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Total synthesis of (+)-tanikolide, a toxic and antifungal δ-lactone, utilizing bromoalkene intermediates conveniently synthesized from vicinal dibromoalkane by regioselective elimination

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Abstract—Stereoselective total synthesis of (+)-tanikolide, a bioactive δ-lactone marine natural product, was successfully accomplished by using regioselective HBr elimination reaction of 3-acyloxy-1,2-dibromoalkanes, Pd-mediated coupling reaction, and the Sharpless asymmetric epoxidation as key steps.

(+)-Tanikolide (**1**)[1] is a biologically active δ-lactone natural product isolated from the lipid extract of the marine cyanobacterium, *Lyngbia majuscula*, collected in Tanikeli Island, Madagascar. The structural character of **1** is a chiral quaternary carbon center with a hydroxymethyl group and a multicarbon chain, similar to that of (−)-malyngolide **2**.[2] **1** exhibited antifungal activity against *Candida albicans*, along with LD_{50} 3.6 μg/mL against brine shrimp and 9.0 μg/mL against snail.[1] To understand the structure–activity relationship, synthetic studies of **1** have been reported as follows.[3] The first total synthesis of (+)-**1** was achieved by using a catalytic asymmetric hydrogen transfer reaction of a tricyclic alcohol.[3a] Methodologies using the ring-closing metathesis (RCM) for construction of the δ-lactone moiety as key steps were reported for the total synthesis of (+)-**1** by two groups.[3c,d]

Recently, we developed an efficient highly regioselective HBr elimination reaction of 2-bromo-1-alkenes synthesized from the corresponding 3-aryloxy- or 3-acyloxy-1,2-dibromoalkanes under mild basic conditions. By employing this methodology and the transition metal-mediated coupling reaction, the total synthesis of biologically active natural products was reported: when 3-*O*-substituted-1-alkyl-1,2-dibromoalkanes were submitted to this elimination reaction, the *syn*- and *anti*-orientated derivatives provided the same *trans*-eliminated process.[4] As an additional demonstration of the regioselective elimination reaction, we describe herein stereoselective total synthesis of **1** using our regioselective HBr elimination reaction of 3-*O*-substituted-1-alkyl-1,2-dibromoalkane derivatives,[4] Pd-mediated coupling reaction,[5] and the Sharpless asymmetric epoxidation as the key steps (Fig. 1).[6]

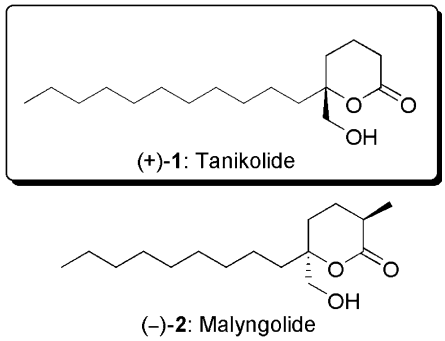

Figure 1. Structures of tanikolide **1** and malyngolide **2**.

Keywords: Antifungal lactone; Bromoalkene; Tanikolide; Regioselective elimination; *Lyngbia majuscula*.
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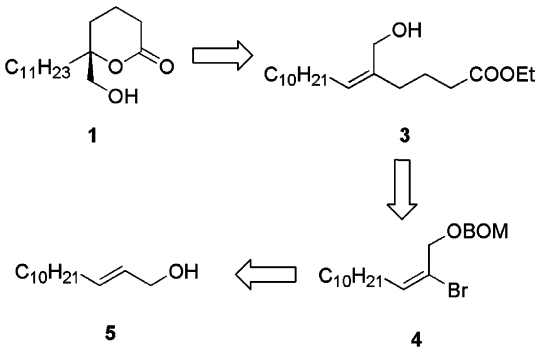
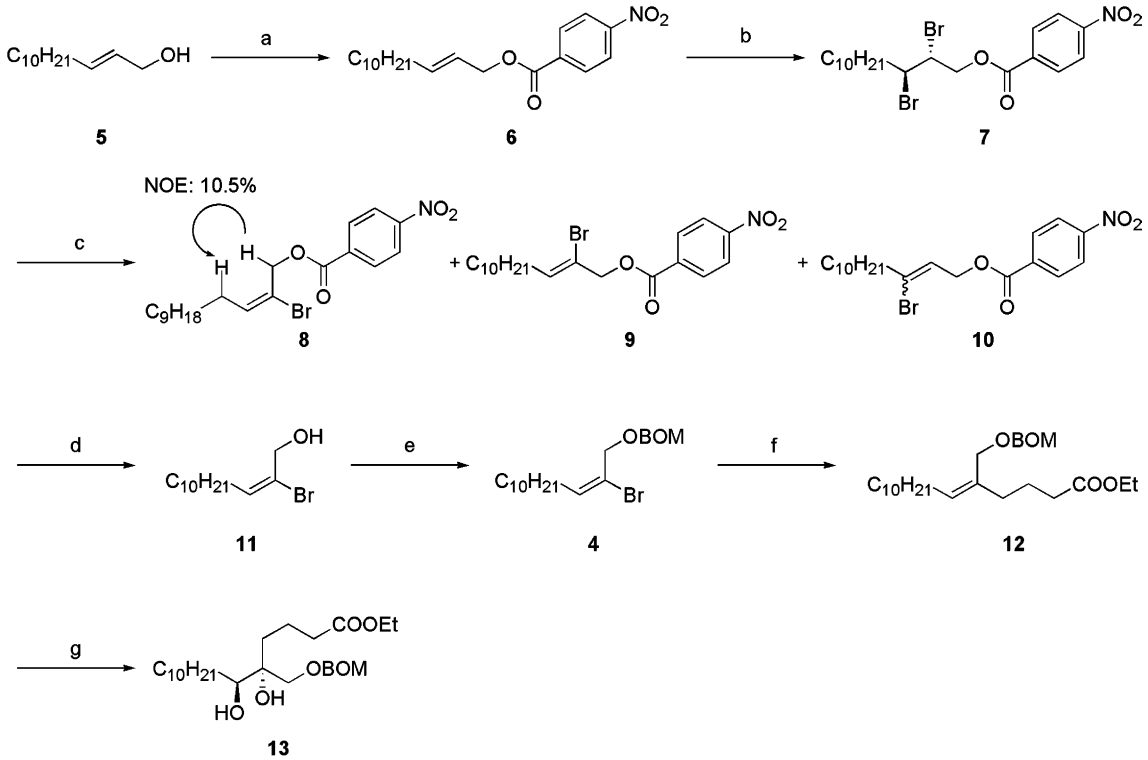


Scheme 1. Retrosynthesis of **1**.

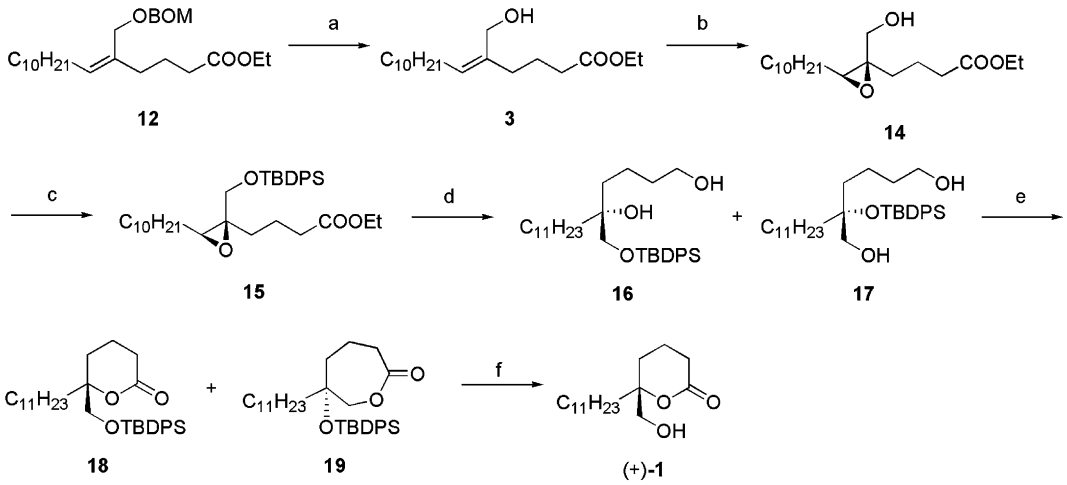
Retrosynthetic analysis indicated that **1** would be constructed from **3** by using the Sharpless asymmetric epoxidation[6] and lactonization (Scheme 1). The allyl alcohol **3** may be synthesized by the Pd-mediated coupling reaction[5] from bromoalkene **4**, readily available by bromination of alkene **5**, and the following regioselective HBr elimination reaction.[4]

Along this line, synthesis of **1** commenced with acylation of **5** (Scheme 2). As the regioselectivity and yield of our HBr elimination reaction were regulated by the electron-withdrawing effect of the *O*-functional groups at the adjacent position of the vicinal dibromoalkyl moiety,[4] we selected a *p*-nitrobenzoyl group, carrying a strong electron-withdrawing effect, as an acyl moiety. Acylation of **5** gave the corresponding ester **6** in quantitative yield, which was submitted to bromination with Pyr.-HBr_3 to yield the racemic *anti*-dibromide **7** in 95% yield. Regioselective *trans*-elimination of the vicinal dibromide carrying the acyloxy group at the adjacent position with DBU[4] provided the bromoalkene derivatives **8**, **9**, and **10** in 94% yield (**8**:**9**:**10** = 60:1:1), the stereochemistry of which was determined by the NOE experiments. The *p*-nitrobenzoyl group was converted into a BOM ether, due to the fact that allyl acylates produce a π-allyl complex under the Pd-mediated coupling conditions.[7] Thus, hydrolysis under basic conditions, followed by chromatographic separation, afforded **11** in 94% yield, which was etherified with BOMCl–$^{i}Pr_2NEt$ to give **4** in 98% yield. The desired Pd-coupling reaction[5] was achieved by using $Pd(dppf)Cl_2$ to give **12** in 73% yield. In the next oxidation step, the Sharpless asymmetric dihydroxylation[8] did not proceed at low temperature. Upon reacting at ambient temperature, the induced enantioselectivity of the oxidation product **13** was less than 50% ee.[9]

Accordingly, we employed the Sharpless asymmetric epoxidation[6] for construction of a chiral quaternary carbon center (Scheme 3). Cleavage of the BOM group of **12** under acidic conditions afforded the allyl alcohol **3** in 80% yield. The asymmetric epoxidation of **3** was achieved by the general protocol of the Sharpless epoxidation[6] to give **14** in 99% yield as 92–94% ee,[9] which upon TBDPS etherification gave **15** in quantitative yield. Reductive opening of the epoxy ring of **15** was achieved with $LiEt_3BH$ at 60 °C to give a 1:1 mixture of diol **16** and the silyl-migrated isomer **17** in 94% yield,



Scheme 2. Reagents and conditions: (a) *p*-$NO_2C_6H_4COCl$, Pyr., CH_2Cl_2, rt (100%). (b) Pyr.-HBr_3, AcOH, rt (95%). (c) DBU, DMF, 50 °C (94%; **8**:**9**:**10** = 60:1:1). (d) LiOH, dioxane, 0 °C (94%). (e) BOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, rt (98%). (f) 5 mol% $Pd(dppf)Cl_2$, $BrZnCH_2CH_2CH_2COOEt$, THF–PhMe, 90 °C (73%). (g) AD-mix-α, aq $^{t}BuOH$, rt (85%).



Scheme 3. Reagents and conditions: (a) concd HCl, EtOH, 50 °C (80%). (b) (−)-DET, TBHP, $Ti(O^iPr)_4$, CH_2Cl_2, −30 °C (99%). (c) TBDPSCl, Imd, DMF, rt (100%). (d) $LiEt_3BH$, THF, 60 °C (94%; **16**:**17** = 1:1). (e) PCC, MS4A, CH_2Cl_2, 0 °C (60%; **18**:**19** = 6:1). (f) TBAF, THF, rt (87%).

which underwent lactonization with PCC to give a 6:1 mixture of the six-membered ring lactone **18** and the seven-membered ring lactone **19** in 60% yield. Finally, treatment of the mixture with TBAF afforded (+)-**1** in 87% yield, $[\alpha]_D^{22}$ +1.9 (*c* 1.0, $CHCl_3$) {lit.,[1] $[\alpha]_D^{25}$ +2.3 (*c* 0.65, $CHCl_3$)}. The synthetic (+)-**1** was identical to the natural product under the full range of spectroscopic data.[1]

In conclusion, the total synthesis of (+)-**1**, a toxic and antifungal metabolite, was accomplished by utilizing our efficient and simple bromoalkene synthesis by the regioselective HBr elimination reaction. As demonstrated, our approach is applicable to other congeners. Further investigation is in progress.

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9. The optical purity was determined by 400 MHz ^1H NMR spectra of the corresponding MTPA ester.