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New strategy for the synthesis of phosphatase inhibitors TMC-69-6H and analogs

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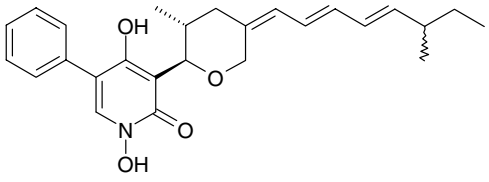
Abstract—An efficient method for the synthesis of antitumor TMC-69-6H and related analogs which have been demonstrated to be phosphatase (PTP1B, VHR, and PP1) inhibitors, is reported. This strategy involves two key steps: a diastereoselective aldol reaction and a one-pot tandem ring-closing and cross metathesis for the construction of the pyran moiety.

Isolated from the fermentation broth of a mitosporic fungus, *Chrysosporium* sp. TC 1068, labile TMC-69 (**1**) was described as a new antitumoral antibiotic.[1] Its hexahydro derivative TMC-69-6H (**2**), with improved stability, was prepared by Khono. These two compounds TMC-69 (**1**) and TMC-69-6H (**2**) showed cytotoxic activities in vitro against various tumor cell lines (IC_{50} values of 0.1–1.87 μM). Compound **2** induced significant prolongation of survival time of mice transplanted with B16 melanoma as well as P388 leukemia (ILS value of 58.1% at a dose of 3 mg/kg). Moreover, TMC 69-6H (**2**) was found to have inhibitor activity against Cdc25A and B phosphatases (dose dependent inhibition of Cdc24A activity with an IC_{50} of 3.1 μM).[2] Cdc25 phosphatases are classified as dual-specificity protein phosphatases that act as keys regulators of the cell cycle progression and mitogenic signaling pathways. These phosphatases which are overexpressed in many human tumors constitute potential targets for drug discovery.

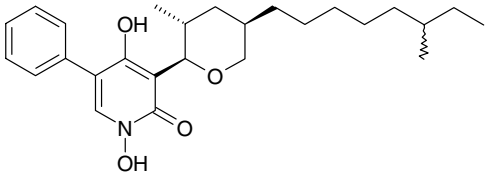
The first total synthesis of TMC-69-6H and analogs was described by Fürstner et al.[3] All these compounds were evaluated for their biological activity,[4] but the previously reported strong inhibition of Cdc25A and B phosphatases was not confirmed. It should be noted that antitumor activity of TMC-69-6H remains undisputed. Fürstner found that TMC-69-6H and congeners exhibit pronounced activities against the tyrosine protein phosphatase PTP1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1. PTP1B is a key regulator of insulin–receptor activity[5] and is expected to enhance insulin sensitivity and act as effective therapeutics for the treatment of Type II diabetes, insulin resistance, and obesity. Phosphatase PP1 plays an important role in the regulation of the cell cycle.[6]

In spite of a completely different selectivity profile, these compounds constitute a promising new class of selective phosphatase inhibitors (see Scheme 1).



TMC-69

1



TMC-69-6H

2

Scheme 1. TMC-69 and TMC-69-6H.

Keywords: TMC-69-6H; Antitumor activity; PTP1B inhibitor; Diastereoselective aldolization; Metathesis.
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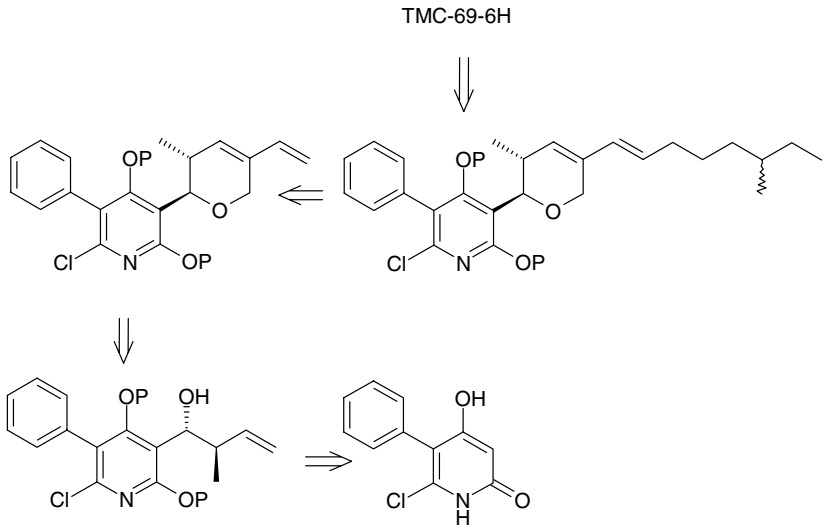
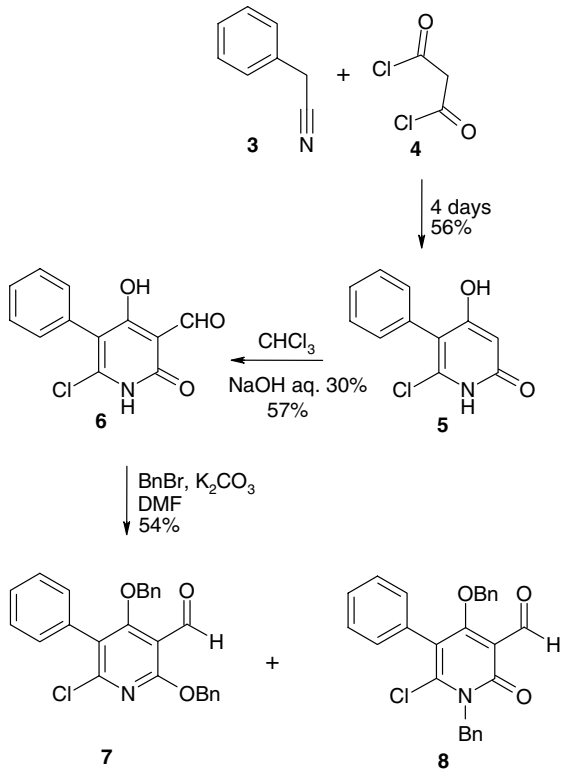


Scheme 2. Retrosynthetic analysis.

We now report a new flexible strategy for the diastereoselective synthesis of TMC-69-6H and derivatives from pyridone moiety via two key steps, diastereoselective aldolization followed by tandem ring-closing and cross metathesis for the construction of pyran moiety. The key aspects of the retrosynthetic analysis applied in this study are outlined in Scheme 2.

We began our investigation by construction of the pyridone moiety using Davis conditions.[7] Thus, condensation between phenylacetonitrile and maloyldichloride produced the known 6-pyridone **5** in 56% yield (Scheme 3).



Scheme 3. Pyridone synthesis.

Pyridone **5** was submitted to the formylation conditions. The Reimer–Thiemann reaction[8] has been successfully extended to pyridone derivatives (Scheme 3). Electrophilic addition of dichlorocarbene species generated by the action of a base (NaOH) in chloroform in a two-phase system, afforded the desired product **6** in 57% yield.

The alkylation of ambient anions of pyridone has been extensively studied.[9] Whatever the conditions, a separable mixture of di-O-benzylated compound **7** and O- and N-benzylated derivative **8** was isolated (Scheme 3). The preferred di-O-alkylation was observed under typical basic conditions (BnBr, K_2CO_3, DMF) to afford **7** in 54% yield.

Starting from **7**, we investigated a new class of crotylboron reagents and their Lewis acid-promoted additions to carbonyl compounds as described by Thadani and Batey.[10] In a biphasic medium (CH_2Cl_2, H_2O) containing a phase transfer catalyst (nBu$_4$NI), the use of potassium (*E*)-crotyltrifluoroborate **9** led to the formation of *anti*-homocrotyl alcohols (dr > 95%) in 96% yield (Scheme 4).

The (*E*)-crotyltrifluoroborate gave the expected *anti* product. This observation is consistent with the intermediacy of crotylboron difluoride, formed in situ by Lewis acid-promoted removal of fluoride from **9**, and addition via a Zimmerman–Traxler like transition state.[11]

As shown in Scheme 5, propargylic ether **11** was prepared according to the procedure in the literature.[12] Treatment of compound **10** with NaH and propargyl bromide gave enyne **11** in 90% yield.

Metal-catalyzed enyne metathesis seemed to be a convenient approach to achieve the synthesis of the