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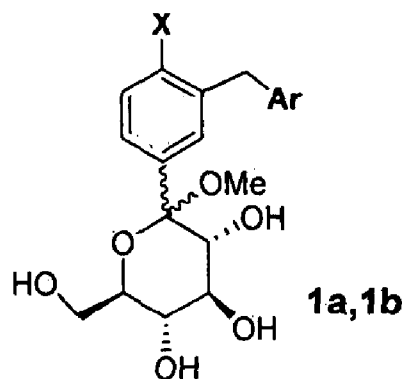
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(54) **Title:** PREPARATION OF INTERMEDIATES FOR THE SYNTHESIS OF CANAGLIFLOZIN AND DAPAGLIFLOZIN



(57) **Abstract:** The present invention relates to a preparation method of the intermediates of structures 1a (for the synthesis of canagliflozin) and 1b (for the synthesis of dapagliflozin), where in structure 1a X is methyl and Ar represents 2-(5-(4-fluorophenyl)-thienyl) and in structure 1b X is chlorine and Ar represents 4-ethoxyphenyl.

Preparation of intermediates for the synthesis of canagliflozin and dapagliflozin

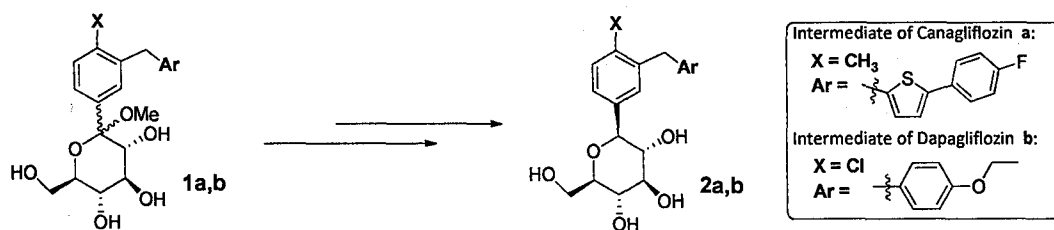
Field of the Invention

The invention relates to a new preparation method of the key intermediates of pharmaceutically active gliflozins, especially canagliflozin and dapagliflozin.

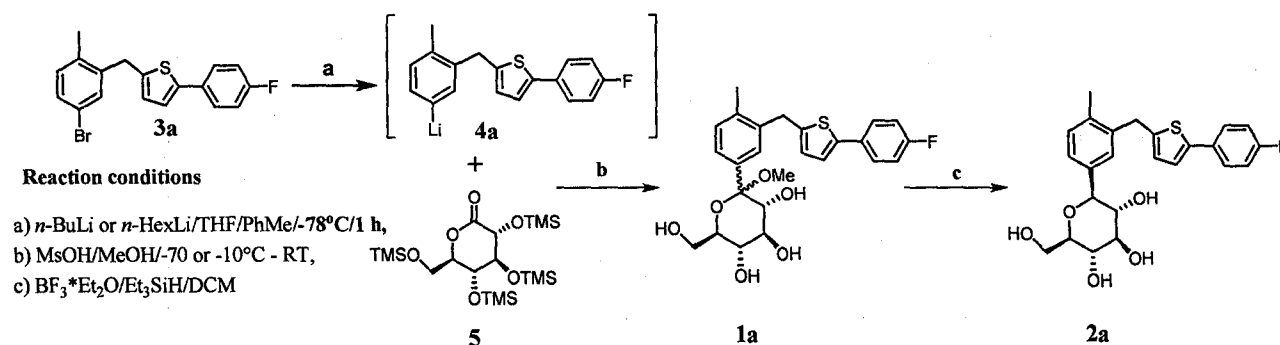
Background Art

In particular, the invention relates to a new preparation method of the key intermediates of structures **1a** and **1b** for the synthesis of canagliflozin of formula **2a** and dapagliflozin of formula **2b** – SGLT2 inhibitors that are used for the treatment of diabetes [Chao, E. C. *Drugs Fut.* **2011**, 36(5), 351; Cole, P., Vicente, M., Castaner, R. *Drugs Fut.* **2008**, 33(9), 745]. See Diagram 1 below.

Diagram 1:



For the preparation of C-glucosides a procedure is generally used wherein aryl lithium is first generated, which is followed by its addition to the protected gluconolactone at -78°C. The adduct is then deprotected and converted to the ketal of structure **1a**, which can be isolated by precipitation. The ketal is then reduced in the presence of a Lewis acid, e.g. by means of triethylsilane to the respective C-glucoside. This methodology, without the conversion to the ketal, was already generally described in the following publication (Kraus, G. A.; Molina, M. T. *J. Org. Chem.*, **1988**, 53, 752-153). With the use of this methodology the syntheses of canagliflozin (WO2005/012326A1) and dapagliflozin (WO2003/099836A1) have also been described. See Diagram 2 below.

Diagram 2: Synthesis of canagliflozin

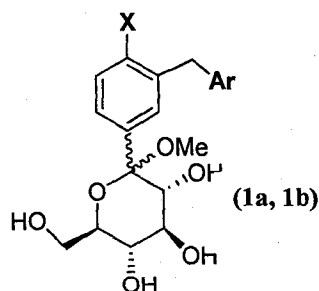
The main technical shortcoming of the mentioned syntheses is the necessity to carry out lithiation under cryogenic conditions (<-65°C) due to instability of aryl lithium reagents at higher temperatures when they decompose. Also, a cooled solution of the respective aryl lithium must be transferred to a cooled gluconolactone solution to achieve a maximum yield and purity of the product. These techniques require the use of costly cooling equipment as well as trained personnel.

The above mentioned disadvantages have been solved e.g. with the use of the so-called turbo-Grignard reagents (e.g. *i*-PrMgCl·LiCl), when the metalation of the iodaryl derivative prepared from the corresponding bromide is carried out at -25°C (WO2010/043682A2).

Another published approach uses a reaction of a diaryl zinc reagent, prepared by a reaction of the aryl lithium **4a** (**Diagram 2**) with zinc chloride, with bromoacetyl glucose, when a tetra-acyl derivative of canagliflozin is directly formed in the reaction (WO2011/047113).

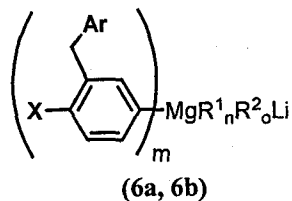
Disclosure of the Invention

The invention relates to a preparation method of the intermediates of structures **1a** (for the synthesis of canagliflozin) and **1b** (for the synthesis of dapagliflozin)

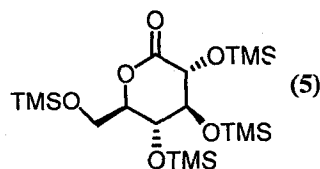


where in structure **1a**, X is methyl and Ar represents 2-(5-(4-fluorophenyl)-thienyl), and in structure **1b**, X is chlorine and Ar represents 4-ethoxyphenyl, which comprises a reaction of the

magnesate reagents of formula **6a** or **6b**,

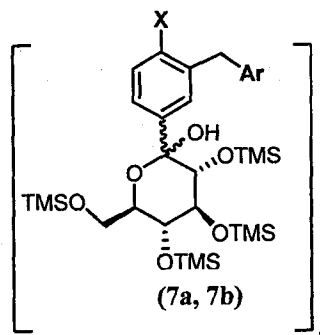


where each of the groups **R**¹ and **R**² is independently a branched or straight C₁ to C₆ alkyl, **m** is an integer from 1 to 3, **n** is an integer from 0 to 1 and **o** is an integer from 0 to 2, with the stoichiometric quantity of the gluconolactone derivative of structure **5**,

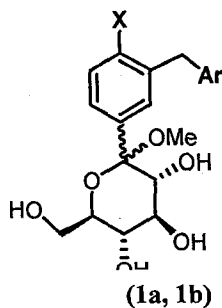


TMS = trimethylsilyl

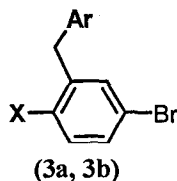
to give the intermediate of structure **7a** or **7b**,



which is converted to the isolable ketal of structure **1a** or structure **1b** through a reaction with methanol in the presence of a suitable organic or inorganic acid.



In the said preparation method, the magnesate reagent of type **6a** or **6b** is prepared through a reaction of the aryl bromide of formula **3a** or **3b**,



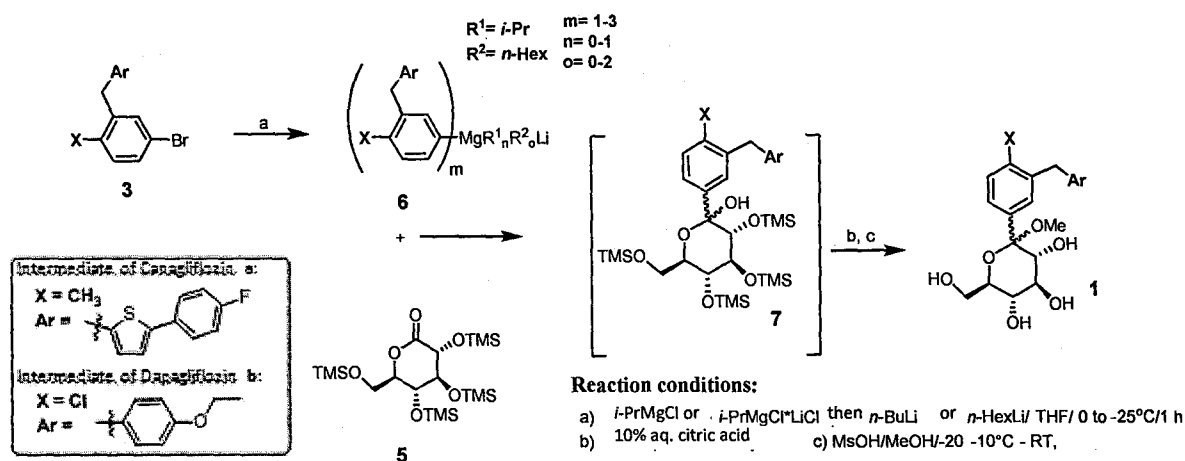
with a C₁ to C₆ alkyl lithium where the alkyl is a straight hydrocarbon chain, in the presence of a C₁ to C₆ alkyl magnesium halide where the alkyl is a direct or branched hydrocarbon chain, X, Ar, m, n and o are as defined above and the molar ratio of the aryl bromide of formula **3** and the alkyl lithium and alkyl magnesium halide is 1:2:1 to 1:0,67:0,33, at the reaction temperature of 0 to -35°C in a suitable ether solvent.

Detailed description of the Invention

The use of magnesate reagents was investigated with the aim to increase the reaction temperature to facilitate industrial production. Magnesates are usually generated through a reaction of the respective aryl halide (Lau, S. Y. W. et al. *Org. Lett.* **2007**, 9, 2239-2242) or heteroaryl halide (Struk, L.; Sośnicki, J. G. *Synthesis* **2012**, 44, 735–746) and lithium trialkyl magnesate, which is generated *in situ* through a reaction of e.g. hexyl lithium and isopropyl magnesium chloride. Although the initial attempts on generation of a triaryl magnesate using this technique did lead to metalation, but the yield and purity of the desired intermediate were very low (< 20%).

Metalation of the aryl bromide of formula **3a** with a turbo-Grignard reagent was not very efficient, the yields were only about 17% at the laboratory temperature overnight. But what was surprisingly found out was that the metalation reaction runs smoothly if a solution of the aryl bromide of formula **3a** or **3b** and a Grignard or turbo-Grignard reagent in the ratio of 1:0.33 to 1:1 equivalents is prepared in advance and then a solution of *n*-hexyl lithium (0.67 to 2.0 equivalents with regard to the aryl bromide) is added to it at a temperature of -25 to -5°C. The magnesates of formula **6a** or **6b** with a different stoichiometry generated this way reacted through addition to TMS-gluconolactone of structure **5** and the resulting crude intermediate products of structure **7a** or **7b** were then converted to the isolable desired key intermediates of structure **1**. See Diagram 3. These intermediates are then converted to the corresponding gliflozins using the reaction described in Diagram 2.

Diagram 3:



The generation of magnesates with different stoichiometric compositions was optimized. A suitable solvent is tetrahydrofuran (THF), but also 2-methyl-THF (MeTHF). Also, two addition methods were tested, i.e. A: addition of a lactone solution to a magnesate solution and B: addition of a magnesate solution to a lactone solution.

Another key factor is the method of processing of the reaction mixture after the addition. The usual method, i.e. addition of a solution of methanesulfonic acid in methanol, led to low yields and low purity of the desired product.

It was surprisingly found out that termination of the reaction with 10% aqueous citric acid, separation of phases and drying of the crude solution of the intermediate product of structure 7 by means of distillation and subsequent reaction with a solution of methanesulfonic acid in methanol led to far better results (see the comparison of batches 1 and 2). Selected results are summarized in Table 1.

Table 1: Preparation of the intermediate for canagliflozin

Batch	Source of Mg (equiv.)	<i>n</i> -HexLi (equiv.)	Solvent (TMSGlu equiv.)	Method of adding	Reaction temperature (magnesium / adding)	Yield of 1a	HPLC purity
1	<i>i</i> -PrMgCl*LiCl	2.1	2-MeTHF (1.3)	A	<-25°C/<-20°C	74%	82.29 %

Batch	Source of Mg (equiv.)	<i>n</i> -HexLi (equiv.)	Solvent (TMSGlu equiv.)	Method of adding	Reaction temperature (magnestation / adding)	Yield of 1a	HPLC purity
	(1.0)						
2	<i>i</i> -PrMgCl*LiCl (1.0)	2.1	2-MeTHF (1.3)	A	<-25°C/<-20°C	62%	55.69 %
3	<i>i</i> -PrMgCl*LiCl (1.0)	2	2-MeTHF (1.3)	A	<-20°C/<-20°C	94%	83.61 %
4	<i>i</i> -PrMgCl (1.0)	2	2-MeTHF (1.05)	A	<-20°C/<-20°C	88%	72.00 %
5	<i>i</i> -PrMgCl (0.33)	0.67	2-MeTHF (1.05)	A	<-20°C/<-30°C	18%	70.00 %
6	<i>i</i> -PrMgCl (0.33)	0.67	2-MeTHF (1.05)	B	<-5°C/<-25°C	53%	72.50 %
7	<i>i</i> -PrMgCl (0.5)	1.05	2-MeTHF (1.05)	A	<-18°C/<-20°C	74%	81.00 %
8	<i>i</i> -PrMgCl (1)	2	THF (1.3)	A	<-25°C/<-25°C	93%	75.00 %

The intermediate for the preparation of dapagliflozin was also prepared using an analogous method; selected results are presented in table 2.

Table 2: Preparation of the intermediate for dapagliflozin

Batch	Source of Mg (equiv.)	HexLi (ekv.)	Solvent (TMSGlu equiv.)	Method of adding	Reaction temperature (magnestation / adding)	Yield of 1b	HPLC purity
1	<i>i</i> -PrMgCl (1.0)	2	THF (1.3)	A	<-25°C/<-20°C	86%	84.7 %
2	<i>i</i> -PrMgCl (0.5)	1	THF (1.3)	A	<-25°C/<-20°C	71%	91.7 %
3	<i>i</i> -PrMgCl (0.34)	0.67	THF (1.3)	A	<-20°C /<-20°C	55%	83.0%

The results presented in Tables 1 and 2 show that with the use of the new synthetic procedure high yields of the intermediates of up to 90% can be achieved in an acceptable purity of approx. 85% at relatively high temperatures that do not require the use of special cryogenic equipment. It is therefore quite obvious that the preparation method in accordance with the present invention represents an efficient and economical synthetic alternative in the preparation of the key intermediates of the synthesis of pharmaceutically active gliflozins, especially canagliflozin and dapagliflozin.

Examples

Example 1:

Two three-necked flasks (100 ml and 50 ml) were dried under N₂ with a hot-air gun and left to cool down under N₂. In one three-necked flask a solution of TMS-gluconolactone (4.2 g, 1.3 equiv.) in 2-MeTHF (10 ml) was prepared under nitrogen.

The aryl bromide of formula 3a (2.5 g, 6.92 mmol) and 2-MeTHF (25 ml) were put in the other three-necked flask under N₂ and the resulting solution was cooled down under N₂ under stirring to -25°C (reaction mixture, bath approx. -25 to -30°C – 70:30 vol. ethylene glycol:ethanol/dry ice). Into the resulting thin suspension a solution of *i*-PrMgCl*LiCl in THF (1.3M, 5.32 ml,

1.0 equiv.) was added by dripping at $< -20^{\circ}\text{C}$, the resulting mixture was further stirred for 15 min. Then, a solution of *n*-HexLi in hexanes (2.3 M, 6.02 ml, 2.0 ekv.) was started to be added, the addition took 10 minutes ($t_{\text{reaction}} < -20^{\circ}\text{C}$ continuously), a green solution was obtained that was further stirred at this temperature for 0.5 h. The course of the metalation reaction was checked by taking of a sample of the mixture (approx. 0.1 ml), which was added to methanol (approx. 0.2 ml) and the mixture was diluted with acetonitrile to the final volume of 2.5 ml. This was followed by HPLC analysis, which showed that the aryl bromide had been completely converted to the magnesate.

Then, at $< -25^{\circ}\text{C}$, addition of a solution of the lactone (4.2 g, 1.3 equiv. in 10 ml of 2-MeTHF) into a solution of the magnesate was started (using a syringe pump, the needle was immersed in the cooled magnesate solution during the addition – for. approx. 0.5 h). Further, the reaction mixture was stirred for approx. 0.75 h and then a 10% aqueous solution of citric acid (30 ml) was added dropwise under stirring. The reaction mixture gradually changed its color from green through orange to yellow; the temperature of the mixture rose to 10°C .

The flask was then withdrawn from the cooling bath and the mixture was intensively stirred for 10-15 min. The mixture was left to stand overnight. The phases were separated, the organic layer was washed with salt brine (5 ml) and evaporated on a rotary vacuum evaporator (hereinafter RVE only, approx. 15 kPa (150 mbar)/ 41°C).

Methanol (20 ml) was added to the honey-like evaporation product. Moderate heating of the mixture was used to prepare a solution into which MsOH (0.1 ml) was added under stirring. The mixture was further stirred under N_2 at the laboratory temperature (hereinafter RT only) for 20 h. Then, a 10% aqueous solution of NaHCO_3 (10 ml) was added to the reaction mixture, the mixture was evaporated, PhMe (20 ml), EtOAc (20 ml) and water (10 ml) were added to the residue. The obtained mixture was shaken, the organic layer was separated and the aqueous phase washed with PhMe (10 ml). The united organic layers were washed with water (5 ml) and then with salt brine (5 ml). The solution was dried over Na_2SO_4 then it was filtered and the solvents were removed on an RVE. The crude product (3.97 g) was dissolved in PhMe (15 ml, under moderate heating) and slowly dripped into stirred *n*-heptane (50 ml) during 30 min at RT. The yellow suspension was then stirred at RT for 1 h and then filtered. The cake was washed with *n*-heptane (2 x 5), dried by suctioned air on frit overnight. The amount of 3.09 g (94%) of a loose yellow solid substance was obtained, HPLC 83,61%.

Example 2:

Two three-necked flasks (100 ml and 50 ml) were dried under N₂ with a hot-air gun and left to cool down under N₂. In one three-necked flask a solution of TMS-gluconolactone (3.39 g, 1.05 equiv.) in 2-MeTHF (10 ml) was prepared under nitrogen.

The aryl bromide of formula **3a** (2.5 g, 6.92 mmol) and 2-MeTHF (25 ml) were put in the other three-necked flask under N₂ and the resulting solution was cooled down under N₂ under stirring to -25°C (reaction mixture, bath approx. -25 to -30°C – 70:30 vol. ethylene glycol:ethanol/dry ice). Into the resulting thin suspension a solution of *i*-PrMgCl in THF (2.0M, 1.73 ml, 0.5 equiv.) was added by dripping at < -20°C, the resulting mixture was further stirred for 15 min. Then, a *n*-HexLi in hexanes (2.3 M, 6.02 ml, 2.0 ekv) was started to be added, the addition took 10 minutes ($t_{\text{reaction}} < -20^\circ\text{C}$ continuously), a green solution was obtained that was further stirred at this temperature for 0.5 h. The course of the metalation reaction was checked by taking of a sample of the mixture (approx. 0.1 ml), which was added to methanol (approx. 0.2 ml) and the mixture was diluted with acetonitrile to the final volume of 2.5 ml. This was followed by HPLC analysis, which showed that the aryl bromide had been completely converted to the magnesate.

Then, at < -25°C, addition of a solution of the lactone into a solution of the magnesate was started (using a syringe pump, the needle was immersed in the cooled magnesate solution during the addition – for. approx. 0.5 h). Further, the reaction mixture was stirred for 1 h and then a 10% aqueous solution of citric acid (30 ml) was added dropwise under intensive stirring. The reaction mixture gradually changed its color from green through orange to yellow; the temperature of the mixture rose to 10°C.

The flask was then withdrawn from the cooling bath and the mixture was intensively stirred for 10 to 15 min. The mixture was left to stand overnight. The phases were separated, the organic layer was washed with salt brine (5 ml) and evaporated on an RVE (approx. 150 mbar/41°C). 2-MeTHF (10 ml) was added to the residue and the mixture was evaporated until dry (repeated twice).

Methanol (20 ml) was added to the honey-like residue and under moderate heating a solution was prepared that MsOH (0.1 ml) was added into under stirring. The obtained mixture was further stirred under N₂ at RT for 20 h.

Then, a 5% aqueous solution of NaHCO₃ (10 ml) was added to the reaction mixture and further 2-MeTHF (30 ml) and water (5 ml) were added. The obtained mixture was shaken and the organic layer was separated. The united organic phases were washed with salt brine (5 ml) and

evaporated under the reduced pressure on an RVE (bath 40°C/150 mbar). The crude product (2.39 g) was dissolved in PhMe (15 ml – moderately heated) and the obtained solution was slowly dripped into stirred *n*-heptane (50 ml) during 30 min at RT. The yellow suspension was then stirred at the laboratory temperature for 2.5 h, which was followed by filtration and washing of the cake with *n*-heptane (2 x 5 ml). The filtration cake was dried by suctioned air on frit overnight. The amount of 2.40 g (73%) of a loose yellow solid substance was obtained, HPLC 81.06%.

Example 3:

Two three-necked flasks (100 ml and 50 ml) were dried under N₂ with a hot-air gun and left to cool down under N₂. In one three-necked flask a solution of TMS-gluconolactone (3.39 g, 1.05 equiv.) in 2-MeTHF (10 ml) was prepared under nitrogen.

The aryl bromide of formula **3a** (2.5 g, 6.92 mmol) and 2-MeTHF (25 ml) were put in the other three-necked flask under N₂ and the resulting solution was cooled down under N₂ under stirring to the temperature of -25°C (reaction mixture, bath approx. -25 to -30°C – 70:30 vol. ethylene glycol:ethanol/dry ice). Into the obtained thin suspension a solution of *i*-PrMgCl in THF (2.0 M, 1.14 ml, 0.33 equiv.) was added by dripping at < -20°C, the obtained mixture was further stirred for 5 min. Then, addition of a solution of *n*-HexLi in hexanes (2.3M, 2.02 ml, 0.67 equiv.) was started. The addition took 10 min (*t*_{reaction} -20°C to -5°C), a green solution was produced, which was further stirred at this temperature for 30 minutes. The course of the metalation reaction was checked by taking of a sample of the mixture (approx. 0.1 ml), which was added to methanol (approx. 0.2 ml) and the mixture was diluted with acetonitrile to the final volume of 2.5 ml. This was followed by HPLC analysis, which showed that the aryl bromide had been completely converted to the magnesate.

The reaction mixture was then cooled down to < -25°C and adding of a solution of the lactone (3.39 g, 1.05 equiv. in 10 ml of 2-MeTHF) into a solution of the magnesate was started (using a syringe pump, the needle was immersed in the cooled magnesate solution – for. approx. 1 h). The reaction mixture was further stirred for approx. 2 h and then a 10% aqueous solution of citric acid (30 ml) was added to it dropwise under intensive stirring. The reaction mixture gradually changed its color from orange to yellow, the temperature of the mixture rose to 10°C.

The flask was then removed from the cooling bath and the obtained mixture was intensively stirred for 15 min. The phases were separated, the organic layer was washed with salt brine (5 ml) and evaporated on an RVE (approx. 150 mbar/41°C).

Methanol (20 ml) was added to the honey-like residue and under moderate heating a solution was prepared that MsOH (0.1 ml) was added into under stirring; the obtained mixture was further stirred under N₂/at RT for 20 h.

Then, a 10% aqueous solution of NaHCO₃ (10 ml) was added to the reaction mixture, the solvents were evaporated on an RVE, PhMe (20 ml), EtOAc (20 ml) and water (10 ml) were added to the residue. The mixture was shaken, the organic layer was separated and the aqueous phase washed with PhMe (10 ml). The united organic layers were washed with water (5 ml) and then with salt brine (5 ml). The organic solution was dried over Na₂SO₄ and then it was filtered and the solvents were removed on an RVE. The crude product was dissolved in PhMe (15 ml – moderately heated) and slowly dripped into stirred *n*-heptane (50 ml) during 30 min at RT. The yellow suspension was then stirred at RT for 1 h and then filtered. The obtained cake was washed with *n*-heptane (2 x 5 ml), dried by suctioned air on frit overnight. The amount of 0.60 g (18%) of a loose yellow solid substance was obtained, HPLC 70.00%.

Example 4:

Two three-necked flasks (100 ml and 50 ml) were dried under N₂ with a hot-air gun and left to cool down under N₂. In one three-necked flask a solution of TMS-gluconolactone (3.39 g, 1.05 equiv.) in 2-MeTHF (10 ml) was prepared under nitrogen.

The aryl bromide of formula **3a** (2.5 g, 6.92 mmol) and 2-MeTHF (25 ml) were put in the other three-necked flask under N₂ and the resulting solution was cooled down under N₂ under stirring to -5°C (reaction mixture). Into the obtained thin suspension a solution of *i*-PrMgCl in THF (2.0M, 1.14 ml, 0.33 equiv.) was added by dripping at < -5°C, the obtained mixture was further stirred for 5 min. Then, addition of a solution of *n*-HexLi in hexanes (2.3 M, 2.02 ml, 0.67 equiv.) was started. The addition took 10 min (*t*_{reaction} -5°C), a green solution was created, which was further stirred at this temperature for 20 minutes. The course of the metalation reaction was checked by taking of a sample of the mixture (approx. 0.1 ml), which was added to methanol (approx. 0.2 ml) and the mixture was diluted with acetonitrile to the final volume of 2.5 ml. This was followed by HPLC analysis, which showed that the aryl bromide had been completely converted to the magnesate.

A cannula was then used to transfer the magnesate solution (during 30 minutes) to a lactone solution (3.39 g, 1.05 equiv. in 10 ml of 2-MeTHF) cooled down to $< -25^{\circ}\text{C}$. The obtained orange reaction mixture was further stirred for approx. 2 h and then a 10% aqueous solution of citric acid (30 ml) was added to the mixture dropwise under intensive stirring. The reaction mixture gradually changed its color from orange to yellow, the temperature of the mixture rose to 10°C .

The flask was then removed from the cooling bath and the mixture was intensively stirred for 15 min. The phases were separated, the organic layer was washed with salt brine (5 ml) and evaporated on an RVE (approx. 150 mbar/ 41°C).

Methanol (20 ml) was added to the honey-like residue and under moderate heating a solution was prepared that MsOH (0.1 ml) was added into under stirring. The obtained mixture was further stirred under N_2 /at RT for 3 h.

10% aqueous NaHCO_3 (10 ml) was added to the reaction mixture and the solvents were evaporated on an RVE. PhMe (20 ml), EtOAc (20 ml) and water (10 ml) were added to the residue. The mixture was shaken, the organic layer was separated and the aqueous phase washed with PhMe (10 ml). The united organic layers were washed with water (5 ml) and then with salt brine (5 ml). The mixture was dried over Na_2SO_4 and then it was filtered and the solvents were removed on an RVE. The crude product was dissolved in PhMe (15 ml – moderately heated) and slowly dripped into stirred *n*-heptane (50 ml) during 30 min at RT. The yellow suspension was then stirred at RT for 1 h and then filtered. The obtained cake was washed with *n*-heptane (2 x 5 ml), dried by suctioned air on frit overnight. The amount of 1.73 g (53%) of a loose yellow solid substance was obtained, HPLC 72.50%.

Example 5:

To a solution of the aryl bromide of formula **3b** (5 g) in dry THF (50 ml) cooled down to -25°C a solution of *i*-PrMgCl in THF (2.0M, 7.67 ml, 1 equiv) was added by dripping under N_2 . After 15 min a solution of *n*-HexLi in hexanes (2.3 ml, 13.35 ml, 2 equiv.) was added to the reaction mixture in the course of 45 min. The aryl bromide was completely converted to the magnesate after 0.5 h (HPLC). Then, a solution of TMS-lactone (9.4 g) in THF (15 ml) was added to the reaction mixture by dripping during 45 min by means of a syringe pump (the needle leaning against the flask wall so that the solution could flow down the wall and get cooled). After 2 h (5% content of the debrominated derivative – HPLC) a 10% aqueous solution of citric

acid (100 ml) was added to the reaction mixture, the temperature of the reaction mixture was increased to 20°C and then it was further intensively stirred for 0.5 h. The organic layer was separated and washed with salt brine (100 ml), dried over MgSO₄ and evaporated until dry on a vacuum evaporator. A residue with the weight of 12 g was obtained, which was dissolved in MeOH (150 ml). MeSO₃H (0.4 ml) was added to the reaction mixture and the obtained reaction mixture was stirred overnight. In the morning, the amount of 100 ml of a 10% solution of NaHCO₃ was added to the reaction mixture and the reaction mixture was stirred for 0.5 h. After partial evaporation on a vacuum evaporator 100 ml of toluene and 100 ml of water were added to the obtained thick slurry. The organic layer was washed with 100 ml of salt brine and dried over MgSO₄ and then concentrated to the volume of approx. 40 ml. During 15 min, this solution was added by dripping to 100 ml of *n*-heptane under intensive stirring at the room temperature. The white precipitate was then aspirated, washed with 20 ml of *n*-heptane and dried overnight in a vacuum dryer at 35°C/180 mbar. The amount of 5.8 g of the product was obtained in the yield of 86%, HPLC purity was 84.7%.

Example 6:

To a solution of the aryl bromide of formula **3b** (5 g) in dry THF (50 ml) cooled down to -25°C a solution of *i*-PrMgCl in THF (2.0M, 3.83 ml, 0.5 equiv.) was added by dripping under N₂. After 15 min a solution of *n*-HexLi in hexanes (2.3M, 6.97 ml, 1 equiv.) was added to the reaction mixture during 45 min. The aryl bromide was completely converted to the magnesate after 0.5 h (HPLC). Then, a solution of TMS-lactone (9.4 g) in THF (15 ml) was added to the reaction mixture by dripping during 45 min by means of a syringe pump (the needle leaning against the flask wall so that the solution could flow down the wall and get cooled). After 2 h (5% content of the debrominated derivative – HPLC) a 10% aqueous solution of citric acid (100 ml) was added to the reaction mixture, the temperature of the reaction mixture was increased to 20°C and then it was further intensively stirred for 0.5 h. The organic layer was separated and washed with salt brine (100 ml), dried over MgSO₄ and evaporated until dry on a vacuum evaporator. A residue with the weight of 12 g was obtained, which was dissolved in MeOH (150 ml). MeSO₃H (0.4 ml) was added to the reaction mixture and the obtained reaction mixture was stirred overnight. In the morning, the amount of 100 ml of a 10% solution of NaHCO₃ was added to the reaction mixture and the reaction mixture was stirred for 0.5 h. After partial evaporation on a vacuum evaporator 100 ml of toluene and 100 ml of water were added to the obtained thick

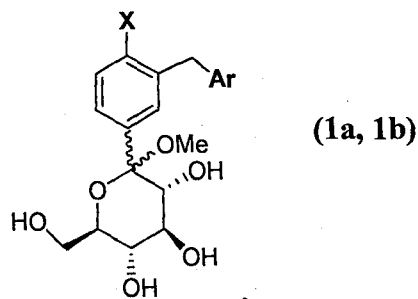
slurry. The organic layer was washed with 100 ml of salt brine and dried over MgSO_4 and then concentrated to the volume of approx. 40 ml. During 15 min, this solution was added by dripping to 100 ml of *n*-heptane under intensive stirring at the room temperature. The white precipitate was then aspirated, washed with 20 ml of *n*-heptane and dried overnight in a vacuum dryer at 35°C/180 mbar. The amount of 4.8 g of the product was obtained in the yield of 71%, HPLC purity 91.7%.

Example 7:

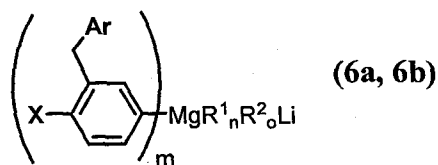
To a solution of the aryl bromide of formula 3b (5 g) in dry THF (50 ml) cooled down to -25°C a solution of *i*-PrMgCl in THF (2.0M, 2.61 ml, 0.34 equiv) was added by dripping under N_2 . After 15 min a solution of *n*-HexLi in hexanes (2.3 M, 4.47 ml, 0.67 equiv.) was added to the reaction mixture during 45 min. The aryl bromide was completely converted to the magnesate after 0.5 h (HPLC). Then, a solution of TMS-lactone (9.4 g) in THF (15 ml) was added to the reaction mixture by dripping during 45 min by means of a syringe pump (the needle leaning against the flask wall so that the solution could flow down the wall and get cooled). After 2 h (5% content of the debrominated derivative – HPLC) a 10% aqueous solution of citric acid (100 ml) was added to the reaction mixture, the temperature of the reaction mixture was increased to 20°C and then it was further intensively stirred for 0.5 h. The organic layer was separated and washed with salt brine (100 ml), dried over MgSO_4 and evaporated until dry on a vacuum evaporator. A residue with the weight of 12 g was obtained, which was dissolved in MeOH (150 ml). MeSO_3H (0.4 ml) was added to the reaction mixture and the obtained reaction mixture was stirred overnight. In the morning, the amount of 100 ml of a 10% solution of NaHCO_3 was added to the reaction mixture and the reaction mixture was stirred for 0.5 h. After partial evaporation on a vacuum evaporator 100 ml of toluene and 100 ml of water were added to the obtained thick slurry. The organic layer was washed with 100 ml of salt brine and dried over MgSO_4 and then concentrated to the volume of approx. 40 ml. During 15 min, this solution was added by dripping to 100 ml of *n*-heptane under intensive stirring at the room temperature. The white precipitate was then aspirated, washed with 20 ml of *n*-heptane and dried overnight in a vacuum dryer at 35°C/180 mbar. The amount of 3.7 g of the product was obtained in the yield of 55%, HPLC purity was 83.0%.

Claims

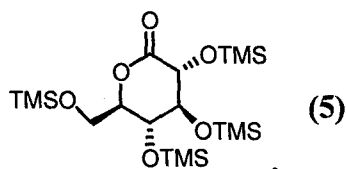
1. A method of preparing the intermediates of structures **1a** and **1b** in the synthesis of canagliflozin or dapagliflozin,



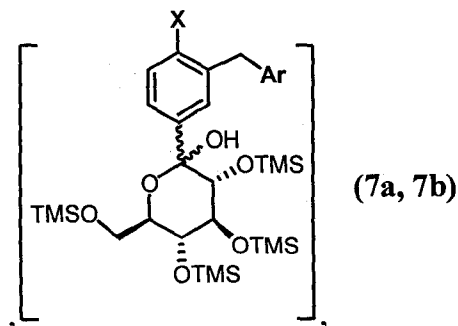
where in structure **1a**, **X** is methyl and **Ar** represents 2-(5-(4-fluorophenyl)-thienyl), and in structure **1b**, **X** is chlorine and **Ar** represents 4-ethoxyphenyl, which comprises a reaction of the magnesate reagents of formula **6a** or **6b**,



wherein each of the groups R^1 and R^2 is independently a branched or straight C_1 to C_6 alkyl, **m** is an integer from 1 to 3, **n** is an integer from 0 to 1 and **o** is an integer from 0 to 2, with the stoichiometric quantity of the gluconolactone derivative of structure **5**,

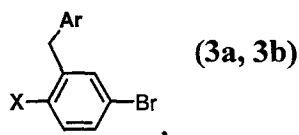


producing the intermediate of structure **7a** or **7b**,



which is converted to the isolable ketal **1a** or **1b** through a reaction with methanol in the presence of a suitable organic or inorganic acid.

2. The method of preparing in accordance with claim 1, characterized in that the magnesate reagent of formula **6a** or **6b** is prepared through a reaction of the aryl bromide of formula **3a** or **3b**,



with a C₁ to C₆ alkyl lithium where the alkyl is a straight hydrocarbon chain, in the presence of a C₁ to C₆ alkyl magnesium halide where the alkyl is a direct or branched hydrocarbon chain, **X**, **Ar**, **m**, **n** and **o** are defined in claim 1 and the molar ratio of the aryl bromide of formula **3** and the alkyl lithium and alkyl magnesium halide is 1:2:1 to 1:0.67:0.33, at the reaction temperature of 0 to -35°C in a suitable ether solvent.

3. The method of preparing in accordance with claim 2, characterized in that the suitable ether solvent is tetrahydrofuran or 2-methyltetrahydrofuran.

4. The method of preparing in accordance with claim 2, characterized in that the molar ratio of the aryl bromide of formula **3** and the aryl lithium and alkyl magnesium halide is 1:2:1 and the solvent is 2-methyltetrahydrofuran.

5. The method of preparing in accordance with claims 1 to 4, characterized in that **Ar** and **X** correspond to the definition in claim 1 and **R**¹ is isopropyl and **R**² is *n*-hexyl.

6. The method of preparing in accordance with claims 1 to 5, characterized in that the C₁ to C₆ alkyl lithium is *n*-hexyllithium and the C₁ to C₆ alkyl magnesium halide is isopropyl magnesium chloride.

7. The method of preparing in accordance with claims 1 to 6, characterized in that the suitable organic or inorganic acid is methanesulfonic acid.

8. The method of preparing the intermediates of structures **1a** or **1b** in accordance with any one of the preceding claims, characterized in that the reaction mixture containing the intermediate of structure **7** is processed by addition of an aqueous solution of citric acid before the addition of the solution of the above mentioned acid in methanol and the organic phase is subsequently dried.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000103

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07H1/00 C07H15/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/043682 A2 (JANSSEN PHARMACEUTICA NV [BE]; MITSUBISHI TANABE PHARMA CORP [JP]; FIL) 22 April 2010 (2010-04-22) cited in the application page 61, line 5 - page 62, line 15 page 109 - page 110; example 11 -----	1,5-8
X	WO 2013/152476 A1 (THERACOS INC [US]; XU BAIHUA [US]; LV BINHUA [CN]; XU GE [CN]; SEED BR) 17 October 2013 (2013-10-17) paragraph [0263] - paragraph [0269] ----- -/--	1,5-8



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

15 November 2016

Date of mailing of the international search report

23/11/2016

Name and mailing address of the ISA/

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Mezzato, Stefano

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000103

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	STEPHEN Y. W. LAU ET AL: "Magnesiation of Electron-Rich Aryl Bromides and Their Use in Nickel-Catalyzed Cross-Coupling Reactions", ORGANIC LETTERS , 14(23), 6012-6015 CODEN: ORLEF7; ISSN: 1523-7052, vol. 9, no. 11, 1 May 2007 (2007-05-01), pages 2239-2242, XP055318723, ISSN: 1523-7060, DOI: 10.1021/o1070841b cited in the application page 2241; tables 3-4 -----	1-8

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International application No

PCT/CZ2016/000103

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