Synthesis and Diversification of Pyridone Dipeptide Chromophores

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Received 18 May 2006; revised 14 June 2006

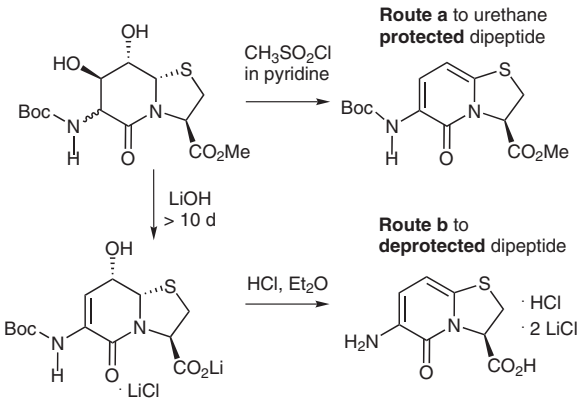
Abstract: An improved synthetic protocol transforms D-aldurono-lactone via a bicyclic dipeptide lactam **2** into pyridone dipeptides with either Boc- or Fmoc-protecting groups **5** or **6**. Regioselective bromination of **5** yields dipeptide **10** which is further diversified in Pd-catalyzed cross coupling reactions. This late diversification of a common peptide precursor makes a maximum number of rigid dipeptide chromophores accessible. The dipeptides **11**, **12**, and **13** exemplify a general strategy of accessing conformationally locked peptide chromophores as tools for chemical biology.

Key words: amino acids, fused-rings, pyridones, thiazolidine lactams, cross-coupling

Side-chain-to-backbone ring structures are incorporated in oligopeptides as local conformational constraints for the purpose of altering the bioactivity profile of the peptide.[1] In the majority of cases, the suitably protected mono- or bicyclic dipeptide building blocks are obtained from two amino acid precursors, whose side-chain functionalities are consumed for the formation of the fused ring system.[2] Decorated bicyclic dipeptide lactams demand an extra functional group on each amino acid making their synthesis more laborious.[3] Synthetic strategies which rely on common precursors are desirable but hardly developed.[4] In the example presented here, the side-chain diversification is achieved by cross-coupling reactions between a halogenated 2-pyridone and diverse boronic acids. The fused pyridone chromophore which becomes part of the peptide backbone has been efficiently accessible by the elimination of two equivalents of water from the bicyclic condensation product between an uronic acid and cysteine (Scheme 1).

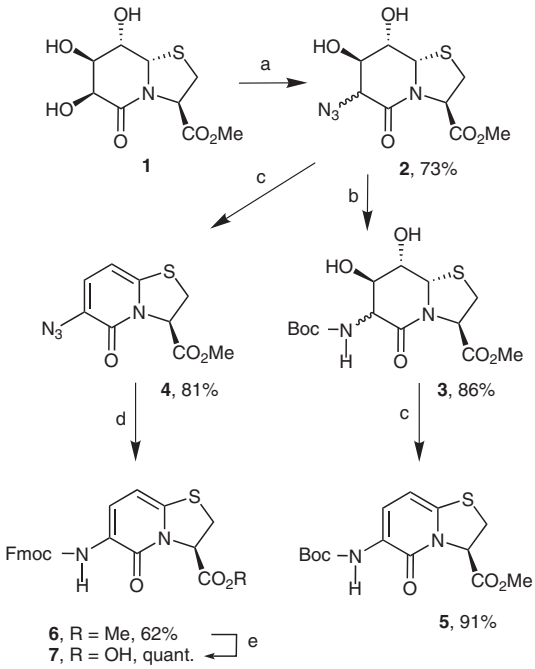
It was already shown that such a dehydration can be provoked during peptide synthesis without requiring extra synthetic transformations (route b in Scheme 1).[5] Yet, for the several-fold introduction of this bicyclic 2-pyridone into a 36mer neuropeptide (Biochemistry Leipzig, A. Beck-Sickinger) we were urged to develop a building block which is amenable for solid-phase peptide synthesis (route a in Scheme 1). The following protocol is more efficient than the original procedure and additionally allows the desired side-chain diversification. The precursor **1** (Scheme 2) is available on gram scale in a one-pot protocol from commercial D-glucuronic acid and L-cysteine methyl ester hydrochloride.

SYNTHESIS 2006, No. 19, pp 3224–3230
Advanced online publication: 02.08.2006
DOI: 10.1055/s-2006-942546; Art ID: T08106SS



Scheme 1

Regioselective activation of the α-hydroxy group,[6] followed by azide substitution (**2**, 73%) and reduction under Staudinger conditions[7] led to the Boc-protected dipeptide **3** (86%) as a mixture of diastereomers along published procedures.[8] The reduction proceeded with comparable yields using H_2 and Pd/C in methanol or H_2S in pyridine. The remaining two hydroxyls in **2** and in **3** assume *pseu-*



Scheme 2 *Reagents and conditions*: a) 1. Tf_2O, CH_2Cl_2/Py, 2. NaN_3, DMF; b) Ph_3P, THF–H_2O, Boc_2O; c) MsCl (3 equiv), Et_3N, CH_2Cl_2/Py; d) 1. H_2, Pd/C, MeOH, 2. Fmoc-ONSu, $NaHCO_3$, acetone; e) aq 6 N HCl, AcOH

do-axial orientations thereby facilitating their elimination, independently of the stereochemistry at C-6. The first elimination could be achieved under basic conditions leading to the dehydroamino acid which yielded the aromatized ring under acidic conditions. Both eliminations occurred together in a fast and clean transformation in the presence of three equivalents of mesyl chloride and triethylamine in isolated yields of 81% (**4**) and 91% (**5**), respectively. Single crystals of **5** were obtained from ethyl acetate/petroleum ether.[9] The new protocol yields the protected pyridone in a single synthetic transformation and avoids the slow first elimination step of the old protocol (route b in Scheme 1). Syrupy aromatic azide **4** cannot be stored for longer time. Immediate hydrogenation (H_2 and Pd/C) in methanol led to the corresponding amine which was subsequently protected with Fmoc-ONSu in acetone in the presence of $NaHCO_3$ (**6**, 62% yield). Recrystallization from ethanol yielded single crystals which were suitable for X-ray analysis (Figure 1).[10] The N-protected carboxylic acid **7** could be generated quantitatively by acidic ester hydrolysis of **6** in 6 N aqueous HCl/acetic acid without detectable racemization. Compound **7** is a storable solid as necessary for solid-phase peptide synthesis and it was used in several Fmoc protocols without problems.[11]

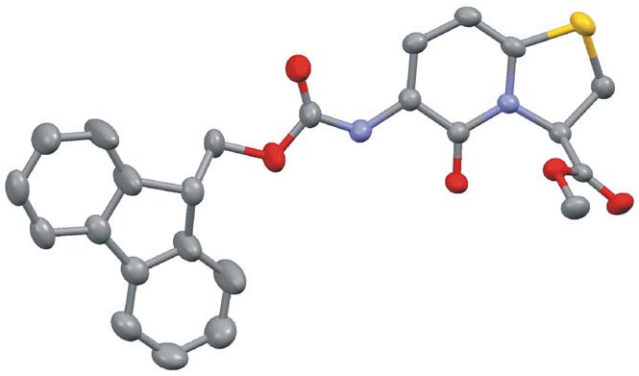


Figure 1 Crystal structure of **6**

In order to examine the handling of the building block with the Boc strategy, we assembled a cyclic peptide in solution with standard coupling and deprotection cycles using **5** as starting compound. During this synthesis the methyl esters were saponified under basic conditions (1 N LiOH/MeOH) and the Boc group was cleaved under acidic conditions with HCl/Et_2O. Acylation of the amino group which has a low basicity because of its aniline-like character was achieved with the coupling reagent (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), NMM as base and DMF as solvent in 93% yield. Cyclization was carried out with 1-hydroxy-7-azabenzotriazole (HOAT), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and 1,3,5-collidine in DMF applying the dilution method[12] (yield: 57%). C_i (**8**) and C_2-symmetric (**9**) hexapeptides were obtained (Figure 2), thus showing that the addition of base must be handled carefully to avoid epimerization of C-3. Nevertheless this is a well-known property in this substance class which should be avoided without big effort.[13]

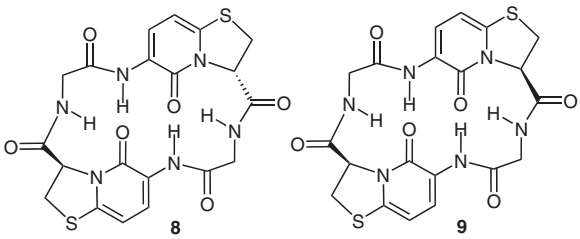
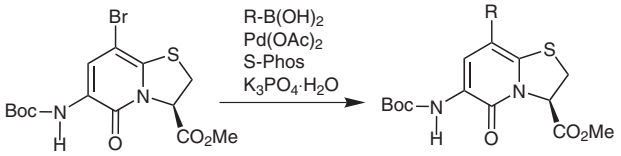


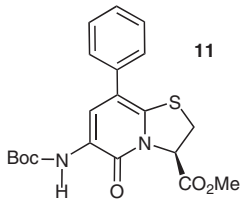
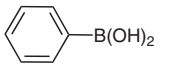
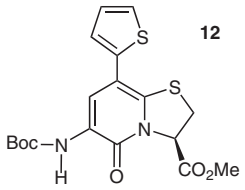
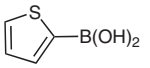
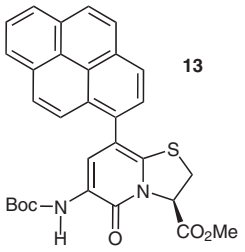
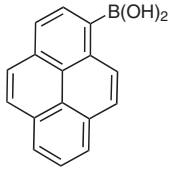
Figure 2 Hexapeptides **8** and **9**

Bromination of **5** by NBS in refluxing CCl_4 proceeded with excellent selectivity to give the substituted 2-pyridone **10** (Table 1) in 95% isolated yield. This halogenated dipeptide is a good starting material for cross-coupling reactions, opening a wide range of further derivatization possibilities at C-8 with the aim of altering the luminescence properties of the dipeptide. Introduction of an iodine substituent gave much lower yields, therefore we concentrated on the cross-coupling reactions of bromide **10**.

Phenylboronic acid was chosen in order to investigate the reactivity of **10** in Suzuki–Miyaura cross-coupling reactions. We tried several coupling conditions with different Pd species [tetrakispalladiumtriphenylphosphine, $Pd(OAc)_2$, $PdCl_2$ together with triphenylphosphine], different bases (Na_2CO_3, $NaHCO_3$, DIPEA), and different solvents (dioxane, DME, THF) without satisfactory results. Finally, the conditions published by Buchwald et al.[14] seemed adequate for bromide **10** using 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) as ligand, $Pd(OAc)_2$ as Pd source, $K_3PO_4 \cdot H_2O$ as base in THF (Table 1). Water was added in the case of thiophene-2-boronic acid to the reaction mixture to increase the solubility of the boronic acid. The required ligand was obtained according to literature procedures from 1,3-dimethoxybenzene, 2-bromochlorobenzene and dicyclohexylphosphoryl chloride.[15] The advantage of this method over the above-named is the complete conversion of the starting material **10**, formation of less by-product **5** and thus an easier work-up procedure. Thienyl-substituted 2-pyridone **12** was introduced in a 36mer peptide by solid-phase peptide synthesis[11] (Biochemistry Leipzig, M. Haack, A. Beck-Sickinger) without loss of stereochemical information after aqueous acidic cleavage of the methyl ester together with the Boc group and subsequent introduction of the Fmoc protecting group under standard conditions using Fmoc chloroformate. NMR spectra of pyrene substituted **13** recorded at 300 K showed a double signal set because of its axial chirality. Coalescence of the methyl ester ^1H NMR signals occurred between 350 and 360 K (500 MHz, $\Delta\delta$ = 20 Hz at 300 K).

Table 1 Suzuki–Miyaura Cross-Coupling of Pyridone Bromide **10**[a]



Product	Boronic acid	Conditions, yield (%)[b]
 **11**		THF, 80 °C, 4.25 h 86
 **12**		THF/H_2O, 80 °C, 5.5 h 95
 **13**		THF, 95 °C, 8.5 h 71[c]

[a] Reaction conditions: **10** (1 equiv), boronic acid (3 equiv), $K_3PO_4·H_2O$ (3 equiv), $Pd(OAc)_2$ (5 mol%) and S-Phos (10 mol%).
[b] Isolated yield.
[c] 2 equiv of boronic acid and $K_3PO_4·H_2O$ were used.

In order to diversify the chromophores of this class of 2-pyridones, the thiaproline **5** was oxidized either with an equimolar amount or with an excess of *m*-chloroperbenzoic acid. The former yielded a mixture of crystalline **14** and light pink oily **15** in a ratio of 1:2.3, which is explained with coordination of the reagent to the carbonyl oxygen of the methyl ester of **5**. The latter resulted in the corresponding sulfone **16** (Figure 3). Suitable crystals for X-ray analysis could be obtained from **14** by recrystallization from ethanol so that **14** and **15** could be identified reliably (**14**).[16] The fluorescence quantum yield of each oxidized product was five to six times higher than for **5**, probably because of the missing quenching of the S1 lone pairs. Further details are discussed elsewhere.[11]

In conclusion, an efficient protocol is presented here towards bicyclic dipeptide lactams wherein a pyridone chromophore is an integral part of the peptide backbone. This rigid pyridone dipeptide can anchor various chromophores at the peptide backbone in a predictable relative orientation. The peptides depicted in Table 1 are UV-labels with selected CD-absorption and luminescence properties. The photochemical properties of bioactive peptides

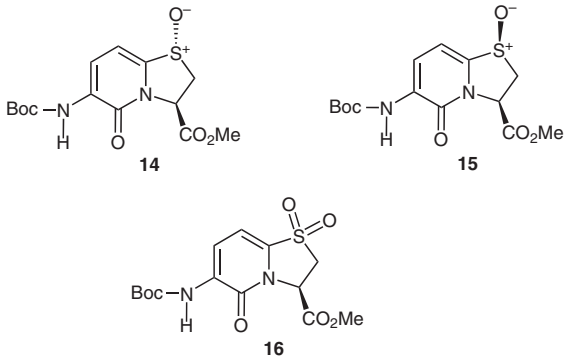


Figure 3 Compounds **14**–**16**

are under study. This new synthetic entry to highly substituted fused 2-pyridones could find applications in the fields of cytotoxic alkaloids,[17a] acetylcholine receptor ligands[17b] or other enzyme inhibitors.[17c]

Solvents were purified according to standard procedures. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm) at a pressure of 0.4 bar. TLC was performed on Merck silica gel aluminum plates, $60F_{254}$. Compounds were visualized by treatment with a solution of $(NH_4)_6Mo_7O_{24}·4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL) or ninhydrin (2 g) in MeOH (200 mL) and heating at 150 °C. All compounds were of white to yellowish color unless stated otherwise indicated. NMR spectra were recorded with Bruker Avance 400, 500 or 600 spectrometers. TMS, or the resonance of the residual solvent (DMSO-d_6: δ = 2.49), was used as internal standard. Diastereomeric groups are marked with t (low-field shift) and h (high-field shift). All ^{13}C assignments are based on inverse CH correlations (HMQC and HMBC). Mass spectra were taken on a Finnigan MAT 95 spectrometer. FT-IR spectra were recorded on a Bruker IFS 88 spectrometer. Elemental analyses were obtained with an Elementar Vario III analyzer. Melting points were measured on a Büchi 530 apparatus.

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 (2)

Compound **1** (6.43 g, 24.4 mmol) was dissolved in a mixture of anhyd CH_2Cl_2 (125 mL) and anhyd pyridine (25 mL). At a reaction temperature of –50 °C, a solution of Tf_2O (4.6 mL, 26.9 mmol) in CH_2Cl_2 (4.6 mL) was added over a period of 15 min. The mixture was allowed to warm up to r.t. over 1 h 45 min and stirred for another 45 min at r.t. After the addition of a solution of Tf_2O (0.4 mL, 2.4 mmol) in CH_2Cl_2 (0.4 mL) and keeping at r.t. for 45 min, the mixture was treated with ice (75 mL). The product was extracted with EtOAc (3 × 100 mL) and the combined organic phases were dried (Na_2SO_4). After evaporation of the solvent, the brown residue was taken up in DMF (200 mL) and NaN_3 (3.18 g, 49.7 mmol) was added. The mixture was stirred at r.t. for 18 h, concentrated under vacuum and partitioned between H_2O and EtOAc (1:2, 150 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL, 6 × 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (EtOAc–toluene, 3:1) to afford **2** (5.15 g, 73%) as a pale-brown syrup; R_f 0.43. For analytical data, see lit.[8]

Methyl (3*R*/*S*,6*R*/*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 (3)

Diastereomeric **2** (4.21 g, 14.6 mmol) and Ph_3P (5.75 g, 21.9 mmol) were dissolved in THF–H_2O (10:1, 110 mL). The solution was

stirred for 20 h at r.t. and Boc_2O (3.82 g, 21.9 mmol) was added. Stirring at r.t. was continued for 12 h, the solution was concentrated under vacuum and the product was isolated by flash column chromatography (EtOAc–toluene, 3:1) to yield 4.54 g (86%) of diastereomeric **3** as a pale-yellow solid. For analytical data, see ref.[8]

Methyl (3*R*)-6-Azido-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (4)

Compound **2** (2.6 g, 9.0 mmol) was dissolved in a mixture of anhyd CH_2Cl_2 and anhyd pyridine (1:1, 100 mL). Et_3N (3.8 mL, 27 mmol) was added and the solution was cooled to 0 °C in an ice-bath. $MeSO_2Cl$ (2.1 mL, 27 mmol) was injected via syringe under vigorous stirring over ca. 5 min. The ice-bath was removed after 20 min and the mixture was stirred at r.t. for additional 40 min. Excess reagent was quenched with ice (75 mL), and after addition of NaCl (1.5 g), the aqueous phase was extracted with CH_2Cl_2 (2 ×). The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. Purification by flash chromatography (EtOAc–toluene, 1:3) yielded **4** (1.84 g, 81%) as a brown oil; R_f 0.5; $[\alpha]_D^{24}$ –270 (c = 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.05 (d, $^3J_{7\text{-H},8\text{-H}}$ = 7.8 Hz, 1 H, 7-H), 6.31 (d, $^3J_{8\text{-H},7\text{-H}}$ = 7.8 Hz, 1 H, 8-H), 5.61 (dd, $^3J_{3\text{-H},2\text{-H}^t}$ = 9.0 Hz, $^3J_{3\text{-H},2\text{-H}^h}$ = 2.0 Hz, 1 H, 3-H), 3.94 (dd, $^2J_{2\text{-H}^t,2\text{-H}^h}$ = 12.0 Hz, $^3J_{2\text{-H}^t,3\text{-H}}$ = 9.0 Hz, 1 H, 2-H^t), 3.74 (s, 3 H, OCH_3), 3.65 (dd, $^2J_{2\text{-H}^h,2\text{-H}^t}$ = 12.0 Hz, $^3J_{2\text{-H}^h,3\text{-H}}$ = 2.0 Hz, 1 H, 2-H^h).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.1 (CO_2CH_3), 156.9 (5-CO), 143.9 (8a-C), 127.4 (7-C), 123.1 (6-C), 99.5 (8-C), 62.7 (3-C), 53.0 (OCH_3), 31.7 (2-C).

MS (EI, 70 eV): m/z = 252.0 [M]$^+$.

Methyl (3*R*)-6-[(*tert*-Butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (5)

Compound **3** (5.03 g, 13.8 mmol) was dissolved in a mixture of anhyd CH_2Cl_2 and anhyd pyridine (1:1, 60 mL). Et_3N (6.7 mL, 48.6 mmol) was added and the solution was cooled to 0 °C in an ice-bath. $MeSO_2Cl$ (3.2 mL, 41.6 mmol) was injected via syringe under vigorous stirring over ca. 5 min. The ice-bath was removed after 20 min and the mixture was stirred at r.t. for additional 20 h. Excess reagent was quenched with ice (75 mL), and after the addition of NaCl (2 g), the aqueous phase was extracted CH_2Cl_2 (2 ×). The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. Purification by flash chromatography (EtOAc–toluene, 1:1) yielded **5** (4.12 g, 91%) as an oil; R_f 0.58. Recrystallization from EtOAc–petroleum ether (bp 40–60 °C) gave colorless crystals; mp 117 °C; $[\alpha]_D^{24}$ –268 (c = 1, MeOH).

IR (KBr): 3270, 3113, 2984, 1750, 1737, 1712, 1638, 1586, 1508, 1357, 1220, 1153, 1071, 767, 725 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.74 (d, $^3J_{7\text{-H},8\text{-H}}$ = 7.7 Hz, 1 H, 7-H), 7.72 (s, 1 H, NH), 6.30 (d, $^3J_{8\text{-H},7\text{-H}}$ = 7.8 Hz, 1 H, 8-H), 5.61 (dd, $^3J_{3\text{-H},2\text{-H}^t}$ = 8.7 Hz, $^3J_{3\text{-H},2\text{-H}^h}$ = 1.9 Hz, 1 H, 3-H), 3.92 (dd, $^2J_{2\text{-H}^t,2\text{-H}^h}$ = 12.0 Hz, $^3J_{2\text{-H}^t,3\text{-H}}$ = 8.7 Hz, 1 H, 2-H^t), 3.71 (s, 3 H, OCH_3), 3.61 (dd, $^2J_{2\text{-H}^h,2\text{-H}^t}$ = 12.0 Hz, $^3J_{2\text{-H}^h,3\text{-H}}$ = 1.9 Hz, 1 H, 2-H^h), 1.44 (s, 9 H, t-C_4H_9).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.4 (CO_2CH_3), 165.3 (5-CO), 152.4 (t-BuO*C*O), 138.9 (8a-C),124.6 (6-C), 123.3 (7-C), 99.3 (8-C), 79.9 [*C*(CH_3)$_3$], 62.8 (3-C), 52.9 (OCH_3), 31.6 (2-C), 27.9 [3 C, C(*C*H_3)$_3$].

EI-MS (70 eV, positive): m/z = 326.2 [M]$^+$.

Anal. Calcd for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.58; S, 9.82. Found: C, 51.61; H, 5.39; N, 8.42; S, 9.37.

Methyl (3*R*)-6-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (6)

Compound **5** (1.42 g, 5.6 mmol) was dissolved in MeOH (80 mL). Pd/C (0.15 g) was added and the suspension was stirred for 20 h under a H_2 atmosphere (1 atm). The mixture was filtered through a pad of Kieselguhr and the solvent was evaporated. ^{1}H NMR of the crude product confirmed the quantitative reduction of **4**. The formed amine (260 mg, 1.15 mmol) was dissolved in acetone (40 mL) followed by the addition of Fmoc-*N*-oxysuccinimide (590 mg, 1.73 mmol) and $NaHCO_3$ (96 mg, 1.15 mmol). The mixture was stirred at r.t. for 5 d. Aq 1 N HCl was added until pH 5, acetone was evaporated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated. Flash chromatography (EtOAc–toluene, 1:1, R_f 0.59) yielded **6** as a yellowish oil. Recrystallization from EtOH gave 320 mg (62%) of colorless crystals; mp 158 °C; $[\alpha]_D^{24}$ –204.6 (c = 1, MeOH).

IR (KBr): 3377, 3038, 2961, 1734, 1650, 1599, 1506, 1448, 1356, 1301 1202, 1078, 758, 737 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.63 (br, 1 H, NH), 7.89 (m, 2 H, Fmoc-H$_{arom}$), 7.78 (m, 2 H, Fmoc-H$_{arom}$), 7.67 (br, 1 H, 7-H), 7.41 (m, 2 H, Fmoc-H$_{arom}$), 7.33 (m, 2 H, Fmoc-H$_{arom}$), 6.27 (d, $^3J_{8\text{-H},7\text{-H}}$ = 7.3 Hz, 1 H, 8-H), 5.60 (dd, $^3J_{3\text{-H},2\text{-H}^t}$ = 8.9 Hz, $^3J_{3\text{-H},2\text{-H}^h}$ = 2.0 Hz, 1 H, 3-H), 4.37 (d, $^3J_{\text{Fmoc-H}^{sec},\ \text{Fmoc-H}^{tert}}$ = 6.9 Hz, 2 H, Fmoc-H$_{sec}$), 4.27 (t, $^3J_{\text{Fmoc-H}^{tert},\ \text{Fmoc-H}^{sec}}$ = 7.0 Hz, 1 H, Fmoc-H$_{tert}$), 3.92 (dd, $^2J_{2\text{-H}^t,2\text{-H}^h}$ = 11.9 Hz, $^3J_{2\text{-H}^t,3\text{-H}}$ = 8.9 Hz, 1 H, 2-H^t), 3.72 (s, 3 H, OCH_3), 3.62 (dd, $^2J_{2\text{-H}^h,\ 2\text{-H}^t}$ = 11.9 Hz, $^3J_{2\text{-H}^h,\ 3\text{-H}}$ = 2.1 Hz, 1 H, 2-H^h).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.4 (CO_2CH_3), 156.5 (5-CO), 153.5 (Fmoc-CO), 143.6, 140.7 (4 C, fluorenyl-C^{quat}), 140.0 (8a-C), 127.7 (2 C, fluorenyl), 127.1 (2 C, fluorenyl), 125.4 (fluorenyl), 125.3 (fluorenyl), 125.3 (7-C), 124.3 (6-C), 120.1 (2 C, fluorenyl), 99.0 (8-C), 66.3 (Fmoc-C^{sec}), 62.8 (3-C), 52.9 (OCH_3), 46.4 (Fmoc-C^{tert}), 31.6 (2-C).

CI-MS (positive): m/z = 449.0 [M + H]$^+$.

Anal. Calcd for $C_{24}H_{20}N_2O_5S$: C, 64.27; H, 4.49; N, 6.25. Found: C, 63.53; H, 4.45; N, 6.17.

(3*R*)-6-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxyic Acid (7)

Compound **6** (572 mg, 1.28 mmol) was dissolved in AcOH (120 mL) and aq 6 N HCl (75 mL). The solution was stirred for 7 d at r.t. and was heated 5 times for 6 h to 50 °C. The solvent was evaporated and the residue was co-evaporated 3 times with aq 1 N HCl. ^{1}H NMR showed quantitative cleavage of the methyl ester; mp 235 °C (dec.); $[\alpha]_D^{24}$ –141 (c = 1, MeOH).

IR (KBr): 3331, 2950, 2605, 1722, 1632, 1576, 1509 1205, 1185, 1073, 756 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.24 (br s, 1 H), 7.89 (m, 2 H, Fmoc-H$_{arom}$), 7.75 (m, 2 H, Fmoc-H$_{arom}$), 7.6 (br s, 1 H), 7.41 (m, 2 H, Fmoc-H$_{arom}$), 7.33 (m, 2 H, Fmoc-H$_{arom}$), 6.10 (br s, 1 H, 8-H), 5.15 (d, $^3J_{3,2\text{-H}^t}$ = 8.2 Hz, 1 H, 3-H), 4.41 (br s, 2 H, Fmoc-CH$_2$), 4.28 (pt, $^3J_{\text{Fmoc-CH, Fmoc-CH2}}$ = 6.9 Hz, 2 H, Fmoc-CH), 3.71 (dd, $^3J_{2\text{-H}^t,3}$ = 8.2 Hz, $^2J_{2\text{-Hgem}}$ = 11.0 Hz, 1 H, 2-H^t), 3.63 (d, $^2J_{2\text{-Hgem}}$ = 11.0 Hz, 1 H, 2-H^h).

^{13}C NMR (HMQC, DMSO-d_6): δ = 127.4, 126.8, 124.9, 119.8 (Fmoc-CH$_{arom}$), 97.7 (C-8), 66.0 (Fmoc-CH$_2$), 65.7 (C-3), 46.4 (Fmoc-CH), 33.3 (C-2).

MS (ESI): m/z = 433.0 [M – H]$^-$, 867.4 [2 M – H]$^-$.

Cyclic Hexapeptides 8 and 9

The linear deprotected hexapeptide H_2N-gly-(thiazolopyridone)-gly-(thiazolopyridone)-CO_2H·2LiCl hydrochloride (80 mg, 0.154

mmol) was dissolved in DMF (800 mL) and treated with HOAT (32 mg, 0.23 mmol), HATU (88 mg, 0.23 mmol), 1,3,5-collidine (0.2 mL, 188 mg, 1.5 mmol) and stirred for 4 days at r.t. Evaporation of the solvent and purification of the crude product by flash column chromatography ($CHCl_3$–MeOH, 5:1, R_f 0.45) yielded a mixture of **8** and **9** (44 mg, 57%). The mixture could be separated by preparative HPLC. The $[\alpha]_D$ values could not be specified exactly because of the very bad solubility of both products in all of the tested solvents. Nevertheless the measured values could be taken qualitatively to identify **8** as a *meso* compound and **9** as the expected chiral product.

MS (ES, positive, product mixture): *m*/*z* = 503.2 $[M + H]^+$, 509.0 $[M + Li]^+$, 520.2 $[M + NH_4]^+$.

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IR (KBr): 3371, 3268, 1679, 1635, 1585, 1522, 1235, 764 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.22 (dd, $^3J_{Gly\text{-}NH,Gly\text{-}H^t}$ = 7.7 Hz, $^3J_{Gly\text{-}NH,Gly\text{-}H^h}$ = 5.0Hz, 2 H, Gly-NH), 8.89 (s, 2 H, Bic-NH), 7.95 (d, $^3J_{7\text{-}H,8\text{-}H}$ = 8.0 Hz, 2 H, 7-H), 6.33 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 8.0 Hz, 2 H, 8-H), 5.19 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.8 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 7.7 Hz, 2 H, 3-H), 4.18 (dd, $^2J_{Gly\text{-}H^t,Gly\text{-}H^h}$ = 16.6 Hz, $^3J_{Gly\text{-}H^t,Gly\text{-}NH}$ = 7.7 Hz, 2 H, Gly-H^t), 3.84 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 11.5 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 9.0 Hz, 2 H, 2-H^t), 3.62 (dd, $^2J_{Gly\text{-}H^h,Gly\text{-}H^t}$ = 16.5 Hz, $^3J_{Gly\text{-}H^h,Gly\text{-}NH}$ = 4.7 Hz, 2 H, Gly-H^h), 3.45 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 11.5 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 7.7 Hz, 2 H, 2-H^h).

^{13}C NMR (HMQC, DMSO-d_6): δ = 127.5 (7-C), 98.7 (8-C), 65.7 (3-C), 43.7 (Gly-C), 30.7 (2-C).

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IR (KBr): 3459, 3339, 3288, 1639, 1589, 1513, 1237, 769 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.17 (pt, ^3J = 5.9 Hz, 2 H, Gly-NH), 8.94 (s, 2 H, Bic-NH), 8.23 (d, $^3J_{7\text{-}H,8\text{-}H}$ = 8.0 Hz, 2 H, 7-H), 6.27 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 8.0 Hz, 2 H, 8-H), 5.35 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.8 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 5.9 Hz, 2 H, 3-H), 3.95 (dd, $^2J_{Gly\text{-}H^t,Gly\text{-}H^h}$ = 17.3 Hz, $^3J_{Gly\text{-}H^t,Gly\text{-}NH}$ = 6.6 Hz, 2 H, Gly-H^t), 3.86 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 11.5 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.9 Hz, 2 H, 2-H^t), 3.79 (dd, $^2J_{Gly\text{-}H^h,Gly\text{-}H^t}$ = 17.3 Hz, $^3J_{Gly\text{-}H^h,Gly\text{-}NH}$ = 5.5 Hz, 2 H, Gly-H^h), 3.45 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 11.5 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 6.0 Hz, 2 H, 2-H^h).

^{13}C NMR (HMQC, DMSO-d_6): δ = 124.4 (7-C), 98.7 (8-C), 64.9 (3-C), 43.7 (Gly-C), 30.7 (2-C).

Methyl (3*R*)-8-Bromo-6-[(*tert*-butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (10)

Compound **5** (1.30 g, 3.99 mmol) was dissolved in CCl_4 and NBS (781 mg, 4.39 mmol) was added. The mixture was refluxed for 8 h, the solvent evaporated and the product purified by flash column chromatography (EtOAc–toluene, 2:3, R_f 0.52); yield: 1.533 g (95%); colorless solid; mp 171 °C (dec.); $[\alpha]_D^{24}$ –262.6 (*c* = 1, MeOH).

IR (KBr): 3412, 3348, 2978, 1755, 1730, 1647, 1586, 1490, 1365, 1221, 1149, 1091, 762 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.0 (s, 1 H, NH), 7.87 (s, 1 H, 7-H), 5.76 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.9 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 2.0 Hz, 1 H, 3-H), 3.97 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 12.0 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.9 Hz, 1 H, 2-H^t), 3.72 (s, 3 H, OCH_3), 3.67 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 12.0 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 2.0 Hz, 1 H, 2-H^h), 1.44 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.0 (CO_2CH_3), 155.1 (5-CO), 152.2 (*t*-BuO*C*O), 139.0 (8a-C), 125.8 (6-C), 124.7 (7-C), 90.3 (8-C), 80.3 [$C(CH_3)_3$], 64.5 (3-C), 53.0 (OCH_3), 31.4 (2-C), 27.8 [3 C, $C(CH_3)_3$].

MS (PI-DCI): *m*/*z* = 405.0 $[M_1 + H]^+$, 407.0 $[M_2 + H]^+$.

Anal. Calcd for $C_{14}H_{17}BrN_2O_5S$: C, 41.49; H, 4.23; N, 6.91. Found: C, 41.46; H, 4.23; N, 6.95.

Methyl (3*R*)-8-Phenyl-6-[(*tert*-butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (11)

Compound **10** (200 mg, 0.494 mmol), phenylboronic acid (180 mg, 1.48 mmol), $K_3PO_4 \cdot H_2O$ (340, mg, 1.48 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and S-Phos (21 mg, 0.051 mmol) were filled into a dry 5 mL flask under argon. The flask was evacuated and backfilled with argon three times before anhyd THF (2 mL) was added. The flask was sealed, and the mixture was heated to 80 °C for 4.25 h. H_2O (10 mL) was added, the aqueous phase extracted with EtOAc (2 ×) and the combined organic phases dried (Na_2SO_4). The solvent was evaporated and flash chromatography [toluene–EtOAc (4:1); R_f 0.22 (8:1)] yielded 170 mg (86%) of **11** as a colorless solid; mp 169 °C; $[\alpha]_D^{22}$ –40 (*c* = 1, $CHCl_3$).

IR (KBr): 3409, 2977, 1751, 1723, 1649, 1599, 1505, 1487, 1402, 1368, 1227, 1151, 1088, 165, 701 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.94 (s,1 H, 7-H), 7.88 (s, 1 H, NH), 7.50–7.33 (m, 5 H, C_6H_5), 5.71 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.9 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 1.9 Hz, 1 H, 3-H), 3.87 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 11.9 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.8 Hz, 1 H, 2-H^t), 3.74 (s, 3 H, OCH_3), 3.62 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 11.9 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 1.8 Hz, 1 H, 2-H^h), 1.44 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.3 (CO_2CH_3), 155.6 (5-CO), 152.4 (*t*-BuOCO), 137.5 (C_{arom}), 136.7 (8a-C), 128.9, 127.5, 127.3 (CH_{arom}), 125.5 (6-C), 124.1 (7-C), 113.1 (8-C), 80.1 [$C(CH_3)_3$], 63.1 (3-C), 53.0 (OCH_3), 31.2 (2-C), 27.9 [3 C, $C(CH_3)_3$].

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}N_2O_5S$ + Na: 425.1142; found: 425.1145.

Methyl (3*R*)-8-(2-Thienyl)-6-[(*tert*-butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (12)

Compound **10** (400 mg, 0.988 mmol), thiophene-2-boronic acid (379 mg, 2.96 mmol), $K_3PO_4 \cdot H_2O$ (680 mg, 2.96 mmol), $Pd(OAc)_2$ (11.8 mg, 0.05 mmol) and S-Phos (44.5 mg, 0.099 mmol) were filled into a Schlenk tube under argon. Degassed THF (3 mL) and H_2O (1 mL) were added. The tube was sealed and the mixture was heated to 80 °C for 4 h. H_2O (10 mL) was added, the aqueous phase extracted with EtOAc (2 ×) and the combined organic phases were dried (Na_2SO_4). The crude mixture was purified by flash chromatography [toluene–EtOAc (4:1), R_f 0.18 (8:1)] to afford 383 mg (95%) of **12** as a colorless solid; mp 182 °C; $[\alpha]_D^{20}$ –227 (*c* = 1, $CHCl_3$).

IR (KBr): 3407, 3116, 2976, 1754, 1725, 1642, 1603, 1490, 1439, 1368, 1219, 1152, 1087, 695 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.06 (s,1 H, 7-H), 7.92 (s, 1 H, NH), 7.58 (dd, $^3J_{thienyl\text{-}5\text{-}H,thienyl\text{-}4\text{-}H}$ = 5.1 Hz, $^3J_{thienyl\text{-}5\text{-}H,thienyl\text{-}3\text{-}H}$ = 1.2 Hz, 1 H, thienyl-5-H), 7.18 (dd, $^3J_{thienyl\text{-}3\text{-}H,thienyl\text{-}4\text{-}H}$ = 3.6 Hz, $^3J_{thienyl\text{-}3\text{-}H,thienyl\text{-}5\text{-}H}$ = 1.2 Hz, 1 H, thienyl-3-H), 7.15 (dd, $^3J_{thienyl\text{-}4\text{-}H,thienyl\text{-}5\text{-}H}$ = 5.1 Hz, $^3J_{thienyl\text{-}4\text{-}H,thienyl\text{-}3\text{-}H}$ = 3.6 Hz, 1 H, thienyl-4-H), 5.73 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.9 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 1.8 Hz, 1 H, 3-H), 3.94 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 11.9 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.9 Hz, 1 H, 2-H^t), 3.75 (s, 3 H, OCH_3), 3.69 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 11.9 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 1.8 Hz, 1 H, 2-H^h), 1.47 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.3 (CO_2CH_3), 155.4 (5-CO), 152.4 (*t*-BuOCO), 139.1 (thienyl-C^{quat}), 136.5 (8a-C), 127.9 (thienyl-4-C), 125.38, 125.45 (6-C, thienyl-5-C), 124.8 (thienyl-3-C), 123.0 (7-C), 107.0 (8-C), 80.2 [$C(CH_3)_3$], 63.1 (3-C), 53.0 (OCH_3), 31.5 (2-C), 27.9 [3 C, $C(CH_3)_3$].

MS (ESI): *m*/*z* = 409.0 $[M + H]^+$, 431.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}N_2O_5S_2$ + Na: 431.0706; found: 431.0701.

Methyl (3*R*)-8-(1-Pyrenyl)-6-[(*tert*-butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (13)

Compound **10** (300 mg, 0.74 mmol), pyrene-1-boronic acid (364 mg, 1.48 mmol), $K_3PO_4 \cdot H_2O$ (340 mg, 1.48 mmol), $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) and S-Phos (30.4 mg, 0.074 mmol) were filled into a dry Schlenk tube under argon. The tube was evacuated and backfilled with argon before anhyd THF (1.5 mL) was added. The tube was sealed, and the mixture was heated to 85 °C for 3.5 h and another 5 h at 100 °C. H_2O was added and the aqueous phase was extracted with EtOAc (4 ×). The combined organic phases were dried (Na_2SO_4) and the crude mixture was purified by flash chromatography [toluene–EtOAc (4:1); R_f 0.27 (8:1)] to give 278 mg (71%) of **13** as a colorless solid; mp 236 °C; $[\alpha]_D^{24}$ –201 (*c* = 1, $CDCl_3$).

IR (KBr): 3264, 2976, 1746, 1716, 1635, 1587, 1496, 1438, 1397, 1366, 1218, 1151, 1080, 852 cm^{-1}.

^1H NMR (500 MHz, 370 K, DMSO-d_6): δ = 8.38–7.65 (m, 10 H), 5.79 (m, 1 H, 3-H), 3.94 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 11.9 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.6 Hz, 1 H, 2-H^t), 3.84 (s, 3 H, OCH_3), 3.58 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 11.9 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 2.3 Hz, 1 H, 2-H^h), 1.45 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, 298 K, $CDCl_3$, double signal set): δ = 168.4 (CO_2CH_3), 156.7 (5-CO), 152.8 (*t*-BuO*C*O), 136.7 (8a-C), 133–124.5 (28 signals), 114.4 (8-C), 81 [$C(CH_3)_3$], 64.0, 63.9 (3-C), 53.6 (OCH_3), 32.2, 32.2 (2-C), 28.4 [3 C, $C(CH_3)_3$].

MS (ESI): *m*/*z* = 549.2 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}N_2O_5S$ + Na: 549.1455; found: 549.1457.

(1*R*,3*R*)-Methyl 6-*tert*-Butoxycarbonylamino-1,5-dioxo-2,3-dihydro-5*H*-1,3-thiazolo[3,2-*a*]pyridine-3-carboxylate (14) and (1*S*,3*R*)-Methyl 6-*tert*-Butoxycarbonylamino-1,5-dioxo-2,3-dihydro-5*H*-1,3-thiazolo[3,2-*a*]pyridine-3-carboxylate (15)

Compound **5** (1.33 g, 4.07 mmol) was dissolved in EtOAc (50 mL). The solution was cooled in an ice-bath and MCPBA (70%, 1 g, 4.07 mmol) was added. The cooling bath was removed after 3 h and the solution was extracted with aq 1 N $NaHCO_3$ and with H_2O (2 ×). The combined aqueous phases were extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. Flash chromatography (EtOAc–toluene, 3:1) yielded 447 mg (32%) of crystalline **14** and 968 mg (69%) of pale-pink syrup **15**.

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Mp 198 °C (dec.); $[\alpha]_D^{24}$ –243 (*c* = 1, MeOH).

IR (KBr): 3325, 3107, 2979, 1758, 1722, 1648, 1598, 1506, 1366, 1340, 1248, 1219, 1148, 1058, 960, 776, 688 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.20 (s, 1 H, NH), 8.03 (d, $^3J_{7\text{-}H,8\text{-}H}$ = 7.7 Hz, 1 H, 7-H), 7.1 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 7.7 Hz, 1 H, 8-H), 5.61 (dd, $^3J_{3\text{-}H,2\text{-}H^t}$ = 6.3 Hz, $^3J_{3\text{-}H,2\text{-}H^h}$ = 7.4 Hz, 1 H, 3-H), 3.89 (dd, $^3J_{2\text{-}H^t,3\text{-}H}$ = 6.3 Hz, $^3J_{2\text{-}H^t,2\text{-}H^h}$ = 13.6 Hz, 1 H, 2^t-H), 3.72 (dd, $^3J_{2\text{-}H^h,3\text{-}H}$ = 7.4 Hz, $^3J_{2\text{-}H^h,2\text{-}H^t}$ = 13.6 Hz, 1 H, 2^h-H), 3.71 (s, 3 H, OCH_3), 1.46 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.3 (CO_2CH_3), 154.6, 152.0 (5-CO, *t*-BuO*C*O), 142.4 (8a-C), 131.8 (6-C), 119.9 (7-C), 107.9 (8-C), 80.8 [$C(CH_3)_3$], 61.2 (3-C), 53.0 (OCH_3), 52.4 (2-C), 27.8 [3 C, $C(CH_3)_3$].

MS (ESI): *m*/*z* = 343.1 $[M + H]^+$, 365.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}N_2O_6S$ + Na: 365.0778; found: 365.0779.

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$[\alpha]_D^{24}$ –196 (*c* = 1, MeOH).

IR (KBr): 3384, 2955, 2929, 1728, 1650, 1607, 1505, 1368, 1217, 1155, 1052, 957, 771 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.18 (s, 1 H, NH), 8.00 (d, $^3J_{7\text{-}H,8\text{-}H}$ = 7.6 Hz, 1 H, 7-H), 7.16 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 7.6 Hz, 1 H, 8-H), 5.83 (dd, $^3J_{3\text{-}H,2\text{-}H^h}$ = 1.2 Hz, $^3J_{3\text{-}H,2\text{-}H^t}$ = 8.7 Hz, 1 H, 3-H), 3.75 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 14.4 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 8.7 Hz, 1 H, 2-H^t), 3.68 (s, 3 H, OCH_3), 3.62 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 14.4 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 1.2 Hz, 1 H, 2-H^h), 1.47 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.9 (CO_2CH_3), 154.5, 152.0 (5-CO, *t*-BuO*C*O), 141.7 (8a-C), 132.2 (6-C), 119.1 (7-C), 108.2 (8-C), 80.8 [$C(CH_3)_3$], 61.3 (3-C), 52.8, 52.3 (OCH_3, 2-C), 27.8 [$C(CH_3)_3$].

MS (ESI): *m*/*z* = 365.0 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}N_2O_6S$ + Na: 365.0778; found: 365.0782.

Methyl (3*R*)-6-[(*tert*-Butoxycarbonyl)amino]-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate 1,1-Dioxide (16)

To a solution of **5** (320 mg, 0.99 mmol) in EtOAc (20 mL) was added MCPBA (70%, 970 mg, 3.95 mmol). The solution was stirred at r.t. for 18 h and neutralized with Et_3N while the color changed from red to blue. The solvent was evaporated and after flash chromatography [EtOAc–toluene (3:2), R_f 0.56] to give 349 mg (98%) of **16** as a pale-pink solid; mp 106 °C; $[\alpha]_D^{24}$ –219.1 (*c* = 1, MeOH).

^1H NMR (600 MHz, DMSO-d_6): δ = 8.36 (s, 1 H, NH), 8.04 (d, $^3J_{7\text{-}H,8\text{-}H}$ = 7.7 Hz, 1 H, 7-H), 7.05 (d, $^3J_{8\text{-}H,7\text{-}H}$ = 7.7 Hz, 1 H, 8-H), 5.67 (dd, $^3J_{3\text{-}H,2\text{-}H^h}$ = 9.4 Hz, $^3J_{3\text{-}H,2\text{-}H^t}$ = 1.7 Hz, 1 H, 3-H), 4.26 (dd, $^2J_{2\text{-}H^t,2\text{-}H^h}$ = 13.9 Hz, $^3J_{2\text{-}H^t,3\text{-}H}$ = 1.7 Hz, 1 H, 2-H^t), 4.13 (dd, $^2J_{2\text{-}H^h,2\text{-}H^t}$ = 13.9 Hz, $^3J_{2\text{-}H^h,3\text{-}H}$ = 9.4 Hz, 1 H, 2-H^h), 3.73 (s, 3 H, OCH_3), 1.46 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.7 (CO_2CH_3), 153.9, 152.1 (5-CO, *t*-BuO*C*O), 133.6 (8a-C), 133.0 (6-C), 119.3 (7-C), 101.9 (8-C), 80.9 [$C(CH_3)_3$], 45.2 (3-C), 53.3 (OCH_3), 50.5 (2-C), 27.8 [3 C, $C(CH_3)_3$]; mp 106 °C; $[\alpha]_D^{24}$ –219.1 (*c* = 1, MeOH).

EI-MS (70 eV, positive): *m*/*z* = 358.0 $[M]^+$.

Anal. Calcd for $C_{14}H_{18}N_2O_7S$: C, 46.92; H, 5.06; N, 7.82; S, 8.95. Found: C, 46.81; H, 4.93; N, 7.44; S, 8.06.

Acknowledgment

The authors thank Dr. M. Zabel (Fachbereich Chemie, Universität Regensburg) for crystal structure analysis of compounds **5** and **6**. This work was supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*.

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