Synthesis of SGLT2 Inhibitors by Means of Copper-Mediated Coupling Reactions with Grignard Reagents

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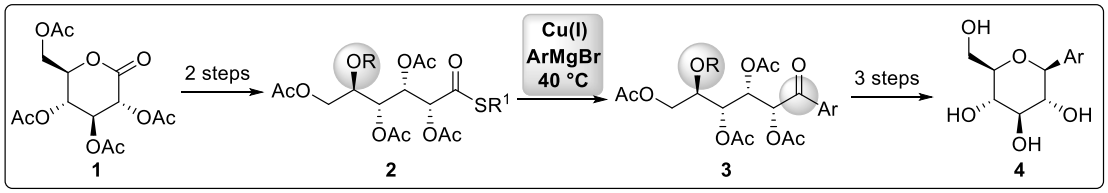
SGLT2 inhibitors such as canagliflozin (Invokana®), dapagliflozin (Farxiga®), and empagliflozin (Jardiance®) have received considerable attention as an anti-diabetes drug.[1] They have β-*C*-arylglycoside as the key structural motif. Several approaches have been devised especially for carbon−carbon bond formation to construct a β-*C*-arylglycoside skeleton. However, they suffer from drawbacks of such as need of cryogenic conditions, expensive and/or hazardous reagents and poor functional group compatibility which restricted their application to industrial large-scale production.[2] In our previous studies, improved synthesis of SGLT2 inhibitors based on ketone synthesis employing Grignard reagents and copper(I) salts has been reported.[3] Even though it can be conducted under mild reaction conditions, use of benzyl protecting group was a major drawback in terms of high cost and less atom economy for deprotection step.

To address the challenge, the present study was planned to use easily cleavable acetyl protected intermediates. Synthesis of acetyl protected thioester **2** was achieved by treatment of tetra-*O*-Ac-D-gluconolactone **1** with thiol and ^{i}PrMgCl. Then, compound **2** was treated with diarylcuprates generated in situ from copper(I) salts and aryl Grignard reagents to give ketone **3**. From **3**, deprotection, cyclization and silane reduction provided desired SGLT2 inhibitors **4**.



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