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Nitro-Mannich reaction and intramolecular 1,3-dipolar cycloaddition route to acylpyrrolidinones: Synthesis of a tetramic acid and (+)-laccarin

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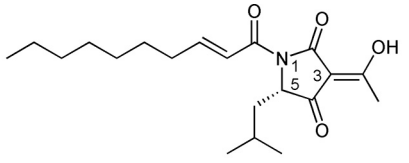
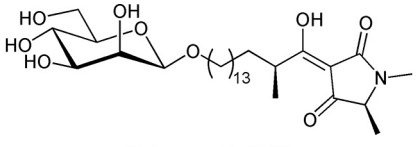
ABSTRACT

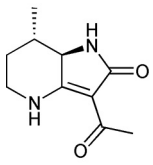
An efficient synthetic pathway to acylpyrrolidinones via a nitro-Mannich reaction, followed by the intramolecular 1,3-dipolar cycloaddition of a nitrile oxide to an alkyne was developed. The syntheses of a leucine-derived tetramic acid and natural tetramide (+)-laccarin were achieved in five steps using aldehydes, 2-alkynamides and nitromethane as the carbon sources.

Introduction

To date, numerous acylpyrrolidinones have been isolated from bacterial and fungal sources. This class of compounds exhibits various biological activities owing to their different substitution patterns, mainly at the N-1, C-3 and C-5 positions. For instance, the tetramic acid reutericyclin (**1**, Fig. 1) is a potent antibiotic isolated from *Lactobacillus reuteri*.[1] The jellyfish-derived fungus *Epicoccum purpurascens* produces epicoccamide D (**2**), which has a mannosylated fatty acid side chain.[2] (+)-Laccarin (**3**) is a unique mushroom-derived tetramide that exhibits cyclic AMP phosphodiesterase inhibitory activity.[3,4] The tetramide quinolactacin A2 (**4**) inhibits tumor necrosis factor production.[5–7] The biological activities and structural characteristics of acylpyrrolidinones, especially tetramic acid, have attracted much interest, and several method for synthesizing these compounds have been reported in the literature.[8–15] However, most of these methods use amino acids as the starting materials, strongly limiting the substituents that can be added at the C-5 position. Accordingly, to synthesize various C-5 substituted acylpyrrolidinones, we developed an alternative method that utilizes different starting materials. We also attempted to prepare (+)-laccarin using a similar methodology to demonstrate its utility







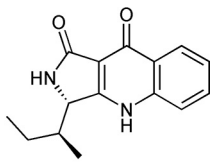


Fig. 1. Structures of naturally occurring 3-acylpyrrolidinones.

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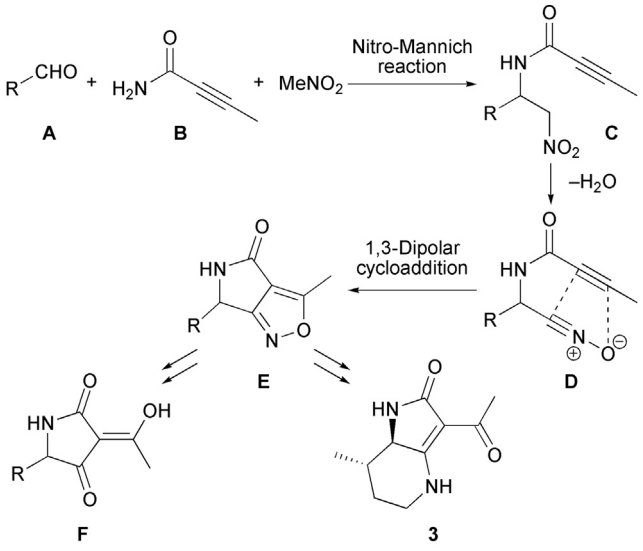
for synthesis of this class of natural products.[16,17] To our knowledge, only one report of the synthesis of (+)-laccarin has appeared in the literature by Gallagher et al.[18]

Results and discussion

Our synthetic strategy of acylpyrrolidinones is shown in Scheme 1. Three simple and easily accessible carbon-based compounds, namely aldehydes **A**, 2-alkynamides **B** and nitromethane, were chosen as the starting materials. This choice allows the C-5 substituent to be changed by selecting the appropriate aldehyde. A nitro-Mannich reaction[19] of these three compounds affords the *N*-(α-alkyl-β-nitroethyl)amide **C**. The nitromethyl group, is subsequently converted into a nitrile oxide, which further reacts with an alkyne via an intramolecular 1,3-dipolar cycloaddition reaction to give the pyrrolo[3,4-*c*]isoxazol-4-one **E**. The desired acylpyrrolidinones, such as compound **F** or **3**, is finally obtained by the reductive cleavage of the N–O bond, followed by the requisite conversion, i.e., imine hydrolysis or cyclization.

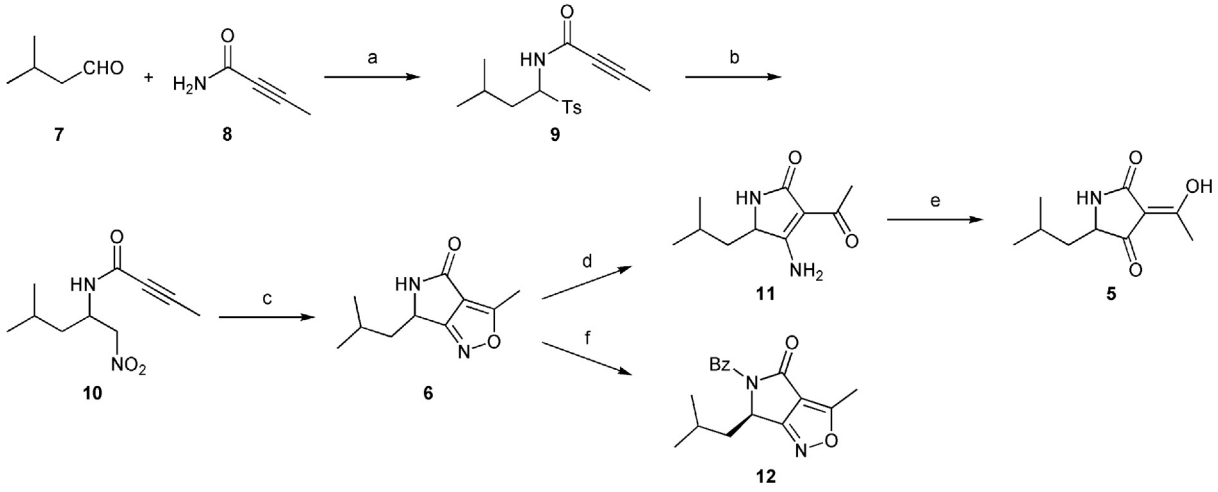


Scheme 1. Synthetic strategy of acylpyrrolidinone.

First, we decided to demonstrate the efficiency of our strategy by synthesizing the tetramic acid core of reutericyclin **5** via **6**, which is a key intermediate in Jones' synthesis of reutericyclin analogues.[13–15]

The synthesis of these compounds is shown in Scheme 2. The nitro-Mannich reaction was carried out in a stepwise manner via an α-amidosulfone intermediate, which is a convenient precursor for *N*-acylimine synthesis.[20] The three-component coupling of isovaleraldehyde (**7**), but-2-ynamide (**8**) and *p*-toluenesulfinic acid gave the α-amidosulfone **9**. This compound was then reacted with nitromethane under basic conditions; specifically they were treated with aqueous potassium hydroxide in tetrahydrofuran (THF) at 0 °C to give the desired nitro-Mannich product **10** in 57% yield. The use of higher reaction temperature or a longer reaction time resulted in a decreased yield because of the degradation of product. However, using a quaternary ammonium chloride catalyst was quite effective; the addition of 20 mol% of benzyltriethylammonium chloride (BTEAC) afforded the desired product **10** in 84% yield.[21] After the nitro-Mannich product was obtained, nitrile oxide formation and intramolecular 1,3-dipolar cycloaddition reactions were performed. Treating **10** with phenyl isocyanate and triethylamine at ambient temperature for 24 h afforded pyrrolo[3,4-*c*]isoxazol-4-one **6** in 84% yield. According to Jones' procedure,[13–15] compound **6** was converted to the tetramide **11** via catalytic hydrogenation. Finally, the tetramic acid core of reutericyclin **5** was synthesized by the microwave-assisted hydrolysis of the enamine moiety. The overall yield of the five steps from isobutyraldehyde and but-2-ynamide was 40%. It should be noted that the asymmetric nitro-Mannich reaction of **9** could be conducted. The use of the asymmetric catalyst *N*-benzylquininium chloride at −45 °C gave optically enriched (+)-**10** in 78% e.e.[22] The absolute configuration of the major enantiomer was determined to be *R*, after conversion of (+)-**10** into (−)-**12**, by comparing the specific rotation of (−)-**12** to the reported value of its enantiomer; synthetic **12**: $[\alpha]_D^{24}$ −208 (*c* 0.45, $CHCl_3$), (*S*)-**12**: $[\alpha]_D^{rt}$ +158.7 (*c* 15.0 × 10^{-3}, $CHCl_3$).[15] This finding suggests that this methodology could be applicable to the synthesis of optically active compounds.

After demonstrating the efficiency of nitro-Mannich/1,3-dipolar cycloaddition route to acylpyrrolidinones, (+)-laccarin was synthesized as shown in Scheme 3. (*S*)-4-Benzyloxy-2-methylbutanal (**13**, <90% e.e.), which could be synthesized from commercially available 1-benzyloxy-2-iodoethane in two steps (67% yield),[23] was utilized in the nitro-Mannich/1,3-dipolar cycloaddition



Scheme 2. Synthesis of the tetramic acid derivative **5** and (*R*)-**12**. Reagents and conditions: (a) *p*-tolSO_2H, $MgSO_4$, CH_2Cl_2, 84%; for (±)-**5**: (b) $MeNO_2$, KOH, BTEAC, THF, 0 °C, 84%; (c) PhNCO, Et_3N, toluene, 84%; (d) H_2, Pd-C, EtOH, quant.; (e) 2 M aq. NaOH, THF, microwave, 68%; for (*R*)-**12**: (b) $MeNO_2$, KOH, *N*-benzylquininium chloride, THF, −45 °C, (*R*)-**10**: 76%, 78% e.e.; (c) PhNCO, Et_3N, toluene, (*R*)-**6**: 84%; (f) *n*-BuLi, BzCl, THF, −78 °C to 0 °C, (*R*)-**12**: 99%.