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Multigram Synthesis of 1-*O*-Acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-L-pyrrolosamine

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Abstract

A synthesis of 1-*O*-acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-L-pyrrolosamine (**7**), which constitutes a protected form of the *N,N*-dimethyl-L-pyrrolosamine residues found within the antiproliferative bacterial metabolites (–)-lomaiviticins A and B (**1** and **2**, respectively), is reported. The synthetic route to **7** proceeds in eight steps and 13% overall yield from (*E*)-crotyl alcohol. The protected carbohydrate **7** is envisioned to be a useful derivative for syntheses of **1** and **2**.

Keywords

lomaiviticin; natural products; carbohydrate; synthesis

Main Text

(–)-Lomaiviticins A (**1**) and B (**2**, Figure 1) are complex bacterial metabolites that were first isolated in 2001 from a strain of *Salinispora pacifica*.¹ (–)-Lomaiviticin A (**1**) is a potent inhibitor of cultured human cancer cell proliferation, with half-maximal inhibitory potencies in the low nanomolar–picomolar range.^{1a} The cytotoxic effects of **1** derive from induction of double-strand breaks in DNA.²

(–)-Lomaiviticins A (**1**) and B (**2**) possess dimeric *C*₂-symmetric structures, each of which contain two diazofluorene functional groups.³ They are related to the natural monomeric diazofluorenes known as the kinamycins (not shown), which have been isolated from various strains of *Streptomyces*.⁴ (–)-Lomaiviticin A (**1**) contains two L-oleandrose residues and two *N,N*-dimethyl-L-pyrrolosamine residues. Several groups have initiated synthetic studies toward **1** and **2**.⁵ Our laboratory reported a synthesis of (–)-lomaiviticin aglycon (**3**).⁵ⁱ We also reported a strategy to prepare *N,N*-dimethyl-*O*-allyl-D-pyrrolosamine (**5**) and *O*-allyl-L-oleandrose (**6**) in three steps from ethyl (2*E*,4*R*,5*R*)-4,5-epoxy-2-hexenoate (**4**) and ethyl (2*E*,4*S*,5*S*)-4,5-epoxy-2-hexenoate (*ent*-**4**), respectively (Scheme 1).^{5e} The

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epoxides **4** and **ent-4** were prepared in 41% yield and 96% ee by Shi epoxidation of ethyl sorbate, as previously described.⁶ Distinct strategies to prepare protected forms of the aminosugar residues of **1** and **2** have also been reported by the Shair laboratory.^{5c,5h}

Several issues render our route to **5** and **6** inadequate for syntheses of (–)-lomaiviticins A and B (**1** and **2**). First, it was revealed^{1b} that both carbohydrate residues of **1** are of the L-form. This calls for implementation of the Shi ketone derived from the unnatural sugar L-fructose to obtain **ent-4**.⁷ L-Fructose itself was synthesized from L-sorbose by a multistep sequence.⁸ Second, although the Shi epoxidation was singularly effective in accessing **4** and **ent-4**, 0.3 equiv of the chiral ketone was required to achieve high conversions, rendering the process impractical on large scales. Third, we have observed that the dialkylamino and *O*-allyl substituents of **5** are incompatible with certain steps in our synthesis of the diazofluorene function of the targets. To address these issues, we have developed a synthesis of 1-*O*-acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-L-pyrrolosamine (**7**), which constitutes a protected form of *N,N*-dimethyl-L-pyrrolosamine. The route to **7** proceeds in eight steps, 13% overall yield, and readily provides multigram quantities of product.

As an alternative to the Shi protocol, we applied a sequence comprising Sharpless epoxidation of (*E*)-crotyl alcohol,⁹ followed by oxidation and in situ chain extension (Scheme 2).¹⁰ Decagram quantities of **ent-4** were readily obtained in 48% yield and 86% ee by this two-step sequence.

With large quantities of **ent-4** in hand, we explored its opening with protected dialkylamine nucleophiles (Scheme 3). After some experimentation, the use of (3,4-dimethoxybenzyl)methylamine was determined to be optimal for the epoxide opening and subsequent steps. Heating solutions of **ent-4** and (3,4-dimethoxybenzyl)methylamine in ethanol at 55 °C formed the aminoalcohol **9** in 60% yield on a 19 g scale. Attempts to directly convert the ester **9** to the corresponding aldehyde **11** by treatment with di-*iso*-butylaluminum hydride (DIBAL-H, two equiv) provided low yields of **11** along with unreacted **9** and the corresponding allylic alcohol, as is frequently observed in the partial reduction of unsaturated esters. To circumvent this, an alternative two-step sequence was implemented. Treatment of **9** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of *iso*-propyl magnesium chloride–lithium chloride complex¹¹ generated the Weinreb amide **10** (92%, 17 g scale).¹² Reduction of **10** with DIBAL-H (2.1 equiv) was relatively clean, as determined by LC/MS and TLC analysis; however, the work-up step required careful optimization. Stirring the product mixture with solutions of Rochelle's salt at ambient temperature provided variable amounts of the aldehyde **11**, the hemiaminal **12**, the 1,3-diene **13**, and the aminoaminal **14** (Figure 2). Performing the workup at 0 °C largely suppressed the formation of **13**. However, **11** and **14** were formed in approximately equimolar ratios, and chromatographic purification of the mixture formed large amounts of **13**. Various approaches involving addition of electrophilic scavengers (to sequester the liberated *N,O*-dimethylhydroxylamine) proved only marginally beneficial until a control experiment demonstrated that the addition of sodium carbonate (2.2 equiv) to the product mixture, originally introduced to neutralize acidic by-products, increased the purity of the

product. Under these conditions, the aldehyde **11** was obtained in 80% yield, as determined by ^1H NMR analysis of the unpurified product mixture against an internal standard. We surmise that alkaline conditions promote the breakdown of **12** and inhibit the formation of **13** and **14**, which may occur via an iminium ion intermediate.

Stirring solutions of the unpurified aldehyde **11** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 equiv) in *p*-methoxybenzyl alcohol (5.0 equiv) induced diastereoselective 1,4-addition of the alcohol (**11**→**15**) and concomitant cyclization to provide the reducing sugar **16** (Scheme 4). A single C-3 diastereomer was obtained in the addition step (^1H NMR analysis). The reducing sugar **16** could be isolated, but removal of excess *p*-methoxybenzyl alcohol was problematic on scale. To circumvent this, the product mixture was treated directly with acetic anhydride and pyridine to provide the glycosyl acetate **17**, which was readily purified by flash-column chromatography. By this approach, **17** was formed in 61% overall yield from the Weinreb amide **10** on a 14 g scale. The final product was obtained by removal of the dimethoxybenzyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 83%, 12 g scale) and acylation of the resulting secondary amine with 9-fluorenylmethoxycarbonyl chloride (FmocCl, 98%, 6.9 g scale). By this sequence, quantities as large as 11.4 g of **7** have been prepared in one pass.

In summary, we have reported a synthesis of 1-*O*-acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-L-pyrrolosamine (**7**), which constitutes a protected form of the *N,N*-dimethyl-L-pyrrolosamine residues of (–)-lomaiviticins A and B (**1** and **2**, respectively). The synthetic route to **7** proceeds in eight steps and 13% overall yield from the inexpensive reagent (*E*)-crotyl alcohol and addresses issues of scalability and functional group compatibility encountered in our earlier work. The protecting group scheme contained in **7** is anticipated to be suitable for the synthesis of lomaiviticins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of (-)-lomaiviticin A (**1**), (-)-lomaiviticin B (**2**), and (-)-lomaiviticin aglycon (**3**).

Scheme 1.

Prior route to the carbohydrate residues of (–)-lomaiviticins A and B (**1** and **2**, respectively) and the structure of 1-*O*-acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-*L*-pyrrolosamine (**7**).

Scheme 2.

Synthesis of ethyl (2*E*,4*S*,5*S*)-4,5-epoxy-2-hexenoate (*ent*-4) from (*E*)-crotyl alcohol.

Scheme 3.
Synthesis of the aminoaldehyde **11**.

Figure 2.
Side-products identified in the reduction of the Weinreb amide **10**.

Scheme 4.

Conversion of the aminoaldehyde **11** to 1-*O*-acetyl-3-*O*-(4-methoxybenzyl)-4-*N*-(9-fluorenylmethoxycarbonyl)-4-*N*-methyl-L-pyrrolidine (**7**).