Efficient Synthesis of Differently Protected Lanthionines via β-Bromoalanine Derivatives

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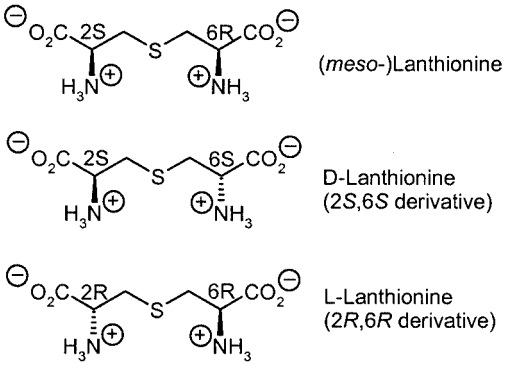
Lanthionines, thioether-linked alanines, are readily available from differently protected β-bromoalanine and cysteine derivatives under phase-transfer conditions at pH 8.5. Racemisation or elimination of starting materials or products was not observed. Also base-sensitive protecting groups, such as, for instance, the Fmoc group, were compatible with this procedure, thus conveniently permitting the synthesis of orthogonally protected lanthionines.

Introduction

Lanthionine,[1] a non-standard amino acid that consists of two alanines linked by a thioether bridge (Scheme 1), has been incorporated into the peptidoglycan to replace the *meso*-diaminopimelate (DAP),[2] the essential amino acid used for crosslinking the bacterial cell wall. It is also a key constituent of bioactive peptide lantibiotics,[3] a group of bactericidal peptides that are produced by, and mainly act against, Gram-positive bacteria. Given the fact that widespread antibiotic resistance has become a serious threat to public health,[4] lantibiotics represent an attractive class of antibacterial agents for new drug discovery.[5] On the other hand, compared to the labile disulfide bridge of cystine in natural or unnatural cyclic peptide sequences, the monosulfide bridge of lanthionine provides more constrained peptide structures with greater biostability. Therefore, the synthesis of lanthionine building blocks and the introduction of the lanthionine structure as novel peptidomimetics into various drug families has received significant interest.[6,7] For instance, the lanthionine moiety has been incorporated into the sandostatin molecule and the resulting lanthionine-sandostatin octapeptides were good drug candidates based on their high and selective binding affinities for somatostatin receptor SSTR5 and their increased stability against enzymatic degradation.[7e]



Scheme 1. Structure of lanthionines

Biosynthetically, lanthionine derivatives are created by the Michael-type addition of a cysteine residue to a dehydroalanine (Dha) residue, which is highly stereoselective, giving *meso*-lanthionine.[8] Hence, a variety of investigations have focused on the biomimetic conjugate addition of cysteine derivatives to dehydroalanine derivatives. Unfortunately, diastereoisomers (or one unpredictable diastereomer) were normally produced during this addition. For example, coupling between Fmoc-Cys-OAll and Boc-Dha-OMe gave rise to two isomers in a 2:3 ratio.[6e] Another strategy for making lanthionine peptides is based on Harpp's synthesis of lanthionine itself, which involves the desulfurisation of cystine peptides by treatment with $P(Et_2N)_3$. However, a low yield and the symmetrical disulfide were obtained instead of the desired lanthionine peptides when unsymmetrical cystine peptides were desulfurised.[6g][6h] Furthermore, this strategy was proven impractical for solid-phase synthesis.[6e] Hence, a number of approaches based on alanyl β-cation equivalents have been developed to synthesise lanthionine derivatives. However, ring-opening of 2-aziridinecarboxylate gave predominantly the β-amino acid with a cysteinyl group at the α-position and yields of the desired lanthionines of less than 37%.[6f,9] β-Chloroalanines were also investigated as alanyl β-cation equivalents to construct lanthionines, however, because of the harsh conditions employed, racemisation was observed.[6h,6i] Moreover, most base-sensitive protecting groups would not withstand these conditions; thus, orthogonally protected lanthionines appear impossible to be prepared in this way.

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In contrast, Goodman et al. reported the synthesis of lanthionine building blocks through the ring-opening of the Cbz-L/D-serine-β-lactone as key intermediate.[6b] Although β,β-dimethyllanthionines were produced in high yields, lanthionines were obtained in much lower yields due to the non-regioselective attack of the primary thiolate anions on both the carbonyl and the β-methylene positions of the β-lactones. Also ring opening of the β-lactones with Fmoc-Cys-OAll was not successful,[6c] which otherwise could lead to lanthionines suitable for Fmoc-based solid-phase peptide synthesis (SPPS).

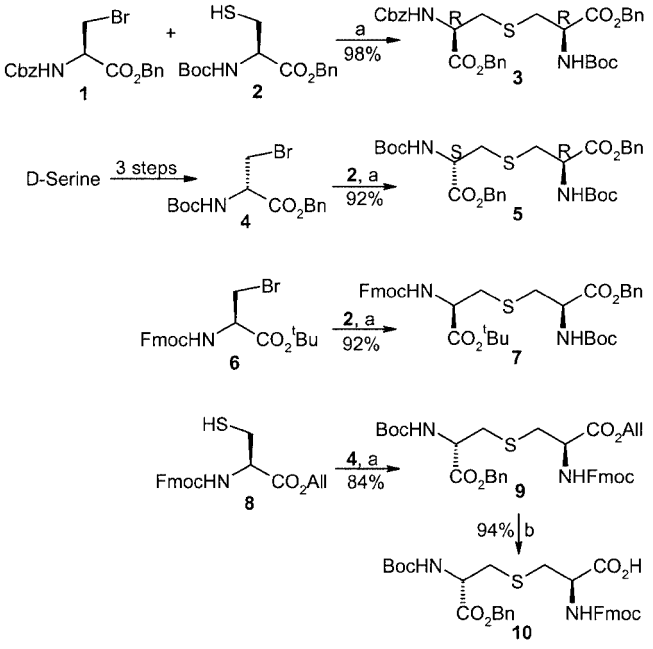
Interestingly, several very recent investigations have focused on the preparation of orthogonally protected lanthionines via β-iodoalanine derivatives.[6c][6d] Dugave et al. were the first to utilise *N*-trityl β-iodoalanate to construct lanthionines;[6c] however, later, Tabor and co-workers demonstrated that this strategy for the synthesis of lanthionines is problematic,[6d] as nor-lanthionines are produced instead of lanthionines. In addition, the essential *N*-trityl group,[10] which was used to suppress the elimination reaction of β-iodoalanines, complicated this strategy.

Under these circumstances, the development of a new and efficient synthesis of lanthionine derivatives seems to be of interest. As part of our ongoing program on the synthesis of DAP-containing muramyl peptides,[11] we decided to pursue approaches to lanthionines because of their biological importance. We wish to report here a new and efficient synthesis of protected lanthionines via β-bromoalanine derivatives.

Results and Discussion

To the best of our knowledge, β-bromoalanine derivatives have not been used to synthesise lanthionines, although they appear to be optimal alanyl β-cation equivalents because under mild basic conditions they exhibit the desired high reactivity towards good nucleophiles without leading to elimination as we experienced in related investigations. Thus, recently, β-bromoalanine-containing peptides have been successfully used as electrophiles to construct *S*-linked glycopeptides.[12] Based on this work, coupling between bromide **1**[13] (Scheme 2) and Boc-Cys-OBn **2**[14] was performed in the presence of tetrabutylammonium hydrogensulfate (TBAHS) in ethyl acetate and an aqueous solution of $NaHCO_3$ at pH 8.5, i.e. phase-transfer conditions (PTC). As expected, protected L-(2*R*,6*R*)-lanthionine **3** was obtained in an almost quantitative yield, which had never been achieved in other attempts at alanyl β-cation-equivalent-mediated lanthionine synthesis.[6] More importantly, no trace of the (2*S*,6*R*)-diastereoisomer of **3** could be detected by NMR spectroscopy; that is, in the present mild two-phase system, the elimination-Michael addition process did not take place. In addition, unlike β-iodoalanine-mediated lanthionine synthesis, which led to a significant amount of undesired aziridine formation,[6c] no trace of aziridine was observed.

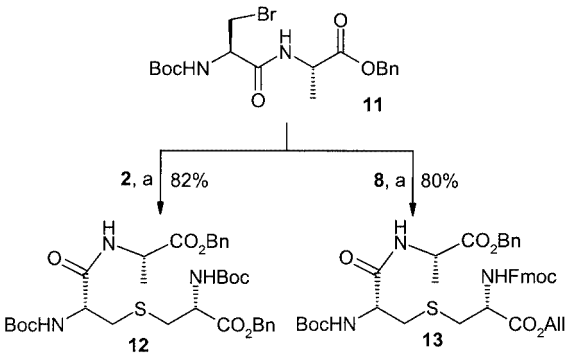
In order to obtain *meso*-lanthionines, D-bromoalanine **4** was prepared from D-serine in three steps,[13] and subjected, together with **2**, to the above-described conditions. Again, the desired protected *meso*-lanthionine **5** was isolated from the reaction mixture in excellent yield (92%), as shown in Scheme 2. Conceivably, **5** can be easily deprotected to afford *meso*-lanthionine. Hence, by utilizing β-bromoalanine derivatives, we were able to establish a concise and efficient access to lanthionines.



Scheme 2. (a) Reagents and conditions: (a) pH 8.5 solution of $NaHCO_3$, TBAHS, EtOAc; (b) $[Pd(PPh_3)_4]$, *N*-methylaniline, THF

For the defined synthesis of peptidoglycan mimetics, an orthogonal protecting group pattern is required for the functional group. Hence, the exposure of bromide **6**[12] to **2** under the same PTC conditions led to a 92% yield of differently protected L-lanthionine **7**. Similarly, the coupling of bromide **4** and Fmoc-Cys-OAll **8**[15] under two-phase conditions, also smoothly afforded the interesting compound **9**, as an orthogonally protected *meso*-lanthionine. This, together with the above-described ready formation of **7**, is an especially promising result, as it demonstrated the compatibility of the *N*-Fmoc group under the present conditions. Unlike the studies with β-iodoalanine derivatives,[6d] no trace of nor-lanthionine was produced using our procedure. Sulfide **9** was further treated with $[Pd(PPh_3)_4]$ and *N*-methylaniline[16] for selective deallylation to yield *meso*-(2*S*,6*R*)-lanthionine-derived compound **10** in a 94% yield, which could be used in Fmoc-based SPPS. It is noteworthy that **10** could previously not reliably be prepared using a β-iodoalanine derivative as building block.[6c,6d]

To further extend the scope and utility of this procedure, we have explored additional examples, as shown in Scheme 3. Bromodipeptide **11**[12] was exposed to cysteine derivatives **2** and **8**, respectively, in the presence of TBAHS in a mixture of ethyl acetate and aqueous $NaHCO_3$ (pH, 8.5); the desired lanthionine containing peptides **12** and **13** were produced readily in 82% and 80% yields, respectively,



Scheme 3. Reagents and conditions: (a) pH 8.5 solution of $NaHCO_3$, TBAHS, EtOAc

without observable contamination of the epimerised peptides.[17]

In summary, a new and efficient route for the synthesis of protected lanthionines, including orthogonally protected lanthionines, is presented. These compounds could be used as building blocks for the construction of lantibiotics. The high yields, the mild conditions, and the compatibility of this approach with common peptide protecting groups are attractive features, compared with previous methods. Extended studies on the scope of the reaction and application of this method are currently underway.

Experimental Section

General Remarks: Unless otherwise stated, all moisture-sensitive reactions were performed in oven-dried glassware under nitrogen using dry solvents. Solvents were evaporated under reduced pressure while maintaining the water bath temperature at below 40 °C. All reactions were monitored by thin-layer chromatography (TLC) by using silica gel 60 F_{254} and the compounds visualised by UV light (254 nm), iodine or by treatment with 0.2% ninhydrin in ethanol or with 10% H_2SO_4 in methanol, followed by heating at 150 °C. Flash chromatography was performed with the indicated solvent system using 30−60 μm silica gel at a pressure of 0.3−0.4 bar. Optical rotations were measured at 25 °C with a Perkin−Elmer 241/MC polarimeter (1-dm cell). NMR spectra were recorded with Bruker AC 250 (250 MHz) instruments by using tetramethylsilane as an internal standard. MS spectra were recorded with a MALDI-kompakt (Kratos) instrument in the positive mode by using 2,5-dihydroxybenzoic acid in dioxane as a matrix. Elemental analyses were performed in the Microanalysis unit at the Fachbereich Chemie, Universität Konstanz. Yields refer to chromatographically pure compounds and are calculated based on reagents consumed.

Benzyl *N*-*tert*-Butoxycarbonyl-β-bromo-D-alaninate (4): Triphenylphosphane PPh_3 (3.15 g, 12.0 mmol) was added portionwise to a solution of Boc-D-Ser-OBzl (1.77 g, 5.99 mmol) and carbon tetrabromide CBr_4 (3.16 g, 9.53 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min, then treated with Et_2O and the resulting precipitate was removed by filtration and washed several times with Et_2O. The combined diethyl ether solution was washed, successively with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/EtOAc, 10:1 → 6:1) to give **4** (1.53 g) as a white solid in a 71% yield: TLC R_f = 0.62 (petroleum ether/EtOAc, 2:1). $[\alpha]_D$ = −5.2 (*c* = 1.0; $CHCl_3$). $[\alpha]_D$ = +21 (*c* = 1.0; MeOH), {$[\alpha]_D$ = −22 (*c* = 1.0; MeOH) for the L-isomer (ref.[13])}. ^1H NMR ($CDCl_3$): δ = 7.35 (m, 5 H), 5.46 (d, *J* = 7.8 Hz, 1 H), 5.22 (m, 2 H), 4.79 (dt, *J* = 8.0, 3.3 Hz, 1 H), 3.84 (dd, *J* = 10.5, 3.2 Hz, 1 H), 3.71 (dd, *J* = 10.5, 3.5 Hz, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.8, 154.7, 134.7, 128.3, 128.0, 79.9, 67.4, 53.8, 33.6, 27.9 ppm. MALDI MS: *m*/*z* = 380.2 [M + Na^+]. $C_{15}H_{20}BrNO_4$ (358.2): calcd. C 50.29, H 5.63, N 3.91; found C 50.51, H 5.70, N 3.88.

General Procedure for the Synthesis of Sulfides 3, 5, 7, 9, 12 and 13: To a solution of the appropriate bromide (0.21 mmol) and the corresponding cysteinyl thiol (0.2 mmol) in EtOAc (3 mL) was added a pH 8.5 solution of $NaHCO_3$ (3 mL) followed by the addition of TBAHS (272 mg, 0.8 mmol). The mixture was vigorously stirred at room temperature for 12 h, then diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, concentrated in vacuo to give a residue, which was purified by flash column chromatography to afford the corresponding sulfide.

Dibenzyl (2*R*,6*R*)-N^2-(Benzyloxycarbonyl)-N^6-(*tert*-butoxycarbonyl)-lanthionate (3): Compound **3** was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 5:1), as a colourless viscous oil (122 mg, 98%): TLC R_f = 0.41 (petroleum ether/EtOAc, 2:1). $[\alpha]_D$ = +1.5 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.33 (m, 15 H), 5.69 (d, *J* = 7.7 Hz, 1 H), 5.37 (d, *J* = 8.0 Hz, 1 H), 5.21≈5.06 (m, 6 H), 4.55 (m, 2 H), 2.92 (m, 4 H), 1.42 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.5, 170.2, 155.7, 155.1, 136.1, 135.0, 134.9, 128.6, 128.5, 128.4, 128.2, 128.1, 80.2, 67.6, 67.5, 67.1, 53.8, 53.4, 35.4, 35.3, 28.2 ppm. MALDI MS: *m*/*z* = 645.5 [M + Na^+], 661.5 [M + K^+]. $C_{33}H_{38}N_2O_8S·0.5H_2O$ (631.7): calcd. C 62.74, H 6.22, N 4.43; found C 62.68, H 6.18, N 4.56.

Dibenzyl (2*S*,6*S*)-N^2,N^6-Bis(*tert*-butoxycarbonyl)lanthionate (5): 5 was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 6:1 → 4:1) as a white amorphous solid (108 mg, 92%): TLC R_f = 0.59 (petroleum ether/EtOAc, 2:1). ^1H NMR ($CDCl_3$) δ 7.34 (m, 10 H), 5.41 (d, *J* = 6.9 Hz, 2 H), 5.15 (s, 4 H), 4.53 (m, 2 H), 2.93 (m, 4 H), 1.43 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.5, 155.1, 135.0, 128.5, 128.4, 128.3, 80.1, 67.3, 53.3, 35.3, 28.2 ppm. MALDI MS: *m*/*z* = 611.7 [M + Na^+], 627.5 [M + K^+]. $C_{30}H_{40}N_2O_8S$ (588.7): calcd. C 61.21, H 6.85, N 4.76; found C 61.24, H 6.93, N 4.73.

1-*O*-Benzyl 7-*O*-*tert*-Butyl (2*R*,6*R*)-N^2-(*tert*-Butoxycarbonyl)-N^6-(fluoren-9-ylmethoxycarbonyl)lanthionate (7): 7 was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 5:1) as a colourless viscous oil (124 mg, 92%): TLC R_f = 0.48 (petroleum ether/EtOAc, 2:1). $[\alpha]_D$ = +5.7 (*c* = 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.4 Hz, 2 H), 7.43−7.28 (m, 9 H), 5.65 (d, *J* = 7.7 Hz, 1 H), 5.41 (d, *J* = 7.6 Hz, 1 H), 5.17 (s, 2 H), 4.57 (m, 1 H), 4.46 (m, 1 H), 4.38 (d, *J* = 7.1 Hz, 2 H), 4.22 (t, *J* = 7.0 Hz, 1 H), 3.02 (d, *J* = 4.9 Hz, 2 H), 2.96 (m, 2 H), 1.47 (s, 9 H), 1.43 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6, 169.4, 155.7, 155.1, 143.83, 143.77, 141.3, 135.0, 128.6, 128.5, 128.4, 127.7, 127.1, 125.1, 119.9, 83.0, 80.2, 67.5, 67.1, 54.3, 53.5, 47.1, 35.6, 28.3, 27.9 ppm. MALDI MS: *m*/*z* = 699.5 [M + Na^+].

7-*O*-Allyl 1-*O*-Benzyl (2*S*,6*R*)-N^2-(*tert*-Butoxycarbonyl)-N^6-(fluoren-9-ylmethoxycarbonyl)lanthionate (9): Compound **9** was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 4:1) as a white amorphous solid (112 mg, 84%). TLC R_f = 0.43 (petroleum ether/EtOAc, 2:1). $[\alpha]_D$ = +2.6 (*c* = 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.76 (d, *J* = 7.3 Hz, 2 H),

7.63 (m, 2 H), 7.42−7.27 (m, 9 H), 5.87 (m, 2 H), 5.41−5.15 (m, 5 H), 4.65−4.57 (m, 4 H), 4.38 (m, 2 H), 4.22 (t, J = 7.0 Hz, 1 H), 2.99 (m, 4 H), 1.44 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6, 170.0, 155.7, 155.1, 143.8, 143.7, 141.3, 134.9, 131.2, 128.6, 128.5, 128.4, 127.7, 127.1, 125.1, 119.9, 119.2, 80.3, 67.5, 67.2, 66.4, 53.8, 53.5, 47.1, 35.8, 35.4, 28.2 ppm. MALDI MS: m/z = 683.5 [M + Na^+], 699.6 [M + K^+]. $C_{36}H_{40}N_2O_8S{\cdot}0.5H_2O$ (669.8): calcd. C 64.56, H 6.17, N 4.18; found C 64.53, H 6.10, N 4.06.

[1-*O*-Benzyl (2*R*,6*R*)-N^2,N^6-Bis(*tert*-butoxycarbonyl)lanthion-7-yl]-L-alanine Benzyl Ester (12): Compound **12** was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 3:1 → 2:1) as a colourless viscous oil (109 mg, 82%): TLC R_f = 0.36 (petroleum ether/EtOAc, 1.4:1). [α]$_D$ = −0.5 (c = 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.35 (m, 10 H), 7.03 (br. d, 1 H), 5.63 (br. d, 1 H), 5.45 (br. s, 1 H), 5.19 (s, 2 H), 5.16 (q-like, 2 H), 4.60 (m, 2 H), 4.26 (br. s, 1 H), 3.01 (d, J = 5.3 Hz, 2 H), 2.97 (dd, J = 13.8, 5.4 Hz, 1 H), 2.75 (dd, J = 13.8, 6.6 Hz, 1 H), 1.45 (s, 9 H), 1.44 (s, 9 H), 1.40 (d, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.2, 170.8, 169.9, 155.3, 135.2, 135.0, 128.5, 128.3, 128.2, 128.0, 80.2, 80.0, 67.3, 67.0, 53.8, 48.2, 35.3, 28.2 ppm. MALDI MS: m/z = 682.4 [M + Na^+], 698.4 [M + K^+]. $C_{33}H_{45}N_3O_9S$ (659.8): calcd. C 60.07, H 6.87, N 6.37; found C 59.96, H 6.72, N 6.28.

[1-*O*-Allyl (2*R*,6*R*)-N^6-(*tert*-Butoxycarbonyl)-N^2-(fluoren-9-ylmethoxycarbonyl)lanthion-7-yl]-L-alanine Benzyl Ester (13): Compound **13** was obtained, after purification by flash column chromatography (petroleum ether/EtOAc, 3:1 → 2:1) as a colourless viscous oil (117 mg, 80%): TLC R_f = 0.15 (petroleum ether/EtOAc, 1.7:1). [α]$_D$ = +8.3 (c = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H), 7.63 (d, J = 7.3 Hz, 2 H), 7.42−7.27 (m, 9 H), 7.09 (d, J = 6.3 Hz, 1 H), 6.21 (d, J = 5.9 Hz, 1 H), 5.91 (m, 1 H), 5.53 (d, J = 6.6 Hz, 1 H), 5.39−5.24 (m, 2 H), 5.15 (q-like, 2 H), 4.71−4.56 (m, 4 H), 4.38 (m, 3 H), 4.24 (t, J = 7.0 Hz, 1 H), 3.07 (d, J = 4.4 Hz, 2 H), 3.04 (dd, J = 14.0, 4.4 Hz, 1 H), 2.83 (dd, J = 14.0, 6.7 Hz, 1 H), 1.43 (s, 9 H), 1.42 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.3, 170.5, 169.9, 156.1, 155.4, 143.8, 143.7, 141.2, 135.2, 131.2, 128.5, 128.4, 128.1, 127.6, 127.0, 125.1, 119.9, 119.1, 80.4, 67.3, 67.1, 66.4, 54.4, 53.9, 48.3, 47.0, 35.5, 35.1, 28.2 ppm. MALDI MS: m/z = 754.8 [M + Na^+], 770.7 [M + K^+]. $C_{39}H_{45}N_3O_9S{\cdot}0.5H_2O$ (740.9): calcd. C 63.23, H 6.26, N 5.67; found C 63.18, H 6.07, N 5.79.

1-*O*-Benzyl (2*S*,6*R*)-N^2-(*tert*-Butoxycarbonyl)-N^6-(fluoren-9-ylmethoxycarbonyl)lanthionate (10): *N*-Methylaniline (32 μL, 0.29 mmol) and tetrakis(triphenylphosphane)palladium (12 mg, 0.01 mmol) were added to a solution of **9** (63 mg, 0.095 mmol) in THF (3.2 mL) at room temperature. The reaction mixture was protected from light and stirred for 1 h. The mixture was then diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic layer was dried with $MgSO_4$, concentrated and subjected to flash column chromatography (CH_2Cl_2/MeOH, 30:1 → 20:1) to give **10** (55 mg, 94%): TLC R_f = 0.34 (CH_2Cl_2/MeOH, 10:1). [α]$_D$ = +8.9 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.68 (d-like, 2 H), 7.54 (br. s, 2 H), 7.26 (m, 9 H), 5.09 (br. s, 2 H), 4.52−4.14 (m, 5 H), 3.00 (m, 4 H), 1.36 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.0, 156.8, 156.2, 155.4, 144.0, 143.8, 141.2, 135.1, 132.2, 128.7, 128.5, 127.6, 127.0, 125.2, 119.8, 82.2, 80.2, 67.3, 54.6, 53.7, 47.0, 35.1, 29.7, 28.2 ppm. MALDI MS: m/z = 643.6 [M + Na^+]. $C_{33}H_{36}N_2O_8S$ (620.7): calcd. C 63.86, H 5.85, N 4.51; found C 63.81, H 6.11, N 3.86.

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[1] [1a] M. J. Horn, D. B. Jones, S. J. Ringel, *J. Biol. Chem.* **1941**, *138*, 141−149. [1b] T. Shiba, T. Wakamiya, K. Fukase, A. Sano, K. Shimbo, Y. Ueki, *Biopolymers* **1986**, *25*, S11−S19.
[2] C. Richaud, D. Mengin-Lecreulx, S. Pochet, E. J. Johnson, G. N. Cohen, P. Marlière, *J. Biol. Chem.* **1993**, *268*, 26827−26835.
[3] S. Burrage, T. Raynham, G. Williams, J. W. Essex, C. Allen, M. Cardno, V. Swali, M. Bradley, *Chem. Eur. J.* **2000**, *6*, 1455−1466 and references cited therein.
[4] J. Travis, *Science* **1994**, *264*, 360−362.
[5] H. G. Sahl, G. Bierbaum, *Annu. Rev. Microbiol.* **1998**, *52*, 41−79.
[6] For the synthesis of lanthionine or methyllanthionine derivatives, see: [6a] N. D. Smith, M. Goodman, *Org. Lett.* **2003**, *5*, 1035−1037. [6b] H. Shao, S. H. H. Wang, C. W. Lee, G. Ösapay, M. Goodman, *J. Org. Chem.* **1995**, *60*, 2956−2957. [6c] C. Dugave, A. Ménez, *Tetrahedron: Asymmetry* **1997**, *8*, 1453−1465. [6d] M. F. Mohd Mustapa, R. Harris, J. Mould, N. A. L. Chubb, D. Schultz, P. C. Driscoll, A. B. Tabor, *Tetrahedron Lett.* **2002**, *43*, 8359−8362. [6e] J. M. Probert, D. Rennex, M. Bradley, *Tetrahedron Lett.* **1996**, *37*, 1101−1104. [6f] K. Nakajima, H. Oda, K. Okawa, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 520−522. [6g] F. Cavelier-Frontin, J. Daunis, R. Jacquier, *Tetrahedron: Asymmetry* **1992**, *3*, 85−94. [6h] D. N. Harpp, J. G. Gleason, *J. Org. Chem.* **1971**, *36*, 73−80. [6i] I. Photaki, I. Samouilidis, S. Caranikas, L. Zervas, *J. Chem. Soc., Perkin Trans. 1* **1979**, 2599−2605. [6j] T. Wakamiya, Y. Oda, K. Fukase, T. Shiba, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 536−539.
[7] Besides ref. 3, for more examples of synthesis of lanthionine/(di)-methyllanthionine-containing peptides, see: [7a] A. K. Galande, A. F. Spatola, *Lett. Peptide Science* **2002**, *8*, 247−251. [7b] Y. Rew, S. Malkmus, C. Svensson, T. L. Yaksh, N. N. Chung, P. W. Schiller, J. A. Cassel, R. N. DeHaven, M. Goodman, *J. Med. Chem.* **2002**, *45*, 3746−3754 and references cited therein. [7c] G. Ösapay, M. Goodman, *J. Chem. Soc., Chem. Commun.* **1993**, 1599−1600. [7d] A. Polinsky, M. G. Cooney, A. Toy-Palmer, G. Ösapay, M. Goodman, *J. Med. Chem.* **1992**, *35*, 4185−4194. [7e] G. Ösapay, L. Prokai, H. S. Kim, K. F. Medzihradszky, D. H. Coy, G. Liapakis, T. Reisine, G. Melacini, Q. Zhu, S. H. H. Wang, R. H. Mattern, M. Goodman, *J. Med. Chem.* **1997**, *40*, 2241−2251. [7f] T. J. Baker, Y. Rew, M. Goodman, *Pure Appl. Chem.* **2000**, *72*, 347−354. [7g] T. Wakamiya, K. Shimbo, A. Sano, K. Fukase, T. Shiba, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2044−2049. [7h] K. Fukase, T. Wakamiya, T. Shiba, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2505−2508. [7i] K. Fukase, M. Kitazawa, A. Sano, K. Shimbo, S. Horimoto, H. Fujita, A. Kubo, T. Wakamiya, T. Shiba, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2227−2240. [7j] J. P. Mayer, J. Zhang, S. Groeger, C. F. Liu, M. A. Jarosinski, *J. Peptide Res.* **1998**, *51*, 432−436. [7k] H. Zhou, W. A. van der Donk, *Org. Lett.* **2002**, *4*, 1335−1338.
[8] [8a] L. Ingram, *Biochim. Biophys. Acta* **1970**, *224*, 263−265. [8b] N. Schnell, K. D. Entian, U. Schneider, F. Gotz, H. Zähner, R. Kellner, G. Jung, *Nature* **1988**, *333*, 276−278.
[9] Y. Hata, M. Watanabe, *Tetrahedron* **1987**, *43*, 3881−3888.
[10] Presumably, the *N*-trityl group is essential for β-iodoalanine derivatives to protect the α-centre from base-promoted racemisation, see: [10a] R. J. Cherney, L. Wang, *J. Org. Chem.* **1996**, *61*, 2544−2546. [10b] C. Dugave, A. Menez, *J. Org. Chem.* **1996**, *61*, 6067−6070.
[11] N. Kubasch, R. R. Schmidt, *Eur. J. Org. Chem.* **2002**, 2710−2726.
[12] X. Zhu, R. R. Schmidt, *Chem. Eur. J.*, submitted.
[13] D. H. R. Barton, Y. Hervé, P. Potier, J. Thierry, *Tetrahedron* **1988**, *44*, 5479−5486.
[14] B. M. Trost, R. Braslau, *J. Org. Chem.* **1988**, *53*, 532−537.
[15] E. Dauty, J. S. Remy, T. Blessing, J. P. Behr, *J. Am. Chem. Soc.* **2001**, *123*, 9227−9234.
[16] H. Waldmann, H. Kunz, *Liebigs. Ann. Chem.* **1983**, 1712−1725.
[17] Careful inspection of the ^{1}H NMR spectra of **12** and **13** did not reveal any contamination of the epimerised peptide.

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