz), 7.49 (br s, 1H), 7.38–7.26 (m, 3H), 7.25–7.18 (m, 3H), 4.39 (s, 2H), 4.09 (ddd, 1H, J = 8.6, 7.4, 5.2 Hz), 3.56 (dd, 1H, J = 10.3, 5.2 Hz), 3.51 (dd, 1H, J = 10.3, 7.4 Hz); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.1, 149.2, 147.0, 137.7, 128.0, 127.4, 127.3, 124.1, 71.9, 70.2, 56.2; IR (ATR): ν 3415, 3203, 3095, 2867, 1684, 1673, 1530, 1343, 1165, 1091 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{16}H_{17}N_3O_6S$ [(M + H)$^+$]: 380.0916; found: 380.0922.

(*S*)-3-(Benzyloxy)-2-(4-nitro-*N*-(prop-2-yn-1-yl)phenylsulfonamido)propanamide 25. To a solution of **24** (1.81 g, 4.78 mmol) and K_2CO_3 (1.98 g, 14.3 mmol) in DMF (24 mL) was added propargyl bromide (1.1 mL, 14.6 mmol) at 0 °C. After stirring for 0.5 h, the mixture was allowed to warm to room temperature, and stirred for 2.5 h. The resulting mixture was diluted in Et_2O, washed with H_2O once and brine four times. The organic layer was dried over $MgSO_4$, filtered, and concentrated. After purification by silica gel column chromatography ($CHCl_3$–MeOH = 30 : 1), the obtained product was recrystallized from MeOH–toluene–hexane to afford **25** (1.33 g, 69%) as a colorless solid: $[\alpha]_D^{26}$ +8.4 (c 0.50, acetone); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19 (dt, 2H, J = 8.9, 2.0 Hz), 8.08 (dt, 2H, J = 8.9, 2.0 Hz), 7.52 (br s, 1H), 7.32–7.20 (m, 4H), 7.19–7.14 (m, 2H), 4.61 (dd, 1H, J = 4.9, 7.7 Hz), 4.49–4.29 (m, 4H), 3.83–3.72 (m, 2H), 3.18 (dd, 1H, J = 2.3, 2.3 Hz); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.4, 149.5, 145.2, 137.6, 128.9, 128.0, 127.7, 127.5, 124.0, 79.7, 74.9, 72.1, 68.3, 59.0, 34.5; IR (ATR): ν 3464, 3282, 1683, 1525, 1362, 1350, 1340, 1311, 1157, 1131, 1095, 1088 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{19}H_{19}N_3O_6S$ [(M + H)$^+$]: 418.1073; found: 418.1074.

(*S*)-3-((Benzyloxy)methyl)-4-((4-nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 26. To a solution of **25** (49.0 mg, 0.117 mmol) in 1,2-DCE (1.2 mL) was added $PtCl_2$ (6.3 mg, 0.024 mmol) one portion. The mixture was stirred at room temperature for 19 h, and then heated at 50 °C for 24 h, 80 °C for 24 h. After cooling to room temperature, the resulting mixture was filtrated through Celite and washed with acetone and MeOH. The filtrate was concentrated. After purification by silica gel column chromatography (hexane–acetone = 2 : 1 and 3 : 2, twice), the crude product was recrystallized from hexane–acetone to afford **26** (30.3 mg, 62%) as a colorless oil: $[\alpha]_D^{26}$ +14.4 (c 0.050, acetone); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.05 (d, 1H, J = 5.7 Hz), 8.22 (dt, 2H, J = 9.2, 2.3 Hz), 8.00 (dt, 2H, J = 9.2, 2.3 Hz), 7.29–7.20 (m, 3H), 7.14–7.08 (m, 2H), 5.57–5.49 (m, 1H), 4.88 (ddd, 1H, J = 10.3, 5.2, 2.3 Hz), 4.71 (dd, 1H, J = 9.7, 4.6 Hz), 4.41–4.30 (m, 3H), 3.86–3.74 (m, 2H), 3.68 (dd, 1H, J = 10.9, 4.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6): δ170.2, 149.6, 144.4, 137.3, 128.5, 128.1, 127.6, 124.2, 122.2, 107.8, 71.8, 65.1, 62.0, 43.1; IR (ATR): ν 3332, 1692, 1663, 1527, 1368, 1348, 1337, 1310, 1160, 1087 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{19}H_{19}N_3O_6S$ [(M + H)$^+$]: 418.1073; found: 418.1078.

(*S*)-3-(Benzyloxy)-*N*-methyl-2-(4-nitrophenylsulfonamido)propanamide 29. To a solution of **24** (3.50 g, 8.86 mmol) was added 40% aq. $MeNH_2$ (45 mL) at room temperature, and stirred at the same temperature for 18 h. The resulting solution was concentrated. The obtained residue was recrystallized from MeOH–acetone–hexane to afford **29** (2.73 g, 78%) as a yellow solid: $[\alpha]_D^{24}$ +53.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (dt, 2H, J = 2.3, 9.2 Hz), 7.96 (dt, 2H, J = 2.3, 9. 2 Hz), 7.39–7.31 (m, 3H), 7.23–7.16 (m, 2H), 6.62 (d, 1H, J = 3.4 Hz), 5.85 (br s, 1H), 4.50 (d, 1H, J = 12.0 Hz), 4.38 (d, 1H, J = 12.0 Hz), 3.83–3.76 (m, 2H), 3.41 (dd, 1H, J = 6.9, 8. 6 Hz), 2.78 (d, 3H, J = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.7, 150.2, 144.8, 136.6, 128.7, 128.5, 128.4, 128.0, 124.4, 73.63, 69.34, 55.5, 26.5; IR (ATR) ν 3398, 3321, 3243, 3102, 2868, 1651, 1605, 1525,1442, 1349, 1311 cm^{-1}; HRMS (FAB$^+$) Calcd for $C_{17}H_{19}N_3O_6S$ [(M + H)$^+$]: 394.1073; found: 394.1092.

(*S*)-3-(Benzyloxy)-*N*-methyl-2-(4-nitro-*N*-(prop-2-yn-1-yl)-phenylsulfonamido)propanamide 31a. To a solution of **29** (2.63 g, 6.69 mmol) and K_2CO_3 (2.78 g, 20.1 mmol) in DMF (34 mL) was added propargyl bromide (1.5 mL, 20 mmol) at 0 °C. After stirring for 0.5 h, the mixture was allowed to warm to room temperature, and stirred for 17 h. The resulting mixture was quenched with saturated aq. NH_4Cl, and extracted with $CHCl_3$ three times. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel column chromatography (hexane–EOAc = 2 : 1) afforded **36a** (2.35 g, 81%) as an orange solid: $[\alpha]_D^{24}$ −29.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02–7.92 (m, 4H), 7.31–7.21 (m, 3H), 7.06–6.98 (m, 2H), 6.61 (br s, 1H), 4.64 (dd, 1H, J = 5.2, 9.2 Hz), 4.31–4.21 (m, 4H), 4.27 (d, 1H, J = 10.9 Hz), 4.02 (dd, 1H, J = 5.2, 10.9 Hz), 3.87 (dd, 1H, J = 10.9, 10.9 Hz), 2.83 (d, 3H, J = 5.2 Hz), 2.27 (t, 1H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.2, 149.9,144.4, 136.7,129.0, 128.3, 128.2, 128.1, 123.5, 77.6, 73.8, 73.5, 66.9, 60.1, 34.3, 26.3; IR (ATR) ν 3412, 3389, 3156, 2942, 2872, 1668, 1607, 1527, 1454, 1412, 1403, 1348, 1313 cm^{-1}; HRMS (FAB$^+$) Calcd for $C_{20}H_{21}N_3O_6S$ [(M + H)$^+$]: 432.1229; found: 432.1215.

(*S*)-3-(Benzyloxy)-2-(*N*-(3-(furan-2-yl)prop-2-yn-1-yl)-4-nitrophenylsulfonamido)-*N*-methylpropanamide 31b. To a solution of **29** (304 mg, 0.773 mmol) and K_2CO_3 (320 mg, 2.32 mmol) in DMF (4.0 mL) was added ((4-bromobut-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane[33] (excess) at 0 °C. After stirring for 0.5 h, the mixture was allowed to warm to room temperature, and stirred for 17 h. The resulting mixture was diluted with EtOAc, washed with H_2O twice and brine twice. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 3 : 2) afforded **31b** (253 mg, 57%) as a colorless oil: $[\alpha]_D^{27}$ −17.7 (c 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00–7.93 (m, 4H), 7.32–7.21 (m, 3H), 7.02 (dd, 2H, J = 7.4, 1.7 Hz), 6.60 (d, 1H, J = 4.0 Hz), 4.64 (dd, 1H, J = 9.2, 5.2 Hz), 4.28 (d, 1H, J = 10.9 Hz), 4.25 (dd, 1H, J = 4.0, 2.3 Hz), 4.22 (d, 1H, J = 10.9 Hz), 4.18 (dd, 2H, J = 1.7, 1.7 Hz), 4.03 (dd, 1H, J = 10.9, 5.2 Hz), 3.85 (dd, 1H, J = 10.9, 9.2 Hz), 2.84 (d, 3H, J = 4.6 Hz), 0.90 (s, 9H), 0.09 (d, 6H, J = 1.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 149.9, 144.5, 136.8, 129.0, 128.3, 128.3, 128.1, 123.5, 84.6, 78.3, 73.5, 67.0, 60.2, 51.4, 34.8, 26.4, 25.7, 18.3, −5.29, −5.33; IR (ATR): ν 3411, 3106, 2956, 2929, 2858, 1674, 1529, 1348, 1313, 1254, 1164, 1088 cm^{-1}; HRMS (FAB$^+$): Calcd for $C_{27}H_{37}N_3O_7SSi$ [(M + H)$^+$]: 576.2200; found: 576.2207.

(*S*)-3-(Benzyloxy)-*N*-methyl-2-(4-nitro-*N*-(3-phenylprop-2-yn-1-yl)phenylsulfonamido)propanamide 31c. To a solution of **29** (764 mg, 2.02 mmol) and K_2CO_3 (835 mg, 6.04 mmol) in DMF

(10 mL) was added propargyl bromide (0.45 mL, 6.0 mmol) at 0 °C. After stirring for 1 h, the mixture was allowed to warm to room temperature, and stirred for 17.5 h. The resulting mixture was diluted with Et_2O, washed with H_2O once and brine five times. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude product.

To the mixture of the above alkyne and CuI (38.4 mg, 0.201 mmol) in Et_3N (10 mL) and THF (10 mL) was added PhI (0.34 mL, 3.04 mmol) and $Pd(PPh_3)_4$ (233 mg, 0.202 mmol) at room temperature. After the mixture was stirred for 7 h at 50 °C, the resulting mixture was concentrated. The residue was filtrated through Celite, and washed with hexane–EtOAc (3 : 2). Purification by silica gel column chromatography (hexane–EtOAc = 3 : 2) afforded **31c** (496 mg, 49% over 2 steps) as a yellow amorphous solid: $[\alpha]_D^{27}$ −25.3 (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dt, 2H, *J* = 9.2, 2.3 Hz), 7.90 (dt, 2H, *J* = 9. 2, 2.3 Hz), 7.37–7.32 (m, 1H), 7.32–7.23 (m, 4H), 7.23–7.15 (m, 4H), 6.94 (d, 2H, *J* = 6.9 Hz), 6.61 (d, 1H, *J* = 4.6 Hz), 4.72 (dd, 1H, *J* = 9.2, 5.2 Hz), 4.45 (d, 1H, *J* = 1.1 Hz), 4.31 (d,1H, *J* = 10.9 Hz), 4.21 (d, 1H, *J* = 10.9 Hz), 4.09 (dd, 1H, *J* = 10.9, 5.2 Hz), 3.96 (dd, 1H, *J* = 10.9, 9.2 Hz), 2.83 (d, 3 H, *J* = 5.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 149.83, 144.7, 136.7, 131.5, 129.1, 129.0, 128.4, 128.29, 128.25, 128.1, 123.6, 121.7, 85.9, 82.7, 73.6, 67.1, 60.36, 35.3, 26.5; IR (ATR): ν 3416, 3102, 2938, 2873, 1674, 1528, 1490, 1348, 1313, 1165, 1091 cm^{-1}; HRMS (FAB^+): Calcd for $C_{26}H_{25}N_3O_6S$ [$(M + H)^+$]: 508.1542; found: 508.1545.

(*S*)-3-(Benzyloxy)-2-(*N*-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-4-nitrophenylsulfonamido)-*N*-methylpropanamide 31d. To the mixture of **31a** (2.89 g, 6.70 mmol) and CuI (128 mg, 0.672 mmol) in Et_3N (17 mL) and THF (17 mL) was added 2-bromofuran[34] (1.48 g, 10.1 mmol) and $Pd(PPh_3)_4$ (774 mg, 0.670 mmol) at room temperature. After the mixture was stirred for 5 h at 50 °C, the resulting mixture was concentrated. The residue was filtrated through Celite, and washed with hexane–EtOAc (3 : 2). Purification by silica gel column chromatography (hexane–EtOAc = 3 : 2) afforded **31d** (2.34 g, 71%) as a yellow oil: $[\alpha]_D^{27}$ −17.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (dt, 2H, *J* = 9.2, 2.3 Hz), 7.90 (dt, 2H, *J* = 9.2, 2.3 Hz), 7.38–7.36 (m, 1H), 7.29–7.22 (m, 2H), 7.22–7.15 (m, 2H), 6.97–6.91 (m, 2H), 6.52 (d, 1H, *J* = 4.0 Hz), 6.48 (d, 1H, *J* = 3.4 Hz), 6.38 (dd, 1H, *J* = 3.4, 1.7 Hz), 4.70 (dd, 1H, *J* = 9.2, 4.6 Hz), 4.57 (d, 1H, *J* = 18.9 Hz), 4.40 (d, 1H, *J* = 18.9 Hz), 4.29 (d, 1H, *J* = 10.9 Hz), 4.21 (d, 1H, *J* = 10.9 Hz), 4.02 (dd, 1H, *J* = 10.9, 4.6 Hz), 3.90 (dd, 1H, *J* = 10.9, 9.2 Hz), 2.84 (d, 3H, *J* = 5.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 149.9, 144.6, 144.1, 136.7, 135.7, 129.1, 128.2, 128.2, 123.6, 116.0, 111.0, 87.4, 76.1, 73.6, 67.0, 60.5, 35.0, 26.4; IR (ATR): ν 3417, 3329, 3107, 2945, 2871, 1670, 1528, 1348, 1313, 1212, 1165, 1091 cm^{-1}; HRMS (FAB^+): Calcd for $C_{24}H_{23}N_3O_7S$ [$(M + H)^+$]: 498.1335; found: 498.1336.

(*S*)-3-((Benzyloxy)methyl)-1-methyl-4-((4-nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 32a. To a solution of **31a** (102 mg, 0.235 mmol) in 1,4-dioxane (1.2 mL) was added $PtCl_2$ (12.4 mg, 0.0466 mmol) in one portion. The mixture was stirred at 70 °C for 72 h. After cooling to room temperature, the resulting mixture was filtrated through Celite and washed with acetone. The filtrate was concentrated. Purification by silica gel column chromatography (hexane–acetone = 5 : 2) afforded **32a** (56.6 mg, 56%) as a colorless solid: $[\alpha]_D^{24}$ −17.1 (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15 (d, 2H, *J* = 8.6 Hz), 7.93 (d, 2H, *J* = 8.6 Hz), 7.31–7.26 (m, 3H), 7.16–7.15 (m, 2H), 5.65 (d, 1H, *J* = 10.6 Hz), 4.96 (tt, 2H, *J* = 11.5, 3.9 Hz), 4.44 (d, 1H, *J* = 11.5 Hz), 4.41–4.37 (m, 1H), 4.36 (d, 1H, *J* = 11.5 Hz), 3.92–3.89 (m, 2H), 3.82 (dd, 1H, *J* = 10.6, 5.4 Hz), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.8, 149.9, 144.9, 136.8, 129.1, 128.6, 128.4, 128.2, 127.9, 123.8, 109.8, 73.1, 65.7, 62.3, 43.6, 37.2; IR (ATR) ν 3104, 3068, 3036, 2869, 1655, 1606, 1529, 1455, 1376, 1349 cm^{-1}; HRMS (FAB^+) Calcd for $C_{20}H_{21}N_3O_6S$ [M^+]: 431.1151; found: 431.1142.

(*S*)-3-((Benzyloxy)methyl)-7-(furan-2-yl)-1-methyl-4-((4-nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 32b. To a solution of **31b** (234 mg, 0.406 mmol) in 1,4-dioxane (4.0 mL) was added $PtCl_2$ (10.8 mg, 0.0406 mmol) in one portion. The mixture was stirred at 70 °C for 12 h. After cooling to room temperature, the resulting mixture was filtrated through Celite and washed with acetone. The filtrate was concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 2 : 1) afforded **32b** (17.0 mg, 7%) as a colorless oil: $[\alpha]_D^{27}$ −59.9 (*c* 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (dt, 2H, *J* = 8.6, 2.3 Hz), 8.05 (dt, 2H, *J* = 8.6, 2.3 Hz), 7.37–7.25 (m, 5H), 5.69 (dd, 1H, *J* = 7.4, 7.4 Hz), 4.88 (dd, 1H, *J* = 9.2, 6.3 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.09 (d, 1H, *J* = 14.3 Hz), 4.05 (dd, 1H, *J* = 12.0, 7.4 Hz), 3.97 (d, 1H, *J* = 14.3 Hz), 3.81–3.69 (m, 2H), 3.27 (dd, 1H, *J* = 12.0, 7.4 Hz), 2.91 (s, 3H), 0.88 (s, 9H), 0.05 (d, 6H, *J* = 2.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.3, 150.3, 145.5, 143.1, 137.6, 128.9, 128.4, 127.82, 127.7, 124.4, 110.4, 72.9, 70.6, 64.4, 61.9, 42.5, 31.7, 25.7, 25.6, 18.2, −5.5; IR (ATR): ν 2956, 2929, 2857, 1662, 1532, 1349, 1170, 1089 cm^{-1}; HRMS (FAB^+): Calcd for $C_{27}H_{37}N_3O_7SSi$ [$(M + H)]^+$: 576.2200; found: 576.2203.

(*S*)-3-((Benzyloxy)methyl)-1-methyl-4-((4-nitrophenyl)sulfonyl)-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 32c. To a solution of **31c** (480 mg, 0.946 mmol) in 1,2-DCE (5.0 mL) was added $PtCl_2$ (25.2 mg, 0.0947 mmol) in one portion. The mixture was stirred at 70 °C for 22 h. After cooling to room temperature, the resulting mixture was filtrated through Celite and washed with acetone. The filtrate was concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 2 : 1) afforded **32c** (358 mg, 75%) as a yellow amorphous solid: $[\alpha]_D^{27}$ −97.4 (*c* 2.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (dt, 2H, *J* = 9.2, 2.3 Hz), 8.10 (dt, 2H, *J* = 9.2, 2.3 Hz), 7.44–7.38 (m, 1H), 7.38–7.32 (m, 4H), 7.32–7.27 (m, 5H), 5.82 (dd, 1H, *J* = 8.0, 8.0 Hz), 4.97 (dd, 1H, *J* = 10.3, 6.3 Hz), 4.51 (dd, 1H, *J* = 24.6, 12.0 Hz), 4.23 (dd, 1H, *J* = 11.5, 8.0 Hz), 3.81 (dd, 1H, *J* = 9.7, 9.7 Hz), 3.71 (dd, 1H, *J* = 9.7, 6.3 Hz), 3.33 (dd, 1H, *J* = 11.5, 7.4 Hz), 2.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.5, 150.4, 148.0, 142.8, 137.4, 134.3, 129.9, 129.1, 128.9, 128.4, 127.8, 127.6, 127.0, 124.5, 112.0, 73.1, 70.6, 64.2, 42.8, 34.3; IR (ATR): ν 3102, 3068, 3033, 2923, 2866, 1662, 1530, 1383, 1348, 1312, 1169, 1086,

1052 cm^{-1}; HRMS (FAB^+): Calcd for $C_{26}H_{25}N_3O_6S$ [$(M + H)^+$]: 508.1542; found: 508.1528.

(*S*)-3-((Benzyloxy)methyl)-7-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-4-((4-nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 32d. To a solution of **31d** (405.7 mg, 0.82 mmol) in 1,2-DCE (6 mL) was added $PtCl_2$ (22 mg, 0.082 mmol) in one portion. The mixture was stirred at 70 °C for 18 h. After cooled to room temperature, the resulting mixture was filtrated through Celite and washed with acetone. The filtrate was concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 8 : 2) afforded **36d** (234 mg, 58%) as a yellow oil, and recovered starting material **31d** (121 mg, 31%). **32d**: $[\alpha]_D^{28}$ −19.0 (*c* 0.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, 2H, *J* = 8.6 Hz), 8.08 (d, 2H, *J* = 8.6 Hz), 7.44 (s, 1H), 7.35–7.20 (m, 6H), 6.43 (dd, 1H, *J* = 2.9, 1.7 Hz), 6.32 (d, 1H, *J* = 3.4 Hz), 6.02 (dd, 1H, *J* = 8.0, 8.0 Hz), 4.90 (dd, 1H, *J* = 9.2, 6.9 Hz), 4.46 (d, 2H, *J* = 7.4 Hz), 4.22 (dd, 1H, *J* = 11.5, 8.0 Hz), 3.77–3.62 (m, 2H), 3.32 (dd, 1H, *J* = 11.5, 7.4 Hz), 2.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.34, 150.4, 147.8, 144.0, 142.9, 138.1, 137.5, 129.0, 128.4, 127.7, 127.6, 124.5, 111.7, 110.5, 110.5, 73.2, 70.8, 64.3, 42.4, 34.7; IR (ATR): ν 3107, 3033, 2924, 2866, 1664, 1530, 1489, 1400, 1348, 1310, 1219, 1168, 1086, 1052 cm^{-1}; HRMS (FAB^+): Calcd for $C_{24}H_{23}N_3O_7S$ [$(M + H)^+$]: 498.1335; found: 498.1332.

(*S*)-3-((Benzyloxy)methyl)-1-methyl-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 33. To a solution of **32d** (564 mg, 1.13 mmol) and K_2CO_3 (314 mg, 2.27 mmol) in MeCN (10 mL) was added PhSH (0.18 mL, 1.7 mmol) at room temperature. After stirring for 4.5 h, the resulting mixture was diluted with EtOAc, washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 2 : 1 to $CHCl_3$–MeOH = 10 : 1) afforded **33** (340 mg, 96%) as a yellow oil: $[\alpha]_D^{28}$ +94.1 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.40 (m, 1H), 7.35–7.23 (m, 5H), 6.44 (dd, 1H, *J* = 3.4, 1.7 Hz), 6.37 (d, 1H, *J* = 3.4 Hz), 6.18 (dd, 1H, *J* = 7.7, 7.7 Hz), 4.56 (d, 2H, *J* = 4. 9 Hz), 3.89–3.80 (m, 2H), 3.72 (dd, 1H, *J* = 9.2, 7.4 Hz), 3.50 (dd, 1H, *J* = 13.2, 7.7 Hz), 3.41(dd, 1H, *J* = 13.2, 7.7 Hz), 3.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 148.8, 143.0, 138.1, 136.6, 128.3, 127.9, 127.6, 115.8, 111.4, 108.9, 73.6, 70.3, 56.4, 41.4, 33.2; IR (ATR): ν 3317, 2925, 2864, 1668, 1559, 1490, 1455, 1374, 1220, 1156, 1100, 1065 cm^{-1}; HRMS (FAB^+): Calcd for $C_{18}H_{20}N_2O_3$ [$(M + H)^+$]: 313.1552; found: 313.1554.

(*S*)-3-((Benzyloxy)methyl)-1,4-dimethyl-7-phenyl-4,5-dihydro-1*H*-1,4-diazepin-2(3*H*)-one 34. To a solution of **33** (298 mg, 0.953 mmol) in MeOH (5.0 mL), MeCN (5.0 mL) and 35% aq. CH_2O (2.0 mL) was added AcOH (0.27mL, 4.8 mmol) and $NaBH_3CN$ (300 mg, 4.8 mmol) at room temperature. After stirring for 16 h, the resulting mixture was quenched with 2M aq. NaOH and brine, extracted with EtOAc, and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 1 : 3 to 1 : 4) afforded **34** (247 mg, 79%) as a colorless oil: $[\alpha]_D^{28}$ +54.5 (*c* 0.09, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 1H, *J* = 1.7 Hz), 7.35–7.23 (m, 5H), 6.46–6.43 (m, 1H), 6.38 (d, 1H, *J* = 3.4 Hz), 6.19 (dd, 1H, *J* = 7. 7, 7.7 Hz), 4.55 (dd, 2H, *J* = 28.6, 12.0 Hz), 3.90–3.82 (m, 1H), 3.73–3.65 (m, 2H), 3.25 (dd, 1H, *J* = 12.0, 7.4 Hz), 3.09 (s, 3H), 3.06 (dd, 1H, *J* = 12.0, 7.4 Hz), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 148.6, 143.2, 138.0, 137.6, 128.3, 128.0, 127.6, 113.7, 111.5, 109.3, 73.5, 68.0, 62.7, 51.6, 40.6, 33.1; IR (ATR): ν 3031, 2946, 2858, 2788, 1668, 1489, 1454, 1377, 1305, 1207, 1154, 1099, 1067, 1015 cm^{-1}: HRMS (FAB^+): Calcd for $C_{19}H_{22}N_2O_3$ [M^+] 326.1630; found: 326.1630.

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