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Convergent synthesis of potent COX-2 inhibitor inotilone

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Abstract—The first synthesis of potent COX-2 inhibitor inotilone is reported. The convergent route features a Mukaiyama aldol condensation that generates the target without the use of protecting groups or a separate dehydration step. The approach also highlights a superior regioselective preparation of 1-bromo-2,4-pentanedione involving a bis(silyl enol ether) and NBS.
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Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular treatments for prevalent inflammatory ailments including arthritis and musculoskeletal pain. In recent years, a specific class of NSAIDs, the cyclooxygenase-2 (COX-2) inhibitors, has sparked intense clinical investigation because of their remarkable cancer chemopreventive activity versus colorectal,[1] breast,[2] and several other cancer cell types.[3] COX-2 inhibitors also elicit potentiation of tumor response to radiation therapy and may ultimately find use as an adjuvant treatment.[4] Celecoxib, the most prescribed selective COX-2 inhibitor in the United States, has also shown efficacy in the treatment of Lou Gehrig's disease.[5] Despite the promising, and in some cases singular, medical benefits offered by COX-2 inhibitors, several have indicated increased cardiovascular risk that warrants caution for applications involving chemoprevention. Recent studies suggest that cardiovascular risk may not be a class effect and that the risk is likely dose dependent.[6] Hence, potent and highly selective COX-2 inhibitors are desired as safer alternatives to the COX inhibitors currently available.

Hertweck and co-workers recently reported several new phenylpropanoid polyketide metabolites from the mushroom *Inonotus* sp.[7] An unusual 5-methyl-3(2*H*)-furanone derivative, inotilone (**1**), showed a COX-2 enzyme assay IC_{50} value of 0.03 μM (Fig. 1). This potency rivals that of the marketed inhibitors meloxicam and nimesulide[8] and is superior to rofecoxib.[9] Importantly, inotilone proved a poor inhibitor of hydroxysteroid dehydrogenase, xanthine oxidase, and displayed an order of magnitude lower IC_{50} value for COX-2 than COX-1. Thus, its potency, selectivity, and low molecular weight make it an attractive target for further investigation.

Our goal was to synthesize inotilone using a convergent approach conducive to analog preparation. Winkler's route to 5-alkyl-3-furanones (**3**) seemed particularly attractive as we envisioned the comparable furanone portion of inotilone could be readily coupled with 3,4-dihydroxy benzaldehyde under acidic conditions to afford **1** without phenol protection (Scheme 1).[10] Winkler et al. also showed that the silyl enol ether of **3** could undergo addition with various aldehydes using one of several Lewis acids, thus portending a promising outcome to our planned late stage coupling step.

Although inspired by the protocol highlighted in Scheme 1, the preparation of the 5-methyl-3(2*H*)-furanone (**8**) featured in inotilone necessitated important modifications from those reported to furnish **3**. We were initially dissatisfied with published routes to 1-halo-2,4-diones. The chloride could be prepared in one step using acetone lithium enolate and ethyl chloroacetate in only

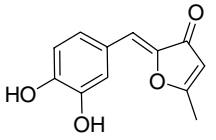

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Figure 1. Potent and selective COX-2 inhibitor inotilone.

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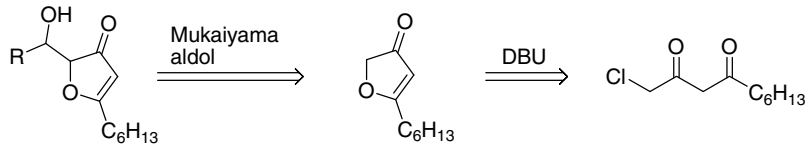

2 3 4

Scheme 1. The Winkler et al. approach to 3(2*H*)-furanone 3 and its use in Mukaiyama aldol reactions.[10]

poor yield (<40%).[11] Meanwhile attempted regioselective bromination of 2,4-pentanedione using hexabromocyclopentadiene resulted in an assortment of 1- and 3-bromoacetylacetone and polybrominated products that were difficult to separate.[12] Direct iodination also furnished an unacceptable mixture of sensitive regioisomeric iodo-2,4-diones.[13] However, treatment of bis(silyl enol ether) **6**[14] with NBS afforded the desired 1-bromo-2,4-pentanedione **7** in quantitative yield (Scheme 2). The reaction proceeds rapidly and is equally efficient on scales from 1 to 25 g.

Attempted cyclization of **7** using DBU proved problematic, primarily due to the moderate volatility of **8** and the arduous removal of the hydrophilic product from water during work-up. We modified Winkler's protocol by conducting the cyclization with K_2CO_3 in ether. Rapid filtration of the crude reaction mixture through Celite and rotary evaporation of the filtrate at 23 °C provided pure **8** without the need for aqueous work-up or purification. The furanone was subsequently treated with LDA and TMSCl to give **9**, which may be purified by simple distillation if desired.

The Mukaiyama aldol reaction between trimethylsilyloxyfuran **9** and 3,4-dihydroxy benzaldehyde was realized using 4.0 equiv of $BF_3{\cdot}Et_2O$ in THF at −30 °C. Fewer equivalents led to poor conversion, as did employment of $Ti(OiPr)_4$ or Et_2AlCl as the Lewis acid. The reaction can also be conducted at room temperature with only a modest decrease in yield (60%) while temperatures lower than −30 °C offer no advantage. Elimination of the intermediate β-hydroxyl group occurs in situ or during work-up, as the crude reaction mixture shows no evidence of the hydroxyl functionality by ^1H NMR. It is notable that the (*Z*)-alkene is the only observed isomer, presumably because of the destabilizing interaction between the furanone carbonyl and the aromatic C_6 hydrogen in the (*E*)-diastereomer of **1**. All characterization data and NOESY correlations of synthetic **1** coincide with those reported by Hertwick.[7]

Herein we described the first synthesis of potent COX-2 inhibitor inotilone. The natural product was prepared from commercially available materials in six steps and ~50% overall yield. The approach is amenable to scale-up, conducive to analog preparation, and features a high yielding new method for 1-bromoacetylacetone (**7**) preparation. The synthesis and biological activities of numerous inotilone analogs will be reported once completed.

Acknowledgements

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Supplementary data

Experimental procedures, NMR spectra, and HRMS data are provided for compounds **1** and **7**–**9**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.166.

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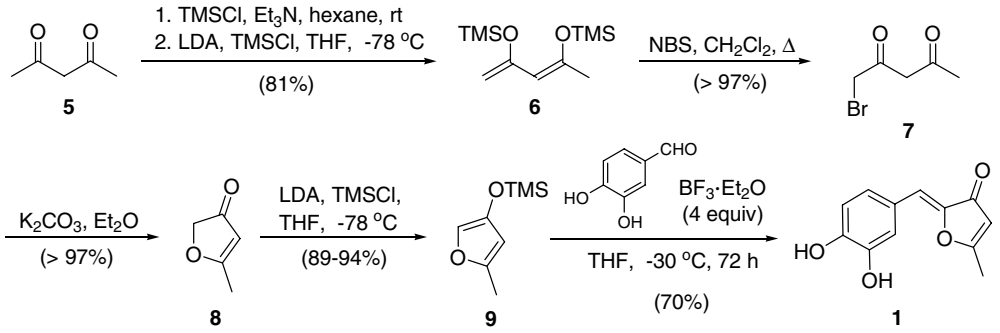

5 6 7 8 9 1

Scheme 2. Route to the total synthesis of inotilone.

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