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Process Development of Selectively Benzoylated and Fluorinated Glycosyl Donors

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Abstract:

Route selection, process development and large-scale preparation of selectively benzoylated and fluorinated D-glucopyranoses, required as glycosyl donors for the synthesis of the SGLT inhibitor SAR7226, are discussed.

Introduction

Sodium-glucose transporters (SGLT) are a family of proteins that have an important role in transporting glucose across cellular membranes against a concentration gradient. These proteins are predominantly expressed in intestinal mucosa (SGLT1) and kidney tubules (SGLT1 and SGLT2) where they mediate intestinal absorption and renal reabsorption of glucose.[1] SAR7226 (**1**) emerged as a promising SGLT1/SGLT2 inhibitor, potentially useful for the treatment of diabetes,[2] and multikilogram quantities of the drug substance were required to support preclinical and clinical activities.

Scheme 1 illustrates a retrosynthetic, convergent approach to **1** that features the coupling of two advanced intermediates, hydroxypyrazole **2** and glycosyl donor **6** to afford the SAR7226 backbone structure. Intermediate **2** is derived from monoalkylation of ethyl 4,4,4-trifluoroacetoacetate (**3**) with 4-methoxybenzyl chloride (**4**) followed by treatment with benzylhydrazine (**5**). Glycosyl donor **6** is derived from a suitable galactosugar **8** that is selectively protected, fluorinated with inversion at the C-4 position, and then manipulated at the anomeric position.

Several synthetic routes and iterations were successfully demonstrated from kilo scale up to pilot-plant scale as the target molecule progressed to clinical development and increasing quantities of drug substance were required. The ultimate goal was to establish an economical and industrializable synthesis of SAR7226. This paper summarizes the process development of glycosyl donor synthons **6**.

Discussion

Development of Glycosyl Donor 6a from 8a. Methyl α-D-galactose monohydrate (**8a**) was chosen as the substrate for early development because it had been used successfully for small deliveries of **1** and was readily available in multikilogram quantities (Scheme 2). The objectives for the first pilot-plant campaigns were to demonstrate a scaleable synthesis of **1** and deliver drug substance rapidly. The first step in the synthesis of **6a** involved selective tribenzoylation at the 2-, 3-, and 6-positions of **8a** using benzoyl chloride in pyridine. Low reaction temperatures (≤0 °C), commonly employed in the literature,[3] were found to be unnecessary. Comparable selectivities were achieved at 20 °C, with the added benefit of shorter reaction times. A total of 4.7 equiv of BzCl were necessary to achieve an optimal distribution of products, typically 85:12:3 normalized HPLC area % (A%) ratio of the desired product, the tetrabenzoylated byproduct, and underbenzoylated intermediates, respectively. The tetrabenzoylated byproduct was more soluble and easier to remove than the underbenzoylated intermediates. To mitigate overbenzoylation, the reaction was continued until the amount remaining of each of two underbenzoylated intermediates was <3.0 A%. An isolation process that minimized the carryover of impurities and provided high-purity product directly from the reaction mixture without a separate recrystallization was developed. Thus, after water quench, extraction into toluene, and aqueous washes to remove benzoic acid and pyridine, the organic phase was partially concentrated and diluted with *n*-heptane to facilitate crystallization of **7a**. Four batches, providing a total of 147 kg of **7a**, were produced in an average yield of 73% and with >98.8 A% purity.

The next step involved the fluorination of **7a** with inversion of configuration at the C-4 position to afford **9**.[4] During early development, diethylaminosulfur trifluoride (DAST) was replaced with bis(2-methoxyethyl)aminosulfur trifluoride (BAST), a more thermally stable fluorinating reagent.[5] The fluorination process likely proceeds through the activated intermediate **12** (Figure 1), analogous to DAST.[4] Upon heating, the resulting activated hydroxyl at C-4 is displaced by fluoride ion with inversion in a highly selective manner.[6] A significant competing reaction pathway is elimination to give the olefin **13**.

A limited screening of solvents established THF as a suitable solvent for the fluorination step. The addition of neat BAST was exothermic and was performed at ambient temperature to

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(1) Idris, I.; Donnelly, R. *Diabetes, Obes. Metab.* **2009**, *11*, 79.

(2) (a) Frick, W.; Glombik, H.; Kramer, W.; Heuer, H.; Brummerhop, H.; Plettenburg, O. U.S. Patent 2005/0014704 A1, 2005 (WO2004052902; CAN 141:38810). (b) Frick, W.; Glombik, H.; Kramer, W.; Heuer, H.; Brummerhop, H.; Plettenburg, O. U.S. Patent 2004/0259819 A1, 2004 (WO2004052903; CAN 141:38811).

(3) (a) Williams, J. M.; Richardson, A. C. *Tetrahedron* **1967**, *23*, 1369. (b) Reist, E. J.; Spencer, R. R.; Calkins, D. F.; Baker, B. R.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2312. (c) Rye, C. S.; Withers, S. G. *J. Am. Chem. Soc.* **2002**, *124*, 9756.

(4) Card, P. J. *J. Org. Chem.* **1983**, *48*, 393.

(5) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048, and references cited therein.

(6) None of the 4-F epimer of **9** was detected in the product or in the filtrate by ^{19}F NMR spectroscopy.

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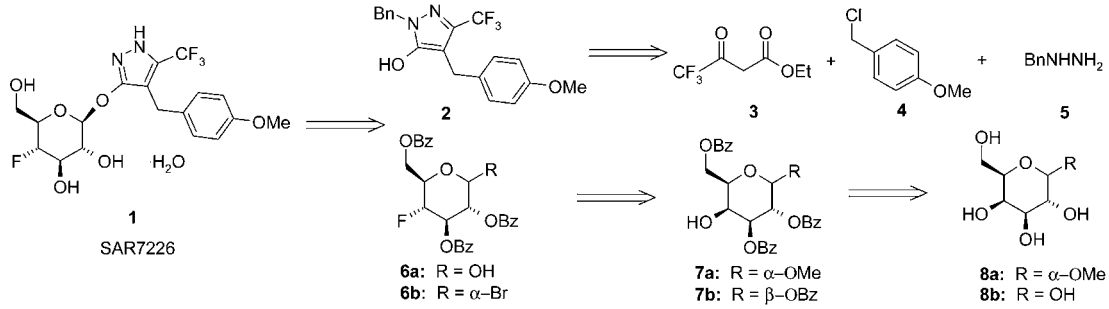
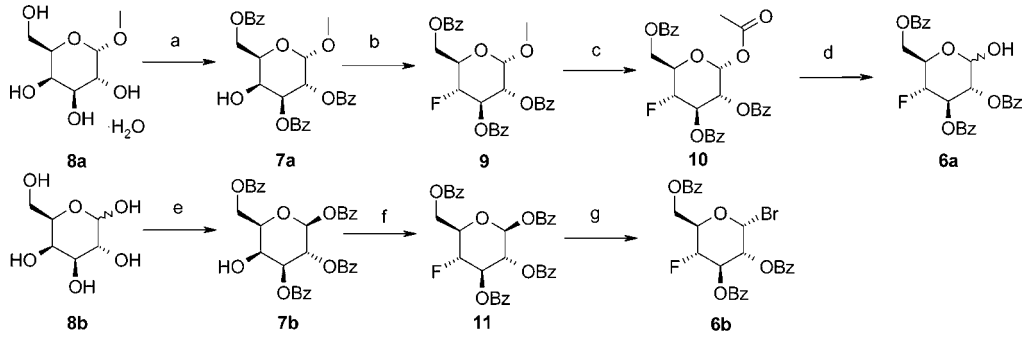
Scheme 1. **Retrosynthesis of SAR7226**



Scheme 2. **Synthesis of glycosyl donors 6a and 6b**[a]



[a] Reagents and conditions: a) BzCl, pyr, 20 °C, 73%; b) BAST, THF, 52 °C, 80%; c) AcOH/Ac_2O/H_2SO_4, 50 °C, 58%; d) $NH_2CH_2CH_2NH_2$/AcOH, THF, 20 °C, quant.; e) BzCl/pyr/Bz_2O, NMP, 45%; f) BAST, 2-MeTHF, 52 °C, 77%; g) HBr/AcOH, 55 °C, ≥ 96%.

provide the activated alcohol in a facile manner. The reaction was then heated at 50 °C to complete the fluorination. Typically, a 5:1 ratio of fluorinated product **9** to olefin **13** was achieved. Attempts to substantially improve the selectivity were unsuccessful. Heating rate and reaction temperature marginally affected the ratio of product to olefin. After a water quench, extractive workup using toluene, partial concentration of the organic phase, and crystallization upon addition of *n*-heptane, a total of 382 kg of **9** was isolated as a white solid in seven batches in 80% average yield, and containing ≤3 A% of olefin **13**, the limit for ensuring suitable downstream chemistry.

A key issue for the fluorination process was the safe handling of neat BAST on large scale in the pilot plant. For the initial batches (61-mol scale), BAST was purchased in bottles and first transferred in a fume hood to a Teflon-coated tank prior to use in the plant. On subsequent larger scales (227-mol scale), the hazards and the extra processing steps associated with predispensing the material were eliminated. The neat BAST was supplied in reusable 100-L pressure vessels constructed of perfluoroalkoxy copolymer resin (PFA).[7,8]

Conversion of **9** to **10** was performed using acetic acid, acetic anhydride, and sulfuric acid as the reagent system.[2] Depending on conditions, varying ratios of three products were obtained: the desired product **10** as a mixture of α- and *β*-anomers and an impurity tentatively assigned (NMR) as an open-chained tribenzoylated and triacylated compound. It was not necessary to separate the anomers of **10** because both yield **6a** upon deacylation.[9] From a process chemistry perspective, however, the α-anomer was preferred in order to maximize yields because it was more readily recoverable (the *β*-anomer was much more soluble) and avoided inefficiencies often encountered when isolating from mixtures. An isolation procedure that removed the impurity from this complex mixture was developed. After an extractive workup using toluene and addition of 2-propanol as an antisolvent, **10** was isolated at 0 °C as a white solid in an average yield of 59% (222 kg total, five batches) consisting of a 9:1 or better mixture of α-/*β*-anomers and containing only about 0.6 A% of the open-chain impurity.

The development of a selective anomeric deacylation of **10** was a critical step in implementing a coupling strategy based on activation of **6a** followed by coupling with hydroxypyrazole **2**.[10] For lab campaigns, selective deacylation was achieved using hydrazine hydrate as base. Prior to pilot-plant scale, an effort was made to replace hydrazine hydrate with a less hazardous reagent (Table 1). Ammonia and morpholine were less chemoselective and generated partially debenzoylated impurities. Ammonium acetate gave poor conversion. Ethylenediamine showed some potential, although a small amount of debenzoylation was detected. In comparison, ethylenediamine as its less basic monoacetate salt[11] in THF proved to be a very regioselective reagent for deacylation, and was employed on scale up. The workup was designed to allow process telescoping with the subsequent coupling step to improve overall efficiency and to

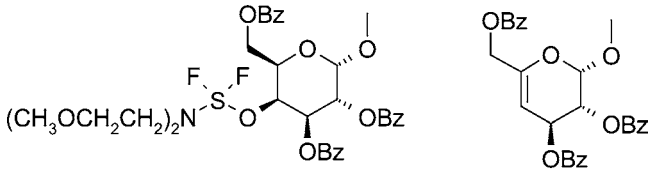
(7) BAST was manufactured by Air Products and Chemicals, Inc. (www.airproducts.com) and sold as Deoxo-fluor. The containers were obtained from Entegris, Inc. (www.entegris.com).

(8) Independent corrosivity studies have not yet been performed. Air Products and Chemicals, Inc. has a history of successfully manufacturing BAST and performing BAST reactions in Hastelloy equipment. Accordingly, the BAST reactions and quenches (HF generated) were performed in the pilot plant in Hastelloy C276 equipment.

(9) In the subsequent deacetylation step, a 4:1 mixture of α/*β*-anomers of **6a** is obtained regardless of anomeric composition of starting **10**.

(10) Poor conversions (<10 A%) resulted in attempts to directly couple **10** or **11** with **2** in the presence of Lewis acids.

(11) Zhang, J.; Kováč, P. *J. Carbohydr. Chem.* **1999**, *18*, 461.



12 13

Figure 1. **BAST intermediate and elimination byproduct.**

avoid a difficult isolation of the anomeric mixture of **6a**. Initially, dichloromethane (DCM) was employed as the extraction solvent. However, it was difficult to completely remove the THF in the DCM phase after water washes and concentration. Residual THF interfered with the downstream chemistry (acetimidate coupling with pyrazole **2**) by competing with the Lewis acid catalyst employed in the coupling step. This issue was overcome by replacing DCM with toluene for extractive workup. THF was then effectively removed (limit of 0.1 wt %) during partial concentration of the toluene phase. The resulting toluene solution of **6a** (quantitative yield, > 99.5 A% purity) was used directly in the coupling step.

The four-step synthesis of **6a** was shown to be reliable and reasonably robust, and a total of 202 kg was prepared in the early pilot-plant campaigns, most of which was elaborated to prepare 90 kg of SAR7226. The campaign objectives were achieved: a scaleable synthesis of **1** employing glycosyl donor **6a** was developed, enabling accelerated delivery of API to support preclinical and early clinical studies. However, the long-term goal was to establish an industrializable synthesis of **1**.[12] This implies:

- technical scalability and good robustness of the processes
- good overall yield and process productivity (space-time-yield)
- acceptable process safety and industrial hygiene
- tolerable waste generation (environmental impact minimized)
- availability of all materials on commercial scale
- acceptable chemical and physical quality of the drug substance: impurities are avoided or controlled
- freedom to operate from an intellectual property standpoint exists or is manageable (e.g., licensing)
- acceptable cost of goods (CoG); API target cost not exceeded after full process optimization

Using these criteria, the overall process to synthesize **1** via glycosyl donor **6a** was assessed. Reasonable assumptions were projected for yield improvements, streamlining workups and isolations, proper selection and minimization of solvents (e.g., minimizing both volume and total number of different solvents in the overall synthesis and optimizing solvent recoverability), and anticipated commercial prices of materials. The exercise was a means to identify potentially insurmountable hurdles to industrialization that would help define whether significant efforts were warranted, e.g., the need for an alternative synthesis route rather than just routine optimization of existing chemistry. In this context, the major criteria for industrialization were deemed achieved, or were projected to be achievable after full optimization, with the exception of CoG of the API.

The material cost to manufacture **6a**, based on projected bulk prices for key materials, was determined to be about 3-fold higher than the target cost for an economical glycosyl donor. The three major cost contributors in the synthesis of **6a** were low yield for the conversion of **9** to **10**, the cost of the BAST, and the high cost of α-methyl galactose (**8a**). Several improvements in the existing synthesis that favorably impacted the cost of **6a** were shown to be feasible, but were not fully developed in time for the first pilot-plant campaign. For example, a direct conversion of **9** to **6a** was developed and nonaflyl fluoride[13] was identified as a cost-effective replacement for BAST. However, even with these improvements, it was evident that the cost target would not be achievable and that a synthesis employing a significantly more economical starting sugar substrate was required.

Development of Glycosyl Donors from Galactose (8b). It may seem surprising that the unit cost for bulk quantities of α-methyl galactose (**8a**) is high because it is prepared industrially from readily available and inexpensive galactose (**8b**)[14] using conventional Fischer glycosylation reaction conditions, namely, MeOH as solvent in the presence of an acid catalyst. However, this glycosylation produces an equilibrium mixture of ~3:1[15] of the desired pyranoside **8a** and its *β*-anomer together with α- and *β*-furanoside impurities and the open-chain dimethyl acetal adduct. In-house attempts to substantially improve this selectivity by screening a variety of conditions and acid catalysts were unsuccessful.[16] Isolating pure **8a** from a mixture of products has proven to be difficult.[15] The need for repeat recrystallizations[17] together with low recoveries when crystallizing from mixtures has contributed to the high commercial price for **8a**.

Attention therefore shifted to developing alternative substrates. It occurred to us that tetrabenzoyl galactose could be a viable synthon.[10] The strategy for synthesizing a suitable glycosyl donor would be similar to that used for the previous substrate: blocking of all positions other than the 4-OH, followed by fluorination and then manipulation at the anomeric position to generate the desired synthon. Whereas tribenzoylation of **8a**, containing a methoxy group fixed in the α-anomeric position, is well behaved and reasonably selective, the analogous regioselective 1,2,3,6-tetrabenzoylation (and regioselective tetraa-

(12) For a recent discussion on assessing and selecting synthesis routes, see: Parker, J. S.; Bower, J. F.; Murray, P. M.; Patel, B.; Talavera, P. *Org. Process Res. Dev.* **2008**, *12*, 1060, and references cited therein. For a review of process chemistry objectives, see: Zhang, T. Y. *Chem. Rev.* **2006**, *106*, 2583.

(13) Vorbrüggen, H. *Synthesis* **2008**, 1165.

(14) Price ranges for bulk quantities: 6−9 €/mol for galactose and 115−155 €/mol for methyl α-D-galactose monohydrate. The primary feedstock for these substrates is cow's milk (certified for human consumption).

(15) (a) Mowery, D. F., Jr.; Ferrante, G. R. *J. Am. Chem. Soc.* **1954**, *76*, 4103. (b) Dale, J. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1930**, *52*, 2534. (c) Pater, R. H.; Coelho, R. A.; Mowery, D. F., Jr. *J. Org. Chem.* **1973**, *38*, 3272.

(16) Ratios improved slightly to 4:1 at elevated temperatures (120 °C, under pressure) in attempts to adapt concepts from reports that achieved 12:1 α/*β* selectivity using microwave-assisted Fischer glycosylation conditions: (a) Bornaghi, L. F.; Poulsen, S.-A. *Tetrahedron Lett.* **2005**, *46*, 3485. (b) Nüchter, M.; Ondruschka, B.; Lautenschläger, W. *Synth. Commun.* **2001**, *31*, 1277.

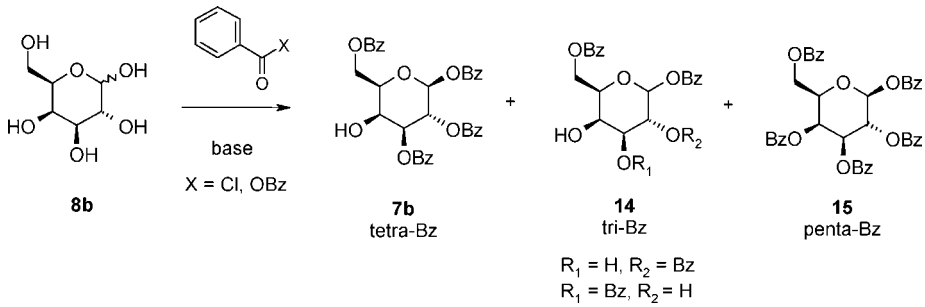
(17) The *β*-anomer is not suitable for use in this instance because it impacts selectivity in the benzoylation step and would lead to mixtures that interfere with isolations in downstream chemistry.

Table 1. **Selectivity of anomeric deacylation of 10**

base (equiv)	equiv	solvent	temp (°C)	time (h)	**10** (A%)	**6a** (A%)	impurities[a] (A%)
$NH_2NH_2 \cdot H_2O$	1.1	THF	0	5	0	100	0
NH_4OAc	2.4[b]	THF/MeOH/H_2O[c]	35	45	8	87	5
NH_3	7.5	THF/MeOH[d]	0	6	0.3	96	3.7
$NH_2CH_2CH_2NH_2$	1.0	THF	22	3	2	94	4
$NH_2CH_2CH_2NH_2$/AcOH	1.2/1.4	THF	22	21	0	100	0
$NH_2CH_2CH_2NH_2$/AcOH	1.2/1.4	DCM	22	21	23	71	6
$NH_2CH_2CH_2NH_2$/AcOH	1.2/1.4	MTBE	22	21	45	52	3
morpholine	1.3	toluene	35	26	1	98	1

[a] Combined debenzoylated impurities. [b] Only 10% conversion with 1.2 equiv of NH_4OAc and absence of MeOH. [c] 9:8:1; no reaction in absence of MeOH. [d] 7:3 ratio.

Scheme 3. **Tetrabenzoylation of 8b**



cylations in general)[18] of **8b** is complicated by several factors. First, **8b** is comprised of α/β-anomers and ring-opened species, which would generate complex mixtures of products and provide challenges in isolation and purification. Second, **8b** is a poorly soluble compound, leading to heterogeneous reaction conditions, at least at the onset of the reaction. As a result, although there is some differentiation between the five hydroxy groups in the molecule,[3a,19] reported yields and selectivities for this tetrabenzoylation have been generally poor, and isolations have often included chromatography.[20]

Benzoylations of carbohydrates are traditionally conducted using pyridine as solvent.[21] Preliminary experiments showed that regioselectivity could be improved by using NMP as solvent with pyridine as base, presumably because of slightly improved solubilization of **8b** in NMP. A mixture of products resulted, including the desired tetra-Bz **7b**, underbenzoylated species, designated tri-Bz **14**, and the overbenzoylated species, penta-Bz **15** (Scheme 3). Early probes suggested that benzoic anhydride gave slightly better regioselectivity than benzoyl chloride. The difference in reactivity of these benzoylating reagents has been rationalized to be due to the nature of the reacting species. In the case of benzoyl chloride, benzoyl

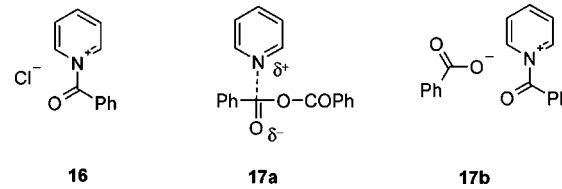


Figure 2. **Benzoylating species.**

pyridinium chloride **16** is the highly reactive species (Figure 2). In contrast, the reactive species in the case of benzoic anhydride is species **17a** or perhaps the benzoyl pyridinium benzoate **17b** in which case the lack of ionic character (**17a**) or steric demands lead to improved differentiation of the hydroxy groups.[19,22] However, benzoylations with benzoic anhydride were sluggish, even at elevated temperatures, and initially this reagent did not appear to be a viable choice from the point of view of efficiency and processability on a pilot-plant time scale.

To address these issues, it was found that an approach using both benzoyl chloride and benzoic anhydride in tandem had merit and led to improvements to the regioselective tetrabenzoylation of **8b**. The basis of the tandem approach was to use an initial deficient amount of benzoyl chloride which would benzoylate the more active hydroxy groups (e.g., at the 1- and 6-positions) to start the process and solubilize the substrate, then the less reactive but more selective benzoic anhydride would benzoylate the less active hydroxy groups and complete the intended tetrabenzoylation.

Indeed, after a series of experiments, this proposal demonstrated real potential. It should be noted that because of the challenges galactose presented as a substrate, mixtures of the

(18) In preliminary screens, benzoylation appeared to have more potential for selectivity than alternative acylations, such as acetylation or pivaloylation. Also, see: Lindhorst, T. K. *Essentials of Carbohydrate Chemistry and Biochemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2003; p 49.

(19) Generally, anomeric-OH and primary-OH are most reactive, and equatorial-OH is more reactive than axial-OH. Based on analogy with benzoylation of methyl α-D-galactopyranoside, 6-OH > 2-OH ≈ 3-OH > 4-OH. See: Haines, A. H. Relative Reactivities of Hydroxyl Groups in Carbohydrates. In *Advances in Carbohydrate Chemistry and Biochemistry*; Tipson, R. S., Horton, D., Eds.; Academic Press: New York, 1976; Vol. 33, pp 11−109.

(20) Reported yield after chromatography is 38%. (β-anomer not reported): (a) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1982**, *110*, 261. (b) Kováč, P.; Taylor, R. B. *Carbohydr. Res.* **1987**, *167*, 153.

(21) Pyridine (or alternative base) in this instance also serves as acyl transfer reagent (via *in situ* generated benzoyl pyridinium species) and as HCl acceptor.

(22) Selective acylations using acid anhydrides: (a) Horton, D.; Lauterback, J. H. *J. Org. Chem.* **1969**, *34*, 86. (b) Chen, C.-T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C.-H.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1188.

Table 2. **Selective tetrabenzoylation of 8b[a,b]**

entry	solvent	BzCl (equiv)	Bz_2O (equiv)	time (h)	**14** (A%)	**15** (A%)	**7b** (A%)
1	pyridine	3.0	1.5	3	7	72	15
2	butanone	5.0	0	3	8	40	21
3	CH_3CN	2.9	1.5	17	8	45	42
4	NMP	4.6	0	5	2	19	56
5	DMPU	2.9	1.5	25	15	6	62
6	TMU	2.9	1.5	25	15	8	63
7	DMF	2.9	1.5	19	6	16	64
8	DMEU	2.9	1.5	25	12	10	67
9	NMP	2.9	1.5	26	5	13	71
10	DMA	2.9	1.5	19	8	10	72
11	NMP[c]	3.05	1.5	19	7	9	72
12	DMA[c]	3.05	1.5	14	7	7	75

[a] Conditions: 20 °C (5 °C for entries 1 and 2), 5.5 equiv of pyr (pyr as solvent for entry 1). [b] Raw A% HPLC conversions. [c] Conditions predicted by DoE data.

desired **7b**, underbenzoylated species **14**,[23] and overbenzoylated **15** were obtained even under the best conditions. Apart from the selectivity of tetrabenzoylation of galactose, one of the major challenges during process development was isolation of **7b** with purity suitable for downstream chemistry from the complex mixture of products. Fortunately, under this tandem protocol, high selectivity at the anomeric center was observed. The β:α selectivity improved from about 82:18 to ≥97:3 as the reaction proceeded, likely due to *in situ* thermodynamic anomerization caused by benzoic acid or pyridine hydrochloride that were generated during benzoylation.[24] This facilitated higher recovery of **7b**. Screening experiments showed that a balance of selectivity and conversion was required to facilitate isolation. The reaction was allowed to proceed until HPLC analysis indicated a product distribution of about 70% **7b**, 10% **14**, and 12% **15**. Allowing the reaction to further benzoylate **14** was counterproductive because it led to increased overbenzoylation of **7b**, and product tended to oil out during isolation when levels of **15** exceeded 15 A%.

Further process development efforts focused on the selectivity, conversion, and a balanced reaction profile by evaluating several parameters, including the preferred amounts of benzoyl chloride versus benzoic anhydride, solvent, and base. The preferred amount of total benzoylating reagent was 4.4 equiv comprising 2.9 equiv of BzCl and 1.5 equiv of Bz_2O. Performance in a variety of solvents is summarized in Table 2. DMA and NMP as solvents gave the highest conversions to **7b** with high selectivity for the β-anomer. BzCl as sole benzoylation reagent in NMP gave only 56% conversion to **7b** (entry 4). A separate screening confirmed pyridine as the best base with respect to tetra/penta selectivity, overall conversion to **7b**, anomeric selectivity, and processability. The main product obtained with pyridine as solvent was **15**.

With the base established as pyridine, the total amount of benzoylating agent set at ~4.5 equiv, the target selectivity set at <15 A% **15**, and the solvents narrowed to NMP or DMA by previous screenings, final optimizations were performed using design of experiments (DoE) techniques. The factors investigated in a second-order central composite response surface design were amount of BzCl (2.9−3.2 equiv), dilution (7−13 v/w parts solvent), and reaction time (14−24 h). The objective was to maximize **7b** while holding **15** to <15 A%. Results are depicted in the three-dimensional response surface plots for the desired **7b** and **15** byproducts (Figure 3). The parameters that had the greatest influence on selectivity were dilution and equivalents of BzCl. The amount of **7b** reached highest levels when using 8−11 parts solvent and about 3.0−3.1 equiv of BzCl. Levels of **15** increased with increasing amounts of BzCl and decreasing amounts of NMP. The study predicted that use of 10 parts of NMP and about 3.05 equiv of BzCl would achieve the targets for selectivity, conversion, and byproduct distribution. This prediction was confirmed by experiments (Table 2, entry 11). Finally, in a parallel DoE study, DMA as solvent gave slightly better selectivity compared to NMP. However, due to greater industrial hygiene limitations anticipated for DMA, NMP was selected as the solvent for subsequent optimizations and scale up.

The optimized, tandem benzoylating reaction sequence was as follows: benzoyl chloride (3.05 equiv) was added to a suspension of **8b**, NMP and pyridine. After 2 h at 20 °C, benzoic anhydride[25] (1.5 equiv) was added. The reaction was judged complete after ≥14 h at 47 °C to give a mixture containing 5−9 A% of **14**, 8−11 A% of **15**, and 65−70 A% of **7b**. The process proved to be robust with consistent performance during scale up.

The challenge that remained was isolating **7b** from the rather complex reaction mixture. This was alleviated to some extent because the products predominately equilibrated to their β-anomers under the reaction conditions. Extensive studies were performed to find a robust isolation process to overcome the propensity of the product to oil out of solution and to limit the carryover of **15**. Work-up consisted of adding toluene, quenching with water to destroy the excess Bz_2O, separating, and washing. The organic layer was concentrated to about half volume, and then product was crystallized by dilution with *n*-heptane. Seeding was employed to crystallize the first pilot-plant batch but was found to be unnecessary and was not employed in subsequent batches. After drying, **7b** was obtained as a white solid in 41−46% yield corrected for ≥93 wt % purity (≤2% each of **14**, α-tetra-Bz anomer, and **15**) and with quality suitable for downstream chemistry without need for recrystallization. This process, starting with inexpensive **8b**, represents significant improvement in terms of yield, selectivity, and ease of isolation of **7b** compared with previously reported procedures. Overall, the scale up of the selective tetrabenzoylation was successful, and the reaction and isolation processes proved to be robust: a total of 630 kg of **7b** was manufactured in consistent fashion at two separate facilities.

The next step that needed attention was fluorination of **7b** to give the corresponding 4-fluoroglucopyranose **11**. A variety of fluorinating systems, including BAST, SO_2F_2, TEA·HF, pyridine·HF, TBAF, and inorganic fluoride sources CsF and

(23) Tentative structural assignments. Attempts to isolate tri-Bz species for characterization were unsuccessful.

(24) In addition, the steric demands of tetrabenzoylation may override anomeric effects. For acid-catalyzed anomerization, see: (a) Pacsu, E. *Chem. Ber.* **1928**, *61*, 1508. (b) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825. (c) Isbell, H. S.; Frush, H. L. *J. Org. Chem.* **1958**, *23*, 1309. (d) See ref 16a.

(25) Bz_2O can also be charged prior to BzCl, where it is an unreactive bystander until the reaction is heated to 47 °C. Alternatively, Bz_2O can be generated *in situ* from BzCl and water.

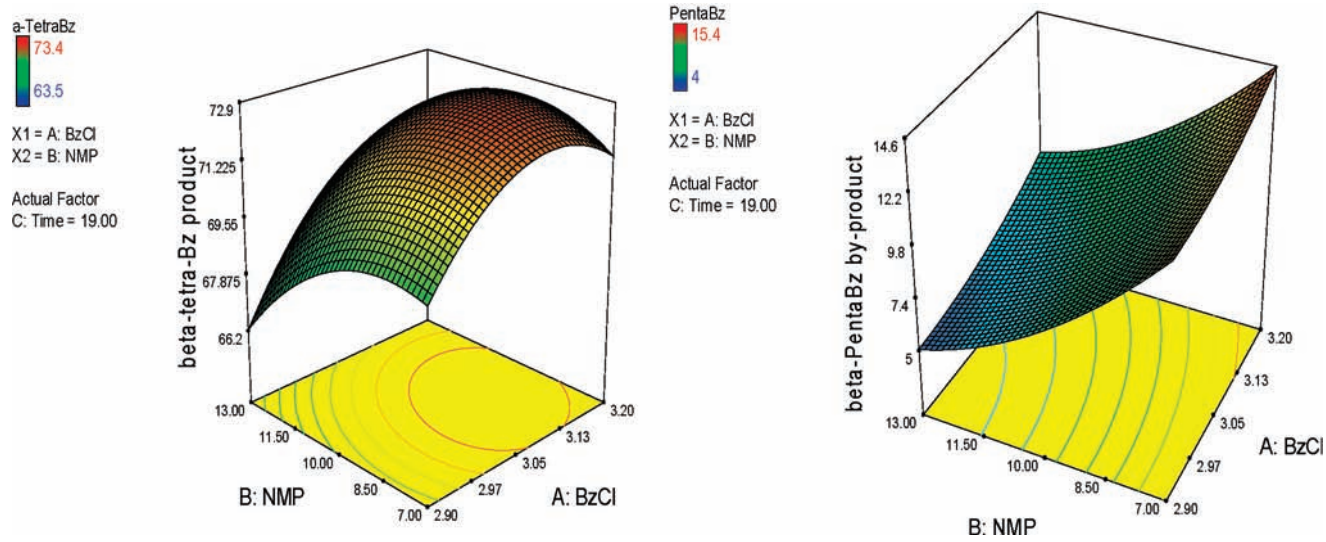
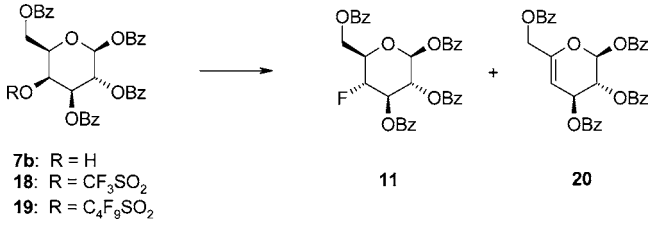


Figure 3. **Effect of amounts of BzCl and NMP on conversion to desired product 7b and byproduct 15.**

Scheme 4. **Fluorination of tetrabenzoylated substrates**



7b: R = H
18: R = CF_3SO_2
19: R = $C_4F_9SO_2$

KF, were evaluated using three related potential substrates (Scheme 4), **7b**, the triflate **18**,[26] and the nonaflate **19**.[27] Analogous to the methyl galactose route, elimination to give the corresponding olefin **20**[28] was a competing side reaction observed in all cases. In some cases, product/olefin ratios were poor, especially for the activated substrates. The best reagent was BAST with substrate **7b** (2-MeTHF, 50 °C) which provided a 85:15 ratio of product/olefin. It was desirable to continue screening fluorinating reagents and conditions in order to replace BAST. However, to achieve short-term API supplies, we chose to continue to optimize the BAST fluorination while further development of alternatives was explored in parallel.

Dioxane as solvent gave the best product/olefin ratio, 87:13. However, because of the lack of significant superiority over other ether solvents and because of process safety (peroxide formation) and industrial hygiene issues, this solvent was not pursued further. 2-MeTHF was selected as the preferred solvent for scale up compared to other solvents screened due to the relatively good product/olefin distribution (85:15) and its suitability for extractive workup. BAST was added at 20 °C, and then the temperature was linearly increased to 55 °C over 2 h. The rationale for this heating profile was to provide a reasonable balance between reaction rate and olefin formation. The fluorination was complete after 3 h at 55 °C. After quenching with water and an extractive workup, the final organic phase was treated with 1-butanol to crystallize **11** as a white solid in 74−78% yield and >98.5 A% purity.[29]

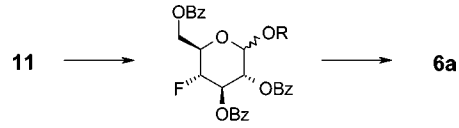
1-BuOH proved to be an ideal antisolvent for the crystallization,[30] providing a high level of robustness in the synthesis because it efficiently solubilized and removed olefin **20** and other impurities that were generated in varying amounts, while still affording a relatively high recovery of **11**. For example, relatively impure substrate **7b** (85 A%) can be tolerated. The underbenzoylated impurities that were carried over in **7b** were mostly retained in the 1-BuOH filtrate after fluorination and isolation, and the overbenzoylated impurities were reduced by ~5 fold to <1 A%, achieving a purity of >98 A%[31] in the isolated **11**. The drawback with using less-pure **7b** was the need to compensate with additional amounts of BAST to complete the fluorination reaction.

With the fluorinated intermediate in hand, the plan was to adapt the selective deacylation procedure previously used for **10** to the new substrate **11** to afford glycosyl donor **6a**. However, selective anomeric debenzoylation was much slower and more challenging compared to the anomeric acetyl group in the former case. Thus, selective anomeric debenzoylation of **11** was studied using organic and inorganic bases, including ethylenediamine/AcOH, methylamine, and KOH. The best conditions (ethylenediamine/AcOH as base, 22 °C, 60 h) afforded only a 63 A% conversion to **6a**, along with 30 A% unreacted **11** and 7 A% overdebenzoylated impurities, indicating that debenzoylation at nonanomeric positions was competitive with anomeric debenzoylation.

Because the direct conversion of **11** to **6a** was inefficient, synthesis alternatives were desired. It was found that **11** can be converted cleanly to either **10** (Ac_2O/AcOH/H_2SO_4, 95% yield)

(26) Prepared by treating **7b** with Tf_2O in DCM in the presence of pyridine.
(27) Prepared by treating **7b** with perfluorobutanesulfonyl fluoride in the presence of DBU.
(28) Olefin **20** was confirmed by comparison to an authentic sample prepared from **18** by treatment with DBU in DCM and was consistent with reported ^{1}H NMR data: Blattner, R.; Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. I* **1980**, 1535.
(29) Fluorination occurred highly selectively with inversion at C-4. None of the 4-epimer was detected in the product or the filtrate compared to an authentic sample of the epimer synthesized independently.
(30) 2-PrOH provided a similar performance, but was not employed in any other step in the synthesis of **1** in the route starting from **8b**. In contrast, 1-BuOH was determined to be essential in a subsequent step in downstream chemistry. Therefore, 1-BuOH was selected as the preferred solvent because it minimized the total number of solvents employed in the overall synthesis and enhanced the opportunity for solvent recovery.
(31) Isolated **11** needed to have a purity ≥98 A% to ensure acceptable quality of downstream products.

Scheme 5. **Indirect conversion of 11 to 6a**



10: R = Ac
20: R = Tf

or **20** (TFA/trifluoroacetic anhydride, cat. TfOH, 97 A% yield), and that these intermediates could be then converted in high yield to **6a** (Scheme 5). Although these variations showed synthetic utility, the improvements in yield were offset by the extra processing steps that were entailed.

Glycosyl donor **6a** was shown to be a reliable synthon for the synthesis of SAR7226 in the first pilot-plant campaigns. Under standard coupling conditions,[32] **6a** was treated with an excess of trichloromethylacetonitrile, and the resulting acetimidate was coupled with pyrazole **2** in the presence of a Lewis acid. A major limitation was waste/environmental concerns due to the formation of trichloroacetamide as a byproduct of the acetimidate coupling. Therefore, in parallel, efforts were made to identify a more suitable alternative glycosyl donor.[10] In the meantime, the coupling of the bromo sugar **6b** by reaction with alkoxides had shown feasibility in the synthesis of a back-up compound, and a decision was made to investigate and develop **6b** for the large-scale synthesis of **1**.

On lab scale, **6b** was prepared by treatment of **11** in DCM with HBr in AcOH.[2] On scale up, AcOH replaced DCM as solvent. The process was optimized for equivalents of HBr, volume of AcOH solvent, and temperature. Quantitative conversion to **6b** was achieved using 4 equiv of HBr in AcOH at 55 °C (to improve solubility of the substrate). Work-up consisted of a water quench followed by partitioning with toluene. The organic phase was given a series of washes to remove AcOH and benzoic acid and then was azeotropically dried by partial concentration under reduced pressure. Two methods of isolation were developed. After partial concentration, **6b** could be isolated in 87−91% yield and >99 A% purity as a white solid by crystallization from toluene/*n*-heptane. For industrial hygiene and yield/efficiency reasons, after partial concentration, **6b** was isolated as a solution in 2-MeTHF/toluene in ≥96% yield (≥96.8 A% purity, exclusively α-anomer). This solution was directly used in the pilot plant in the coupling step as part of a successful campaign that demonstrated the utility of **6b** in the synthesis of **1**. The estimated cost to manufacture **6b** was 80% of the limit target cost for the glycosyl donor needed for the production of SAR7226, about 3-fold lower compared to that for **6a** on a mole-to-mole basis, primarily because its manufacture was more concise and it was prepared from a more economical sugar substrate.

Conclusions

Process development efforts towards two glycosyl donors applicable to the synthesis of SAR7226 were reported. The first glycosyl donor, **6a**, was prepared in four chemical steps in about 32% overall yield. Although this synthesis proved to be scalable and was used to prepare 90 kg of SAR7226 (**1**), the route suffered from CoG issues, primarily due to high material costs for the α-methyl galactose (**8a**) starting material. As a result, a second glycosyl donor, **6b**, was developed starting from the more economical substrate, galactose (**8b**). A key aspect in the synthesis of **6b** was the development of a highly selective tetrabenzoylation of galactose using benzoyl chloride and benzoic anhydride as reagents in tandem. The new synthesis reproduced lab-scale expectations, and no major issues were encountered during scale up. Overall, a total of 157 kg of **6b** was prepared, which was subsequently coupled with **2** to provide **1**. The estimated cost to manufacture **6b** was significantly less than that for **6a** by a factor of 3, and as a result, CoG was no longer deemed a limitation in the manufacture of **1**.

Experimental Section

Methyl 2,3,6-Tri-*O*-benzoyl-α-D-galactopyranoside (7a).[3a,b] Benzoyl chloride (74.4 kg, 529 mol) was added over 2 h to a suspension of **8a** (24.0 kg, 113 mol) in pyridine (160 kg) at 9 ± 3 °C. The mixture was heated at 18 ± 3 °C for 4 h. The reaction was cooled to 10 °C, and water (190 kg) was added over 30 min while allowing the temperature to rise to 21 ± 3 °C. The mixture was stirred for ≥1 h to quench the benzoyl chloride−pyridine complex. Toluene (190 kg) was added, and after 15 min, the phases were separated. The organic layer was washed with 8% aq $NaHCO_3$ (2 × 281 kg), 1 N HCl (2 × 190 kg), and then with water (190 kg) at 25 °C. The toluene phase (249 kg) was partially concentrated (70−170 Torr, jacket temperature <90 °C) by collecting 51 kg distillate. After venting with nitrogen, toluene (33 kg) was added to give a target concentration of approximately 3.5 v/w parts of toluene based on the theoretical yield of product. The batch was adjusted to 70 °C and *n*-heptane (91 kg) was added at 70 ± 3 °C over 34 min. The solution was cooled to 61 °C over 20 min, at which point crystallization was confirmed. The mixture was held at about 61 °C for 20 min and then was cooled to 25 °C over 2 h and held for 1 h. After filtration, washing with a mixture of *n*-heptane (31 kg) and toluene (60 kg), and drying (<100 Torr, 45 °C), **7a** was obtained as a white solid (40.5−43.5 kg, 71−76% yield, ≥ 98.8 A% by HPLC[33]). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.85 (br s, 1H, O*H*), 3.45 (s, 3H, OCH_3), 4.35 (apparent t, J = 6.4 Hz, 1H, *H-5*), 4.41 (m, 1H, *H-4*), 4.58−4.68 (m, 2H, *H-6*), 5.22 (d, J = 3.3 Hz, 1H, *H-1*), 5.69−5.73 (m, 2H, *H*-2 and *H-3*), 7.33−7.56 (m, 9H, Ar-*H*), 7.96−8.05 (m, 6H, Ar-*H*).

Methyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside (9).[2] Bis(2-methoxyethyl)amino sulfur trifluoride (BAST, 54 kg, 244 mol) was added over 47 min from a PFA-lined pressure tank to **7a** (115 kg, 227 mol) in THF (414 kg) in a Hastelloy C276 reactor while maintaining 20 ± 5 °C. The resulting solution was heated and held at 52 °C for 3 h. The mixture was cooled to 10 °C, and water (460 kg) was added (initially slowly) over 50 min while maintaining <25 °C. Toluene (400 kg) was added, and the mixture stirred for 15 min. The organic layer was separated and washed with water

(32) Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343.

(33) Zorbax Eclipse C8, 4.6 mm × 150 mm, 3.5 μ, 220 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: 40/60/0.1 for 2 min, linear ramp over 13 min to 10/90/0.1. Relative retention times: tetrabenzoylated adduct of **8a**, 0.95; **7a**, 1.00.

(180 kg) and 6% aq $NaHCO_3$ (390 kg), followed by water (2 × 180 kg). The toluene solution was partially concentrated (70−170 Torr, jacket temperature <90 °C) by collecting 500 kg of distillate. After releasing the vacuum with nitrogen, the batch was adjusted to 60 °C to ensure dissolution of solids; a sample was taken to confirm solvent composition (≤5 wt % THF relative toluene). The batch was cooled to 45 °C, and *n*-heptane (150 kg) was added over 1 h at 40 ± 5 °C. The batch was cooled to 20 ± 5 °C over 40 min, held at 20 ± 5 °C for 1 h, and then was filtered, washed with *n*-heptane (150 kg), and dried (<100 Torr, 45 °C) to give **9** as a white solid (91.7 kg; 79.4% yield, 97.2 A% by HPLC[34]). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.47 (s, 3H, OC*H*$_3$), 4.33 (m, 1H, *H-5*), 4.60−4.74 (m, 2H, *H-6*), 4.78 (ddd, J = 50.0, 10.0, 10.0 Hz, 1H, *H-4*), 5.17 (apparent t J = 3.5 Hz, 1H, *H-1*), 5.21 (dd, J = 10.1, 3.6 Hz, 1H, *H-2*), 6.12 (ddd, J = 15.5, 9.0, 9.0 Hz, 1H, *H-3*), 7.35−7.60 (m, 9H, Ar-*H*), 7.98−8.11 (m, 6H, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$, δ): −196.52 (dd, J = 50.9, 15.7 Hz).

1-*O*-Acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucose (10).[2] Acetic acid (74.0 kg, 1233 mol) was charged over 10 min to a suspension of **9** (130.0 kg, 255 mol) in acetic anhydride (507 kg, 4966 mol) while maintaining 20 ± 3 °C. Sulfuric acid (96%, 78 kg, 764 mol) was added over 42 min while maintaining <35 °C. The reaction was gradually heated to 50 °C and held for 1 h. The mixture was cooled to 44 °C, diluted with toluene (676 kg), and then cooled to 16 °C. Water (300 kg) was carefully added over 49 min while maintaining <28 °C. The mixture was stirred for 1 h at 20 °C. The organic layer was separated, partitioned with ethyl acetate (210 kg) and water (330 kg), and then stirred for 30 min at 23 °C. The organic layer was separated and washed with 6% aq $NaHCO_3$ (690 kg, then 350 kg) and water (330 kg), then was concentrated (50−150 Torr, jacket temperature <80 °C) to a volume of about 325 L. The vacuum was released using nitrogen. The batch was cooled, and 2-propanol (830 kg) was added over 56 min at 30−40 °C. The suspension was cooled to 20 °C over 30 min, then to 0 °C over 2 h and held for 40 min. After filtering, washing with 2-propanol (210 kg), and drying (<100 Torr, 45 °C), **10** was obtained as a white product (73−80 kg, 53−58% yield, ≥99.2 A% by HPLC[35]) as a ∼9:1 or better mixture of α-/β-anomers.[36] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.20 (s, 3H, C*H*$_3$), 4.40−4.45 (m, 1H, *H-5*), 4.62−4.73 (m, 2H, *H-6*), 4.85 (ddd, J = 50.4, 9.6, 9.3 Hz, 1H, *H-4*), 5.42 (dd, J = 10.5, 3.6 Hz, 1H, *H-2*), 6.09−6.19 (m, 1H, *H-3*), 6.55 (m, 1H, *H-1*), 7.33−7.59 (m, 9H, Ar-*H*), 7.90 (d, 2H, J = 8.4 Hz, Ar-*H*), 8.00 (d, 2H, J = 8.4 Hz, Ar-*H*), 8.07 (d, 2H, J = 8.4 Hz, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$, δ): −196.20 (dd, J = 50.8, 14.1 Hz).

2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-D-glucose (6a).[2] Acetic acid (11.5 kg, 191 mol) was added to a solution of **10** (73.1 kg, 136 mol) in THF (482 kg) at about 0 °C. Ethylenediamine (9.9 kg, 164 mol) was added over 20 min while maintaining 0−6 °C. The mixture was heated to 20 °C over 30 min and then maintained at about 20 °C for 15 h. The reaction was cooled to 0 °C and then diluted with toluene (310 kg). Water (370 kg) was added over 19 min while keeping the temperature <20 °C. The batch was stirred for 20 min at 20 °C, and then the phases were allowed to separate. The organic layer was washed with 1 N hydrochloric acid (180 kg), water (2 × 290 kg), 5% aq $NaHCO_3$ (380 kg), and water (2 × 370 kg) to achieve pH ≤ 7 for the final water wash. The organic layer was partially concentrated (50−150 Torr, jacket temperature <80 °C) by collecting about 325 kg distillate. The batch was cooled, and toluene (950 kg) was added. Residual water and THF were removed by collecting 506 kg of distillate. The resulting solution, containing 0.3 wt % THF (target: ≤0.1 wt %), was diluted with 352 kg of toluene and then partially concentrated by collecting 371 kg of distillate. After venting and cooling to 20 °C, the resulting solution contained ≤0.1 wt % THF, ≤0.05 wt % water (KF), and 67.4 kg of **6a** (theoretical yield,[37] >99.5 A% HPLC[38]), and was used directly in the coupling step. α-Anomer (major): ^{1}H NMR, (500 MHz, DMSO-d_6, δ): 4.48−4.68 (m, 3H, *H-5*, *H-6*), 5.05 (ddd, J = 50.9, 9.7, 9.5 Hz, 1H, *H-4*), 5.20 (m, 1H, *H-2*), 5.49 (apparent q, J = 4.2, 3.6 Hz, 1H, *H-1*), 5.99 (ddd, J = 14.7, 9.7, 9.5 Hz, 1H, *H-3*), 7.45−7.71 (m, 9H, Ar-*H*), 7.54 (m, 1H, O*H*), 7.84−8.08 (m, 6H, Ar-*H*); ^{19}F NMR (282 MHz, DMSO-d_6, δ): −198.75 (dd, J = 50.9, 14.7 Hz). β-Anomer (minor): ^{1}H NMR, (400 MHz, DMSO-d_6, δ): 4.48−4.68 (m, 3H, *H-5*, *H-6*), 5.01 (ddd, J = 50.9, 9.7, 9.5 Hz, 1H, *H-4*), 5.19 (m, 1H, *H-2*), 5.21 (m, 1H, *H-1*), 5.93 (ddd, J = 14.7, 9.2, 8.6 Hz, 1H, *H-3*), 7.45−7.71 (m, 9H, Ar-*H*), 7.52 (m, 1H, *OH*), 7.84−8.08 (m, 6H, Ar-*H*); ^{19}F NMR (376 MHz, DMSO-d_6, δ): −199.50 (dd, J = 50.9, 14.7 Hz).

1,2,3,6-Tetra-*O*-benzoyl-β-D-galactopyranose (7b). Benzoyl chloride (105 kg, 747 mol) was added over a period of 72 min to a suspension of D-galactose (44.0 kg, 244 mol), NMP (458 kg), and pyridine (107.0 kg, 1352 mol) while maintaining a temperature of 18−22 °C.[39] The reaction has held at about 20 °C for 2 h, and then a solution of benzoic anhydride (83.6 kg, 369 mol) in NMP (37 kg) was added over 31 min at 18−22 °C. The suspension (pyridine·HCl had precipitated) was held at 18−22 °C for 1 h, and was then warmed to 47 °C over 0.5 h to give a pale-yellow solution. After 26 h at 47 °C, the reaction was judged complete (<9.0 A% tribenzoylated species remained), and the solution was cooled to 22 °C. The mixture was diluted with toluene (190 kg), and then water (290 kg) was added over 30 min while maintaining <30 °C. The batch was warmed to 47 °C and held for 1 h to hydrolyze the

(34) Zorbax Eclipse C8, 4.6 mm × 150 mm, 3.5 μ, 230 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: 40/60/0.1 for 8 min, linear ramp over 1 min to 30/70/0.1. Relative retention times: **7a**, 0.65; **9**, 1.00.

(35) Zorbax Eclipse C8, 4.6 mm × 150 mm, 3.5 μ, 220 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: linear ramp over 11 min from 40/60/0.1 to 30/70/0.1. Relative retention times: ***β*-10**, 0.94; **10**, 1.00; **9**, 1.12.

(36) The reported NMR data correspond to the α-anomer. Important chemical shifts for the minor β-anomer are: ^{1}H NMR: δ 2.02 (s, 3H, C*H*$_3$), 6.02 (m, 1H, *H*-1); ^{19}F NMR: −199.26 (dd, J = 51.9, 14.1 Hz).

(37) HPLC assay data (wt/wt) from lab-scale batches consistently demonstrated quantitative yield for this process.

(38) Zorbax Eclipse C8, 4.6 × 150 mm, 3.5 μ, 230 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: linear ramp over 20 min from 50/50/0.1 to 15/85/0.1. Retention times: **6a** anomers, 9.5 and 10.6 min; **10**, 13.6 min.

(39) Adding BzCl at lower temperatures did not improve selectivity. Best selectivity was observed with fast addition (≤1 h on pilot-plant scale).

excess benzoic anhydride. After cooling to 20 °C, the phases were separated. The organic phase was washed with 6% aq $NaHCO_3$ (2 × 370 kg), diluted with toluene (150 kg) and washed with water (3 × 350 kg). The toluene phase was separated and azeotropically dried by collecting about 300 kg of distillate (70−150 Torr, jacket temperature <80 °C). After the vacuum was released with nitrogen, the batch was diluted with toluene (277 kg). The solution was heated to 75 °C, and *n*-heptane (97 kg) was added over a period of 25 min at 70−80 °C. The solution was cooled to 50 °C and held for 3 h. Crystallization commenced within 30 min. The suspension was cooled to 10 °C over a period of 5 h, held at 10 °C for 3 h, cooled to −10 °C over ≥2 h, held at −10 °C for 2 h, and then was warmed to 20 °C over 30 min and held for 3 h. After filtering, rinsing with a mixture of toluene (110 kg) and *n*-heptane (36 kg), and drying (<100 Torr, 50 °C), **7b** was obtained as a white solid (59.7−65.6 kg corrected for ∼94 A% HPLC,[40] 41−45% yield). NMR (500 MHz, DMSO-d_6, δ): 4.39 (dd, J = 5.8, 3.4 Hz, 1H, *H-4*), 4.53 (m, 2H, *H-6*), 4.59 (m, 1H, *H-5*), 5.68 (dd, J = 10.6, 3.4 Hz, 1H, *H-3*), 5.91 (dd, J = 10.6, 8.2 Hz, 1H, *H-2*), 5.95 (br d, 1H, O*H*), 6.39 (d, J = 8.2 Hz, 1H, *H-1*), 7.40−7.70 (m, 12H, Ar-*H*), 7.85−8.00 (m, 8H, Ar-*H*).

1,2,3,6-Tetra-*O*-benzoyl-4-deoxy-4-fluoro-β-D-glucose (11). A mixture of **7b** (83 kg, 78 kg corrected for 94 A% purity, 131 mol) and 2-MeTHF (190 kg) in a Hastelloy C276 reactor was heated at 45 °C until dissolution was achieved, and then the solution was cooled to 20 °C. BAST (37.4 kg, 169 mol) was added over a period of ≤60 min while maintaining 15−25 °C. The reaction mixture was heated to 52 °C over 2 h and then held at 52 °C for 2−3 h. The mixture was cooled to 20 °C and then carefully quenched with water (180 kg) over 45 min while maintaining 15−25 °C. The phases were separated. The organic layer was washed for 30 min with 6% aq $NaHCO_3$ (390 kg). The aqueous phase was diluted with 5% aq NaCl (100 kg) prior to separation. The organic phase was diluted with 2-MeTHF (71 kg) and washed with 5% aq NaCl (190 kg). The resulting milky solution was heated to 57 °C. 1-Butanol (440 kg) was added over 2 h to crystallize the product while maintaining 57−60 °C. After cooling to 20 °C over 2 h, further cooling and holding at 5 °C for 1 h, filtering, washing with 1-butanol (2 × 60 kg, 15 °C) and drying (<100 Torr, 50 °C), 58−61 kg of **11** was obtained as a white solid (74−78% yield, >98.5 A% by HPLC[41]). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.30 (dddd, J = 9.5, 4.5, 2.5, 2.5 Hz, 1H, *H-5*), 4.63 (ddd, J = 12.5, 4.3, 1.0 Hz, 1H, *H-6*), 4.75 (ddd, J = 12.5, 2.5, 1.5 Hz, 1H, *H-6′*), 4.93 (ddd, J = 50.1, 9.5, 9.0, 1H, *H-4*), 5.77 (dd, J = 9.5, 8.3 Hz, 1H, *H-2*), 5.98 (ddd, J = 14.1, 9.5, 9.0 Hz, 1H, *H-3*), 6.23 (d, J = 8.3 Hz, 1H, *H-1*), 7.30−7.60 (m, 12H, Ar-*H*), 7.95 (d, J = 7.8 Hz, 2H, Ar-*H*), 8.02 (apparent t, J = 7.8 Hz, 4H, Ar-*H*), 8.05 (d, J = 7.8 Hz, 2H, Ar-*H*); ^{19}F NMR (282 MHz, $CDCl_3$, δ): −199.00 (dd, J = 50.8, 14.1 Hz).

2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranosyl Bromide (6b).[3c] A solution of hydrogen bromide (95 kg of 33 wt % HBr in AcOH, 388 mol, 4.0 equiv) was charged in 22 min to a suspension of **11** (58 kg, 96.9 mol) and AcOH (180 kg) while maintaining 20−30 °C. The mixture was heated to 55 °C over about 1 h and then held at 55 °C for 4 h. The suspension was cooled, and water (410 kg) was added over 60 min while maintaining <20 °C. Toluene (626 kg) was added, the temperature was adjusted to 20 °C, and the phases were separated. The organic layer was washed with water (2 × 300 kg) and 6% aq $NaHCO_3$ (410 kg). The organic layer was washed with water (2 × 300 kg, to pH ≤7) and then concentrated (70−170 Torr, jacket T <80 °C) to a volume of about 260 L. After venting the reactor with nitrogen and cooling to 20 °C, the resulting thick slurry was dissolved in 2-MeTHF (230 kg) to give a solution containing 51.9 kg of **6b** (as determined by wt % HPLC analysis, ≥ 96.8 A% HPLC,[42] 96.1% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.60−4.80 (m, 3H, *H-5*, *H-6*), 4.89 (ddd, J = 50.5, 9.6, 9.0 Hz, 1H, *H-4*), 5.23 (ddd, J = 10.1, 4.2, 0.9 Hz, 1H, *H-2*), 6.21 (ddd, J = 13.5, 10.0, 9.3 Hz, 1H, *H-3*), 6.76 (br dd, J = 3.9, 3.1 Hz, 1H, *H-1*), 7.39−7.64 (m, 9H, Ar-*H*), 7.99−8.11 (m, 6H, Ar-*H*); ^{19}F NMR (376 MHz, $CDCl_3$, δ): −197.00 (dd, J = 50.5, 13.5 Hz).

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(40) Zorbax Eclipse XDB-C8, 4.6 mm × 150 mm, 3.5 μ, 230 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: linear ramp over 5 min from 50/50/0.1 to 45/55/0.1, then linear ramp over 15 min to 10/90/0.1. Relative retention times: **14**, 0.51; **7b**, 1.00; **15**, 1.32.

(41) Zorbax Eclipse XDB-C8, 4.6 mm × 150 mm, 3.5 μ, 230 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: 40/60/0.1 for 1 min, linear ramp over 16 min to 20/80/0.1. Relative retention times: **7b**, 0.73; **11**, 1.00.

(42) Zorbax Eclipse XDB-C8, 4.6 mm × 150 mm, 3.5 μ, 230 nm, 35 °C, water/ACN/TFA, 1 mL/min, gradient program: linear ramp over 16 min from 50/50/0.1 to 20/80/0.1. Relative retention times: **6b**, 1.00; **11**, 1.06.