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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02932 • Publication Date (Web): 06 Dec 2019

Rearrangement of Threonine and Serine-Based *N*-(3-Phenylprop-2-yn-1-yl) Sulfonamides Yields Chiral Pyrrolidin-3-ones

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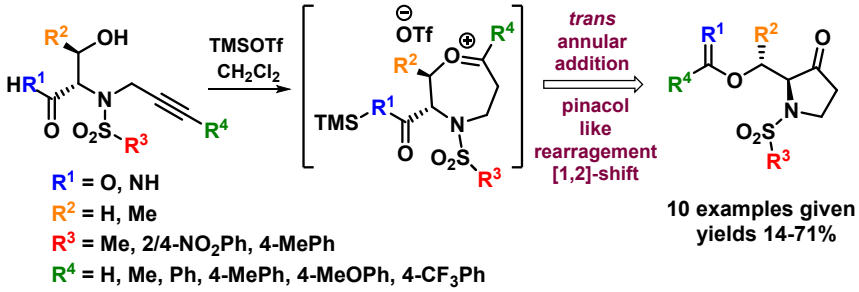


Keywords: rearrangement, hydroalkoxylation, threonine pyrrolidine

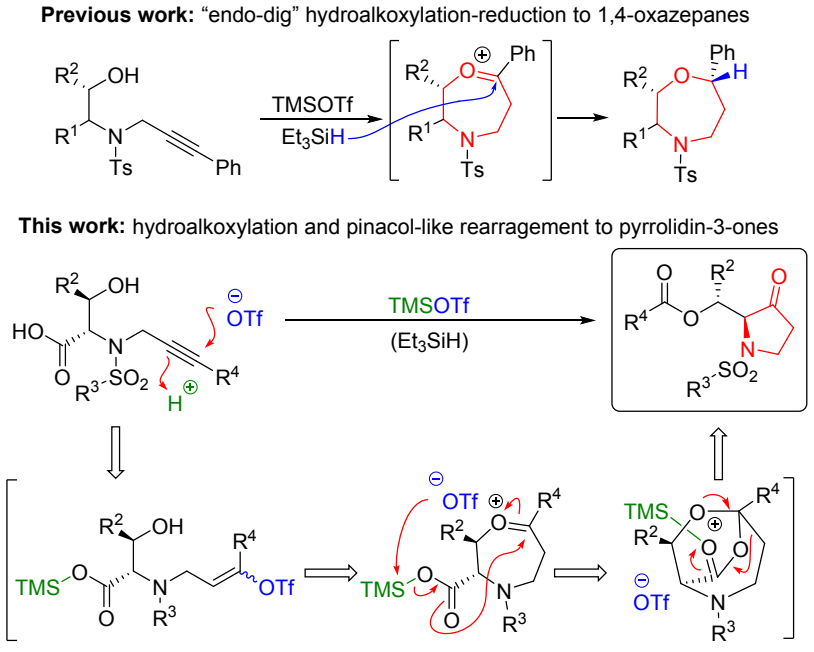
Abstract

N-(3-phenylprop-2-yn-1-yl)-sulfonamides derived from serine and threonine were synthesized using solid-phase synthesis and subjected to reaction with trimethylsilyl trifluoro-methanesulfonate (TMSOTf). In contrast to the previously reported formation of 1,4-oxazepanes, this reaction afforded pyrrolidin-3-ones. A mechanistic explanation for this unexpected outcome is proposed, and the limitations and scope of the rearrangement are outlined.

Introduction

N-Substituted 2/4-nitrobenzenesulfonamides are excellent synthetic intermediates for preparing diverse nitrogenous heterocycles.[1,2] Recently, substantial attention has been paid to *N*-phenacyl-2/4-nitrobenzenesulfonamides derived from natural amino acids, especially serine and threonine, as the cyclization of these compounds stereoselectively yields various chiral morpholine derivatives.[3,4] Based on the synthetic potential of internal alkynols in the field of catalyzed intramolecular hydroalkoxylations,[5–10] we switched from *N*-phenacyl to *N*-(3-phenylprop-2-yn-1-yl) analogues and applied the previously reported reaction[11] to potentially synthesize functionalized 1,4-oxazepanes amenable to further diversification (Scheme 1).

Scheme 1. Different reactivity of *N*-(3-phenylprop-2-yn-1-yl)sulfonamides



For full reaction mechanism see **Scheme 4**.

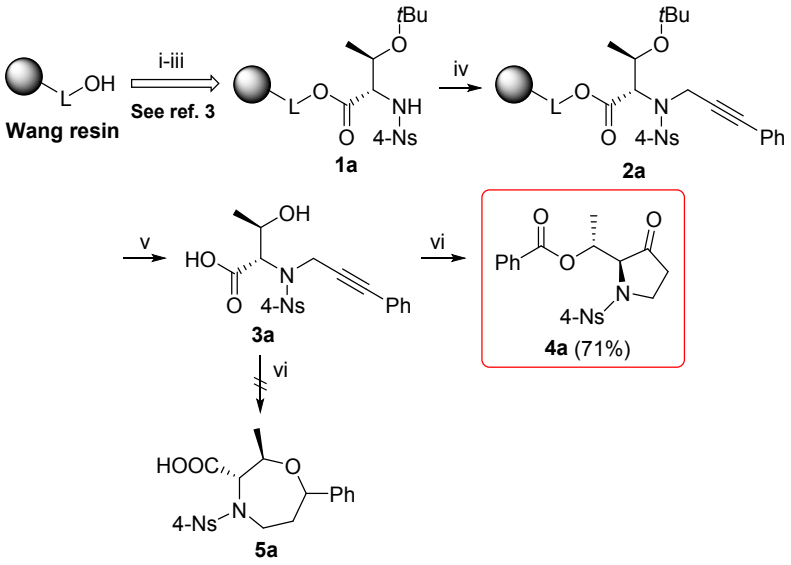
Surprisingly, completely different reaction outcomes were obtained, and the isolated compounds were identified as pyrrolidin-3-one derivatives. Inspired by this unusual result and, considering the limited number of synthetic routes leading to chiral pyrrolidin-3-ones despite their occurrence in

biologically active compounds,[12–17] we decided to explore the limitations and scope of the rearrangement and provide an insight to reaction mechanism.

Results and Discussion

By analogy to previously reported *N*-phenacyl analogues,[3] corresponding phenylalkynol **3a** was prepared using a convenient solid-phase synthesis process. Briefly, Wang resin was acylated with Fmoc-Thr-(O*t*Bu)-OH, subjected to Fmoc-cleavage, and reacted with 4-nitrobenzenesulfonyl chloride (4-NsCl). Resulting sulfonamide **1a** was alkylated with 3-phenylprop-2-yn-1-ol using a Mitsunobu alkylation. Cleavage from resin **2a** with trifluoroacetic acid (TFA) was followed by spontaneous cleavage of the *t*-butyl ether. Intermediate **3a** was obtained in excellent crude purity (≥ 90%, calculated from LC-UV traces) and prior to the final transformation, it was purified by semipreparative HPLC and fully characterized (Scheme 2). Even with the efficacy of solid-phase synthesis, consisting particularly in the rapid production of compounds *via* multi-step reaction sequences with minimal hands-on-time,[18] it should be noted that the corresponding intermediate **3a** can also be easily obtained using traditional solution-phase synthesis starting from threonine with a suitably protected carboxylic group. Intermediate **3a** was reacted with TMSOTf and Et_3SiH to obtain 1,4-oxazepane **5a**. We applied previously reported conditions[11] (i.e., 2 equiv TMSOTf and 1 equiv Et_3SiH in anhydrous CH_2Cl_2) and generated a highly pure compound (≥90%, LC-UV-MS traces), with a molecular mass corresponding to expected product **5a**. However, its ^1H and $^{13}C\{^1H\}$ NMR spectra were not consistent with the structure of **5a**. For example, the $^{13}C\{^1H\}$ signal at 210.6 ppm indicating a carbonyl group could not be assigned to any carbon atom in **5a**. For this reason, a set of 1D and 2D NMR spectra, including ^1H-^{15}N HMBC, was collected and carefully analyzed.

Scheme 2. Synthesis of starting material **3a** and its TMSOTf-mediated rearrangement to **4a**[a]



[a]Reagents and conditions: (i) Fmoc-Thr(O^{t}Bu)OH, 1-hydroxybenzotriazole (HOBt), 4-(dimethylamino)pyridine (DMAP), diisopropylcarbodiimide (DIC), dimethylformamide (DMF), CH_2Cl_2, 24 h, rt; (ii) 50% piperidine/DMF, 30 min, rt; (iii) 4-NsCl, 2,6-lutidine, CH_2Cl_2, 24 h, rt; (iv) 3-phenylprop-2-yn-1-ol, triphenylphosphine (TPP), diisopropyl azodicarboxylate (DIAD), tetrahydrofurane (THF), 24 h, rt; (v) 50% trifluoroacetic acid (TFA)/CH_2Cl_2, 1 h, rt; (vi) TMSOTf/Et_3SiH (2:1), anhydrous CH_2Cl_2, 24 h, 0 °C.

The structure of **4a** was determined by means of ^{1}H, ^{13}C{^{1}H}, APT, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C{^{1}H} HSQC, ^{1}H-^{13}C{^{1}H} HMQC, ^{1}H-^{13}C{^{1}H} HMBC and ^{1}H-^{15}N HMBC. See Supplementary Information for the complete set of 1D and 2D spectra. Figure 1 summarizes ^{1}H-^{13}C{^{1}H} and ^{1}H-^{15}N long-range correlations. We identified benzoyl, 4-Nosyl, pyrollidin-3-onyl and CH_3-CH-O moieties. ^{1}H-^{13}C{^{1}H} HMBC spectrum provided H^{13}-C14 correlation. At the same time, H^{13} was also correlated to C3 and N1 of pyrollidin-3-one moiety. Although, ^{1}H-^{15}N four-bond correlation was not observed between 4-Nosyl protons and N1, the scaffold structure was confirmed by NOE correlations between 4-Nosyl protons and protons H^2, H_a^4, H_b^4, H_a^5, H_b^5 and H^{21} (see Supporting Information for more details). NOE correlations were also observed between benzoyl protons and protons H^2 and H^{21} (Figure 1).

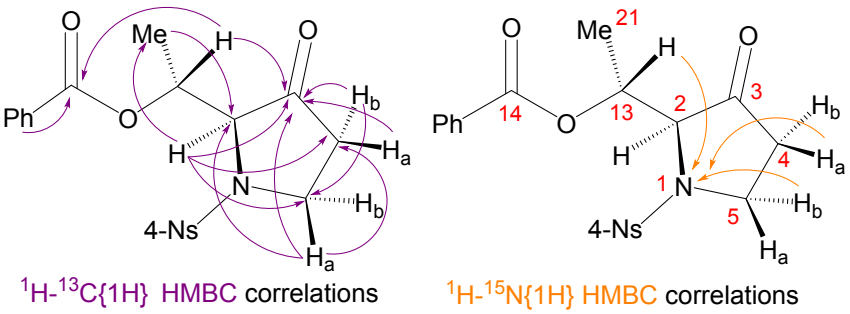
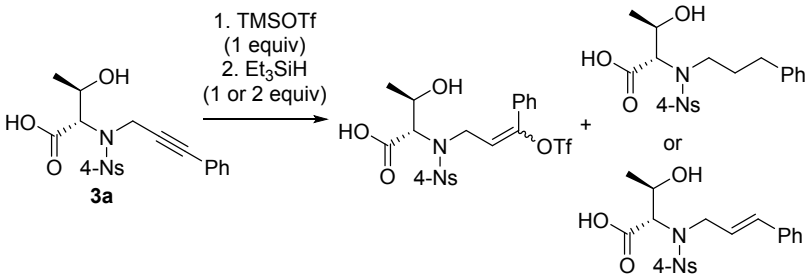


Figure 1. Selected correlations for 2D NMR analysis of rearrangement product **4a** (all correlations are displayed in Supporting Information, Figures S48 and S49).

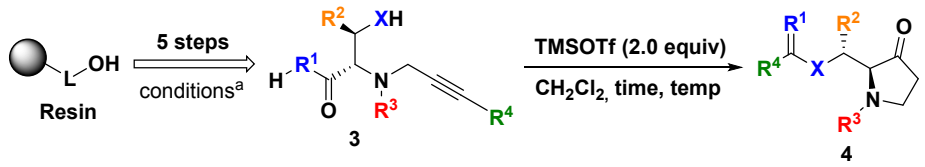
The reaction conditions were further modified to investigate their impact on the reaction outcome (see Supporting Information for details, Table S3): (i) the same reagents in the same ratio (2 equiv TMSOTf and 1 equiv Et_3SiH) were added in the opposite order and gave the same results; (ii) same reagents in the opposite ratio (1 equiv TMSOTf and 2 equiv Et_3SiH) led only to a mixture of the corresponding enol triflate and the reduced analogues of compound **3a** with double (at room temperature) or single (at 0 °C) bonds (Scheme 3); (iii) the same reagents in an equimolar ratio (1 equiv TMSOTf and 1 equiv Et_3SiH) again yielded a mixture of enol triflate, alkene and alkane derivatives; (iv) reaction with 2 equiv TMSOTf gave solely compound **4a**. The last experiment shows that Et_3SiH is not involved in the conversion of **3a** to **4a**; thus, it was omitted from the reaction mixture in further studies. Finally, we tested the reaction of compound **3a** with $TiCl_4$ and $BF_3{\cdot}OEt_2$ as the alternative Lewis acids. Treatment with $TiCl_4$ did not provide the rearrangement product while the reaction with $BF_3{\cdot}OEt_2$ led to the formation of compound **4a**; however, the reaction was slower compared to TMSOTf.

Scheme 3. Outcomes using the conditions (ii) and (iii) (for more details see in the text)



The structure-reactivity relationship of the rearrangement was further studied using a series of variously substituted starting materials (Table 1). First, we used different sulfonyl chlorides (2-NsCl, mesyl chloride and tosyl chloride) to evaluate the effect of the R^3 group (intermediates **3a**-**d**). Similarly, different phenylalkynols bearing electron-donating (Me and OMe) or electron-withdrawing (CF_3) substituents were used, and these reactants resulted in different R^4 substituents (intermediates **3e**-**g**). 2-Butynol (intermediate **3h**) and propargyl alcohol (intermediate **3i**) were also included as alternatives to phenylalkynols. Fmoc-Thr(O^{t}Bu)-OH was replaced with Fmoc-Ser(O^{t}Bu)-OH to modify the R^2 position (intermediate **3j**). Finally, Rink amide resin was used instead of Wang resin, and this afforded carboxamide intermediate **3k**. Table 1 shows the observed scope and limitations of the transformation to products **4**.

Table 1: Rearrangement of **3** to **4**: Limitations and scope[a-e]



entry	final cmpd	X	R^1	R^2	R^3	R^4	time [h]	temp [°C]	crude purity [%][b]	yield [%][c]
1	**4a**	O	O	Me	4-Ns	Ph	24	23	96	71
2	**4b**	O	O	Me	2-Ns	Ph	24	23	96	41
3	**4c**	O	O	Me	Ms	Ph	24	23	92	40
4	**4d**	O	O	Me	Ts	Ph	24	23	80	50
5	**4e**	O	O	Me	4-Ns	4-MePh	24	23	76	30
6	**4f**	O	O	Me	4-Ns	4-MeOPh	24	23	81	42
7	**4g**	O	O	Me	4-Ns	4-CF_3Ph	24	40	56	18
8	**4h**	O	O	Me	4-Ns	Me	72	23	75	33
9	**4i**	O	O	Me	4-Ns	H	72	23	43	NI[d]
10	**4j**	O	O	H	4-Ns	Ph	72	23	51	14
11	**4k**	O	NH	Me	4-Ns	Ph	72	23	60	14
12	**4l**	S	O	H	4-Ns	Ph	24	23	NP[e]	NP[e]

[a]In analogy with ref. 3 and Scheme 2. For detailed reaction conditions see Supporting Information. [b]Overall crude purity determined by HPLC after the entire reaction sequence (6 steps) prior to final purification. [c]Isolated overall (6 steps) yield calculated from the loading of the starting resin. [d]NI = not isolated, compound proved to be unstable during the HPLC purification process. [e]NP = not prepared.

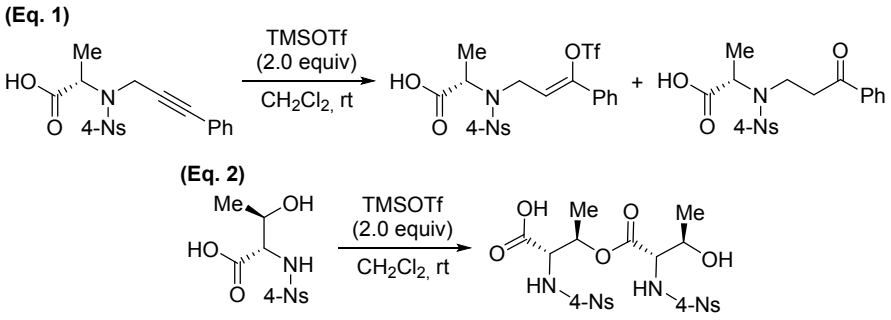
It was observed that the reaction times and crude purities depended strongly on the starting materials. As expected, the electron-withdrawing group substituted arylalkyne **3g** (CF_3) slowed the

conversion and a significant amount of the corresponding enol triflate intermediate was detected after 24 h. In this case, a higher temperature (40 °C) was necessary to push the conversion of the starting material to the final product **4g**. Longer reaction times were required when alkyl (**3h**) or hydrogen-bearing (**3i**) alkynes were used. Similarly, serine-based (**3j**) rearrangement precursor yielded the desired product **4j** in 48 h and 14% overall yield.[19] Replacement of carboxylic acid with the corresponding amide also led to the slow transformation. Finally, the rearrangement of amide **3k** to imidoester **4k** (carboxylic acid replaced with the amide) was also rather sluggish and yielded the desired product in 14% overall yield. Typically, in these cases the corresponding enol triflates and/or ketones were still detected in the reaction mixtures (9-28%, calculated from their LC-UV-MS traces). The isolated yields were somewhat compromised in several cases, which was caused by difficult chromatography and careful removal of impurities with similar retention times to products. Finally, to further extend applicability of the disclosed reaction sequence, the sulfanyl analogue of **3a** was prepared from protected cysteine. However, no traces of the desired pyrrolidinone **4l** were detected.

As previously reported,[11] the reaction of similar intermediates promoted by TMSOTf proceeds *via* an intramolecular hydroalkoxylation to the 1,4-oxazepines (Scheme 1), and in the presence of an external nucleophile (such as Et_3SiH), it gives the corresponding 1,4-oxazepanes. In the case of intermediates **3**, we expected the similar reaction course, but the reaction outcome suggested that at the 1,4-oxazepine stage, the carboxylate/carboxamide as an internal nucleophile added in a trans-annular manner. Competitive experiments with Et_3SiH indicated that the intramolecular addition is favored over the intermolecular one. The following pinacol-like rearrangement and ring opening of the cyclic hemiacetal resulted in the formation of the pyrrolidin-3-one scaffold. Although careful monitoring of the reaction mixture was performed using LC-UV-MS, we were able to detect only rearranged products **4** along with the corresponding enol triflates as presumed reaction intermediates. We have tried to support the proposed reaction mechanism by several control reactions (Scheme 4, Eq. 1 and 2). First, the reaction substrate without the phenylprop-2-yn-1-yl moiety was treated with TMSOTf (Eq. 2). In this case only intermolecular esterification[20] occurred. Next, an intermediate without the hydroxy group (synthesized from Fmoc-Ala-OH) was reacted with TMSOTf (Eq. 1). In this case only the enol triflate derivative along with the corresponding ketone

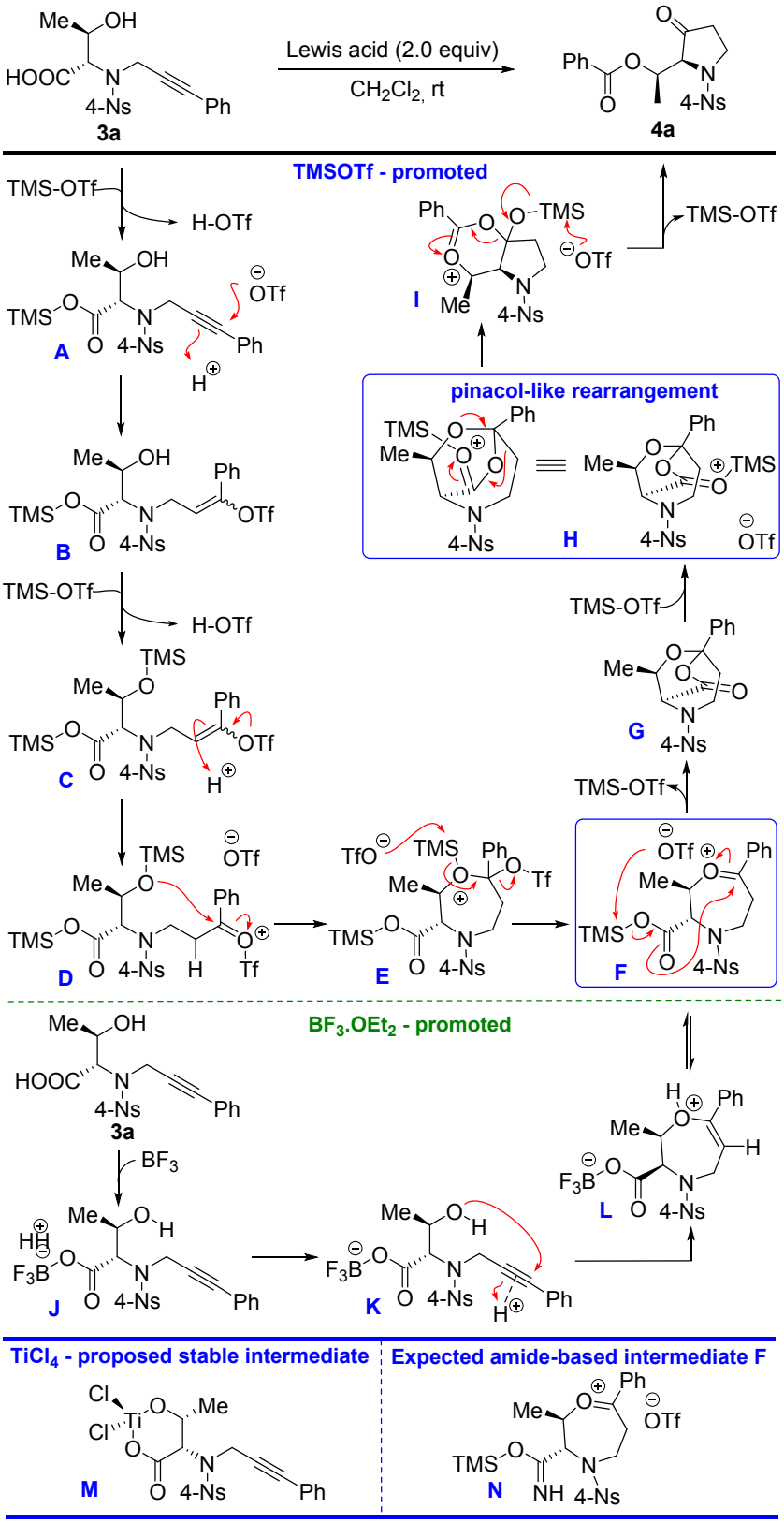
was produced. These results strongly suggest that both, the hydroxy group and alkynyl moiety are mandatory to trigger the rearrangement.

Scheme 4: Control experiments designed to identify essential functional groups of the molecule; products determined using LC-UV-MS traces



In addition, reaction shown in Scheme 4, Eq. 1, supports our reaction mechanism since the hydroxy group is not required to form the enol triflate intermediate **C**. Our results also suggested that even though in the case of TMSOTf the reaction proceeds *via* enol triflate **B**, the key intermediate for the cyclization and the subsequent rearrangement is the oxonium intermediate **F** (Scheme 5). Our speculation is based on the previously observed $BF_3 \cdot OEt_2$ promoted rearrangement of **3a** to **4a**. Under such conditions, no enol triflate intermediate **B** can be formed.

Scheme 5: Plausible mechanism of the rearrangement


Lewis acid (2.0 equiv)
CH2Cl2, rt
3a
4a
TMSOTf - promoted
pinacol-like rearrangement
BF3.OEt2 - promoted
TiCl4 - proposed stable intermediate
Expected amide-based intermediate F

Taking into account all these observations, we believe that the first step of the TMSOTf-promoted rearrangement is the reaction between TMSOTf and carboxylic acid of **3a**. In situ generated triflic acid (TfOH) then adds to alkyne to yield the enol triflate intermediate **B**.[21] The second equivalent of TMSOTf then reacts with the hydroxy group of **B** to yield the silylated alcohol **C** and another equivalent of TfOH. TfOH-mediated enol triflate hydrolysis yields the intermediate **D** that further undergoes the intramolecular 7-*exo*-*trig* cyclization to yield, upon TMS group release, the key oxonium intermediate **F**. Trans-annular cyclization of carboxylic acid to oxonium yields strained acetal intermediate **G** that is well organized for Lewis acid promoted C-C bond fragmentation reaction. Finally, rearranged hemiacetal intermediate **H** opens up to yield the desired product **4a**.

Similarly, the oxonium intermediate **F** can be formed if BF_3 is used to trigger the reaction. We expect that in the first step, the BF_3 reacts with the carboxylic acid of **3a**.[22] Generated intermediate **J** then undergoes proton-activated intramolecular 7-*endo*-*dig* cyclization of hydroxy group oxygen to alkyne. Finally, the proton transfer generates the key oxonium intermediate **F**. Observed incapacity of $TiCl_4$ to promote the rearrangement of **3a** can be rationalized by the intermediate **M** formation (hydroxy group is not available for intramolecular cyclization reaction). Proposed reaction mechanism also rationalizes longer reaction times observed during the formation of compounds **4g**-**i** bearing alkynes substituted with electron-deficient aryl group or with alkyl (lower stabilization of δ^+ Markovnikov addition-type intermediate). Similarly, trans-annular cyclization of the corresponding TMS-amide intermediate **N** is slower than in the case of the corresponding acid due to lower nucleophilicity of the nitrogen atom in **N**.

Conclusion

To summarize, we have discovered an unexpected rearrangement of *N*-(3-phenylprop-2-yn-1-yl) sulfonamides that yielded novel chiral derivatives of pyrrolidin-3-ones. The starting materials are readily available by either solution-phase or solid-phase synthesis and furnish the target compounds mostly in good or acceptable crude purities and yields. The reported reaction is broadly applicable in the case of the pyrrolidine scaffold and therefore can be utilized for the simple

preparation of diversely substituted products. Its application to more complex compounds and diverse starting materials can be further studied in the future.

Experimental section

General Information. Solvents and chemicals were purchased from Sigma-Aldrich (Milwaukee, WI), Acros Organic (Geel, Belgium) and Fluorochem (Hadfield, United Kingdom). Wang resin (100-200 mesh, 1% DVB, 1.4 mmol/g) and Rink resin (100-200 mesh, 1% DVB, 0.6 mmol/g) were obtained from AAPPTec (Louisville, KY). Solid-phase synthesis was carried out in plastic reaction vessels (syringes, each equipped with a porous disk) using a manually operated synthesizer (Torviq, Niles, MI). All reactions were carried out at ambient temperature (23 °C) unless stated otherwise; when the reactions required a heating at higher temperature, the heating was performed in oil bath at specific temperature (see for each derivative separately below in the text). Synthesis of *N*-sulfonamides (**1a-l**) was performed according to previously reported procedure.[3] The LC-MS analyses were carried out on UHPLC-MS system consisting of UHPLC chromatograph Acquity with photodiode array detector and single quadrupole mass spectrometer (Waters), using X-Select C18 column with the mobile phase consisting of 10 *m*M ammonium acetate (AmAc) in H_2O and MeCN. The ESI source operated at discharge current of 5 *μ*A, vaporizer temperature of 350 °C and capillary temperature of 200 ˚C. For the LC/MS analysis, a sample of resin (~5 mg) was treated with TFA in DCM, the cleavage cocktail was evaporated under a stream of nitrogen, and cleaved compounds extracted into MeCN (1 mL). Purification was carried out on C18 reverse phase semi preparative HPLC chromatography with the gradient of 10 *m*M aqueous AmAc and MeCN, flow rate 15 mL/min or by normal phase by silica gel chromatography. Residual solvents (H_2O and ammonium acetate buffer) was lyophilized by the ScanVac Coolsafe 110-4 working at -110 °C. All NMR spectra were performed with using ECA400II or ECX500 spectrometers (JEOL RESONANCE, Tokyo, Japan) at magnetic field strength of 9.39 T or 11.75 T corresponding to ^{1}H, $^{13}C\{^{1}H\}$ and ^{15}N resonance frequencies of 399.78 MHz or 500.16 MHz, 100.53 MHz or 125.77 MHz and 50.7 MHz at 27 ºC. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are

reported in Hertz (Hz). The signals of MeCN-d_3, $CDCl_3$ and MeOH-d_4 were set at 1.94 ppm, 7.26 ppm and 3.31 ppm, respectively, in ^{1}H NMR spectra and at 118.26 ppm, 77.36 ppm and 49.15 ppm, respectively, in $^{13}C\{^1H\}$ NMR spectra. ^{15}N chemical shifts were referenced to external 90% formamide in DMSO-d_6 (112.00 ppm).[23] The assignment of ^{1}H, $^{13}C\{^1H\}$ and ^{15}N signals was done by $^{13}C\{^1H\}$ APT, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-$^{13}C\{^1H\}$ HSQC, ^{1}H-$^{13}C\{^1H\}$ HMQC, ^{1}H-$^{13}C\{^1H\}$ HMBC and ^{1}H-^{15}N HMBC. Abbreviations in NMR spectra: br. s – broad singlet, s – singlet, d – doublet, dd – doublet of doublets, ddd – doublet of doublets of doublets, dddd – doublet of doublets of doublets of doublets, t – triplet, m – multiplet. HRMS analysis was performed using LC-MS (Dionex Ultimate 3000) with Orbitrap Elite high-resolution mass spectrometer (Thermo Exactive plus) operating at positive full scan mode (120 000 FWMH) in the range of 100-1000 m/z with electrospray ionization working at 150 °C and the source voltage of 3.6 kV. The acquired data were internally calibrated with phthalate as a contaminant in MeOH (m/z 297.15909). IR spectra were measured by DRIFT (Diffuse Reflectance Infrared Fourier Transform) on a Thermo Nicolet AVATAR 370 FTIR spectrometer. Absorbance peaks (wavenumbers) are reported in reciprocal centimeters (cm^{-1}) and transmittances (T) are reported in percentages (%). Specific optical rotations were measured on Automatic Compact Polarimeter POL-1/2 (ATAGO, Japan) with LED Light Source and 589 nm interference filter at 24 °C. The length of cuvette was 2 cm and specific optical rotations are reported as follows: $[\alpha]_D^T$, concentration (g/ml) and solvent. Melting points were measured by Boetius stage apparatus (WEB Analytik, Dresden, Germany) and they are reported in Celsius degrees (°C).

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

General procedure for Sonogashira coupling to prepare alkylating agents. $Pd(PPh_3)_2Cl_2$ and CuI were suspended in degassed TEA under nitrogen. Then aryl iodide was added followed

by propargyl alcohol and the reaction was stirred intensively for 5-22 h at room temperature for derivatives **II-III** or heated at 60 °C in oil bath for 22 h for derivative **IV**. Then the reaction mixture was filtrated over Celite, washed with fresh TEA and purified by silica gel chromatography in EtOAc/hexane.

3-(*p*-tolyl)prop-2-yn-1-ol II. According to the general procedure, $Pd(PPh_3)_2Cl_2$ (483 mg, 0.69 mmol, 1 mol%) and CuI (262 mg, 1.38 mmol, 2 mol%) were suspended in degassed TEA (325 mL) under nitrogen. Then 4-iodotoluene (15.0 g, 68.80 mmol, 1.0 equiv) was added followed by propargyl alcohol (4.4 mL, 75.68 mmol, 1.1 equiv) and the reaction was stirred intensively for 5 h at room temperature. Then the reaction mixture was filtrated over Celite, washed with fresh TEA and purified by silica gel chromatography in EtOAc/hexane (3/7; v/v), R_f = 0.5, yielded pale brown solid (5.2 g, 35.616 mmol, 51%). HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (br. d, *J* = 8.0 Hz, 2H), 7.12 (br. d, *J* = 8.0 Hz, 2H), 4.49 (s, 2H), 2.35 (s, 3H), 1.79 (br. s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 139.0, 131.9, 129.4, 119.8, 86.9, 86.2, 52.0, 21.8. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{10}H_{11}O$ $[M+H]^+$ 147.0804, found 147.0805. Other spectral and physical properties (mp 33.0–34.0 °C and IR data) concur with published data.[24]

3-(4-methoxyphenyl)prop-2-yn-1-ol III. According to the general procedure, $Pd(PPh_3)_2Cl_2$ (150 mg, 0.21 mmol, 1 mol%) and CuI (81 mg, 0.42 mmol, 2 mol%) were suspended in degassed TEA (101 mL) under nitrogen. Then 4-iodoanisole (5.0 g, 21.4 mmol, 1.0 equiv) was added followed by propargyl alcohol (1.4 mL, 23.50 mmol, 1.1 equiv) and the reaction was stirred intensively for 22 h at room temperature. Then the reaction mixture was filtrated over Celite, washed with fresh TEA and purified by silica gel chromatography in EtOAc/hexane (3/7; v/v), R_f = 0.4, yielded pale brown solid (3.1 g, 19.136 mmol, 89%). HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (br. d, *J* = 6.9 Hz, 2H), 6.83 (br. d, *J* = 6.9 Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 1.85 (br. s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 160.1, 133.5, 115.0, 114.3, 86.2, 86.0, 55.6, 52.0. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{10}H_{11}O_2$ $[M+H]^+$ 163.0754, found 163.0755. Other spectral and physical properties (mp 63.1–63.5 °C and IR data) concur with published data.[25]

3-(4-trifluoromethyl)phenyl)prop-2-yn-1-ol IV. According to the general procedure, $Pd(PPh_3)_2Cl_2$ (129 mg, 0.18 mmol, 1 mol%) and CuI (70 mg, 0.36 mmol, 2 mol%) were suspended in degassed TEA (86.4 mL) under nitrogen. Then 4-iodobenzotrifluoride (2.7 mL, 18.38 mmol, 1.0 equiv) was

added followed by propargyl alcohol (1.2 mL, 20.21 mmol, 1.1 equiv) and the reaction was stirred intensively for 22 h at 60 °C in oil bath. Then the reaction mixture was filtrated over Celite, washed with fresh TEA and purified by silica gel chromatography in EtOAc/hexane (3/7; v/v), R_f = 0.5, yielded waxy yellow solid (3.56 g, 17.800 mmol, 97%). HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (br. d, *J* = 8.4 Hz, 2H), 7.53 (br. d, *J* = 8.4 Hz, 2H), 4.52 (s, 2H), 1.80 (br. s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 132.3, 130.6 (q, *J* = 32.8 Hz), 126.7, 125.6 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 271.8 Hz), 90.0, 84.7, 51.9. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{10}H_6F_3O$ $[M-H]^-$ 199.0365, found 199.0359. Other spectral and physical properties (mp 40.0–41.1 °C and IR data) concur with published data.[24]

General procedure for the Mitsunobu alkylation 2a-l. Resin **1a-l** (500 mg) was washed three times with DCM, anhydrous DMF and anhydrous THF, and solution of alcohol (3.00 mmol) and triphenylphosphine (TPP, 787 mg, 3.00 mmol) in anhydrous THF (5 mL) was added. The syringe with resin and reaction solution was connected by a plastic clutch with the second syringe containing a solution of DIAD (591 *μ*L, 3.00 mmol) in anhydrous THF (5 mL). The syringes were cooled to -20 °C, their content was mixed together and shaken for 24 h at room temperature. The resulting resin was washed three times with anhydrous THF and DCM.

Cleavage from the resin and removal of the *t*Bu protecting group 3a-l. The resin **2a-l** (500 mg) was shaken in TFA/anhydrous DCM (5 mL, 50%) for 1 h at room temperature. Then the resin was washed three times with fresh cleavage cocktail (5 mL) and combined washes were evaporated using a stream of nitrogen. The crude product was purified by reverse-phase semipreparative HPLC or by silica gel chromatography (see Supporting Information, Table S1).

(-)-*N*-((4-nitrophenyl)sulfonyl)-*N*-(3-phenylprop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3a. Pale orange amorphous solid (46.8 mg, 0.112 mmol, 82%). The crude product was purified by silica gel chromatography in DCM/MeOH (9/1; v/v) + 1% HCOOH, R_f = 0.6. HPLC purity 98%. Cleaved from 325 mg of resin **2a** (0.420 mmol/g, 0.137 mmol of substrate). ^{1}H NMR (400 MHz, MeCN-d_3): δ = 8.22 (d, *J* = 9.2 Hz, 2H), 8.12 (d, *J* = 9.2 Hz, 2H), 7.24-7.34 (m, 5H), 4.58 (s, 2H), 4.44-4.47 (m, 2H), 3.91 (br. s, 1H), 1.24 (d, *J* = 6.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, MeCN-d_3): δ = 172.6, 151.0, 146.9, 132.3, 130.0, 129.5, 129.4, 124.9, 123.4, 87.0, 84.7, 68.4, 66.8, 38.1, 20.6. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{19}H_{17}N_2O_7S$ $[M-H]^-$ 417.0751, found 417.0756. IR

(DRIFT): $\bar{\nu}$ = 3528, 3251, 3106, 2979, 2931, 1724, 1685, 1605, 1528, 1442, 1401, 1344, 1308, 1157, 1088, 854, 822 cm^{-1}. $[\alpha]_D^{24}$ = -43.2° (c = 0.00110 g/mL, MeCN).

(-)-*N*-((2-nitrophenyl)sulfonyl)-*N*-(3-phenylprop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3b. White amorphous solid (29.2 mg, 0.070 mmol, 21%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 98%. Cleaved from 622 mg of resin **2b** (0.524 mmol/g, 0.326 mmol of substrate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1H), 7.46-7.53 (m, 3H), 7.16-7.25 (m, 5H), 5.84 (br. s, 1H), 4.75 (d, *J* = 18.6 Hz, 1H), 4.67 (d, *J* = 18.6 Hz, 1H), 4.57-4.58 (m, 1H), 4.50 (d, *J* = 4.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 174.9, 148.2, 134.0, 133.6, 132.1, 132.0, 131.8, 128.8, 128.6, 124.4, 122.6, 86.0, 85.3, 68.7, 67.0, 38.0, 20.2. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{19}H_{17}N_2O_7S$ [M-H]$^-$ 417.0751, found 417.0759. IR (DRIFT): $\bar{\nu}$ = 3209, 2979, 1720, 1541, 1346, 1440, 1159, 1124, 756, 691 cm^{-1}. $[\alpha]_D^{24}$ = -21.0° (c = 0.00119 g/mL, MeCN).

(-)-*N*-(methylsulfonyl)-*N*-(3-phenylprop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3c. White amorphous solid (14.7 mg, 0.047 mmol, 12%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 401 mg of resin **2c** (0.524 mmol/g, 0.210 mmol of substrate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.33 (m, 2H), 7.17-7.22 (m, 3H), 4.92 (br. s, 1H), 4.56 (d, *J* = 18.3 Hz, 1H), 4.48 (d, *J* = 18.3 Hz, 1H), 4.39-4.46 (m, 1H), 4.32 (d, *J* = 3.8 Hz, 1H), 3.05 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 174.7, 132.0, 129.1, 128.8, 122.4, 85.4, 85.4, 68.0, 66.2, 41.5, 37.2, 20.2. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{14}H_{16}NO_5S$ [M-H]$^-$ 310.0744, found 310.0750. IR (DRIFT): $\bar{\nu}$ = 3521, 3492, 3005, 2253, 2145, 2000, 1749, 1711, 1361, 1421, 1092 cm^{-1}. $[\alpha]_D^{24}$ = -87.5° (c = 0.00012 g/mL, MeCN).

(-)-*N*-((2-nitrophenyl)sulfonyl)-*N*-(3-phenylprop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3d. White amorphous solid, 27.1 mg (31%, 0.112 mmol). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 435 mg of resin **2d** (0.524 mmol/g, 0.228 mmol of substrate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.2 Hz, 2H), 7.15-7.26 (m, 7H), 5.16 (br. s, 1H), 4.69 (d, *J* = 18.9 Hz, 1H), 4.54 (d, *J* = 18.9 Hz, 1H), 4.45 (m, 2H), 2.28 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 174.3, 144.0, 137.3, 131.9, 129.8, 128.8, 128.5, 128.2, 122.6, 85.8, 85.0, 77.7, 77.4, 77.0, 68.0, 36.6, 22.3, 21.8, 20.0.

HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{20}H_{20}NO_5S$ $[M-H]^-$ 386.1057, found 386.1065. IR (DRIFT): $\bar{\nu}$ = 3508, 3234, 3055, 2980, 2922, 1915, 1704, 1442, 1327, 1152, 1090, 811, 756 cm^{-1}. $[\alpha]_D^{24}$ = -20.2° (c = 0.00104 g/mL, MeCN).

(-)-*N*-((4-nitrophenyl)sulfonyl)-*N*-(3-(4-trifluoromethyl)phenyl)prop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3g. White amorphous solid (70.0 mg, 0.144 mmol, 69%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 482 mg of resin **2g** (0.734 mmol/g, 0.354 mmol of substrate). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.27 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 7.57 (br. d, *J* = 7.6 Hz, 2H), 7.43 (br. d, *J* = 7.6 Hz, 2H), 4.72 (d, *J* = 18.9 Hz, 1H), 4.63 (d, *J* = 18.9 Hz, 1H), 4.41-4.54 (m, 2H), 1.35 (d, *J* = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, MeOH-d_4): δ = 173.2, 151.5, 147.5, 133.2, 131.2 (q, *J* = 32.8 Hz), 130.5, 128.4, 126.4 (d, *J* = 4.2 Hz), 125.5 (q, *J* = 271.3 Hz), 125.1, 90.0, 83.7, 68.6, 38.2, 21.0. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{20}H_{18}F_3N_2O_7S$ $[M+H]^+$ 487.0781, found 487.0784. IR (DRIFT): $\bar{\nu}$ = 3104, 2983, 2936, 2871, 1925, 1726, 1529, 1404, 1348, 1322, 1159, 1123, 1089, 1066, 1016, 843, 740 cm^{-1}. $[\alpha]_D^{24}$ = -44.4° (c = 0.00422 g/mL, MeCN).

(-)-*N*-(but-2-yn-1-yl)-*N*-((4-nitrophenyl)sulfonyl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3h. Pale yellow-white amorphous solid (85.2 mg, 0.239 mmol, 73%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 498 mg of resin **2h** (0.656 mmol/g, 0.327 mmol of substrate). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.36 (d, *J* = 9.1 Hz, 2H), 8.16 (d, *J* = 9.1 Hz, 2H), 4.39-4.45 (m, 1H), 4.28-4.36 (m, 3H), 3.38-3.24 (1H), 1.66 (s, 3H), 1.26 (d, *J* = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (400 MHz, MeOH-d_4): δ = 174.3, 151.5, 147.8, 130.4, 124.9, 81.2, 76.5, 68.4, 37.4, 20.7, 3.2. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{14}H_{17}N_2O_7S$ $[M+H]^+$ 357.0751, found 357.0751. IR (DRIFT): $\bar{\nu}$ = 3106, 3041, 2980, 2935, 2230, 1706, 1527, 1347, 1309, 1089, 830, 759 cm^{-1}. $[\alpha]_D^{24}$ = -74.55° (c = 0.00100 g/mL, MeCN).

(-)-*N*-((4-nitrophenyl)sulfonyl)-*N*-(prop-2-yn-1-yl)-(2*S*,3*R*)-2-amino-3-hydroxybutyric acid 3i. White amorphous solid (28.1 mg, 0.082 mmol, 33%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 400 mg of resin **2i** (0.621 mmol/g, 0.248 mmol of substrate). ^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.35 (d, *J* = 9.2 Hz, 2H), 8.15 (d, *J* = 9.2 Hz, 2H), 4.54 (dd, *J* = 18.6, 2.5 Hz, 1H), 4.32-4.36 (m, 2H), 4.23 (d, *J* = 5.2 Hz, 1H), 2.55

(t, *J* = 2.5 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, MeOH-d_4): δ = 175.0, 151.6, 147.4, 130.4, 125.0, 81.8, 73.6, 69.1, 68.8, 37.2, 20.8. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{13}H_{15}N_2O_7S$ $[M+H]^+$ 343.0594, found 343.0594. IR (DRIFT): $\bar{\nu}$ = 3211, 3105, 2970, 2940, 2231, 1717, 1528, 1433, 1349, 1309, 1158, 1090, 830, 741 cm^{-1}. $[\alpha]_D^{24}$ = -88.5° (c = 0.00013 g/mL, MeCN).

(-)-*N*-((4-nitrophenyl)sulfonyl)-*N*-(3-phenylprop-2-yn-1-yl)-(*S*)-2-amino-3-hydroxybutyric acid 3j. White amorphous solid (32.4 mg, 0.080 mmol, 30%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 98%. Cleaved from 522 mg of resin **2j** (0.515 mmol/g, 0.267 mmol of substrate). ^1H NMR (500 MHz, MeOH-d_4): δ = 8.25 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.20-7.29 (m, 5H), 4.63 (d, *J* = 18.6 Hz, 1H), 4.57 (dd, *J* = 7.2, 5.8 Hz, 1H), 4.48 (d, *J* = 18.6 Hz, 1H), 4.08 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.91 (dd, *J* = 11.4, 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, MeOH-d_4): δ = 175.1, 151.4, 148.3, 132.7, 130.4, 129.6, 129.5, 125.0, 124.1, 86.5, 85.5, 65.6, 63.1, 36.9. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{18}H_{17}N_2O_7S$ $[M+H]^+$ 405.0751, found 405.0751. IR (DRIFT): $\bar{\nu}$ = 3042, 2240, 1738, 1580, 1532, 1349, 1167, 1156, 1058, 816 cm^{-1}. $[\alpha]_D^{24}$ = -29.6° (c = 0.00108 g/mL, MeCN).

(-)-(2*S*,3*R*)-3-hydroxy-2-((4-nitro-*N*-(3-phenylprop-2-yn-1-yl)phenyl)sulfonamido)butanamide 3k. White amorphous solid (32.4 mg, 0.078 mmol, 30%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. Cleaved from 715 mg of resin **2k** (0.359 mmol/g, 0.257 mmol of substrate). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.32-7.35 (m, 1H), 7.26-7.29 (m, 2H), 7.14-7.16 (m, 2H), 6.41 (br. s, 1H), 5.69 (br. s, 1H), 4.83 (d, *J* = 18.9 Hz, 1H), 4.61 (d, *J* = 18.9 Hz, 1H), 4.42 (qd, *J* = 6.4 Hz, 1H), 4.25 (d, *J* = 7.4 Hz, 1H), 2.58 (br. s, 1H), 1.22 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 171.1, 150.5, 145.9, 131.7, 129.7, 129.5, 128.9, 124.3, 121.3, 86.5, 83.6, 66.0, 65.6, 35.6, 19.7. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{19}H_{20}N_3O_6S$ $[M+H]^+$ 418.1067, found 418.1069. IR (DRIFT): $\bar{\nu}$ = 3502, 3486, 3386, 3351, 3189, 3115, 3100, 3078, 3038, 3009, 2980, 2940, 2248, 1932, 1878, 1674, 1606, 1530, 1419, 1344, 1309, 1159, 1089, 1026, 855, 821 cm^{-1}. $[\alpha]_D^{24}$ = -40.2° (c = 0.00107 g/mL, MeCN).

General conditions for rearrangement of 3a-l to pyrrolidin-3-ones 4a-l. (a) TMSOTf – promoted rearrangement (see Supporting Information, Scheme S1, Table S2-3). For derivative **4a**: To a stirred solution of **3a** (58 mg, 0.14 mmol, 1.0 equiv) in anhydrous DCM (1.5 mL) cooled to 0 °C, TES was slowly added dropwise (22 μL, 0.14 mmol, 1.0 equiv) followed by addition of TMSOTf (52 μL mg, 0.28 mmol, 2.0 equiv). After 24 h, the reaction mixture was washed with saturated solution of $NaHCO_3$/DCM (3×5 mL), dried with anhydrous $MgSO_4$, filtrated and evaporated to dryness. For derivatives **4a-l**: To the crude product **3a-l** (cleaved from 500 mg resin), TMSOTf (380 μL, 2.10 mmol, 2.0 equiv) in anhydrous DCM (5 mL) was added and shaken for specific reaction time and temperature (see later in the text and Supporting Information, Table S2). The reaction mixture was evaporated under a stream of nitrogen, the residual material was dissolved in anhydrous DCM (5 mL) and washed three times with saturated solution of $NaHCO_3$. The organic layer was separated, dried with anhydrous $MgSO_4$, evaporated to dryness and the crude samples were purified by reverse-phase semi preparative HPLC chromatography. **(b) $BF_3.OEt_2$ – promoted rearrangement** (see Supporting Information, Scheme S1, Table S3): To the crude product **3a** (cleaved from 100 mg resin), $BF_3.OEt_2$ (52 μL, 0.42 mmol, 2.0 equiv) in anhydrous DCM (1 mL) was added and shaken for 2.5 h, 24 h and 48 h at room temperature. The DCM layer was washed three times with saturated solution of $NaHCO_3$. dried with anhydrous $MgSO_4$, evaporated to dryness and analyzed by LC-UV-MS. Conclusion: The observed conversion was 10% after 48 hours calculated from the HPLC-UV traces (205-400 nm). **(c) $TiCl_4$ – promoted rearrangement** (see Supporting Information, Scheme S1, Table S3): To the crude product **3a** (cleaved from 100 mg resin), $TiCl_4$ (46 μL, 0.42 mmol, 2.0 equiv) in anhydrous DCM (1 mL) was added and shaken for 2.5 h, 24 h and 48 h at room temperature. The sample for HPLC analysis was obtained by the same procedure as for $BF_3.OEt_2$. Conclusion: The desired product was not detected.

(+)-(^{13}*R*)-1-((^{2}*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ether benzoate 4a. Reaction conditions: 24 h at room temperature. White amorphous solid (40.9 mg, 0.098 mmol, 71%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^{1}H NMR (500 MHz, MeCN-d_3): δ = 8.34 (d, J = 8.9 Hz, 2H, $HC^{8,10}$), 8.10 (d, J = 8.9 Hz, 2H, $HC^{7,11}$), 7.93-7.95 (m, 2H, $HC^{16,20}$), 7.60-7.63 (m, 1H, HC^{18}), 7.47-7.49 (m, 2H, $HC^{17,19}$), 5.54 (qd, J = 6.5, 4.0 Hz, 1H, HC^{13}), 4.12 (ddd, J = 4.0, 1.0, 1.0 Hz, 1H, HC^{2}), 4.02 (ddd, J = 12.4, 10.0, 3.3 Hz, 1H,

H_aC^5), 3.88 (ddd, *J* = 12.4, 9.5, 7.7 Hz, 1H, H_bC^5), 2.31 (dddd, *J* = 18.8, 7.7, 3.3, 1.0 Hz, 1H, H_aC^4), 2.04 (dddd, *J* = 18.8, 10.5, 9.5, 1.0 Hz, 1H, H_bC^4), 1.47 (d, *J* = 6.5 Hz, 3H, HC^{21}). $^{13}C\{^1H\}$ NMR (126 MHz, MeCN-d_3): δ = 210.6 (C3), 166.3 (C14), 151.8 (C9), 144.0 (C6), 134.4 (C18), 130.7 (C15), 130.3 (C16,20), 129.8 (C7,11), 129.6 (C17,19), 125.9 (C8,10), 72.1 (C13), 67. (C2), 46.5 (C5), 37.1 (C4), 17.1 (C21). ^{15}N NMR (51 MHz, MeCN-d_3): δ = 102.7 (N1); 366.9 (N12). See Supporting Information for detailed assignments. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 7.89-7.91 (m, 2H), 7.54-7.58 (m, 1H), 7.40-7.43 (m, 2H), 5.57 (qd, *J* = 6.6, 4.6 Hz, 1H), 4.07 (br. d, *J* = 4.6 Hz, 1H), 4.00 (ddd, *J* = 12.2, 9.9, 3.8 Hz, 1H), 3.89 (ddd, *J* = 12.2, 9.1, 7.8 Hz, 1H), 2.42 (ddd, *J* = 18.6, 7.8, 3.8 Hz, 1H), 2.24 (ddd, *J* = 18.6, 9.1, 7.8 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 208.8, 165.7, 150.7, 143.9, 133.8, 129.9, 129.8, 128.9, 128.9, 125.0, 77.6, 77.4, 77.1, 70.9, 66.4, 45.7, 36.9, 17.3. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{19}H_{17}N_2O_7S$ $[M-H]^-$ 417.0751, found 417.0757. IR (DRIFT): $\bar{\nu}$ = 2874, 1940, 1828, 1763, 1714, 1529, 1452, 1347, 1270, 1222, 1164, 1088, 855, 713 cm^{-1}. $[\alpha]_D^{24}$ = +61.2° (c = 0.00165 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-((2-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl benzoate 4b. Reaction conditions: 24 h at room temperature. Pale yellow amorphous solid (47.6 mg, 0.114 mmol, 41%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.92-7.93 (m, 2H), 7.67-7.70 (m, 2H), 7.62-7.64 (m, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 5.56 (qd, *J* = 6.4, 4.0 Hz, 1H), 4.29 (br. d, *J* = 4.0 Hz, 1H), 4.23 (ddd, *J* = 12.3, 9.5, 3.5 Hz, 1H), 3.93 (ddd, *J* = 12.3, 9.9, 8.0 Hz, 1H), 2.49 (ddd, *J* = 18.6, 9.5, 9.5 Hz, 1H), 2.42 (ddd, *J* = 18.6, 8.0, 3.5 Hz, 1H), 1.46 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 209.4, 165.7, 148.5, 134.7, 133.6, 132.7, 132.3, 132.1, 130.0, 129.9, 128.8, 124.9, 71.4, 67.1, 45.8, 37.2, 17.5. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{19}H_{19}N_2O_7S$ $[M+H]^+$ 419.0907 found 419.0907. IR (DRIFT): $\bar{\nu}$ = 2979, 2937, 1921, 1765, 1717, 1542, 1450, 1347, 1262, 1225, 1192, 1087, 805, 741, 708 cm^{-1}. $[\alpha]_D^{24}$ = +173.3° (c = 0.00118 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-(mesylsulfonyl)-3-oxopyrrolidin-2-yl)ethyl benzoate 4c. Reaction conditions: 24 h at room temperature. Gray-white amorphous solid (47.1 mg, 0.151 mmol, 40%). The crude product

was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95-7.97 (m, 2H, $HC^{10,14}$), 7.56-7.59 (m, 1H, HC^{12}), 7.43-7.46 (m, 2H, $HC^{11,13}$), 5.54 (qd, *J* = 6.5, 4.0 Hz, 1H, HC^{7}), 4.15 (br. d, *J* = 4.0 Hz, 1H, HC^{2}), 4.14 (ddd, *J* = 12.0, 10.0, 2.6 Hz, 1H, H_aC^{5}), 3.81 (ddd, *J* = 12.0, 10.0, 7.7 Hz, 1H, H_bC^{5}), 2.93 (s, 3H, HC^{6}), 2.68 (ddd, *J* = 18.8, 11.0, 10.0 Hz, 1H, H_aC^{4}), 2.50 (ddd, *J* = 18.8, 7.7, 2.6 Hz, 1H, H_bC^{4}), 1.51 (d, *J* = 6.5 Hz, 3H, HC^{15}). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 210.3 (C3), 165.7 (C8), 133.7 (C12), 123.0 (C9), 129.9 (C10,14), 128.9 (C11,13), 71.4 (C7), 66.2 (C2), 45.3 (C5), 38.9 (C6), 37.4 (C4), 17.6 (C15). ^{15}N NMR (51 MHz, $CDCl_3$): δ = 99.2 (N1). See Supporting Information for detailed assignments. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{14}H_{18}NO_5S$ $[M+H]^+$ 312.0900 found 312.0899. IR (DRIFT): $\bar{\nu}$ = 2963, 2934, 1918, 1757, 1716, 1452, 1340, 1265, 1195, 1149, 1086, 1029, 776, 710 cm^{-1}. $[\alpha]_D^{24}$ = +469.1° (c = 0.00081 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-3-oxo-1-tosylpyrrolidin-2-yl)ethyl benzoate 4d. Reaction conditions: 24 h at room temperature. White amorphous solid (80.4 mg, 0.208 mmol, 50%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92-7.97 (m, 2H), 7.75 (br. d, *J* = 8.3 Hz, 2H), 7.53-7.58 (m, 1H), 7.40-7.45 (m, 2H), 7.33 (br. d, *J* = 8.3 Hz, 2H), 5.63 (qd, *J* = 6.4, 3.4 Hz, 1H), 4.00 (br. d, *J* = 3.4 Hz, 1H), 3.96 (ddd, *J* = 12.7, 9.9, 3.0 Hz, 1H), 3.86 (ddd, *J* = 12.7, 9.6, 7.7 Hz, 1H), 2.42 (s, 3H), 2.21 (ddd, *J* = 18.5, 7.7, 3.0 Hz, 1H), 1.94 (ddd, *J* = 18.5, 9.9, 9.6 Hz, 1H), 1.55 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 210.7, 165.7, 144.9, 134.9, 133.6, 130.6, 130.1, 129.9, 128.8, 127.8, 71.9, 66.80, 45.8, 36.5, 21.9, 17.3. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{20}H_{22}NO_5S$ $[M+H]^+$ 388.1213 found 388.1213. IR (DRIFT): $\bar{\nu}$ = 2996, 2939, 2903, 1926, 1763, 1709, 1449, 1164, 1088, 821, 751, 716 cm^{-1}. $[\alpha]_D^{24}$ = +76.4° (c = 0.00121 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl 4-methylbenzoate 4e. Reaction conditions: 24 h at room temperature. White amorphous solid (24.5 mg, 0.057 mmol, 30%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.76 (br. d, *J* = 8.2 Hz, 2H), 7.20 (br. d, *J* = 8.2 Hz, 2H), 5.53 (qd, *J* = 6.4, 4.6 Hz, 1H), 4.07 (br. d, *J* = 4.6 Hz, 1H), 4.03 (ddd, *J* = 12.0, 9.9, 3.5 Hz, 1H), 3.88 (ddd, *J* = 12.0, 9.5, 7.6 Hz, 1H), 2.43 (ddd, *J* = 18.7, 7.6, 3.5

Hz, 1H), 2.40 (s, 3H), 2.26 (ddd, *J* = 18.7, 9.9, 9.5 Hz, 1H), 1.51 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 208.9, 165.8, 150.6, 144.7, 144.1, 129.9, 129.6, 128.8, 127.0, 125.0, 70.6, 66.5, 45.6, 36.9, 22.0, 17.4. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{20}H_{21}N_2O_7S$ $[M+H]^+$ 433.1064 found 433.1064. IR (DRIFT): $\overline{\nu}$ = 2980, 2961, 2874, 1935, 1763, 1707, 1528, 1452, 1346, 1309, 1266, 1165, 1086, 752, 734 cm^{-1}. $[\alpha]_D^{24}$ = +50.0° (c = 0.00131 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl 4-methoxybenzoate 4f. Reaction conditions: 24 h at room temperature. Pale yellow amorphous solid (55.0 mg, 0.118 mmol, 42%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.83 (br. d, *J* = 8.9 Hz, 2H), 6.87 (br. d, *J* = 8.9 Hz, 2H), 5.52 (qd, *J* = 6.6, 4.6 Hz, 1H), 4.06 (br. d, *J* = 4.6 Hz, 1H), 4.02 (ddd, *J* = 12.9, 9.8, 3.4 Hz, 1H), 3.89 (ddd, *J* = 12.9, 9.3, 7.7 Hz, 1H), 3.85 (s, 3H), 2.42 (ddd, *J* = 18.6, 7.7, 3.4 Hz, 1H), 2.25 (ddd, *J* = 18.6, 9.8, 9.3 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 208.9, 165.5, 164.1, 150.7, 144.1, 132.0, 128.8, 125.0, 122.1, 114.1, 70.4, 66.5, 55.8, 45.6, 36.9, 17.4. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{20}H_{19}N_2O_8S$ $[M-H]^-$ 447.0857 found 447.0846. IR (DRIFT): $\overline{\nu}$ = 1940, 1766, 1701, 1529, 1510, 1345, 1313, 1255, 1165, 1087, 1026, 854, 735 cm^{-1}. $[\alpha]_D^{24}$ = +34.2° (c = 0.00130 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl 4-(trifluoromethyl)-benzoate 4g. Reaction conditions: 24 h , heating at 40 °C in oil bath. White amorphous solid (21.7 mg, 0.045 mmol, 18%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 98%. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.6 Hz, 2H), 8.08 (br. d, *J* = 8.6 Hz, 4H), 7.70 (br. d, *J* = 8.2 Hz, 2H), 5.63 (qd, *J* = 6.5, 4.6 Hz, 1H), 4.01 (br. d, *J* = 4.6 Hz, 1H), 3.88-3.91 (m, 2H), 2.42 (ddd, *J* = 18.6, 7.9, 4.4 Hz, 1H), 2.22 (ddd, *J* = 18.6, 10.4, 9.2 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 208.3, 164.7, 150.9, 143.3, 135.3 (q, *J* = 32.8 Hz), 133.1, 130.4, 129.1, 125.9 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 273.0 Hz), 125.1, 71.5, 65.9, 45.6, 36.9, 16.9. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{20}H_{16}F_3N_2O_7S$ $[M-H]^-$ 485.0625 found 485.0614. IR (DRIFT): $\overline{\nu}$ = 2980, 2961, 1943, 1765, 1718, 1530, 1411, 1323, 1269, 1165, 1087, 1016, 856, 757 cm^{-1}. $[\alpha]_D^{24}$ = +55.7° (c = 0.00114 g/mL, MeCN).

(+)-(*R*)-1-((*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl acetate 4h. Reaction conditions: 72 h at room temperature. Pale yellow amorphous solid (32.1 mg, 0.090 mmol, 33%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 98%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.3 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 2H), 5.33 (qd, *J* = 6.3, 3.7 Hz, 1H), 3.91 (br. d, *J* = 3.7 Hz, 1H), 3.88 (ddd, *J* = 18.6, 10.2, 3.7 Hz, 1H), 3.82 (ddd, *J* = 12.3, 8.6, 7.7 Hz, 1H), 2.35 (ddd, *J* = 18.6, 7.7, 3.7 Hz, 1H), 2.10 (ddd, *J* = 18.6, 10.2, 9.1 Hz, 1H), 2.01 (s, 3H), 1.41 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 209.0, 170.0, 150.9, 143.7, 129.1, 125.2, 71.2, 66.3, 45.7, 36.8, 21.3, 17.0. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{14}H_{17}N_2O_7S$ $[M+H]^+$ 357.0751 found 357.0751. IR (DRIFT): $\bar{\nu}$ = 2982, 2962, 2876, 1815, 1763, 1709, 1532, 1351, 1309, 1238, 1168, 1089, 856 cm^{-1}. $[\alpha]_D^{24}$ = +103.2° (c = 0.00109 g/mL, MeCN).

(+)-(*S*)-(1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)methyl benzoate 4j. Reaction conditions: 72 h at room temperature. White amorphous solid (15.8 mg, 0.039 mmol, 14%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 97%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.70-7.74 (m, 2H), 7.512-7.58 (m, 1H), 7.35-7.40 (m, 2H), 4.78 (dd, *J* = 11.7, 3.4 Hz, 1H), 4.57 (dd, *J* = 11.7, 2.6 Hz, 1H), 4.15 (dd, *J* = 3.4, 2.6 Hz, 1H), 3.97 (ddd, *J* = 10.2, 8.6, 6.3 Hz, 1H), 3.75 (ddd, *J* = 10.2, 8.0, 8.0 Hz, 1H), 2.66-2.72 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 207.7, 165.7, 150.5, 144.1, 134.0, 129.6, 129.1, 128.9, 128.6, 124.9, 64.0, 62.3, 44.9, 37.0. HRMS (ESI-TOF, neg.): *m/z* calcd for $C_{18}H_{15}N_2O_7S$ $[M-H]^-$ 403.0594 found 403.0599. IR (DRIFT): $\bar{\nu}$ =2979, 2959, 2896, 1948, 1762, 1721, 1522, 1344, 1265, 1162, 1147, 1094, 855, 712, 687 cm^{-1}. $[\alpha]_D^{24}$ = +56.5° (c = 0.00114 g/mL, MeCN).

(+)-*N*-(*R*)-1-((*S*)-1-((4-nitrophenyl)sulfonyl)-3-oxopyrrolidin-2-yl)ethyl benzamide 4k. Reaction conditions: 72 h at room temperature. Pale white-pink amorphous solid (21.2 mg, 0.051 mmol, 14%). The crude product was purified by semipreparative HPLC chromatography. HPLC purity 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.87-7.93 (m, 2H), 7.53-7.59 (m, 1H), 7.38-7.45 (m, 2H), 5.57 (dq, *J* = 6.3, 3.8 Hz, 1H), 4.07 (br. d, *J* = 3.8 Hz, 1H), 4.00 (ddd, *J* = 12.2, 9.9, 3.9 Hz, 1H), 3.90 (ddd, *J* = 12.2, 9.5, 8.0 Hz, 1H), 2.42 (ddd, *J* = 18.4, 8.0, 3.9 Hz, 1H), 2.24 (ddd, *J* = 18.4, 9.9, 9.5 Hz, 1H), 1.53 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.8, 165.8, 143.9, 133.8, 129.9, 129.8, 128.9, 128.9, 125.0, 70.9, 66.4,

45.7, 36.9, 17.3. HRMS (ESI-TOF, pos.): *m/z* calcd for $C_{19}H_{20}N_3O_6S$ $[M+H]^+$ 418.1067 found 418.1067. IR (DRIFT): $\bar{\nu}$ = 2980, 2961, 1935, 1765, 1528, 1451, 1345, 1311, 1265, 1165, 1086, 855, 757, 711 cm^{-1}. $[\alpha]_D^{24}$ = +69.4° (c = 0.00142 g/mL, MeCN).

Supporting Information Available

Supporting information contains details of analytical results along with spectroscopic data for the synthesized compounds. This material is available free of charge *via* the Internet.

Acknowledgements

This work was supported by an internal grant from Palacký University (IGA_PrF_2019_027) and the Ministry of Health of the Czech Republic (17-31834A). Jiří Pospíšil is greateful for support from European Regional Development Fund-Project “Centre for Experimental Plant Biology” (no. CZ.02.1.01/0.0/0.0/16_019/0000738). Dr. Hiroyuki Koshino, (RIKEN, Japan) is acknowledged for his confirmation of the final structure **4a** using NMR data.

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