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Divergent synthesis of (+)-tanikolide and its analogues employing stereoselective rhodium(II)-catalyzed reaction

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ABSTRACT

In this study, we described the divergent synthesis of (+)-tanikolide and its analogues, such as (4*S*)- and (4*R*)-hydroxytanikolides, and nortanikolide, employing a stereoselective dirhodium(II)-catalyzed reaction to construct the quaternary chiral center of tanokolides. The key steps involve (a) a dirhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement, (b) an *N*-heterocyclic carbene-catalyzed ring-expansion lactonization of tetrahydrofurfural, or (c) an oxidative cleavage of tetrahydrofuran-5-methanol to γ-lactone using a 2-iodobenzamide catalyst. This route would provide high flexibility for analogue synthesis because the long side chain can be introduced at a later stage in the synthesis.

1. Introduction

(+)-Tanikolide (**1**, Fig. 1) and (−)-malyngolide, which are δ-lactones with alkyl long chains and hydroxymethyl groups at C5, were isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Tanikeli Island, Madagascar[1] and the shallow water variety of *Lyngbya Majuscula*,[2] respectively. Interestingly, the stereochemistries of these natural products are opposite in comparison with C5 and alkyl side chains of different lengths. Additionally, malyngolide possesses a methyl group at C2. With respect to their biological activities, tanikolide exhibits strong toxicity against brine shrimp and snails and malyngolide displays an antimicrobial activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*.[2] Furthermore, tanikolide exhibits antifungal activity against *Candida albicans*,[1] while malyngolide shows no activity against it.[1] Since there is a clear difference in their biological activities in spite of their structural similarities, their analogues, possessing slightly different substituents, may lead to new promising candidates for drug discovery.

In terms of potent biological activities and structural features of (+)-tanikolide and (−)-malyngolide, there have been a large number of reports on the total syntheses of these natural products[3–13] and their analogues.[6n,o] One of the key steps is the stereoselective construction of the quaternary carbon center at C5, which has been accomplished using several different approaches, such as aldol reactions,[3] allylation of ketones such as Keck allylation,[4] addition of Grignard reagents to ketones,[5] epoxidation–epoxide opening,[6] Sharpless asymmetric dihydroxylation,[7] sigmatropic rearrangement,[8] 1,3-dipolar cycloaddition of nitronate and acrolein,[9] asymmetric intramolecular cyclopropanation,[10] bromolactonization,[11] asymmetric allylic alkylation,[12] and others.[13] However, most of these examples are application and demonstration of synthetic methodologies to construct a synthetically challenging quaternary carbon center. To the best of our knowledge, there is only one example of the divergent synthesis of their analogues.[6n,o]

One of the most direct and powerful methods for construction of substituted cyclic ethers is tandem intramolecular oxonium ylide formation from α-diazocarbonyl compounds under catalysis by dirhodium(II) or copper complexes and [2,3]-sigmatropic rearrangement.[14] The synthetic utility of the tandem reaction has been demonstrated through the synthesis of a wide range of natural products.[15] We have reported a stereoselective, copper-catalyzed oxonium ylide formation–rearrangement of α-diazo ketone for the synthesis of the C3–C12 portion of laulimalide.[16] We have also disclosed that a dirhodium(II)-catalyzed tandem reaction of diazoketoesters proceeds with excellent stereoselectivity[17] and is applicable to the synthesis of 2-*epi*-cinatrin C_1 dimethyl ester.[18] As a

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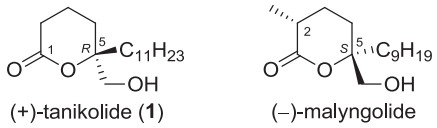


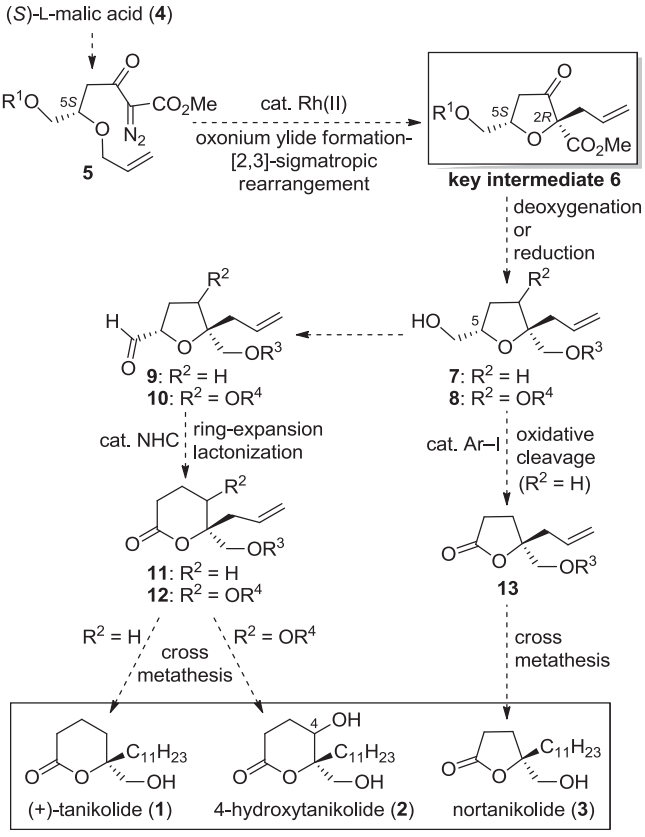
Fig. 1. Structure of (+)-tanikolide (**1**) and (−)-malyngolide.

part of our work in the development of oxonium ylide rearrangement and its application to the synthesis of biologically active compounds, we herein report a divergent synthesis of (+)-tanikolide and its analogues, such as 4-hydroxy- and nortanikolides.[19]

2. Results and discussion

2.1. Synthetic strategy

Our synthetic plan for (+)-tanikolide (**1**) and its analogues, 4-hydroxytanikolides (**2**), and nortanikolide (**3**), is illustrated in Scheme 1. We have already reported the stereoselective dirhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of 5-allyloxy-2-diazo-3-oxocarboxylate.[17,20] From this observation, we can expect to stereoselectively obtain (2*R*,5*S*)-dihydrofuranone **6**, which has the same configuration at C2 as that of tanikolide, by the dirhodium(II)-catalyzed reaction of (5*S*)-diazoketoester **5**. The diazoester **5** can be prepared from (*S*)-L-malic acid (**4**). The obtained dihydrofuranone **6** could be a key synthetic intermediate for **1**–**3**. In addition, introduction of the alkyl side chain could be conducted at a later stage of the synthesis using cross metathesis to easily synthesize analogues with various side chains. Deoxygenation of the keto group in **6**, followed by the oxidation of the resultant tetrahydrofuran-5-methanol **7** ($R^2 = H$), could provide tetrahydrofurfural **9**. Subsequently, *N*-heterocyclic carbene (NHC)-catalyzed ring-expansion of aldehyde **9**, prepared from the hydroxymethyl group in **7**, to δ-lactone **11**[21] and the following cross metathesis would result in the completion of the total synthesis of **1**. Reduction of ketone **6** could afford the alcohol **8** ($R^2 = OR^4$), which should be converted into **2** in the same manner as that of **7** into **1**. Noranalogue **3** could be synthesized from **7** by an oxidative cleavage reaction[22] and cross metathesis. Consequently, in this synthesis, the C5 hydroxymethyl group plays the following important roles: construction of the C2 chiral center, ring-expansion from γ-lactone to δ-lactone, and oxidative cleavage.

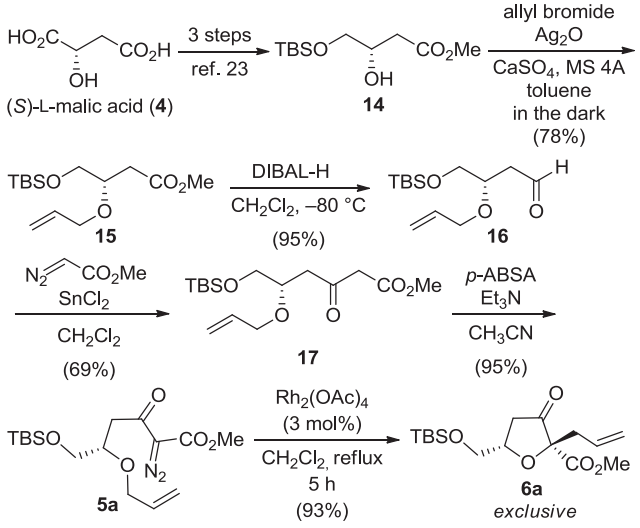


Scheme 1. Synthetic strategy for (+)-tanikolide (**1**) and its analogues **2** and **3**.

2.2. Total synthesis of (+)-tanikolide

The synthesis of the key intermediate **6a** from (*S*)-L-malic acid (**4**) was investigated as shown in Scheme 2. Conversion of **4** into silyloxyalcohol **14** was conducted in the usual manner.[23] Allylation of the hydroxy group in **14** was accomplished by the treatment with allyl bromide, silver(I) oxide, calcium sulfate, and a molecular sieve (MS) 4 Å for 24 h in the dark, which afforded allyl ether **15** in 78% yield. After the reduction of ester **15** into aldehyde **16** with diisobutylaluminum hydride (DIBAL-H), the resultant **16** was converted to diazoketoester **5a** via β-ketoester **17** by treatment of **16** with methyl diazoacetate with $SnCl_2$ and subsequent diazo transfer from *p*-acetoamidobenzenesulfonyl azide (*p*-ABSA) to **17**. The rhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of **5a** yielded dihydrofuranone **6a** with perfect stereoselectivity. The reaction of diazoketoester **5a** with 3 mol% of dirhodium(II) tetraacetate in refluxing dichloromethane for 5 h produced the corresponding dihydrofuranone **6a** as the sole product in 93% yield.

With the key synthetic intermediate **6a** in hand, we next examined the deoxygenation of the keto group in dihydrofuranone **6a** (Scheme 3). After conversion of **6a** to alcohol **18** by treatment with sodium borohydride in tetrahydrofuran (THF), the reaction of **18** with Martin sulfurane or Burgess reagents did not proceed at all. Next, we examined the Barton–McCombie deoxygenation of alcohol **18**. Treatment of **18** with 1,1′-thiocarbonyldiimidazole in benzene under reflux provided the corresponding thiocarbamate **19** in 95% yield. The reaction of **19** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave a complex mixture of products. Since all the attempts to deoxygenate 3-



Scheme 2. Stereoselective synthesis of key intermediate **6a**.