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Stereoselective sulfoxide formation from a thioproline derivative†

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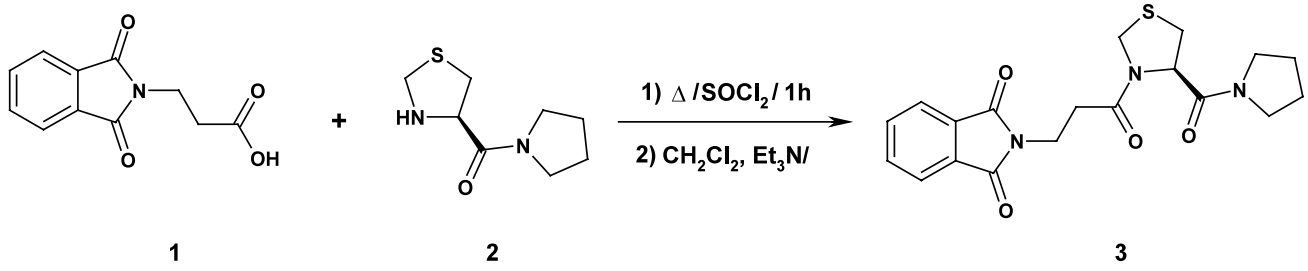
Abstract—Oxidation of the PEP inhibitor, thioprolylpyrrolidine derivative **3** affords a mixture of the two possible *trans*- and *cis*-sulfoxide isomers **4** and **5**. 3-Chloroperbenzoic acid oxidation resulted almost exclusive formation of the *trans*-isomer (α-sulfoxide, **4**, d.e. >99% in $CHCl_3$), whereas when $NaIO_4$ was used the *cis* isomer (β-sulfoxide, **5**) was also obtained, the ratio of the isomers varying with the reaction conditions applied. The structures of the separated isomers **4** and **5** were assigned on the basis of the aromatic solvent-induced shifts (ASIS) in the NMR spectra.

1. Introduction

Prolyl-oligopeptidase (PEP; EC 3.4.21.26) seems to play an important role[1,2] in the degradation of neuropeptides capable of changing the performance in learning and memory tasks in both animals and humans. Its inhibitors are therefore promising drug candidates for the treatment and prevention of diseases[3,4] with associated memory loss, such as Alzheimer's disease and senile dementia.

A potent class of PEP inhibitors contains a prolylpyrrolidine moiety,[3,5] which is thought to be crucial for enzyme recognition.[6] Several structural changes have been made in the prolylpyrrolidine moiety, e.g. replacement of one of the pyrrolidine methylene groups with a sulfur atom[7–9] or sulfoxide group[10] in order to increase the biological activity and/or water solubility.[11]

Whereas the stereoselective chemical oxidation of sulfur centers to afford sulfoxides has been widely investigated[12–15] (the stereoselectivity rarely exceeds 95% e.e.), that of thioproline is not explored. The oxidation of *Z*-thioprolylpyrrolidine has recently been reported[10] using 3-chloroperbenzoic acid (MCPBA), but no structural characterization of the product was described. In our PEP inhibitor project[16] we have developed a highly stereoselective oxidation of the model compound, 2-{3-oxo-3-[(4*R*)-4-(1-pyrrolidinylcarbonyl)-1,3-thiazolidin-3-yl]propyl}-1*H*-isoindole-1,3-(2*H*)-dione **3** and elucidated the structures of the diastereomeric *S*-oxides **4** and **5** formed in the reaction.



1 **2** **3**

Scheme 1. Synthesis of thioprolylpyrrolidine **3**.

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† Dedicated to Professor András Messmer on the occasion of his 80th birthday.

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2. Results and discussion

2.1. Chemistry

(1,3-Dioxo-1*H*-isoindole-2-yl)propionic acid **1** was prepared according to the literature method[17] starting from 1*H*-isoindole-1,3-dione and 3-aminopropionic acid. Reaction of propionyl chloride, formed from **1** with $SOCl_2$ and (4*R*)-4-(1-pyrrolidinylcarbonyl)-1,3-thiazolidine hydrochloride salt[18] in the presence of NEt_3 in CH_2Cl_2 gave the desired thioprolylpyrrolidine **3** in good yield (Scheme 1). When **3** was oxidized with $NaIO_4$ in aqueous MeOH, the corresponding sulfoxide isomers **4** and **5** were obtained respectively with moderate diastereoselectivity, which varied slightly with temperature (see Table 1). The diastereomeric sulfoxides **4** and **5** were separated by means of column chromatography. The diastereoselectivity increased when MCPBA was used as the oxidant in MeOH. Excellent diastereoselectivity was achieved in $CHCl_3$ with MCPBA for sulfoxide **4**. In this case the diastereoselectivity seemed to be little dependent on the temperature. The ratio of the isomers **4** and **5** were determined from the crude reaction mixtures by use of an RP-HPLC method (see Section 4).

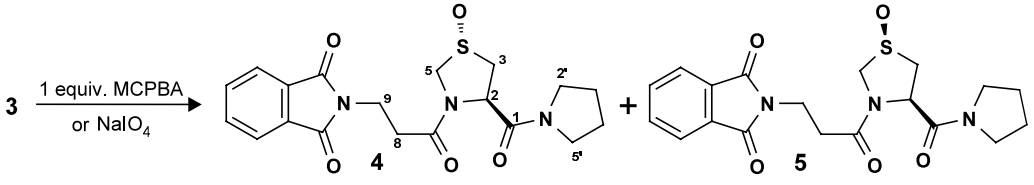
2.2. Structure elucidation

The RP-HPLC study of the products demonstrated that the two isomers (a major one and a minor one) were obtained in different ratios. Four sets of signals were observed in the ^1H and ^{13}C NMR spectra of the products, since both isomers exhibit hindered rotation around the thioproline amide bond resulting in separate signals for the *trans* and *cis* amide rotamers (see Scheme 2). The sulfoxide isomers **4** and **5** were separated by column chromatography in order to simplify their structural assignment by NMR. Their structures could be identified via the aromatic solvent-induced shifts (ASIS),[19] where solvation by benzene results in a chemical shift decrease. The ASIS values are calculated by subtracting the measured chemical shifts in C_6D_6 from the values determined in $CDCl_3$. Lower ASIS values are therefore expected for hydrogens on the side of the thioproline on which the oxygen atom is situated than for the hydrogens on the opposite side, because during solvation the benzene molecules avoid the negatively charged oxygen atom of the sulfoxide moiety.

The assignments of the ^1H NMR signals of the two isomers **4** and **5** were supported by 2D NOESY measurements. The assignment of the *trans* amide rotamers **4t** and **5t** was based on the NOE interaction between the C(5)–H_2 and C(8)–H_2 methylene protons, which proved that the *trans* amide rotamer is the predominant form in $CDCl_3$ and C_6D_6 solutions. The NOESY exchange peaks helped to identify the signals of the corresponding *cis* amide rotamers **4c** and **5c**. The assignments of the hydrogens of the diastereotopic C(5)–H_2 and C(3)–H_2 methylene groups were based on their NOESY cross-peak intensity ratios in the knowledge of the α-steric position of 2-H. The full assignment was performed in $CDCl_3$ and also in C_6D_6. The chemical shifts in $CDCl_3$ together with the ASIS values are listed in Table 2.

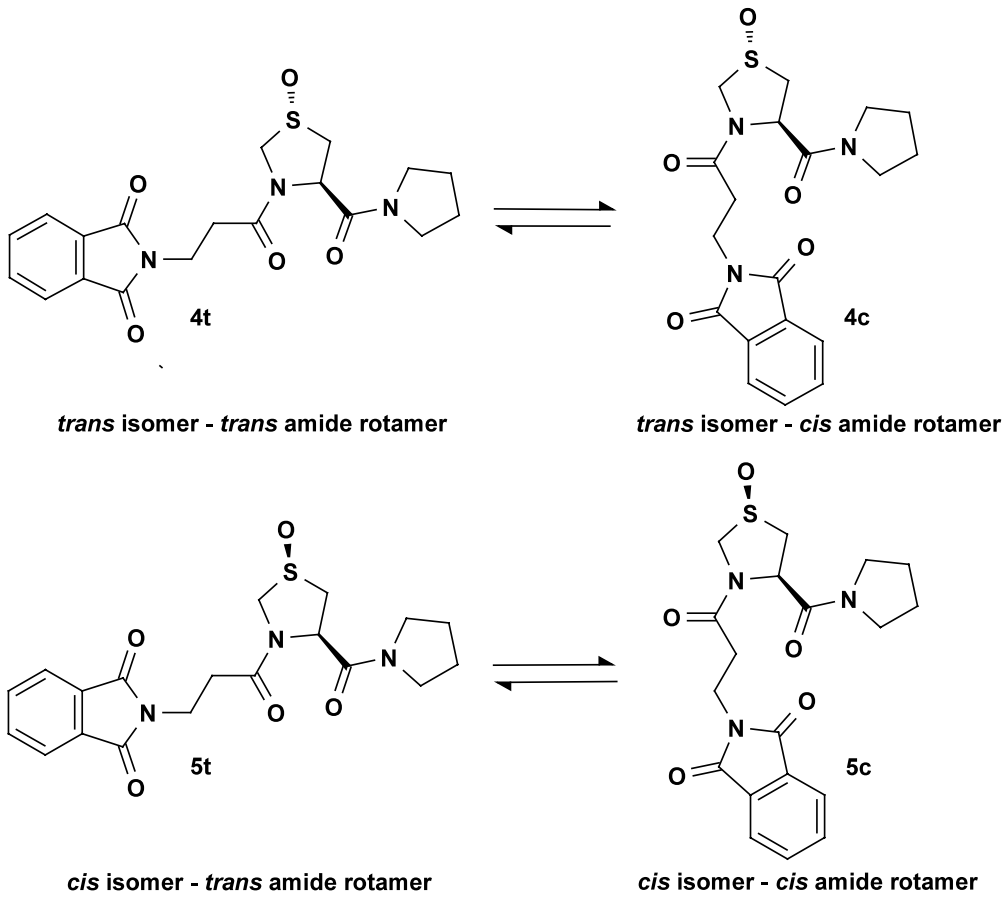
The ASIS data on both *trans*- and *cis*-amide rotamers of the minor isomer **5** unambiguously prove that the configuration of the sulfoxide bond is β because the induced shifts of the β-protons are smaller than those of the α-hydrogen; the minor isomer has therefore the *cis* structure **5**. We observed intense NOE cross-peaks between 2-H and 2′-H_2 methylene protons in the NOESY spectra of both **4t** and **5t** amide rotamers. As thoroughly analyzed earlier in the case of a prolylpyrrolidine derivative[20] this interaction indicates that the N–C(1)–C(2)–N torsion angle in the predominant conformation is about 115°. This in turn means that the amide group connected to C(1) also points in the β-direction. The benzene molecules therefore prefer to solvate the α-side of the thiazolidinyl ring **5** so as to avoid interaction with the negatively charged oxygens of the sulfoxide and amide moieties.

Table 1. Oxidation of the thioprolylpyrrolidine **3** to the α/β-sulfoxide isomers **4** and **5**



Oxidant	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)	D.e.[a] (%)	α-Sulfoxide **4**	β-Sulfoxide **5**
$NaIO_4$	Aq. MeOH	0	8	54	79.0	89.5	10.5
		25	8	77	73.4[b]	89.7	10.3
		50	8	80	71.0	85.5	14.5
MCPBA	$CHCl_3$	0	7	65	99.6	99.8	0.2
		25	7	68	99.6[b]	99.8	0.2
		50	7	72	96.6	99.3	0.7
	MeOH	25	7	80	92.7	96.4	3.6

[a] Diastereomeric excess determined by HPLC analysis.
[b] The ^1H NMR spectra of the crude reaction mixtures indicated a similar isomer ratio.



Scheme 2. Amide rotamers of **4** and **5** isomers.

Table 2. The ^{1}H NMR chemical shifts in $CDCl_3$ and the ASIS values[a] of the thioprolyl ring of the **4** and **5** isomers (ppm)

Isomer	Rotamer		H-2α	H-3α	H-3β	H-5α	H-5β
trans	*trans*	**4t**	5.63 (0.20)	3.26 (0.66)	3.19 (0.59)	4.86 (0.68)	4.47 (0.68)
α-sulfoxide	*cis*	**4c**	5.30 (0.28)	3.56 (0.73)	2.97 (0.91)	5.52 (0.10)	4.19 (0.54)
cis	*trans*	**5t**	5.10 (0.41)	3.77 (0.71)	3.02 (0.29)	5.18 (0.64)	4.47 (0.20)
β-sulfoxide	*cis*	**5c**	4.90 (0.40)	3.79 (0.70)	3.15 (0.25)	5.60 (0.24)	4.30 (0.03)

[a] The ASIS values are given in brackets.

The ASIS values for the *cis* amide rotamer of isomer **4** support the α-steric position of the sulfoxide oxygen, while no significant differences were measured for the *trans* amide rotamer between the ASIS data on the α- and β-hydrogens. We explain this phenomena by the competitive effect of the sulfoxide oxygen and the amide oxygen connected to C(1) during solvation, since the former points to the α-, and the later one to the β-direction. Similarly larger differences were observed in the ASIS values of the *cis* isomer as for the *trans* form during the NMR study of *N*-acetyl-4-methoxycarbonyl-1,3-thiazolidine-1-oxide,[21] where the isomeric structure was unambiguously elucidated by X-ray crystallographic analysis.[22]

2.3. Discussion of the origin of the stereoselectivity

The origin of the observed diastereoselectivity might be given if the participation of the sterically encumbered C(1) carboxamide moiety is assumed. First, its position adjacent to the reaction center allows the oxidant to approach from the less hindered α-face of the substrate **3** resulting in a higher amount of α-sulfoxide **4**. Furthermore, the negatively charged oxygen atom in the amide moiety might unfavorably interact with the aromatic part of a reagent such as MCPBA analogously with the effect observed in C_6D_6 during the ASIS measurement. Consequently, higher diastereomeric excesses were obtained for **4** with MCPBA than with $NaIO_4$.

3. Conclusion

In conclusion, the oxidation of thioprolylpyrrolidine derivative **3** to the corresponding sulfoxides **4** and **5** proceeded with excellent diastereoselectivity when MCPBA was applied for the oxidation of thioproline

moiety. The biological activities of these oxygenated derivatives will be reported elsewhere.

4. Experimental

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, $\delta=0$ (TMS), in DMSO-d_6, $CDCl_3$ and C_6D_6 solvents). Chemical shifts are expressed in ppm, J values are given in Hz. All 2D NOESY NMR spectra were recorded in $CDCl_3$ and C_6D_6 solvents using the standard Bruker pulse sequences.

The reversed phase HPLC tests were carried out on a Waters instrument controlled by Millennium[32] software. The samples were dissolved in acetonitrile ($c=1$ mg/mL) then filtered through a 0.45 μm membrane filter, and 10 μL of this solution was injected onto the column by using a Waters 717 autosampler. Reversed phase chromatographic conditions were as follows: stationary phase: Inertsil ODS2, 5 μm, 250×4.0 mm; gradient elution with a mixture of acetonitrile and 25 mM NaH_2PO_4 solution (pH 3.0 with cc. H_3PO_4). Linear gradient: acetonitrile content from 5 to 65% during 50 min. Flow rate: 1 mL/min. Detection wavelength: 207 nm. The *trans* isomer **4** eluted at 27.8 min, while the *cis* isomer **5** eluted at 28.5 min.

4.1. (1,3-Dioxo-1,3-dihydroisoindole-2-yl)propionic acid 1

(1,3-Dioxo-1,3-dihydroisoindole-2-yl)propionic acid **1** was prepared according to the literary procedure,[17] starting from 1*H*-isoindole-1,3-dione and 3-aminopropionic acid in 87–91% yield, mp: 149–151°C.

4.2. 2-{3-oxo-3-[(4*R*)-4-(1-Pyrrolidinylcarbonyl)-1,3-thiazolidine-3-yl]propyl}-1*H*-iso-indole-1,3(2*H*)-dione 3

A mixture of (1,3-dioxo-1,3-dihydroisoindole-2-yl)-propionic acid **1** (2.36 g, 10.77 mmol) and $SOCl_2$ (10 mL) was heated under reflux for 1 h. The excess $SOCl_2$ was removed by distillation under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and added to a solution of (4*R*)-4-(1-pyrrolidinylcarbonyl)-1,3-thiazolidine HCl salt[18] (2.40 g, 10.77 mmol) in CH_2Cl_2 (30 mL) and Et_3N (2.73 g, 3.74 mL, 26.9 mmol) at −5°C. The resulting solution was stirred at room temperature for 3 h and washed with 30% aqueous citric acid, water, saturated aqueous $NaHCO_3$ and brine, consecutively. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The resulting solid was crystallized from $CHCl_3$/*n*-hexane to give the product **3** (3.13 g, 74%); mp: 172–174°C); $[\alpha]_D^{20}=-91.4$ ($c=1$, EtOH). ^{1}H NMR (DMSO-d_6) δ (ppm) *trans* amide rotamer **3t**: 1.7–2.0 (m, 4H, H-3′a,b, H-4′a,b), 2.72, 2.88 (ddd, $J=16.5$, 9.2, 6.2 Hz, 1H; ddd, $J=16.5$, 9.2, 6.2 Hz, 1H, H-8a,b), 2.97 (dd, $J=11.6$, 5.6 Hz, 1H, H-3β), 3.2–3.7 (m, 5H, H-3α, H-2′a,b, H-5′a,b), 3.76 (m, 2H, H-9a,b), 4.47 (d, $J=8.8$, Hz, 1H, H-5β), 4.77 (d, $J=8.8$ Hz, 1H, H-5α), 4.93 (dd, $J=7.6$, 5.6 Hz, 1H, H-2α), 7.8–8.0 (m, 4H, aromatic hydrogens); ^{1}H NMR (DMSO-d_6) δ (ppm) *cis* amide rotamer **3c**: 1.7–2.0 (m, 4H, H-3′a,b, H-4′a,b), 2.40, 2.65 (ddd, $J=16.0$, 9.2, 7.0 Hz, 1H; ddd, $J=16.0$, 8.7, 5.7 Hz, 1H, H-8a,b), 3.13 (dd, $J=11.6$, 3.8 Hz, 1H, H-3β), 3.2–3.7 (m, 5H, H-3α, H-2′a,b, H-5′a,b), 3.76 (m, 2H, H-9a,b), 4.33 (d, $J=9.6$, Hz, 1H, H-5β), 4.76 (d, $J=9.6$ Hz, 1H, H-5α), 5.07 (dd, $J=7.4$, 3.8 Hz, 1H, H-2α), 7.8–8.0 (m, 4H, aromatic hydrogens). The ratio of amide rotamers **3t** and **3c** in DMSO-d_6: 68:32 (in C_6D_6: 92:8). Anal. calcd for $C_{19}H_{21}N_3SO_4$: C, 58.90; H, 5.47; N, 10.85. Found: C, 58.79; H, 5.10; N, 10.92%.

4.3. 2-{3-[(1*R*,4*R*)-1-Oxido-4-(1-pyrrolidinylcarbonyl)-1,3-thiazolidine-3-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione 4

To a stirred solution of compound **3** (0.97 g, 2.5 mmol) in chloroform (10 mL) was slowly added MCPBA (0.72 g, 2.5 mmol). After stirring at 25°C for 7 h, aqueous $NaHCO_3$ was added to the reaction mixture. The aqueous layer was extracted with $CHCl_3$ (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The yellow foam residue was purified by column of silica gel with $CHCl_3$–MeOH 40:1 as eluent. The α-sulfoxide isomer **4** was obtained. Compound **4** α-sulfoxide (0.64 g, 63%; a white powder; mp: 74–75°C); $[\alpha]_D^{20}=-84.5$ ($c=1$, EtOH). ^{1}H NMR ($CDCl_3$) δ (ppm) α-sulfoxide *trans* amide rotamer **4t**: 1.8–2.2 (m, 4H, H-3′a,b, H-4′a,b), 2.81 (ddd, $J=15.5$, 9.3, 6.1 Hz, 1H, H-8a), 2.92 (ddd, $J=15.5$, 9.3, 6.1 Hz, 1H, H-8b), 3.19 (dd, $J=13.8$, 7.5 Hz, 1H, H-3β), 3.26 (ddd, $J=13.8$, 7.5, 2.1 Hz, 1H, H-3α), 3.3–3.6 (m, 4H, H-2′a,b, H-5′a,b), 4.04 (m, 2H, H-9ab), 4.47 (d, $J=12.0$ Hz, 1H, H-5β), 4.86 (dd, $J=12.0$, 2.1 Hz, 1H, H-5α), 5.63 (t, $J=7.5$ Hz, 1H, H-2α), 7.6–7.9 (m, 4H, aromatic hydrogens); ^{1}H NMR ($CDCl_3$) δ (ppm) α-sulfoxide *cis* amide rotamer **4c**: 1.8–2.2 (m, 4H, H-3′a,b, H-4′a,b), 2.7 (m, 1H, H-8a), 2.9 (m, 1H, H-8b), 2.97 (dd, $J=\sim13$, 8.2 Hz, 1H, H-3β), 3.56 (ddd, $J=\sim13$, 8.2, 2.7 Hz, 1H, H-3α), 3.3–3.6 (m, 4H, H-2′a,b, H-5′a,b), 3.9–4.2 (m, 2H, H-9a,b), 4.19 (d, $J=13.0$ Hz, 1H, H-5β), 5.52 (dd, $J=13.0$, 2.7 Hz, 1H, H-5α), 5.30 (t, $J=8.2$ Hz, 1H, H-2α), 7.6–7.9 (m, 4H, aromatic hydrogens), the ratio of **4t** and **4c**: 94:6; ^{1}H NMR (C_6D_6) δ (ppm) α-sulfoxide *trans* amide rotamer **4t**: 1.0–1.5 (m, 4H, H-3′a,b, H-4′a,b), 2.41 (ddd, $J=15.2$, 9.2, 6.0 Hz, 1H, H-8a), 2.59 (ddd, $J=15.2$, 9.2, 6.0 Hz, 1H, H-8b), 2.60 (m, 2H, H-3α,β), 2.68 (dt, $J=10.2$, 7.3 Hz, 1H, H-5′b), 3.12 (dt, $J=12.1$, 6.7 Hz, 1H, H-2′b), 3.32 (dt, $J=12.1$, 6.7 Hz, 1H, H-2′a), 3.68 (dt, $J=10.2$, 7.3 Hz, 1H, H-5′a), 3.79 (d, $J=12.1$ Hz, 1H, H-5β), 3.88 (ddd, $J=14.8$, 8.9, 6.0 Hz, 1H, H-9a), 4.04 (ddd, $J=14.8$, 8.9, 6.0 Hz, 1H, H-9b), 4.18 (dd, $J=12.1$, 1.6 Hz, 1H, H-5α), 5.43 (t, $J=7.5$ Hz, 1H, H-2α), 6.7–6.9, 7.3–7.5 (m, 4H, aromatic hydrogens); ^{1}H NMR (C_6D_6) δ (ppm) α-sulfoxide *cis* amide rotamer **4c**: 1.0–1.5 (m, 4H, H-3′a,b, H-4′a,b), 2.06 (m, 1H, H-3β), 2.83 (m, 1H, H-3α), 3.01 (m, 1H, H-5′a), 3.50 (m, 1H, H-2′a), 3.65 (m, 1H, H-5β), 5.02 (m, 1H, H-2α), 5.42 (m, 1H, H-5α), 6.6–6.9, 7.3–7.7 (m, 4H, aromatic hydrogens), the ratio of **4t** and **4c**: 96:4. Anal. calcd for $C_{19}H_{21}N_3SO_5$: C, 56.56; H, 5.25; N, 10.42; S, 7.93. Found: C, 56.43; H, 5.23; N, 10.38; S, 7.88%.

4.4. 2-{3-[(1*S*,4*R*)-1-Oxido-4-(1-pyrrolidinylcarbonyl)-1,3-thiazolidine-3-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione 5

To a stirred solution of compound **3** (2.55 g, 6.58 mmol) in MeOH (15 mL) and H_2O (5 mL) at 50°C was added a solution of $NaIO_4$ (1.54 g, 7.24 mmol) and the resulting mixture was stirred at the same temperature for 8 h. The white precipitate formed was filtered off. MeOH was removed and the remaining aqueous solution was extracted with $CHCl_3$ (5×10 mL). The combined organic phases were dried over $MgSO_4$. The organic solvent was removed in vacuo and the residue was purified by column of silica gel with $CHCl_3$–MeOH 40:1 as eluent to afford the α-sulfoxide **4** (1.68 g; 63%) and β-sulfoxide **5** (0.12 g; 5%) isomers: compound **5** β-sulfoxide (0.12 g, 5%; white powder; mp: 104–105°C). Anal. calcd for $C_{19}H_{21}N_3SO_5$: C, 56.56; H, 5.25; N, 10.42; S, 7.93. Found: C, 56.38; H, 5.21; N, 10.34; S, 7.88%. ^{1}H NMR ($CDCl_3$) δ (ppm) β-sulfoxide *trans* amide rotamer **5t**: 1.8–2.2 (m, 4H, H-3′a,b, H-4′a,b), 2.75–2.86 (m, 2H, H-8a,b), 3.02 (dd, J=12.5, 7.1 Hz, 1H, H-3β), 3.40 (ddd, J=13.8, 9.4, 7.9 Hz, 1H, H-5′b), 3.45 (dt, J=12.3, 7.0, 7.0 Hz, 1H, H-2′b), 3.56 (dt, J=12.3, 7.0, 7.0 Hz, 1H, H-2′a), 3.77 (dd, J=12.5, 8.4 Hz, 1H, H-3α), 3.81 (ddd, J=13.8, 9.4, 7.0 Hz, 1H, H-5′a), 4.01 (t, J=7.5 Hz, 2H, H-9a,b), 4.47 (d, J=10.2 Hz, 1H, H-5β), 5.10 (dd, J=8.4, 7.1 Hz, 1H, H-2α), 5.18 (d, J=10.2 Hz, 1H, H-5α), 7.6–8.0 (m, 4H, aromatic hydrogens); ^{1}H NMR ($CDCl_3$) δ (ppm) β-sulfoxide *cis* amide rotamer **5c**: 1.8–2.2 (m, 4H, H-3′a,b, H-4′a,b), 2.70 (m, 2H, H-8a,b), 3.15 (dd, J=13.8, 7.5 Hz, 1H, H-3β), 3.79 (m, 1H, H-3α), 4.30 (d, J=10.9 Hz, 1H, H-5β), 4.90 (m, 1H, H-2α), 5.60 (d, J=10.9 Hz, 1H, H-5α), 7.6–8.0 (m, 4H, aromatic hydrogens), the ratio of **5t** and **5c**: 87:13; ^{1}H NMR (C_6D_6) δ (ppm) β-sulfoxide *trans* amide rotamer **5t**: 1.1–1.4 (m, 4H, H-3′a,b, H-4′a,b), 2.3–2.5 (m, 2H, H-8a,b), 2.65 (ddd, J=14.0, 9.2, 7.1 Hz, 1H, H-5′b), 2.73 (dd, J=12.4, 6.9 Hz, 1H, H-3β), 3.06 (dd, J=12.4, 8.5 Hz, 1H, H-3α), 3.16 (dt, J=11.9, 7.9, 7.9 Hz, 1H, H-2′b), 3.30 (ddd, J=14.0, 10.1, 7.2 Hz, 1H, H-5′a), 3.33 (dt, J=11.9, 7.0, 7.0 Hz, 1H, H-5′b), 3.75–4.0 (ddd, J=14.2, 8.4, 6.6 Hz, ddd, J=14.2, 8.6, 5.9 Hz, 2H, H-9a,b), 4.27 (d, J=10.3 Hz, 1H, H-5β), 4.54 (d, J=10.3 Hz, 1H, H-5α), 4.69 (dd, J=8.5, 6.9 Hz, 1H, H-2α), 6.90–6.97, 7.42–7.51 (m, 4H, aromatic hydrogens); ^{1}H NMR (C_6D_6) δ (ppm) β-sulfoxide *cis* amide rotamer **5c**: 1.1–1.4 (m, 4H, H-3′a,b, H-4′a,b), 2.60 (m, 2H, H-8a,b), 2.90 (dd, J=12.8, ~7 Hz, 1H, H-3β), 3.09 (m, 1H, H-3α), 4.27 (m, 1H, H-5β), 4.50 (t, J= ~7 Hz, 1H, H-2α), 5.36 (d, J=11.4, Hz, 1H, H-5α), 6.90–6.97, 7.42–7.51 (m, 4H, aromatic hydrogens), the ratio of **5t** and **5c**: 93:7.

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