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A new synthetic approach to the lactol moiety of halichoblelide

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ABSTRACT

A stereoselective approach to the γ-lactol moiety of halichoblelide is described starting from commercially available (*R*)-3-butyn-2-ol. The key step is the hydroboration of a chiral protected 1,2-butadien-3-ol and its addition to furfural.

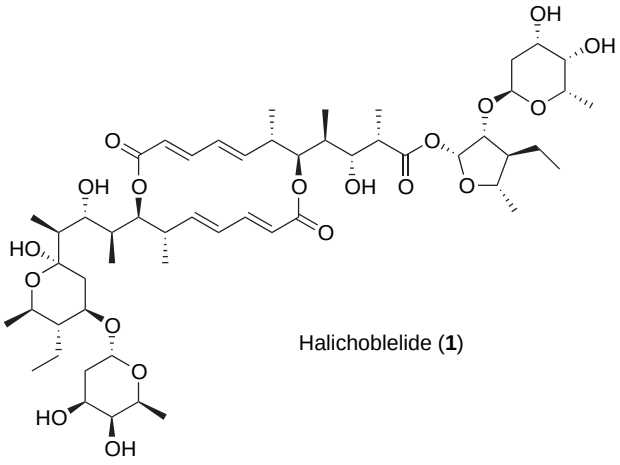
1. Introduction

In 2002, Numata and co-workers isolated halichoblelide (**1**),[1] a new cytotoxic macrodiolide obtained from a strain of *Streptomyces hygroscopicus* OUPS-N92, which inhabits the gastrointestinal tract of the fish *Halichoeres bleekeri* (Fig. 1).

The biological activity test of **1** revealed potent cytotoxicity against the murine cell line P388 (ED_{50} 0.63 μg/ml) and 39 human cancer cell lines (mean log GI_{50} −5.25).

Some years later, Kuwahara and co-workers embarked on the total synthesis of halichoblelide and reported the synthesis of the glycosyl lactol moiety (**2**) incorporated in **1**.[2] In fact, substructure **2** is the only synthetic fragment of halichoblelide described in the literature (Fig. 2).

Very recently, we developed a new stereoselective approach to 2-vinyl-1,3-diols based on the hydroboration of protected 2,3-alkadien-1-ols, followed by the addition of an aldehyde.[3] The *syn*,*syn* configuration observed in the products can be explained in terms of a transient (*E*)-alkenylborane generated in the hydroboration step. We envisaged that our methodology could be applied in the synthesis of the lactol moiety of **2** (**3** in Scheme 1). Thus, lactol **3** could be obtained from lactone **4**, which could be easily prepared from a *syn*,*syn*-2-vinyl-1,3-diol **5**.



Halichoblelide (**1**)

Fig. 1. Structure of halichoblelide (**1**).

2. Results and discussion

We took advantage of our experience in the synthesis of 2-vinyl-1,3-diols to prepare diol **5** (Scheme 2). Thus, we protected quantitatively the commercially available (*R*)-3-butyn-2-ol as *tert*-butyldimethylsilyl ether (**6**). We homologated the protected alkyne with formaldehyde under Ma's conditions,[4] to afford allene **7** in 82% yield.

At this point allene **7** was hydroborated with dicyclohexylborane and added to an aromatic aldehyde to yield the desired

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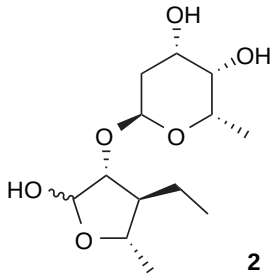
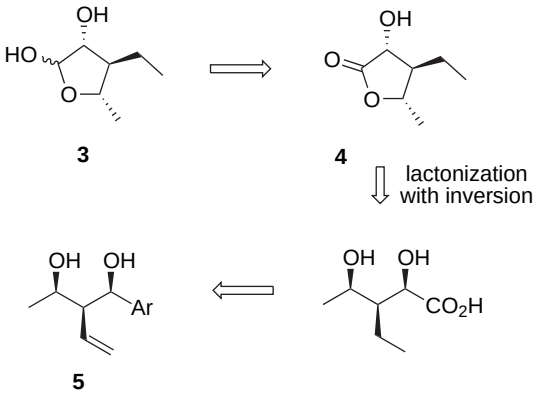
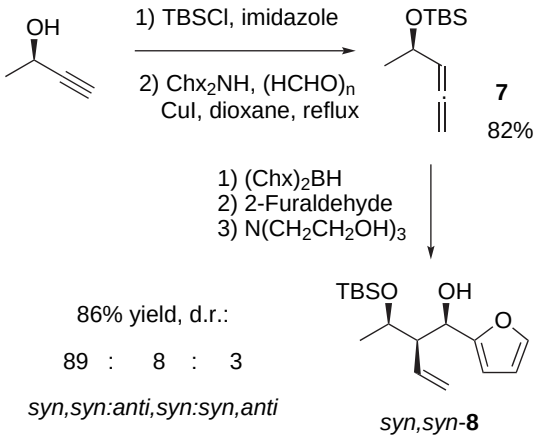


Fig. 2. Glycosyl lactol **2**.



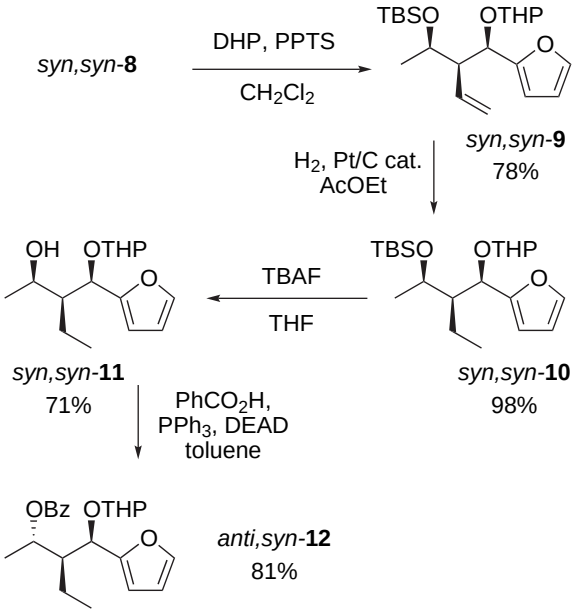
Scheme 1. Retrosynthetic analysis of lactol **3**.



Scheme 2. Synthesis of alcohol **8**.

protected 2-vinyl-1,3-diol. Furfural was considered as a good candidate because it can be easily oxidized to a carboxyl group. Under these conditions we obtained diol **8** in good yield and with high stereoselectivity. The major isomer *syn*,*syn*-**8** was easily isolated from the mixture of stereoisomers (86% yield).

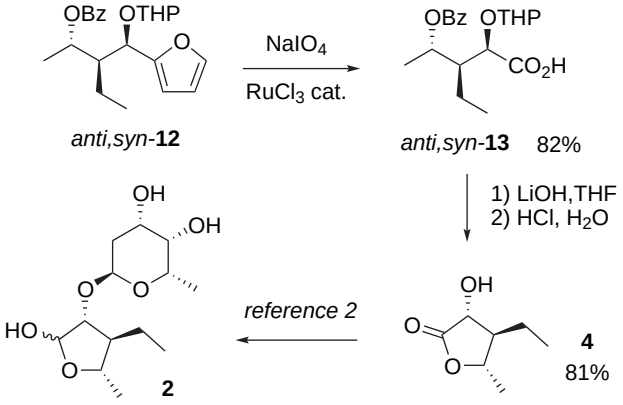
Protection of the free hydroxyl group of *syn*,*syn*-**8** as a tetrahydropyranyl (THP) yielded the corresponding adduct (*syn*,*syn*-**9**) in 78% yield (Scheme 3). The alternative protection of this alcohol as an acetate was troublesome since the acetyl migrated during the later TBS deprotection step. Hydrogenation of the olefin *syn*,*syn*-**9** was achieved almost quantitatively with Pt/C as catalyst, to afford *syn*,*syn*-**10**. Deprotection of TBS yielded the monoprotected diol *syn*,*syn*-**11**. After oxidation of the furan to a carboxyl group, we planned to activate the free hydroxyl group and cyclize to the lactone by an S_N2 process. However, any attempt to activate this alcohol as a sulfonate was unsuccessful, since the transient sulfonate



Scheme 3. Synthesis of benzoate *anti*,*syn*-**12**.

always decomposed. Alternatively, the inversion was performed easily prior the lactonization step by a Mitsunobu reaction.[5] Under these conditions, benzoate *anti*,*syn*-**12** was obtained in 81% yield. We checked that the assumed inversion had indeed occurred, by comparison with the non-inverted benzoate (prepared from *syn*,*syn*-**11** with benzoyl chloride).

The endgame of this synthesis was the oxidation of the furan moiety with sodium periodate under Ru catalysis[6] to afford acid *anti*,*syn*-**13** in 82% yield (Scheme 4). Deprotection of benzoate under basic conditions followed by acidic treatment caused the hydrolysis of THP group with concomitant cyclization to the final lactone **4** in 81% yield. Transformation of **4** into glycosyl lactol **2** in three steps has been previously reported.[2]



Scheme 4. Oxidation of furane **12** and lactone formation.

The NMR spectroscopic data of lactone **4** were fully consistent with those in the literature.[2] Furthermore, the Mosher ester of **4** indicated a single enantiomer.[7]

3. Conclusion

Lactone **4**, an intermediate in the synthetic approach to halichoblelide, has been synthesized stereoselectively from commercially available (*R*)-3-butyn-2-ol. In the context of natural product synthesis, this approach constitutes the first application of our recently described methodology of hydroboration–addition of