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Lanthionine Peptides by *S*-Alkylation with Substituted Cyclic Sulfamidates Promoted by Activated Molecular Sieves: Effects of the Sulfamidate Structure on the Yield

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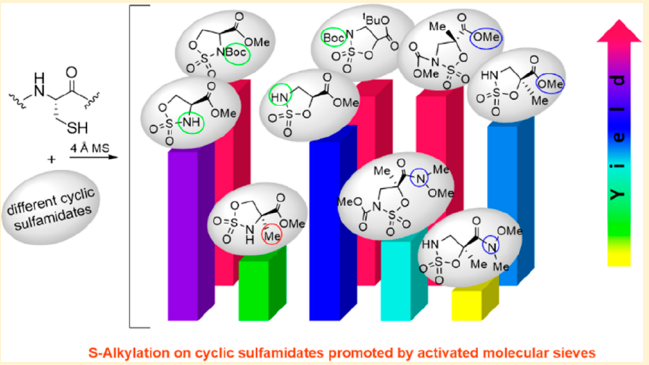
Supporting Information

ABSTRACT: A green and efficient method for preparing lanthionine peptides by a highly chemoselective and stereochemically controlled procedure is presented. It involves an *S*-alkylation reaction, promoted by activated molecular sieves, on chiral cyclic sulfamidates, both *N*-protected and unprotected. Of note, the reaction yield was high also for cyclic sulfamidates bearing a free amine group, while other strategies failed to achieve a ring-opening nucleophilic reaction with *N*-unprotected substrates. To prove the feasibility of the procedure, the synthesis of a thioether ring B mimetic of the natural lantibiotic haloduracin β was performed.



Lantibiotics are peptide molecules characterized by sulfur-containing rings, which are generated during the ribosomal biosynthesis through a 1,4-conjugate addition of cysteine to dehydroalanine or dehydrobutyrine to form the bis-α-amino acid lanthionine or methyllanthionine, respectively.[1−5] They are classified as potent bacteriocins, as they kill bacteria through multiple mechanisms, including inhibition of the synthesis of the cell wall and aggregation with Lipid II to create pores into the cell membrane.[6−9] It is worth noting that bacteria do not easily develop resistance to lantibiotics.

The size and complexity of multicyclic lantibiotics make the biochemical and chemical synthesis of their analogues very difficult. In fact, the focus in this research field is on the rational design of lanthipeptides having enhanced properties together with a reasonable synthetic accessibility.[10−12] In this regard, we have previously reported a novel strategy for synthesizing lanthionine-containing peptides, consisting of an efficient and stereoselective ring-opening nucleophilic reaction performed via *S*-alkylation on cyclic sulfamidates derived from serine. The reaction was promoted by activated molecular sieves (MS) that were a guarantee of mild conditions and did not require any further catalyst. The expected lanthionine-containing products were obtained in good yields and excellent chemoselectivities. Moreover, the very common β-elimination side reaction on the serine sulfamidate, occurring even under slightly basic conditions, was completely prevented.[13]

In this paper, we report about the reactivity of structurally different cyclic sulfamidates derived from α- and β-amino acids under the reaction conditions described above, as it is known that their reactivity strongly depends on their substitution pattern.[14] In particular, we performed the *S*-alkylation by cyclic sulfamidates derived from L-serine, (*S*)-α-methylserine, (*S*)-isoserine, or (*R*)-α-methylisoserine, including their *N*-unprotected/protected versions (Boc-Sulfaser-OMe,[15] H-Sulfaser-OMe,[16] H-SulfaMeSer-OMe, Boc-SulfaIsoser-O^{t}Bu,[17] H-SulfaIsoser-OMe, MeO$_2$C-SulfaMeIsoser-CO$_2$Me and MeO$_2$C-SulfaMeIsoser-N(OMe)Me,[18] H-SulfaMeIsoser-OMe,[19] H-SulfaMeIsoser-N(OMe)Me,[20] Cbz-SulfaIsoser-O^{t}Bu).

The S-alkylation substrate was a cysteine residue already inserted in a peptide sequence. The reaction was promoted by activated molecular sieves (MS), which might assist the sulphydryl proton removal, as previously described.[21−29] Peptide **1** (AcGlyTrpCysHisValAlaNH$_2$) was employed as a model peptide to assess whether the structure of the sulfamidate could affect the chemoselectivity of the reaction. It contains potential nucleophilic groups (tryptophan and histidine ring nitrogens) that may compete with S-alkylation.[13] The reaction was performed under argon atmosphere with 1.2 equiv of sulfamidate reagent, in DMF as the solvent, and in the

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J. Org. Chem. XXXX, XXX, XXX−XXX

presence of 4 Å molecular sieves activated by treatment at 280 °C for 12 h under vacuum. The reaction mixture was kept under stirring overnight at room temperature. Afterward, molecular sieves were removed by centrifugation and the obtained crude product was purified by reversed-phase chromatography. The yield of each product is reported in Table 1, as estimated by the HPLC peak area of the alkylated peptide compared to that of the starting peptide and other byproducts, if any.

Table 1. Yield of the *S*-Alkylation Reaction To Convert Cysteine into Lanthionine

Entry	Peptide	Yield (%)	Time (h)
1a	AcGlyTrp**Lan**HisValAlaNH$_2$	95	12
1b	AcGlyTrp**Lan**^{1}HisValAlaNH$_2$	85	12
1c	AcGlyTrp**Lan**^{2}HisValAlaNH$_2$	<40	12
1d	AcGlyTrp**Lan**^{3}HisValAlaNH$_2$	95	12
1e	AcGlyTrp**Lan**^{4}HisValAlaNH$_2$	90	12
1f	AcGlyTrp**Lan**^{5}HisValAlaNH$_2$	95	12
1g	AcGlyTrp**Lan**^{6}HisValAlaNH$_2$	40	12
1h	AcGlyTrp**Lan**^{7}HisValAlaNH$_2$	80	12
1i	AcGlyTrp**Lan**^{8}HisValAlaNH$_2$	0	12
2l	ValAlaLeu**Lan**^{9}ProNH$_2$ (S–S)	75	12

To confirm that the alkylated product corresponded to the expected lanthipeptide, a detailed structural characterization of compounds **1a**−**1h** was carried out by 2D-NMR. First, full resonance assignment was achieved by means of the sequence-specific method based on the iterative analysis of 2D-TOCSY and 2D-ROESY NMR spectra.[30] Then, the pattern of intralanthionine short distances was assessed by further analysis of rotating frame nuclear Overhauser effect (ROE) peaks.[31] For instance, unambiguous ROE contacts between lanthionine $H_\alpha/H_{\delta1}$, $H_\varepsilon/H_{\beta2}$, and H_α/H_ε were taken as an evidence of lanthionine formation after reaction of peptide **1** with the proper sulfamidate in compound **1b** (Figure 1). The most relevant intralanthionine ROE contacts found for each of the compounds considered is summarized in Table 2.

Scheme 1 depicts the *S*-alkylation of peptide **1** by L-serine-derived sulfamidates, either *N*-protected or unprotected. The yields of peptide **1a**[13] and peptide **1b** were compared to assess the role of *N*-protecting group in the sulfa-serine derivative. Notably, using this new ring-opening reaction promoted by activated molecular sieves, the activation of the sulfamidate group through *N*-functionalization is not critical, as also described by Halcomb et al.[32] for the ring-opening of related analogues with 1-thiocarbohydrates in slightly basic water solution.[18,19] The yields of compounds **1a** and **1b** are comparable and quite high. It is worth noting that, upon the slightly acidic treatment performed during the purification step, the product **1a** is recovered in the totally desulfated form, as usually observed for a lanthipeptide obtained from Boc-SulfaSer-OMe.[13] On the other hand, the sulfate group in product **1b** was retained in higher percentage. This can be attributed to the lack of an electron-withdrawing substituent on the nitrogen such as the *tert*-butoxycarbonyl group, which might inhibit the hydrolysis of the sulfamate group that occurs with an accumulation of negative charge on the nitrogen. This is in line with the observations by Halcomb et al.[32]

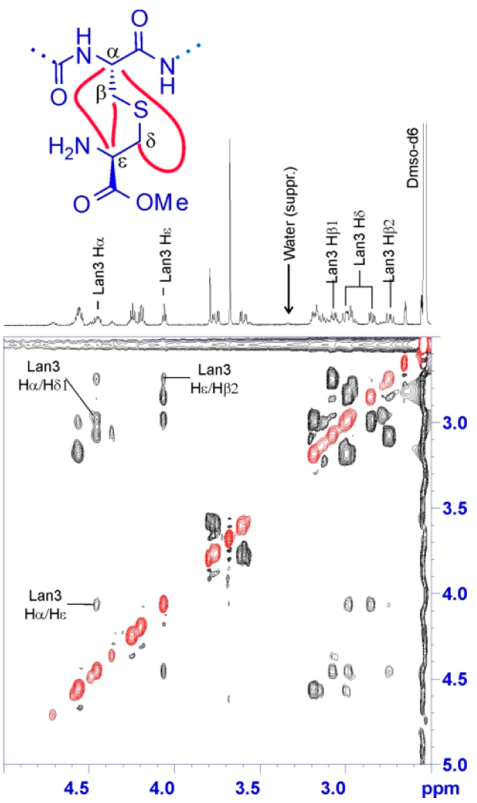

Figure 1. Expansion of the 2D-ROESY NMR spectrum of compound **1b** with assignment of the relevant intralanthionine cross peak. The corresponding short distances are sketched as red lines on the structure shown on the right.

Table 2. Short Interproton Distances within the Lanthionine Side Chain Detected by 2D-ROESY Spectroscopy[a]

compd	ROESY contact
1b	$H_\alpha/H_{\delta1}$; $H_\varepsilon/H_{\beta2}$; H_α/H_ε
1c	$H_\alpha/H_{\delta2}$; H_δ/H_β
1d	$H_\delta/H_{\beta1}$; $H_\delta/H_{\beta2}$; H(O^{t}Bu)/H_α; H(O^{t}Bu)/$H_{\beta1}$; H(O^{t}Bu)/$H_{\beta2}$
1e	H_α/H_δ; $H_\delta/H_{\beta2}$
1f	$H_{\varepsilon2}/H_{\beta1}$; $H_{\varepsilon1}/H_{\beta1}$
1g	$H_{\beta2}/H_{\varepsilon1}$; $H_{\beta2}/H_{\varepsilon2}$; δMe/$H_{\beta2}$; δMe/$H_{\beta3}$
1h	δMe/H_β; H_β/H_ε

[a]See the Supporting Information for atom nomenclature and 2D-NMR spectra.

The *S*-alkylationon peptide **1** was also performed by using a cyclic sulfamidate derived from (*S*)-*α*-methylserine (Scheme 2). The obtained yield revealed a reduced reactivity of the substrate, likely due to the steric hindrance exerted by the *α*-methyl group. The final product **1c**, mainly obtained in the sulfated form as expected, was treated with a 50% solution of TFA in water after the purification step to promote the hydrolysis of the sulfate ester.

Recently, we have designed a versatile synthetic methodology based on the ring-opening of cyclic sulfamidates derived from isoserine via oxygen, nitrogen, or sulfur nucleophilic attack. This procedure was shown to proceed with the total inversion of the configuration at the electrophilic carbon,

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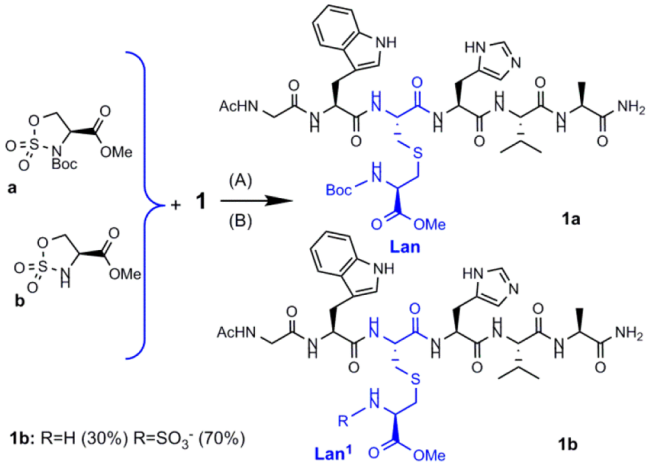
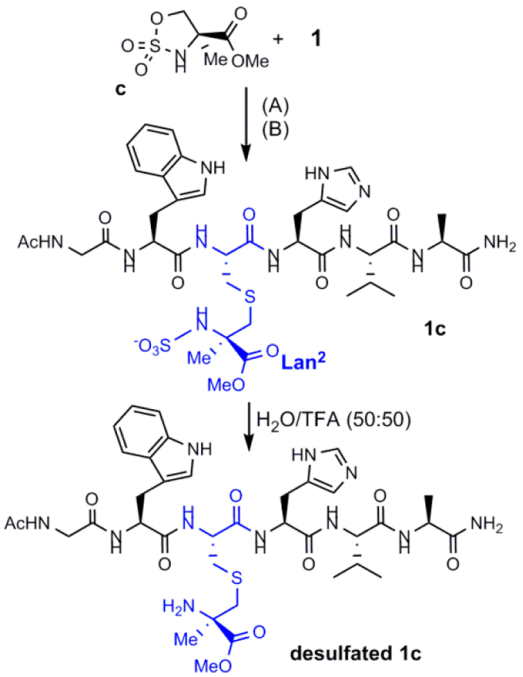
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. *S*-Alkylation of Peptide 1 Performed with Boc-Sulfaser-OMe (a) or H-Sulfaser-OMe (b)[a]



[a]Conditions: (A) 4 Å MS, DMF, rt, 12 h; (B) HPLC purification 0.1% TFA in water.

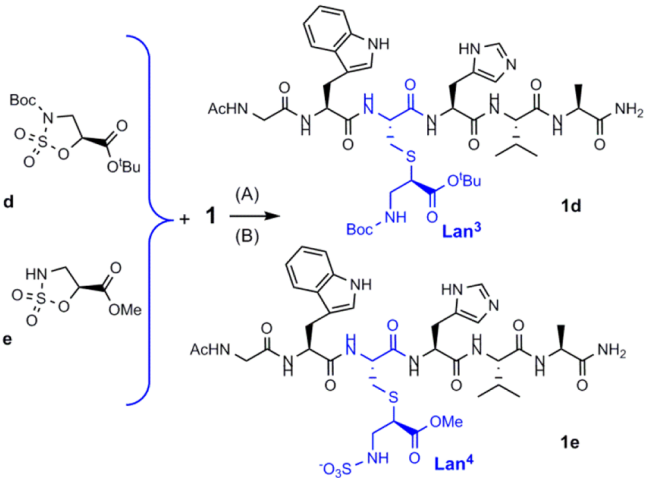
Scheme 2. *S*-Alkylation of Peptide 1 Performed with H-SulfaMeSer-OMe (c)[a]



[a]Conditions: (A) 4 Å MS, DMF, rt, 12 h; (B) HPLC purification 0.1% TFA in water.

preserving the enantiomeric excess of the starting material.[17] This methodology was demonstrated mostly on (*S*)-*N*-Boc isoserine-sulfamidate **d** and used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base to activate the *S*-nucleophiles. Being encouraged by the mild synthetic strategy based on activated molecular sieves for *S*-alkylation with cyclic serine-sulfamidates,[13] we tested such a route to access lanthipeptides incorporating lanthionine mimics featuring isoserine (norlanthionine). With this aim, we analyzed the reactivity of *N*-protected and unprotected (*S*)-isoserine-sulfamidate derivatives **d** and **e**, respectively, with peptide **1** (Scheme 3). The lanthionine-containing peptides **1d** and **1e** were both obtained

Scheme 3. *S*-Alkylation of Peptide 1 Performed with Boc-SulfaIsoser-O^{t}Bu (d) or H-SulfaIsoser-OMe (e)[a]



[a]Conditions: (A) 4 Å MS, DMF, rt, 12 h; (B) HPLC purification 0.1% TFA in water.

in high yields, despite the absence of the *N*-protecting group for peptide **1e**. This result is in agreement with what was found for the serine-sulfamidate derivatives **a** and **b** (Scheme 1). In both cases, the nucleophilic attack occurred with complete inversion of configuration at the reacting center, and competitive elimination or deprotection reactions were not observed. This feature can be due not only to the specific architecture of this unnatural amino acid but also to the mild reaction conditions of the employed *S*-alkylation methodology.

Following this line to obtain new lanthipeptide analogues, we challenged the problem of S-alkylation with (*R*)-α-methylisoserine-sulfamidates that incorporate a quaternary electrophilic center on the cyclic sulfamidate. In this regard, derivatives **f** and **g** (N-protected, ester or amide derivatives) and **h** and **i** (N-unprotected, ester or amide derivatives) were considered. These ring-opening reactions give access to new lanthipeptides incorporating lanthionine mimics based on α-methylisoserine (α-methylnorlanthionine).[17] The yields of the final lanthipeptides were found to be strongly dependent on the type of protecting group on the sulfamidate carboxylic function. Compounds **1f** and **1h**, both having methyl ester protection on the sulfamidate carboxyl function, gave high and comparable yields. On the other hand, as previously described,[18,19,33] compounds **1g** and **1i** having amide protection on the carboxyl function gave low or undetectable yields, respectively. Of note, in all cases the nucleophilic attack occurred with complete inversion of configuration at the quaternary reacting center, and again competitive elimination or deprotection reactions were not observed in any case.

The results obtained in terms of final lanthipeptide yields are as follows. The protection of the sulfamidate carboxylic function as ester or amide definitely affects the efficiency of the *S*-alkylation reaction. This is clear from the low yield of compound **1g** (Scheme 4, Table 1) as compared to the high yield of the esterified analogue **1f**. The effect of the protecting group is even more evident for compound **1i**, which has the carboxylic function in the amide form and was obtained in an undetectable yield that forbids its final characterization (Scheme 5, Table 1).

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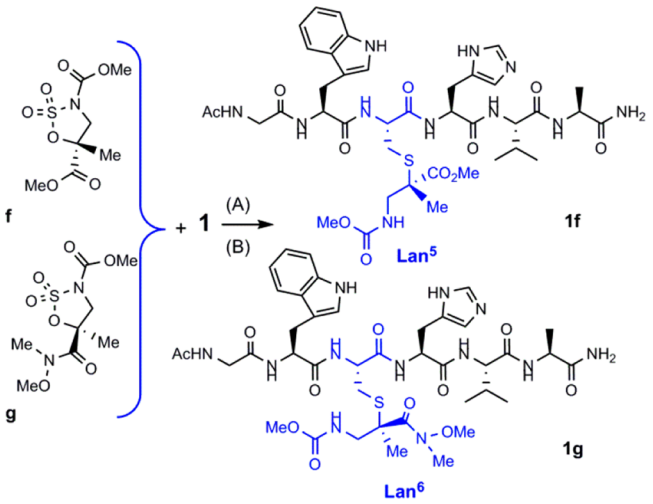
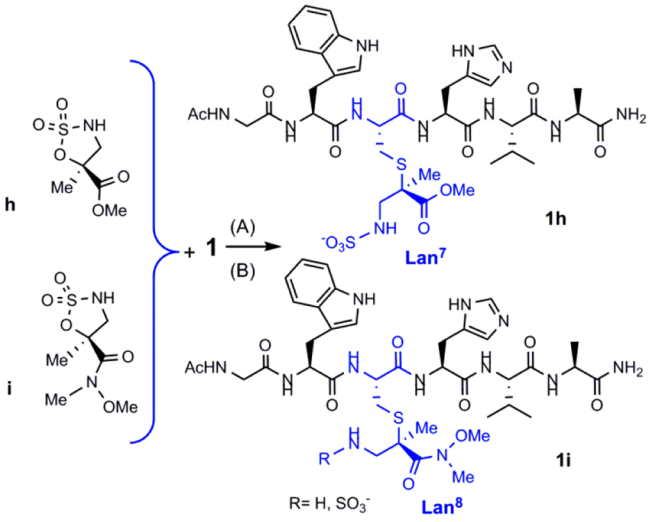
Scheme 4. Chemoselective *S*-Alkylation of Peptide 1 Performed with MeO_2C-SulfaMeIsoser-CO_2Me (f) or MeO_2C-SulfaMeIsoser-N(OMe)Me (g)[a]



[a]Conditions: (A) 4 Å MS, DMF, rt, 12 h; (B) HPLC purification 0.1% TFA in water.

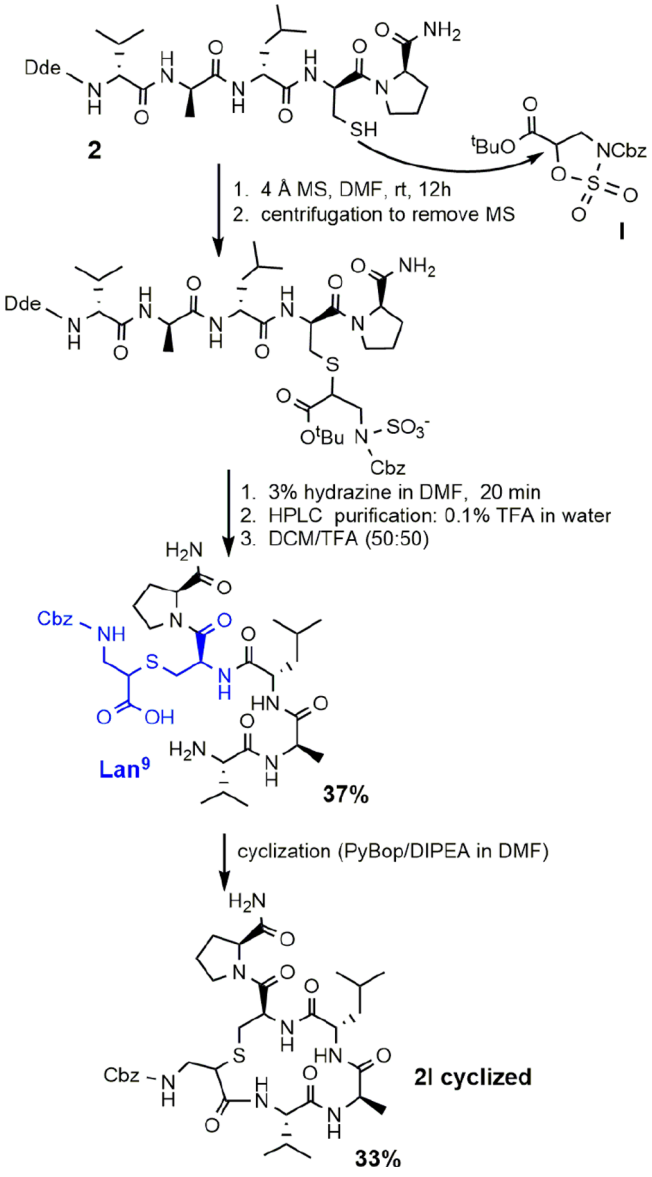
Scheme 5. Chemoselective *S*-Alkylation of Peptide 1 Performed with H-SulfaMeIsoser-OMe (h) or H-SulfaMeIsoser-N(OMe)Me (i)[a]



[a]conditions: (A) 4 Å MS, DMF, rt, 12 h; (B) HPLC purification 0.1% TFA in water.

We next extended this synthetic protocol to access cyclic lanthipeptide **2l**, which can be regarded as a mimetic ring B of the bioactive lantibiotic haloduracin *β*, whose synthesis has been reported previously.[13] This new mimetic features the incorporation in its skeleton of the unnatural norlanthionine instead of natural lanthionine. As shown in Scheme 6, the *S*-alkylation of the peptide **2** with Cbz-SulfaIsoser-O^{t}Bu **l** was characterized by a high yield, in line with the results obtained for other sulfamidates derived from (*S*)-isoserine (Scheme 3). The removal of the Dde group (3% hydrazine solution in DMF) and of the acid labile *tert*-butyl of the carboxylic function (DCM/TFA, 50:50) allowed the cyclization of the lanthipeptide. The successful formation of the haloduracin *β* ring B analogue was assessed by 2D-NMR spectroscopy (^{1}H

Scheme 6. Synthetic Strategy for Preparing Ring B of Haloduracin *β* Containing the Norlanthionine



and ^{13}C NMR assignments in the Supporting Information). Most importantly, the 2D ^{1}H, ^{13}C-HMBC spectrum showed heteronuclear correlations that could be unambiguously assigned to V1 H_α/Lan5 C = O, Lan5 H_δ/Lan5 C_β, and Lan5 H_β/Lan5 H_δ, confirming the proper conversion of cysteine into norlanthionine, and the proper ring closure (see the Supporting Information for spectral data and atom nomenclature).

In summary, the investigation of the reactivity of serine-based sulfamidates toward S-alkylation by using a cysteine-containing peptide as the substrate and activated molecular sieves as the promoters has been expanded to a number of structurally different, substituted cyclic sulfamidates,. The very good yields obtained for many of the obtained lanthipeptides proved the wide applicability and good efficiency of the proposed synthetic approach. The most interesting results were gained by employing *N*-unprotected sulfamidates that still could be incorporated into peptide sequences with excellent yields. Concerning the protection of the carboxylic group, it

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J. Org. Chem. XXXX, XXX, XXX−XXX

was confirmed that while the ester group favors the nucleophilic ring-opening reaction, the amide functionality lowers the final yield. Many valuable findings were seized by the present work, which would allow us to plan the full synthesis of new lanthibiotic analogues in the near future.

EXPERIMENTAL SECTION

Materials and Methods. Fmoc protected amino acids, Rink Amide MBHA resin, *N*-hydroxybenzotriazole (HOBT), and benzotriazol-1-yl-oxy-trispyrrolidinophosphonium (PyBOP) were purchased from Calbiochem-Novabiochem (Laufelfingen, Switzerland); piperidine and diisopropylethylamine (DIPEA) were purchased from Fluka (Milwaukee, WI); all solvents were purchased from Aldrich (St Louis, MI) or Fluka (Milwaukee, WI) and were used without further purification, unless otherwise stated. Molecular sieves type 4 Å (beads, diameter 1.6 mm) were purchased from Aldrich and activated by heating at 280 °C for 4 h under vacuum.

For all of the RP-HPLC procedures the system solvent used was H_2O 0.1% TFA (A) and CH_3CN 0.1% TFA (B), and detection was performed at 210 and 280 nm. Analytical RP-HPLC runs were carried out on a HP Agilent Series 1100 apparatus using a Phenomenex (Torrance, CA) Kinetex column (5 μm C18 100 A- 60 × 4.60 m) with a flow rate of 1.0 mL min^{-1} and a linear gradient starting from 5% to 70% B in 10 min; preparative RP-HPLC was carried out on HP Agilent Series 1200 apparatus using a Phenomenex (Torrance, CA) Gemini column (5 μm NX-C18 110 Å- 150 × 21.2 mm, AXIA) with a flow rate of 15 mL min^{-1} and a linear gradient starting from 5% to 70% B in 20 min.

LC-ESI-TOF-MS analyses was performed with an Agilent 1290 Infinity LC System coupled to an Agilent 6230 TOF LC/MS System (Agilent Technologies, CernuscoSulNaviglio, Italy). The system solvent used was: H_2O 0.05% TFA (A) and CH_3CN 0.05% TFA (B); Phenomenex (Torrance, California) Jupitercolumn (3 μm C18 300 Å- 150 × 2.0 mm); linear gradient starting from 5% to 70% B in 20 min and detection at 210 and 280 nm

NMR spectra were acquired with a Bruker Avance spectrometer operating at 14 T (corresponding to a proton Larmor frequency of 600 MHz), equipped with an inverse Z-gradient 5 mm BBI probe. Temperature was set to 300.0 K, and controlled within ±0.1 K by means of the BTO2000 VTU system. Samples were dissolved in 600 μL of DMSO-d_6 (99.9 atom %). The residual solvent resonance at 2.54 ppm was used as a secondary reference for chemical shift calibration. Resonance assignment was based on the analysis of homonuclear 2D-TOCSY and 2D-ROESY NMR spectra. 2D-TOCSY spectra were acquired with the Bruker mlevphpr pulse program (homonuclear Hartman−Hahn transfer by means of the MLEV17 sequence[34]) in the phase-sensitive mode according to the States-TPPI Scheme. Typical acquisition parameters included: 2s relaxation delay, 32−64 scans, 16 dummy scans, 25 Hz bandwidth for the water suppression presaturation pulse (if required), 2048 × 256−400 data points, 13 ppm spectral width (in F2 and F1), and 100 ms mixing time. Data were treated with squared cosine window functions (both along F2 and F1) prior to complex FT. 2D-ROESY spectra were acquired with the Bruker roesyphpr.2 pulse program in the phase-sensitive mode by the States TPPI Scheme.[35] Typical acquisition and processing parameters were as for 2D-TOCSY spectra, but with a mixing time of 300 msat 2.5 kHzspin-lock field strength, and 64 scans. Spectra were processed by the Bruker Topspin 3.0 software package. Sequence specific assignment was carried out by the Computed Aided Resonance Assigment software package (CARA: R.L.J Keller "The Computer Aided Resonance Assignment", 2004 CANTINA Verlag, Goldau, Switzerland).

Peptide synthesis. Peptide synthesis was carried out manually by solid-phase method using the standard Fmoc-protecting group strategy. Appropriate Fmoc-amino acid derivatives [Fmoc-Ala-OH, Fmoc-Val-OH, Fmoc-Gly-OH, Fmoc-Cys(Trt)-OH, Fmoc-Trp-(Boc)-OH, Fmoc-Leu-OH, Fmoc-His(Trt)-OH, Fmoc-Pro-OH were employed and a Rink Amide MBHA resin (0.7 mmol g^{-1} substitution; 50 μmol scale) was used as solid support, as it releases peptides amidated at *C*-terminus upon acid treatment. All Fmoc-amino acids were activated by in situ PyBop/HOBt//DIPEA activation procedure. Amino acid coupling steps were monitored by Kaiser test after 60 min coupling cycles. Fmoc deprotection was performed with 20% piperidine in DMF for 5 + 10 min. Peptide *N*-terminus was acetylated by treatment with a mixture of acetic anhydride (4.7%) and pyridine (4%) in DMF for 10 min. The cleavage from the solid support and the simultaneous deprotection of all side chains were performed by suspending the fully protected compound-resins in TFA/H_2O/TIS (97:2:1) for 3 h. The peptides were isolated by precipitation into cold diethyl ether and centrifuged to form a pellet.

Cyclic Sulfamidate Synthesis. Boc-SulfaSer-OMe (**a**) was obtained following the procedure previously reported by Rashid Baig et al.[33] H-SulfaSer-OMe (**b**) was obtained following the procedure previously reported by Denoël et al.[34] Boc-SulfaIsoser-O^{t}Bu (**d**) was obtained following the procedure previously reported by us,[28] MeO_2C-SulfaMeIsoser-OMe (**f**) and MeO_2C-SulfaMeIsoser-N(OMe)Me (**g**) were obtained following the procedure previously reported by us.[29] H-SulfaMeIsoser-OMe (**h**) was obtained following the procedure previously reported by us,[27] H-SulfaMeIsoser-N-(OMe)Me (**i**) was obtained following the procedure previously reported by us[35] H-SulfaMeSer-OMe (**c**), H-SulfaIsoser-OMe (**e**), and Cbz-SulfaIsoser-O^{t}Bu (**l**) are new compounds whose synthesis are described as follows.

*H-SulfaMeSer-OMe (**c**).* Sulfamidate Boc-SulfaMeSer-OMe, synthesized according the literature[28] (40 mg, 0.14 mmol), was dissolved in CH_2Cl_2 (1 mL), TFA (1 mL) was added, and the solution was allowed stirring at room temperature until the starting material was consumed by TLC monitoring (1 h). Then the solution was concentrated in vacuo to give sulfamidate **c** (26 mg, 95%) as a colorless oil, without further purification. $[\alpha]^{20}_D$ +4.1 (*c* 1.00 CH_3OH). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_5H_{10}NO_5S$ 196.0274, found 196.0278. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 1.61 (s, 3H, $CH_3\alpha$), 3.83 (s, 3H, CO_2CH_3), 4.37 (d, 1H, *J* = 9.0 Hz, 1 $CH_2\beta$), 4.93 (d, 1H, *J* = 9.0 Hz, 1 $CH_2\beta$). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ (ppm): 21.7 ($CH_3\alpha$), 52.4 (CO_2CH_3), 63.9 ($CH\alpha$), 75.6 ($CH_2\beta$), 171.5 (CO).

*H-SulfaIsoser-OMe (**e**).* Sulfamidate Boc-SulfaIsoser-OMe, synthesized according literature[28] (281 mg, 1.00 mmol), was dissolved in CH_2Cl_2 (4 mL), TFA (2 mL) was added, and the solution was allowed stirring at room temperature until starting material was consumed by TLC monitoring (4 h). Then, the solution was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/EtAcO, 8:2) to give sulfamidate **e** (172 mg, 95%) as a colorless oil. $[\alpha]^{20}_D$ +3.2 (*c* 1.00, $CHCl_3$). HRMS (ESI+) (*m/z*): $[M + Na]^+$ calcd for $C_4H_7NO_5SNa^+$, 203.9943; found 203.9951. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.87 (s, 3H, CO_2CH_3), 3.95−4.12 (m, 1H, $CH_2\beta$), 4.15−4.31 (m, 1H, $CH_2\beta$), 4.72 (br s, 1H, NH), 5.12 (t, 1H, *J* = 7.2 Hz, $CH\alpha$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) = 46.2 ($CH_2\beta$), 54.0 (CO_2CH_3), 73.0 ($CH\alpha$), 165.6 (CO).

*Cbz-SulfaIsoser-O^{t}Bu (**l**).* *tert*-Butyl 2,2,2-trichloroacetimidate (5.0 mL, 27.8) dissolved in cyclohexane (40 mL) was added dropwise to a solution of (*S*)-Cbz-IsoSer-OH, synthesized following the protocol published in the literature[36] (4.109 g, 13.9 mmol), in AcOEt (120 mL) and stirred overnight. The reaction mixture was washed with a saturated solution of $NaHCO_3$ (2 × 100 mL). The organic phase was then concentrated and recrystallized over CH_2Cl_2.After that, supernatant was concentrated and purified by column chromatography (hexane/AcOEt, 6:4) to give a product as a white foam (4.26 g, 84%), corresponding to (*S*)-Cbz-IsoSer-O^{t}Bu. $[\alpha]_D^{25}$ = −16.1 (*c* 1.00, MeOH). HRMS (ESI+) (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{22}NO_5^+$, 296.1498; found 296.1502. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51 (s, 9H, $C(CH_3)_3$), 4.20 (m, 2H, CH_2), 5.05 (t, *J* = 7.30, 1H, H_α), 5.30 (s, 2H, CH_2Ph), 7.86−6.80 (m, 5H, Cbz). ^{13}C NMR (100 MHz, $CDCl^3$) δ (ppm) 27.9 ($C(CH_3)_3$), 47.4 (C_β), 69.7 (CH_2Ph), 73.2 (C_α), 85.5 ($C(CH_3)_3$), 128.2−128.8 (5C, Cbz) 134.3 (Cbz quaternary), 149.5 (NCOO) 163.5 (COO). To a solution of imidazole (1.06 g, 15.7 mmol) in CH_2Cl_2 (15 mL) was slowly

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J. Org. Chem. XXXX, XXX, XXX−XXX

added another solution of thionyl chloride (0.33 mL, 4.7 mmol) in CH_2Cl_2 (5 mL) at 0−5 °C for 15 min. The reaction mixture was then stirred at room temperature for 1 h and then cooled to −10 °C. To this suspension was added a solution of (*S*)-Cbz-IsoSer-O^{t}Bu (768 mg, 2.6 mmol) in CH_2Cl_2 (8 mL) over 30 min at −10 °C, and the mixture was then stirred at room temperature for 2 h. Water (30 mL) was added to this suspension, and the mixture was stirred at room temperature for 10 min. The organic phase was washed with 10% aqueous citric acid (25 mL) and brine (25 mL) and dried over sodium sulfate. The solids were removed by filtration and washed with dichloromethane. The combined filtrates were mixed with a 10% aqueous sodium periodate solution (25 mL), and the mixture was cooled to 0 °C. Ruthenium(III) chloride hydrate (6 mg, 0.26 mmol) was added to the well stirred mixture, and the reaction was vigorously stirred at 0 °C for 2 h and for an additional 2 h at room temperature. The organic phase was washed with a 10% aqueous sodium ascorbate solution (8 mL) and filtered over silica gel. After evaporation of the volatiles, the product was chromatographed using hexane/AcOEt, (7:3) to give the required sulfamidate (*S*)-Cbz-SulfaIsoser-O^{t}Bu (**l**) as a white solid in a 90% yield (836 mg). $[\alpha]_D^{25}$ = +3.2 (*c* 1.00, $CHCl_3$). HRMS ESI+ (*m*/*z*) [M + Na$^+$] calcd for $C_{15}H_{19}NNaO_7S^+$, 380.0774; found 380.0772. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.45 (s, 3H, $C(CH_3)_3$), 3.49−3.59 (m, 2H, CH_2), 3.15−3.18 (m, 1H, H_α), 5.05−5.15 (m, 2H, CH_2Ph), 7.25−7.39 (m, 5H, Cbz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl^3$) δ (ppm) 27.9 ($C(CH_3)_3$), 44.3 (C_β), 66.8 (CH_2Ph), 70.3 (C_α), 83.1 ($C(CH_3)_3$), 128.0−128.5 (5C, Cbz) 136.5 (Cbz, quaternary), 156.5 (NCOO), 172.2 (COO).

General Procedure for Postsynthetic Peptide *S*-Alkylation. Each solution of acetylated peptide in DMF (5 mg/mL) was poured, under argon atmosphere, in a round-bottom flask containing 4 Å molecular sieves (3−3.5 g) previously activated at 280 °C for 4 h under vacuum. After a few minutes, the corresponding cyclic sulfamidate **a**−**i** and **l** (1.2 equiv) was added. The reaction was stirred at room temperature overnight followed by analytical RP-HPLC. The reaction mixture was separated from the molecular sieves by centrifugation, and the precipitate was washed with DMF (0.200−0.500 mL). The final product was purified by RP-HPLC, analyzed by mass spectrometry and fully characterized by NMR spectroscopy.

Compound 1a *(AcGlyTrpLanHisValAlaNH$_2$)*. Synthesized as previously described.[13]

Compound 1b *(AcGlyTrpLan^{1}HisValAlaNH$_2$)*. Peptide **1** (6.4 mg) was reacted with 1.95 mg of **b** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1b**) after RP-HPLC purification: 47% (3.0 mg); HPLC t_R = 14.800 min; ES-MS calcd [M + H]$^+$ 814.3600, found *m*/*z* 814.3662. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.84 (1H, s), 9.00 (1H, s, br), 8.41 (1H, d), 8,22 (1H, d), 8.14 (1H, t), 8.11 (1H, t), 8.07 (1H, d), 7.72 (1H, s), 7.61 (1H, d), 7.45 (1H, s), 7.35 (1H, d), 7.27 (1H, s), 7.18 (1H, s), 7.08 (1H, t), 7.00−6.99 (2H, m, o), 4.56−4.55 (2H, m, o), 4.45 (1H, m), 4.24 (1H, m), 4.20 (1H, dd), 4.06 (1H, t), 3.76 (1H, dd), 3.67 (3H, s), 3.59 (1H, dd), 3.19−3.16 (3H, m, o), 3.07 (1H, dd), 3.00−2.98 (2H, m, o), 2.85 (1H, dd), 2.74 (1H, dd), 2.05 (1H, m), 1.86 (3H, s), 1.24 (3H, d), 0.90 (3H, d), 0.88 (3H, d).

Compound 1c *(AcGlyTrpLan^{2}HisValAlaNH$_2$)*. Peptide **1** (6.2 mg) was reacted with 2.04 mg of **c** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1c**) after RP-HPLC purification: 19% (1.2 mg). HPLC t_R = 15.160 min. ES-MS: calcd [M + H]$^+$, 828.3821 found *m*/*z* 828.3801. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.82 (1H, s), 8.91 (1H, s, br), 8.35 (1H, d), 8.23 (1H, d), 8.07 (1H, t), 8.02 (1H, br, o), 8.01 (1H, d, o), 7.71 (1H, d), 7.61 (1H, d), 7.42 (1H, s, br), 7.35 (1H, d), 7.20 (1H, s, br), 7.18 (1H, s), 7.09 (1H, t), 6.98 (2H, m, o), 4.57−4.50 (3H, m, o), 4.23 (1H, m), 4.17 (1H, t), 3.78 (1H, dd), 3.64 (3H, s), 3.62 (1H, dd), 3.19−3.14 (5H, m, o), 2.99 (1H, dd), 2.93 (1H, d), 2.76 (1H, dd), 2.06 (1H, m), 1.84 (3H, s), 1.51 (3H, s), 1.25 (3H, d), 0.91 (3H, d), 0.88 (3H, d).

Compound 1d *(AcGlyTrpLan^{3}HisValAlaNH$_2$)*. Peptide **1** (5.3 mg) was reacted with 2.88 mg of **d** in the presence of activated molecular sieves and under argon atmosphere. The reaction mixture was stirred at room temperature for overnight.

Yield (**1d**) after RP-HPLC purification: 51% (2.7 mg). HPLC t_R = 19.90 min. ES-MS: calcd [M + H]$^+$, 956.4680, found *m*/*z* 956.4811. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.85 (1H, s), 8.98 (1H, br), 8.39 (1H, d), 8.19 (1H, d), 8.13−8.11 (3H, m, o), 7.88 (1H, d), 7.61 (1H, d), 7.39 (1H, br), 7.36 (1H, d), 7.28 (1H, s), 7.18 (1H, s), 7.09 (1H, t), 7.04−7.01 (3H, m, o), 4.71 (1H, q), 4.56 (1H, dt), 4.40 (1H, q), 4.25 (1H, m), 4.19 (1H, dd), 3.77 (1H, dd), 3.59 (1H, dd), 3.42 (dd), 3.34 (m, overlapping with water), 3.18 (2H, m, o), 3.11 (1H, dd), 3.04−3.02 (2H, m, o), 2.96 (1H, dd), 2.88 (1H, dd), 2.04 (1H, m), 1.84 (3H, s), 1.44 (9H, s), 1.40 (9H, s), 1.25 (3H, s), 0.91 (3H, d), 0.88 (3H, d).

Compound 1e *(AcGlyTrpLan^{4}HisValAlaNH$_2$)*. Peptide **1** (6.0 mg) was reacted with 1.83 mg of **e** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1e**) after RP-HPLC purification: 47% (2.8 mg); HPLC t_R = 14.740 min. ES-MS: calcd [M + H]$^+$, 814.3600 found *m*/*z* 814.3679. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.84 (1H, s), 8.98 (1H, br), 8.48 (1H, br), 8.25 (1H, d), 8.16 (2H, m, o), 8.08 (1H, br), 7.76 (1H, d), 7.60 (1H, d), 7.45 (1H, br), 7.35 (1H, d), 7.25 (1H, s, br), 7.18 (1H, s), 7.09 (1H, t), 6.99 (2H, m, o), 4.55−4.53 (2H, m, o), 4.43 (1H, q), 4.24 (1H, m), 4.19 (1H, dd), 3.90 (1H, t), 3.76 (1H, dd), 3.69 (3H, s), 3.60 (1H, dd), 3.29 (1H, dd), 3.17−3.16 (3H, m, o), 3.08 (1H, dd), 2.98−2.97 (2H, m, o), 2.88 (1H, dd), 2.05 (1H, m), 1.85 (3H, s), 1.24 (3H, d), 0.90 (3H, d), 0.87 (3H, d).

Compound 1f *(AcGlyTrpLan^{5}HisValAlaNH$_2$)*. Peptide **1** (9.1 mg) was reacted with 3.9 mg of **f** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1f**) after RP-HPLC purification: 48% (4.4 mg); HPLC t_R = 15.66 min;. ES-MS: calcd [M + H]$^+$, 886.3801, found *m*/*z* 886.3824. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.85 (1H, s), 8.98 (1H, br), 8.35 (1H, d), 8.28 (1H, d), 8.14−8.11 (3H, overlapping multiplets), 7.85 (1H, 1H, d), 7.61 (1H, d), 7.39 (1H, br), 7.36 (1H, d), 7.31 (1H, t), 7.29 (1H, br), 7.18 (1H, s), 7.09 (1H, t), 7.02 (1H, s, o), 7.00 (1H, t, o), 4.71 (1H, m), 4.56 (1H, dt), 4.33 (1H, m), 4.24 (1H, m), 4.20 (1H, dd), 3.78 (1H, dd), 3.69 (3H, s), 3.59 (1H, dd, o), 3.57 (3H, s), 3.52 (1H, dd), 3.40 (1H, dd), 3.17 (1H, dd), 3.12 (1H, dd), 3.01 (1H, dd), 2.95−2.93 (2H, m, o), 2.88 (1H, dd), 2.05 (1H, m), 1.84 (3H, s), 1.36 (3H, s), 1.24 (3H, d), 0.91 (3H, d), 0.88 (3H, d).

Compound 1g *(AcGlyTrpLan^{6}HisValAlaNH$_2$)*. Peptide **1** (8.7 mg) was reacted with 4.13 mg of **g** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1g**) after RP-HPLC purification: 25% (1.6 mg). HPLC t_R = 15.49 min; ES-MS: calcd [M + H]$^+$, 915.4185, found *m*/*z* 915.4297. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.83 (1H, s), 8.96 (1H, br), 8.33 (1H, d), 8.21 (1H, d), 8.12 (1H, d) 8.10 (1H, t, o), 8.07 (1H, d, o), 7.86 (1H, d), 7.61 (1H, d), 7.38 (1H, br, o), 7.36 (1H, d, o), 7.25 (1H, br), 7.17 (1H, s), 7.09 (1H, t), 7.01 (1H, t, o), 6.99 (1H, s), 6.89 (1H, t), 4.71 (1H, m), 4.56 (1H, dt), 4.34 (1H, m), 4.25 (1H, m), 4.20 (1H, dd), 3.77 (1H, dd), 3.71 (3H, s), 3.60 (1H, dd, o), 3.57 (4H, overlapping s and m), 3.42 (m, overlapping with water), 3.18 (3H, s, o), 3.17 (1H, dd, o), 3.10 (1H, dd), 3.01 (1H, dd), 2.96 (1H, dd), 2.86 (1H, m), 2.80 (1H, m), 2.05 (1H, m), 1.85 (3H, s), 1.44 (3H, s), 1.25 (3H, d), 0.91 (3H, d), 0.88 (3H, d).

Compound 1h *(AcGlyTrpLan^{7}HisValAlaNH$_2$)*. Peptide **1** (6.5 mg) was reacted with 2.14 mg of **h** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature overnight.

Yield (**1h**) after RP-HPLC purification: 40% (2.6 mg). HPLC t_R = 15.252 min. ES-MS: calcd [M + H]$^+$, 828.3800 found *m*/*z* 828.3804. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): 10.86

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J. Org. Chem. XXXX, XXX, XXX−XXX

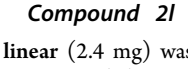
(1H, d), 8.97 (1H, br), 8.27 (1H, d, o), 8.25 (1H, d, o), 8.14 (1H, d, o), 8.12 (1H, d, o), 8.09 (1H, d, o), 7.77 (1H, d), 7.59 (1H, d), 7.39 (1H, br, o), 7.35 (1H, d, o), 7.26 (1H, s, br), 7.23 (1H, s), 7.09 (1H, t), 7.00 (1H, t, o), 6.99 (1H, s, br, o), 4.61 (1H, m), 4.45 (1H, m), 4.28 (1H, m, o), 4.23 (1H, m, o), 4.16 (1H, m, o), 3.82 (1H, dd), 3.69 (3H, s), 3.63 (1H dd), 3.19 (1H, m, o), 3.17 (1H, m, o), 3.15 (1H, m, o), 3.14 (1H, m, o), 3.08 (1H, m, o), 3.01 (1H, m, o), 2.86 (2H, m), 2.04 (1H, m), 1.86 (3H, s), 1.37 (3H, s), 1.24 (3H, d), 0.90 (3H, d). 0.87 (3H, d).

Compound 1i *(AcGlyTrpLan^{8}HisValAlaNH$_2$)*. Peptide **1** (8.1 mg) was reacted with 3.06 mg **i** in the presence of activated molecular sieves and under argon atmosphere. The reaction was stirred at room temperature for overnight.

Yield (**1i**): not detectable.

Synthetic Strategy of VALCP_SulfaIsoser. The synthesis of the peptide chain was performed following the general procedure described in a previous paragrph (100 μmol scale). After removal of the Fmoc group at the N-terminus of the peptidyl-resin, the Dde was introduced in the solid phase by reaction with Dde−OH (10 equiv; 182.2 mg) previously dissolved in DMF. The shaking was kept for 90 min. After the cleavage of the peptide from the resin, the S-alkylation was performed by reacting 6.7 mg of **2** with 4.32 mg of **l** (Cbz-SulfaIsoser-O^{t}Bu), following the protocol previously described. Then, the molecular sieves were removed and 80 μL of hydrazine were added to 2.5 mL of the reaction mixture. The obtained ∼3% hydrazine solution was kept under stirring for 20 min at room temperature, it allowed the removal of the Dde protecting group at the N-terminus. After preparative RP-HPLC, the peptide **H-ValAlaLeuLan^{9}ProNH$_2$** (2.5 mg) was freed from the ^{t}Bu group by employing a mixture of TFA/DCM (50:50; V_{tot}= 3 mL) and keeping the reaction mixture under stirring for 1 h. After removal of the solvent in vacuo, the cyclization reaction, in order to obtain **2l cyclized**, was performed in DMF using the PyBop/DIPEA (1:2) activation protocol. The stirring was kept for 5 h. The crude product was purified by preparative RP-HPLC, analyzed by mass spectrometry and NMR spectroscopy.

Compound 2l linear *(H-ValAlaLeuLan^9 (O^{t}Bu)ProNH2)*. Yield (**1l linear**) after RP-HPLC purification: 37% (2.5 mg). HPLC: t_R = 18.980 min. ES-MS: calcd $[M + H]^+$, 778.4120, found m/z 778.4133.

Compound 2l cyclized (). Peptide **2l linear** (2.4 mg) was cyclized using 1.87 mg of PyBop, and 1 μL of DIPEA and the reaction was stirred for 5 h.

Yield (**2l**) after RP-HPLC purification: 33% (0.8 mg). Analytical HPLC t_R = 20.690 min. ES-MS: calcd $[M + H]^+$, 704.3400, found m/z 704.3430. White solid. ^{1}H NMR δ, ppm (600 MHz, DMSO-d_6, 298 K): ^{1}H NMR (DMSO-d_6, 298 K). 8.06 (1H, d), 7.95 (1H, d), 7.90 (1H, d), 7.82 (1H, d), 7.56 (1H, t), 7.41−7.33 (5H, m, o), 7.22 (1H, s) 6.97 (1H, s), 5.06 (2H, m), 4.66 (1H, dd), 4.20 (1H, dd), 4.16−4.15 (2H, m, o), 4.00 (1H, t), 3.68−3.65 (2H, m, o), 3.56 (1H, m), 3.33 (m, overlapping with water), 3.14 (1H, dd), 2.72 (1H, dd), 2.06−2.05 (2H, m, o), 1.92−1.85 (3H, m, o), 1.62−1.54 (3H, m, o), 1.33 (3H, d), 0.91−0.88 (12H, m, o).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02306.

LC−MS spectra of *S*-alkylated compounds; tables with proton chemical shifts (ppm) of *S*-alkylated compounds; NMR spectra of *S*-alkylated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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