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D- and L-Erythrose as sources of chiral quaternary carbon centers. Total synthesis of (−)-malyngolide and (+)-tanikolide

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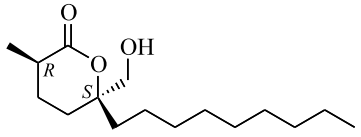
Dedicated with appreciation to Professor D. N. Nicolaides on the occasion of his 65th birthday

Abstract—A highly efficient and versatile approach was applied for the total synthesis of the marine natural products (−)-malyngolide and (+)-tanikolide from isopropylidene L- and D-erythrose, using a common strategy.

(−)-Malyngolide **1** and (+)-tanikolide **2** (Fig. 1) are marine metabolites isolated from the lipid extract of a blue–green algae, cyanobacterium *Lyngbya majuscula* from species collected from the coasts of Hawaii[1] and Tanikeli island, Madagascar,[2] respectively. Biological evaluation showed that **1** exhibits significant antibacterial activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, whereas **2** is a toxic and antifungal agent. Both compounds share similar skeletal features, a δ-lactonic moiety incorporating a chiral quaternary center, and a multicarbon side-chain, along with a hydroxymethyl group. However, they differ in the absolute stereochemistry of the quaternary carbon and the length of the aliphatic chain. Additionally, **1** incorporates in its structure a methyl group α to the carbonyl, thus generating a second chiral center, with *R*-configuration.



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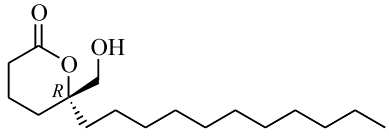

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Figure 1. Structures of (−)-malyngolide and (+)-tanikolide.

The interesting activity of **1** combined with the challenge to selectively construct a stereogenic quaternary carbon has prompted several groups to address the total synthesis of this molecule.[3,4] Besides the earliest approaches which led to racemic products, an array of methodology was successfully employed, including chiral pool, chiral auxiliary and catalytic asymmetric syntheses as well as enzymes to obtain optically active material. Considerable work[4,5] has also been reported for the preparation of **2** despite the fact that the latter was relatively recently isolated. Although previous accomplishments confronted the synthesis of **1** and **2** in diverse and elegant ways, most of them lack the ability to prepare both natural products following a short, efficient and relatively simple pathway.

In accordance with our continuing synthetic efforts[6] towards molecules with intriguing characteristics and usefulness we also embarked on the preparation of **1** and **2**. The structural similarities between these compounds led us to design a common retrosynthetic strategy (Scheme 1). Thus, we envisioned that desired products could be obtained upon lactonization of precursors **4** which in turn could derive from unsaturated systems **5** through elimination of one oxygen substituent and hydrogenation. Finally, intermediates **5** could be considered as double olefination products of protected erythroses **6**.

Keywords: (−)-malyngolide; (+)-tanikolide; erythrose; total synthesis; δ-lactone; quaternary center.

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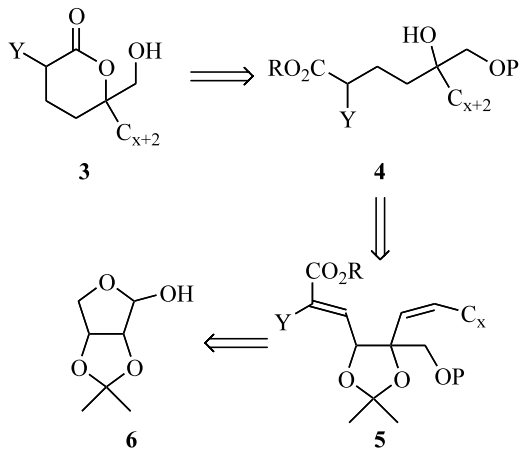


Scheme 1. Retrosynthetic analysis.

Readily available isopropylidene L- and D-erythrose (**7** and **15**, Schemes 2 and 3) served as the appropriate chirons for this approach.[7] Installation of the hydroxymethyl group and construction of the chiral quaternary center was first achieved via an aldol reaction with formaldehyde.[6k,8] Alcohols **8** and **16** were then selectively protected under forcing conditions to prepare trityl ethers **9** and **17**, respectively.

Subsequently, a Wittig reaction with the unstable phosphonium ylides derived from octyl and decyl bromides was used on the masked aldehydes to introduce the side chain. It is worth noting that these reactions required a rather high temperature, probably due to stereochemical hindrance from the adjacent quaternary carbon substituent. Olefins **10** and **18** were isolated in excellent yields as mixtures of *Z*- and *E*-isomers (ratios of ca. 2:1 and 7:3, respectively).

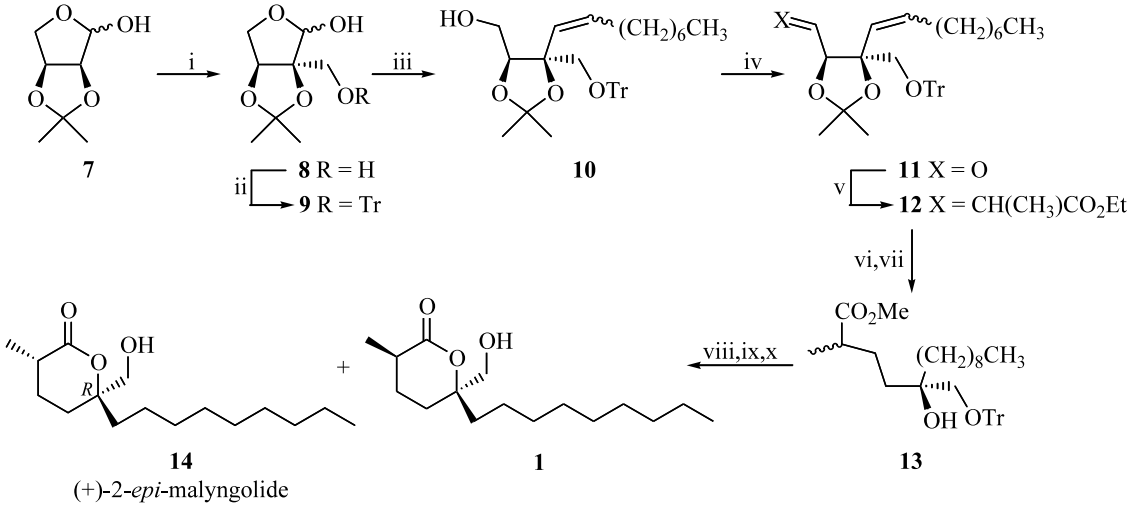
The second double bond was constructed using a Wittig olefination as well, on aldehydes **11** and **19**. These were easily obtained upon Swern oxidation of **10** and **18** and used without purification. In this case the required stable ylides were employed. Whereas the geometrical outcome was poor for disubstituted alkene **20**, the corresponding trisubstituted **12** was isolated as a single *E*-isomer. In any case, stereochemistry of the double bonds was of no importance since both were hydrogenated later on.

A magnesium reductive elimination[9] was then utilized for the concomitant C-2 double bond migration and the removal of the unnecessary oxygen substituent of **12** and **20**. During this process a complicated mixture of partially hydrogenated products was formed which was simply hydrogenated on Pd/C, giving methyl esters **13**, as a mixture of epimers,[10] and **21**, respectively.

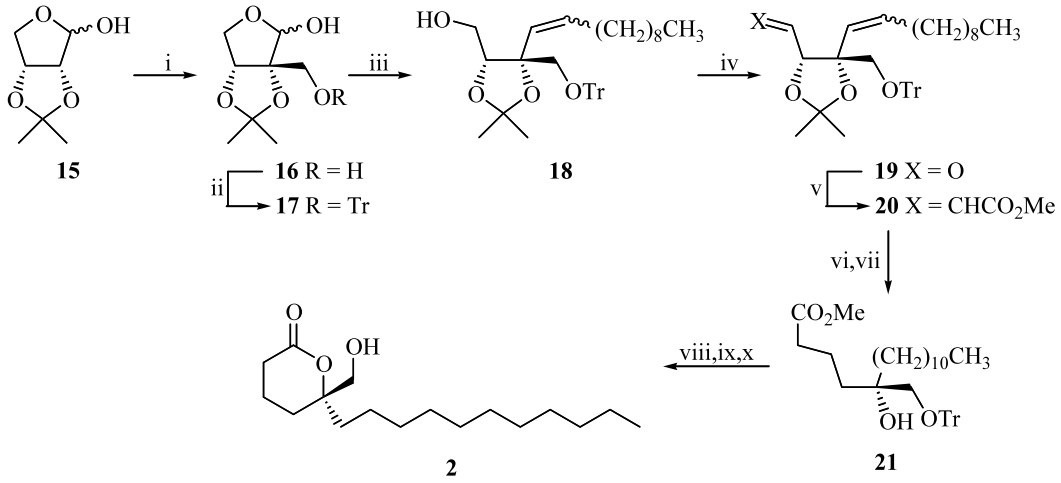
Intermediates **13** and **21** were practically one step away from the desired targets. The successful final steps included initially acid treatment for removal of the trityl group. This deprotection was optimized, after some experimentation, with formic acid in anhydrous ether. Saponification of the ester group and finally lactonization upon refluxing in chloroform followed, without isolation of any of the intermediates.

In contrast, a reverse sequence involving saponification as the first step and subsequent detritylation with formic acid led also to the partial formation of the primary alcohol formates.

By applying this procedure to hydroxy ester **13** a mixture of (−)-malyngolide **1** and (+)-2-*epi*-malyngolide **14** in a ratio of ca. 1:1 was formed. Pure products were obtained after separation by column chromatography and exhibited physical and spectroscopic data identical



Scheme 2. Synthesis of (−)-malyngolide **1**. *Reagents and conditions*: (i) HCHO, K_2CO_3, MeOH, 65°C, 82%; (ii) TrCl, Py, 60°C, 87%; (iii) $Ph_3P^+(CH_2)_7CH_3Br^-$, *n*BuLi, THF, 0°C to room temperature, 97%; (iv) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, −55°C to room temperature; (v) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, room temperature, 87% overall from **10**; (vi) Mg, MeOH, room temperature; (vii) H_2, Pd/C, MeOH, room temperature, 65% overall from **12**; (viii) HCO_2H, Et_2O, room temperature; (ix) NaOH, MeOH, room temperature; (x) $CHCl_3$, 60°C, 40% of **1**, 45% of **14** overall from **13**.



Scheme 3. Synthesis of (+)-tanikolide **2**. *Reagents and conditions*: (i) HCHO, K_2CO_3, MeOH, 65°C, 87%; (ii) TrCl, Py, 60°C, 86%; (iii) $Ph_3P^+(CH_2)_9CH_3Br^-$, *n*BuLi, THF, 0°C to room temperature, 92%; (iv) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, −55°C to room temperature; (v) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, room temperature, 90% overall from **18**; (vi) Mg, MeOH, room temperature; (vii) H_2, Pd/C, MeOH, room temperature, 60% overall from **20**; (viii) HCO_2H, Et_2O, room temperature; (ix) NaOH, MeOH, room temperature; (x) $CHCl_3$, 60°C, 80% overall from **21**.

with those reported in the literature.[1,4b] {for **1**: $[\alpha]_D = -13.4$ (*c* 0.8, $CHCl_3$), lit.[1] $[\alpha]_D = -13.0$ (*c* 2, $CHCl_3$); for **14**: $[\alpha]_D = +12.1$ (*c* 1, $CHCl_3$), lit.[3e] $[\alpha]_D = +12.3$ (*c* 1, $CHCl_3$)}. It is however known that the unnatural epimer could be isomerized to the natural one upon treatment with *t*BuOK in DMSO, leading to ca. 1:1 mixtures.[3a,11]

Accordingly, hydroxy ester **21** provided in a very good overall yield, (+)-tanikolide **2** which was also found to have identical physical and spectroscopic properties with those reported in the literature.[2] {$[\alpha]_D = +2.2$ (*c* 0.75, $CHCl_3$), lit. $[\alpha]_D = +2.3$ (*c* 0.7, $CHCl_3$)}.

The work described in this article presents a short and efficient synthetic approach towards the preparation of (−)-malyngolide **1** and (+)-tanikolide **2** making use of readily available, multigram quantities of L- and D-erythrose derived chirons and employing a common retrosynthetic plan. The overall yields for both targets are over 30% [taking into account that (+)-2-*epi*-malyngolide is epimerized to the natural product] in a ten-step sequence involving a minimum number of purifications and relatively simple and inexpensive procedures.

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