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Synthesis of the *N*-(*tert*-butyloxycarbonyl)-*O*-triisopropylsilyl-D-pyrrolosamine glycal of lomaiviticins A and B via epimerization of L-Threonine

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ABSTRACT

An efficient synthesis of the *N*-(*tert*-butyloxycarbonyl)-*O*-triisopropylsilyl-D-pyrrolosamine glycal of lomaiviticin A (1) and lomaiviticin B (**2**) is described. The synthesis is highlighted by the epimerization of the L-threonine-derived oxazolidine **10** to oxazolidine **11**. This key epimerization reaction, which serves to establish the correct relative configuration of the carbohydrate unit, was made possible only after conformational analysis indicated that substituted oxazolidines may adopt conformations that preclude enolization.

In 2001, He and co-workers reported the isolation and characterization of lomaiviticin A (**1**) and lomaiviticin B (**2**) (Fig. 1).[1] These molecules are potent growth inhibitors against 24 cultured human cancer cell lines (GI_{50} = 0.01–98 ng/ml). The cytotoxicity patterns of **1** and **2** in a 24 cell line panel of human cancer cells are unique, suggesting that they have novel mechanisms of action.

In addition to their potent activity in cells, **1** and **2** are unprecedented C_2-symmetric structures. They share identical core structures, but lomaiviticin A is glycosylated at C3 and C3′ while the C3 and C3′ carbinols of lomaiviticin B are engaged as ketals with C1 and C1′. The C4 and C4′ carbinols of **1** and **2** are glycosylated with rare *N*,*N*-dimethylpyrrolosamine carbohydrates. Both **1** and **2** possess a diazobenzofluorene ring system that evokes comparisons to the kinamycin family of natural products.[2] Progress toward the synthesis of **1** and **2** has been reported,[3] including our approach to the central ring system of lomaiviticin A using a stereoselective oxidative enolatedimerization of a 7-oxanorbornanone.[4]

Recently, the synthesis of the *N*,*N*-dimethylpyrrolosamine carbohydrate found in both **1** and **2** has been addressed by our group[5] as well as Herzon and co-workers.[6] In this Letter, we describe an alternative synthesis of the *N*,*N*-dimethylpyrrolosamine sugar that utilizes an interesting and useful epimerization reaction.

Our initial synthesis plan is outlined in Scheme 1. We targeted a suitably protected glycal that could ultimately be converted to a glycosyl donor. The retrosynthetic analysis began from glycal **3** which would be obtained via cycloisomerization of **4**. Alkynol **4** would be accessed from methyl ester **5**, which could be derived from the amino acid D-*allo*-threonine (**6**).

An initial challenge to this synthesis plan was the limited commercial availability of D-*allo*-threonine **6**.[7] Given the potential utility of this amino acid in organic synthesis, it was not surprising that several methods are available for its preparation.[8] Despite the availability of these methods, we were interested in devising a more efficient strategy to access this important amino acid. Specifically, we sought to develop a strategy where L-threonine **7** could be epimerized at the amino stereocenter to provide the desired D-*allo*-threonine configuration since **7** is readily available (Scheme 2).

Our revised plan was to start the synthesis route outlined in Scheme 1 with L-threonine (**7**) instead of its more expensive diastereomer **6**. We surmised that the enolate of the L-threonine-derived oxazolidine **8** would be protonated from the *si*-face, providing the desired configuration at the amino stereocenter. This epimerization strategy offered two distinct advantages over the approaches previously reported in the literature. First, our synthesis would begin from **7**, a cheap and readily available starting material. Second, this strategy provides an alternative to undertaking a separate synthesis to procure multigram quantities of D-*allo*-threonine by utilizing an intermediate in our proposed route to the target glycal **3**.

Toward this end, L-threonine was readily converted to oxazolidine **8** (Scheme 3). Initially, we chose to carry out a control experiment to test the feasibility of the approach outlined in Scheme 2. Oxazolidine **8** was treated with LDA at −78 °C followed by exposure to MeI. The purpose of using MeI in this control experiment was twofold. While serving to confirm the facial selectivity of the alkylation (and ultimately, the protonation), this experiment would also allow us to unambiguously confirm if enolization was achieved.[9] Surprisingly, after oxazolidine **8** was treated with LDA at −78 °C followed by MeI the starting material was recovered unchanged.

Though we acknowledged the possibility that the enolate was too hindered to be alkylated with MeI, we considered this scenario to be unlikely.[10] It seemed more probable that the enolate had not been formed. This observation can be rationalized by considering possible conformations of oxazolidine **8** (Fig. 2). An important consideration to the following analysis is that the carbamate will

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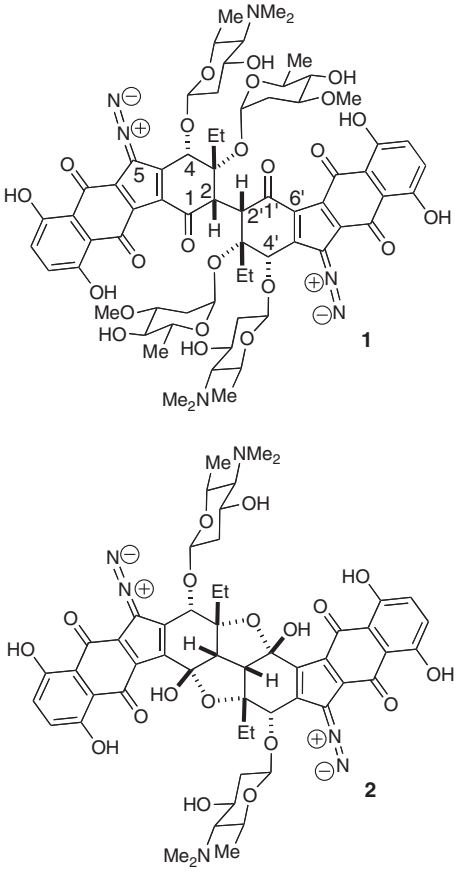
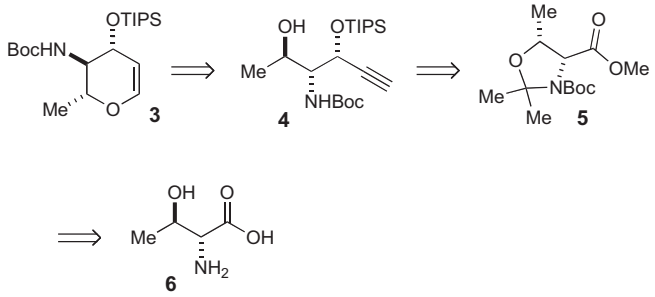
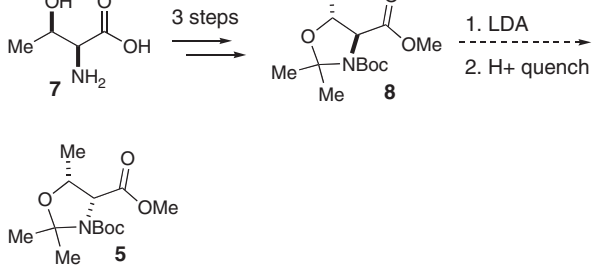


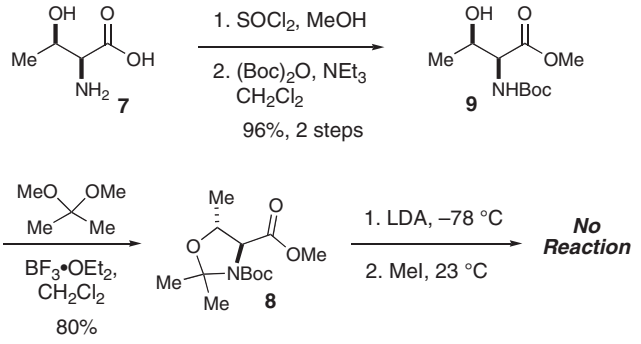
Figure 1. Lomaiviticin A (**1**) and lomaiviticin B (**2**).



Scheme 1. Retrosynthetic analysis.



Scheme 2. Proposed epimerization of L-threonine.



Scheme 3. Synthesis of epimerization precursor.

possess double bond character. In conformer **I**, the hydrogen α to the ester is placed in plane with the carbamate in order to minimize allylic strain. This forces the ester into a pseudo-axial position and introduces an unfavorable *syn*-pentane interaction between the ester and the methyl substituent cis to the ester. An alternative conformer (**II**) is one in which the ester is placed in a pseudo-equatorial position, thereby alleviating the *syn*-pentane interaction. However, in order to minimize unfavorable steric interactions with the carbamate, the ester rotates about the C–C bond (shown in red). As a consequence of this bond rotation, the α-hydrogen is no longer stereoelectronically aligned for deprotonation.

This conformational analysis indicates that enolization will only take place if conformer **I** could be accessed. Using this analysis as a guide we sought to redesign the substrate such that the *syn*-pentane interaction would be alleviated. We rationalized this would be done most effectively by replacing the methyl group cis to the methyl ester with a proton.

Toward that end, methyl ester **9** was treated with pivaldehyde under acidic conditions to afford oxazolidine **10** (Scheme 4). With the *syn*-pentane interaction now removed, we were pleased to discover that exposure of **10** to LDA followed by a reverse quench with AcOH/MeOH afforded the fully epimerized product in quantitative yield.[11] This result strongly supports the assertion

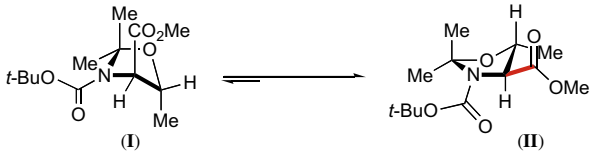
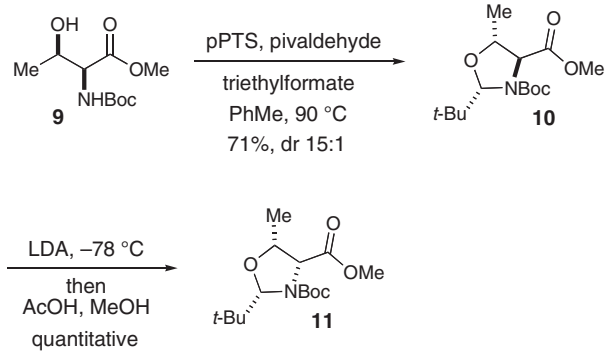
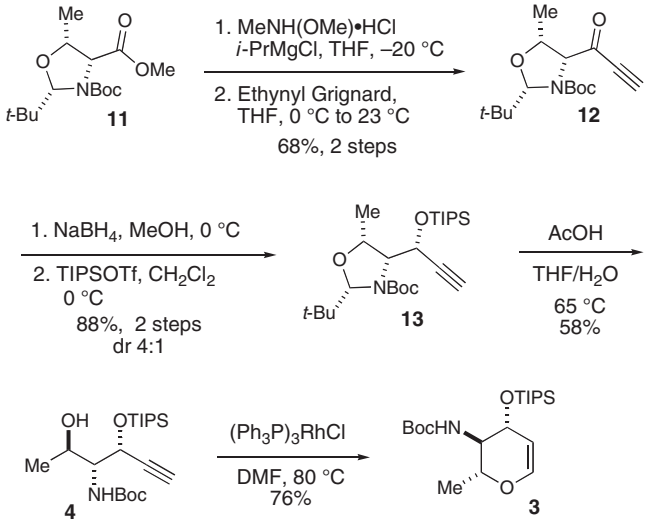


Figure 2. Conformational analysis of oxazolidine **8**.



Scheme 4. Synthesis of revised epimerization substrate.



Scheme 5. Synthesis of glycal **3**.

that enolization was precluded because of unfavorable non-covalent interactions described in Figure 2.

After the successful epimerization[12] of **10**, oxazolidine **11** was converted to a Weinreb amide followed by treatment with ethynyl Grignard (Scheme 5). The ynone **12** was reduced to the corresponding propargyl alcohol with $NaBH_4$.[13] The resulting carbinol was protected as a TIPS ether and the oxazolidine was cleaved under acidic conditions. The resulting alkynol underwent cycloisomerization[14] in the presence of Wilkinson's catalyst to provide glycal **3** in 76% yield.[15]

In conclusion, we have developed an efficient synthesis of the *N*-(*tert*-butyloxycarbonyl)-*O*-triisopropylsilyl-D-pyrrolosamine glycal of lomaiviticin A (**1**) and lomaiviticin B (**2**). Our synthesis is highlighted by the epimerization of the L-threonine derived oxazolidine **10** to oxazolidine **11**, which possesses the desired relative configuration. This epimerization reaction was made possible only after control experiments indicated that substituted oxazolidines may adopt conformations that preclude enolization. Glycal **3** will ultimately be converted to a suitable glycosyl donor for the glycosylation of the aglycones of **1** and **2**. These results will be reported in due course.

Acknowledgments

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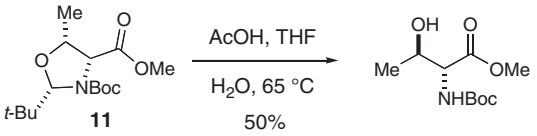
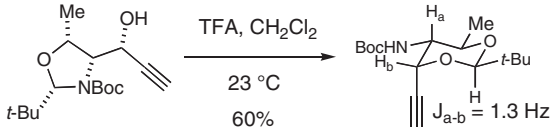
References and notes

1. He, H.; Ding, W.-D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362–5363.
2. (a) Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207–2208; (b) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209–2210; (c) Marco-Contrelles, J.; Molina, M. T. *Curr. Org. Chem.* **2003**, *7*, 1433–1442.
3. (a) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076–2081; (b) Zhang, W.; Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2008**, *10*, 1939–1941; (c) Nicolaou, K. C.; Nold, A. N.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5860–5862.
4. Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684.
5. Moris, W. J.; Shair, M. D. *Org. Lett.* **2008**, *11*, 9–12.
6. Gholap, S. L.; Woo, C. M.; Ravikumar, P. C.; Herzon, S. B. *Org. Lett.* **2009**, *11*, 4322–4325.
7. Recently, the production of D-*allo*-threonine has been discontinued by Sigma–Aldrich.
8. (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42; (b) Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765–6768; (c) Pons, D.; Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 5023–5026; (d) Beaulieu, P. L. *Tetrahedron Lett.* **1991**, *32*, 1031–1034; (e) Blaskovich, M. A.; Lajoie, G. A. *Tetrahedron Lett.* **1993**, *34*, 3837–3840; (f) Fischer, P. M.; Sandosham, J. *Tetrahedron Lett.* **1995**, *36*, 5409–5412; (g) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582–2583; (h) Lloyd-Williams, P.; Sanchez, A.; Carulla, N.; Ochoa, T.; Giralt, E. *Tetrahedron* **1997**, *53*, 3369–3382; (i) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Eur. J. Org. Chem.* **2000**, 1443–1449.
9. The product resulting from protonation of the enolate from the *re*-face would be identical to the starting material. Therefore, we would not be able to unambiguously determine whether this product was a result of *re*-face protonation or failure to achieve enolate formation.
10. Similar serine-derived oxazolidines have been alkylated with MeI: Brunner, M.; Saarenketo, P.; Straub, T.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2004**, 3879–3883.
11. The resulting oxazolidine **11** was cleaved under acidic conditions. The ^1H NMR of the resulting β-hydroxy-α-amino ester matched the known ^1H NMR of the of *N*-Boc-L-*allo*-threonine methyl ester:



Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185–4188.
12. *Experimental procedure for epimerization of oxazolidine* **10**: To a solution of diisopropylamine (20 ml, 143 mmol) in THF (252 ml) at −78 °C was added *n*BuLi (53 ml, 126 mmol) dropwise. The resulting LDA solution was allowed to stir at −78 °C for 10 min. A solution of oxazolidine **10** (15.5 g, 57.2 mmol) in THF (114 ml) was added to the cooled solution (−78 °C) of LDA dropwise over 20 min. The resulting pale yellow solution was allowed to stir at −78 °C for 2 h. The enolate solution was transferred to a rapidly stirring mixture of AcOH (78 ml) in MeOH (200 ml) at −78 °C and allowed to stir for 5 min. The reaction mixture was diluted with EtOAc (200 ml), washed with saturated $NaHCO_3$ (3 × 100 ml), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford oxazolidine **11** (15.5 g, quantitative). Characterization data for **11**: ^1H NMR (600 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.57–4.55 (d, J = 7.1 Hz, 1H), 4.28–4.24 (ddd, J = 6.5, 7.1, 12.7 Hz, 1H), 3.76 (s, 3H), 1.49 (s, 9H), 1.35–1.34 (d, J = 6.5 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 155.5, 96.9, 74.3, 64.1, 51.8, 36.8, 28.4, 26.5, 26.3, 16.0. HRMS (ESI) Mass calcd for $C_{15}H_{27}NO_5$ [M+Na]$^+$, 324.1781. Found 324.1793.
13. The stereochemistry of the $NaBH_4$ reduction was confirmed by treating the resulting propargyl alcohol with TFA in CH_2Cl_2:



Villard, R.; Fotiadu, F.; Buono, G. *Tetrahedron: Asymmetry* **1998**, *9*, 607–611.
14. Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483.
15. *Characterization data for* **3**: ^1H NMR (600 MHz, $CDCl_3$) δ 6.35–6.34 (d, J = 6.3 Hz, 1H), 4.84–4.83 (m, 1H), 4.67–4.65 (m, 1H), 4.20–4.18 (ddd, J = 3.4, 9.7, 11.6 Hz 1H), 4.17–4.16 (br s, 1H), 3.70 (m, 1H), 1.47 (s, 9H), 1.46–1.45 (d, J = 6.4 Hz, 3H), 1.14–1.13 (m, 3H), 1.10–1.09 (d, J = 6.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ155.1, 143.3, 103.0, 79.6, 74.0, 66.1, 55.5, 28.5, 18.2, 17.9, 12.5. HRMS (ESI) Mass calcd for $C_{20}H_{39}NO_4Si$ [M+Na]$^+$, 408.2540. Found 408.2533.