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Hydrazine derivative synthesis by trifluoroacetyl hydrazide alkylation

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ABSTRACT:

N'-Alkyl hydrazides were effectively synthesized by routes featuring installation, alkylation and removal of a trifluoroacetyl group. A set of amino acid derived hydrazides were respectively acylated using trifluoroacetic anhydride and the resulting trifluoroacetyl hydrazides were alkylated with alcohols in Mitsunobu reactions and with alkyl halides under alkaline conditions. Removal of the trifluoroacetyl group was affected respectively under reductive and hydrolytic conditions to provide the respective *N*'-alkyl hydrazides. This three-step process may be performed without isolation of intermediates to yield *N*'-alkyl hydrazide after a single chromatographic purification.

Keywords: hydrazine, hydrazide, carbazate, Mitsunobu reaction, azapeptide, azasulfurylpeptide, alkylation, lactam

Introduction

Hydrazine functionality is present in various natural and synthetic products (Figure 1).[1,2] In nature, hydrazine components are found in linear structures, including antibiotic metabolites from *Streptomyces,* such as Elaiomycin (**1**),[3,4] and cyclic analogs, such as the Nigeglanine family of pyridazinoindazolium alkaloids (e.g., **2**).[5] Synthetic hydrazine derivatives include pesticides (e.g., **3**) and drugs (e.g., **4-6**),[2,6] and have been pursued for applications in heterocycles, lubricants, polymers, dyestuffs and photographic products.[7,8] Moreover, hydrazine analogs of peptides, so-called azapeptides (e.g., **7**) have been used to induce turn secondary structures and to improve pharmacokinetic properties.[6,9]

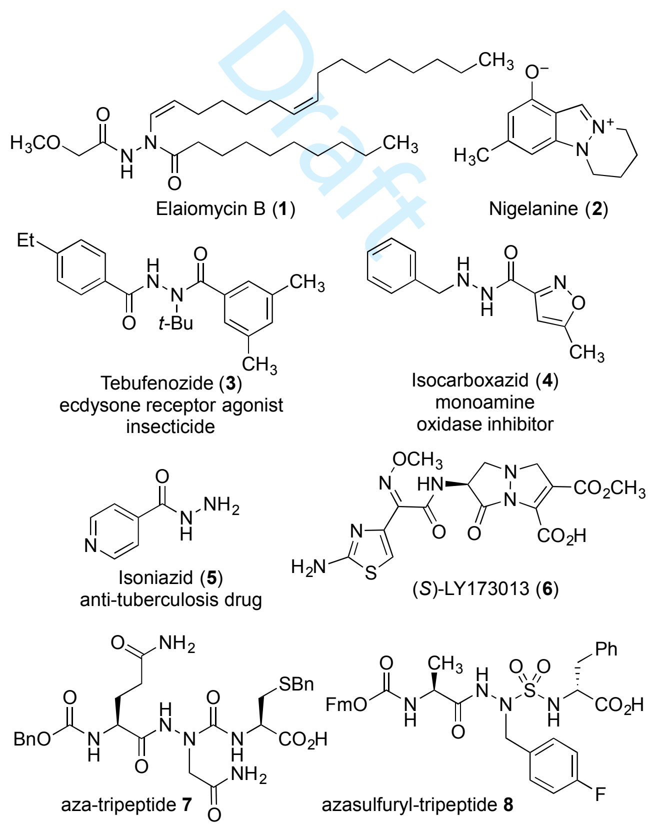
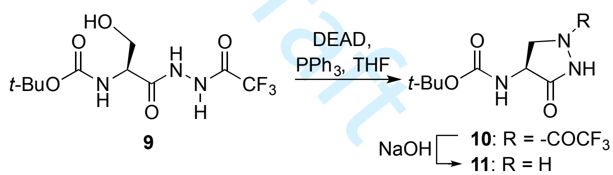


Figure 1. Representative natural and synthetic hydrazine products

The value of hydrazine derivatives has evoked significant interest in synthetic methods for the selective functionalization of the dinitrogen structure.[2,7,9] Several recent approaches have given access to specific hydrazine analogs, some exhibiting significant utility. For example, alkynyl hydrazides have been synthesized by addition of lithium acetylides to sterically hindered diazodicarboxylates, and employed in the synthesis of various heterocycles.[10] Cope-type hydroamination of alkenes and alkynes with hydrazine analogs has provide access to hydrazone and alkyl hydrazide derivatives.[11] 3-(2-Benzoyl-1-alkyl- and aryl-hydrazinyl)propanoates were prepared from Morita–Baylis–Hillman ketones by a one step process featuring a Michael addition followed by base mediated *C*- to *N*-acyl migration.[12] In addition, *N*'-allylic carbazates have been prepared by palladium catalyzed displacements of enantiomerically enriched allylic amines with retention of configuration.[13] In the interest to develop general practical means for functionalizing hydrazine derivatives, many strategies have employed regioselective alkylation using electron deficient derivatives, including arylsulfonyl hydrazides,[8,14] carbazates,[15,16] *N*-acyl hydrazones,[17,18] and semicarbazones.[9,19] Among these strategies, several have employed the Mitsunobu reaction to accomplish alkylation with alcohols under mild conditions.[14,16,19] Such alkylation strategies can surmount issues of over alkylation with reactive electrophiles. However, after hydrazine alkylation, selective removal of electron deficient groups such as sulfonamides can prove challenging.

The trifluoroacetamide has been employed in Mitsunobu chemistry as an effective pronucleophile to accomplish intramolecular ring closure for the synthesis of aspidospermidine alkaloids and pipecolinic acid residues in peptides,[20,21] and to achieve intermolecular alkylation with methanol for *N*'-methylation of peptides,[22] in part because of effective mild conditions for subsequent amine liberation by reduction with sodium borohydride.[23] Trifluoro-acetyl hydrazides have been employed for the synthesis of 2-trifluoromethyl 1,3,4-oxadiazoles.[24] To the best of our knowledge, the use of trifluoro-acetyl hydrazides to prepare hydrazine derivatives has been limited to an intramolecular cyclization to prepare the enantiomerically pure pyrazolidin-3-one precursor **11** of the bicyclic pyrazolidinone antibacterial agent LY173013 (**6**).[25] Trifluoro-acetylation of L- and D-*N*-(Boc)serine hydrazides with *S*-ethyl trifluoro-thioacetate, intramolecular Mitsunobu cyclization and hydrolysis with sodium hydroxide provided *S*- and *R*-pyrazolidinones **11**, which were converted to the respective bicycles, of which only the *S*-enantiomer exhibited antibacterial activity (Scheme 1).[25]

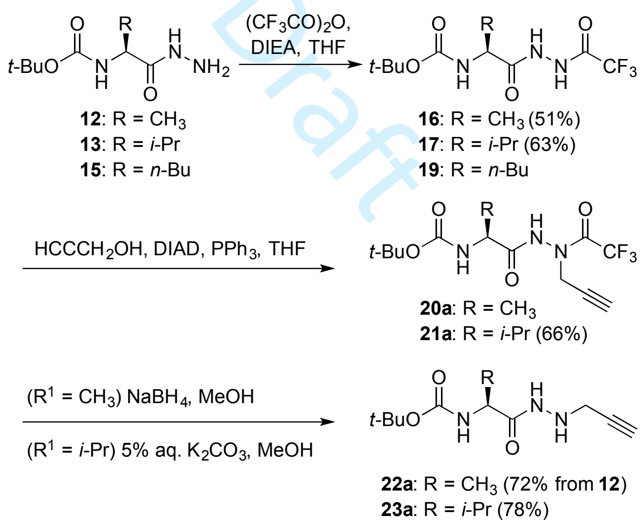


Scheme 1. Pyrazolidinone synthesis from trifluoro-acetyl hydrazide.[25]

Inspired by the intramolecular precedent,[25] the potential to utilize intermolecular alkylation of trifluoro-acetyl hydrazides has now been investigated using a variety of amino acid derivatives. Amino acid *N*'-alkyl hydrazides have found significant use in the preparation of tripeptide analogs bearing central semicarbazide and aminosulfamide residues as precursors for the preparation of the aza- and azasulfurylpeptides.[26,27] The synthesis of amino acid *N*'-alkyl hydrazides has however necessitated synthesis of alkyl hydrazine precursors in solution, prior to amino acylation with a suitably protected amino acid precursor.[26,27] Offering potential to generate a series of amino acid *N*'-alkyl hydrazides from a common precursor, the presented method is expected to find significant utility for the solution phase construction of these valuable precursors.

Results and Discussion

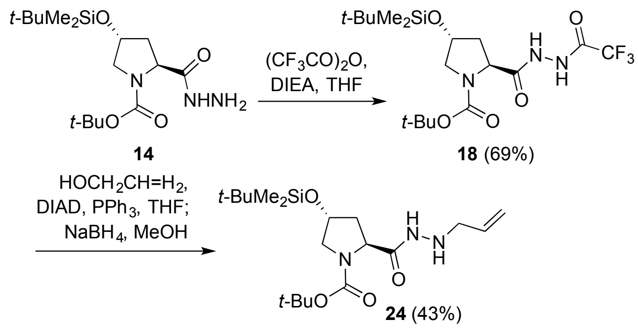
Initially, *N*-(Boc)-alanine, valine and 4-*tert*-butyldimethylsiloxyproline hydrazides (**12-14**, Schemes 2 and 3) were prepared by routes featuring hydrazinolysis of the corresponding methyl esters.[28] In addition, *N*-(Boc)-aminohexanoyl hydrazide (**15**) was prepared from (*S*)-*N*-(Boc)homoallylglycine methyl ester (Boc-Hag-OMe) by heating in a solution of aqueous hydrazine in methanol for 24 h, which caused concomitant olefin reduction.[29]



Scheme 2. Three-step synthesis of *N*'-alkyl hydrazides by way of Mitsunobu reaction on trifluoro-acetyl hydrazide

Trifluoro-acetylation of hydrazides **12-15** was performed by treatment with trifluoroacetic anhydride (1.1 eq.) and DIEA (1.2 eq.) in THF as a solvent at 0 °C and warming to room temperature, followed by aqueous work-up (Scheme 2). For characterization purposes, trifluoroacetyl hydrazides **16-18** were isolated by chromatography in 51-69% yields.

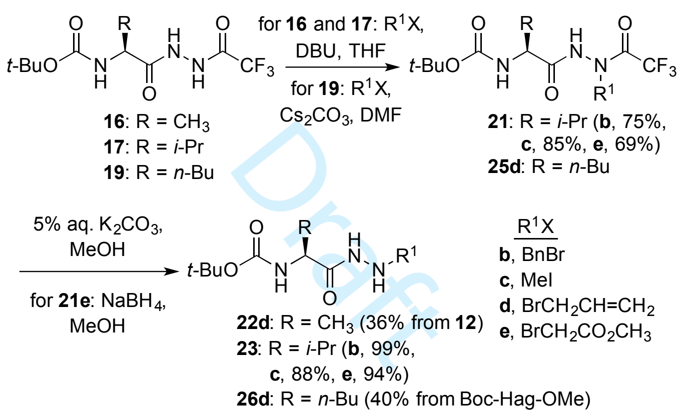
Trifluoroacetyl hydrazides (e.g., **16**) were however sufficiently pure for use in next step without any further purification. The choice of using trifluoroacetic anhydride instead of *S*-ethyl trifluoro-thioacetate was made based in part on cost. In addition, attempts to trifluoro-acetylate *N*-Boc-alanine hydrazide (**12**) with ethyl trifluoroacetate in THF failed at both rt and reflux, and starting material was recovered.



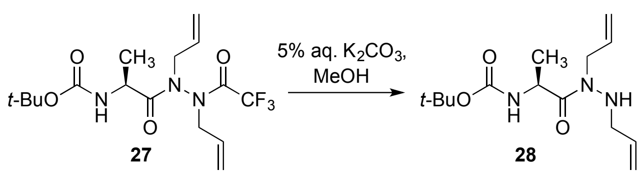
Scheme 3. Synthesis of *N*'-allyl hydroxyproline hydrazide **24** by way of Mitsunobu reaction

Mitsunobu alkylation of trifluoroacetyl hydrazides **16-18** was performed in THF by treating sequentially with triphenylphosphine (1.2 eq.), the respective alcohol (2-propyn-1-ol and 2-propen-1-ol, 1.2 eq.) at 0 °C, followed by dropwise addition of diisopropyl azodicarboxylate (DIAD, 1.2 eq.). After ice bath removal and reaction mixture warming to room temperature, monitoring by TLC showed consumption of starting material and formation of a new less polar product. After Mitsunobu alkylation, *N*'-trifluoroacetyl *N*'-propargyl *N*-(Boc)valine hydrazide **21a** was isolation by chromatography in 66% yield from **17**. Alternatively, without isolation, the Mitsunobu reaction mixture was diluted with MeOH, cooled to 0 °C and treated with sodium borohydride to reduce off the trifluoroacetyl group.[23] After a final purification by column chromatography, the three-step transformation of *N*-(Boc)alanine hydrazide **12** to *N*'-propargyl hydrazide **22a** was accomplished in 72 % overall yield (Scheme 2). For comparison, only 42 % yield of *N*'-propargyl hydrazide **22a** was obtained after chromatography of the reaction mixture from alkylation of alanine hydrazide **12** with propargyl bromide (0.9 eq.) and DIEA (2.0 eq.) in DMF, due in part to significant dialkylated product and recovered starting material. Use of a higher stoichiometry of propargyl bromide gave greater dialkylated product. After Mitsunobu alkylation and reductive cleavage of the *N*'-trifluoroacetyl siloxyproline hydrazide **18**, *N*'-allyl hydrazide **24** was isolated by chromatography in 43 % overall yield over two steps. Alternatively, the trifluoroacetyl group was removed from hydrazide **21a** by hydrolysis using a 5% aqueous solution of potassium carbonate in methanol to provide *N*'-propargyl *N*-(Boc)valine hydrazide (**23a**) in 78% yield.[30]

As described above, in reactions of unprotected hydrazides and carbazates, over alkylation with alkyl halides is an inherent problem necessitating chromatography to separate recovered starting and bis-alkylated materials from the mono-alkylated product.[31,32] Alkylation of *N*'-trifluoroacetyl hydrazides **17** and **19** was thus explored using different bases and reactive electrophiles: benzyl bromide, iodomethane, allyl bromide and methyl bromoacetate (Scheme 4). In THF, valine hydrazide **17** reacted with benzyl bromide and DIEA or K_2CO_3 as base giving *N*'-benzyl *N*'-trifluoroacetyl hydrazide **21b** with low conversion (ca. <10%). Employment of the stronger soluble amidine base 1,8-diazabicyclo[5.4. 0]undec-7-ene (DBU) in the alkylation of hydrazide **17** with benzyl bromide in THF at 50°C gave complete conversion to **21b** and 75% yield after chromatography. Employing DBU in THF conditions, *N*'-trifluoroacetyl hydrazide **17** was also reacted with iodomethane and methyl bromoacetate to give respectively *N*'-methyl *N*'-trifluoroacetyl hydrazides **21c** and **21e** in 85% and 69% yields after chromatography. Removal of the trifluoroacetyl group from purified hydrazides **21b** and **21c** using a 5% aqueous solution of potassium carbonate in methanol provided cleanly *N*'-benzyl and *N*'-methyl *N*-(Boc)valine hydrazides (**23b** and **23c**) in high yields. On the other hand, reductive cleavage of the trifluoroacetyl hydrazide **21e** with sodium borohydride provided *N*'-methoxycarbonylmethyl hydrazide **23e** in 94% yield without affecting the ester side chain. In addition, *N*'-allyl *N*-(Boc)alanine hydrazide (**22d**) was synthesized in three-steps from hydrazide **12** in 36% overall yield after chromatography of the reaction mixture from sequential treatments with trifluoroacetic anhydride and allyl bromide using DBU as base in THF, followed by hydrolytic cleavage.

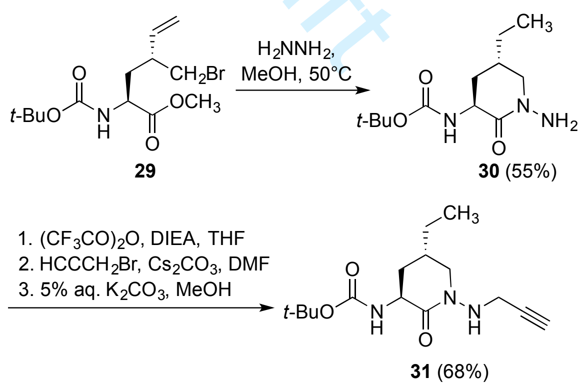


Scheme 4. Synthesis of *N*'-alkyl hydrazides by alkylation of trifluoroacetyl hydrazides



Scheme 5. Synthesis of *N*'*N*''-diallyl hydrazide **28**

N'-Allyl *N*-(Boc)aminohexanoyl hydrazide (**26d**) was isolated in 40% yield after single chromatography of the residue from a four-step sequence featuring hydrazinolysis of *N*-(Boc)-homoallylglycine methyl ester (Boc-Hag-OMe), treatment of hydrazide **15** with trifluoroacetic anhydride and DIEA in THF to give trifluoroacetyl hydrazide **19**, *N*'-alkylation with allyl bromide and Cs_2CO_3 in DMF to provide *N*'-allyl hydrazide **25d** and trifluoroacetyl group removal using 5% aqueous K_2CO_3 in MeOH. In DMF, hydrazide **17** reacted with benzyl bromide and Cs_2CO_3, but gave mono-alkylated **21b** contaminated with significant bis-alkylation product which was observed by TLC as a less polar product and characterized by the corresponding molecular ion [m/z = 508 (M+H) and 530 (M+Na)] in the spectrometric analysis. Pursuing dialkylation, *N*'*N*"-diallyl *N*-(Boc)alanine hydrazide (**28**) was synthesized from *N*-(Boc)alanine hydrazide (**12**) by a route featuring acylation with trifluoroacetic anhydride and K_2CO_3 in DMF, followed by alkylation with allyl bromide and K_2CO_3 in DMF heated to 65°C for 48 h. The corresponding *N*'*N*"-diallyl *N*'-trifluoroacetyl *N*-(Boc)alanine hydrazide (**27**) was isolated in 23% yield after aqueous work-up and chromatography, and hydrolytically converted to *N*'*N*"-diallyl hydrazide **28** using 5% aqueous K_2CO_3 in MeOH, followed by chromatography in 73% yield (Scheme 5).



Scheme 6. Synthesis of *N*'-propargyl 1,3-diamino-δ-lactam **31**

In the context of our efforts to prepare peptide turn mimics, *N*'-alkyl hydrazides from 1,3-diamino-δ-lactams (e.g., **31**) are being pursed to create constrained dipeptide structures that combine the covalent restrictions of α-amino-δ-lactam (Adl) residues with the stereoelectronic constraints of azapeptides.[33,34] Treatment of (2*S*,4*S*)-methyl 2-*N*-(Boc)amino-4-(bromomethyl)hex-5-enoate (**29**) with hydrazine in methanol overnight effected hydrazinolysis, lactam formation and olefin reduction to provide (3*S*,5*S*)-1,3-diamino-5-ethyl-δ-lactam (**30**, Scheme 6). 1,3-Diamino-δ-lactam **30** was converted into *N*'-propargyl hydrazide **31** in 68% overall yield after chromatography of the mixture from a three-step process featuring trifluoroacetylation using trifluoroacetic anhydride and DIEA in THF, *N*'-alkylation with propargyl bromide in presence of Cs_2CO_3 in DMF and removal of the trifluoroacetyl group using 5% aqueous K_2CO_3 in MeOH.

Conclusion

The trifluoroacetyl group has proven to be an effective activator and blocker of hydrazine nitrogen in the synthesis of *N*'-substituted hydrazides of a series of different amino acid derivatives. Conveniently generated by acylation with trifluoroacetic anhydride, trifluoroacetyl hydrazides were selectively alkylated using both alcohols in Mitsunobu reactions and alkyl halides under alkaline conditions. Finally, the trifluoroacetyl group was effectively removed using reductive conditions with sodium borohydride in methanol as well as under hydrolytic conditions using aqueous potassium carbonate in methanol. Although the intermediates may be isolated after each reaction of the three-step sequence, they are usually sufficiently pure such that only a single chromatography may be employed to isolate the final *N*'-alkyl hydrazide. Surmounting issues of over alkylation by employment of the relatively inexpensive and orthogonally removable trifluoroacetyl group, this method should find general utility for the synthesis of hydrazine derivatives in natural products and synthetic intermediates in medicinal chemistry and peptide science.

Experimental Section

General

Unless specified, all reactions were performed under argon atmosphere. All glassware was stored in the oven or flame-dried and let cool under inert atmosphere prior to use. Anhydrous solvents were obtained either by filtration through drying columns (DCM, THF, MeCN, DMF) in a GlassContour system (Irvine, CA) or by distillation over CaH_2 (MeOH, $CHCl_3$). All other starting materials, reagents and chemicals were purchased from commercial suppliers and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on silica gel plates, which were visualized under UV light (254 nm) and by staining with $KMnO_4$, 2,4-dinitrophenylhydrazine (DNPH) and bromocresol green. Flash chromatography[35] was performed using either 230-400 mesh silica gel from SiliCycle Inc. or on a CombiFlash instrument from Teledyne using RediSep Gold columns. Nuclear magnetic resonance spectra (^{1}H, ^{13}C and COSY NMR) were recorded either on Bruker AMX 300, AV 400, AVII 400 or AMX 500 spectrometers. Specific rotations were determined on a Perkin-Elmer 341 polarimeter at 589 nm sodium-D line using a 0.5 dm cell and are reported as follow $[\alpha]_{\lambda}^{\text{temperature (°C)}}$, concentration ($c$ in g/100 mL), and solvent. High resolution mass spectrometry (HRMS) was performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Analytical supercritical fluid chromatography (SFC) was perfomed by the Laboratoire d'analyse et de separation chirale par SFC de l'Université de Montréal and reported as follow: temperature, backpressure and retention time (R*t*).

(2*S*,4*R*)-*N*-Boc-4-(*tert*-butyldimethylsilyloxy)proline hydrazide (14) A solution of *N*-Boc-hydroxyproline methyl ester (500 mg, 2.04 mmol, 1 eq.) in 10 mL of DCM at 0 °C was treated with imidazole (278 mg, 4.08 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (338 mg, 2.24 mmol, 1.1 eq.). After stirring at room temperature for 4 h, the reaction mixture was filtered and washed with DCM. The filtrate and washings were washed with 10% aq. HCl (10 mL), aq. saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated to a colorless liquid which without further purification, was dissolved in methanol (5 mL), treated with hydrazine hydrate (2 mL), and stirred at room temperature for 20 h, when complete consumption of starting material (R_f = 0.42, 30% EtOAC in hexane) was indicated by TLC. The volume was concentrated. The reduced volume was partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated to afford hydrazide **14** as white solid (571 mg, 1.59 mmol, 78 %): mp 139-142°C; R_f 0.48 (10% MeOH in DCM); $[\alpha]_D^{25}$ −35.2 (*c* 0.6, MeOH); FT-IR (neat) ν_{max} 3329, 3230, 3069, 2929, 2877, 2857, 1690 cm^{-1}. A 2:1 mixture of *trans*- and *cis*-prolyl carbamate isomers was observed based on integration of the hydrazide CONH signals at 8.14 and 7.46 ppm. Proton and carbon NMR signals of the minor isomer are written respectively in brackets and parentheses. ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1H), [7.46 (br s, 1H)], 4.36 (m, 2H), 3.86 (br s, 2H), 3.39 (m, 2H), 2.28 (m, 1H), 2.00 (m, 1H), 1.42 (s, 9H), 0.84 (s, 9H), 0.04 (overlapping s, 6H); $^{13}C[^1H]$ NMR (126 MHz, $CDCl_3$) δ (173.5), 172.7, 156.1, (154.7), 80.7, 70.5, (69.9), (59.0), 57.5, (55.2), 55.0, 37.5, 28.5, 25.8, 18.0, -4.8, (-4.7); HRMS (ESI^+) calcd *m/z* for $C_{16}H_{34}N_3O_4Si$ $[M+H]^+$, 360.2313 found 360.2301.

***N'*-Trifluoroacetyl *N*-(Boc)alanine hydrazide** (**16**) Employing the protocol for the synthesis of valine trifluoroacetyl hydrazide **17** described below, Boc-Ala-$NHNH_2$ (**12**, 0.34 g, 1.67 mmol), DIEA (0.25 mL, 1.43 mmol) and trifluoroacetic anhydride (0.18 mL, 1.31

mmol) were reacted in THF (10 mL). Purification by column chromatography on silica gel using 80% ethyl acetate in hexane as eluent and evaporation of the collected fractions afforded trifluoro-acetyl hydrazide **16** (256 mg, 51%) as white solid: R*f* 0.76 (80% EtOAc in hexane); mp 80.4-82.6; $[\alpha]^{23}_{D}$ –2.2 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ : 9.65 (br s, 1H), 9.59 (br s, 1H), 5,31 (br s, 1H), 4.44-4.37 (m, 1H), 1.45-1.42 (overlapping s and d, 12H); $^{13}C[^1H]$ NMR (300 MHz, $CDCl_3$) δ : 171.56, 156.06, 155.48-154.41(q), 121.16-111.36 (q), 81.16, 48.59, 28.17, 17.49. HRMS (ESI^+) calcd m/z for $C_{10}H_{16}F_3N_3O_4Na$ $[M+Na]^+$ 322.0984, found: 322.0985.

***N'*-Trifluoroacetyl *N*-(Boc)valine hydrazide** (**17**) A 0°C solution of *N*'-(Boc)valine hydrazide (10 g, 43.2 mmol) in anhydrous THF (40 mL) was treated with DIEA (9 mL, 51.8 mmol, 1.2 equiv.) followed by trifluoroacetic acid anhydride (6.6 mL, 4.76 mmol, 1.1 equiv), and stirred for 30 min. The ice bath was removed. The reaction mixture warmed to room temperature with stirring for 1 h, when complete consumption of starting material was observed by TLC (R*f* 0.52, 50% EtOAc in hexane). The volatiles were evaporated. The residue was dissolved in DCM, and washed with water (20 mL). The aqueous layer was extracted twice with DCM (20 mL). The organic layers were combined, washed with brine, dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of 0-100% EtOAc in hexane. Evaporation of the collected fractions afforded trifluoroacetyl hydrazide **17** (8.85 g, 63%) as a white foam: R*f* 0.63 (50% EtOAc in hexane); mp 151-153 °C; $[\alpha]_D^{25}$ –0.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3305, 3182, 1726, 1683, 1634, 1498, 1292, 1249, 1153, 1020, 639, 447 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 10.07 – 9.77 (m, 2H), 5.54 (d, *J* = 9.2 Hz, 1H), 4.29 – 4.00 (m, 1H), 2.05 (d, *J* =

2.4 Hz, 1H), 1.42 (s, 9H), 1.10 – 0.91 (overlapping d, 6H); $^{13}C[^{1}H]$ NMR (126 MHz, $CDCl_3$) δ 170.6, 156.4, 154.7 (q), 115.5 (q), 80.8, 58.5, 30.9, 28.2, 19.0, 18.3. HRMS (ESI^+) calcd m/z for $C_{12}H_{20}F_3N_3O_4Na$ $[M+Na]^+$ 350.1298, found: 350.1295

(2*S*,4*R*)-*N*-Boc-4-(*tert*-Butyldimethylsilyloxy)proline *N'*-trifluoroacetylhydrazide (18)

A solution of (2*S*,4*R*)-*N*-Boc-4-(*tert*-butyldimethylsilyloxy)proline hydrazide (**14**, 571 mg, 1.59 mmol, 1 eq.) in THF (15 mL) was cooled to 0°C and treated with DIEA (0.60 mL, 3.50 mmol, 2.2 eq.) and trifluoroacetic anhydride (0.44 mL, 3.18 mmol, 2 eq.). The ice bath was removed. The reaction mixture warmed to room temperature with stirring for 1.5 h. The volatiles were evaporated in vacuo. The residue was dissolved in EtOAc, washed with water, and dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel eluting with a gradient of 30-60% EtOAc in hexane. Evaporation of the collected fractions provided the trifluoro-acetyl hydrazide **18** (501 mg, 1.10 mmol, 69%) as a white solid: R_f = 0.41 (50% EtOAc in hexane); mp 60-62°C, $[\alpha]_D^{25}$ –58.1 (*c* 1.02, MeOH); FT-IR (neat) ν max 3235, 2955, 2931, 2859, 1746, 1671 cm^{-1}. A 2:1 mixture of *trans*- and *cis*-prolyl carbamate isomers was observed based on the integration of the CF_3CONH signals at 9.75 and 9.37 ppm. Proton and carbon NMR signals of the minor isomer are written respectively in brackets and parentheses. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (br s, 1H), 9.75 (br s, 1H) [9.37 (br s, 1H)], 4.44 (m, 2H), 3.45 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.34 (m, 1H), 2.26 (m, 1H), 2.04 (m, 1H), 1.43 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H); $^{13}C[^{1}H]$ NMR (126 MHz, $CDCl_3$) δ 170.7 (171.5), 156.4, 155.0 (q, *J* = 38.7 Hz), 115.7 (q, *J* = 287.1 Hz), 81.5, 70.3 (69.8), 57.3, 55.1, 37.7, 28.4 (28.1), 25.72, 18.0, -4.9 (-4.8); HRMS (ESI^+) calcd *m/z* for $C_{18}H_{32}F_3N_3O_5SiNa$ $[M+Na]^+$, 478.1955 found 478.1946.

N'-Propargyl-N'-trifluoroacetyl N-(Boc)valine hydrazide (21a). Trifluoroacetyl hydrazide **17** (500 mg, 1.53 mmol) was dissolved in 5 mL of THF, cooled to 0 °C, and treated with triphenylphosphine (481mg, 1.83 mmol) and propargyl alcohol (106 μL, 1.83 mmol), followed by dropwise addition of di-isopropyl azodicarboxylate (DIAD, 361 μL, 1.83 mmol). The ice bath was removed, and the reaction mixture warmed to rt. After 7.5 h, TLC showed disappearance of the starting material spot and formation of a less polar product spot. The volatiles were removed under reduced pressure. The residue was purified on a Combiflash instrument by eluting with 20% EtOAc in hexane as solvent system. Evaporation of the collected fractions gave trifluoroacetyl hydrazide **21a** as white solid (366 mg, 66%): mp 160 °C, $[\alpha]_D^{25}$ –3.7 (*c* 1, $CHCl_3$); R*f* 0.25 (20% EtOAc in hexane); FT-IR (neat) ν max 3320, 3268, 2982, 2962, 1721, 1677, 1522, 1157, 694, 632; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 5.12 (br m, 1H), 4.91 (br m, 1H), 4.18 (br m, 2H), 2.30 (s, 1H), 2.20 (m, 1H), 1.44 (s, 9H), 0.98 (overlapping d, J = 5.0, 5.0 Hz, 6H); ^{13}C[^{1}H] NMR (125 MHz, $CDCl_3$) δ 171.6, 157.6 (q), 156.4, 115.6 (q), 81.0, 75.5, 74.6, 58.0, 37.9, 30.1, 28.3, 19.4, 17.1; HRMS m/z calcd for $C_{15}H_{23}F_3N_3O_4Na$ $[M+Na]^+$, found 388.1455, found, 388.1467,

N'-Benzyl-N'-trifluoroacetyl N-(Boc)valine hydrazide (21b). A solution of trifluoroacetamide **17** (100 mg, 0.31 mmol) in 2 mL of anhydrous THF was treated with benzyl bromide (0.04 mL, 0.34 mmol, 1.1 equiv.) and DBU (0.091 mL, 0.62 mmol, 2 equiv.). The resulting solution was heated to 50°C and stirred overnight. The reaction mixture was cooled to room temperature, concentrated in vacuo. The residue was dissolved in DCM (5 mL) and washed with water (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL).

The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (15% EtOAc in hexane). Evaporation of the collected fractions afforded *N*'-benzyl hydrazide **21b** (95 mg, 75 %) as white solid: R*f* 0.72 (40% EtOAc in hexane); mp 158-160 °C; $[\alpha]_D^{25}$ –2.76 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3318, 3224, 2978, 1723, 1676, 1522, 1233, 1217, 1149, 698, 635, 510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.39 – 7.21 (m, 5H), 5.18 – 4.98 (m, 1H), 3.90 (dd, J = 9.0, 6.9 Hz, 1H), 2.93 – 2.73 (m, 1H), 2.11 (h, J = 6.8 Hz, 1H), 1.38 (s, 9H), 0.92 (overlapping d, J = 7.1 Hz, 6H); $^{13}C[^1H]$ NMR (75 MHz, $CDCl_3$) δ 171.3, 158.3, 156.0, 133.7, 129.0, 128.6, 117.8, 113.9, 80.7, 58.4, 52.2, 29.7, 28.1, 19.2, 17.6. HRMS (ESI⁺) calcd m/z for $C_{19}H_{26}F_3N_3O_4Na$ $[M+Na]^+$ 440.1768, found: 440.1775.

***N*'-Methyl-*N*'-trifluoroacetyl *N*-(Boc)valine hydrazide (21c).** Employing the same protocol as described for the synthesis of *N*'-benzyl-*N*'-trifluoroacetyl hydrazide **21b**, *N*'-trifluoroacetyl hydrazide **17** (100 mg, 0.31 mmol) in THF (2 mL) was treated with methyl iodide (0.02 mL, 0.34 mmol, 1.1 equiv.) and DBU (0.091 mL, 0.62 mmol, 2 equiv.) at 50°C. After purification of the residue by column chromatography, *N*'-methyl-*N*'-trifluoroacetyl hydrazide **21c** (88 mg, 85%) was afforded as a white solid: R*f* 0.44 (30% EtOAc in hexane); mp 140-142 °C; $[\alpha]_D^{25}$ −4.1 (*c* 1, $CHCl_3$; FT-IR (neat) ν max 3319, 3259, 2963, 1726, 1676, 1522, 1153, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 5.32 (d, *J* = 9.3 Hz, 1H), 4.03 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.22 (s, 3H), 2.22 – 2.01 (m, 1H), 1.42 (s, 9H), 0.98 (t, *J* = 6.5 Hz, 6H); $^{13}C[^1H]$ NMR (126 MHz, $CDCl_3$) δ 171.5, 158.0 (q), 156.4, 115.9 (q), 80.8, 58.3, 36.5, 30.4, 28.1, 19.2, 18.0. HRMS (ESI⁺) calcd m/z for $C_{13}H_{22}F_3N_3O_4Na$ $[M+Na]^+$ 364.1455, found: 364.1467.

_N_’-Methoxycarbonylmethyl-_N_’-trifluoroacetyl-_N_-(Boc)valine hydrazide (21e). Employing the same protocol as described for the synthesis of *N*’-benzyl-*N*’-trifluoroacetyl hydrazide **21b**, *N*’-trifluoroacetyl hydrazide **17** (100 mg, 0.31 mmol) in THF (2 mL) was treated with methyl bromoacetate (0.032 mL, 0.34 mmol, 1.1 equiv.) and DBU (0.091 mL, 0.62 mmol, 2 equiv.) at 50°C. After purification of the residue by column chromatography, *N*’-methoxycarbonylmethyl-*N*’-trifluoroacetyl hydrazide **21e** (84 mg, 69%) was afforded as a white solid: R*f* 0.59 (40% EtOAc in hexane); mp 139-142°C; $[\alpha]_D^{25}$ −2.4 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3376, 3239, 2965, 2363, 2344, 1747, 1686, 1510, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 3.92-3.67 (m, 2H), 3.77 (s, 3H), 2.14 (m, 1H), 1.43 (s, 9H), 0.96 (overlapping d, *J* = 6.8, 5.5 Hz, 6H); $^{13}C[^1H]$ NMR (126 MHz, $CDCl_3$) δ 171.9, 168.3, 158.4 (q), 156.2, 115.8 (q), 81.0, 59.3, 52.9, 49.0, 29.6, 28.3, 19.3, 18.0; HRMS (ESI+) calcd m/z for $C_{15}H_{24}F_3N_3O_6Na$ $[M+Na]^+$ 422.1509, found: 422.1523.

_N_’-Propargyl _N_-(Boc)alanine hydrazide (22a). A 0 °C solution of Boc-Ala-$NHNH_2$ (**12**, 0.24 g, 1.19 mmol) in 10 mL of THF was sequentially treated with diisopropylethylamine (DIEA, 0.25 mL, 1.43 mmol) and trifluoroacetic anhydride (0.18 mL, 1.31 mmol). After 30 min, the ice bath was removed. The reaction mixture warmed to rt. After consumption of starting material was evidenced by TLC [R*f* 0.30 (75% EtOAc in hexane, visualized with $KMnO_4$))] the volatiles were evaporated. The residue was dissolved in EtOAc, washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford trifluoro-acetyl hydrazide **16**, which was dissolved in 10 mL of THF, cooled to 0 °C, and treated sequentially with triphenylphosphine (0.37 g, 1.43 mmol) and propargyl alcohol (0.08 mL, 1.43 mmol), followed by dropwise addition of di-isopropyl azodicarboxylate (DIAD, 0.28 mL, 1.43 mmol). The ice bath was removed. After 1h, the reaction mixture warmed to rt, when hydrazide **16** was completely consumed as evidenced by disappearance of the $KMnO_4$ positive spot on TLC [R*f* 0.57 (75% EtOAc in hexane, visualized with $KMnO_4$))]. The reaction mixture was treated with MeOH (10 mL), cooled to 0 °C, treated with sodium borohydride (90.0 mg, 2.38 mmol), agitated for 30 min, treated with a second portion of $NaBH_4$ (45 mg, 1.19 mmol) and stirred for 2h when complete consumption of trifluoroacetyl hydrazide **20a** and formation of *N*'-propargyl hydrazide **22a** were observed by TLC [R*f* 0.35 (75% EtOAc in hexane, visualized with $KMnO_4$)] and LC-MS {m/z calculated for $C_{11}H_{19}N_3O_3Na$, $[M+Na]^+$ = 264.1, found 264.1; RT = 8.04 min, analytical RP-HPLC on XTerraTM column 3.5 μm (2.1 x 50 mm) using a gradient of 10-90% MeOH [0.1% formic acid (FA)] in water (0.1% FA) over 9 min}. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography eluting with a gradient of 50-80% EtOAc in hexane. Evaporation of the collected fractions gave *N*'-propargyl hydrazide **22a** (203 mg, 72 % overall yield over three steps from **12**) as white foam: $[\alpha]^{20}_D$ –26.2° (*c* 1.0 in $CHCl_3$); FT-IR (neat) ν max 3304, 3184, 3056, 2971, 1725, 1682, 1635, 1519, 1499, 1368, 1316, 1292, 1248, 1153, 1046, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 5.42 (d, *J* = 7.6 Hz, 1H), 4.82 (s, 1H), 4.21 – 4.16 (m, 1H), 3.57 (s, 2H), 2.21 (t, *J* = 2.4 Hz, 1H), 1.39 (s, 9H), 1.32 (d, *J* = 7.1 Hz, 3H); $^{13}C[^1H]$ NMR (75 MHz, $CDCl_3$) δ 172.8, 155.7, 80.4, 80.0, 72.8, 49.0, 41.1, 28.6, 18.8; HRMS m/z calculated for $C_{11}H_{20}N_3O_3$ $[M+H]^+$ 242.1499; found 242.1494.

Alternatively, a 0 °C solution of Boc-Ala-$NHNH_2$ (**12**, 0.51 g, 2.53 mmol) in 10 mL of DMF was treated with diisopropylethylamine (DIEA, 0.88 mL, 5.06 mmol) and propargyl bromide (0.26 mL, 2.23 mmol, 80 wt % in toluene) and stirred for 30 min. The ice bath was removed. After warming to room temperature with stirring overnight, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 X 100 mL). The combined organic layers were dried using Na_2SO_4, filtered, and concentrated in vacuo to a residue, which was purified by silica gel chromatography eluting with a gradient of 30-80% EtOAc in hexane. Evaporation of the collected fractions gave *N*'-propargyl hydrazide **22a** (0.26 g, 42% yield) as white foam exhibiting identical spectroscopic properties as material prepared from the sequence above.

***N*'-Allyl *N*-(Boc)alanine hydrazide (22d)** A 0 °C solution of Boc-Ala-$NHNH_2$ (**12**, 0.134 g, 0.50 mmol) in THF (7 mL) was treated with DBU (95 µL, 0.64 mmol) followed dropwise by trifluoroacetic anhydride (89 µL, 0.55 mmol). After 30 min, the ice bath was removed. The reaction mixture warmed to rt. After consumption of starting material was evidenced by TLC (R*f* 0.11, 80% EtOAc in hexane), the reaction mixture was treated sequentially with more DBU (0.134 mL, 0.90 mmol) and allyl bromide (0.12 µL, 1.34 mmol), and heated with stirring at 65 °C. After 48 h, TLC analysis indicated complete consumption of hydrazide **16** (R*f* 0.76, 80% EtOAc in hexane) by the disappearance of the $KMnO_4$ positive spot. The reaction mixture was diluted with MeOH (12 mL), treated with 5% aqueous K_2CO_3 (5 mL) and heated at reflux for 30 min, when TLC indicated complete consumption of the less polar spot (R*f* 0.79, 80 % EtOAc in hexane). The reaction volume was reduced under vacuum. The reduced volume was extracted with DCM (15 mL). The aqueous phase was extracted with DCM (5 mL x 3), dried over $MgSO_4$, filtered and evaporated to a residue, which was purified by silica gel chromatography eluting with a gradient of 20-80 % EtOAc in hexane. Evaporation of the collected fractions gave *N*'-allyl *N*-(Boc)alanine hydrazide (**22d**, 44 mg, 36% overall yield from **12**) as a white solid: R*f* 0.62 (50 % EtOAc in hexane); mp 78.6-80.1 °C; $[\alpha]^{23}_{D}$ –3.3 (*c*

0.37, $CHCl_3$); FT-IR (neat) ν max 3439, 3181, 3080, 2981, 2930, 1703, 1669, 1482, 1440, 1159, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 5.82-5.97 (m, 2H), 5.15-5.29 (m, 3H), 3.41-3.43 (d, *J* = 6.6 Hz, 2H), 1.43 (s, 9H), 1.29-1.31 (d, *J* = 7.0 Hz, 3H); $^{13}C[^1H]$ NMR (75 MHz, $CDCl_3$) δ 171.7, 171.0, 133.2, 119.3, 71.9, 59.9, 46.2, 28.4, 28.3; LRMS m/z calculated for $C_{11}H_{21}N_3O_3K$ $[M+K]^+$ 266.4.

***N*'-Propargyl *N*-(Boc)valine hydrazide (23a)** A solution of trifluoroacetyl hydrazide **21a** (150 mg, 0.41 mmol) in MeOH (15 mL) was treated with a 5% aqueous solution of K_2CO_3 (15 mL), heated at reflux for 30 min and cooled to rt. The volume was reduced under reduced pressure. The reduced volume was extracted with EtOAc (3 × 20 mL). The organic phases were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with a gradient of 20-50% EtOAc in hexane. Evaporation of the collected fractions gave *N*"-propargyl hydrazide **23a** as white solid (86 mg, 78 %): mp 117-118 °C; $[\alpha]_D^{25}$ –3.3 (*c* 1, $CHCl_3$); R*f* 0.24 (40% EtOAc in hexane); FT-IR (neat) ν max 3707, 3327, 3292, 3256, 2972, 2844, 1686, 1659, 1521, 1303, 1169, 1017, 643; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 5.61 (d, *J* = 9.3 Hz, 1H), 4.92 (s, 1H), 3.91 (t, *J* = 8.3 Hz, 1H), 3.54 (m, 2H), 2.17 (t, *J* = 2.3 Hz, 1H), 1.95 (m, 1H), 1.35 (s, 9H), 0.87 (overlapping d, *J* = 7.5, 7.0 Hz, 6H); $^{13}C[^1H]$ NMR (125 MHz, $CDCl_3$) δ 171.3, 155.7, 79.8, 79.5, 72.4, 58.3, 40.6, 31.0, 28.2, 19.0, 18.1; HRMS m/z calculated for $C_{13}H_{23}N_3O_3Na$ $[M+Na]^+$ 292.1632, found 292.1641.

***N*'-Benzyl *N*-(Boc)valine hydrazide (23b)** As described for *N*'-propargyl hydrazide **23a**, a solution of *N*'-trifluoroacetyl hydrazide **21b** (50 mg, 0.12 mmol) and MeOH (12.5 mL) was treated at reflux with a 5% aqueous K_2CO_3 solution (5 mL). Evaporation of the dried organic layer after aqueous work-up afforded quantitatively *N*'-benzyl hydrazide **23b** as white solid: R*f* 0.58 (60% EtOAc in hexane); mp 150-152 °C; $[\alpha]_D^{25}$ –1.6 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3317, 2967, 1689, 1669, 1526, 1245, 1168, 877, 698, 655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 4.96 (s, 1H), 3.99 (s, 2H), 3.80 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.20 – 2.02 (m, 1H), 1.44 (s, 9H), 0.92 (overlapping d, *J* = 8.4, 6.8 Hz, 6H); ^{13}C[^{1}H] NMR (126 MHz, $CDCl_3$) δ 171.2, 155.8, 137.4, 128.9, 128.5, 127.7, 80.1, 58.7, 55.9, 30.8, 28.4, 19.2, 17.9. HRMS (ESI$^+$) calcd m/z for $C_{17}H_{28}N_3O_3$ [M+H]$^+$ 322.2125 found: 322.2123.

***N*'-Methyl *N*-(Boc)valine hydrazide (23c)** As described for *N*'-propargyl hydrazide **23a**, a solution of *N*'-trifluoroacetyl hydrazide **21c** (44 mg, 0.1 mmol) and MeOH (12 mL) was treated at reflux with a 5% aqueous K_2CO_3 solution (8 mL). Evaporation of the dried organic layer after aqueous work-up afforded *N*'-methyl hydrazide **23c** as white solid (28 mg, 88 %): R*f* 0.2 (90% EtOAc in hexane); mp 83-86 °C; $[\alpha]_D^{25}$ –1.0 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3285, 2965, 2931, 2362, 2342, 1654, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 5.24 (d, *J* = 9.3 Hz, 1H), 4.60 (s, 1H), 3.85 (dd, *J* = 9.1, 6.9 Hz, 1H), 2.61 (s, 3H), 2.07 (m, 1H), 1.44 (s, 9H), 0.94 (overlapping d, *J* = 6.8, 5.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 155.9, 80.0, 58.7, 39.2, 30.9, 28.3, 19.2, 18.1; LRMS m/z calculated for $C_{11}H_{23}N_3O_3K$ [M+K]$^+$ 284.

***N*'-Methoxycarbonylmethyl-*N*-(Boc)valine hydrazide (23e)** A 0°C solution of trifluoroacetyl hydrazide **21e** (33 mg, 0.08 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (6 mg, 0.16 mmol, 2 equiv.), stirred at room temperature for 30 min, and treated again with another equivalent of $NaBH_4$, after mass spectrometry revealed remaining starting material. The ice bath was removed. After stirring for 1 h, the reaction mixture warmed to room temperature. The volatiles were concentrated under vacuum. The residue was partitioned between DCM and water. The aqueous layers were washed twice with DCM (2 X 10 mL). The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to afford **23e** (24 mg, 94%): R*f* 0.3 (50% EtOAc in hexane); mp 139-142°C; $[\alpha]_D^{25}$ –0.44 (*c* 1, $CHCl_3$); FT-IR (neat) ν max 3292, 2965, 2360, 2343, 1744, 1685, 1655, 1162, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.09 (d, 1H), 3.90 – 3.62 (m, 2H), 3.74 (s, 3H), 2.08 (m, 1H), 1.43 (s, 9H), 0.96 – 0.89 (overlapping d, *J* = 6.0, 6.0, 6H); HRMS (ESI+) calcd *m/z* for $C_{13}H_{25}N_3O_5Na$ $[M+Na]^+$ 326.1686, found: 326.1691.

(*2S,4R*)-Boc-4-(*tert*-Butyldimethylsiloxy)proline *N'*-allylhydrazide (24) A 0 °C solution of trifluoroacetyl hydrazide **18** (202 mg, 0.44 mmol, 1 eq.) in THF (5 mL) was treated with triphenylphosphine (138 mg, 0.52 mmol, 1.2 eq.) and allyl alcohol (0.04 mL, 0.52 mmol, 1.2 eq.), followed by dropwise addition of diisopropyl azodicarboxylate (DIAD, 0.10 mL, 0.52 mmol, 1.2 eq.). The ice bath was removed. The reaction mixture warmed to room temperature over 1.5 h, when TLC indicated complete consumption of trifluoroacetyl hydrazide **18** (R_f 0.42, 50% EtOAc in hexane). The reaction mixture was diluted with 5 mL of MeOH, cooled to 0°C, treated with sodium borohydride (24.9 mg, 0.66 mmol, 1.5 eq.), stirred 30 min, and treated again with $NaBH_4$ (16.6 mg, 0.44 mmol, 1 eq.). After stirring 15 min, water was added to the reaction mixture, which was concentrated under reduced pressure. The concentrated volume was extracted with EtOAc (3 x 5 mL). The organic layer was combined, dried over $MgSO_4$, and evaporated to a residue that was purified by column chromatography on silica gel using a gradient from 30-80% EtOAc in hexane. Evaporation of the collected fractions provided *N'*-allyl hydrazide **24** (76 mg, 0.19 mmol, 43%): R_f = 0.57

(70% EtOAc in hexane); $[\alpha]_D^{25}$ –59.6 (*c* 0.51, MeOH); FT-IR (neat) ν_{max} 3288, 3079, 2954, 2929, 2886, 2857, 1670 cm^{-1}; the proton NMR data indicated a 2:1 mixture of *trans*- and *cis*-prolyl carbamate isomers based on integration of the hydrazide CONH signals at 8.31 and 7.47 ppm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (br s, 1H), [7.47 (bs s, 1H)], 5.84 (ddt, *J* = 16.7, 10.3, 6.3 Hz, 1H), 5.2 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 8.3 Hz, 1H), 4.37 (m, 2H), 3.61–3.23 (m, 4H), 2.38 (m, 1H), [2.19, (m 1H)], [2.03, (m 1H)], 1.94 (m, 1H), 1.44 (s, 9H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C[^{1}H] NMR (126 MHz, $CDCl_3$) δ 171.1, 156.3, 134.3, 118.4, 80.8, 70.6, 57.5, 54.9, 54.7, 36.9, 28.5, 25.8, 18.0, -4.8; HRMS (ESI$^+$) calcd *m/z* for $C_{19}H_{38}N_3O_4Si$ [M+H]$^+$, 400.2620 found 400.2626.

***N'*-Allyl *N*-(Boc)aminohexanoyl hydrazide (26d)** A solution of (*S*)-N-(Boc)homoallylglycine methyl ester (Boc-Hag-OMe, 500 mg, 2.1 mmol, 1 equiv., prepared according to reference 36) in 1:1 MeOH (8 mL) / aqueous hydrazine (8 mL, 50-60%) was heated at 70°C for 24h. The volatiles were removed under vacuum to give hydrazide **15** as white foam, which was used without further purification: R*f* 0.42 (5% MeOH in DCM); $[\alpha]_D^{24}$ –22.6 (*c* 1 , MeOH); FT-IR (neat) ν max 3306, 2958, 2872, 1663, 1531, 1455, 1168 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (br s, 4H), 4.00 (t, *J* = 6.1 Hz, 1H), 1.77-1.67 (m, 1H), 1.64-1.55 (m, 1H), 1.46 (s, 9H), 1.42-1.28 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C[^{1}H] NMR (126 MHz, $CDCl_3$) δ 175.3, 158.6, 81.4, 55.6, 34.1, 29.9, 29.6, 24.2, 15.1. HRMS (ESI$^+$) calcd *m/z* for $C_{11}H_{23}N_3O_3Na$ [M+Na]$^+$ 268.1632, found 268.1630.

A solution of hydrazide **15** (500 mg, 2.45 mmol, 1.1 eq) in THF (20 mL) was cooled to 0°C, treated with DIEA (0.429 mL, 4.93 mmol, 1.2 eq) followed by trifluoroacetic anhydride (0.314 mL, 2.24 mmol, 1.1 eq), and stirred for 30 min. The ice bath was removed. The reaction mixture warmed to room temperature with stirring for 30 min. The volatiles were evaporated. The residue was dissolved in EtOAc (20 mL), washed with of water (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a trifluoroacetyl heydrazide **19** as white foam, which was used without further purification.

A solution of trifluoroacetyl hydrazide **19** (100 mg, 0.29 mmol, 1 equiv.) in DMF (5 mL) was treated with Cs_2CO_3 carbonate (103.93 mg, 0.319 mmol, 1.1 eq), heated to 50°C for 10 min, treated with allyl bromide (0.04 mL, 0.319 mmol, 1.1 eq) and stirred for 18 h at 50°C. The reaction mixture was cooled to room temperature, treated with water (5 mL), and extracted with EtOAc (2 x 7 mL). The organic layers were combined and evaporated to a residue, which was taken up in MeOH (10 mL), treated with 5% aqueous K_2CO_3 (10 mL) and heated at 50°C for 45 min. The volume was decreased under reduced pressure, and partitioned between EtOAc (15 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The organics layers were combined, dried over $MgSO_4$, filtered and evaporated. Purification of the residue by chromatography on silica gel using a gradient of 30-40% EtOAc in hexane, and evaporation of the collected fractions gave *N*'-allyl hydrazide **26d** as white crystals (33 mg, 0.12 mmol, 40%): mp 76°C, R*f* 0.35 (50% EtOAc in hexane); $[\alpha]_D^{24}$ –36.2 (*c* 0.7, $CHCl_3$); FT-IR (neat) ν max 3319, 2942, 2831, 1743, 1449, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 5.88-5.78 (m, 1H), 5.20 (m, 2H), 5,14 (d, *J* = 10.2, 1H), 4.76 (br s, 1H), 4.01 (m, 1H), 3.42 (d, *J* = 6.1 Hz, 2H), 1.85-1.71 (m, 1H), 1.61-1.52 (m, 1H), 1.42 (s, 9H), 1.35-1.25 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H); $^{13}C[^{1}H]$ NMR (126 MHz, $CDCl_3$) δ 172.0, 156.0, 134.4, 118.7, 80.4, 54.9, 53.5, 32.6, 28.6, 28.0, 22.7, 14.1. HRMS (ESI$^+$) calcd *m/z* for $C_{14}H_{28}N_3O_3$ $[M+H]^+$ 286.2125, found 286.2129.

***N'*-Diallyl *N*-(Boc)alanine hydrazide (28).** A 0 °C solution of Boc-Ala-$NHNH_2$ (**12**, 100 mg, 0.50 mmol) in DMF (5 mL) was treated with potassium carbonate (76 mg, 0.55 mmol) followed dropwise by trifluoroacetic anhydride (77 µL, 0.55 mmol). After 30 min, the ice bath was removed. The reaction mixture warmed to rt. After consumption of starting material was evidenced by TLC (R*f* 0.11, 80 % EtOAc in hexane), the reaction mixture was filtered, and the filtrate was partitioned between DCM (15 mL) and water (5 mL). The organic phase was washed with water (5 × 5 mL), dried over $MgSO_4$, filtered and evaporated to afford trifluoroacetyl hydrazide **16** as a yellow oil, which was dissolved in DMF (5 mL), treated sequentially with K_2CO_3 (0.092 g, 0.67 mmol) and allyl bromide (0.18 mL, 2.0 mmol), and heated with stirring at 65°C. After 48 h, TLC analysis indicated complete consumption of hydrazide **16** (R*f* 0.76, 80% EtOAc in hexane) by the disappearance of the $KMnO_4$ positive spot. The reaction mixture was partitioned between DCM (15 mL) and water (5 mL). The organic phase was washed with water (5 × 5 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography eluting with a gradient of 20-80% EtOAc in hexane. Evaporation of the collected fractions gave *N'N''*-diallyl *N'*-trifluoroacetyl *N*-(Boc)alanine hydrazide (**27**, 44 mg, 23% overall yield from **12**) as a translucid oil (R*f* 0.82, 80 % EtOAc in hexane), which was dissolved in MeOH (12mL), treated with 5% aqueous K_2CO_3 (5 mL) and heated at reflux for 30 min. The reaction mixture was cooled to room temperature. The volatiles were removed under vacuum. The reduced volume was diluted with DCM (15 mL). The aqueous phase was separated, washed with DCM (5 mL x 3), dried over $MgSO_4$, filtered and evaporated to a residue, which was purified by silica gel chromatography eluting with a gradient of 20-80% EtOAc in hexane. Evaporation of the collected fractions gave *N'N''*-diallyl *N*-(Boc)alanine hydrazide (**28**, 24 mg, 73% overall yield from **27**) as a translucid oil: R*f* 0.65 (50 % EtOAc in hexane); $[\alpha]^{23}_{D}$ –3.7 (*c* 0.36, $CHCl_3$); FT-IR (neat) ν max 3424, 3288, 2992, 2926, 1715, 1695, 1651, 1498, 1399, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81-5.94 (m, 1H), 5.65-5.78 (m, 1H), 5.07-5.35 (m, 6H), 4.30-4.36 (dd, *J* = 5.3, 5.7 Hz, 1H), 4.05-4.13 (m, 1H), 3.64-3.68 (m, 1H), 3.41-3.48 (m, 2H), 1.43 (s, 9H), 1.29-1.31 (d, *J* = 6.8 Hz, 3H); $^{13}C[^{1}H]$ NMR (75 MHz, $CDCl_3$) δ 177.9, 175.5, 132.8, 131.3, 119.6, 118.9, 51.3, 46.6, 45.4 28.4, 28,2, 19,3; HRMS m/z calcd for $C_{14}H_{25}N_3O_3$ $[M+H]^+$ 284.1965, found 284.1969.

(2*S*,4*R*)- and (2*S*,4*S*)-Methyl 2-*N*-(Boc)amino-4-(bromomethyl)-hex-5-enoates [(2*S*,4*R*)- and (2*S*,4*S*)-29] Bromides (2*S*,4*R*)- and (2*S*,4*S*)-**29** were prepared from *N*-(Boc)-3-iodoalanine methyl ester (20 g, 60.7 mmol) and *trans*-1,4-dibromo-2-butene (16.9 g, 80 mmol, 1.3 equiv.) using the protocol previously described for the synthesis of the corresponding chlorides in reference 37. First to elute was bromide (2*S*,4*S*)-**29** as green oil (6.2 g, 30%); Rf 0.5 (10% EtOAc in hexane, 3 times eluted, visualized with $KMnO_4$); $[\alpha]_D^{25}$ 8.4 (*c* 1.2, $CHCl_3$); FT-IR (neat) ν_{max} 3368, 2979, 1698, 1504, 1436, 1365, 1159, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73-5.66 (m, 1H), 5.20-5.16 (m, 2H), 5.12-5.04 (m, 1H,), 4.41-4.35 (m, 1H), 3.76 (s, 3H), 3.51-3.48 (dd, 1H, *J* = 9.6, 5.5), 3.43-3.40 (dd, 1H, *J* = 10.1, 5.5), 2.60-2.54 (m, 1H), 2.16-2.11 (m, 1H), 1.78-1.72 (m, 1H), 1.46 (s, 9H); $^{13}C[^{1}H]$ NMR (125 MHz, $CDCl_3$) δ 173.0, 155.2, 138.2, 117.6, 80.1, 52.3, 51.4, 41.5, 37.5, 35.8, 28.3; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{22}BrNO_4Na$ 358.0624, found 358.06333. Next to elute was bromide (2*S*,4*R*)-**29** as a green oil (8.2 g, 40%); R*f* 0.4 (10% EtOAc in hexane, 3 times eluted, visualized with $KMnO_4$); $[\alpha]_D^{25}$ 10.1 (*c* 1.3, $CHCl_3$); FT-IR (neat) ν_{max} 3380, 2980, 1705, 1508, 1435, 1365, 1159, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.64 (m, 1H), 5.28-5.21 (m, 2H), 4.93-4.91 (d, 1H, *J* = 9.2), 4.36-4.32 (m, 1H), 3.76 (s, 3H), 3.45-3.42 (dd, 1H, *J* = 10.0, 5.5), 3.37-3.34 (dd, 1H, *J* = 10.0, 6.7), 2.61-2.54 (m, 1H), 1.93-1.88 (m, 2H), 1.46 (s, 9H); ^{13}C[^{1}H] NMR (125 MHz, $CDCl_3$) δ 173.3, 155.4, 137.5, 118.4, 80.1, 52.4, 51.6, 42.3, 37.6, 36.0, 28.3; HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{13}H_{22}BrNO_4Na$ 358.0624 found 358.0627.

(3*S*,5*S*)-1,3-Diamino-5-ethyl-δ-lactam [(3*S*,5*S*)-30] A solution of bromide (2*S*,4*S*)-**29** (250 mg, 0.3 mmol) in a 1:1 volume ration of MeOH (5 mL) and hydrazine hydrate (5 mL) was heated to 50°C overnight, when complete disappearance of starting material was observed by TLC (R*f* 0.17, 100% EtOAc). The volatiles were removed under vacuum, and the residue was purified by flash column chromatography eluting with 80-100% EtOAc in hexane. Evaporation of the collected fractions provided (3*S*,5*S*)-1,3-diamino-5-ethyl-δ-lactam [(3*S*,5*S*)-**30**] as off-white solid (106 mg, 55%): R*f* 0.17 (100% EtOAc, visualized with $KMnO_4$); $[\alpha]_D^{25}$ 32.6 (*c* 0.6, $CHCl_3$); FT-IR (neat) ν_{max} 3680, 3289, 2967, 1716, 1626, 1523, 1366, 1253, 1163, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.49 (s, 1H), 4.11-4.07 (m, 1H), 3.56 (ddd, 1H, *J* = 11.9, 5.7, 1.5), 3.17-3.15 (t, 1H, *J* = 11.6), 2.52-2.49 (d, 1H, *J* = 13.2), 1.98-1.95 (m, 1H), 1.48 (s, 9H), 1.42-1.40 (m, 3H), 0.98 (t, 3H, *J* = 7.5); ^{13}C[^{1}H] NMR (125 MHz, $CDCl_3$) δ 168.4, 155.9, 79.7, 56.8, 51.5, 34.3, 33.5, 28.4, 26.5, 11.2; HRMS (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{12}H_{23}N_3O_3Na$ 280.1631 found 280.1626.

(3*S*,5*S*)-*N'*-Propargyl 1,3-diamino-δ-lactam (31) A 0°C solution of 1,3-diamino-δ-lactam (3*S*,5*S*)-**30** (150 mg, 0.6 mmol) in anhydrous THF (6 mL) was treated with DIEA (90.4 mg, 0.7 mmol, 1.2 equiv.) followed by trifluoroacetic anhydride (245 mg, 1.2 mmol, 2 equiv.), and stirred at 0°C for 30 min. The ice bath was removed. The reaction mixture warmed to room temperature. After 1 h, TLC (R*f* 0.39, 40% EtOAc in hexane) indicated complete consumption of starting material. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with water. The aqueous layer was washed with EtOAc (5 mL x 2). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated. Without further purification, the residue was dissolved in anhydrous DMF (4 mL) treated with Cs_2CO_3 (285 mg, 0.87 mmol, 1.5 equiv.) followed by propargyl bromide (80% wt. in toluene, 104 mg, 0.87 mmol, 1.5 equiv.). After heat at 50°C with stirring overnight, the reaction mixture exhibited complete consumption of starting material by TLC (R*f* 0.7, 40% EtOAc in hexane). The reaction mixture was cooled to room temperature, and partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with water (10 mL x 4) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Without further purification, the residue was dissolved in MeOH (15 mL) treated with 5% aqueous K_2CO_3 (6 mL) and heated at reflux for 30 min, when complete consumption of starting material was observed by TLC (R*f* 0.32, 40% EtOAc in hexane). The volatiles were removed under vacuum. The reduced volume was diluted with DCM (15 mL). washed with water (5 mL x 3), dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography using 30% EtOAc in hexane. Evaporation of the collected fractions provided (3*S*,5*S*)-*N*'-propargyl 1,3-diamino-δ-lactam (**31**) as an oil (117 mg, 68%): R*f* 0.32 (40% EtOAc in hexane, visualized with $KMnO_4$); $[\alpha]_D^{25}$ 46.6 (*c* 0.7, $CHCl_3$); FT-IR (neat) ν_{max} 3706, 3680, 3283, 2972, 2865, 2075, 1707, 1642, 1455, 1364, 1163, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67-5.65 (t, 1H, *J* = 5.2), 5.36 (s, 1H), 4.14 (dt, 1H, *J* = 5.5, 4.8), 3.68-3.64 (m, 3H), 3.15-3.13 (t, 1H, *J* = 11.5), 2.52-2.49 (d, 1H, *J* = 16.2), 2.26-2.25 (t, 1H, *J* = 2.5), 1.98-1.96 (m, 1H), 1.48 (s, 9H), 1.43-1.33 (m, 3H), 0.98 (t, 3H, *J* = 7.5); $^{13}C[^{1}H]$ NMR (125 MHz, $CDCl_3$) δ 172.8, 155.2, 138.2, 117.6, 80.1, 59.6, 52.3, 51.4, 41.5, 37.5, 35.8, 28.3, 18.7; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{15}H_{25}N_3O_3Na$ 318.1788 found 318.1777.

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Figure titles

Figure 1. Representative natural and synthetic hydrazine products

Scheme titles

Scheme 1. Pyrazolidinone synthesis from trifluoro-acetyl hydrazide.

Scheme 2. Three-step synthesis of *N*'-alkyl hydrazides by way of Mitsunobu reaction on trifluoro-acetyl hydrazide

Scheme 3. Synthesis of *N*'-allyl hydroxyproline hydrazide **24** by way of Mitsunobu reaction

Scheme 4. Synthesis of *N*'-alkyl hydrazides by alkylation of trifluoroacetyl hydrazides

Scheme 5. Synthesis of *N*'*N*''-diallyl hydrazide **28**

Scheme 6. Synthesis of *N*'-propargyl 1,3-diamino-δ-lactam **31**

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