Side-Chain-Functionalized Dipeptides Derived from 6,5-Fused Bicyclic Thiazolidinlactams

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Condensation of D-arabinuronolactone (**2**) with L-cysteine methyl ester yields the bicyclic thiazolidinlactam **3** as a single diastereoisomer with the new bridgehead stereocenter in the (*S*) configuration. Regioselective activation of the α-hydroxy group leads to the triflate **4** without requiring protecting groups on the residual hydroxy groups. Subsequent azide exchange, reduction, and Boc protection, yields the epimeric dipeptide mimetics **6** and **7**. Compound **3** forms the single acetonide **9**, which permits the regioselective alkylation of the γ-hydroxy group of the bicyclic framework. Subsequent deprotection and exchange of the α-hydroxy functionality against a Boc-protected amino group (**13**) demonstrates the regioselective side-chain modification of bicyclic dipeptides.

Introduction

Amino acids that are derived from sugar precursors combine the polyfunctional character of carbohydrates with the polyamide backbone of peptides.[1] Furanoid or pyranoid sugar amino acids restrict the dynamics about peptide torsional angles and, as a consequence, the monocyclic amino acids can stabilize structural motifs in peptides.[2] Fused rings exert an even stronger local structural control by freezing several torsions within bi- or oligocyclic frameworks.[3] The peptide mimetics described here combine the molecular diversity of sugars with the rigidity of fused heterocyclic rings. The synthesis of 7,5-fused ring systems and their structural properties within oligopeptides have been described recently.[4] Here we investigate the possibility of constraining the relative ring sizes further and we describe the regioselective modification of hydroxy groups. The L,L-,[5] D,L-,[6] and L,D-configured[7] dipeptides that are constrained within hexahydrothiazolo[3,2-*a*]pyridin-5-one ring systems find application as active-site inhibitors of enzymes. The uronic acid derived dipeptides described here bear additional functional groups that mimic the side chains of serine and threonine. Regioselective alkylation of the hydroxy groups introduces alternative amino acid side chains and opens access to different dipeptide mimetics that are derived from a common precursor.

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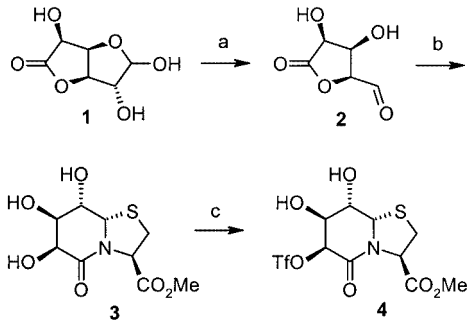
Results and Discussion

Synthesis

Periodate cleavage of D-glucurono-3,6-lactone (**1**) yields D-arabinurono-2,5-lactone (**2**),[8] which combines with L-cysteine methyl ester to give the bicyclic thiazolidinlactam **3** (Scheme 1). The annulation reaction is spontaneous in water containing a few percent of pyridine.[4] The yield of this two-step reaction is limited by the preparation of the oily sugar lactone **2**, which was not isolated but immediately condensed with L-cysteine methyl ester in a highly diastereoselective reaction. The different nucleophilicities of the hydroxy groups of **3** regulate the third selective reaction step, which is the formation of triflate **4** with 1.1 equiv. of triflic anhydride. Crystals of **4** were grown from ethyl acetate and the (*S*) configuration at the bridgehead stereocenter was proven by X-ray structural analysis.



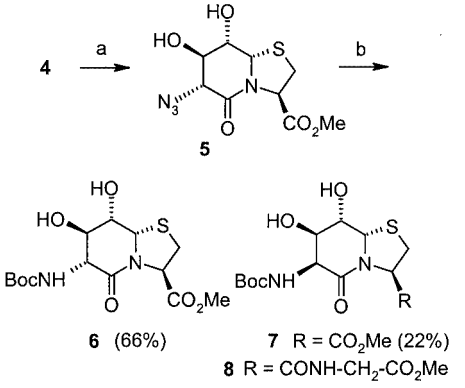
Scheme 1. a) $NaIO_4$, 0.05 M Na_2HPO_4, 0 °C to room temp.; b) HCl·H-Cys-OMe, H_2O/pyridine (10:1) (65 % both steps); c) Tf_2O, CH_2Cl_2/pyridine (10:1), −30 °C to room temp. (78%)

The triflate is displaced with inversion of configuration by an azido group in CH_2Cl_2 to yield **5** (Scheme 2). Alternatively, the reaction of **4** with sodium azide can be performed with a comparable yield in DMF as solvent without the necessity of adding a crown ether. The S_N2-type reaction is accompanied by an inversion of the α-stereocenter in contrast to the double inversion − and thus overall retention of configuration − that was observed in the case of the 7,5-membered rings and explained by the destabilized axial orientation of the azido group.[4c] Such destabilization is absent in the more planar 6,5-membered fused rings, and the 6-H proton is found on the same side of the six-membered ring as the bridgehead proton 8a-H as determined from the ROESY spectrum of **5** (Figure 1). Subsequent reduction of **5** with hydrogen sulfide is accompanied by the epimerization of the α-carbon atom. The two diastereoisomeric amines were protected with Boc anhydride and then separated by flash chromatography to yield the D,L-configured dipeptide **6** and the L,L-dipeptide **7**. Reduction of the azide **5** with $Na_2S_2O_3$, TMSCl, and NaI in acetonitrile at room temperature for 30 min,[9] followed by Boc protection of the amine, gave **6** without formation of the diastereoisomer **7**.

The transformation of **3** to azide **5** can be performed by a one-pot reaction in an overall 62% yield without isolation of the intermediate triflate **4**, which reduces the number of synthetic steps from the commercial sugar lactone to the fully protected dipeptide to only four. Similarly, the transformation of **4** to the Boc-protected dipeptides can be performed without requiring workup of the intermediate.

The carboxy terminus of **7** (or **6**) is deprotected upon saponification with LiOH, and HCl/Et_2O sets the amino terminus free. Coupling products are then obtained under the standard conditions of peptide synthesis. Only the tripeptide **8** is presented here, which has interesting conformational properties as discussed below.

Synthetic strategies towards bicyclic peptidomimetics start generally from two amino acids of which the side chain functionalities are consumed in the formation of the bicyclic ring.[3] In a similar manner, the strategy presented here consumes the aldehyde functionality of the uronic acid in the formation of the fused rings. The two remaining hydroxy groups allow for subsequent synthetic modifications



Scheme 2. a) NaN_3, CH_2Cl_2, 15-crown-5, room temp. (92%); b) H_2S, H_2O/pyridine (1:2), then Boc_2O, DIPEA, CH_2Cl_2

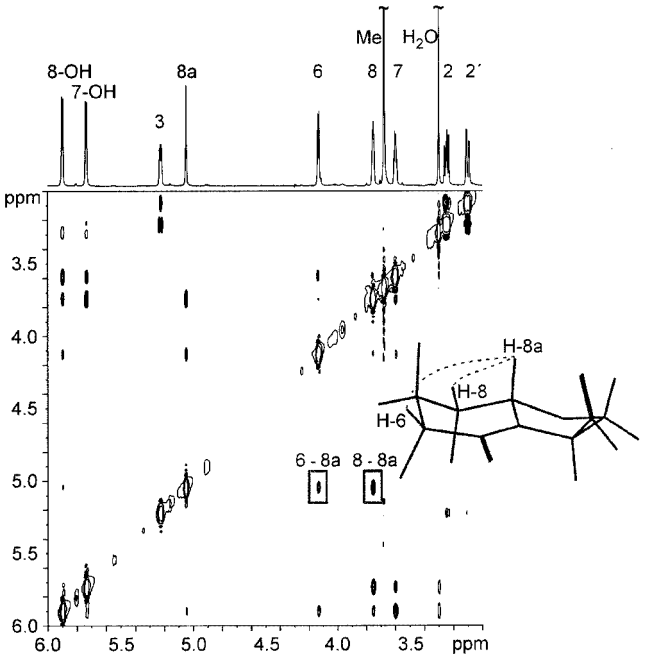
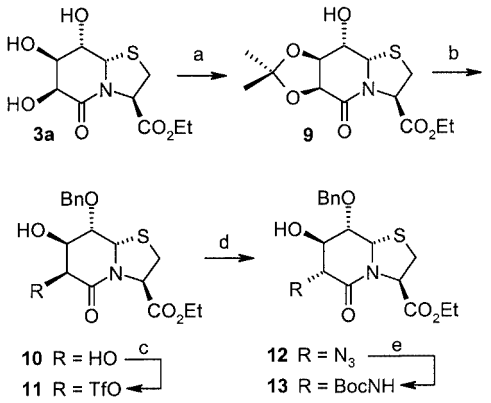


Figure 1. ROESY spectrum (600 MHz, 300 K, 4 kHz pulsed spin lock, 200 ms mixing time) of the azide **5** in [D_6]DMSO; the small ^3J coupling constants within the six-membered ring, namely $^3J_{6,7} = 5.2$, $^3J_{7,8} < 2$, and $^3J_{8,8a} = 1.5$ Hz, are caused by the relative gauche arrangement of the four ring protons; the strongest NOE is observed between the neighbouring protons 8-H and 8a-H; the intense NOE between protons in the positions 6 and 8a proves that both protons are found on the same side of the ring; the full assignment is given in the Exp. Sect.

by serving as anchoring points for encoded amino acid side chains. For example, Hirschmann et al. showed that an *O*-benzyl group attached to a sugar scaffold can mimic the phenylalanine side chain.[10] The regioselective modification of one of the two hydroxy groups of **3** forms the basis for the synthesis of a wide range of side-chain-modified dipeptides. Various peptidomimetics are then accessible form the common precursor **3**. Branching of the synthetic strategy after the synthesis of the fused ring system is another advantage of the uronic acid based synthesis over amino acid based strategies, in which each new bicyclic dipeptide requires a new amino acid precursor; examples of syntheses of more than one bicyclic peptide from a common precursor remain exceptions.[11] Compound **3** forms a single acetonide (**9**, Scheme 3) that permits the differentiation between the 7-OH and the 8-OH groups and, hence, **9** becomes the key intermediate for the regioselective modification of the side chain.

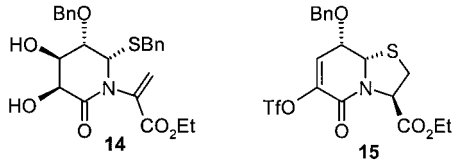
Benzylation of **9**, followed by deprotection of the acetonide, yielded the monoalkylated derivative **10**. The reaction sequence of triflation (→ **11**) and azide exchange yielded the azide **12**, which was transformed by reduction and Boc protection into the crystalline D,L-dipeptide **13** in an 87% yield. Additionally, the epimeric L,L-dipeptide (11%) was separated by flash chromatography.

The side products (**14** and **15**) formed in the two low-yielding steps were separated and characterized. Both result from eliminations and yield dehydro amino acids. The side



Scheme 3. a) acetone, H^+ (89%); b) i. BnBr, NaH, DMF, ii. TFA/H_2O/EtOH (34%); c) Tf_2O, DMAP, CH_2Cl_2/pyridine (10:1) (38%); d) NaN_3, 15-crown-5, CH_2Cl_2 (83%); e) H_2S, H_2O/pyridine (1:2), then Boc_2O, DIPEA, CH_2Cl_2 (87%)

product **14** from the benzylation reaction is separable from **10** after cleavage of the acetonide group. Only the stereoisomer that retains the configuration of the former bridgehead stereocenter is observed. This was an unexpected reaction, because the thioproline sulfur atom does not act as a nucleophile in reactions with other electrophiles. Therefore, we expect that a change in the reaction conditions will permit a better differentiation between the secondary hydroxy group and the thiazolidin lactam sulfur atom. A second side product resulting from elimination is observed upon the triflation of **10**. The DMAP present in the reaction mixture leads to the formation of **15**, which was not formed from the reaction conducted in the absence of DMAP as shown by the high yield of triflate **4**.



Structural Analysis

The crystal structures of **6** and **7** are shown in Figure 2. The planarized six-membered rings keep both hydroxy substituents in pseudoaxial orientations with O−C−C−O torsional angles of ca. 180° for **7** and **8** and ca. −150° for **6** and **13** (Figure 3).

Thiazabicycloalkane amino acids like the β-turn dipeptide (BTD)[12] **7**, its diastereoisomer **6**, or the *O*-alkylated **13**, mimic dipeptides consisting of the amino acids i and $i+1$. The 6,5-fused heterocyclic rings lock three sequential peptide backbone torsions ψ_i, ω_i, and φ_{i+1} (φ = CO−N−C_α−CO, ω = N−CO−C_α−N, ψ = C_α−CO−N−C_α).[13] Torsion Ψ_i is constrained within an extended conformation and the observed values for φ_{i+1} are the ones expected for (thio)proline (Table 1). The amino and carboxy terminal torsions of the bicyclic ring φ_i and ψ_{i+1} assume preferred orientations, although varying over a wider range. Surprisingly, the largest variation of φ_i is found in the two molecules in the asymmetric unit in the crystal structure of **8**. The carboxy termini (torsion ψ_{i+1}) assume extended conformations with the exception of **6**, which is flipped by 180°. Conformational mobility is expected for this exocyclic torsion in solution. NMR spectroscopy corroborates the ring conformations found in the solid state; the ^3J coupling constants are listed in the Exp. Sect.

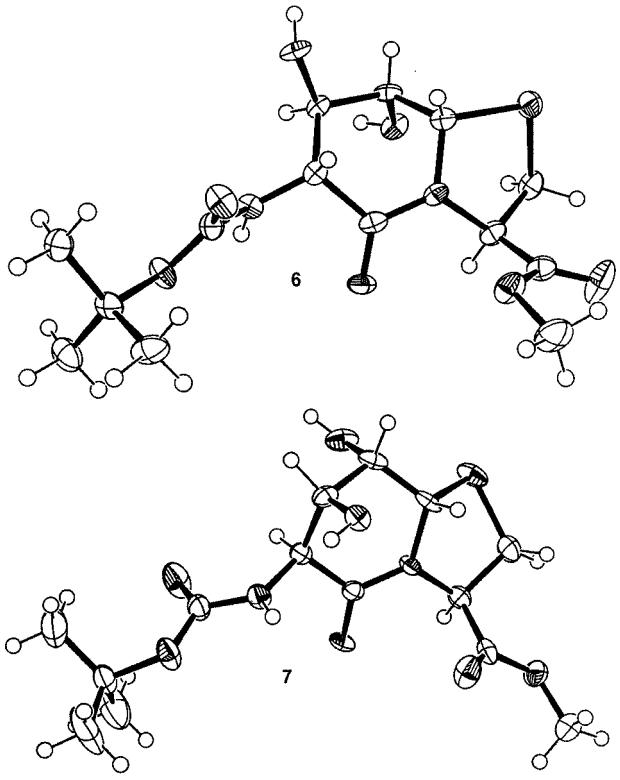


Figure 2. Crystal structures of the protected dipeptides **6** and **7**

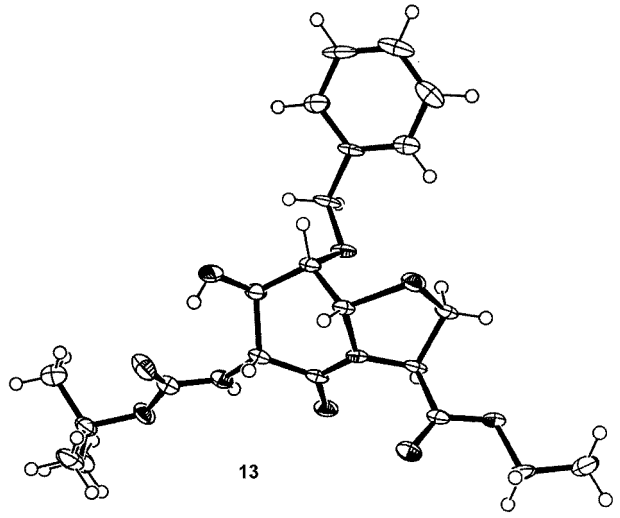


Figure 3. Crystal structure of side-chain-functionalized **13**

Table 1. Representative torsion angles of the solid-state structures; compounds **6** and **13** represent D,L-configured dipeptides while all others mimic L,L-dipeptides; structures **8** (1) and **8** (2) are the two molecules in the asymmetric unit of the crystal; the values for BTD were taken from the literature (ref.[12b])

	φ_i	ψ_i	φ_{i+1}	ψ_{i+1}
6	105.0°	175.1°	−96.6°	30.1°
13	156.3°	178.7°	−96.0°	−169.9°
7	−110.9°	−142.3°	−76.3°	−172.3°
8 (1)	−151.9°	−148.0°	−70.1°	144.3°
8 (2)	−78.1°	−164.3°	−77.2°	162.4°
BTD	−104.3°	−157.0°	−66.5°	−197.0°

Conclusion

A straightforward synthetic strategy yields 6,5-fused carbodipeptides in D,L- (major) and L,L-configured (minor) diastereoisomers, respectively. No side-chain protection is necessary during the synthesis or in the subsequent peptide coupling steps. Selective synthetic transformations of hydroxy groups, excellent solubility, and a tendency to form crystals, make these carbohydrate-derived dipeptides a promising new class of peptidomimetics. The dipeptide analogs described here are derived from a single bicyclic precursor that is accessible in large quantities and that can serve as a starting point for the synthesis of dipeptides with diverse side-chain functionalities.

Experimental Section

General Remarks: Solvents were purified according to standard procedures. Flash chromatography was performed on J. T. Baker silica gel 60 (0.040−0.063 mm) at a pressure of 0.4 bar. Thin layer chromatography was performed on Merck silica gel plastic plates, $60F_{254}$; compounds were visualized by treatment with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL) and heating at 150 °C. Optical rotations were measured with a Perkin−Elmer polarimeter 241 in a 1-dm cell at 22 °C. NMR spectra were recorded with a Bruker AC 400 or a Bruker DRX 600. TMS, or the resonance of the residual solvent ([D$_6$]DMSO: δ = 2.49 ppm), was used as internal standard. Diasterotopic proton pairs that could not be assigned stereochemically are characterized as highfield (h) and lowfield (l) in the ^{1}H NMR data. FAB mass spectra were acquired with a Finnigan MAT 312 in the positive mode, using NBA as the matrix. CCDC-183964 (**4**), -154782 (**6**), -183443 (**7**), -183963 (**8**), and -183444 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Methyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-6,7,8-Trihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (3): γ-Glucuronolactone (5.0 g, 28.4 mmol) and $NaIO_4$ (7.9 g, 36.9 mmol, 1.3 equiv.) were dissolved in aqueous Na_2HPO_4 (0.05 M, pH = 7.5, 50 mL). An ice bath was used to keep the reaction temperature below 30 °C. MeOH (50 mL) was added after 1 h causing a white precipitate to form. The suspension was stirred for another 12 h at room temp., the precipitate was filtered off, and the solvent was evaporated. The residue was dissolved in H_2O/pyridine (10:1, 110 mL). After addition of L-cysteine methyl ester (5.0 g, 29.1 mmol), the solution was stirred at room temp. for 4 d. The solvent was evaporated and the residue was dissolved in MeOH. Compound **3** (4.87 g, 18.5 mmol, 65%) was obtained as a colorless solid after flash chromatography with $CHCl_3$/MeOH (3:1) (R_f = 0.65). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 5.60 (d, $^3J_{8\text{-OH},8}$ = 5.1 Hz, 1 H, 8-OH), 5.40 (d, $^3J_{7\text{-OH},7}$ = 3.5 Hz, 1 H, 7-OH), 5.31 (d, $^3J_{6\text{-OH},6}$ = 6.1 Hz, 1 H, 6-OH), 5.16 (d, $^3J_{8a,8}$ = 2.6 Hz, 1 H, 8a-H), 4.87 (dd, $^3J_{3,2proS}$ = 5.4, $^3J_{3,2proR}$ = 7.6 Hz, 1 H, 3-H), 4.07 (dd, $^3J_{6,6\text{-OH}}$ = 6.0, $^3J_{6,7}$ = 3.6 Hz, 1 H, 6-H), 4.01 (m, 1 H, 7-H), 3.93 (m, 1 H, 8-H), 3.63 (s, 3 H, OCH_3), 3.30 (m, 1 H, 2-H^{proR}), 3.03 (dd, $^3J_{2proS,3}$ = 5.28, $^2J_{gem}$ = 11.44 Hz, 1 H, 2-H^{proS}) ppm. ^{13}C NMR: δ = 170.51, 169.02 (C-5, CO_2), 71.03 (C-7), 66.93 (C-6), 66.77 (C-8), 64.64 (C-8a), 60.35 (C-3), 52.22 (OCH_3), 31.23 (C-2) ppm. $[\alpha]_D^{24}$ = −214 (*c* = 1, MeOH). FAB-MS: *m*/*z* = 264 [M + H]$^+$, 527 [2 M + H]$^+$. $C_9H_{13}NO_6S$ (263.27): calcd. C 41.06, H 4.98, N 5.32; found C 40.23, H 5.05, N 5.18.

Analytical Data of the Ethyl Ester 3a: ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 5.60 (d, $^3J_{8\text{-OH},8}$ = 5.0 Hz, 1 H, 8-OH), 5.38 (d, $^3J_{7\text{-OH},7}$ = 3.5 Hz, 1 H, 7-OH), 5.30 (d, $^3J_{6\text{-OH},6}$ = 6.2 Hz, 1 H, 6-OH), 5.17 (d, $^3J_{8a,8}$ = 2.9 Hz, 1 H, 8a-H), 4.85 (dd, $^3J_{3,2proS}$ = 5.3, $^3J_{3,2proR}$ = 7.9 Hz, 1 H, 3-H), 4.1 (m, 3 H, CH_2CH$_3$, 6-H), 4.01 (m, 1 H, 7-H), 3.93 (m, 1 H, 8-H), 3.30 (m, 1 H, 2-H^{proR}), 3.01 (dd, $^3J_{2proS,3}$ = 5.0, $^2J_{gem}$ = 11.2 Hz, 1 H, 2-H^{proS}), 1.19 (t, $^3J_{Et}$ = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR: δ = 170.0, 169.0 (C-5, CO_2), 70.1 (C-7), 66.6 (C-6), 66.5 (C-8), 64.3 (C-8a), 60.6 (CH_2CH$_3$), 60.1 (C-3), 30.9 (C-2), 13.6 (CH$_2$CH_3) ppm. $[\alpha]_D^{24}$ = −151 (*c* = 1, MeOH). FAB-MS: *m*/*z* = 278 [M + H]$^+$, 300 [M + Na]$^+$. $C_{10}H_{15}NO_6S$ (277.29): calcd. C 40.23, H 5.05, N 5.18; found C 43.32, H 5.45, N 5.05.

Methyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-7,8-Dihydroxy-5-oxo-6-(trifluoromethanesulfonyloxy)hexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (4): Compound **3** (950 mg, 3.6 mmol) was dissolved in pyridine (50 mL) and CH_2Cl_2 (5 mL). At a reaction temperature of −40 °C a catalytic amount of DMAP was added together with Tf_2O (900 μL, 5.4 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was maintained at −40 °C for 30 min, then at room temperature for 30 min, and then poured onto ice (50 mL). The product was extracted with ethyl acetate (1 × 100 mL, 2 × 50 mL) and the combined organic phases were dried ($MgSO_4$). After flash chromatography (ethyl acetate/toluene, 4:1), compound **4** (1.14 g, 2.9 mmol, 81%) (R_f = 0.72) was obtained. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.47 (d, ^3J = 3.7 Hz, 1 H, OH), 6.18 (br. s, 1 H, OH), 5.32 (d, $^3J_{6,7}$ = 3.5 Hz, 1 H, 6-H), 5.20 (d, $^3J_{8a,8}$ = 2.4 Hz, 1 H, 8a-H), 4.95 (dd, $^3J_{3,2h}$ = 5.7, $^3J_{3,2l}$ 7.5 Hz, 1 H, 3-H), 4.36 (m, 1 H, 7-H), 4.11 (m, 1 H, 8-H), 3.69 (s, 3 H, OCH_3), 3.40 (dd, $^2J_{gem}$ = 11.5, $^3J_{2l,3}$ = 7.7 Hz, 1 H, 2-H^l), 3.11 (dd, $^2J_{gem}$ = 11.4, $^3J_{2h,3}$ = 5.5 Hz, 1 H, 2-H^h) ppm. ^{13}C NMR: δ = 169.70, 160.66 (C-5, CO_2), 82.37 (C-6), 69.73 (C-7), 66.84 (C-8), 64.54 (C-8a), 60.62 (C-3), 52.49 (OCH_3), 31.30 (C-2) ppm. PI-DCI-MS: *m*/*z* = 413 [M + NH_4]$^+$. $C_{10}H_{12}F_3NO_8S_2$ (395.34): calcd. C 30.38, H 3.06, N 3.54; found C 30.00, H 3.08, N 2.95.

Methyl (3*R*,6*R*,7*R*,8*S*,8a*S*)-6-Azido-7,8-dihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (5): NaN_3 (700 mg, 10.8 mmol) and 15-crown-5 (2 mL, 8.2 mmol) were added to a solution of triflate **4** (2.00 g, 3.05 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temp for 14 h and then H_2O (20 mL) was added. The aqueous phase was extracted twice with

ethyl acetate and the combined organic phases were dried ($MgSO_4$). Flash chromatography (ethyl acetate/toluene, 3:1) yielded the azide **5** (1.34 g, 4.65 mmol, 92%) (R_f = 0.43).

One-Pot Synthesis of 5: Compound **3** (1 mmol) was dissolved in pyridine/CH_2Cl_2 (3:2, 5 mL) and cooled to −40 °C. DMAP (catalytic amount) was added followed by Tf_2O (0.2 mL, 1.22 mmol) in CH_2Cl_2 (0.5 mL). The solution was stirred at −40 °C for 45 min, at −20 °C for 45 min, and then at room temp. for 45 min. The solution was then cooled to −10 °C before NaN_3 (100 mg, 1.54 mmol) and 15-crown-5 (300 μL, 334 mg, 1.52 mmol) were added. After 1 h at this temperature, the solution was stirred for 3 d at room temp. The red-brown solution was concentrated and dissolved in H_2O/ethyl acetate (1:2, 30 mL). The aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried ($MgSO_4$) and **5** (177 mg, 0.62 mmol, 62%) was obtained as a clear syrup after flash chromatography (ethyl acetate/toluene, 3:1) (R_f = 0.43). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 5.90 (d, $^3J_{7\text{-OH},7}$ = 4.7 Hz, 1 H, 7-OH), 5.73 (d, $^3J_{8\text{-OH},8}$ = 4.57 Hz, 1 H, 8-OH), 5.22 (dd, $^3J_{3,2l}$ = 6.9, $^3J_{3,2h}$ = 2.82 Hz, 1 H, 3-H), 5.04 (d, $^3J_{8a,8}$ = 1.5 Hz, 1 H, 8a-H), 4.13 (d, $^3J_{6,7}$ = 5.2 Hz, 1 H, 6-H), 3.75 (m, 1 H, 8-H), 3.68 (s, 3 H, OCH_3), 3.60 (m, 1 H, 7-H), 3.26 (dd, $^3J_{2l,3}$ = 7.0, $^2J_{gem}$ = 11.3 Hz, 1 H, 2-H^l), 3.10 (dd, $^3J_{2h,3}$ = 2.9, $^2J_{gem}$ = 11.30 Hz, 1 H, 2^h-H) ppm. ^{13}C NMR: δ = 169.82, 165.12 (C-5, CO_2), 73.76 (C-7), 71.55 (C-8), 64.15 (C-6), 62.86 (C-8a), 61.38 (C-3), 52.52 (OCH_3), 31.18 (C-2) ppm. $[\alpha]_D^{24}$ = −57.3 (*c* = 1, $CHCl_3$). FAB-MS: *m*/*z* = 289 [M + H]$^+$, 577 [2 M + H]$^+$. $C_9H_{12}N_4O_5S$ (288.28): calcd. C 37.50, H 4.20, N 19.44; found C 37.24, H 4.40, N 18.18.

Methyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-6-*tert*-Butoxycarbonylamino-7,8-dihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (6) and Methyl (3*R*,6*R*,7*R*,8*S*,8a*S*)-6-*tert*-Butoxycarbonylamino-7,8-dihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (7): Azide **5** (1.15 g, 4 mmol) was dissolved in pyridine/H_2O (2:1, 150 mL). H_2S was bubbled through the solution for 10 min, and then the mixture was stirred at room temp. for 14 h. The solvent was evaporated and the crude product was dissolved in CH_2Cl_2. Boc_2O (1.2 g, 5.5 mmol) and DIPEA (0.7 mL, 4.0 mmol) were added and the reaction mixture was stirred at room temp. for 14 h. The solution was concentrated under vacuum and the products isolated by flash chromatography (ethyl acetate/toluene, 10:1) to yield **6** (950 mg, 2.62 mmol, 66%) (R_f = 0.56) and **7** (310 mg, 0.86 mmol, 22%) (R_f = 0.43).

Alternative Preparation of 6: Azide **5** (100 mg, 0.35 mmol) and NaI (80 mg, 0.53 mmol 1.5 equiv.) were dissolved in dry MeCN (5 mL) and the solution stirred for 5 min before TMSCl (70 μL, 0.53 mmol) was added; a red-brown suspension was formed. After 30 min at room temp., 10% $Na_2S_2O_3$ was added dropwise until a yellow color was observed. The solvent was evaporated and the dry residue was dissolved in dry CH_2Cl_2. While cooling in an ice bath, DIPEA (70 μL) and Boc_2O (115 mg, 0.53 mmol, 1.5 equiv.) were added. After stirring the solution for 3 d at room temp., the solvent was evaporated and the residue was dissolved in ethyl acetate/H_2O (2:1, 30 mL). The aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Compound **6** (56 mg, 0.15 mmol, 44.5%) was obtained as a yellow solid after flash chromatography (ethyl acetate/toluene, 5:1) (R_f = 0.53).

Analytical Data of 6: ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 6.84 (d, $^3J_{NH,6}$ = 9.1 Hz, 1 H, NH), 5.61 (d, $^3J_{8\text{-OH},8}$ = 4.8 Hz, 1 H, 8-OH), 5.44 (d, $^3J_{7\text{-OH},7}$ = 5.3 Hz, 1 H, 7-OH), 5.15 (dd, $^3J_{3,2l}$ 7.0, $^3J_{3,2h}$ = 2.6 Hz, 1 H, 3-H), 5.06 (d, $^3J_{8a,8}$ = 1.2 Hz, 1 H, 8a-H), 3.96 (dd, $^3J_{6,NH}$ = 9.4, $^3J_{6,7}$ = 6.8 Hz, 1 H, 6-H), 3.75 (m, 1 H, 8-H), 3.66 (s, 3 H, OCH_3), 3.61 (m, 1 H, 7-H), 3.24 (dd, $^3J_{2l,3}$ = 7.3, $^3J_{2l,2h}$ = 11.2 Hz, 1 H, 2-H^l), 3.06 (dd, $^3J_{2h,3}$ = 2.9, $^3J_{2h,2l}$ = 11.4 Hz, 1 H, 2-H^h), 1.39 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR: δ = 170.20, 166.93 (C-5, CO_2), 155.73 (CO*t*Bu), 77.96 (C_q *t*Bu), 73.56 (C-7), 73.27 (C-8), 63.04 (C-8a), 61.23 C-3), 56.83 (C-6), 52.43 (OCH_3), 31.27 (C-2), 28.20 (CH_3 *t*Bu) ppm. M.p. 172 °C. $[\alpha]_D^{24}$ = −86 (*c* = 1, $CHCl_3$). FAB-MS: *m*/*z* = 363 [M + H]$^+$. $C_{14}H_{22}N_2O_7S$ (362.40): calcd. C 46.40, H 6.12, N 7.73; found C 46.46, H 6.15, N 7.67.

Analytical Data of 7: ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 6.34 (d, $^3J_{NH,6}$ = 9.7 Hz, 1 H, NH). 5.74 (d, $^3J_{8\text{-OH},8}$ = 4.7 Hz, 1 H, 8-OH), 5.62 (d, $^3J_{7\text{-OH},7}$ = 3.8 Hz, 1 H, 7-OH), 5.15 (d, $^3J_{8,8a}$ = 2.6 Hz, 1 H, 8-H), 4.84 (dd, $^3J_{2,3}$ = 7.3, $^3J_{2',3}$ = 5.9 Hz, 1 H, 3-H), 4.44 (dd, $^3J_{6,NH}$ = 9.7, $^3J_{6,7}$ = 2.9 Hz, 1 H, 6-H), 3.92−3.96 (m, 2 H, 7-H, 8-H), 3.64 (s, 3 H, OCH_3), 3.31 (dd, $^2J_{2,2'}$ = 11.4, $^3J_{2,3}$ = 7.6 Hz, 1 H, 2-H^l), 3.02 (dd, $^2J_{2,2'}$ = 11.4, $^3J_{2',3}$ = 5.6 Hz, 1 H, 2-H^h), 1.39 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR: δ = 170.41, 166.54 (C-5, CO_2), 155.67 (CO*t*Bu), 78.11 (C_q *t*Bu), 70.94 (C-7) 66.16 (C-8), 64.51 (C-8a), 60.64 (C-3), 52.16 (OCH_3), 50.97 (C-6), 31.12 (C-2), 28.10 (CH_3 *t*Bu) ppm. $[\alpha]_D^{24}$ = −96.1 (*c* = 1, $CHCl_3$). FAB-MS: *m*/*z* = 363 [M]$^+$. $C_{14}H_{22}N_2O_7S$ (362.40): calcd. C 46.40, H 6.12, N 7.73; found C 46.38, H 6.14, N 7.71.

Analytical Data of Methyl {[(3*R*,6*S*,7*R*,8*S*,8a*S*)-(6-*tert*-Butoxycarbonylamino-7,8-dihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-3-yl)carbonyl]amino}acetate (8): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.30 (t, $^3J_{GlyNH,H\alpha}$ = 6.2 Hz, 1 H, Gly-NH), 6.31 (d, $^3J_{BocNH,6}$= 9.1 Hz, 1 H, BocNH), 5.71 (d, $^3J_{8\text{-OH},8}$ = 4.7 Hz, 1 H, 8-OH), 5.57 (d, $^3J_{7\text{-OH},7}$ = 3.5 Hz, 1 H, 7-OH), 5.17 (d, $^3J_{8a,8}$ = 1.8 Hz, 1 H, 8a-H), 4.88 (dd, $^3J_{3,2l}$ = 7.3, $^3J_{3,2h}$ = 5.6 Hz, 1 H, 3-H), 4.38 (dd, $^3J_{6,NHBoc}$ = 9.7, $^3J_{6,7}$ = 2.9 Hz, 1 H, 6-H), 3.93 (m, 1 H, 7-H), 3.90 (m, 1 H, 8-H), 3.88 (dd, $^2J_{H\alpha,H\alpha'}$ = 17.6, $^3J_{H\gamma,NH}$ = 5.9 Hz, 1 H, Gly-H$^l_\gamma$), 3.82 (dd, $^2J_{H\alpha,H\alpha'}$ = 17.6, $^3J_{H\alpha,NH}$ = 5.9 Hz, 1 H, Gly-H$^h_\alpha$), 3.62 (s, 3 H, OCH_3), 3.21 (dd, $^2J_{gem}$ = 11.4, $^3J_{2l,3}$ = 7.6 Hz, 1 H, 2-H^l), 2.99 (dd, $^2J_{gem}$ = 11.2, $^3J_{2h,3}$ = 5.0 Hz, 1 H, 2-H^h), 1.38 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR: δ = 170.08, 169.98, 166.21 (C-5, CO_2, CONH), 155.66 (CO*t*Bu), 78.14 (C_q *t*Bu), 70.47 (C-7), 66.32 (C-8), 64.79 (C-8a), 61.17 (C-3), 51.70 (OCH_3), 50.96 (C-6), 40.57 (Gly-C_α), 31.28 (C-2), 28.14 (CH_3 *t*Bu) ppm. PI-DCI-MS: *m*/*z* = 437 [M + NH_4]$^+$.

Ethyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-8-Hydroxy-6,7-isopropylidene-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (9): Ethyl ester **3a** (1.6 g, 5.77 mmol) was dissolved in acetone (50 mL) and the reaction vessel was cooled in an ice bath. Concentrated sulfuric acid (0.5 mL) was added and the reaction mixture was stirred for 15 min at 0 °C and then 45 min at room temp. The precipitate that formed during neutralization with sodium carbonate was isolated and subjected to flash-chromatography (ethyl acetate/toluene, 5:1) to give **9** (1.63 g, 5.14 mmol, 89%) (R_f = 0.53) as a yellow solid. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 5.79 (d, $^3J_{8\text{-OH},8}$ = 5.0 Hz, 1 H, 8-OH), 5.21 (dd, $^3J_{3,2h}$ = 2.6, $^3J_{3,2l}$ = 6.5 Hz, 1 H, 3-H), 4.99 (s, 1 H, 8a-H), 4.44 (d, $^3J_{6,7}$ = 6.5 Hz, 1 H, 6-H), 4.41 (dd, $^3J_{7,6}$ = 6.5, $^3J_{7,8}$ = 2.9 Hz, 1 H, 7-H), 4.11 (m, 2 H, CH_2CH$_3$), 3.93 (m, 1 H, 8-H), 3.13 (dd, $^3J_{2l,3}$ = 6.8, $^2J_{gem}$ = 11.4 Hz, 1 H, 2-H^l), 3.06 (dd, $^3J_{2h,3}$ = 2.6, $^2J_{gem}$ = 11.2 Hz, 1 H, 2-H^h), 1.39 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.18 (t, $^3J_{Et}$ = 7.0 Hz, 3-H, CH_2CH_3) ppm. ^{13}C NMR: δ = 169.21, 164.73 (C-5, CO_2), 109.67 (C_q^{Isopr}), 75.89 (C-6), 73.24 (C-7), 67.51 (C-8), 61.40 (*C*H$_2$CH$_3$), 61.24 (C-8a), 61.16 (C-3), 30.46 (C-2), 26.20, 24.34 (CH_3^{Isopr}), 13.88 (CH_2CH_3) ppm. $[\alpha]_D^{24}$ = −85.9 (*c* = 1, $CHCl_3$). FAB-MS: *m*/*z* = 318 [M + H]$^+$. $C_{13}H_{19}NO_6S$ (317.36): calcd. C 47.52, H 5.65, N 4.62; found C 49.21, H 5.82, N 4.23.

Ethyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-8-Benzyloxy-6,7-dihydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (10): Alcohol **9** (1.2 g, 3.8 mmol) was dissolved in DMF (50 mL), followed by the addition of benzyl bromide (1.5 mL, 12.6 mmol). The reaction vessel was cooled in an ice bath, NaH (70 mg, 2.9 mmol) was added, the mixture was stirred for 30 min, and then the ice bath was removed. Twice more, NaH (40 mg, 1.7 mmol) was added in intervals of 30 min. The solvent was evaporated, then toluene was added and evaporated. The dried residue was dissolved in ethyl acetate/H_2O (4:1, 250 mL). The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried ($MgSO_4$). At this stage, separation of **10** from the side product was not possible by flash chromatography (ethyl acetate/toluene, 4:5) (R_f = 0.5). The acetonide was cleaved using TFA (15 mL) in EtOH (10 mL) and H_2O (0.7 mL). The solvent was evaporated after 15 h at room temp. and flash chromatography (ethyl acetate/toluene, 5:1) of the residue yielded **10** (470 mg, 1.28 mmol, 34%) (R_f = 0.36) and the side product **14** (115 mg, 0.25 mmol, 7%) (R_f = 0.43). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.35 (m, 5 H, Ph), 5.57 (d, $^3J_{7\text{-OH},7}$ = 3.8 Hz, 1 H, 7-OH), 5.45 (d, $^3J_{6\text{-OH},6}$ = 5.9 Hz, 1 H, 6-OH) 5.24 (d, $^3J_{8a,8}$ = 2.6 Hz, 1 H, 8a-H), 4.91 (dd, $^3J_{3,2h}$ = 5.0, $^3J_{3,2l}$ 7.6 Hz, 1 H, 3-H), 4.69 (m, 2 H, PhC*H*$_2$), 4.17 (m, 1 H, 7-H), 4.11 (m, 2 H, C*H*$_2$CH$_3$), 4.05 (dd, $^3J_{6,6\text{-OH}}$ = 5.9, $^3J_{6,7}$ = 3.5 Hz, 1 H, 6-H), 3.99 (dd, $^3J_{8,8a}$ = 2.6, $^3J_{8,7}$ = 4.7 Hz, 1 H, 8-H), 3.31 (m, 1 H, H^l), 3.05 (dd, $^2J_{gem}$ = 11.4, $^3J_{2h,3}$ = 5.0 Hz, 1 H, 2-H^h),1.19 (t, $^3J_{Et}$ = 7.3 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 169.85, 168.92 (C-5, CO_2), 138.09, 128.27, 127.66, 127.63 (Ph), 74.61 (C-8), 72.71 (PhCH$_2$), 68.75 (C-7), 67.37 (C-6), 63.32 (C-8a), 60.99 (*C*H$_2$CH$_3$), 60.06 (C-3), 31.39 (C-2), 13.97 (CH$_2$*C*H$_3$) ppm. $[\alpha]_D^{24}$ = −197.4 (*c* = 1, CHCl$_3$). FAB-MS: *m*/*z* = 368 [M + H$^+$], 390 [M + Na]$^+$. $C_{17}H_{21}NO_6S$ (367.42): calcd. C 55.57, H 5.76, N 3.81; found C 56.30, H 5.57, N 3.90.

Analytical Data of the Minor Product

Ethyl 2-[(2*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-2-benzylsulfanyl-4,5-dihydroxy-6-oxopiperidin-1-yl]acrylate (14): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.30 (m, 10 H, Ph), 6.24 (s, 1 H, 3-H^l), 5.74 (s, 1 H, 3-H^h), 5.48 (d, $^3J_{4\text{-OH},4}$ = 3.8 Hz, 1 H, 4-OH), 5.25 (d, $^3J_{5\text{-OH},5}$ = 5.3 Hz, 1 H, 5-OH), 5.09 (d, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.65 (m, 2 H, PhCH$_2$), 4.37 (pt, $^3J_{5,5\text{-OH}/7}$ = 4.4 Hz, 1 H, 5-H), 4.1 (m, 3 H, 7-H, C*H*$_2$CH$_3$), 3.89 (pt, $^3J_{3,2/4}$ = 4.4 Hz, 1 H, 3-H), 3.85 (d, $^2J_{gem}$ = 12.9 Hz, 1 H, PhCH$_2$S), 3.76 (d, $^2J_{gem}$ = 12.6 Hz, 1 H, PhCH$_2$S), 1.17 (t, $^3J_{Et}$ = 7.3 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 171.27, 163.14 (C-6, CO_2), 138.16, 137.94 137.76 (Ph, C-2), 128.85, 128.44, 128.25, 127.72, 127.66, 127.06 (Ph), 123.36 (C-3 acrylic ester), 79.63 (C-3), 72.22 (O*C*H$_2$Ph), 69.62 (C-4), 67.62 (C-5), 65.80 (C-2), 60.83 (*C*H$_2$CH$_3$), 36.03 (S*C*H$_2$Ph), 13.90 (CH$_2$*C*H$_3$) ppm. $[\alpha]_D^{24}$ = −53.2 (*c* = 1, CHCl$_3$). FAB-MS: *m*/*z* = 480 [M + Na]$^+$, 502 [M + 2 Na$^+$ − H$^+$]$^+$, 630 [M + 2 Na + I]$^+$.

Ethyl (3*R*,6*S*,7*R*,8*S*,8a*S*)-8-benzyloxy-7-hydroxy-5-oxo-6-(trifluoromethanesulfonyloxy)hexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (11): Compound **10** (450 mg, 1.2 mmol) and DMAP (9 mg) were dissolved in CH_2Cl_2 (50 mL). The solution was cooled to −30 °C and Tf_2O (300 μL, 1.8 mmol, 1.5 equiv.) was added. The solution was cooled to −50 °C and pyridine (3 mL) was added. The mixture was warmed to room temperature, stirred for 2 h, and then the solvent was evaporated. The residue was dissolved in ethyl acetate (100 mL) and H_2O (20 mL), and the aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried ($MgSO_4$). Flash chromatography (toluene/ethyl acetate, 5:1) yielded **11** (228 mg, 0.46 mmol, 38%) (R_f = 0.26) and the side product **15** (217 mg, 0.45 mmol, 37%) (R_f = 0.54). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.35 (m, 5 H, Ph), 6.61 (d, $^3J_{7\text{-OH},7}$ = 3.8 Hz, 1 H, 7-OH), 5.27 (d, $^3J_{8a,8}$ = 2.1 Hz, 1 H, 8a-H), 5.24 (d, $^3J_{6,7}$ = 3.2 Hz, 1 H, 6-H), 5.00 (dd, $^3J_{3,2h}$ = 5.3, $^3J_{3,2t}$ = 7.6 Hz, 1 H, 3-H), 4.77 (d, $^2J_{gem}$ = 12.0 Hz, 1 H, PhCH$_2$), 4.70 (d, $^2J_{gem}$ = 11.7 Hz, 1 H, PhCH$_2$), 4.42 (m, 1 H, 7-H), 4.1 (m, 2 H, C*H*$_2$CH$_3$), 3.40 (dd, $^2J_{gem}$ = 11.4, $^3J_{2l,3}$ = 7.6 Hz, 1 H, 2-H^l), 3.14 (dd, $^2J_{gem}$ = 11.4, $^3J_{2h,3}$ = 5.3 Hz, 1 H, 2-H^h), 1.19 (t, $^3J_{Et}$ = 7.0 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 169.05, 160.62 (C-5, CO_2), 137.58, 128.41, 127.99, 127.82 (Ph), 82.23 (C-6), 74.37 (C-8), 73.36 (*C*H$_2$Ph), 67.77 (C-7), 63.12 (C-8a), 61.35 (*C*H$_2$CH$_3$), 60.34 (C-3), 31.44 (C-2), 13.92 (CH$_2$*C*H$_3$) ppm. FAB-MS: *m*/*z* = 500 [M + H]$^+$, 522 [M + Na]$^+$. $C_{18}H_{20}F_3NO_8S_2$ (499.48): calcd. C 43.28, H 4.04, N 2.80; found C 43.53, H 4.30, N 2.75.

Analytical Data of the Side Product Ethyl (3*R*,8*S*,8a*S*)-8-Benzyloxy-5-oxo-6-(trifluoromethanesulfonyloxy)-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (15): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.30 (m, 6 H, Ph), 5.29 (d, $^3J_{8a,8}$ = 2.9 Hz, 1 H, 8a-H), 5.26 (dd, $^3J_{3,2l}$ = 6.5, $^3J_{3,2h}$ = 1.8 Hz, 1 H, 3-H), 4.72 (d, $^2J_{gem}$ = 11.4 Hz, 1 H, CH$_2$Ph), 4.69 (d, $^2J_{gem}$ = 11.4 Hz, 1 H, CH$_2$Bn), 4.39 (dd, $^3J_{8,8a}$ = 3.2, $^3J_{8,7}$ = 6.5 Hz, 1 H, 8-H), 4.15 (m, 2 H, CH$_2$Et), 3.34 (dd, $^2J_{gem}$ = 11.4, $^3J_{2l,3}$ = 6.8 Hz, 1 H, 2-H^l), 3.22 (dd, $^2J_{gem}$ = 11.4, $^3J_{2h,3}$ = 2.1 Hz, 1 H, 2-H^h), 1.19 (t, $^3J_{Et}$ = 7.0 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 168.69, 154.78 (5-CO, CO_2), 141.31 (C-6), 137.76 (C-Ph), 128.47 (C-7), 128.32, 127.80, 127.65 (Ph), 72.15 (*C*H$_2$Ph), 69.06 (C-8), 63.79 (C-8a), 61.60 (*C*H$_2$CH$_3$), 61.24 (C-3), 32. 87 (C-2), 13.83 (CH$_2$*C*H$_3$) ppm.

Ethyl (3*R*,6*R*,7*R*,8*S*,8a*S*)-6-Azido-8-benzyloxy-7-hydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (12): Compound **11** (200 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (30 mL) and then NaN_3 (50 mg, 0.77 mmol) and 15-crown-5 (100 μL, 0.51 mmol) were added and the mixture was stirred at room temp. for 16 h. H_2O (10 mL) was added and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and flash chromatography (toluene/ethyl acetate, 2:1) yielded **12** (130 mg, 0.33 mmol, 83%) (R_f = 0.37) as an oil. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.35 (m, 5 H, Ph), 6.06 (d, $^3J_{7\text{-OH},7}$ = 5.0 Hz, 1 H, 7-OH), 5.22 (dd, $^3J_{3,2l}$ = 7.0, $^3J_{3,2h}$ = 2.6 Hz, 1 H, 3 H), 5.17 (d, $^3J_{8a,8}$ = 2.1 Hz, 1 H, 8a-H), 4.71 (d, $^2J_{gem}$ = 11.7 Hz, 1 H, CH$_2$Ph), 4.62 (d, $^2J_{gem}$ = 12.0 Hz, 1 H, CH$_2$-Ph), 4.31 (d, $^3J_{6,7}$ = 5.9 Hz, 1 H, 6-H), 4.13 (m, 2 H, C*H*$_2$CH$_3$), 3.80 (m, 1 H, 7-H), 3.75 (pt, $^3J_{8,8a/7}$ = 2.6 Hz, 1 H, 8-H), 3.23 (dd, $^2J_{gem}$ = 11.4, $^3J_{2l,\ 3}$ = 7.0 Hz, 1 H, 2-H^l), 3.13 (dd, $^2J_{gem}$ = 11.4, $^3J_{2h,3}$ = 2.6 Hz, 1 H, 2-H^h), 1.19 (t, $^3J_{Et}$ = 7.0 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 169.11, 164.70 (C-5, CO_2), 137.85, 128.26, 127.62, 127.53 (Ph), 79.39 (C-8), 71.69 (*C*H$_2$Ph), 71.06 (C-7), 64.06 (C-6), 61.82 (C-8a), 61.37 (*C*H$_2$CH$_3$) 61.20 (C-3), 31.55 (C-2), 13.97 (CH$_2$*C*H$_3$) ppm. $[\alpha]_D^{24}$ = −49.6 (*c* = 1, CHCl$_3$). FAB-MS: *m*/*z* = 393 [M + H]$^+$, 415 [M + Na]$^+$, 565 [M + 2 Na + I]$^+$.

Ethyl (3*R*,6*R*,7*R*,8*S*,8a*S*)-8-Benzyloxy-6-*tert*-butoxycarbonylamino-7-hydroxy-5-oxohexahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (13): Azide **12** (90 mg, 0.23 mmol) was dissolved in pyridine/H_2O (2:1, 23 mL). H_2S was bubbled through the solution for 10 min and then the reaction mixture was stirred at room temp. for 16 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (30 mL). Boc_2O (100 mg, 0.46 mmol) and DIPEA (40 μL) were added and the solution was stirred for 16 h at room temp., before being concentrated in vacuo. The product was isolated by flash chromatography (toluene/ethyl acetate, 2:1) to yield **13** (93 mg, 0.2 mmol, 87%) (R_f = 0.4). ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.30 (m, 5 H, Ph), 7.03 (d, $^3J_{NHBoc,6}$ = 9.1 Hz, 1 H, BocNH), 5.61 (d, $^3J_{7\text{-OH},7}$ = 5.9 Hz, 7-OH), 5.10 (m, 2 H, 3, 8a), 4.69 (d, $^2J_{gem}$ = 11.7 Hz, 1 H, CH$_2$Ph), 4.56 (d, $^2J_{gem}$ = 12.0 Hz, 1 H, CH$_2$Ph), 4.10 (m, 2 H, C*H*$_2$CH$_3$), 4.05 (pt, $^3J_{6,7/NHBoc}$ = 8.2 Hz,

1 H, 6-H), 3.84 (m, 1 H, 7-H), 3.69 (m, 1 H, 8-H), 3.20 (dd, $^2J_{gem}$ = 11.4, $^3J_{2t,3}$ = 7.3 Hz, 1 H, 2-H^l), 3.10 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, 2-H^h), 1.36 (s, 9 H, CH_3 *t*Bu), 1.19 (t, $^3J_{Et}$ = 7.3 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 169.47, 166.64 (C-5, CO_2), 155.80 (CO*t*Bu), 138.01, 128.20, 127.52, 127.48 (Ph), 82.24 (C-8), 77.88 (C_q *t*Bu), 71.32 (CH_2Ph), 70.68 (C-7), 61.65 (C-8a), 61.24 (CH_2CH_3), 61.11 (C-3), 57.26 (C-6), 31.74 (C-2), 28.23 (CH_3 *t*Bu), 13.98 (CH_3CH_3) ppm. FAB-MS: *m*/*z* = 467 [M + H]$^+$, 489 [M + Na]$^+$. $C_{22}H_{30}N_2O_7S$ (466.55): calcd. C 56.63, H 6.48, N 6.00; found C 56.64, H 6.77, N 6.15.

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