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Synthesis of silodosin glucuronide and its deuterated counterpart: solving a problematic *O*-glycosylation of a nitrogen-containing molecule

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Abstract: We report here the first chemical synthesis of silodosin glucuronide, a metabolite of the α_{1A}-adrenoceptor antagonist silodosin, and its deuterium-labeled counterpart. As a key synthetic step, the incorporation of a glucuronosyl unit onto silodosin invariably led to either an undesired orthoester or a complex mixture under an array of standard glycosylation conditions. This problematic *O*-glycosylation may be attributed to the presence of multiple basic groups that could neutralize the acidic activators, decrease the nucleophilicity of a hydroxy group via hydrogen bond or even facilitate acyl migration side reactions. After elaborate tuning of reaction conditions, success was eventually achieved by using perbenzoylated D-glucuronosyl *N*-phenyltrifluroacetimidate (PTFA) as donor in combination with a procedure of sequential addition of TMSOTf. This protocol is potentially general for the glycosylation of other nitrogen-containing small molecule drugs.

Keywords: glucuronide; glycosylation; metabolite; silodosin.

Introduction

Silodosin (**1**), a potent and highly selective α_{1A}-adrenoceptor antagonist, is a marketed drug for the treatment of benign prostatic hyperplasia (BPH) with fewer cardiovascular side effects compared with other α-androgen receptor (AR) antagonists [1]. With respect to chemical structure, silodosin is composed of an indoline core scaffold linked with a catechol head piece and a primary alcohol tail (Scheme 1). A major metabolic pathway of silodosin is *O*-glucuronidation at the primary hydroxyl group via UDP-glucuronosyltransferase-2B7 (UGT2B7) to generate silodosin glucuronide (**2**) (Scheme 1) [2]. As a drug metabolite, glucuronide **2** is in high demand for pharmacokinetic studies and pharmacological evaluations [3]. However, quantities available from tedious isolation are insufficient, and the chemical synthesis of glucuronide **2** has not been reported to date. We present here the first synthesis of silodosin glucuronide (**2**) and its deuterium-labeled counterpart **3**.

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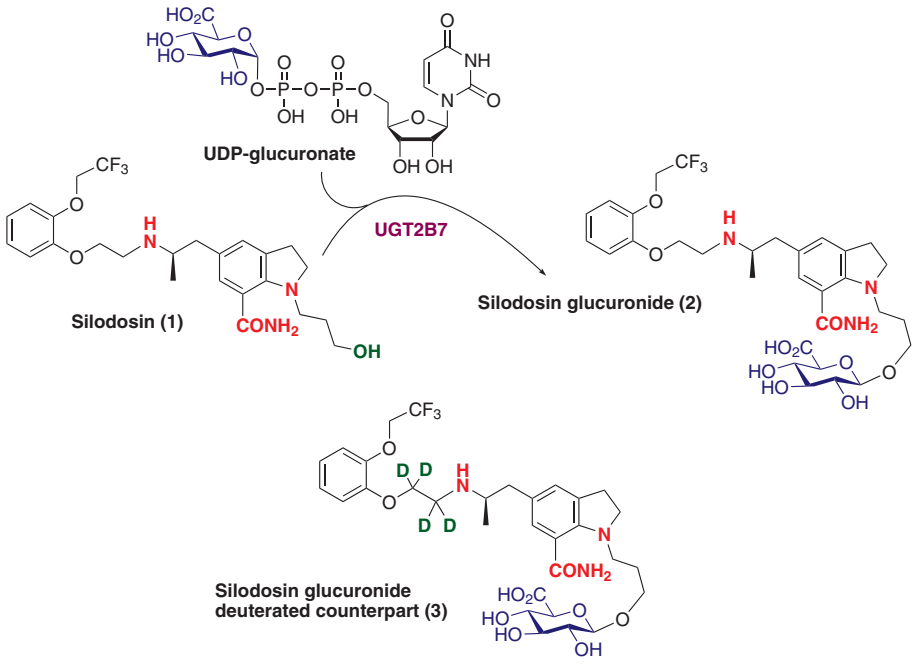
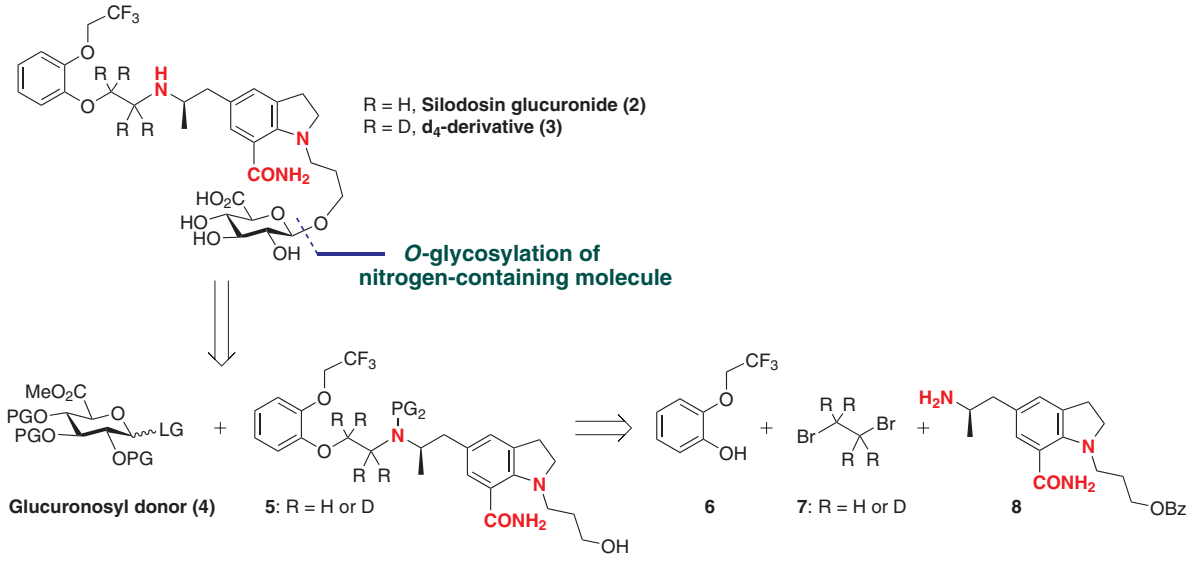
Results and discussion

At first sight, the chemical synthesis of glucuronides **2** and **3** seems to be very straightforward, by the coupling of a glucuronosyl selectively to the primary hydroxyl group of the silodosin moiety via a simple glycosylation (Scheme 2). However, its secondary and tertiary amines might conflict with the glycosylation because most of the activators are strong acids. Indeed, glycosyl acceptors in traditional glycosylations are either simple alcohols or protected saccharide fragments [4]. When the glycosyl acceptor is a complex multi-functionalized molecule, the glycosylation might result in the formation of side products [5, 6]. In such circumstances, elaborate screening of glycosyl donors and activators is critical to the success of glycosylation. Nevertheless, glycosylation of basic nitrogen-containing molecules has been reported in only a few examples and requires much more attention [7]. On the other hand, glycosylation with a glucuronosyl donor usually suffers from the presence of the electron-withdrawing C-6 carboxylate, which gives rise to decreased anomeric reactivity and deficient stability of the oxacarbenium intermediate [8]. We aimed to tackle the anticipated synthetic challenges with the targeted glucuronides **2** and **3**.

Our synthetic plan (Scheme 2) of silodosin glucuronides **2** and **3** suggested a late-stage glycosylation of properly protected silodosin derivatives **5** employing the glucuronosyl donor **4** to construct the β-glucuronosidic linkage. Thus, silodosin derivatives **5** could be protected at the secondary amine to prevent neutralization of the acidic promotor, and the amide ($CONH_2$) group could remain free. In turn, **5** could easily be derived from the

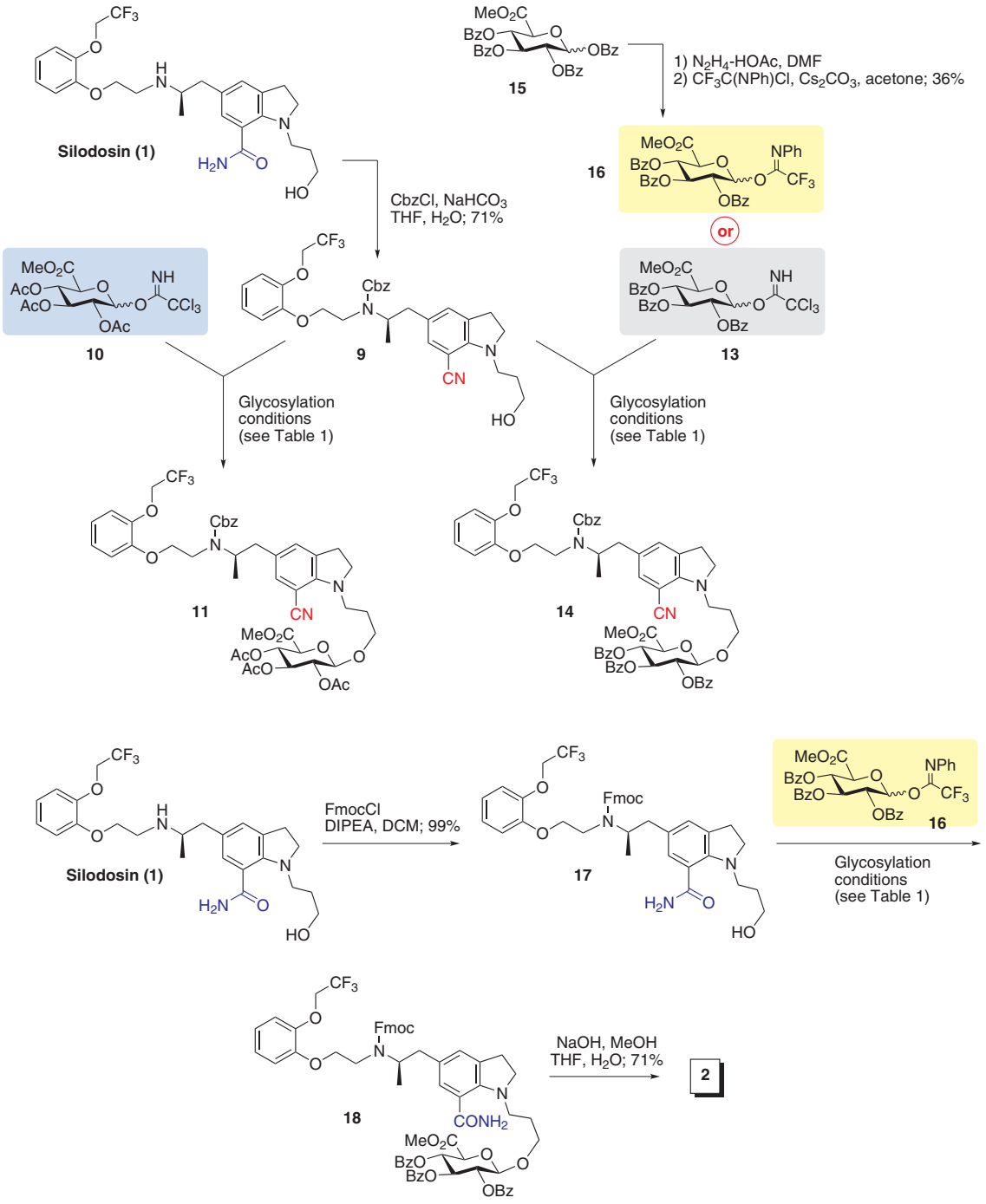


Scheme 1 Metabolism of silodosin by *O*-glucuronidation and the structure of glucuronides **2** and **3**.



Scheme 2 Synthetic plan of glucuronides **2** and **3**.

sequential coupling of fragments **6**, **7** and **8** via alkylation. With the readily prepared glucuronosyl donor **10** [9] in hand, the synthesis of glucuronide **2** commenced from *N*-benzyloxycarbamate (Cbz) protection with commercially available silodosin (**1**) (Scheme 3). To our surprise, the amide ($CONH_2$) group underwent dehydration to cyanide (CN) by treating compound **1** with CbzCl in a mixed solution of THF/H_2O, providing intermediate **9** (71%). As a cyano group can serve as a protecting group of amides, the intermediate **9** was then used for further coupling with peracetylated glucuronosyl trichloroacetimidate **10** (Scheme 3). Our first trial with the glycosylation was performed under the activation of TMSOTf (0.4 eq) at 0°C and the major product obtained was the orthoester [10], an isoform of **11** (Entry 1, Table 1). Increasing the amount of TMSOTf to 1.2 eq for the coupling (Entry 2) promoted rearrangement of the orthoester, resulting in a 15% yield of desired glycoside **11**. Unfortunately, a further increase



Scheme 3 Synthesis of glucuronide **2** by glycosylation.

of the amount of TMSOTf to 1.8 eq (Entry 3) gave rise to significant migration [11] of acetyl from the donor to the primary alcohol, and the use of $BF_3{\cdot}OEt_2$ (1.5 eq) at –10°C provided acetylated compound **9** as the major product (Entry 4).

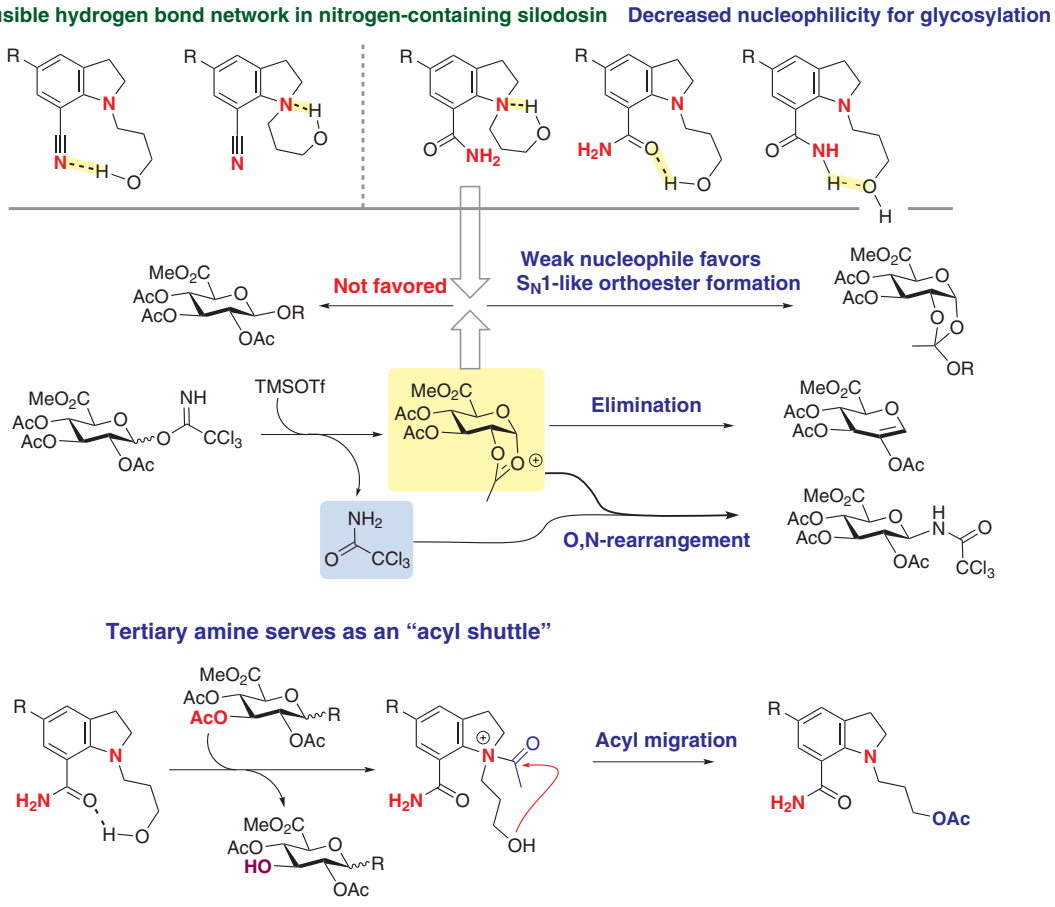
Considering the acid labile property of acetyl ester, we decided to examine the benzoyl (Bz) group as a protecting group on the glycosyl donor. Thus, perbenzoylated glucuronosyl trichloroacetimidate **13** [12] was synthesized according to the literature (Scheme 3). As expected, acyl migration was eliminated by using a benzoylated donor with TMSOTf (0.3 eq) at 0°C (Entry 5). However, the reaction was still not productive due to the formation of the glycosyl amide side product through *O*,*N*-rearrangement [13]. To prevent this side reaction, we turned our attention to the donor *N*-phenyltrifluoroacetimidate (PTFA) [14],

Table 1 Studies on glycosylation of silodosin using glucuronosyl donors.

Entry	Donor	Acceptor	Condition	Desired product (yield)	Side product (yield)
1	**10**	**9**	TMSOTf (0.4 eq), CH_2Cl_2, 0°C, 1 h	**11** (trace)	Orthoester isoform of **11** (73%)
2	**10**	**9**	TMSOTf (1.2 eq), CH_2Cl_2, 0°C, 1 h	**11** (15%)	Orthoester isoform of **11** (48%)
3	**10**	**9**	TMSOTf (1.8 eq), CH_2Cl_2, 0°C, 1 h	**11** (trace)	Acetyl ester of acceptor **9**
4	**10**	**9**	$BF_3{\cdot}OEt_2$ (1.5 eq), CH_2Cl_2, −10°C, 1 h	**11** (trace)	Acetyl ester of acceptor **9**
5	**13**	**9**	TMSOTf (0.3 eq), CH_2Cl_2, 0°C, 1 h	**14** (trace)	Glycosyl amide isoform of **13**
6	**16**	**9**	TMSOTf (0.3 eq), CH_2Cl_2, 0°C, 1 h	**14** (trace)	Orthoester isoform of **14**
7	**16**	**9**	TMSOTf (0.9 eq), CH_2Cl_2, 0°C, 1 h	**14** (47%)	Orthoester isoform of **14**
8	**16**	**17**	TMSOTf (1.2 eq), CH_2Cl_2, 0°C, 1 h	**18** (61%)	Glycal from **16**, benzoyl ester of **17**
9	**16**	**17**	TMSOTf (0.9 eq), CH_2Cl_2, 0°C, 1 h; then TMSOTf (0.3 eq), 0°C, 30 min	**18** (85%)	No significant side product

which is moderately reactive without generating a competing nucleophilic amide-leaving entity. Accordingly, the glucuronosyl PTFA donor **16** was synthesized from **15** [12] by sequential anomeric debenzoylation and treatment with $CF_3C(NPh)Cl/Cs_2CO_3$ (47%). We then investigated the glycosylation of acceptor **9** using **16** as a glycosylating agent. The use of TMSOTf (0.3 eq) at 0°C (Entry 6) still led to the corresponding orthoester as the major product by TLC and MS. However, when the amount of TMSOTf was increased to 0.9 eq (Entry 7), the desired glycoside **14** was obtained in an acceptable 47% yield with only a minor orthoester yield.

To avoid transformation of the cyano group to amide in the final stage, as for the coupling products **11** and **14**, we protected the secondary amine of **1** with fluorenylmethyloxycarbonyl (Fmoc) (Scheme 3). The acceptor **17**

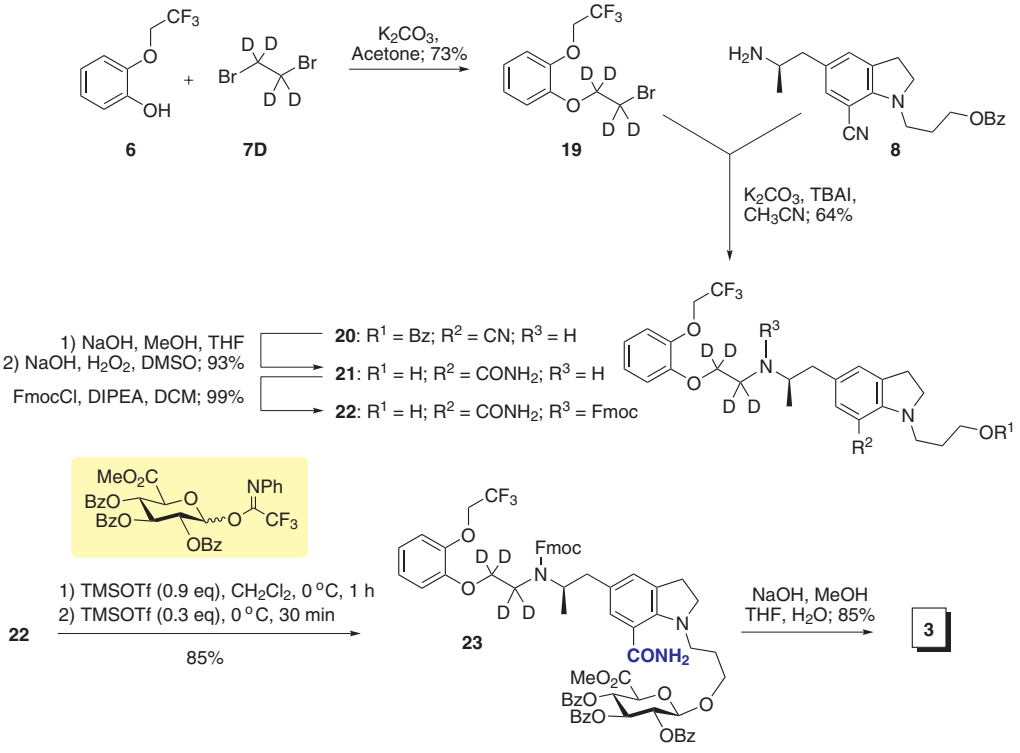


Scheme 4 The plausible side reaction pathways in the glucuronidation of silodosin.

was obtained in a quantitative yield by treatment with FmocCl in the presence of *N*,*N*-diisopropylethylamine (DIPEA). To further enhance the glycosylation yield, 1.2 eq of TMSOTf was utilized for the glycosylation of **16** with **17** (Entry 8) in the hope of complete conversion of the orthoester to glycoside. Indeed, the coupling delivered glycoside **18** in a moderate yield (61%), with glycal as a minor product derived from the elimination of donor **16** and slight benzoyl migration side product. To our delight, the coupling of **16** and **17** was eventually optimized to an 85% yield (Entry 9) by sequentially adding 0.9 eq and 0.3 eq of TMSOTf.

Based on the observation of problematic glycosylations, we hypothesize that the side reactions are imparted by the presence of multiple basic nitrogen groups (Scheme 4) and suggest the following five points: (1) The influence of the tertiary amine is not eliminated because it cannot be protected. (2) The tertiary amine and free amide group might form a hydrogen bond network, which deactivates the primary hydroxyl group and thus favors S_N1-like orthoester formation. (3) The tertiary amine could partially neutralize the acidic promotor, preventing the rearrangement of orthoester to glycoside. (4) Due to the low reactivity of the acceptor hydroxyl group, the competing side reactions, including elimination of the oxacarbenium ion to form glycal and *O*,*N*-rearrangement to give glycosyl amide, could become major reaction pathways; however, this could be reduced by using *N*-phenyltrifluoroacetimidate (PTFA) as donor. (5) The tertiary amine might serve as a nucleophilic 'acyl shuttle' to promote migration of the acyl group, and this could be prevented by using the benzoylated glycosyl donor.

Having established the optimal conditions, the coupling of **16** and **17** was scaled up to gram scale to obtain a sufficient amount of **18**, which was subjected to the one-pot final deprotection of Fmoc, C-6 methyl ester and O-benzoyl ester by using NaOH in a mixed solution of H_2O, MeOH and THF (Scheme 3). Finally, reverse-phase C-18 column purification afforded silodosin glucuronide (**2**) in a 71% yield. The deuterium-labeled counterpart **3** was synthesized in a similar manner using optimal glycosylation conditions (Scheme 5). The deuterium-labeled aglycon **21** was synthesized starting from simple fragments. Thus, the alkylation of 2-*O*-(2,2,2-trifluoroethyl)catechol (**6**) with excess deuterium-labeled 1,2-dibromoethane **7D** in the presence of K_2CO_3 in acetone afforded the monobromide **19** (73%), which was coupled with optically pure amine **8** under basic conditions to provide **20** (64%). Subsequent deprotection of the benzoyl ester and hydrolysis of cyanide gave **21** (93%), which was then protected at the secondary amine by the Fmoc group to deliver **22**. Finally, the glycosylation of **22**



Scheme 5 Synthesis of glucuronide **3**.

with the donor **16** was achieved with a high yield of 85%, and the global deprotection of **23** produced the deuterium-labeled counterpart **3** in an 85% yield.

Conclusion

Silodosin glucuronide (**2**) is a major metabolite of silodosin by *O*-glucuronidation at the primary hydroxyl group. The first synthesis of compound **2** and its deuterium-labeled analogue **3** by late-stage glycosylation of the appropriately protected silodosin derivative with a glucuronosyl donor is reported here. In a challenging step, the coupling of the glucuronosyl compound to the primary alcohol resulted in a range of side reactions under several standard glycosylation conditions. It was proposed that the problematic glycosylations are imparted by the basic nitrogen groups, which could neutralize the acidic activators, decrease the nucleophilicity of the hydroxy group via hydrogen bonds or even facilitate acyl migration side reactions. This problem was solved by elaborate tuning of reaction parameters and conditions, and the best result (85% yield) was achieved by using perbenzoylated D-glucuronosyl *N*-phenyltrifluoroacetimidate (PTFA) as the donor in combination with the sequential addition of 0.9 eq and 0.3 eq of TMSOTf.

Experimental

(R)-Benzyl (1-(7-cyano-1-(3-hydroxypropyl)indolin-5-yl) propan-2-yl)(2-(2-(2,2,2 trifluoroethoxy)phenoxy)ethyl) carbamate (9)

To a solution of **1** (100 mg, 0.20 mmol) in THF/H_2O (1:1, 8 mL) were added Na_2CO_3 (32 mg, 0.3 mmol) and CbzCl (86 µL, 0.6 mmol) at 0°C under nitrogen. The mixture was warmed to room temperature and stirred for 12 h. The mixture was treated with a saturated solution of $NaHCO_3$, extracted with ethyl acetate and the extract was concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–60%, acetone/hexanes) afforded **9** (87 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.31 (m, 5H), 7.11–6.72 (m, 6H), 5.26–5.02 (m, 2H), 4.47–4.28 (m, 2H), 4.21–3.92 (m, 3H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.75–3.46 (m, 6H), 3.03–2.51 (m, 4H), 2.04–1.80 (m, 3H), 1.34–1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 155.6, 151.9, 149.3 and 149.1 (rotamers), 147.2 and 147.0 (rotamers), 136.7 and 136.4 (rotamers), 132.7 and 132.7 (rotamers), 131.2, 129.5 and 129.4 (rotamers), 128.6, 128.1, 127.9, 127.7 and 127.5 (rotamers), 123.9 and 123.9 (rotamers), 123.5 (q, *J* = 279.1Hz), 121.5 and 121.2 (rotamers), 119.9 and 119.8 (rotamers), 116.9 and 116.7 (rotamers), 113.9 and 113.6 (rotamers), 87.5, 67.6 (q, *J* = 35.1 Hz),, 67.4, 67.0, 60.4, 55.5, 53.3, 45.5, 44.0, 40.4 and 39.6 (rotamers), 30.5, 27., 18.75 and 17.8 (rotamers). ESI-HRMS. Calcd for $C_{33}H_{37}F_3N_3O_5$ (M + H)$^+$: *m/z* 612.2685. Found: *m/z* 612.2678.

Orthoester form of 11

Donor **10** (132 mg, 0.27 mmol) and acceptor **9** (87 mg, 0.14 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4-Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under a nitrogen atmosphere, then cooled to 0°C and treated dropwise with TMSOTf (10 µL, 0.4 eq). After stirring at 0°C for 1 h, the mixture was treated with a saturated solution of $NaHCO_3$, extracted with ethyl acetate and the extract was concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–35%, ethyl acetate/hexanes) afforded an orthoester form of **11** (96 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45–7.32 (m, 5H), 7.07–6.76 (m, 6H), 5.91 (d, *J* = 4.5 Hz, 1H), 5.29–5.23 (m, 1H), 5.16 (ddd, *J* = 41.0, 21.5, 16.2 Hz, 3H), 4.42–4.30 (m, 4H), 4.18–4.07 (m, 2H), 4.04–3.91 (m, 1H), 3.79 (s, 3H), 3.68–3.47 (m, 8H), 2.92–2.72 (m, 3H), 2.61–2.52 (m, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 1.96–1.88 (m, 2H), 1.77 (s, 3H), 1.35–1.22 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.4, 168.9, 168.9, 156.4, 155.5, 151.7 and 151.7 (rotamers), 149.3 and 149.1 (rotamers), 147.2 and 147.0 (rotamers), 136.7 and 136.4 (rotamers), 132.7 and 132.7 (rotamers), 131.3, 129.5 and 129.4 (rotamers), 128.6, 128.2 and 128.1 (rotamers), 128.1, 127.9, 127.7 and 127.5 (rotamers), 123.9 and 123.9 (rotamers), 122.4, 121.4 and 121.2 (rotamers), 119.4, 119.4, 116.9 and 116.7 (rotamers), 113.9 and 113.6 (rotamers), 961, 87.7, 73.1, 69.2, 68.3, 68.1, 67.7, 67.5, 67.4, 67.0, 60.6, 55.5, 53.2, 52.7, 45.2, 44.0, 40.4, 39.6, 27.7, 27.3, 21.8, 20.7, 18.7 and 17.9 (rotamers). ESI-HRMS. Calcd for $C_{46}H_{53}F_3N_3O_{14}$ (M + H)$^+$: *m/z* 928.3480. Found: *m/z* 928.3490.

Glucuronide 11

The coupling procedure described above provided compound **11** (20 mg, 15%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.30 (m, 5H), 7.07–6.74 (m, 6H), 5.30–5.21 (m, 2H), 5.18–5.06 (m, 2H), 5.06–5.01 (m, 1H), 4.59 (d, *J* = 7.7 Hz, 1H), 4.41–4.30 (m, 2H), 4.16–3.92 (m, 5H), 3.77 (s, 3H), 3.70–3.47 (m, 7H), 2.94–2.72 (m, 3H), 2.62–2.51 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02–1.90 (m, 2H), 1.28–1.26 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.1, 169.4, 169.3, 167.2, 151.6, 149.3, 149.1, 147.2, 147.0, 141.3, 136.7, 135.7, 132.8, 132.8, 131.2, 131.2, 131.7, 129.5, 129.4, 129.3, 128.6, 128.2, 128.1, 128.1, 128.0, 123.9, 123.9, 121.5, 121.2, 119.5, 116.9, 116.7, 113.9, 113.6, 100.8, 90.3, 72.5, 72.1, 71.3, 69.5, 67.7, 67.6, 67.5, 67.0, 55.5, 53.4, 52.9, 44.8, 43.8, 40.4, 39.6, 27.7, 27.3, 20.7, 20.6, 20.5, 17.9. ESI-HRMS. Calcd for $C_{46}H_{53}F_3N_3O_{14}$ (M + H)$^+$: *m/z* 928.3480. Found: *m/z* 928.3484.

N-Phenyltrifluoroacetimidate (16)

To a solution of **15** (563 mg, 1.0 mmol) in DMF (10 mL) at 0°C was added $N_2H_4 \cdot$ HOAc (230 mg, 2.5 mmol). The mixture was warmed to room temperature and stirred for 1 h, quenched with acetone and concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–35%, ethyl acetate/hexanes) afforded the 1-OH intermediate product (210 mg). This compound was dissolved in acetone (5 mL) at 0°C under nitrogen and the solution was treated with Cs_2CO_3 (197 mg, 0.61 mmol) and $CF_3C(NPh)Cl$ (127 µL, 0.81 mmol). The mixture was filtered and concentrated. Flash chromatography on silica gel (gradient 0–15% ethyl acetate/hexanes) afforded **16** (251 mg, 36% for 2 steps); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06–7.98 (m,

5H), 7.94 (d, J = 7.8 Hz, 2H), 7.61–7.57 (m, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.6 Hz, 4H), 7.36 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.44 (s, 2H), 6.28 (t, J = 9.9 Hz, 1H), 5.79 (t, J = 9.8 Hz, 1H), 5.68 (d, J = 8.7 Hz, 1H), 4.79 (d, J = 8.6 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 165.5, 165.3, 165.2, 142.6, 133.8, 133.7, 133.5, 130.0, 129.9, 129.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 124.5, 119.3, 119.1, 115.9 (dd, J = 571.5, 285.7 Hz), 91.88, 70.96, 70.01, 69.50, 69.25, 53.15; ^{19}F NMR (377 MHz, $CDCl_3$): δ −65.60.

Glucuronide 14

Donor **16** (81 mg, 0.12 mmol) and acceptor **9** (48 mg, 0.08 mmol) were dissolved in anhydrous CH_2Cl_2 (4 mL). Freshly activated 4-Å molecular sieves (170 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to 0°C and TMSOTf (12 µL, 0.9 eq) was added dropwise. After stirring at 0°C for 1 h, the mixture was treated with a saturated solution of $NaHCO_3$, extracted with ethyl acetate and the extract was concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–25%, ethyl acetate/hexanes) afforded **14** (51 mg, 47%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00–7.94 (m, 4H), 7.89 (d, J = 8.0 Hz, 2H), 7.57–7.50 (m, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.43–7.30 (m, 11H), 7.06–6.71 (m, 6H), 5.95 (t, J = 9.5 Hz, 1H), 5.72 (t, J = 9.5 Hz, 1H), 5.62–5.54 (m, 1H), 5.22–5.05 (m, 2H), 4.92 (d, J = 7.5 Hz, 1H), 4.43–4.32 (m, 3H), 4.18–4.06 (m, 3H), 4.04–3.91 (m, 1H), 3.77–3.68 (m, 4H), 3.62–3.40 (m, 5H), 3.36–3.27 (m, 1H), 2.93–2.67 (m, 3H), 2.61–2.49 (m, 1H), 2.02–1.87 (m, 2H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.3, 165.6, 165.2, 165.0, 156.4 and 155.5 (rotamers), 151.7 and 151.6 (rotamers), 149.3 and 149.1 (rotamers), 147.2 and 147.1 (rotamers), 136.7 and 136.4 (rotamers), 133.5, 133.4, 132.8 and 132.8, 131.2, 129.8, 129.8, 129.3 and 129.3 (rotamers), 129.2, 128.8, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 127.9, 127.4 and 127.2 (rotamers), 123.9, 123.9, 123.5 (q, J = 278 Hz), 121.5, 121.2, 116.9, 116.8, 113.9, 113.7, 101.2, 87.2, 72.9, 72.2, 71.7, 70.3, 67.8, 67.53 (q, J = 35 Hz), 67.08, 67.03, 55.55, 53.49, 52.90, 44.7, 40.4, 39.6, 27.9, 27.2, 18.7 and 17.9 (rotamers). ESI-HRMS. Calcd for $C_{61}H_{59}F_3N_3O_{14}$ $(M+H)^+$: m/z 1114.3949. Found: m/z 1114.3981.

(R)-(9*H*-Fluoren-9-yl)methyl (1-(7-carbamoyl-1-(3-hydroxypropyl)indolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate (17)

To a solution of **1** (100 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was added DIEPA (105 µL, 0.60 mmol), and the mixture was stirred for 20 min at 0°C under nitrogen. Then a solution of FmocCl (63 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added over 20 min. The mixture was warmed to room temperature, stirred for 12 h, then concentrated and the residue was purified by flash chromatography on silica gel (gradient 0–60%, acetone/hexanes) to afford **17** (144 mg, 99%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80–7.67 (m, 2H), 7.63–7.43 (m, 2H), 7.43–7.24 (m, 4H), 7.19 (s, 0.5 H, rotamers), 7.08–6.88 (m, 4H), 6.84 (s, 0.5 H, rotamers), 6.77 (d, J = 27 Hz, 1H), 6.70–6.60 (m, 1H), 6.46 (s, 1H), 4.59 (dd, J = 10.7 Hz and 5.3 Hz, 1H), 4.51–4.26 (m, 3H), 4.18–4.05 (m, 1H), 4.02–3.86 (m, 1H), 3.79–3.43 (m, 5H), 3.44–3.32 (m, 1H), 3.30–3.05 (m, 3H), 3.03–2.60 (m, 4H), 2.48–2.27 (m, 1H), 1.79–1.65 (m, 2H), 1.22 (d, J = 6.7 Hz, 1.5 H, rotamers), 1.02 (d, J = 5.3 Hz, 1.5 H, rotamers); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.7 and 171.6 (rotamers), 157.0, 155.8, 149.8 and 149.6 (rotamers), 149.3 and 149.2(rotamers), 147.0, 144.2 and 144.1 (rotamers), 143.9 and 143.8 (rotamers), 141.5 and 141.4 (rotamers), 141.3, 133.6, 129.6 and 129.5 (rotamers), 128.1 and 127.9 (rotamers), 127.8, 127.7, 127.6, 127.1, 127.1, 124.7, 124.6, 124.0, 123.9, 123.6 (q, J = 279 Hz), 121.3, 121.2, 120.1 and 120.0 (rotamers), 119.9, 117.7, 117.1, 117.0, 113.9, 113.6, 67.7 (q, J = 35 Hz), 67.1, 66.7, 66.7, 59.4, 54.7, 53.6, 50.3, 50.2, 47.5 and 47.4 (rotamers), 43.3, 39.9, 30.9, 28.1, 18.6 and 18.2 (rotamers); ^{19}F NMR (377 MHz, $CDCl_3$): δ −73.96 (d, J = 5.6 Hz). ESI-HRMS. Calcd for $C_{40}H_{43}F_3N_3O_6$ $(M+H)^+$: m/z 718.3104. Found: m/z 718.3098.

Glucuronide 18

Donor **16** (202 mg, 0.29 mmol) and acceptor **17** (140 mg, 0.19 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL). Freshly activated 4-Å molecular sieves (500 mg) were added and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to 0°C and TMSOTf (32 µL, 0.176 mmol) was added dropwise. After stirring at 0°C for 1h, additional TMSOTf (11 µL, 0.06 mmol) was added. The mixture was stirred for another 30 min, treated with a saturated solution of $NaHCO_3$, extracted with ethyl acetate and the extract was concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–65%, ethyl acetate/hexanes) afforded **18** (200 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99–7.94 (m, 4H), 7.89 (d, J = 7.8 Hz, 2H), 7.79 (t, J = 6.3 Hz, 1H), 7.70 (d, J = 5.0 Hz, 1H), 7.63–7.44 (m, 5H), 7.42–7.25 (m, 10H), 7.07–6.88 (m, 5H), 6.68–6.59 (m, 1H), 5.96 (t, J = 9.5 Hz, 1H), 5.71 (t, J = 9.5 Hz, 1H), 5.56 (dd, J = 16.5 Hz and 7.8 Hz, 1H), 4.86 (d, J = 7.3 Hz, 1H), 4.70–4.55 (m, 1H), 4.54–4.45 (m, 1H), 4.40–4.31 (m, 3H), 4.27–4.14 (m, 2H),, 4.04–3.92 (m, 2H), 3.70 (s, 3H), 3.57 (d, J = 5.6 Hz, 2H), 3.50 (d, J = 23 Hz, 1H), 3.31–3.17 (m, 3H), 3.08–2.95 (m, 2H), 2.89–2.62 (m, 3H), 2.50–2.26 (m, 1H), 1.87–1.69 (m, 2H), 1.21 (d, J = 6.6 Hz, 1.5 H, rotamer), 0.96 (d, J = 5.2 Hz, 1.5 H, rotamer); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.77 and 169.7 (rotamers), 167.5, 165.7, 165.2, 165.0, 156.7 and 155.7 (rotamers), 149.6 and 149.4 (rotamers), 147.1, 144.1 and 143.9 (rotamers), 141.5 and 141.4 (rotamers), 134.4 and 134.2 (rotamers), 133.5, 133.4, 130.7 and 130.6 (rotamers), 129.8, 129.8, 129.2, 128.8, 128.7, 128.5, 128.4, 128.4, 127.8, 127.6, 127.2, 127.1 and 124.7 (rotamers), 124.0 and 123.9 (rotamers), 123.6 (q, J = 279.3 Hz), 121.3, 121.1, 120.1 and 120.1 (rotamers), 119.9, 118.9 and 118.8 (rotamers), 117.2, 113.9 and 113.7 (rotamers), 101.1, 72.8, 72.1, 71.2, 70.2, 68.2, 67.7 (q, J = 35 Hz), 67.0 and 66.7 (rotamers), 66.7 and 66.6 (rotamers), 552, 53.4, 52.9, 51.2 and 50.9 (rotamers), 47.5, 47.4, 43.7, 40.0, 28.3, 28.0 and 27.9 (rotamers), 18.4 and 18.0 (rotamers); ^{19}F NMR (377 MHz, $CDCl_3$): δ −73.97 (d, J = 11.4 Hz). ESI-HRMS. Calcd for $C_{68}H_{65}F_3N_3O_{15}$ $(M+H)^+$: m/z 1220.4368. Found: m/z 1220.4338.

Glucuronide 2

A solution of **18** (80 mg, 0.07 mmol) in a mixed solvent of MeOH/H_2O (5/1, 2.6 mL) and THF (1 mL) was stirred at 0°C under nitrogen and treated with 3M NaOH (0.87 mL). The mixture was warmed to room temperature, stirred overnight, quenched with acetic acid (205 µL) and concentrated. Flash chromatography on a reversed-phase C18 column (gradient 0–70%, acetonitrile/water) afforded **2** (31 mg, 71%). ^{1}H NMR (400 MHz, MeOD): δ 7.17–6.96 (m, 6H), 4.57 (q, J = 8.6 Hz, 2H), 4.40–4.20 (m, 3H), 4.07–3.91 (m, 1H), 3.67–3.57 (m, 2H), 3.57–3.48 (m, 3H), 3.44 (dd, J = 17.2 Hz and 8.6 Hz, 3H), 3.35–3.21 (m, 4H), 3.06 (dd, J = 13.6 Hz and 5.1 Hz, 1H), 2.99–2.85 (m, 2H), 2.77–2.66 (m, 1H),

1.94–1.78 (m, 2H), 1.30 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ 173.0, 149.0, 148.2, 147.6, 133.9, 128.0, 127.0, 125.3, 124.5 (q, J = 278 Hz), 123.3, 122.3, 118.0, 115.7, 115.3, 103.2, 76.4, 74.9, 73.6, 72.4, 67.3, 66.6 (q, J = 35 Hz), 65.5, 53.1, 48.3, 44.1, 38.5, 27.7, 27.1, 14.9; ^{19}F NMR (377 MHz, MeOD): δ −75.38. ESI-HRMS. Calcd for $C_{31}H_{41}F_3N_3O_{10}$ $(M+H)^+$: m/z 672.2744. Found: m/z 672.2785.

Compound 19

To a solution of **6** (1.0 g, 5.2 mmol) and **7D** (3.0 g, 15.6 mmol) in CH_3CN (20 mL) was added K_2CO_3 (1.44 g, 10.4 mmol) under nitrogen. The mixture was heated under reflux for 16 h, then filtered and concentrated. Flash chromatography on silica gel (gradient 0–10%, ethyl acetate/hexanes) afforded **19** (1.14 g, 73%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11–7.04 (m, 2H), 7.02–6.94 (m, 2H), 4.46 (q, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.1, 147.7, 124.4, 123.6 (q, J = 279 Hz), 122.4, 118.9, 115.4, 68.5 (q, J = 35 Hz). ESI-HRMS. Calcd for $C_{10}H_7D_4BrF_3O_2$ $(M+H)^+$: m/z 303.0146. Found: m/z 303.0137.

Compound 20

To a solution of **8** · L-tartaric acid salt (200 mg, 0.39 mmol) in H_2O (10 mL) was added K_2CO_3 (412 mg, 3.89 mmol) to adjust the pH to 10. The mixture was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, filtered and concentrated to give free amine **8**. To a solution of crude **8** in acetonitrile (20 mL) were added **19** (130 mg, 0.43 mmol), K_2CO_3 (108 mg, 0.78 mmol) and TBAI (7 mg, 0.02 mmol). The mixture was heated at 80°C for 12 h and then cooled to room temperature. The mixture was filtered, washed with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–40%, acetone/hexanes) afforded **20** (145 mg, 64%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.08–7.03 (m, 1H), 7.02–6.96 (m, 3H), 6.95–6.90 (m, 2H), 4.50 (t, J = 6.3 Hz, 2H), 4.34 (q, J = 8.5 Hz, 2H), 3.77 (t, J = 7.2 Hz, 2H), 3.59 (t, J = 8.5 Hz, 2H), 2.99–2.92 (m, 2H), 2.90 (dd, J = 12.8 Hz and 6.4 Hz, 1H), 2.63 (dd, J = 13.6 Hz and 6.4 Hz, 1H), 2.45 (dd, J = 13.6 Hz and 6.9 Hz, 1H), 2.21–2.14 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.6, 151.6, 149.8, 147.5, 132.9, 132.6, 131.5, 130.2, 129.7, 128.4, 128.0, 124.3, 123.6 (q, J = 279 Hz), 121.5, 119.5, 118.1, 114.7, 88.0, 68.1 (q, J = 35 Hz), 62.6, 54.2, 53.4, 45.3, 42.4, 27.3, 27.2, 20.0 . ESI-HRMS. Calcd for $C_{32}H_{31}D_4F_3N_3O_4$ $(M+H)^+$: m/z 586.2831. Found: m/z 586.2837.

Compound 21

To a solution of **20** (118 mg, 0.20 mmol) in a mixed solvent of MeOH (3 mL) and THF (2 mL) was added NaOH (0.4 mL, 1M), and the mixture was stirred at room temperature. After completion as indicated by TLC analysis, the solvent was evaporated. The residue was diluted with water and extracted with ethyl acetate. The extract was dried over Na_2SO_4, filtered and concentrated to give a residue that was used for the next step without purification. The crude product was dissolved in DMSO (4 mL) at 0°C under nitrogen and treated with 5 M NaOH (121 µL) and 30% H_2O_2 (87 µL). The mixture was warmed to room temperature, stirred for 24 h, diluted with water and extracted with ethyl acetate. The extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (gradient 0–10%, MeOH/CH_2Cl_2) afforded **21** (93 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 1H), 7.07–6.93 (m, 4H), 6.93–6.80 (m, 3H), 4.30 (q, J = 8.5 Hz, 2H), 3.69 (t, J = 5.5 Hz, 2H), 3.37 (t, J = 8.5 Hz, 2H), 3.21–3.09 (m, 3H), 3.02–2.86 (m, 3H), 2.68 (dd, J = 13.5 Hz and 6.4 Hz, 1H), 2.51 (dd, J = 13.5Hz and 6.9 Hz, 1H), 1.86–1.69 (m, 2H), 1.06 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 149.8, 149.6, 147.4, 133.9, 130.2, 128.2, 128.0, 124.3, 123.6 (q, J = 278 Hz), 121.5, 118.3, 118.1, 114.7, 68.0 (q, J = 35 Hz), 59.4, 54.4, 53.6, 50.8, 42.5, 21.0, 28.2, 19.8. ESI-HRMS. Calcd for $C_{25}H_{29}D_4F_3N_3O_4$ $(M+H)^+$: m/z 500.2674. Found: m/z 500.2659.

Compound 22

To a solution of **21** (400 mg, 0.80 mmol) in CH_2Cl_2 (12 mL) was added DIEPA (418 µL, 0.24 mmol) and the mixture was stirred at 0°C under nitrogen. Then a solution of FmocCl (224 mg, 0.84 mmol) in CH_2Cl_2 (12 mL) was added over 20 min. The mixture was warmed to room temperature, stirred for an additional 12 h and concentrated. Flash chromatography on silica gel (gradient 0–60%, acetone/hexanes) afforded **22** (569 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.65 (m, 2H), 7.62–7.42 (m, 2H), 7.42–7.25 (m, 4H), 7.17 (s, 0.5 H, rotamor), 7.07–6.86 (m, 4H), 6.82 (s, 1H, rotamor), 6.78–6.59 (m, 2H), 6.24 (s, 1H), 4.64–4.54 (m, 1H), 4.45–4.25 (m, 3H), 4.17–4.00 (m, 1H), 3.70 (d, J = 13.3 Hz, 2H), 3.49 (s, 1H), 3.44–3.30 (m, 1H), 3.25–3.03 (m, 2H), 2.97–2.61 (m, 4H), 2.48–2.27 (m, 1H), 1.98 (s, 1H), 1.80–1.63 (m, 2H), 1.26–1.16 (m, 1.5 H, rotamer), 1.03 (d, J = 6.5 Hz, 1.5 H, rotamer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 and 171.5 (rotamers), 157.0 and 155.9 (rotamers), 149.8 and 149.6 (rotamers), 147.0 and 147.0 (rotamers), 144.2 and 144.1 (rotamers), 143.9 and 143.8 (rotamers), 141.5 and 141.4 (rotamers), 141.3, 133.6, 129.5 and 129.3 (rotamers), 128.0 and 127.9 (rotamers), 127.7, 127.8 and 127.6 (rotamers), 127.1, 127.1, 124.7 and 124.7 (rotamers), 124.8 and 124.6 (rotamers), 124.0 and 123.9 (rotamors), 123.5 (q, J = 278 Hz), 121.3 and 121.2, 120.0 and 120.0 (rotamers), 119.9, 117.5, 117.1 and 117.0 (rotamers), 113.8 and 113.6 (rotamers), 67.7 (q, J = 35 Hz) and 67.7 (q, J = 35 Hz) (rotamers), 66.8 and 66.7 (rotamers), 59.4, 54.5, 53.6, 50.2 and 50.0 (rotamers), 47.5 and 47.4 (rotamers), 39.9, 30.9 and 30.9 (rotamers), 28.1 and 28.1 (rotamers), 18.6 and 18.2 (rotamers). ESI-HRMS. Calcd for $C_{40}H_{39}D_4F_3N_3O_6$ $(M+H)^+$: m/z 722.3355. Found: m/z 722.3360.

Compound 23

Donor **16** (667 mg, 0.96 mmol) and acceptor **22** (464 mg, 0.643 mmol) were dissolved in anhydrous CH_2Cl_2 (7 mL). Freshly activated 4-Å molecular sieves (500 mg) were added and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to 0°C and TMSOTf (105 µL, 0.9 eq) was added dropwise. After stirring at 0°C for 1 h, additional TMSOTf (35 µL, 0.3 eq) was added. The mixture was stirred for another 30 min, treated with a saturated solution of NaHCO3, extracted with ethyl acetate and the extract was concentrated under reduced pressure. Flash chromatography on silica gel (0–65% ethyl acetate/hexanes) afforded **23** (668 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.5 Hz, 4H), 7.88 (d, J = 7.5 Hz, 2H), 7.81–7.74 (m, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.60–7.24 (m, 15H), 7.07–6.86 (m, 5H), 6.68–6.56 (m, 1H), 5.94 (t, J = 9.5 Hz, 1H), 5.83 (s, 1H), 5.70 (t, J = 9.5 Hz, 1H), 5.61–5.50 (m, 1H), 4.85 (d, J = 7.5 Hz, 1H), 4.69–4.55 (m,

1H), 4.53–4.44 (m, 1H), 4.41–4.29 (m, 3H), 4.25–4.14 (m, 2H), 4.04–3.95 (m, 1H), 3.92–3.80 (m, 1H), 3.70 (s, 3H), 3.61–3.51 (m, 1H), 3.33–3.15 (m, 2H), 3.08–2.93 (m, 2H), 2.91–2.60 (m, 3H), 2.45–2.27 (m, 1H), 1.83–1.68 (m, 2H), 1.20 (d, J = 6.5 Hz, 1.5H, rotamer), 0.96 (d, J = 6.5 Hz, 1.5H, rotamer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 and 169.6 (rotamers), 167.4, 165.7, 165.2, 165.0, 156.7 and 155.7 (rotamers), 149.6 and 149.2 (rotamers), 149.4, 147.1, 144.2 and 144.1 (rotamers), 144.0 and 143.9 (rotamers), 141.5 and 141.4 (rotamers), 141.4 and 141.3 (rotamers), 134.4 and 134.2 (rotamers), 133.5, 133.4, 133.3, 130.7 and 130.6 (rotamers), 129.8, 129.8, 129.2, 128.8, 128.7, 128.5, 128.4, 128.4, 128.2, 127.8, 127.7, 127.6, 127.1, 124.7, 124.0, 123.9, 123.58 (q, J = 279 Hz), 121.2, 121.1, 120.1 and 120.1 (rotamers), 119.9, 119.0 and 118.8 (rotamers), 117.2, 113.8, 113.6, 101.1, 72.8, 72.1, 71.7, 70.2, 68.2, 67.7 (q, J = 35 Hz), 66.7 and 66.6 (rotamers), 55.0, 53.4, 52.9, 51.2 and 50.9 (rotamers), 47.5 and 47.4 (rotamers), 40.0, 28.3, 28.0 and 28.0 (rotamers), 18.4 and 18.3 (rotamers). ESI-HRMS. Calcd for for $C_{68}H_{61}D_4F_3N_3O_{15}$: m/z $(M+H)^+$ 1224.4619. Found: m/z 1224.4610.

Compound 3

A solution of **23** (1.14 g, 0.93 mmol) in a mixed solvent of MeOH/H_2O (5/1, 37 mL) and THF (14 mL) was stirred at 0°C under nitrogen, then treated with 3M NaOH (8.3 mL). The mixture was warmed to room temperature, stirred overnight, quenched with acetic acid and concentrated. Flash chromatography on a reversed-phase C18 column (gradient 0–60%, CH_3CN/H_2O) afforded **3** (535 mg, 85%). ^{1}H NMR (400 MHz, MeOD): δ 7.14–7.00 (m, 6H), 4.58 (q, J = 8.6 Hz, 2H), 4.26 (d, J = 7.8 Hz, 1H), 4.04–3.94 (m, 1H), 3.69–3.57 (m, 2H), 3.54 (d, J = 9.4 Hz, 1H), 3.50–3.38 (m, 4H), 3.31–3.21 (m, 3H), 3.05 (dd, J = 13.8 Hz and 5.4 Hz, 1H), 2.99–2.86 (m, 2H), 2.74 (dd, J = 13.8 Hz and 8.6 Hz, 1H), 1.95–1.79 (m, 2H), 1.32 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ 175.5, 173.0, 149.0, 148.1, 147.6, 133.9, 128.0, 126.9, 125.0, 123.9 (q, J = 278 Hz), 123.3, 122.4, 118.0, 115.5, 115.2, 103.2, 76.4, 74.9, 73.6, 72.4, 67.3, 66.5 (q, J = 35 Hz), 55.7, 53.0, 48.1, 38.3, 27.6, 27.0, 14.8; ^{19}F NMR (377 MHz, MeOD): δ –75.41. ESI-HRMS. Calcd for $C_{31}H_{37}D_4F_3N_3O_{10}$ $(M+H)^{3+}$: m/z 676.2995. Found: m/z 676.2987.

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