Synthesis of SGLT2 Inhibitors by Means of Fukuyama Coupling Reaction

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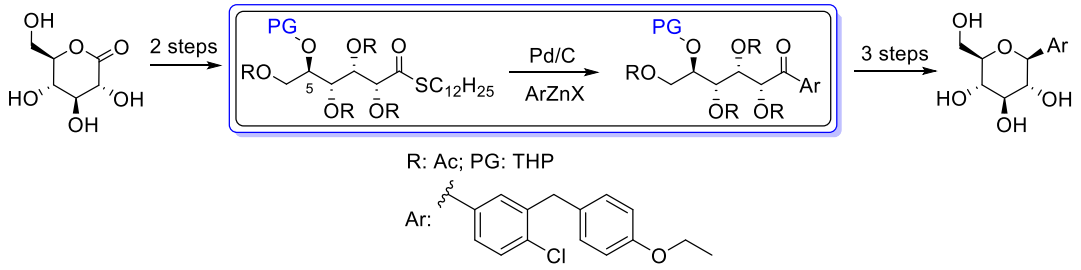
The sodium glucose co-transporter 2 (SGLT2) has received considerable attention in recent years as a target for the treatment of type 2 diabetes mellitus (T2DM)[1,2]. In this context, dapagliflozin currently represents one of the most advanced SGLT2 inhibitor due to its high efficacy and safety. The present study describes a novel synthesis of dapagliflozin via Fukuyama coupling reaction[3] of a D-gluconolactone-derived thioester with aryl zinc reagents producing the corresponding multifunctional aryl ketones in high yield at ambient temperature, followed by THP deprotection, base catalysed cyclization, silane reduction and final deacetylation. This newly developed protocol is highlighted by the high cumulative yields, mild reaction conditions and use of readily removable acetyl protecting groups.



1) J. Talode, D. Kato, H. Nagae, H. Tsurugi, M. Seki, and K. Mashima, *J. Org. Chem.* **2020**, *85*, 12382 2) B. Komoroski, N. Vachharajani, D. Boulton, D. Kornhauser, M. Geraldes, L. Li, M. Pfister *Clinical Pharmacology & Therapeutics* **2009**, *85*(5), 520. 3) M. Seki, M. Hatsuda, Y. Mori, S. Yoshida, S. Yamada, T. Shimizu, *Chem. Eur. J.* **2004**, 10, 6102.