ORGANIC LETTERS

2000
Vol. 2, No. 8
1105−1107

A New Selective Synthesis of the Ile-*allo*-Thr-Gly Tripeptide Fragment of Lysobactin

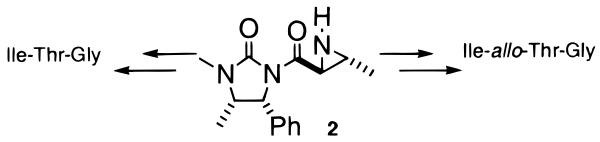
Silvia Armaroli, Giuliana Cardillo,* Luca Gentilucci, Massimo Gianotti, and Alessandra Tolomelli

Dipartimento di Chimica "G.Ciamician" and CSFM-CNR, Università di Bologna, via Selmi 2, 40126 Bologna, Italy

cardillo@ciam.unibo.it

Received February 14, 2000

ABSTRACT



***trans*-Aziridine-2-carboxylic acid derivatives are useful intermediates for the synthesis of threonine or *allo*-threonine through ring expansion and S_N2 displacement, respectively. We describe here the preparation of the Ile-*allo*-Thr-Gly 11 fragment of Lysobactin via the aziridine 9 intermediate.**

Lysobactin[1] **1** was isolated from the fermentation of *Lysobacter* sp. SC13,067 (ATCC 53042) and is a potent agent against Gram-positive bacteria (in vitro). Its efficacy in vivo was compared with that of the antibiotic Vancomycin. Vancomycin and related antibiotics inhibit bacterial cell wall biosynthesis by specific binding to D-alanyl-D-alanine cell wall precursors. The structure of **1** (Figure 1) shows the interesting presence of the glycine-*allo*-threonine-isoleucine tripeptide sequence.

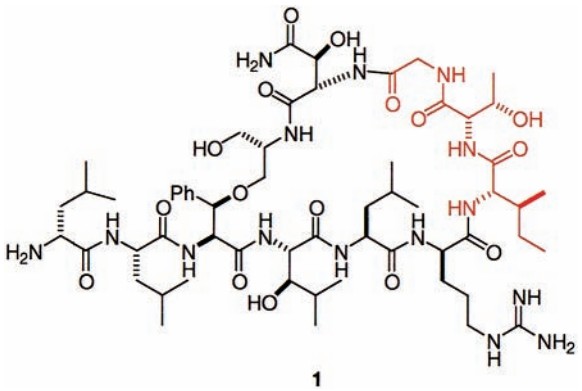


Figure 1. Lysobactin.

We report here our progress toward the synthesis of this tripeptide fragment containing *allo*-threonine with the assigned (2*S*,3*S*) configuration. Our project starts from the idea that the β-hydroxy-α-amino acids in **1** come with the aziridine acyl derivative precursor. These activated aziridine compounds give aziridine ring opening with an inversion of configuration by a proper nucleophile.[2] On the other hand, the aziridine ring expansion reaction gives the corresponding oxazoline as a protected form of the amino alcohol compounds. This reaction occurs with retention of configuration of the starting aziridine derivative stereocenters (Scheme 1).[3]

We explored both of these strategies, showing that a threonine or *allo*-threonine dipeptide sequence may be synthesized from a unique starting aziridine simply by

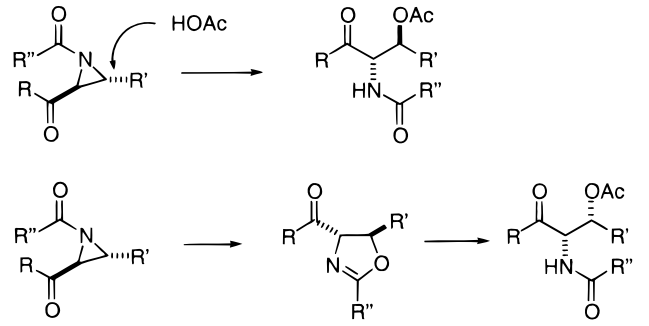
(1) (a) O'Sullivan, J.; McCullough, J. E.; Tymiak, A. A.; Kirsch, D. R.; Trejo, W. H.; Principe P. A. *J. Antibiot.* **1988**, *41*, 1740−1744. (b) Tymiak, A. A.; McCormick, T. J.; Unger, S. E. *J. Org. Chem.* **1989**, *54*, 1149−1157.

(2) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59−68. (d) Dauban, P.; Dubois, L.; Tran Huu Dau, M. E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035−2043.

(3) (a) Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081−3088. (b) Ferraris, F.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568−4569 and references therein.

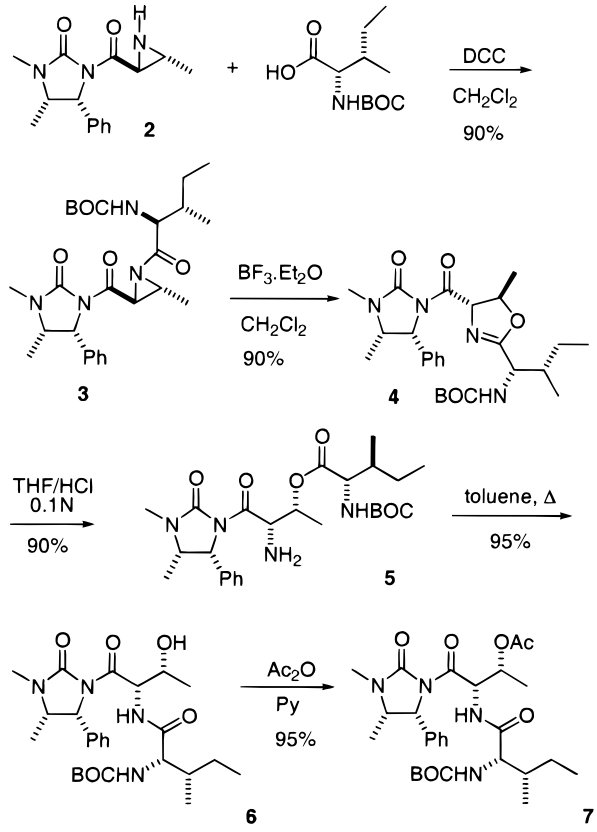
10.1021/ol005659o CCC: $19.00
Published on Web 03/29/2000

Scheme 1. Reactivity of Activated Aziridines



changing the steps of the synthetic sequences. The (2′*S*,3′*R*) aziridine **2** was obtained as the major isomer from a two-step sequence: 1,4-addition of *O*-benzylhydroxylamine to the α,*β*-unsaturated crotonyl derivative followed by cyclization to the corresponding *trans* aziridine[4] through the intermediate enolate.[5] The stereochemical result of the reaction was controlled using (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one as a chiral auxiliary. The synthesis of the isoleucine-threonine derivative is outlined in Scheme 2. The acyl derivative (2*S*,3*R*)-**3**[6] was obtained in 90% yield by treatment of **2** with *N*-BOC-isoleucine and DCC in CH_2Cl_2. After purification by flash chromatography on silica gel, compound **3** was converted to oxazoline (4*S*,5*R*)-**4** in the presence of $BF_3{\cdot}Et_2O$. The oxazoline H_4-H_5 coupling

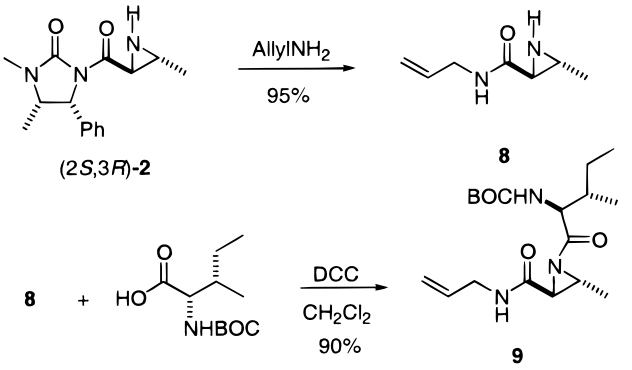
Scheme 2. Synthesis of Dipeptide Derivatives **6** and **7**



constant ($J = 5.7$ Hz) confirmed the *trans* relationship.[7] The hydrolysis of **4** was carried out in THF with 0.1 N HCl, and this gave the ester (2′*S*,3′*R*)-**5** in 90% yield. Nucleophilic intramolecular displacement to the amide (2′*S*,3′*R*)-**6** was performed in toluene at reflux for 3 h. The *O*-acetate **7** was easily prepared by treatment of **6** with acetic anhydride and pyridine in CH_2Cl_2 (Scheme 2).[8]

This sequence leads to the preparation of an Ile-Thr derivative. To obtain Ile-*allo*-Thr, an S_N2 aziridine ring opening is required. However, attempts to promote the ring opening of aziridine **3** by treatment with CH_3COOH failed to give **4** preferentially. This demonstrates that the presence of the chiral auxiliary strongly favors the aziridine to oxazoline ring expansion.[9] For this reason the correct sequence containing (2*S*,3*S*)-*allo*-threonine was obtained by removing the imidazolidinone chiral auxiliary at an earlier stage of the sequence, as outlined in Scheme 3.

Scheme 3. Synthesis of Derivative **9**



The introduction of a masked glycine was achieved by treatment of **2** with neat allylamine[10] at room temperature

(4) For the addition of NH_2OBn, see: (a) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615−5619. For cyclization to *trans* aziridine, see: (c) Cardillo, G.; Casolari, S.; Gentilucci, L.; Tomasini, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1848−1849. (d) Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148−9153.

(5) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

(6) For a review of aziridine-containing peptides, see: (a) Okawa, K.; Nakajima, K. *Biopolymers* **1981**, *20*, 1811−1821. (b) Korn, A.; Rudolph-Böhner, S.; Moroder, L. *Tetrahedron* **1994**, *50*, 1717−1730.

(7) (a) Foglia, T. A.; Gregory, L. M.; Maerker, G. *J. Org. Chem.* **1970**, *35*, 3779−3785. (b) Pines, S. H.; Kozlowski, M. A.; Karady, S. *J. Org. Chem.* **1969**, *34*, 1621−1627.

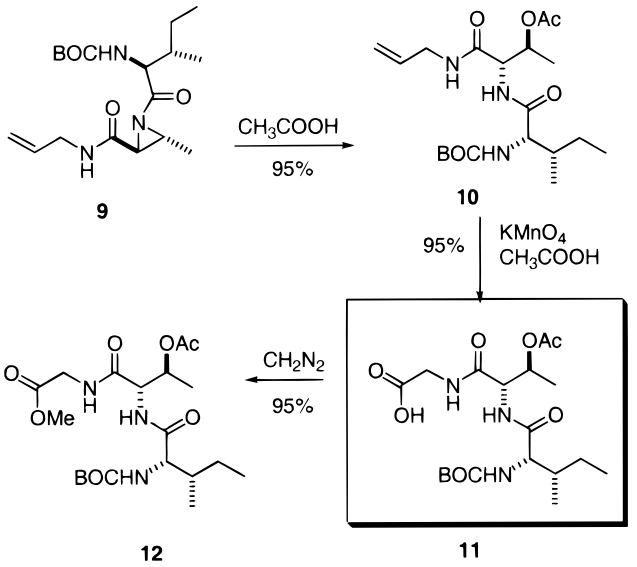
(8) Selected data for **5**: ^{1}H NMR ($CDCl_3$) δ 0.74 (d, 3H, $J = 6.9$ Hz); 0.79 (d, 3H, $J = 6.6$ Hz); 0.80 (t, 3H, $J = 7.2$ Hz); 0.97−1.34 (m, 2H); 1.31 (d, 3H, $J = 6.0$ Hz); 1.45 (s, 9H); 1.62−1.88 (bm, 3H); 2.83 (s, 3H); 3.88−3.96 (m, 2H); 4.84 (d, 1H, $J = 3.3$ Hz); 5.05 (d, 1H, $J = 8.4$ Hz); 5.31 (d, 1H, $J = 9.0$ Hz); 5.38 (dq, 1H, $J = 3.3, 6.0$ Hz); 7.07−7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.5, 14.2, 14.9, 15.1, 25.1, 26.9, 28.4, 37.9, 54.2, 57.8, 59.2, 60.4, 79.4, 127.0, 128.3, 128.5, 135.9, 155.2, 155.3, 170.9, 171.1. $[\alpha]^{20}_D = -46.2$ ($c = 0.6$, $CHCl_3$). **6**: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3H, $J = 6.6$ Hz); 0.88 (t, 3H, $J = 7.5$ Hz); 0.89 (d, 3H, $J = 7.5$ Hz); 1.03−1.31 (m, 2H); 1.19 (d, 3H, $J = 6.3$ Hz); 1.41 (s, 9H); 1.75−1.93 (m, 1H); 2.83 (s, 3H); 3.91−3.98 (m, 1H); 3.98 (dq, 1H, $J = 6.6, 9.3$ Hz); 4.33 (dq, 1H, $J = 2.1, 6.3$ Hz); 5.05 (d, 1H, $J = 8.1$ Hz); 5.34 (d, 1H, $J = 9.3$ Hz); 5.95 (dd, 1H, $J = 2.1, 8.7$ Hz); 6.67 (d, 1H, $J = 8.7$ Hz); 7.13−7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 11.4, 15.1, 15.5, 19.5, 24.8, 28.2, 28.3, 37.3, 54.2, 55.7, 59.2, 59.4, 68.5, 79.8, 126.8, 128.3, 128.7, 136.1, 155.2, 169.9, 171.4, 171.5. $[\alpha]^{20}_D = -45.0$ ($c = 1$, $CHCl_3$).

for 4 h to give the allylamido derivative (2*S*,3*R*)-**8** in 95% yield. The coupling of compound **8** with *N*-BOC-isoleucine was performed in CH_2Cl_2, and (2*S*,3*R*)-**9** was obtained in 90% yield.

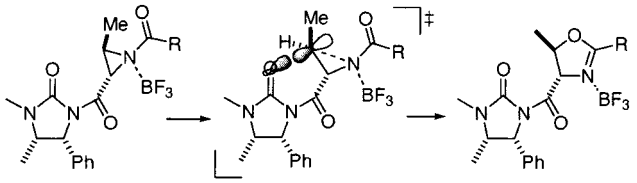
Ring opening of the (2*S*,3*R*)-aziridine derivative **9** was performed in CH_3COOH as reported in the literature.[2b] This reaction proceeded through an S_N2 mechanism, and the *allo*-threonine acetate derivative (2*S*,3*S*)-**10** was isolated in 95% yield. Finally **10** was treated with $KMnO_4/CH_3COOH$[11] in a remarkably clean reaction to give (2*S*,3*S*)-**11**, which was converted to its methyl ester derivative **12** with CH_2N_2 (Scheme 4). The ^1H NMR and ^{13}C NMR of both compounds are consistent with their assigned structures.[12]

In conclusion, our synthetic protocol which starts from the aziridine enabled us to prepare *allo*-Thr- and Thr-containing sequences in a few steps and in a high yield. Since five hydroxyamino acids in the Lysobactin backbone are present in the *syn* or *anti* configuration,[13] our results show a reasonable and encouraging route toward the total synthesis of the macrocyclic lactone.

Scheme 4. Synthesis of Tripeptide **11**



(9) It is generally assumed that the ring expansion of *N*-acylaziridine occurs via a carbocationic-like TS (ref 3a) or a carbocationic intermediate (ref 3b) and is favored by the presence of Lewis acids.



Our semiempirical calculations suggest that the presence of the imidazolidin-2-one substituent could be responsible for the accelerated expansion rate. Indeed, the reactant adopts a preferential conformation in which the endocyclic carbonylic oxygen points toward the aziridine C3′, thus stabilizing the incipient positive charge. This model is in accord with our previous experimental observations that aziridine 2-ester ring expansion is much slower than that of aziridine 2-imide.

(10) Davis, S. G.; Dixon, D. J. *Synlett* **1998**, 963−964.

(11) Itani, H.; Uyeo, S. *Synlett* **1995**, 213.

(12) Selected data for **11**: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H); 1.20−1.40 (m, 1H); 1.25 (m, 3H); 1.39 (s, 9H); 1.41−1.60 (m, 1H); 1.80−2.00 (m, 1H); 2.05 (s, 3H); 3.95−4.18 (m, 3H); 4.92−5.04 (m, 1H); 5.05−5.21 (m, 1H); 5.23−5.40 (d, 1H, J = 7.6 Hz); 7.30−7.45 (m, 1H); 7.46−7.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 11.8, 14.8, 17.0, 20.5, 24.7, 28.3, 33.9, 39.2, 54.2, 59.7, 65.8, 79.0, 155.4, 163.7, 166.2, 166, 4, 181.5. $[\alpha]^{20}_D = -22.0$ (c = 1.0, $CHCl_3$).

(13) For an alternative method for the direct introduction of hydroxyamino acids starting from heterocyclic compounds, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Odriozola, B.; Maneiro, E.; Miranda, J. I.; Urchegui, R. *Chem. Commun*. **1996**, 161−162. (b) Palomo, C.; Cabrè, F.; Ontoria, J. M. *Tetrahedron Lett*. **1992**, *33*, 4819−4822.

Acknowledgment. This work was supported by MURST (60% and Cofin '98) and by the University of Bologna (funds for selected topics "Sintesi e caratterizzazione di biomolecole per la salute umana").

Supporting Information Available: Full experimental details and analytical data for all new compounds (**3**−**12**) and representative ^1H NMR spectra of compounds **3**, **4**, **7**, **8**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005659O