HETEROCYCLES, Vol. 106, No. 12, 2023, pp. 1777 - 1815. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 25th July, 2023, Accepted, 15th September, 2023, Published online, 2nd October, 2023
DOI: 10.3987/REV-23-1013

STRATEGY FOR THE SYNTHESIS OF *C*-ARYL GLUCOSIDES AS SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

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Abstract – Sodium glucose cotransporter 2 (SGLT2) inhibitors are currently the focus of attention in the treatment of diabetes. Since the discovery of the first SGLT inhibitor phlorizin, a natural *O*-aryl glucoside, extensive efforts in the search for selective SGLT2 inhibitors have continued and several *C*-aryl glucosides have been launched onto the market. This review presents routes and strategies collected from both drug discovery chemistry and industrial process chemistry for the synthesis of nine pioneering *C*-aryl glucoside SGLT2 inhibitors (dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, luseogliflozin, tofogliflozin, ertugliflozin, bexagliflozin, and sotagliflozin). The synthetic strategies employed for the construction of the carbon backbone of these inhibitors are classified into four types, and details of various synthetic routes and methods are described.

CONTENTS

1. INTRODUCTION

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been receiving much attention for their role in the treatment of diabetes.[1] The first SGLT inhibitor to be discovered was phlorizin (**1**), which is a natural *O*-aryl glucoside isolated from the bark of apple trees (Figure 1). However, this compound shows non-selective inhibitory activity towards SGLT1 and SGLT2,[2] causing gastrointestinal side effects because SGLT1 exists mainly in the intestine.[3] Furthermore, phlorizin (**1**) is problematic as a drug candidate owing to its metabolic instability (hydrolysis of the *O*-glycosidic bond). Therefore, various compounds have been synthesized to overcome the drawbacks of phlorizin (**1**).

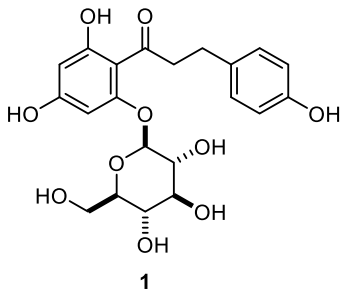

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Figure 1. Structure of phlorizin

Inspired by the structure of phlorizin (**1**), many selective SGLT2 inhibitors have been developed as potential new drugs for the treatment of diabetes. Both *O*-aryl glucoside and *C*-aryl glucoside compounds have been investigated, and *C*-aryl glucosides in particular have met great success.[4]

Various pathways for the synthesis of *C*-aryl glucosides with SGLT2 inhibition activity have been documented in the literature, and several reviews have also been published.[5] The present review deals with the synthesis of *C*-aryl glucoside SGLT2 inhibitors that had been approved as of 2019. The synthetic strategies and methods described here consist of those published in academic journals but not those appearing in patents. All of the *C*-aryl glucosides discussed in this review feature a structure depicted by the general molecule in Figure 2. The structures of individual *C*-aryl glucoside SGLT2 inhibitors are shown in Figure 3.

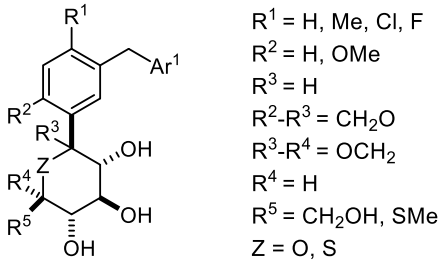


Figure 2. General structure of SGLT2 inhibitors

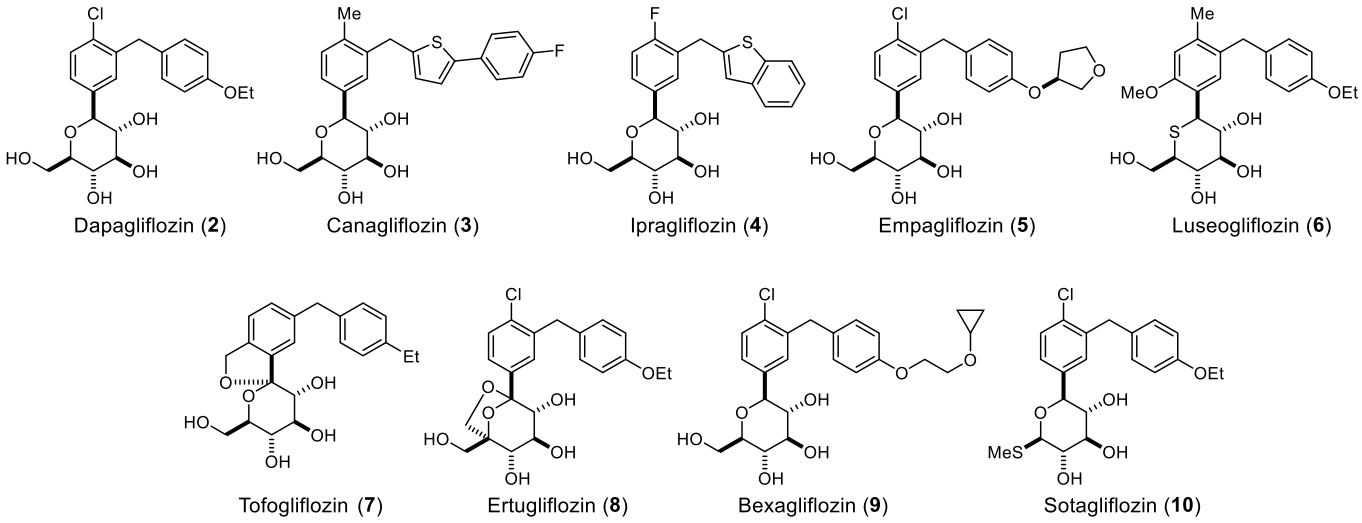


Figure 3. Structures of SGLT2 inhibitors

2. SYNTHETIC STRATEGIES

The four main synthetic strategies and their key reactions are shown in Figure 4.

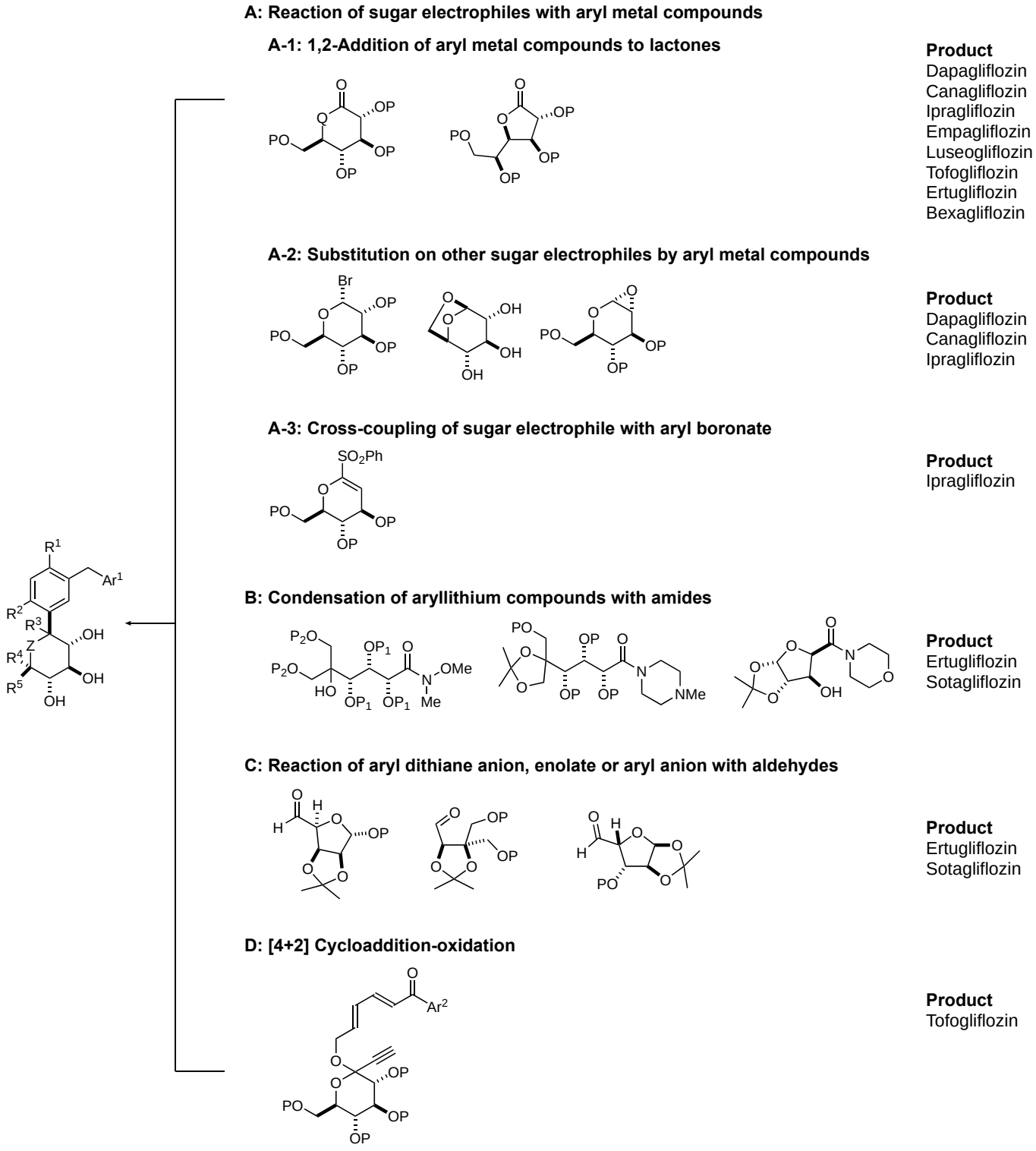


Figure 4. Synthetic strategies: key reactions and substrates

Most *C*-aryl glucosides can be synthesized by way of carbon-carbon bond-forming reactions between sugar electrophiles[6] as sugar moieties and aryl metal compounds as aromatic moieties (A in Figure 4). With this strategy, reactions between several kind of sugar electrophiles and aryl carbanions generated from aryl halides by halogen-metal exchange reactions are carried out to form the desired carbon-carbon bond.[7] In many cases, gluconolactone derivatives are used as the sugar electrophiles for 1,2-addition reactions of aryl carbanions (A-1); this method has been applied to the synthesis of dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, tofogliflozin, ertugliflozin, and bexagliflozin. Thiolactone has been also used (A-1: synthesis of luseogliflozin). In addition, a dihydro-2(*3H*)-furanone derivative has been used as the sugar electrophile for the 1,2-addition reaction (A-1: synthesis of ipragliflozin).[8] Moreover, the use of a glycosyl halide, anhydro-sugar, or glycal epoxide[9] as the sugar electrophile has also been shown to be efficient for the synthesis of *C*-aryl glucosides (A-2: synthesis of dapagliflozin, canagliflozin, and ipragliflozin). More recently, by use of α-oxo-vinylsulfone, cross-coupling with aryl boronate has been demonstrated to afford a *C*-aryl glycal leading to a *C*-aryl glucoside (A-3: synthesis of ipragliflozin).

Condensation of amides, the backbones of which have the necessary oxygen functional groups, with aryl carbanions is another strategy for carbon-carbon bond formation between an aliphatic moiety and an aromatic moiety. Weinreb and piperazine amides have been used to achieve effective condensation (B in Figure 4: synthesis of ertugliflozin). Morpholine amide has also been used (B in Figure 4: synthesis of sotagliflozin).

In a third strategy, formation of the desired carbon-carbon bonds has been attained by 1,2-addition of carbanions/enolates as aryl moieties to chiral aldehydes bearing *O*-functional groups. For example, 1,2-addition of a carbanion generated by the deprotonation of aryl dithiane to tri-oxygenated tetrahydrofuran-carbaldehyde yields a useful intermediate leading to a *C*-aryl glucoside (C in Figure 4: synthesis of ertugliflozin). In addition, 1,2-addition of lithium enolate generated by the deprotonation of an aryl methyl ketone to an aldehyde prepared from L-arabinose affords the desired carbon skeleton (C in Figure 4: synthesis of ertugliflozin). The reaction of an aldehyde derived from L-xylose with aryllithium affords a 1,2-adduct that can be converted into a *C*-aryl glucoside after several steps (C in Figure 4: synthesis of sotagliflozin).

A fourth strategy for the synthesis of a *C*-aryl glucoside involves a reaction without the use of aromatic carbanions or the use of carbanions or enolates bearing aromatic rings mentioned above. The aromatic ring of the *C*-aryl glucoside is constructed by [4+2]cycloaddition of a dienone-yne bearing tetrahydropyran followed by oxidation. Subsequent reduction of the carbonyl group derived from the dienone moiety leads to the desired *C*-aryl glucoside (D in Figure 4: synthesis of tofogliflozin).

3. SYNTHESIS

The strategies involved in the synthesis of the SGLT2 inhibitors examined in this review focus on those that have been described in academic journals; the details of methods described in patents are excluded.[8-10] The synthetic processes discussed here include those of medicinal chemistry and process chemistry. Both approaches are valuable for the creation of new drugs, with medicinal chemistry being useful for the discovery of new drugs and process chemistry being useful for drug preparation on an industrial scale.

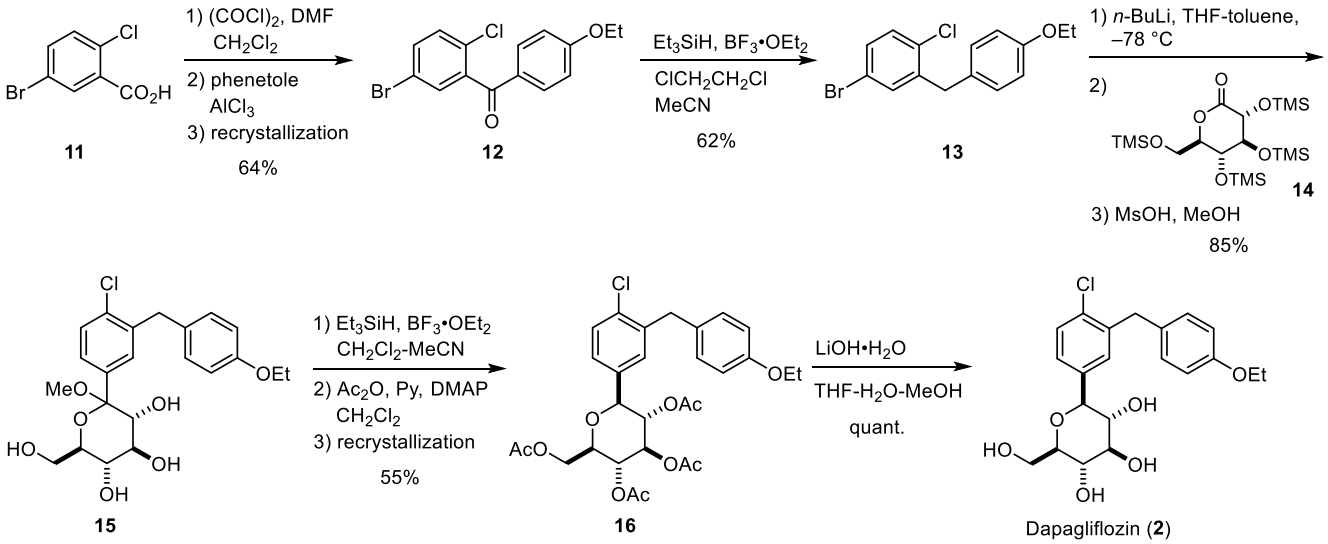
3.1. SUGAR ELECTROPHILES WITH ARYL METAL COMPOUNDS

3.1.1. Lactones with aryl metal compounds

Various *C*-aryl glucoside SGLT2 inhibitors have been synthesized by the 1,2-addition of an aryl carbanion generated from an aryl halide to a protected gluconolactone. The aryl moieties can be in various configurations. In this section, the syntheses of eight SGLT2 inhibitors are described (dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, luseogliflozin, tofogliflozin, ertugliflozin, and bexagliflozin). The synthetic routes of these *C*-aryl glucosides are illustrated in Schemes 1–11.

(1) Dapagliflozin

Among the *C*-aryl glucoside SGLT2 inhibitors depicted in Figure 3, the first to be synthesized was dapagliflozin (**2**); its synthetic route (Scheme 1) appeared in the literature in 2008.[11]



Scheme 1. Synthesis of dapagliflozin (**2**) *via* gluconolactone

The synthetic strategy is as follows: construction of a carbon backbone by connecting a sugar electrophile to an aryl nucleophile, carbon-carbon bond formation by 1,2-addition of an aryl carbanion to a protected

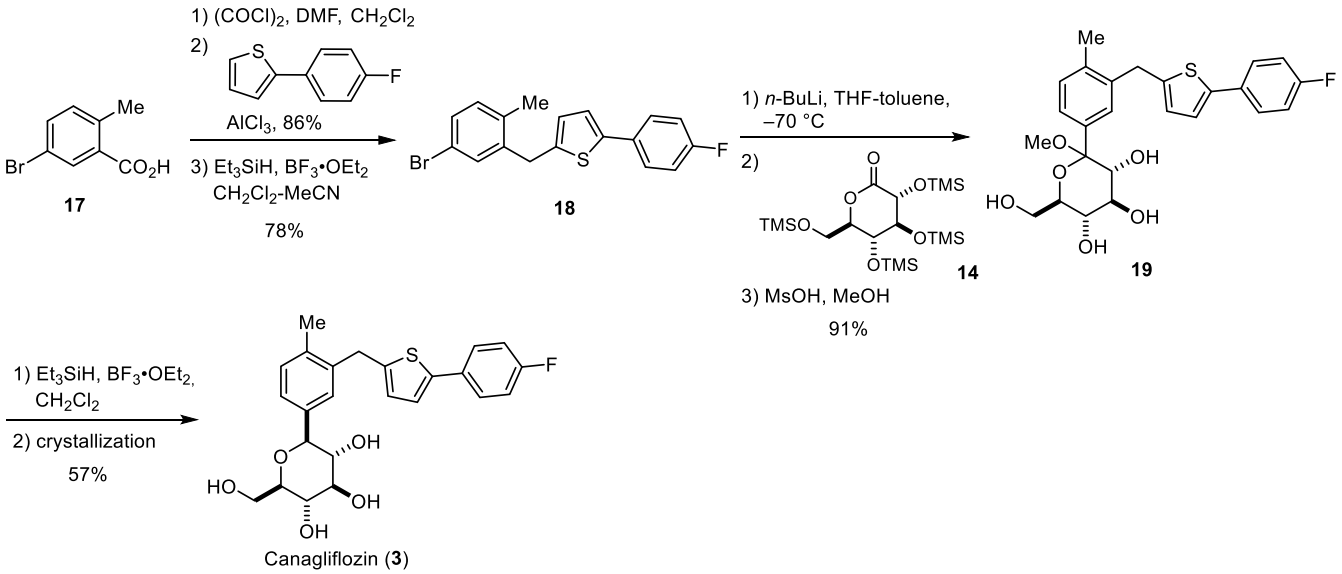
gluconolactone as a sugar electrophile, and generation of a carbanion from an aryl halide by halogen-metal exchange.

The aryl moiety for connecting to the sugar electrophile is prepared by Friedel–Crafts acylation. Acylation catalyzed by $AlCl_3$ of phenetole with 5-bromo-2-chlorobenzoyl chloride generated from commercially available benzoic acid **11** affords *p*-benzophenone **12**. Although the regioselectivity (*para*:*ortho*) is 7 to 1, *para*-**12** is obtained in 64% isolated yield by two times recrystallization. Reduction of the carbonyl group is attained by use of triethylsilane (Et_3SiH) with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) to give the desired diarylmethane **13** in 62% yield.

After lithiation of **13** by bromine-lithium exchange using *n*-butyllithium (*n*-BuLi), 1,2-addition to trimethylsilylgluconolactone **14** under cryogenic conditions followed by treatment with methanesulfonic acid (MsOH) in MeOH affords an anomeric mixture of *O*-methyl lactols **15**. Removal of the anomeric methoxy group is achieved by reduction with a combination of Et_3SiH and $BF_3{\cdot}OEt_2$[12] to afford tetraacetate **16** which is purified by recrystallization to remove the small amount of anomer formed during reduction. Finally, hydrolysis of tetraacetate **16** with aqueous LiOH affords dapagliflozin (**2**) in quantitative yield.

(2) Canagliflozin

Synthesis of canagliflozin (**3**) using this strategy is illustrated in Scheme 2.[13] Here, the aryl moiety of canagliflozin (**3**) is synthesized starting from 5-bromo-2-methylbenzoic acid (**17**).



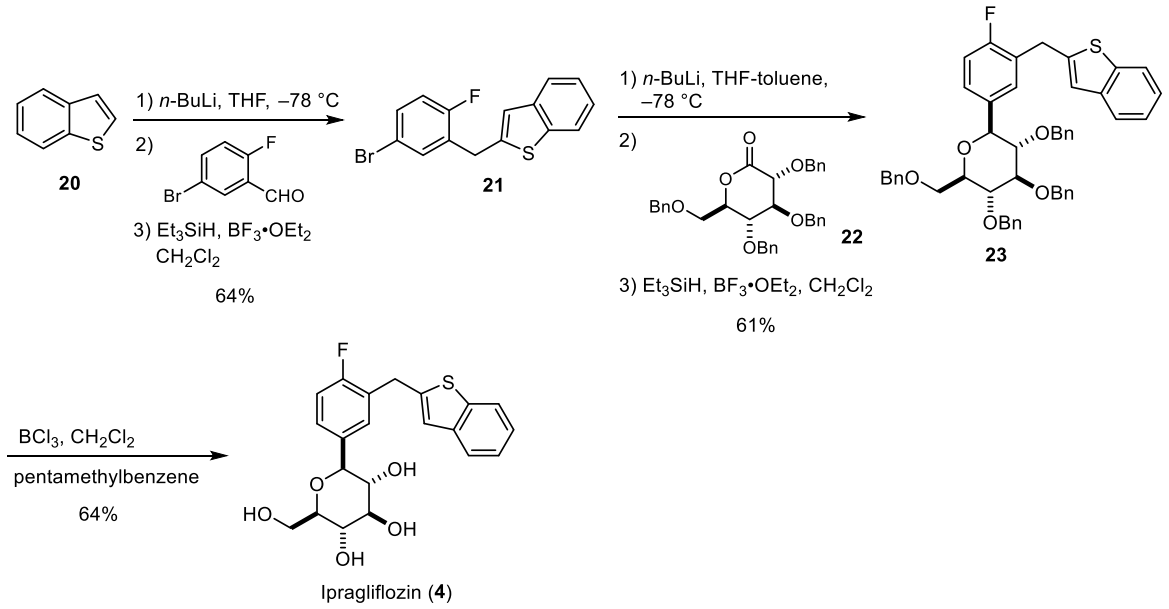
Scheme 2. Synthesis of canagliflozin (**3**) *via* gluconolactone

After conversion of benzoic acid **17** to the corresponding acid chloride, Friedel–Crafts acylation with fluorophenylthiophene using $AlCl_3$ affords aryl ketone in 86% yield. Reduction of the carbonyl group gives the desired aryl bromide **18** in 78% by use of Et_3SiH with $BF_3{\cdot}OEt_2$.

Bromide **18** is treated with *n*-BuLi, and then the resulting lithiated aryl moiety is subjected to 1,2-addition to trimethylsilylgluconolactone **14**. Treatment with MsOH in methanol affords desilylated *O*-methyl lactols **19** in 91% yield. After removal of the anomeric methoxy group, the crude product is purified by crystallization to afford canagliflozin (**3**) in 57% yield.

(3) Ipragliflozin

Synthesis of ipragliflozin (**4**) using this strategy is illustrated in Scheme 3.[14] With this method, ipragliflozin (**4**) is synthesized through direct reduction of lactol (1,2-addition adduct) without preparation of *O*-methyl lactols.



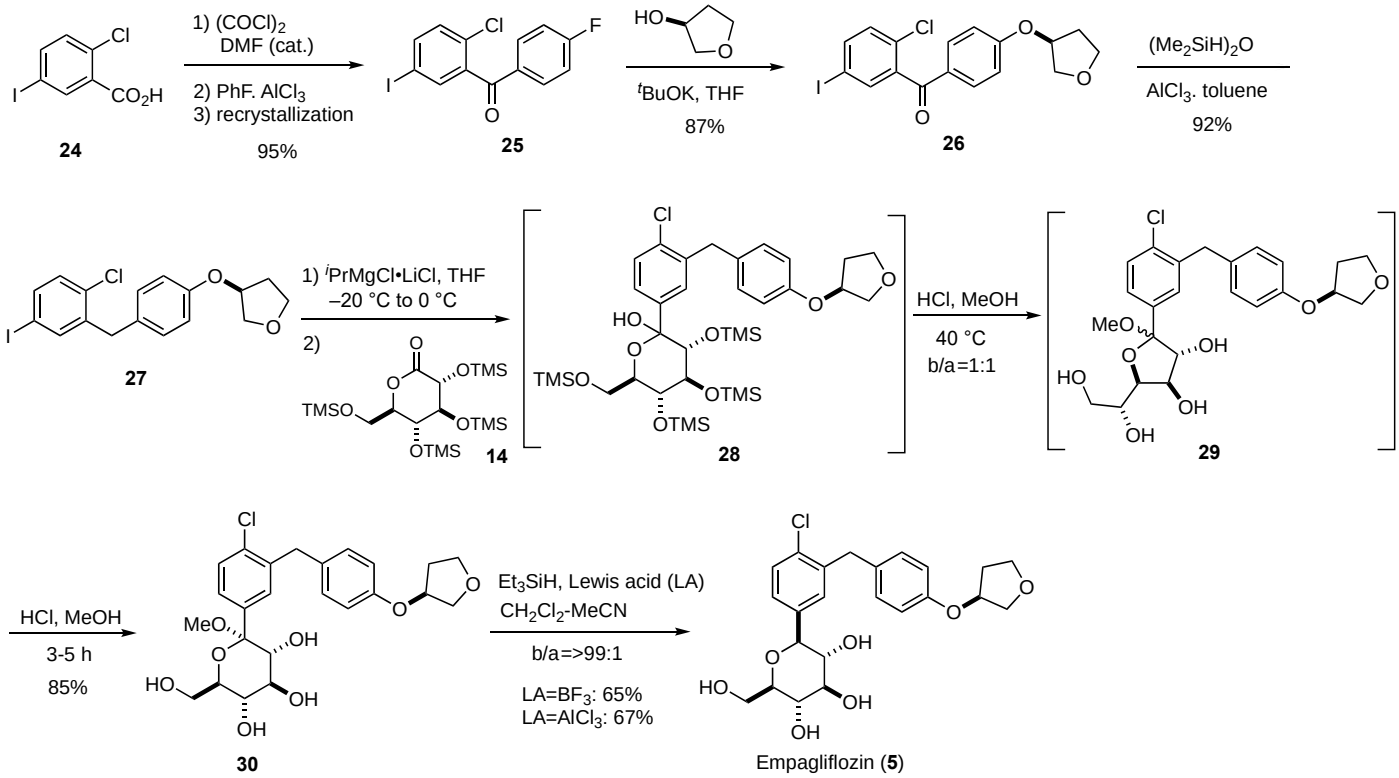
Scheme 3. Synthesis of ipragliflozin (**4**) *via* gluconolactone

Aryl halide **21** is prepared starting from thiophene (**20**) and 5-bromo-2-fluorobenzaldehyde. Deprotonation at the 2-position of thiophene (**20**) with *n*-BuLi followed by 1,2-addition is carried out, and then reduction by use of Et_3SiH with $BF_3{\cdot}OEt_2$ affords the desired aryl bromide **21** in 64% yield as the aryl part of ipragliflozin (**4**).

Bromine-lithium exchange of **21** with *n*-BuLi followed by 1,2-addition to benzylgluconolactone **22** gives a lactol, reduction of which with Et_3SiH and $BF_3{\cdot}OEt_2$ gives benzylated ipragliflozin **23** in 61% yield. Deprotection by use of boron trichloride in the presence of pentamethylbenene affords ipragliflozin (**4)** in 64% yield.

(4) Empagliflozin

Synthesis of empagliflozin **(5**) using this strategy is illustrated in Scheme 4.[15] Formation of *O*-methyl lactol and reduction conditions for removal of the methoxy group with this synthesis are examined in detail.



Scheme 4. Synthesis of empagliflozin (**5**) *via* gluconolactone

Aryl halide **27** is prepared starting from 5-iodo-2-chlorobenzoic acid (**24**) and fluorobenzene. After conversion of benzoic acid **24** to the corresponding acid chloride, the highly regioselective Friedel–Crafts reaction is performed to give fluorobenzophenone **25** in 95% yield after recrystallization. Aromatic substitution of **25** with (*S*)-hydroxytetrahydrofuran under basic conditions gives benzophenone **26** in 87% yield after crystallization. Reduction is achieved by use of tetramethyldisiloxane with aluminum chloride ($AlCl_3$) to give the desired aryl iodide **27** in 92% yield after crystallization.

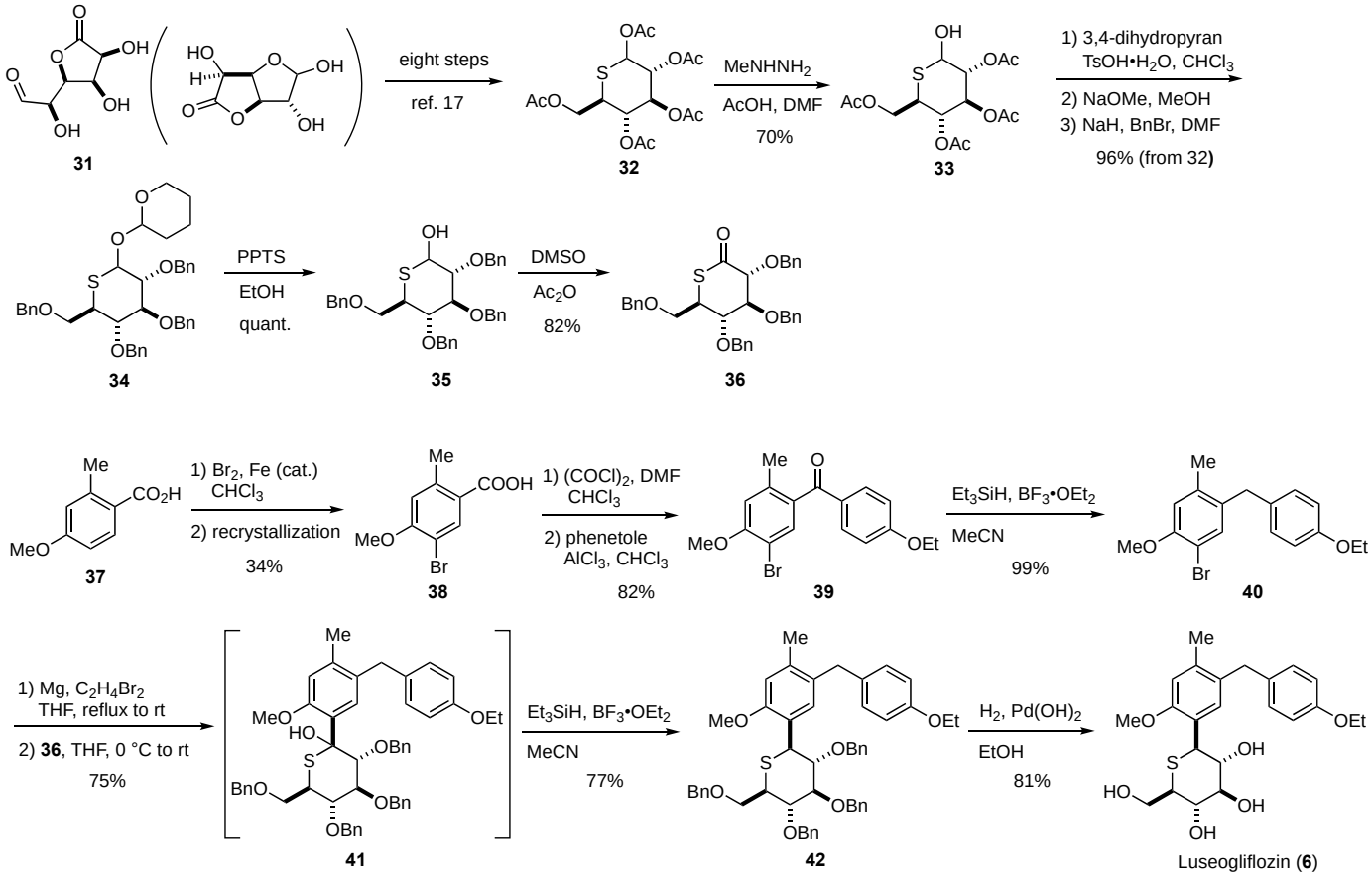
Iodine-metal exchange followed by 1,2-addition to trimethylsilylgluconolactone **14** is attained with isopropylmagnesium chloride/lithium chloride (^{i}PrMgCl·LiCl) complex at −20 °C to 0 °C to give lactol **28**. When ^{i}PrMgCl is used alone, the reaction is sluggish and results in the decomposition of the arylmagnesium chloride. When the corresponding aryl bromide is used instead of aryl iodide **27**, bromine-magnesium exchange with ^{i}PrMgCl·LiCl complex proceeds more slowly.

Treatment of the resulting mixture of lactol **28**, which is obtained by the reaction of aryl iodide **27** with ^{i}PrMgCl·LiCl complex followed by 1,2-addition to **14**, with aqueous HCl in methanol affords methyl furanoketal **29** as an anomeric mixture (β/α=1:1). This five-membered ring compound is converted to *O*-methyl β-pyranoketal **30** over 3 to 5 h. Treatment of the crude **30** (*O*-unprotected; tetrahydroxy compound) with a combination of Et_3SiH and $BF_3{\cdot}OEt_2$ in $MeCN/CH_2Cl_2$ affords β-*C*-glucoside **5** (β/α=>99:1) in 65% yield after crystallization. Careful study has revealed that the water content of the reaction mixture affects

the formation of the furanoside side product. The reaction of **30** by use of $AlCl_3$ gives results comparable to that of $BF_3{\cdot}OEt_2$ (**5**: 67% yield, after crystallization). Interestingly, the reaction with $AlCl_3$ is much less sensitive to water. In contrast to the β/α selectivity for reduction of tetraol **30**, the selectivity in reduction of tetra-*O*-protected derivatives (*O*-acetyls, *O*-benzyls, and *O*-allyls) of **30** were low for which chelation effects are proposed.

(5) Luseogliflozin

Synthesis of luseogliflozin (**6**) using this strategy is illustrated in Scheme 5.[16] This compound contains a sulfur atom in its aliphatic six-membered ring.



Scheme 5. Synthesis of luseogliflozin (**6**) *via* gluconolactone

Commercially available D-glucurono-3,6-lactone **31** is converted into 5-thio-D-glucose penta-*O*-acetate **32** in eight steps according to a method described in the literature.[17] Selective deacetylation at the anomeric position gives alcohol **33**. Protection of the resulting hydroxy group with 3,4-dihydropyran followed by removal of all acetyl groups is performed, and then the resulting hydroxy groups are protected with benzyl bromide to afford ether **34**. Deprotection of the tetrahydropyranyl group by use of pyridinium *p*-

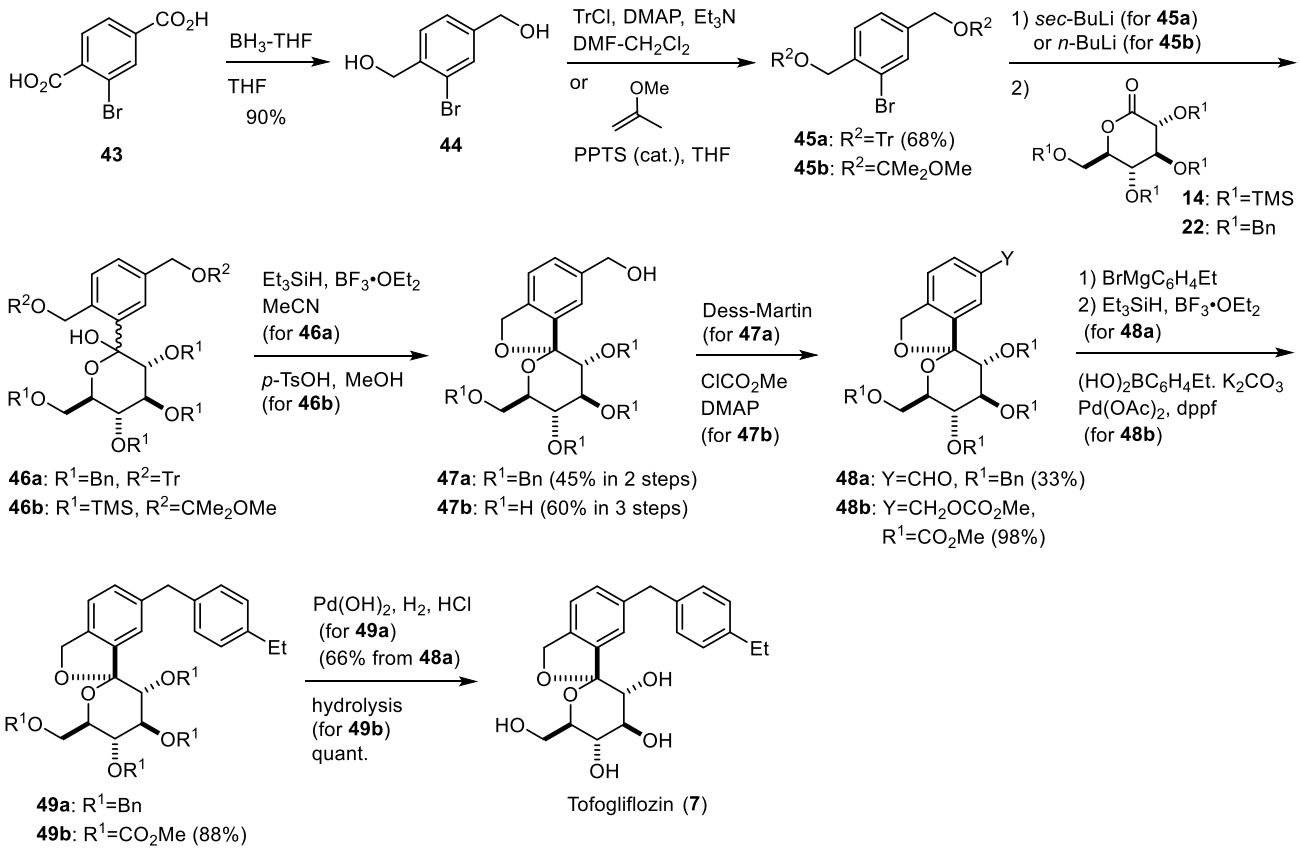
toluenesulfonate followed by oxidation with acetic anhydride-DMSO (Albright–Goldman method)[18] affords the desired thiolactone **36**.

Aryl bromide **40** is prepared from commercially available 4-methoxy-2-methylbenzoic acid **37**.[19] Bromination of **37** with bromine in the presence of Fe (cat.) gives a mixture of 3- and 5-bromo derivatives, from which the desired bromide **38** is isolated by recrystallization (34% yield). Acid chlorination followed by Friedel–Crafts reaction with phenetole gives benzophenone **39** in 82% yield. Reduction of **39** with a combination of Et_3SiH and $BF_3{\cdot}OEt_2$ gives aryl bromide **40** in 99% yield.

Treatment of **40** with magnesium powder gives a Grignard reagent, which is subjected to 1,2-addition to thiolactone **36** to afford thiolactol **41** as a single isomer (anomeric configuration has not been determined). Reduction by use of a combination of Et_3SiH and $BF_3{\cdot}OEt_2$ in MeCN gives benzyl ether **42** (β/α = >96:4). The β-isomer is subjected to hydrogenolysis to afford luseogliflozin (**6**) in 81% yield.

(6) Tofogliflozin

Synthesis of tofogliflozin (**7**) by use of lactones with aryl metal compounds has been achieved in four ways.[20-23] As shown in Figure 3, this compound has a unique spiroketal-dihydroisobenzofuran moiety.



Scheme 6. Synthesis of tofogliflozin (**7**) *via* gluconolactone

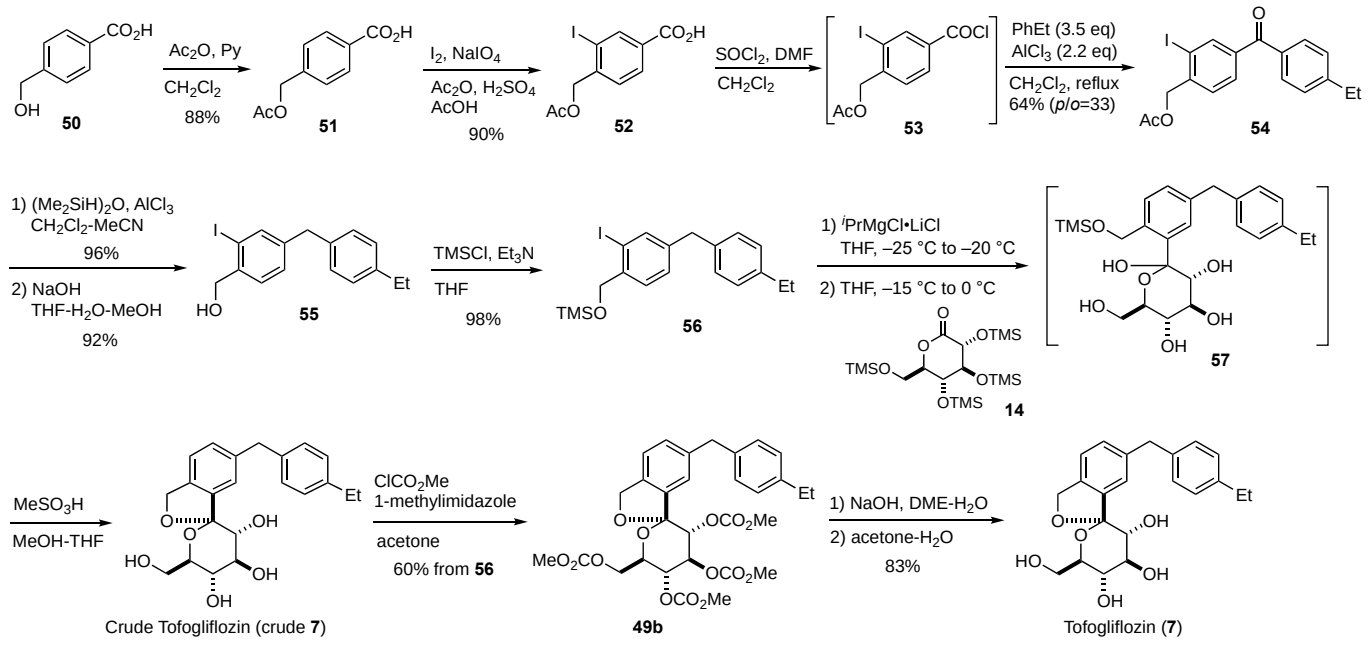
The first synthesis of tofogliflozin (**7**) was accomplished by way of the spiroketal intermediate **47a** by referring to the synthesis of antibiotic papulacandins,[24] which have a similar spiroketal moiety (Scheme 6).[20] In this synthetic route, reduction of commercially available 2-bromoterephthalic acid **43** followed by protection of hydroxyl groups with trityl chloride gives bromobenzyl ether **45a**. Bromine-lithium exchange with *sec*-butyllithium followed by 1,2-addition to benzylgluconolactone **22** gives lactol **46a**. Deprotection of the trityl group and spirocyclization are attained by use of $BF_3{\cdot}OEt_2$ together with Et_3SiH to afford the key intermediate **47a** (45% yield from 1,2-addition) which is then converted to the aldehyde **48a** by Dess–Martin oxidation. Addition of a Grignard reagent (4-ethylphenylmagnesium bromide) followed by reduction of the resulting hydroxy group furnishes penultimate tetrabenzyl ether **49a**. Finally, hydrogenolysis using palladium hydroxide [$Pd(OH)_2$] on activated charcoal/H_2 with HCl affords tofogliflozin (**7**) in 66% (from aldehyde **48a**).

However, the highly viscous properties of the synthetic intermediates with benzyl protecting groups such as **49a** are troublesome and not appropriate for large scale synthesis. Considering that a crystalline penultimate product would be more suitable for quality control of the final product, various protecting groups of **7** were examined. Among the protecting groups screened, introducing a methoxycarbonyl group to **7** was found to afford a crystalline solid **49b**. In addition, pentaol **47b** as the precursor of **48b** is also a stable crystal. Therefore, the synthetic route using crystalline solids **47b** and **49b** was developed as shown in Scheme 6 by the series of compounds labelled "b".[21]

Bromodiol **44** is converted into 2-methoxy-2-propyl ether **45b** with 2-methoxypropene, and then bromine-lithium exchange with *n*-BuLi and subsequent 1,2- addition to trimethylsilylgluconolactone **14** gives lactol **46b**. Removal of all the protecting groups and stereospecific spirocyclization under acidic conditions (*p*-toluenesulfonic acid in MeOH) affords the crystalline pentaol **47b** (60% yield over 3 steps). After permethoxycarbonylation of the five hydroxy groups of **47b** to **48b** by use of methoxycarbonyl chloride and a stoichiometric amount of 4-dimethylaminopyridine (DMAP), an ethylphenyl moiety is introduced by a Suzuki-coupling-type reaction of 4-ethylphenylboronic acid according to Kuwano and Yokogi's method.[25] Use of a combination of palladium acetate and 1,1′-bis(diphenylphosphino)ferrocene (dppf) as catalysts is found to give the best results for this coupling reaction, and crystalline coupling product **49b** is obtained in 88% isolated yield. Hydrolysis with aqueous NaOH affords tofogliflozin (**7**), with >99% purity in quantitative yield.

A synthetic route for tofogliflozin (**7**) partially inspired from empagliflozin[15] synthesis has also been reported.[22] The key reactions are the same as those in the synthesis of empagliflozin: reduction of a biaryl ketone with a silane reagent, and iodine-metal exchange by use of a combination of Grignard reagent and LiCl.

As illustrated in Scheme 7, after acetylation of the hydroxy group of hydroxylmethylbenzoic acid **50**, regioselective iodination with a combination of sodium periodate and iodine according to Lulinski's method gives *m*-iodobenzoic acid **52**.[26] This acid is converted into acid chloride **53**, Friedel–Crafts reaction of which with ethylbenzene gives biaryl ketone **54**. High regioselectivity is attained (*para/ortho* = 33; 64% chemical yield) when 2.2 equivalents of $AlCl_3$ as catalyst along with 3.5 equivalents of ethylbenzene is used. Reduction of biaryl ketone **54** by use of tetramethyldisiloxane [$(Me_2SiH)_2O$] with 3 equivalents of $AlCl_3$ affords biarylmethane in 96% yield. After removal of the acetyl group by hydrolysis, protection of the hydroxy group with trimethylsilyl chloride (TMSCl) gives the aryl moiety **56** in 98% yield. Iodine-metal exchange by use of ^{i}PrMgCl·LiCl complex followed by 1,2-addition to trimethylsilylgluconolactone **14** at −20 °C affords the coupling product **57**. This coupling product **57** is converted into tofogliflozin (**7**) in 71% yield by acidic treatment with MsOH. The reaction temperature is critical for the chemical yield: reactions at −10 °C and 0 °C give the coupling product **57** in yields of 63% and 41%, respectively. When excess Grignard reagent is used, yields of the coupling product decrease: this phenomenon is also observed in the synthesis of empagliflozin (**5**).[15]



Scheme 7. Synthesis of tofogliflozin (**7**) *via* gluconolactone with benzylaryl bromide

A synthetic route featuring a one-pot reaction has also been reported. The regioselective halogen-lithium exchange of homo-dihalogenated benzene derivatives has proven to be an efficient tool for the synthesis of tofogliflozin (**7**).[23] Three-component coupling for construction of a carbon backbone of **7** in a one-pot process by the sequential bromine-lithium exchange reactions of alkoxymethyl-2,4-dibromobenzene is envisioned as illustrated in Figure 5.

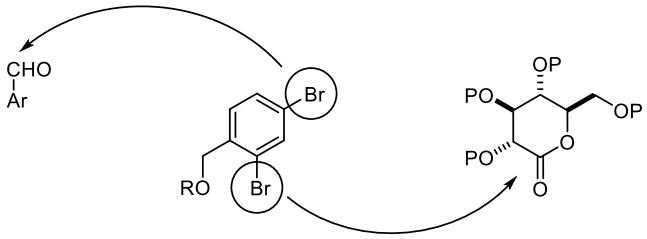
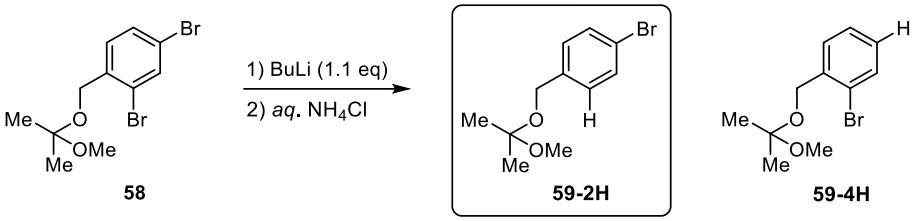


Figure 5. Regioselective/sequential Br-Li exchange/three-component coupling



Scheme 8. Regioselective Br-Li exchange of dibromide

The bromine-lithium exchange reaction of 2,4-dibromo-1-(1-methoxy-1-methylethoxymethyl)benzene (**58**) was expected to occur preferentially at the 2-position because the oxygen atoms of the methoxymethoxy group were expected to coordinate to a lithium atom by the proximity effect.[27] In fact, as illustrated in Scheme 8, it was found that the reaction of **58** with *n*-BuLi followed by quenching with aqueous NH_4Cl afforded a mixture of *para*-bromobenzene **59-2H** and *ortho*-bromobenzene **59-4H** in various ratios depending on the reaction conditions. Reaction in THF at −78 °C gives **59-2H** and **59-4H** in the ratio of 3 to 1. By use of a mixture of toluene and *tert*-butyl methyl ether as solvents,[28] the regioselectivity was improved (**59-2H**/**59-4H** = 9:1). The ratio of **59-2H** to **59-4H** reached 40:1 by slow addition of *n*-BuLi at 0 °C (over 30 min). This interesting phenomenon suggested that dibromide **58** would act as a mediator to increase the overall regioselectivity.[29] A mechanistic rationale for this high regioselectivity is depicted in Figure 6.

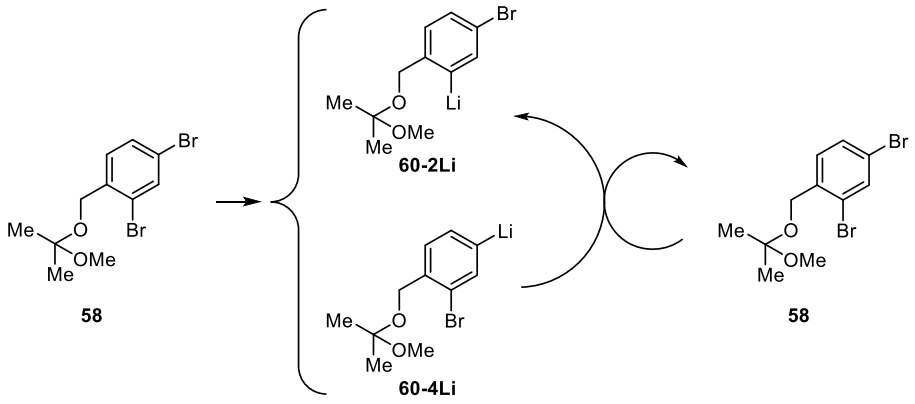
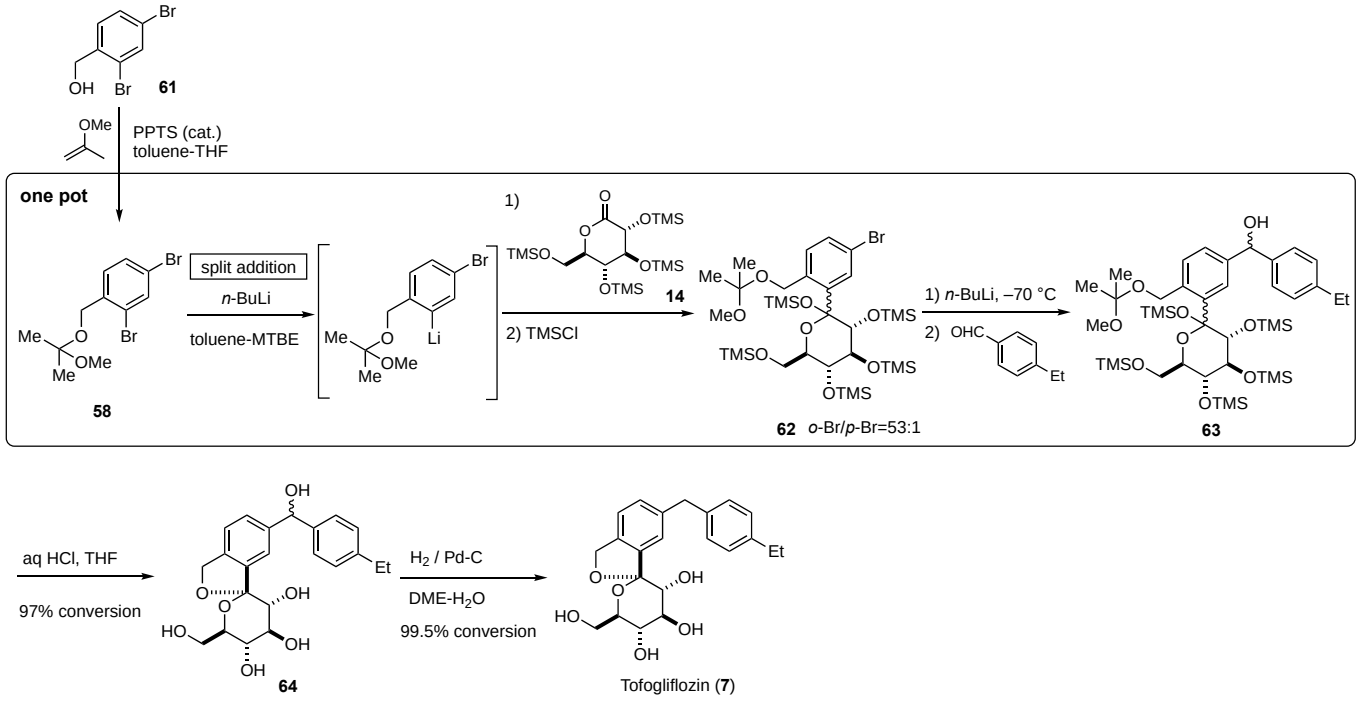


Figure 6. Mechanism of regioselective Br-Li exchange

The slow addition of *n*-BuLi would make a mixture composed of lithiated products and the remaining starting material **58**. The resulting solution would cause a bromine-lithium exchange reaction between *para*-lithiated product **60-4Li** and the remaining starting material **58**. Thus, this process could enrich the desired *ortho*-lithiated product **60-2Li**, because *para*-lithiated product **60-4Li** is converted back to **58**, which could change into *ortho*-lithiated product **60-2Li**.

In order to verify the speculation above, a reaction with excess substrate **58** to *n*-BuLi is carried out. It is found that the reaction in the presence of an additional 0.3 equivalent of **58** to *n*-BuLi used at 0 °C afforded the monobromide **59-2H** derived from *ortho*-lithiated product **60-2Li** with dramatically high selectivity (**59-2H** / **59-4H** = 220:1).

In the one-pot synthetic route, for a more cost-effective synthesis that avoids excessive use of **58**, split addition of *n*-BuLi is carried out to create an environment in which **58** is present during the bromine-lithium exchange. As shown in Scheme 9, a solution of dibromide **58** is prepared from benzyl alcohol **61**; to this solution, 0.8 equivalent of *n*-BuLi at −10 °C to 0 °C is added initially, followed by an additional 0.3 equivalent of *n*-BuLi for completion of bromine-lithium exchange. The mixture is added to trimethylsilylgluconolactone **14** and then treated with TMSCl to afford **62**. The *ortho*-regioselectivity in this 1,2-addition is very high (53:1). A second lithiation with *n*-BuLi followed by addition of 4-ethylbenzaldehyde affords the regioselective double 1,2-addition product **63**. These five operations (from dibromobenzyl ether **58** to the double 1,2-addition product **63**) are accomplished in a one-pot process.



Scheme 9. Synthesis of tofogliflozin (**7**) *via* regioselective Br-Li exchange of dibromide

Further construction of the spiro-ring together with the removal of both the methoxymethylethyl group and the trimethylsilyl group are attained by a telescoping process: treatment of the crude 1,2-addition product **63** with aqueous HCl affords benzhydrol **64** (97% conversion). Hydrogenolysis of **64** by use of 5% Pd on activated charcoal/H_2 affords tofogliflozin (**7**) in 99.5% conversion.

(7) Ertugliflozin

Ertugliflozin (**8**) has a bridged bicyclic ketal moiety. 1,2-Addition of aryl metals to lactones **65**–**67 (**Figure 7), which already have oxygen functionalized substituents set at the C5-position, has been attempted[30]

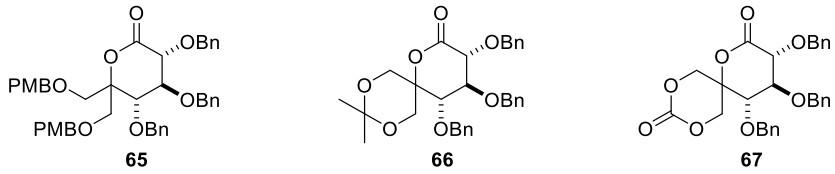
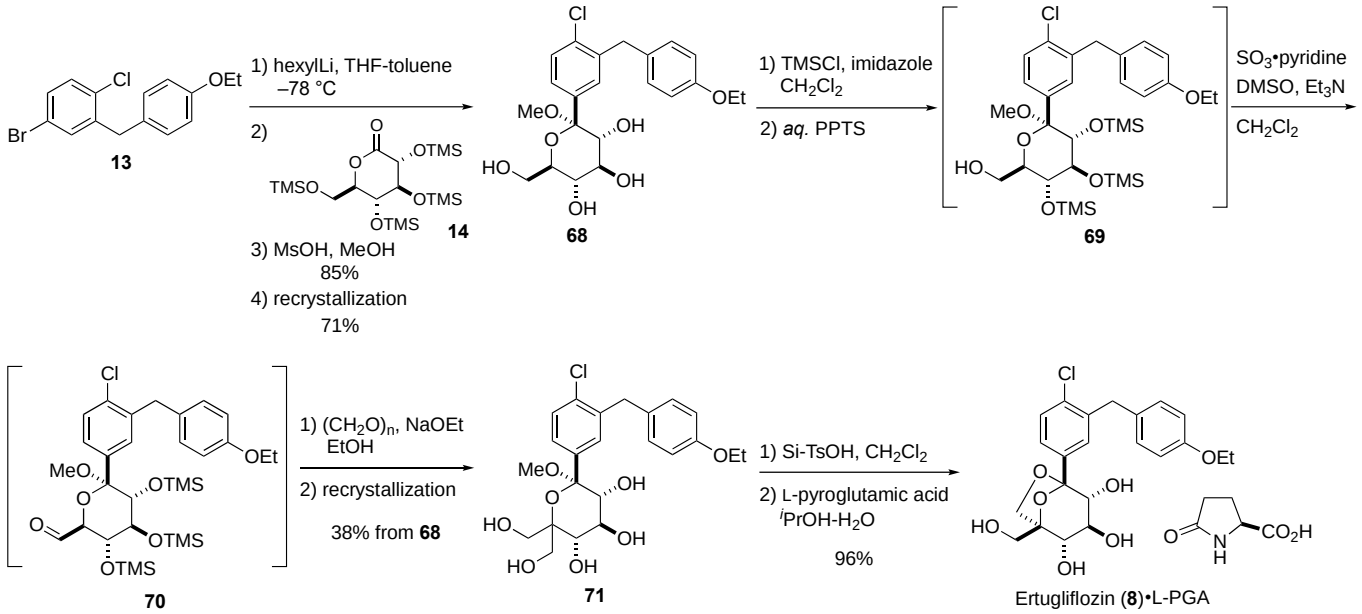


Figure 7. Lactones having substituents at the C5-position

However, the reaction of lactone **65**, which has *p*-methoxybenzyloxy groups, with aryl metals failed to provide the desired adduct: Formation of α,β-unsaturated lactone was observed, presumably due to steric hindrance between the substituents at the C5-position and bulky aryl anions. The reaction of lactone **66**, which has a dimethylacetonide moiety of which at least one carbonyl face would be accessible to nucleophiles, also gave only an elimination product. The reaction of lactone **67**, which has a cyclic carbonate moiety, with an aryllithium afforded the desired 1,2-adduct with no elimination side-product; however, the method for preparing lactone **67** was not simple.

Successful synthesis of ertugliflozin (**8**) by an approach involving lactones was attained by use of trimethylsilylgluconolactone **14**. The synthetic route for **8** with **14** is illustrated in Scheme 10.[30] Bromine-lithium exchange of aryl bromide **13**[11] with *n*-hexyllithium, and subsequent 1,2-addition to trimethylsilylgluconolactone **14** and treatment with MsOH in MeOH affords *O*-methyl lactol **68** in 71% isolated yield after recrystallization. Persilylation of **68** with TMSCl/imidazole, and then selective monodesylilation at the C6-position by use of aqueous pyridinium *p*-toluenesulfonate successfully affords **69**. After the hydroxymethyl group at the C6-position is oxidized by SO_3-pyridine complex with triethylamine and DMSO (Parikh–Doering method),[31] the obtained aldehyde **70** is converted into pentaol **71** by an aldol–crossed-Cannizzaro reaction with formaldehyde in 38% yield from **68** after recrystallization (telescope process). Formation of a bicyclic ketal moiety is accomplished by treatment with SilicaBond tosic acid (Si-TsOH) in CH_2Cl_2. Subsequently, treatment with L-pyroglutamic acid (L-PGA) affords ertugliflozin (**8**)·L-PGA cocrystal in 96% yield.

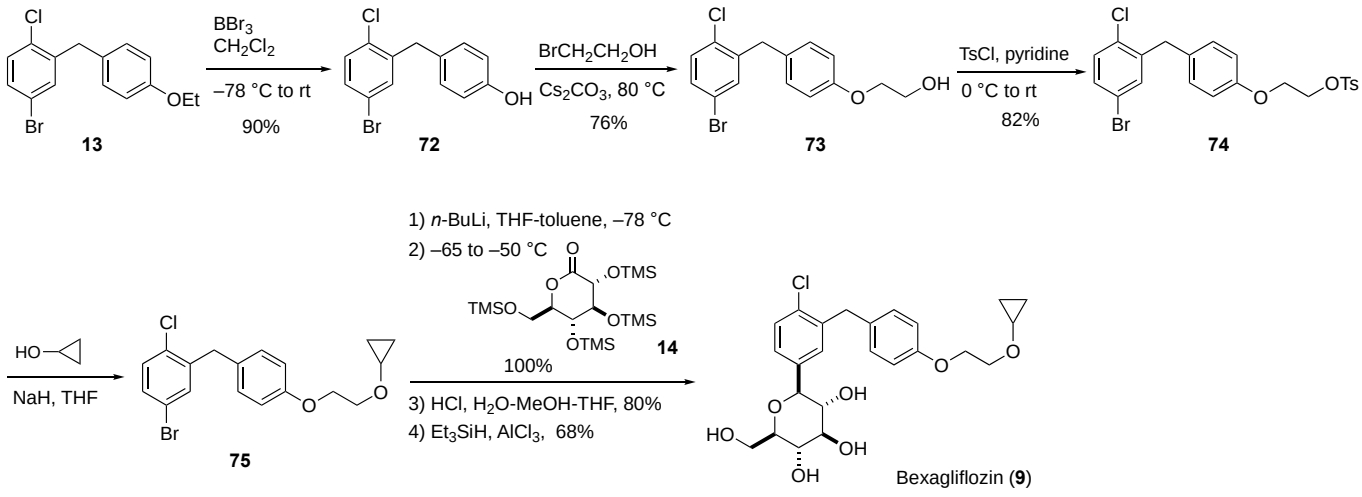


Scheme 10. Synthesis of ertugliflozin (**8**) *via* gluconolactone

(8) Bexagliflozin

Synthesis of bexagliflozin (**9**) using this strategy is illustrated in Scheme 11.[32] Ethoxybenzene derivative **13**, which is prepared according to a method described in the literature,[11] is subjected to de-ethylation by use of boron tribromide to afford phenol **72**. Reaction with bromoethanol gives ether-alcohol **73**, and the hydroxy group is converted into the corresponding tosylate **74** with tosyl chloride. Substitution of the tosylate with cyclopropyl alcohol with sodium hydride as a base affords aryl bromide **75**.

Bromine-lithium exchange of **75** followed by 1,2-addition to trimethylsilylgluconolactone **14**, etherification with MeOH, and reduction by use of Et_3SiH with $AlCl_3$ affords bexagliflozin (**9**).



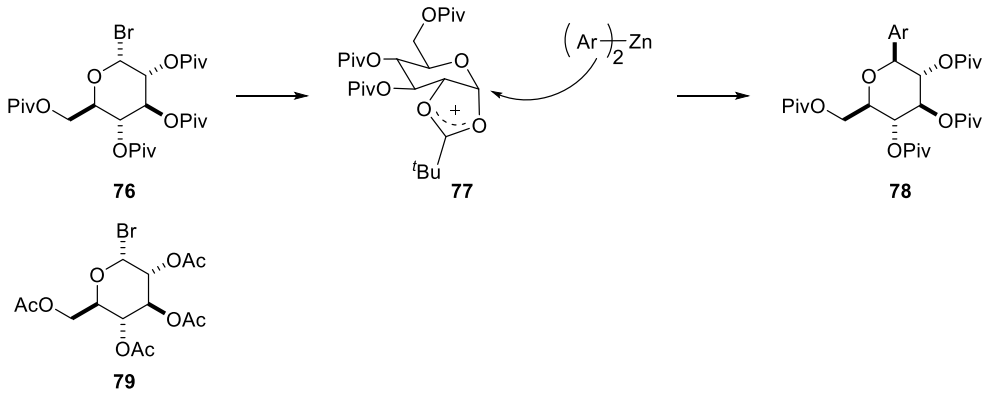
Scheme 11. Synthesis of bexagliflozin (**9**) *via* gluconolactone

3.1.2. Other sugar electrophiles with aryl metal compounds

3.1.2.1. Glycosyl bromide

Some of the *C*-aryl glucosides mentioned above have also been synthesized effectively by use of sugar electrophiles other than lactones. Glycosyl bromide protected as pivaloyl ester **76**, which is a stable crystalline substrate, has proven to be a useful sugar electrophile with which to synthesize dapagliflozin (**2**), canagliflozin (**3**), and ipragliflozin (**4**).[33]

As illustrated in Scheme 12,[34] the reaction of **76** with organozinc compounds prepared from aromatic halides proceeds with β-selectivity to form *C*-aryl glucoside **78**. The selectivity is explained by attack of a nucleophile to a bicyclic intermediate **77** (anchimeric assistance). *O*-Peracetyl glycosyl bromide **79** is also used in the synthesis of canagliflozin (**3**).

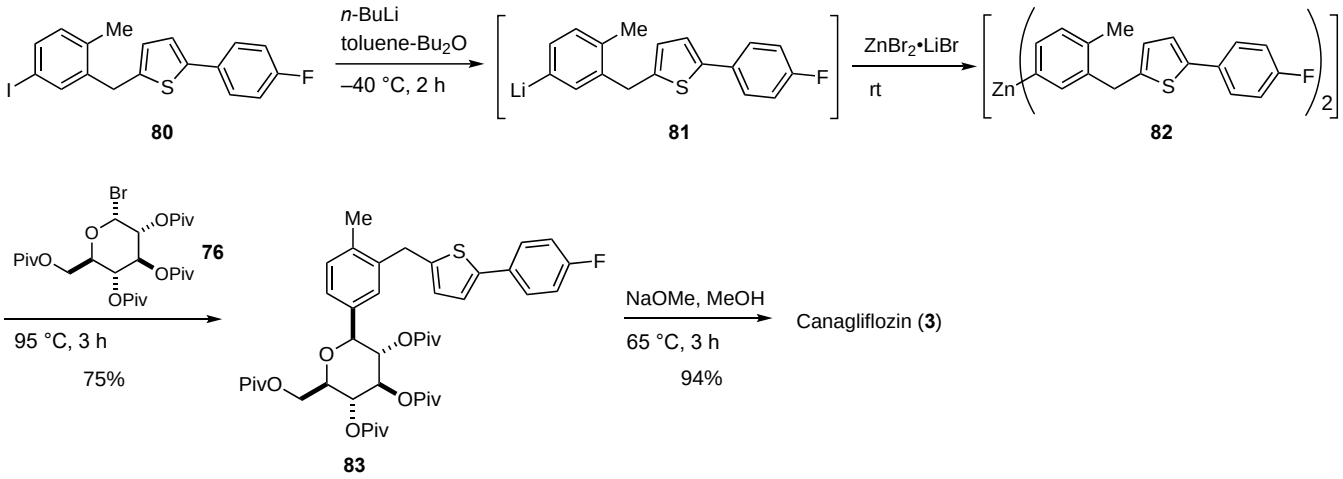


Scheme 12. Mechanism for β-selectivity *via* anomeric oxonium ion

(1) Canagliflozin

(1-1) Synthesis by use of glycosyl bromide pivaloyl ester

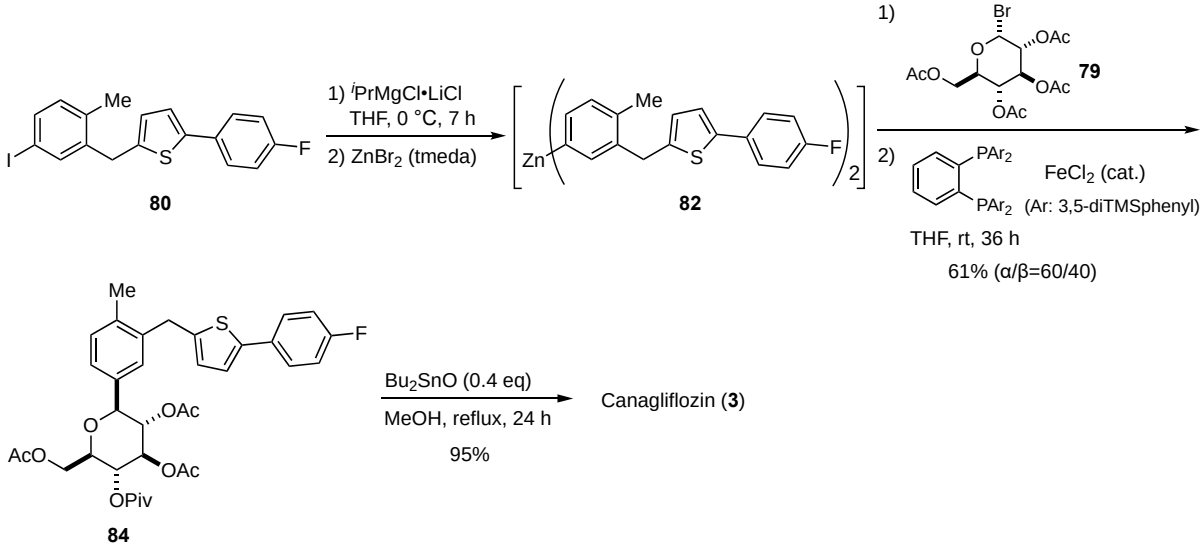
The synthesis of canagliflozin (**3**) by this method is illustrated in Scheme 13.[34] Organozinc compound **82** is prepared from aryl iodide **80** by a sequential lithiation–transmetalation process as follows. Aryl iodide **80** is lithiated by *n*-BuLi in toluene-dibutyl ether at −40 °C to give aryllithium **81**, and then the resulting mixture is treated with zinc bromide/lithium bromide ($ZnBr_2$·LiBr) complex to provide organozinc compound **82**. The reaction of **82** with bromo-sugar **76** at 95 °C affords *C*-aryl glucoside **83** in 75% yield, hydrolysis of which affords canagliflozin (**3**) in 94% yield.



Scheme 13. Synthesis of canagliflozin (**3**) *via* bromo-sugar

(1-2) Synthesis by use of glycosyl bromide acetate

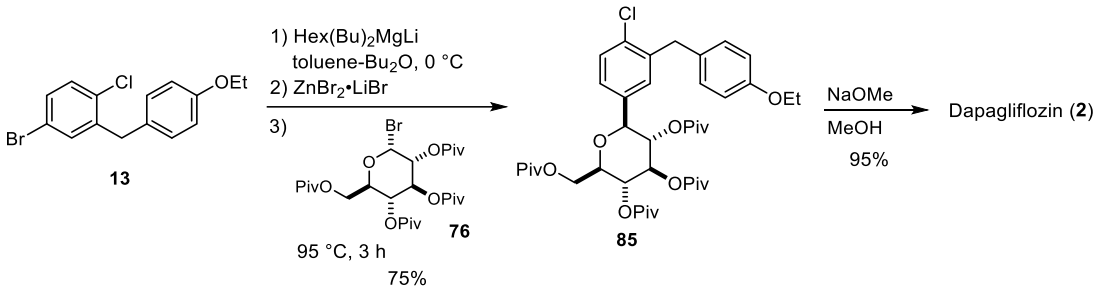
The synthesis of canagliflozin (**3**) has been also accomplished by the reaction of glycosyl bromide **79**. Iron-catalyzed cross coupling of **79** with organozinc compound **82**, which is prepared from aryl iodide **80** with ^{i}PrMgCl·LiCl complex and dibromo(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)zinc [$ZnBr_2$(tmeda)], is used for construction of the carbon-carbon bond between the aryl moiety and the sugar electrophile (Scheme 14).[35] The reaction of **79** with **82** in the presence of catalytic amounts of iron(II) chloride/bidentate phosphine ligand complex in THF at room temperature for 36 h affords the coupling product **84** in 61% yield. The stereoselectivity (α/β) is 60:40. The β-anomer is separated by column chromatography, and subsequent deprotection by use of tin oxide catalyst affords canagliflozin (**3**) in 95% yield.[36]



Scheme 14. Synthesis of canagliflozin (**3**) *via* bromo-sugar with iron catalyst

(2) Dapagliflozin

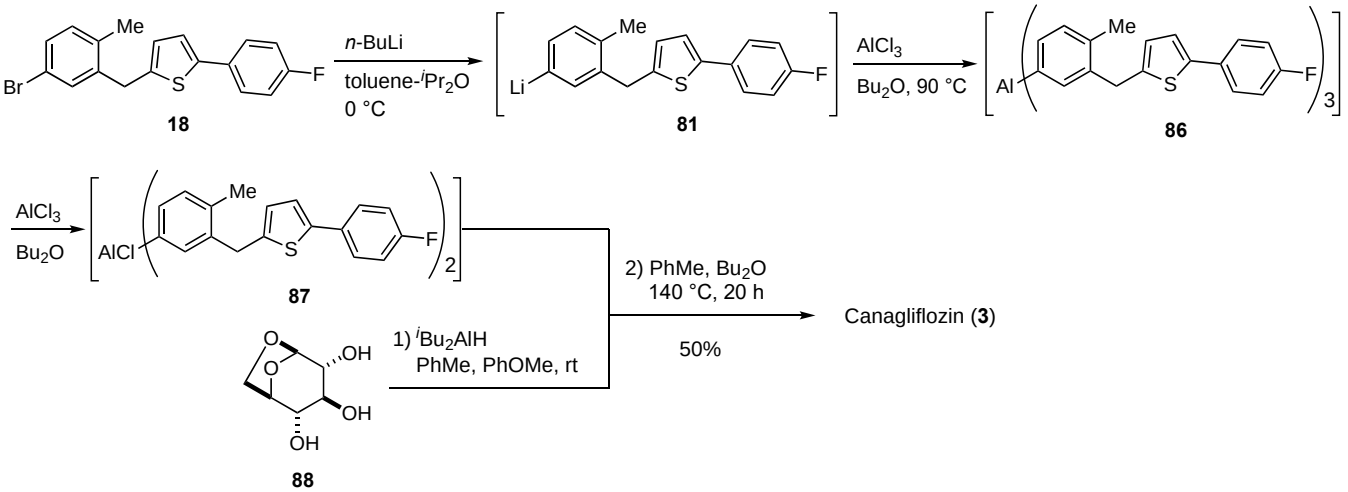
Dapagliflozin (**2**) has been synthesized in a manner similar to the synthesis of canagliflozin (**3**) by use of bromo-sugar **76** (Scheme 15).[34] The bromine-magnesium exchange reaction of aryl bromide **13** with lithium dibutyl(hexyl)magnesate ($Hex(Bu)_2MgLi$) followed by magnesium-zinc exchange with $ZnBr_2$·LiBr complex affords the desired organozinc compound. Subsequently, coupling with **76** at 95 °C is carried out to give the *C*-aryl glucoside **85** in 75% isolated yield. Hydrolysis of **85** with sodium methoxide in MeOH at room temperature affords dapagliflozin (**2**) in 95% yield.



Scheme 15. Synthesis of dapagliflozin (**2**) *via* bromo-sugar

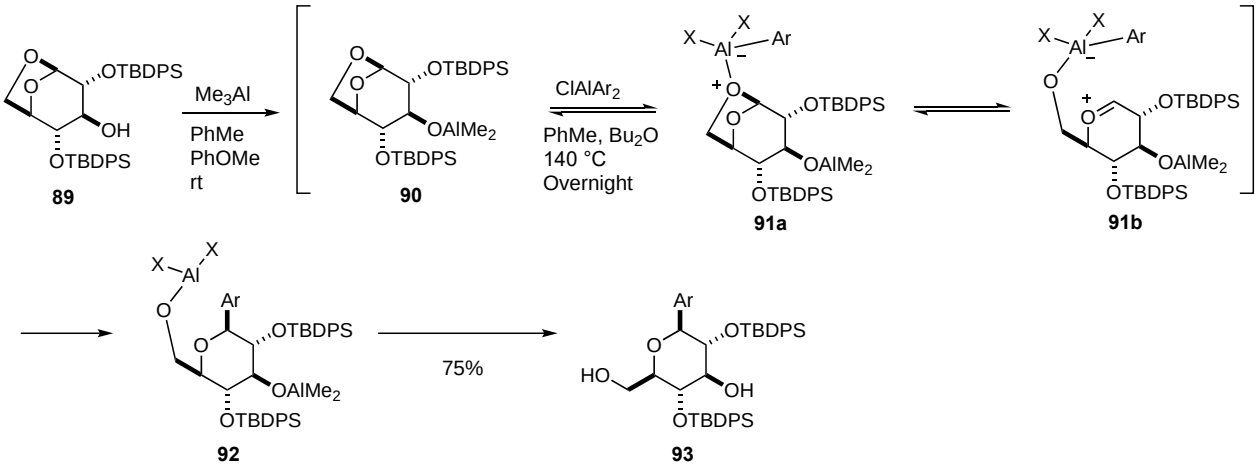
3.1.2.2. Anhydro-sugars

Canagliflozin (**3**) has been synthesized by β-selective arylation of commercially available unprotected 1,6-anhydroglucose **88** with organoaluminum reagent **87**, which is prepared from the corresponding aryl halide **18** by bromine-lithium exchange followed by trans-metalation (Scheme 16).[37]



Scheme 16. Synthesis of canagliflozin (**3**) *via* anhydroglucose

Before arylation, 1,6-anhydroglucose **88** is pretreated with 3 equivalents of diisobutylaluminum hydride in anisole as a solvent having superior solubilizing ability. Subsequently, the resulting mixture together with 2 equivalents of arylaluminum chloride **87** is heated in toluene/Bu_2O at 140 °C for 20 h to give a mixture of canagliflozin (**3**) and unreacted **88** (61% and 33% respectively; determined by high performance liquid chromatography (HPLC) using an internal standard. Purification by column chromatography affords canagliflozin (**3**) in 50% isolated yield.



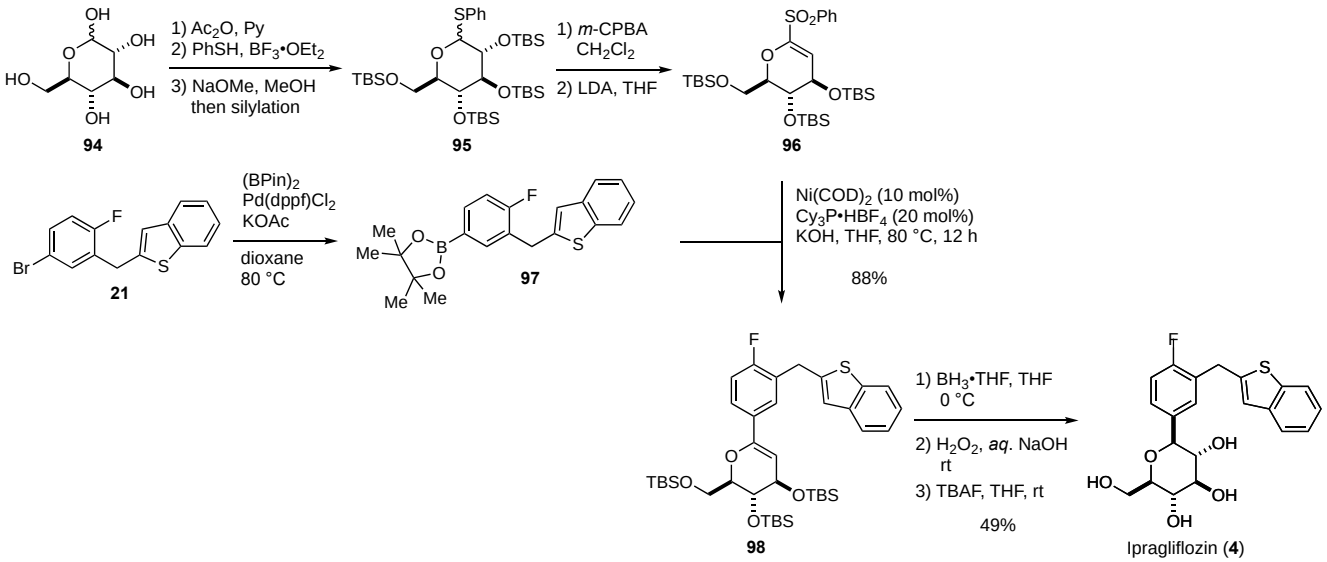
Scheme 17. Mechanism of synthesis of canagliflozin (**3**) *via* anhydroglucose

To understand the stereoselectivity of this reaction, arylation of 2,4-di-*O*-protected 1,6-anhydroglucose **89** was carried out. A reaction mechanism for the arylation of **89** was proposed as described in Scheme 17.[38] Aluminum complex **91a** could be formed by coordination of the C6-O ether linkage of **90**, which would be generated by treatment of **89** with trimethylaluminum, to the organoaluminum reagent ($ClAlAr_2$) as an arylating reagent. Ring opening of **91a** would produce oxocarbenium ion **91b**. Delivery of the aryl group to the α-face of the oxocarbenium ion **91b** would be unfavorable owing to steric hindrance. Favorable β-face attack led to 2,4-di-*O*-protected canagliflozin (**93**) in 75% isolated yield. This compound was converted into canagliflozin (**3**) by desilylation using tetrabutylammonium fluoride in THF.

3.1.3. Sugar electrophile with aryl boronate ester

Ipragliflozin (**4**) has been synthesized by Ni-catalyzed Suzuki–Miyaura cross-coupling of easily synthesized α-oxo-vinylsulfone **96** with aryl boronate ester **97** (Scheme 18).[39] Vinylsulfone **96** is prepared by β-elimination of glycosyl sulfone,[40] which is synthesized from D-glucose (**94**) *via* 1-phenylthio-glycopyranoside (**95**) according to a method described in the literature.[41] Arylboronic acid pinacol ester **97** is prepared from aryl halide **21** by use of a combination of bis(pinacolato)diborane and 1,1′-bis(diphenylphosphino)ferrocene-palladium chloride with potassium acetate (71% after chromatography), according to a procedure described in the literature with slight modification.[42]

Cross-coupling between sulfone **96** and boronate **97** is attained by use of 10 mol% bis(1,5-cyclooctadiene)nickel(0) and 20 mol% tricyclohexylphosphonium tetrafluoroborate as catalysts to afford *C*-aryl glycal **98** in 88% yield after chromatographic purification. Hydroboration/oxidation of **98** followed by deprotection and then chromatographic purification affords ipragliflozin (**4**) in 49% yield over three steps.



Scheme 18. Synthesis of ipragliflozin (**4**) *via* α-oxo-vinylsulfone

3.2. AMIDES WITH ARYL ORGANOMETALLIC COMPOUNDS

(1) Ertugliflozin

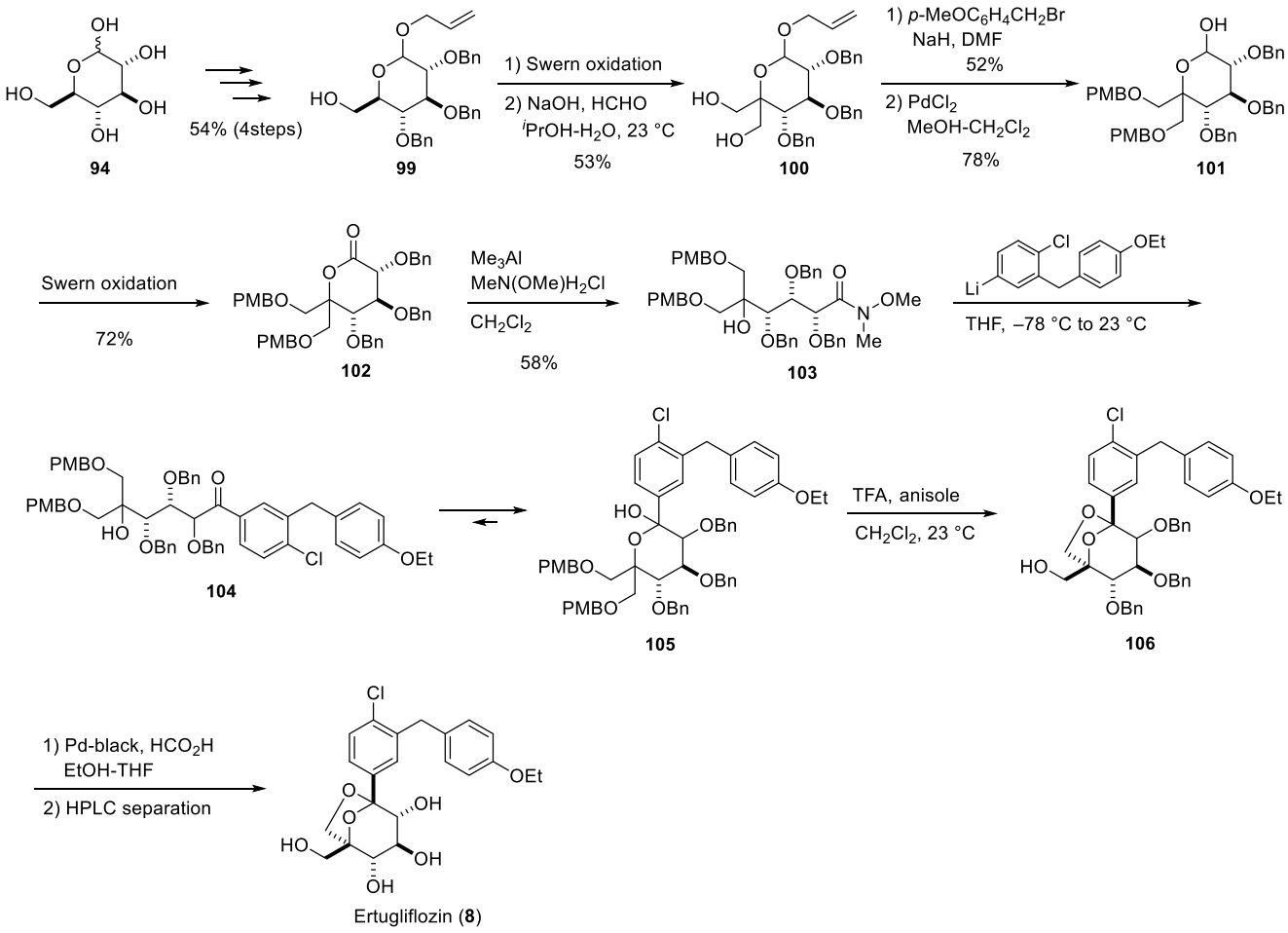
(1-1) Synthesis by use of Weinreb amide with aryllithium

Ertugliflozin (**8**), the structure of which contains a dioxa-bicyclo[3,2,1]octane ring, has been synthesized by way of arylation of a Weinreb amide with aryllithium generated by lithium-bromine exchange of aryl bromide (Scheme 19).[43]

Weinreb amide **103** is prepared starting from D-glucose (**94**). D-Glucose (**94**) is converted into an intermediate **99** according to a method described in the literature (54% for 4 steps).[44] Subsequently, oxidation under Swern conditions followed by a one-pot aldol–Cannizzaro sequence affords a tetrahydropyran having germinal hydroxymethyl groups **100**. After protection of these hydroxymethyl groups as *p*-methoxybenzyl (PMB) ethers, the allyl group is removed with $PdCl_2$ to afford lactol **101** which is then oxidized to lactone **102**. Finally, treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum provides the desired Weinreb amide **103**.

The reaction of amide **103** with aryllithium (see *Section 3.1.1.(7)*) in THF produces cyclic lactol **105** as a diasteromeric mixture *via* the initial condensation product **104**. The epimerization at C-4 is rationalized *via* the formation of an enol or an enol ether intermediate. Removal of *p*-methoxybenzyl groups by

trifluoroacetic acid (TFA) followed by stereoselective intramolecular cyclization gives bicyclic compound **106** as an epimeric mixture. Removal of benzyl groups by hydrogenolysis (over palladium black with formic acid) gives a mixture of epimers at C-4, HPLC separation of which affords the desired ertugliflozin (**8**).

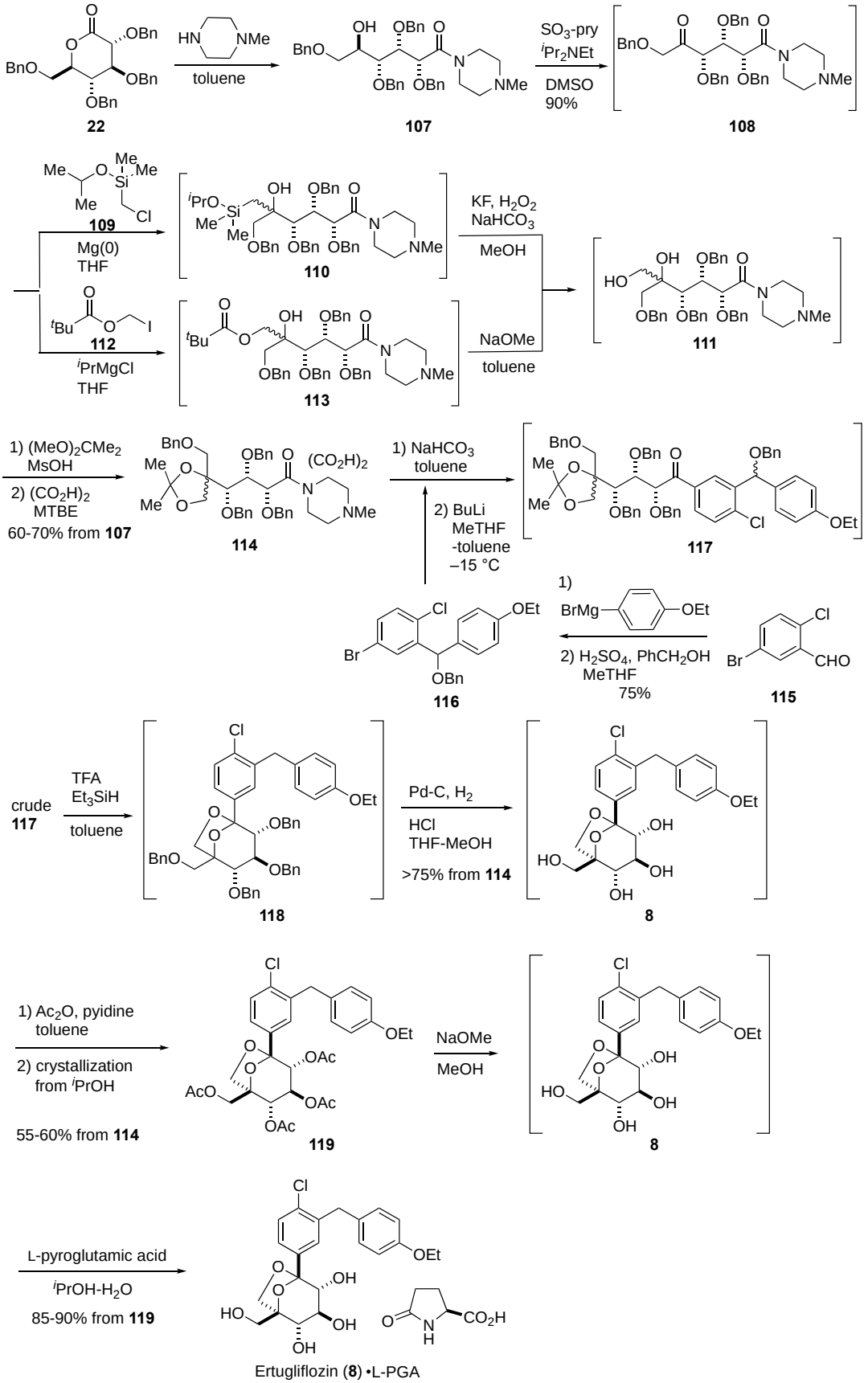


Scheme 19. Synthesis of ertugliflozin (**8**) *via* Weinreb amide

(1-2) Synthesis by use of methylpiperazine amide with aryllithium

The synthetic route of ertugliflozin (**8)** presented above is the first-generation synthesis, designed for preparation on a small scale and which requires HPLC separation for isolation of ertugliflozin **(8)**. An alternative practical synthesis has been developed for scale-up.

As illustrated in Scheme 20,[45] *O*-benzylgluconolactone **22** is converted to methylpiperazine amide **107** by treatment with methylpiperazine. This amide contains a basic nitrogen which enables salt formation. Oxidation of the secondary hydroxy group of **107** is carried out by the Parikh–Doering method (DMSO, pyridine-SO_3 complex)[31] to afford ketoamide **108**. Hydroxymethylation of **108** is attained by 1,2-addition of a Grignard reagent to the ketonic carbonyl group of **108**. Either of two kinds of Grignard reagents is used.



Scheme 20. Synthesis of ertugliflozin (**8**) *via* methylpiperazine amide

In the first method, the Grignard reagent is derived from chloromethylsiloxane **109**, and 1,2-addition of this Grignard reagent to ketoamide **108** at −20 °C gives adduct **110** as a diastereomeric mixture (3:2, both isomers lead to a single product at a later stage). Adduct **110** is subjected to Tamao–Fleming oxidation (potassium fluoride, hydrogen peroxide) to give diol **111**. The second method involves a Grignard reagent prepared from iodomethyl pivalate **112** by iodine-magnesium exchange with ^{i}PrMgCl. 1,2-Addition of this reagent to ketoamide **108** at −78 °C affords the desired adduct **113** as a diastereomeric mixture (95:5), and subsequent treatment with sodium methoxide affords diol **111**. These two nucleophilic hydroxymethylation methods perform in comparable yield (approx. 75% from ketoamide **108**). The hydroxy groups of **111** are converted to dimethylacetonide, and then salt **114** is formed by adding oxalic acid for effective purging of process-related impurities.

This crystalline **114** is converted to the free base, and then condensed with an aryl anion that is prepared by bromine-lithium exchange of bromobenzhydryl ether **116**. Ether **116** is provided by the reaction of 5-bromo-2-chlorobenzaldehyde **115** with 4-ethoxyphenylmagnesium bromide followed by treatment with benzyl alcohol in the presence of H_2SO_4. Only mono-addition to amide **114** takes place to afford **117**, and no detectable epimerization is observed. Subsequent treatment of the crude solution of **117** with Et_3SiH in the presence of TFA gives cyclized products as a mixture of two diastereomers of **118**. Hydrogenolysis of **118** under acidic conditions affords ertugliflozin (**8**) as the only detectable product (>75% overall yield for the three-step sequence).

For purification, crude ertugliflozin (**8**) is transformed to the corresponding tetraacetate **119** by treatment with acetic anhydride and pyridine, which is then crystallized from ^{i}PrOH to obtain pure tetraacetate **119** in 55%–60% yield from amide **114**. Removal of acetyl groups by sodium methoxide in MeOH gives a crude solution of **8**, treatment of which with L-pyroglutamic acid (L-PGA) affords cocrystal (**8**·L-PGA) in 85%–90% yield from tetraacetate **119**.

(2) Sotagliflozin

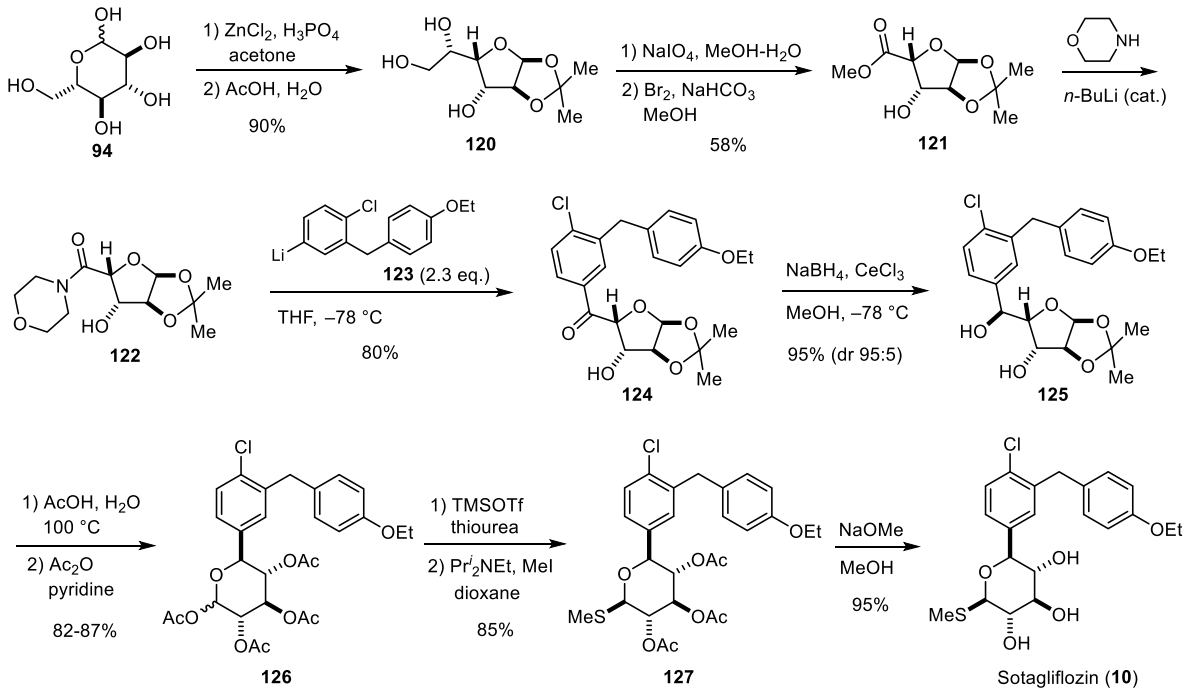
(2-1) Synthesis by use of morpholine amide with aryllithium

Sotagliflozin (**10**) is a dual inhibitor of SGLT2 and SGLT1. This compound has been synthesized (11 steps) *via* amide intermediate **122** starting from L-glucose (**94**) as illustrated in Scheme 21.[46]

L-Glucose (**94**) is converted to bis-acetonide, and then selective deprotection gives triol **120** in 90% yield. Cleavage of the vicinal diol by use of sodium periodate affords an aldehyde, which is oxidized with bromine in MeOH to afford methyl ester **121** in 58% yield. Amidation is carried out by use of morpholine with a catalytic amount of *n*-BuLi to give amide **122**.

Condensation of **122** with aryllithium **123** (see *Section 3.2.(2)-(2-2)*) affords ketone **124** in 80% yield. Ketone **124** is converted into tetraacetate **126** by the same method as the first synthetic route (see

Section 3.3.(2); synthesis *via* aldehyde intermediate). Thiolation of **126** with thiourea catalyzed by trimethylsilyl triflate followed by treatment with methyl iodide in the presence of Hünig base affords methyl sulfide-triacetate **127** in 85% yield. Alcoholysis with sodium methoxide furnishes sotagliflozin (**10**) in 95% yield.

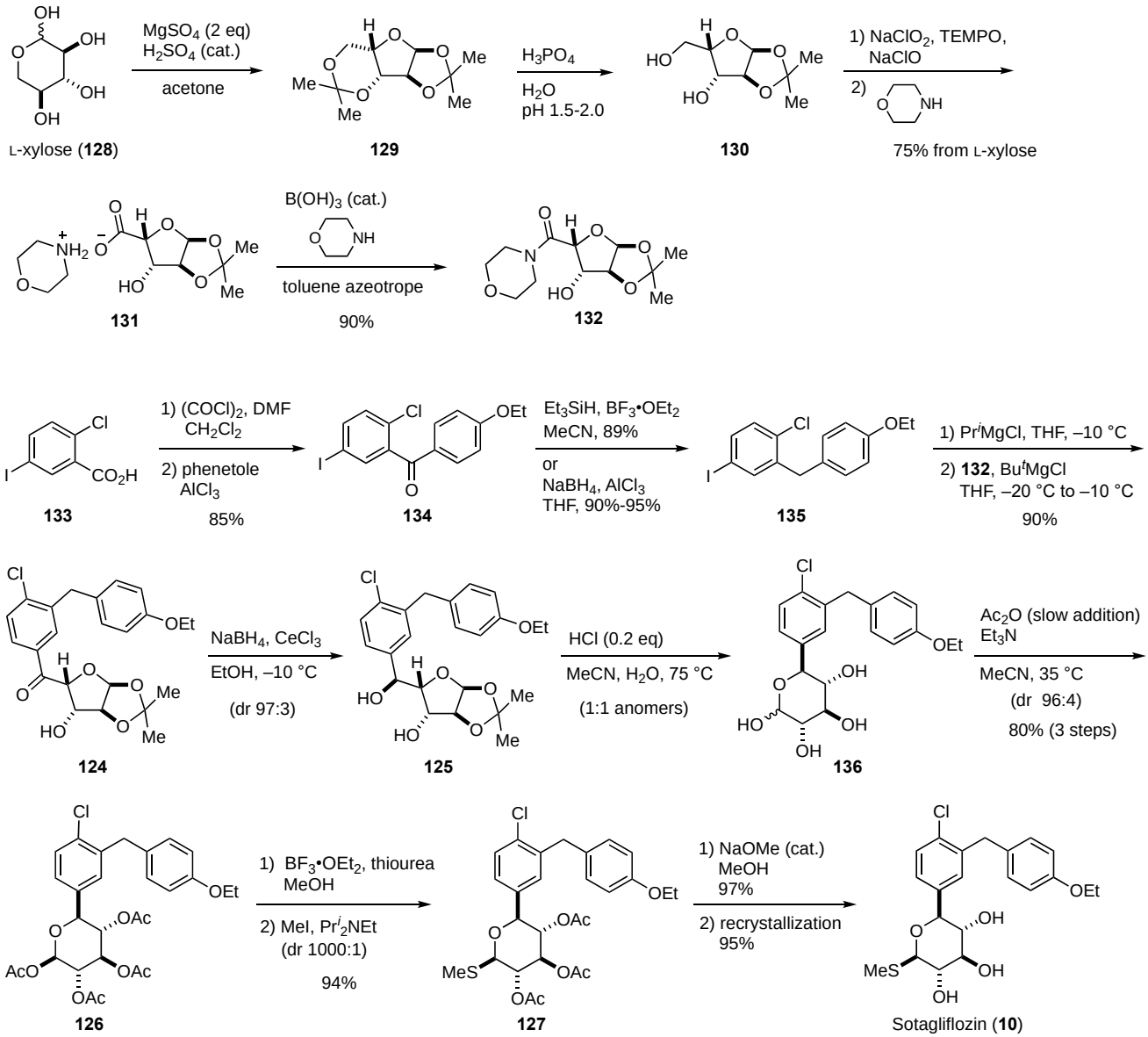


Scheme 21. Synthesis of sotagliflozin (**10**) *via* amide starting from L-glucose

(2-2) Synthesis by use of morpholine amide with arylmagnesium chloride

The synthesis of sotagliflozin (**10**) described above is more concise (overall yield: approx. 30% overall) than that by way of 1,2-addition to an aldehyde (the first synthesis of sotagliflozin, approx. 12% overall yield: see *Section 3.3.(2)*). However, there are some drawbacks such as the use of expensive starting materials/reagents (L-glucose, sodium periodate) and hazardous reagents (Br_2) as well as the fact that the hydroxy group of amide **122** consumes a valuable aryllithium. Therefore, a third synthesis has been developed, as shown in Scheme 22.[46] This synthetic route focuses on the use of crystalline intermediates. L-Xylose (**128**) is converted to bis-acetonide **129** by use of environmentally benign $MgSO_4$ together with a catalytic amount of H_2SO_4. The treatment of **129** with aqueous H_3PO_4 leads to the selective deprotection of the six-membered ring to afford mono-acetonide **130** under controlled pH, reaction temperature, and time. For selective oxidation of the primary alcohol, the use of a combination of trichloroisocyanuric acid and catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) gives rise to a clean reaction (see the first synthesis of sotagliflozin; *Section 3.3.(2)*); however, removal of the cyanuric acid is difficult. On the other hand, oxidation by a combination of sodium chlorite, sodium hypochlorite, and catalytic TEMPO proceeds

effectively to afford the desired carboxylic acid.[47] Because the acetonide moiety is sensitive to acidic conditions, morpholine is added to the crude carboxylic acid and the morpholine salt of carboxylic acid **131** is then isolated as a crystal in 75% yield from L-xylose. Amidation is carried out by use of 20 mol% boric acid in toluene under azeotropic conditions to afford amide **132** as a crystal in 90% yield; this procedure is preferable from the viewpoint of cost and availability on scale, although 3,5-bis(trifluoromethyl)phenylboronic acid is known to be a more efficient catalyst.[48]

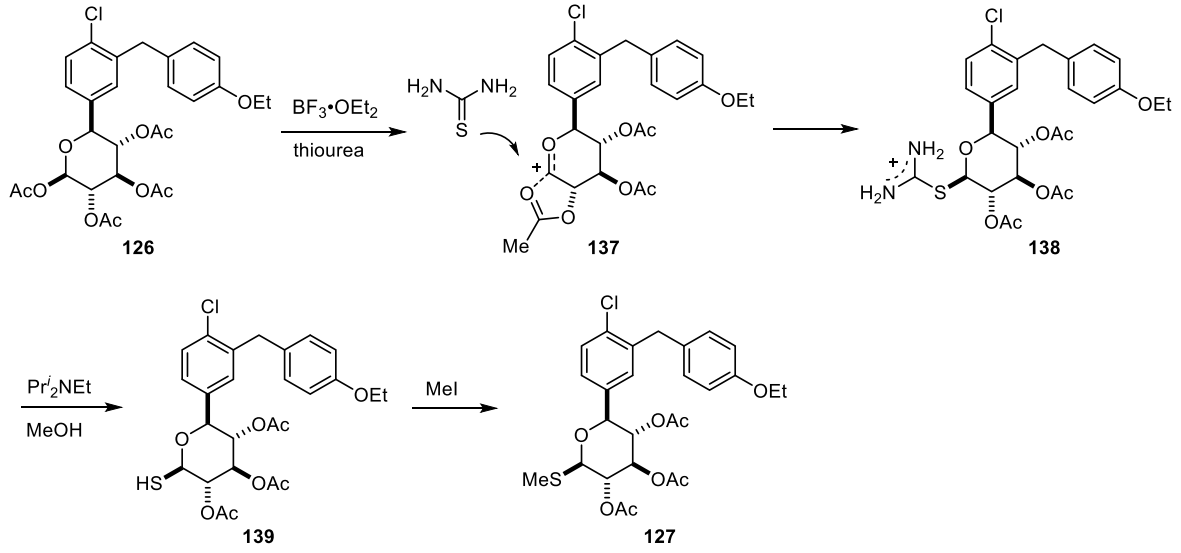


Scheme 22. Synthesis of sotagliflozin (**10**) *via* amide starting from L-xylose

Iodobiarylmethane **135** as the coupling partner for amide **132** is prepared from chloroiodebenzoic acid **133** according to the chemistry of its bromide analogue.[11] Friedel–Crafts acylation of **133** with phenetole in CH_2Cl_2 gives biarylketone **134** in 85% isolated yield; a low moisture level in the reaction mixture (100 ppm in CH_2Cl_2) is critical to obtain high regioselectivity (approx. 100:1). Reduction of ketone **134** is attained

by treatment with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to give iodobiarylmethane **135** in 89% yield. Alternatively, for cost reduction, reduction by a combination of sodium borohydride ($NaBH_4$) and $AlCl_3$ has also been developed, which affords the desired iodide **135** as a crystal in up to 95% yield.

Iodide **135** is converted into arylmagnesium chloride by treatment with ^{i}PrMgCl at −10 °C, and then a condensation reaction with amide **132**, the hydroxy group of which had been deprotonated by *tert*-butylmagnesium chloride in advance, is carried out at −20 °C to −10 °C to afford ketone **124** as a crystal in 90% yield. EtOH is a more effective solvent than MeOH with respect to the stereoselectivity of reduction of the carbonyl group of **124** (dr 97:3 at −10 °C, for reactions in EtOH; see *Sections 3.2.(2)-(2-1)* and *3.3.(2)*). Treatment of alcohol **125** with a catalytic amount of aqueous HCl (0.2 equivalent) in aqueous MeCN leads to deprotection and ring expansion to give tetraol **136** as an anomeric mixture (1:1). Slow addition of acetic anhydride to the anomeric mixture in the presence of triethylamine in MeCN at 35 °C furnishes (9*R*)-tetraacetate **126** as a crystalline product (dr 96:4, 80% isolated yield from ketone **124**). Although thiolation catalyzed by expensive trimethylsilyl triflate has been reported previously (see, *Section 3.2(2)-(2-1)*), thiolation of **126** is achieved more cost-effectively by use of thiourea in the presence of $BF_3{\cdot}OEt_2$. As depicted in Scheme 23, thiolation would proceed stereoselectively *via* oxonium ion **137** stabilized by the neighboring acetate group to give urea-adduct **138**. Thus, the reaction of **138** with Hünig base and methyl iodide in MeOH affords methyl sulfide **127** as a crystal in 94% isolated yield (dr 1000:1). Deprotection is accomplished by a catalytic amount of sodium methoxide in MeOH to afford sotagliflozin (**10**) in 97% yield.



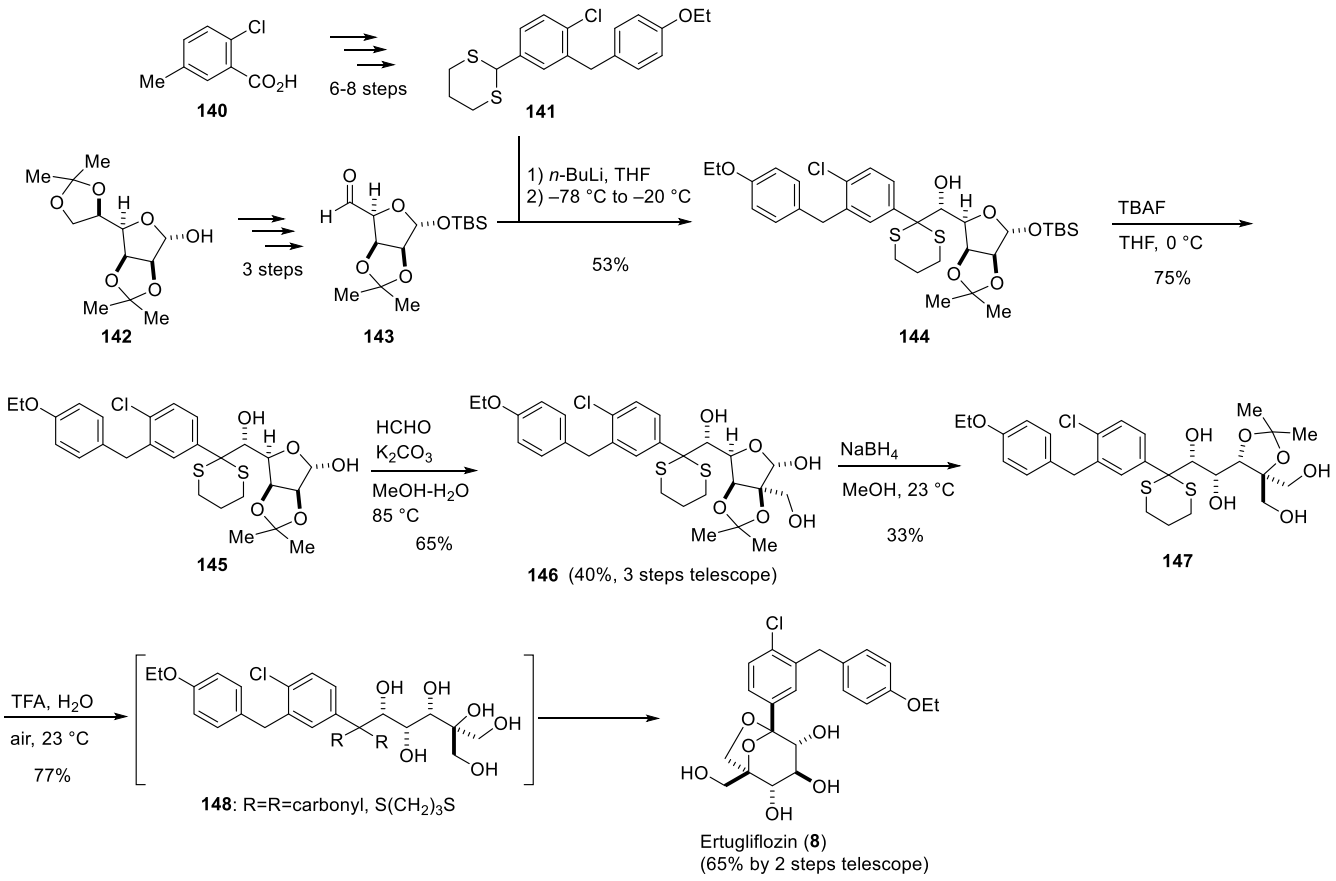
Scheme 23. Stereoselective thiolation

3.3. ALDEHYDE WITH ANIONIC SPECIES

(1) Ertugliflozin

(1-1) Synthesis by use of aldehyde with aryl dithiane anion

Ertugliflozin (**8**) has been synthesized *via* 1,2-adduct **144** obtained from the reaction of crystalline aryl dithiane **141** with aldehyde **143** (Scheme 24).[49] Aldehyde **143** is prepared from diacetone-α-D-mannofuranose **142** in three steps.[50]



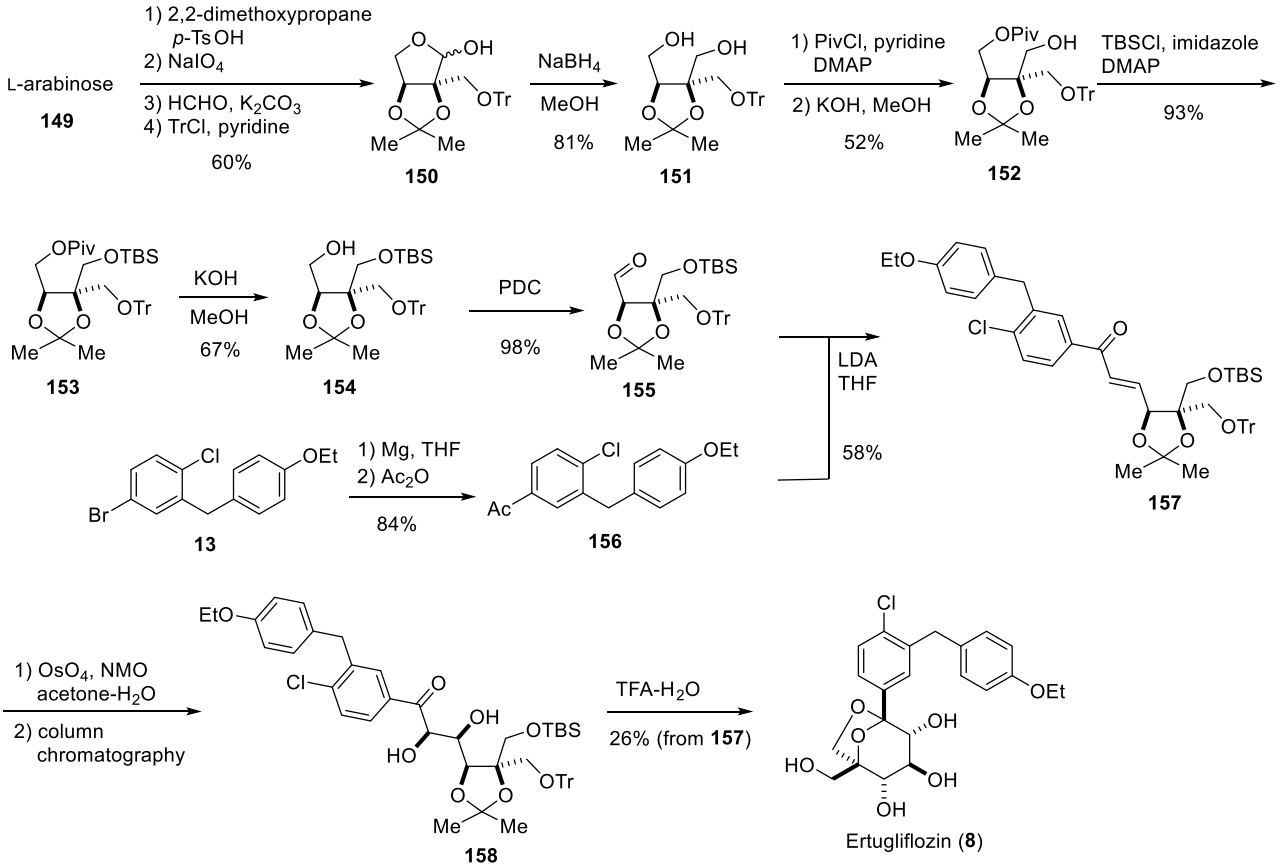
Scheme 24. Synthesis of ertugliflozin (**8**) *via* aldehyde by use of dithiane

As illustrated in Scheme 24, aryl dithiane **141** is prepared from 2-chloro-5-methylbenzoic acid **140** according to a method described in the literature (6–8 steps).[51] After lithiation of **141** with *n*-BuLi, diastereoselective addition to **143** is achieved at low temperature to give a single diastereomer **144** (*Si* face adduct). This selectivity is explained by the Cram chelate model[52] and the Felkin–Anh model.[53] After desilylation of **144** with tetrabutylammonium fluoride to produce **145**, construction of a tetra-substituted carbon center on the tetrahydrofuran ring is accomplished by treating **145** with formaldehyde in the presence of K_2CO_3 in MeOH-H_2O to give lactol **146** in 26% yield over three steps.[54] The yield is improved by a telescoping process: When the reactions in these three steps are carried out without isolating the

intermediates, lactol **146** is obtained in 40% yield (95% purity). Reduction of lactol **146** with $NaBH_4$ in MeOH gives linear tetraol **147** in 33% yield. Deprotection of the acetal-protected diol groups of **147** and subsequent thermodynamically controlled cyclization *via* intermediate **148** takes place cleanly by treatment with TFA/H_2O under air to afford ertugliflozin (**8**) as a single isomer in 77% yield. The modest isolated yield of **147** (33%) is due to the partial decomposition of the borate complex during workup with aqueous NH_4Cl. However, because deprotection/cyclization conditions are suitable for hydrolysis of the strong borate complex, a telescoping process improves the overall yield of **8** from **146** (65%).

(1-2) Synthesis by use of aldehyde with lithium enolate

Ertugliflozin **(8)** has been also synthesized by the reaction of an aldehyde with a lithium enolate generated from the deprotonation of an aryl methyl ketone.[55]



Scheme 25. Synthesis of ertugliflozin (**8**) *via* aldehyde by use of lithium enolate

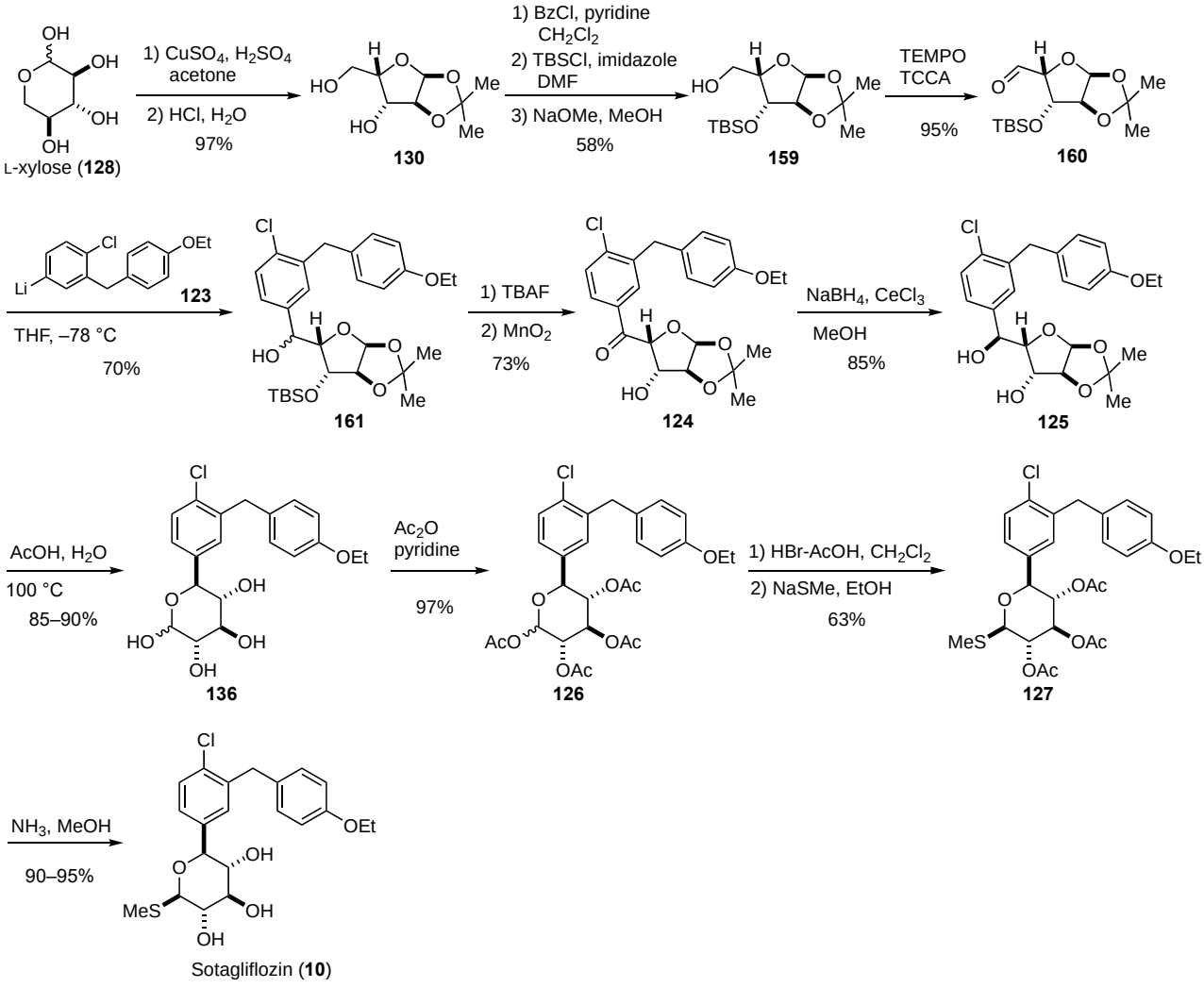
As illustrated in Scheme 25, aldehyde **155** is synthesized *via* reduction/oxidation of an L-erythrose derivative starting from L-arabinose (**149**). L-Arabinose is converted into protected hydroxymethyl L-erythrose **150**[56] in 60% yield, which is then treated with $NaBH_4$ to afford diol **151** in 81% yield. In order to selectively oxidize the hydroxylmethyl group at the C5-position, mono-protection of the diol group is

carried out through three steps: Firstly, diol **151** is treated with pivaloyl chloride for protection of the less hindered hydroxy group; next, the other hydroxy group is silylated by using *tert*-butyldimethylsilyl chloride (TBSCl); finally, hydrolysis with KOH affords the alcohol **154** in 67% yield. Aldehyde **155** is obtained by oxidation of **154** with pyridinium dichromate (PDC) in 98% yield.

Aldol condensation of aldehyde **155** and aromatic methyl ketone **156** (prepared from aryl bromide **13**, see *Section 3.1.1.(1)*) with lithium diisopropylamide (LDA) as a base affords enone **157** in 58% yield. Dihydroxylation by use of osmium tetraoxide/*N*-methylmorpholine *N*-oxide affords a diastereomeric mixture (the ratio of the desired isomer to the undesired isomer is 1:2). Separation by column chromatography gives the desired isomer **158** in 30% yield, which upon deprotection with trifluoroacetic acid affords ertugliflozin (**8**) in 85% yield.

(2) Sotagliflozin

The first synthesis of sotagliflozin (**10**) was attained starting from L-xylose as illustrated in Scheme 26.[46]



Scheme 26. Synthesis of sotagliflozin (**10**) *via* aldehyde

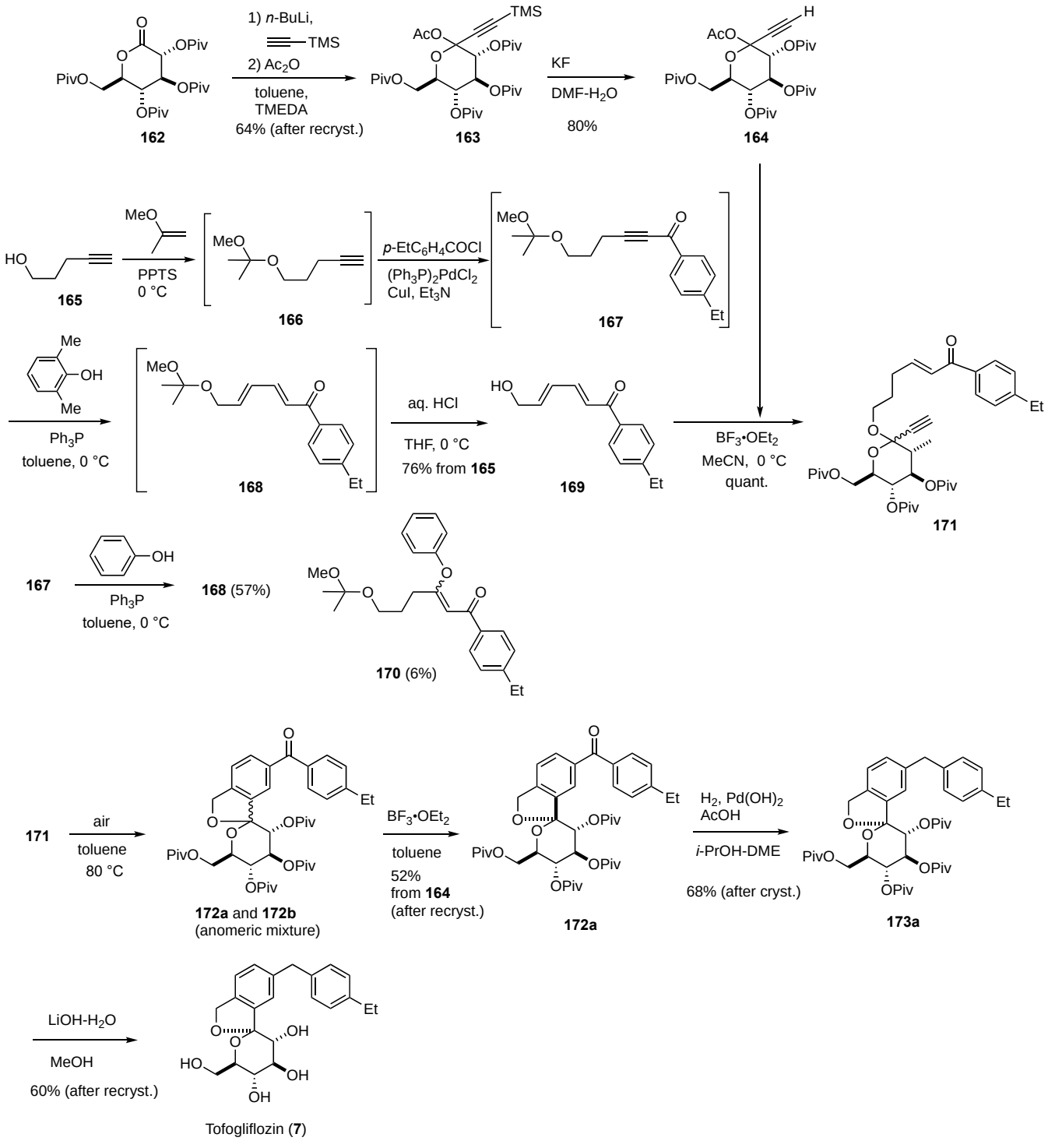
In this synthesis, the hydroxyl groups of L-xylose are first protected as bis-acetonide, and then converted to monoacetonide **130** by selective deprotection of the six-membered acetonide. Reprotection of the primary and secondary alcohols in **130** respectively with benzoyl chloride and TBSCl followed by the removal of the benzoyl group by sodium methoxide gives monoalcohol **159**. Oxidation by a combination of TEMPO and trichloroisocyanuric acid (TCCA) affords aldehyde **160**. 1,2-Addition of aryllithium **123** (see *Section 3.2(2)-(2-2)*) under cryogenic conditions affords benzyl alcohol **161** with low diastereoselectivity, and therefore oxidation of the hydroxy group of **161** is carried out by use of manganese dioxide after removal of the silyl group to give ketone **124**. Diastereoselective reduction of ketone **124** is attained by the Luche method to afford diol **125** (dr: 9/1).[57] Acidic treatment of **125** leads to the removal of the acetonide together with ring expansion to afford tetraol **136** as an anomeric mixture (1:1). These anomers are converted to tetraacetate **126**, which is then treated with hydrobromic acid/acetic acid and sodium thiomethoxide successively to afford triacetate **127**.[58] Deprotection by treatment with ammonia in MeOH furnishes sotagliflozin (**10**).

3.4. [4+2]CYCLOADDITION-OXIDATION

Tofogliflozin (**7**) has been synthesized in various ways, as mentioned in *Section 3.1.1.(6)*. In those cases, nucleophilic aryl metal compounds generated by halogen-metal exchange reactions are utilized to construct a *C*-glucosidic bond, and a dihydroisobenzofuran moiety is formed by cyclization under acidic conditions. Recently, the intramolecular [4+2]cycloaddition of dienone-yne under aerobic conditions has proven to be powerful tool for the synthesis of **7**.[59] This new methodology demonstrates that synthesis of **7** can be attained under noncryogenic conditions.

The synthesis of **7** *via* intramolecular [4+2]cycloaddition is depicted in Scheme 27. Protection of the hydroxy groups of gluconolactone is carried out by use of pivaloyl chloride to give pivaloyl ester **162**. 1,2-Addition of lithium trimethylsilylacetylide in the presence of tetramethylethylenediamine in toluene followed by acetylation of the resulting alkoxide by acetic anhydride affords acetate **163** in 64% yield (after recrystallization).[60] Treatment with KF gives alkyne **164** in 80% yield. Dienylmethyl alcohol **169** is prepared from commercially available 4-pentyn-1-ol (**165**). Protection of the hydroxy group of **165** followed by acylation of the terminal alkyne by use of a palladium-copper catalyst ($(Ph_3P)_2PdCl_2$, CuI) affords alkynone **167**. Treatment of **167** with triphenylphosphine and phenol affords dienone **168**[61] along with phenol adduct **170** as a side-product. When 2,6-dimethylphenol is used as a bulkier and less nucleophilic phenol, formation of the phenol adduct is suppressed, and dienone **168** is obtained as a single geometric isomer (*E*,*E*-configuration). Deprotection is carried out under acidic conditions to furnish the desired dienylmethyl alcohol **169** (76% yield over four steps: telescoping process).

Glucosylation of acetate **164** with dienylmethyl alcohol **169** is attained by treatment with $BF_3{\cdot}OEt_2$ in MeCN at 0 °C to afford dienone-yne compound **171** as a key intermediate.[62] When a toluene solution of **171** is warmed at 80 °C under aerobic conditions, [4+2]cycloaddition products **172a** and **172b** are generated as an anomeric mixture (*ca*. 60:40). Isomerization at the anomeric position is carried out by treatment with $BF_3{\cdot}OEt_2$ in toluene to give the desired spiroketal **172a** having suitable stereochemistry.



Scheme 27. Synthesis of tofogliflozin (**7**) *via* [4+2]cycloaddition

These reactions are achieved by a telescoping process (three steps: 52% yield after recrystallization). Reduction of the carbonyl group of **172a** to methylene is performed by hydrogenolysis by use of 20% $Pd(OH)_2$ on activated charcoal/H_2 to afford pivalate **173a** in 68% yield (after crystallization). Finally, hydrolysis with LiOH affords tofogliflozin (**7**) in 60% yield (after recrystallization).

4. CONCLUSION

This review has described the various methods of synthesis of the *C*-aryl glucosides SGLT2 inhibitors that had been approved up to 2019. All contain structural features in common that can be illustrated as the general molecule shown in Figure 2. The synthetic strategies employed for the construction of the carbon backbone of these inhibitors can be classified into four types (Figure 4): (1) the reaction of sugar electrophiles with aryl metal compounds, (2) the condensation of amides with organometallic compounds, (3) the 1,2-addition of lithium carbanions or enolates to aldehydes, and (4) the [4+2]cycloaddition of yne-dienone compounds.

The synthetic routes presented here have been collected from both drug discovery chemistry and industrial process chemistry. These synthetic methods should provide an abundance of useful knowledge, not only with respect to the preparation of *C*-aryl glucosides but also with respect to the formation of carbon-carbon and carbon-heteroatom bonds with high stereochemical control.

ACKNOWLEDGEMENTS

We thank Dr. Masao Tsukazaki for his suggestions during the preparation of the manuscript. Thanks are also due to Mr. Robert Freeman and Editing Services at Chugai Pharmaceutical Co., Ltd. for their assistance with English usage.

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