Stereoselective Synthesis of Orthogonally Protected α-Methylnorlanthionine
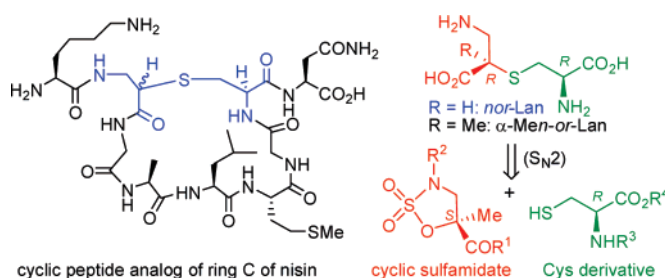
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ABSTRACT

cyclic peptide analog of ring C of nisin
cyclic sulfamidate
Cys derivative

As the unusual amino acid norlanthionine (*nor*-Lan) has previously been incorporated into cyclic peptide analogues of the ring C of lantibiotic nisin, we report here the stereoselective synthesis of the new (*S,R*)- and (*R,R*)-α-methylnorlanthionines (α-Me-*nor*-Lan). The orthogonally protected derivatives of these compounds have also been prepared. The key step in the synthesis of these bisamino acids was the S_N2 opening reaction of the corresponding cyclic sulfamidates with the SH group of appropriately protected L-cysteine derivatives.

The increasing problem of antibiotic resistance has highlighted the imperative demand for novel antimicrobial agents. Lantibiotics, lanthionine- or methyllanthionine-containing antibiotics, such as nisin, duramycin, and subtilin are produced by Gram-positive bacteria[1] and are promising candidates to address this problem. Lanthionine is an unusual bis-α-amino acid that consists of two alanyl residues bridged by a thioether linkage (Figure 1). In contrast to the labile

disulfide bond of cystine, the monosulfur bridge of lanthionine is chemically far stronger. For this reason, thioether-bridged peptides can be regarded as stable analogues of cystine bridges and lanthionine[2] and analogues[3] have therefore been incorporated into medicinally relevant peptides as
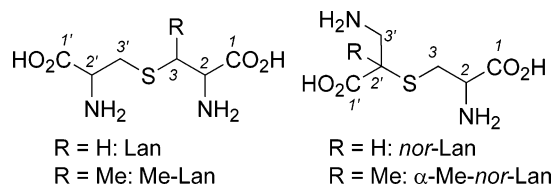

Figure 1. Representation of some lanthionine derivatives.

(1) Reviews: (a) Guder, A.; Wiedemann, I.; Sahl, H.-G. *Biopolymers* **2000**, *55*, 62. (b) van Kraaij, C.; de Vos, W. M.; Siezen, R. J.; Kuipers, O. P. *Nat. Prod. Rep.* **1999**, *16*, 575. (c) Breukink, E.; de Kruijff, B. *Biochim. Biophys. Acta* **1999**, *1462*, 223. (d) Sahl, H.-G.; Bierbaum, G. *Annu. Rev. Microbiol.* **1998**, *52*, 41. (e) Jung, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1051. (f) Chatterjee, Ch.; Paul, M.; Xie, L.; van der Donk, W. A. *Chem. Rev.* **2005**, *105*, 633 and references therein. (g) Patton, G. C.; van der Donk, W. A. *Curr. Opin. Microbiol.* **2005**, *8*, 543.

(2) (a) Ösapay, G.; Prokai, L.; Kim, H.-S.; Medzihradszky, K. F.; Coy, D. H.; Liapakis, G.; Reisine, T.; Melacini, G.; Zhu, Q.; Wang, S. H.-H.; Mattern, R.-H.; Goodman, M. *J. Med. Chem.* **1997**, *40*, 2241. (b) Melacini, G.; Zhu, Q.; Ösapay, G.; Goodman, M. *J. Med. Chem.* **1997**, *40*, 2252. (c) Polinsky, A.; Cooney, M. G.; Toy-Palmer, A.; Ösapay, G.; Goodman, M. *J. Med. Chem.* **1992**, *35*, 4185. (d) Ösapay, G.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1599. (e) Paul, M.; van der Donk, W. A. *Minirev. Org. Chem.* **2005**, *2*, 23. (f) Matteucci, M.; Bhalay, G.; Bradley, M. *Tetrahedron Lett.* **2004**, *45*, 1399. (g) Bregant, S.; Tabor, A. B. *J. Org. Chem.* **2005**, *70*, 2430.
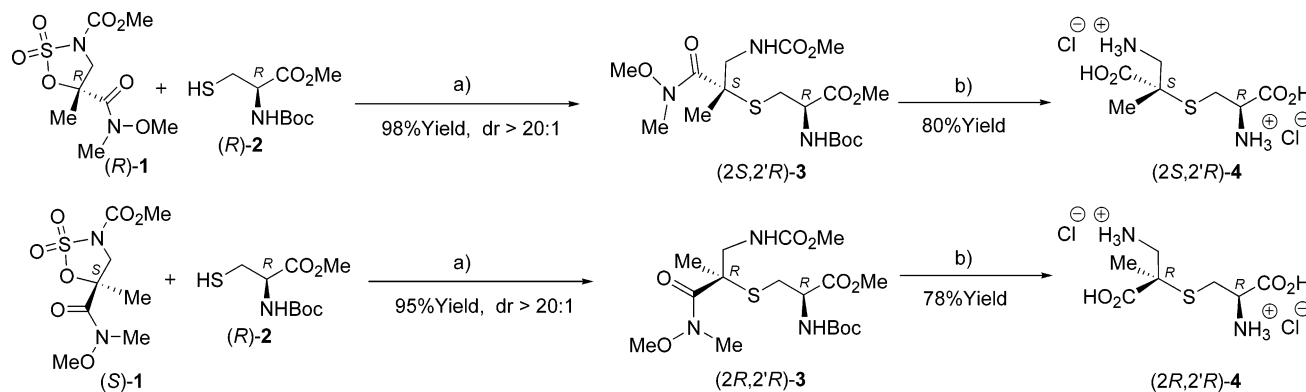
[a] Reagents and conditions: (a) (i) DBU, DMF, 50 °C, 1 h; (ii) 2 N HCl/CH$_2$Cl$_2$ (1:1), 25 °C, 10 h. (b) (i) LiOH·H$_2$O, MeOH/H$_2$O (3:2), 25 °C, 24 h; (ii) 12 N HCl, reflux, 12 h.

conformational constraints. The syntheses of lanthionine (Lan) and methyllanthionine (Me-Lan) monomers for use in peptide synthesis are nontrivial because of the requirement of orthogonal protection of the two amine groups and the two carboxylic acid functions. Despite this, however, several synthetic approaches to these compounds have been described in recent years.[2,4] Nevertheless, the synthesis of the isomer norlanthionine (*nor*-Lan), which consists of an alanyl and a β-alanyl residue (Figure 1), has to the best of our knowledge only been reported by the group of Tabor,[5] and this was incorporated into a cyclic peptide analogue of the ring C of lantibiotic nisin.[6]

In this sense, the development of a new and efficient synthesis of norlanthionine derivatives seems to be of interest. As part of our ongoing program aimed at the synthesis of restricted peptides, we decided to pursue approaches to α-methylnorlanthionines because of their potential biological importance.

We wish to report here new and efficient syntheses of (2*S*,2′*R*)- and (2*R*,2′*R*)-α-methylnorlanthionine (α-Me-*nor*-Lan) in diastereomerically pure form starting from the corresponding cyclic α-methylisoserine-derived sulfamidate as a chiral building block. The preparation of the orthogonally protected derivatives of the target compounds is also

reported. The opening reaction of the starting sulfamidate at the quaternary carbon center with the thiol group of a suitably protected cysteine derivative is the key step in the synthetic pathway.

Initially, and taking into account the excellent results obtained in the opening reaction of the easily accessible chiral building block (*R*)-**1** with nucleophiles,[7] particularly with sulfur nucleophiles,[8] we performed the S$_N$2 reaction with commercial *N*-Boc-L-cysteine methyl ester (*R*)-**2** using DBU as a base and DMF as a solvent at 50 °C for 1 h, followed by acid hydrolysis of the sulfamic acid intermediate. Purification of the crude product by column chromatography gave the corresponding protected α-Me-*nor*-Lan **3** in excellent yield (98%) with a dr > 20:1[9] (Scheme 1).

Bearing in mind that the protecting groups on derivative **3** are not suitable for peptide synthesis, we used this compound to obtain the free α-Me-*nor*-Lan **4**. Weinreb amide hydrolysis of **3** with LiOH, followed by acid hydrolysis with 12 N HCl under reflux gave (2*S*,2′*R*)-α-Me-*nor*-Lan **4** as the hydrochloride derivative. The other diastereoisomer was obtained by the same sequence of reactions but starting from the chiral building block (*S*)-**1** and giving the protected (2*R*,2′*R*)-α-Me-*nor*-Lan **3**, which was hydrolyzed to (2*R*,2′*R*)-α-Me-*nor*-Lan **4** (Scheme 1).

Given that an orthogonal protecting group plan will be required for the future regioselective manipulation of these important diastereomerically pure core residues, α-Me-*nor*-Lan, we considered changing the protecting groups on the starting materials: the chiral sulfamidate-derived building blocks and the cysteine derivatives.

To this end, the amide and carbamate groups of sulfamidate (*R*)-**1** were hydrolyzed to give sulfamidate (*R*)-**5**. The

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(5) (a) Mustapa, M. F. M.; Harris, R.; Mould, J.; Chubb, N. A. L.; Schultz, D.; Driscoll, P. C.; Tabor, A. B. *Tetrahedron Lett.* **2002**, *43*, 8363. (b) Mustapa, M. F. M.; Harris, R.; Bulic-Subanovic, N.; Elliott, S. L.; Bregant, S.; Groussier, M. F. A.; Mould, J.; Schultz, D.; Chubb, N. A. L.; Gaffney, P. R. J.; Driscoll, P. C.; Tabor, A. B. *J. Org. Chem.* **2003**, *68*, 8185.

(6) Mustapa, M. F. M.; Harris, R.; Esposito, D.; Chubb, N. A. L.; Mould, J.; Schultz, D.; Driscoll, P. C.; Tabor, A. B. *J. Org. Chem.* **2003**, *68*, 8193.

(7) (a) Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Chem. Commun.* **2004**, 980. (b) Building block (*R*)-**1** was obtained in two steps from the Weinreb amide of methacrylic acid with an overall yield of 78%.

(8) Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M. *J. Org. Chem.* **2006**, *71*, 1692.

(9) The diastereomeric purity of opening products (2*R*,2′*R*)-**3**, (2*S*,2′*R*)-**3**, (2*S*,2′*R*)-**20**, and (2*R*,2′*R*)-**20** was determined by ^{1}H NMR spectroscopy, and a sole stereoisomer was detected: dr > 20:1.

carboxylic acid function of this compound was transformed into benzyl and allyl esters to obtain sulfamidates (*R*)-**6** and (*R*)-**7**, respectively (Scheme 2).
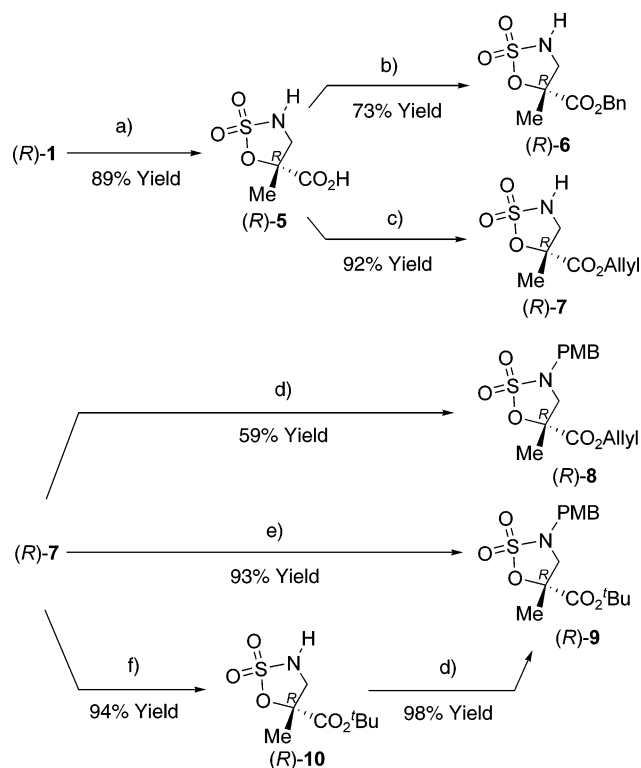
The NH function of compound (*R*)-**7** was protected with the *p*-methoxybenzyl group (PMB) by reaction with *p*-methoxybenzyl bromide (PMB-Br) in the presence of 1.0 equiv of ᵗBuOK as base in THF. This reaction yielded sulfamidate (*R*)-**8** as the major product, accompanied by sulfamidate (*R*)-**9** as a result of the transformation of the allyl ester into the *tert*-butyl ester. Treatment of sulfamidate (*R*)-**7** under the conditions described above, but using 7.5 equiv of ᵗBuOK, gave compound (*R*)-**9** exclusively. Alternatively, compound (*R*)-**9** could also be obtained in two steps from (*R*)-**7**, via (*R*)-**10**, by transesterification and subsequent *N*-alkylation (Scheme 2).

As far as the cysteine derivatives are concerned, commercially available L-cystine bisallyl ester di(*p*-toluensulfonate) salt (2*R*,2′*R*)-**11** was used to give cysteine derivative (*R*)-**13** in two steps. This procedure involved the generation of Boc carbamate (2*R*,2′*R*)-**12** followed by cleavage of the disulfide bond with tri-*n*-butylphosphine (Bu₃P). Moreover, two other protected cysteine derivatives (*R*)-**16** and (*R*)-**19** were synthesized from L-cystines (2*R*,2′*R*)-

14 and (2*R*,2′*R*)-**17**, respectively, which are also commercially available (Scheme 3).
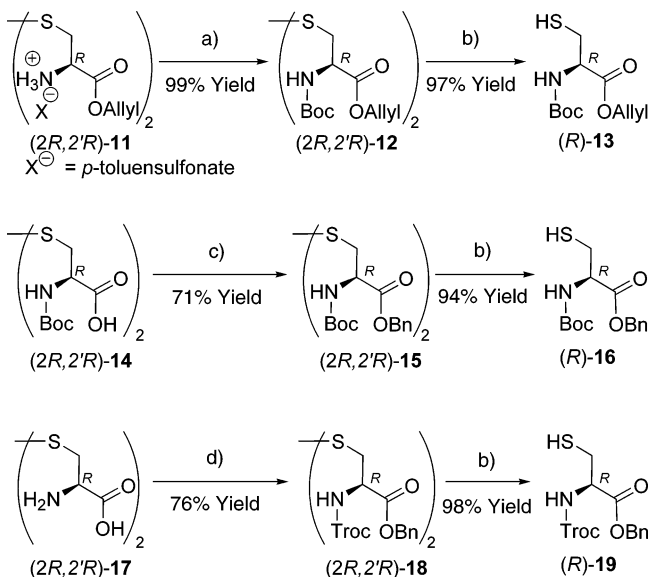
The synthesis of the known cysteine derivative[10] (*R*)-**16** from cystine (2*R*,2′*R*)-**14** was performed by a new procedure that involved esterification of the carboxylic acids with benzyl alcohol in the presence of oxalyl chloride and dichloroethane as a solvent to give (2*R*,2′*R*)-**15**, followed by clean cleavage of the disulfide bridge with Bu₃P (Scheme 3).

On the other hand, the synthetic route to compound (*R*)-**19** from cystine (2*R*,2′*R*)-**17** started from the protection of the amino group as the trichloroethoxycarbonyl (Troc) carbamate in a basic medium. The carboxylic acid groups of the corresponding cystine derivative were then activated as acid chlorides to incorporate the benzyl group as an ester function with benzyl alcohol to give compound (2*R*,2′*R*)-**18**, which was readily transformed into the desired protected cysteine (*R*)-**19** by treatment with Bu₃P (Scheme 3).

In an effort to synthesize orthogonally protected α-Me-*nor*-Lan, we initially explored the use of cysteine (*R*)-**13** as a nucleophile to open cyclic sulfamidate (*R*)-**6** under different conditions. Unfortunately, all attempts failed, probably because of internal attack of SH or NHBoc groups on the allyl ester (as detected by ¹H NMR). Taking this fact into account, we decided to change the protecting groups, i.e., the allyl ester in the sulfamidate building block and the benzyl ester in the cysteine moiety. Moreover, the NH

(10) (a) Humphrey, R. E.; McCrary, A. L.; Webb, R. M. *Talanta* **1965**, *12*, 727. (b) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532.

function of the sulfamidate was protected with the *p*-methoxybenzyl group. Indeed, we assayed the opening reaction of sulfamidate (*R*)-**8** with cysteine (*R*)-**16**, and a complex mixture of several compounds was obtained. Fortunately, these problems were solved by using compound (*R*)-**19** as the protected cysteine and compound (*R*)-**9** as the sulfamidate building block. The S$_N$2 reaction with DBU as the base and DMF as the solvent, followed by acid hydrolysis, gave orthogonally protected α-Me-*nor*-Lan (2*S*,2′*R*)-**20** in excellent yield in diastereomerically pure form (Scheme 4).

Scheme 4. Synthesis of Orthogonally Protected α-Me-*nor*-Lan (2*S*,2′*R*)-**20** and (2*R*,2′*R*)-**20**[a]

(2*S*,2′*R*)-**20**

(2*R*,2′*R*)-**20**
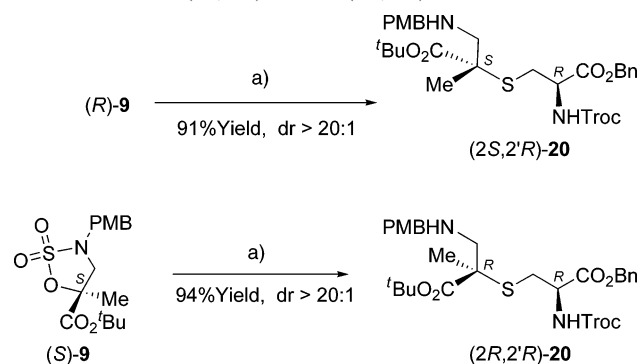
a Reagents and conditions: (a) (i) (*R*)-**19**, DBU, DMF, 50 °C, 1 h; (ii) 20% H$_2$SO$_4$/CH$_2$Cl$_2$ (1:1), 25 °C, 10 h.

In an attempt to obtain the diastereoisomer of α-Me-*nor*-Lan with the (2*R*,2′*R*)-configuration, we synthesized the enantiomer of (*R*)-**9**; the sulfamidate building block (*S*)-**9**

was prepared using the protocol described above but starting from (*S*)-**1**. The opening reaction of (*S*)-**9** with cysteine (*R*)-**19** gave the orthogonally protected α-Me-*nor*-Lan (2*R*,2′*R*)-**20** in diastereomerically pure form (Scheme 4). Evidently, the other two diastereomers of α-Me-*nor*-Lan could be obtained by following the synthetic pathway described here but combining the sulfamidates (*S*)-**9** and (*R*)-**9** with the cysteine moiety (*S*)-**19**.

In summary, we have carried out the stereoselective synthesis of the new (*S*,*R*)- and (*R*,*R*)-α-methylnorlanthionines (α-Me-*nor*-Lan). We have also prepared the orthogonally protected derivatives for peptide synthesis. The key step in the synthetic pathway for these new bisamino acids was the S$_N$2 opening reaction of the corresponding chiral cyclic sulfamidates with the SH group of L-cysteine derivatives. Taking into account that *nor*-Lan-containing peptides show unknown turn conformations, the future inclusion of α-Me-*nor*-Lan into peptides will allow the exploration of conformational space which will probably not be available with the proteinogenic amino acids.

Supporting Information Available: Experimental details, as well as spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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