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A Practical Stereoselective Synthesis and Novel Cocrystallizations of an Amphiphatic SGLT-2 Inhibitor

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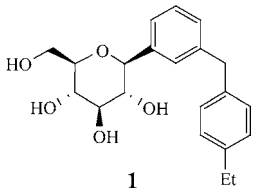
ABSTRACT: A practical synthesis of the SGLT-2 inhibitor *β*-*C*-aryl-D-glucoside (**1**) has been developed. The route employed 2,3,4,6-tetra-*O*-trimethlysilyl-D-glucano-1,5-lactone as the key chiral building block, prepared efficiently from the commercially available, inexpensive raw materials, D-gluconolactone and trimethylsilyl chloride. The salient step in the synthesis is the Lewis acid-mediated stereoselective reduction of a methyl *C*-aryl peracetylated glycoside using a silyl hydride to set the stereochemistry of the crucial anomeric chiral center. Several novel cocrystalline complexes of **1** with L-phenylalanine and L-proline were discovered. Single-crystal structures of these complexes and several synthetic intermediates have been determined. The L-phenylalanine complex was developed and used to purify and isolate the API. All steps were implemented at multikilogram scale.

INTRODUCTION

The synthetic *β*-*C*-arylglucoside (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-ethylbenzyl)-(phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol[1] (**1**) has been identified as a potent and selective *h*SGLT2 inhibitor with potential for the treatment of diabetes.



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To generate material in support of phase I clinical trials, the first-generation Discovery Chemistry synthesis, based on methodology developed by Kishi[2] and Kraus,[3] was used to gain rapid access to compound **1** starting with 2,3,4,5-tetra-*O*-benzyl-D-glucose **2** (Scheme 1).

Lactone (**3**)[4] was prepared from compound **2** via TEMPO/bleach oxidation in >90% yield. On large scale, purification of the syrupy product **3** was not practical; therefore, it was used directly in the next step without purification. The aglycon 3-bromo-(4′-ethyl)-diphenylmethane (**4**) was synthesized using a known two-step process.[5] The lithio-anion derived from **4** was coupled with lactone **3** at −78 °C to obtain lactol **5** as a colorless, neat crystalline compound in 65% yield, >98 A% purity.

The X-ray single-crystal structure[6] of **5** confirmed that a single isomer was obtained, with the hydroxyl in the *α*-configuration.

The key step in this synthesis is the reduction of lactol **5**; typically, this has required sterically hindered silanes[7] in order to obtain high *β*-selectivity. Thus, reduction of **5** using triisopropylsilyl hydride (2 equiv) in the presence of $BF_3{\cdot}Et_2O$ (1.05 equiv) at −40 °C in DCM gave an anomeric mixture of **6a** (*β*-aryl)[6] and **6b** (*α*-aryl) (>20:1 ratio) in ∼63% yield. The *α*-isomer **6b** was purged in a subsequent crystallization. Seeking to further increase the isomer ratio, we screened the reduction of lactol **5** using other, more readily available silanes. This effort was unsuccessful since entities such as water-soluble heptamethylsiloxane, gave good conversion, but poor *β*-selectivity (*α*/*β*, 1:∼4.5). Hydrogenolysis (Pd/C) of the final intermediate **6a** in THF provided **1**. The crude product **1** was isolated as an amorphous foam with typical yield >95−97% and with >94 A% purity.[8] Chromatography was used during early development for further purification. The typical laboratory chromatography yields were >73% and improved 99.3 A%

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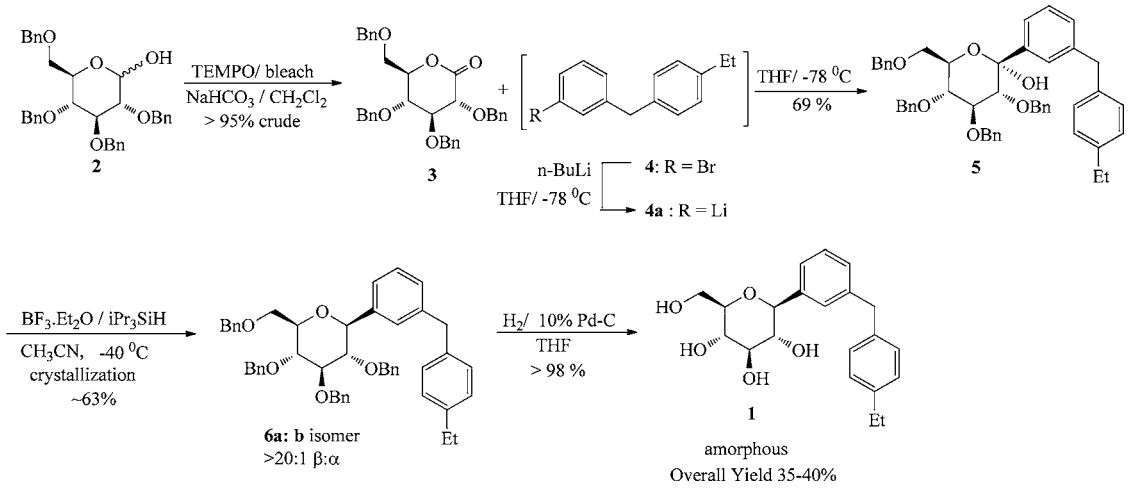
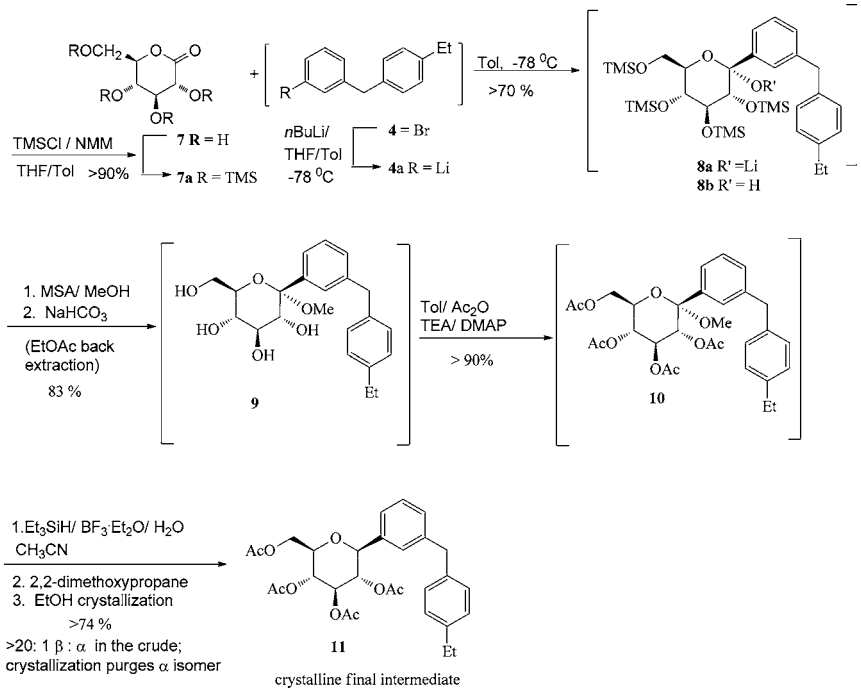
Scheme 1. First-generation synthesis of aryl glucoside 1



Scheme 2. Process R & D synthesis of tetraacetate 11



purity. All of the above steps, except chromatography, were optimized for scale-up in our glass plant (200-L scale).

During our process development of the first-generation synthesis, we identified several disadvantages to using 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **3** as a starting material. For instance, **3** was synthesized from commercially available, but expensive, 2,3,4,6-tetrabenzylglucose **2**. Product **3** was difficult to isolate and purify at multikilogram scale due to its syrupy nature. The crude product also gradually decomposed over several months, thereby limiting its usefulness in a commercial process. The reduction of intermediate lactol **5** required sterically hindered silanes to give favorable *β*-selectivity, and these silanes were expensive and difficult to obtain on commercial scale. More critically, the synthesis of *C*-arylglycosides via 2,3,4,6-tetra-*O*-benzyl gluconolactone **3** required a hydrogenolytic deprotection in the final step of the synthesis. Due to the amorphous nature of **1**, chromatography was required to remove palladium and process impurities. Although this process enabled rapid delivery of supplies to support early toxicology and preclinical studies, the inability to crystallize **1** was of paramount concern.

Despite extensive investigation, a crystalline form of **1** has not been discovered, possibly due to the amphiphatic nature of the molecule. In addition, the amorphous, foamy active pharmaceutical ingredient (API) **1** becomes a tacky or gummy solid on exposure to moisture. A syrupy, noncrystalline, and hygroscopic form presented a formidable challenge to the development team. The lack of sufficient control over the isolation and purification of amorphous **1**, the high cost of goods, and the unfavorable physical characteristics of several intermediates created increased urgency and provided motivation for the development of a new process and a new final form for API **1**.

Recently, we communicated[9] a new methodology for a general stereoselective synthesis of *β*-*C*-arylglucosides in which the benzyl ethers employed in Scheme 1 were replaced by alkyl

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esters. We also demonstrated that Lewis acid-mediated ionic reduction of a peracetylated 1-*C*-arylmethyl-glucoside proceeded with a high degree of selectivity to give *β*-*C*-arylglucosides, despite initial concerns that a 2-acyl group might disfavor the desired stereoselective reduction via intramolecular stabilization of the oxocarbenium ion. In this publication, we provide an application of the development of this new approach to synthesize the *β*-*C*-arylglucoside drug candidate **1** in multikilogram quantities. Furthermore, unique cocrystallizations of API **1** with amino acids as hydrogen-bonded complexes permitted efficient isolation and purification.

RESULTS AND DISCUSSION

While some derivatives of glucose (such as **2**) can be expensive and, as such, not realistic starting materials, we realized the advantages of employing materials from the naturally occurring chiral pool which eliminated the need to control four of the five stereocenters of compound **1**. This suggested we retain the core of **2** or **3** as a starting material and explore protecting-group modifications to circumvent the adverse physical characteristics of the intermediates in the original synthesis. In this manner, proper protecting-group selection could offer cost advantages and improvements to the physical form of certain intermediates for ease of isolation. A final desired change would be the discovery of a simple deprotection method to avoid the use of hydrogenolysis which was required in the first-generation synthesis.

A key need was to identify a means to purify compound **1** as a crystalline API instead of resorting to chromatography. We discovered that peracetylation of **1** yielded the corresponding tetraacetate **11** (see Scheme 2) as a stable and pure crystalline solid that was easy to crystallize and purify. The subsequent deprotection of this material to **1** was facile, and the resulting API purity was very high (>99.9 A%). We recognized the desirable traits of this crystalline derivative for the endgame of our new process. However, there was a concern that acetates would not be compatible with the organometallic chemistry used to generate aglycon **3**. As an alternative, we employed the transient protection of gluconolactone as the per-trimethylsilyl derivative[9] as the trimethylsilyl groups would resist lithioaromatics at low temperature but could also be cleaved during the workup under mildly acidic conditions. Starting with D-gluconolactone **7**, silyl protection was achieved using TMSCl/*N*-methyl morpholine in THF to give **7a**. The workup of this intermediate required a carefully controlled process as its oily nature and sensitivity to moisture precluded easy isolation. Therefore, the reaction mixture was diluted with toluene prior to aqueous washes, and the persilylated lactone **7a** was obtained as a solution. The selection of toluene as solvent was critical as it efficiently extracted the product and enabled azeotropic drying that was needed in the following step.

Aglycon **4** was transmetalated with *n*-BuLi to form the lithiated species **4a** which was reacted at −78 °C with the solution of **7a** prepared above to give lactol **8**. In this transformation, the toluene/THF solvent combination (3.5:1) proved ideal for yield and product purity; in THF solvent, a competing silyl transfer reaction dominates, forming trimethylsilyl-aglycon as a major byproduct.[10]

Lactol **8b** was noncrystalline and problematic to isolate; therefore, the THF/toluene solution of **8b** was quenched into methanol/methanesulfonic acid. This acidic quench served to: (1) neutralize any excess organometallic species, (2) promote in situ trans-ketalization with methanol, and (3) expedite concomitant removal of the TMS protecting groups to produce a crude solution of methyl glycoside **9**. The intermediate **9** was an amorphous, foamy solid. Extensive investigation failed to produce a crystalline form of **9**. Thus, after an aqueous workup, the solution was dried via toluene azeotrope and used into the following step. The toluene solution of **9** was prepared in 83% assay yield and 87 A% purity.

On the basis of our previous investigations, acetate groups were chosen to protect the hydroxyls in **9** as the reduction would provide advantageous crystalline peracetylated **1** (**11**). The toluene solution of **9** was fully acetylated by Ac_2O/TEA and catalyzed by DMAP to generate the tetraacetate **10**. The remaining Ac_2O was quenched by aqueous phosphoric acid and an aqueous wash. After phase separation, the toluene solution was partially concentrated. The dry toluene solution was ready for the key transformation: reduction.

We screened a variety of anomeric reduction conditions, focusing on the original acid-catalyzed silyl hydride process. We investigated both Lewis and Brønsted acids as potential alternatives to $BF_3{\cdot}Et_2O$ along with triethylsilyl hydride as an alternative to the triisopropyl derivative (Table 1). While

Table 1. Study of the reduction of methyl glucoside 10

entry	catalyst[a]	equiv	H_2O (equiv)	conv[b]
	Lewis acid			
1	$BF_3{\cdot}Et_2O$	4	1.2	>99
2	$BF_3{\cdot}Et_2O$	3	1	>99
2	$BF_3{\cdot}Et_2O$	3	<0.1	<20
3	$BF_3{\cdot}Et_2O$	3	1.4	58
4	$BF_3{\cdot}Et_2O$	3	1.75	31
5	$BF_3(H_2O)_2/BF_3$	0.5/3.5	1.2	98.4
4	$ZrCl_4$	3.5	0.15	84
5	$HBF_4{\cdot}Et_2O$	4.0	0.2	>99
6	BF_3.THF	4	1.0	0
7	$ZnCl_2$	2.5	1.2	0
	Brønsted Acid			
8	CF_3SO_3H	2.5	0.15	>99
9	CH_3SO_3H	4.0	2.0	0
10	$CF_3SO_3Si(CH_3)_3$	2.5	0.2	93.4
11	$CF_3SO_3Si(CH_3)_3$	2.5	1.2	>99

[a][**7a**]: 0.04 M, Et_3SiH: 4 equiv, 10 °C, order of addition: Lewis acid + Et_3SiH, then substrate after 40 min. [b]Conversion of *β* to *α* after 110 min determined by HPLC analysis. Typical *β* to *α* ratio was observed >20:1 for all substrates.

several alternative catalysts gave encouraging results, we decided to retain $BF_3{\cdot}Et_2O$ for a combination of cost, product purity and process robustness. The less expensive and more readily available triethylsilyl hydride (Et_3SiH) replaced triisopropylsilyl hydride (iPr_3SiH) since the resulting isomer ratio was similar.

The optimized process starts with dilution of the toluene solution of **10** with acetonitrile followed by reduction with Et_3SiH, $BF_3{\cdot}Et_2O$, and one equivalent of water. Water is critical for the reaction to progress to completion, water and $BF_3{\cdot}OEt_2$ generate a strong Brønsted acid, such as $H^+BF_3OH^-$, which accelerates[11] the formation of an oxa-carbenium ion intermediate. These strongly acidic conditions are essential to compensate for the deactivating effect of the carbohydrate acetoxy-substituents. On the basis of the literature[12] and studies conducted,[9a] we believe that predominant axial hydride attack from the *α*-face on the oxacarbenium ion intermediate provides

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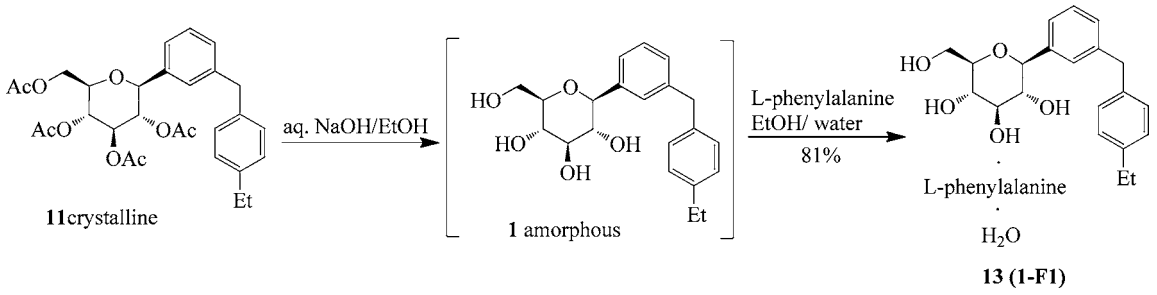
Scheme 3. Synthesis of complex 13



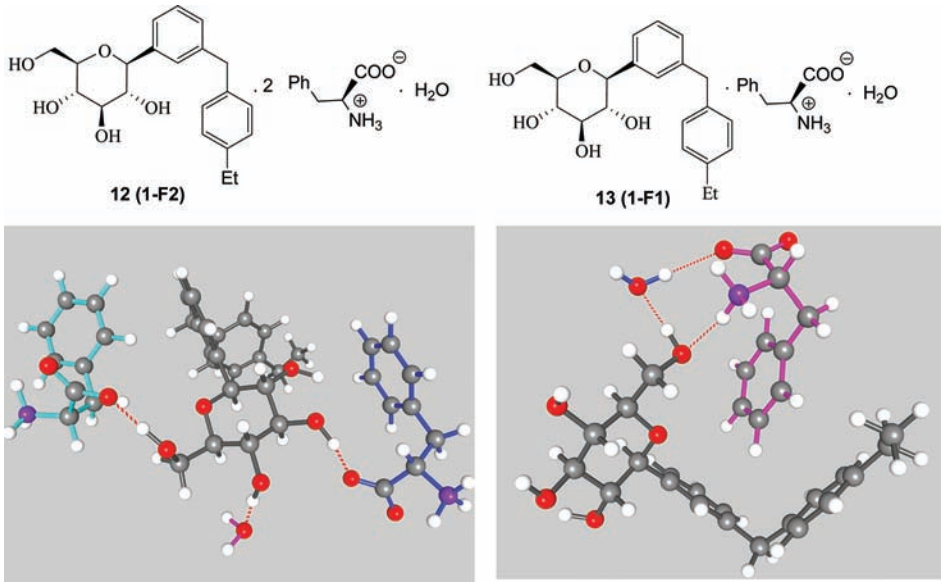


Figure 1. X-ray structure of complexes **12** (**1**-F2) and **13** (**1**-F1).

equatorially substituted β-*C*-arylglucoside **11**[6] as the major product (>20:1 β:α).

The use of Et_3SiH presented safety considerations on multikilogram scale that required attention. Unreacted silyl hydride generated hydrogen gas in spent reaction streams and rendered waste hazardous to store and transport. To mitigate this risk, 2,2-dimethoxypropane was charged to the mature reaction mixture to quench the excess Et_3SiH. After complete disappearance of triethylsilyl hydride was shown by GC analysis, aqueous workup and crystallization of the product from ethanol produced a 74% yield of the final intermediate **11** (98.6 HPLC A% purity). Saponification of tetraacetate **11** (aq NaOH/EtOH) produced API **1** as an amorphous compound (Scheme 3).

To solve the isolation and final crystal form issues of the amorphous, amphiphatic drug substance **1**, we focused on a cocrystallization approach.[13] Although in principle, virtually any pair of molecules may cocrystallize,[14] we reasoned that another amphiphatic cocrystallization component might favorably pack and interact with both the polar hydroxyls and the hydrophobic hydrocarbon regions of **1**, thus enhancing the probability of cocrystallization. We identified several natural amino acids as possible partners for cocrystallization with **1** but concentrated on L-phenylalanine which has a polar and hydrophobic nature similar to that of the drug molecule. These efforts provided two crystal forms (complexes): **12** = form **1**-F2 (composition: 1 mol of **1** + 2 mol of L-phenylalanine +1 mol of water), and **13** = **1**-F1 (composition: 1 mol of **1** + 1 mol of L-phenylalanine +1 mol of water) (see Figure 1). Both forms were fine needles and relatively stable at room temperature (22−25 °C), but when suspended in water, the (**1**-F2) complex **12** dissolved and crystallized as the (**1**-F1) complex **13**. The structures of these hydrogen-bonded complexes could only be solved from synchrotron X-ray diffraction data of the very fine, hair-like crystals.[6] Our studies showed that the 1:1 complex is more stable than the 1:2 complex in water and water-rich environment (e.g., EtOH/H_2O = 17/83). When 1:2 complex was slurried in water it converted to 1:1 complex within hours; similarly, 50/50 mixture of 1:1 complex and 1:2 complexes that were slurried in water (40 °C) for overnight converted to pure 1:1 complex. Crystals of 1:2 complex appear to be long and thin rods, melt at 140−145 °C and lose ~2.5% weight at 100 °C when observed by DSC. This weight loss corresponds to the loss of 1 mol equiv of H_2O. Crystals of the 1:1 complex appear to be fine, hair-like materials or short needles/rods, melt at 100−105 °C, and lose ~3.3% weight at 125 °C. In addition, the **1**-F1 complex provided a significant weight advantage over the **1**-F2 complex. On the basis of these observations form **1**-F1 (**13**) was chosen as the final form for further development.

In addition to L-phenylalanine, several stable crystalline complexes of **1** with D-phenylalanine and L-proline were prepared and their stuctures[6] determined by single-crystal X-ray analysis. The power of such foreign agents as cocrystallization partners in assembling crystal structures of pharmaceutical products—which alone crystallize with difficulty, if at all—has been increasingly recognized in recent years.[15]

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As there was a defined form and a route to a pure API, the development of the multikilogram synthesis only remained. In contrast to the hydrogenation required to cleave the benzyl protecting groups of the final intermediate in the first-generation synthesis (Scheme 1), the final step now required only aqueous base to remove the acetates. The saponification is rapid and irreversible and can be performed under a wide range of reagent concentrations and temperature conditions.

From all our experimental data we have observed that the stereochemical integrity of the product in the final step was very effectively preserved. Essentially no process changes were required to scale up the final intermediate **11** to 64 kg scale. Deacetylation using EtOH/aq NaOH (Scheme 3) followed by neutralization with aq HCl to pH 7 generated a solution of free compound **1** which was converted to the L-phenylalanine complex **13** (**1**-F1) and crystallized as a monohydrate. After filtration and drying, **13** (**1**-F1) was produced with 99.9 A% purity and 80−88% yield (58 kg). This material has been used for clinical investigations.

■ CONCLUSIONS

We have demonstrated a robust and practical synthesis of drug substance **1** on manufacturing scale. The salient features of the synthesis are (a) the replacement of the conventional benzyl protecting group of the chiral sugar synthon by a combination of transitory silyl protection followed by ester protection, (b) demonstration on multikilo scale of the feasibility of ester protection and stereoselective ionic reduction using a less hindered triethylsilyl hydride (Et_3SiH) for the reduction of methyl glycoside **10** to obtain *β*-*C*-arylglucoside **11**, (c) the use of peracetylated *β*-*C*-arylglucoside **11** to control quality for the overall synthesis as it was highly crystalline with good impurity-purging capability, (d) replacement of the hydrogenation operation by a mild ester hydrolysis in the final chemical step, and (e) demonstration of an unusual means for purification via cocrystallization with L-phenylalanine. Problems with oily intermediates were circumvented by conducting the entire synthesis in two telescoped processes. Anti-diabetic activity and other structure−activity relationship data of the SGLT-2 inhibitor **1** will be reported in due course.

■ EXPERIMENTAL SECTION

All new compounds described in the Experimental Section were fully characterized. The experimental outlined below provides representative procedures for what was run in the kilo/pilot-plant facilities. ^1H NMR spectra were obtained at 400 MHz, ^{13}C NMR spectra were obtained at 100 MHz at room temperature (22−25 °C) in $CDCl_3$ or CD_3OD, except as indicated. Chemical shifts are reported in ppm downfield from an internal tetramethylsilane standard or relative to residual solvent signal. Mass spectroscopy was performed using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer. HPLC analysis results are described as area percent (A%). HPLC analysis was performed with a YMC Pack FL-ODS 4.6 mm × 50 mm, 5 μm; The solvent A was 0.2% H_3PO_4 solution, and solvent B was 0.2% acetonitrile; start 100% A and 0% B flow 4 mL/min, Inj Vol 10 μL, UV absorption 210 nm, runtime 20 min 70% acetonitrile containing 0.1% TFA. Also used was YMC S3 ODS-A 44.6 mm × 50 mm at room temperature (22−25 °C); the solvent A was 0.2% H_3PO_4 solution, and solvent B was 90% acetonitrile and 10% water; start 95% A and 5% B to 100% B; flow 2.5 mL/min, Inj Vol 5 μL, UV absorption 220 nm, runtime 10 min. Moisture determinations were performed with a Karl Fisher titrator. For persilylated TMS lactone (**7a**), the gas chromatographic analyses were performed using HP 5890 with FID (He carrier) with a Restek Corp. column: Rtx-5 lot # 7992B, 30 m × 0.32 mm I.D. Initial temperature 200 °C, final temperature 260 °C, rate 5 °C/min, injection volume 1 μL, total run time 15 min. For triethylsilyl hydride, gas chromatographic analysis was performed using instrument HP GC5890 II with FID or equivalent, column: Rtx-5, 30 m × 32 mm I.D., 0.25 μm film thickness; Initial temp. 40 °C, hold for 1 min, rate 1:5 °C/min, final temp. 60 °C, no hold, rate 2:50 °C/min, final temp.: 200 °C, hold for 0.2 min, run time 8 min. Injection port temperature 260 °C, detector temperature 280 °C with He gas carrier. This GC method determines the residual triethylsilyl hydride (TESH) at low ppm level. An external standard calibration was used for quantitation of triethylsilyl hydride in process samples. Detection limit for this GC method is 0.2 ppm triethylsilyl hydride. Initial development scale-up of first-generation reactions (Scheme 1) were conducted in kilo lab with 100- or 200-L size reactors, and new synthesis (Scheme 2) was demonstrated at the pilot plant in typical 2000-L reactors. Purified (deionized) water was used for all plant operations.

2,3,4,6-Tetra-*O*-(phenylmethyl)-1-*C*-[3-[(4-ethylphenyl)methyl]phenyl]glucopyranose (5). A reactor was purged with argon gas and charged sequentially with bromide **4** (4.5 kg), TMEDA (7.1 L), and anhydrous THF (40.5 L). The solution was cooled to −70 to −75 °C, and *n*-BuLi (6.5 L, 2.5 M in hexane) was added while maintaining temperature at −65 to −70 °C range. The orange-red solution became yellow at the end of the addition of *n*-BuLi. HPLC after stirring for 30 min at −70 °C showed disappearance of bromide **4**. A second reactor with a solution of lactone **3** (7.5 kg) in THF (12.5 L) was prepared under argon gas. This solution was transferred in five equal portions to the organometallic solution prepared above at ≤−65 °C. After addition of each portion of the lactone solution over 10 min while maintaining temperature ≤−65 °C, the batch was agitated for 3 min. After the fourth charge, the batch was analyzed for lactone content by HPLC. If the lactone content was >5%, the further charge of the fifth portion of lactone solution was not performed. Otherwise, after charging the fifth portion of lactone solution the batch was agitated further for 30 min at −70 to −75 °C or until the lactone **3** was <5% by HPLC. The cooling was stopped, and a solution of 10% citric acid in water (59.3 L) was added. The temperature of the mixture was allowed warm up to 18 °C over 3−5 h. MTBE (20.2 L) was added, and the mixture was agitated for 10 min. The layers were separated, and the aqueous layer was extracted with MTBE (20.2 L). The organic layers were combined and washed with aqueous saturated $NaHCO_3$ solution (20.2 L) and then with brine (20.2 L). The organic layer was evaporated to give 11.125 kg of oil. The product was dissolved in MeOH (44.5 L), the clear solution was agitated, and water (8.9 L) was added to produce an oily suspension. The temperature of the mixture was kept above 27 °C during this process. Heptanes (133.5 L) was added, and the mixture was stirred for 10 min. The turbid heptanes layer was separated, and the MeOH/water layer was extracted with heptanes (2 × 66.7 L). The heptanes layers were passed through a Celite filter and then concentrated under vacuum to ∼60 L volume. Some oil separated during concentration. The mixture was warmed to 65 °C to dissolve some separated oil and then cooled to 40 °C

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and seeded with **5** (~1%). After the start of crystallization, the batch was cooled to 20 °C and held for 12 h. The mixture was further cooled to 0−5 °C, and then the solids were collected by filtration or by centrifuge. The cake was washed with 0 °C heptanes (3 × 4.5 L) and dried under vacuum at 30 °C to a constant weight to give 7.12 kg (59.4%, >99.00 A%) of compound **5**: Anal. Calcd for $C_{49}H_{50}O_6$: C, 81.86; H, 7.01. Fd. C, 81.66; H, 6.88. HRMS: Calcd for M + H = 717.3580 Da, Measured 717.3590 Da. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.5 Hz), 1.62 (s, 1H), 2.59 (q, 2H, J = 7.5 Hz), 3.56 (d, 1H, J = 9.2 Hz), 3.72−3.75 (dd, 1H, J = 1.8 and 9.2 Hz), 3.81−3.88 (m, 3H), 3.95 (s, 2H), 4.08 (t, 1H, J = 9.2 Hz), 4.16−4.20 (m, 1H), 4.37 (d, 1H, J = 10.5 Hz), 4.55 (d, 1H, J = 12 Hz), 4.65 (d, 1H, J = 6.2 Hz), 4.68 (d, 1H, J = 3.5 Hz), 4.87−4.93 (m, 3H), 6.96 (d, 2H, J = 7.5 Hz), 7.19 (d, 2H, J = 7.5 Hz), 7.21−7.52 (m, 24H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.54, 28.37, 41.60, 68.91, 72.16, 73.33, 75.02, 75.41, 75.67, 77.20, 78.33, 83.44, 85.17, 97.92, 123.92, 126.72, 127.45, 127.55, 127.63, 127.69, 127.93, 128.13, 128.25, 128.29, 128.36, 128.72, 129.14, 137.45, 138.12, 138.26, 138.50, 138.66, 141.28, 141.91, 142.41.

2,3,4,6-Tetra-*O*-(phenylmethyl)-1,5-anhydro-1-C-[3-[(4-ethylphenyl)methyl]phenyl]glucopyranose (6a). To a solution of glucopyranose **5** (1.22 kg) in CH_3CN (21.89 L) at −25 °C was added triisopropylsilane (0.93 L), followed by $BF_3{\cdot}Et_2O$ (0.28 L) at such rate that temperature does not exceed ≤−20 °C. (**Caution:** The reaction is exothermic.) After stirring for 2.5 h at −25 °C, HPLC analysis indicated **5** was ≤0.6 HPLC A%. A saturated aqueous solution of $NaHCO_3$ (9.73 L) was added over 10 min. (**Caution:** Slight foaming due to the evolution of H_2 and CO_2.) The temperature of the mixture increased to −5 °C. MTBE (12.16 L) was added, and the agitation was continued for 10 min at 5 °C. Water (4.86 L) was added to dissolve the precipitated solid, and the layers were separated. The organic layer was washed with aqueous saturated $NaHCO_3$ (9.73 L), and this aqueous wash was extracted with MTBE (4.86 L). The combined organic extracts were washed with brine (9.73 L). The organic layer was evaporated under vacuum to give 1.34 kg of product **6** as mixture of isomers (β:α ~20:1) as an oil. The material was dissolved in MeOH (6.69 L) at room temperature (22−25 °C), and seeds of **6a** (~1%) were added. The suspension was stirred for 2 h at room temperature (22−25 °C) and for 1 h at 0 °C. The crystals were filtered, washed with MeOH (2 × 0.97 L) at room temperature (22−25 °C), and dried under vacuum at 30 °C to a constant weight to give 0.83 kg of product **6a**. The compound was redissolved in heptanes (8.3 L) at 60 °C. The turbid solution was polish filtered at 60 °C, and the filter was washed with heptanes (0.83 L). The filtrate was cooled slowly to 38 °C, and seeds of compound **6a** were added. Crystallization started at 35 °C. The mixture was stirred at room temperature (22−25 °C) for 12 h and then was cooled to 0 °C. After 2 h the crystals were filtered and washed with cold heptanes (2 × 0.83 L). The cake was dried under vacuum to constant weight to yield 0.76 kg (63%, 98.0 A%) of compound **6a**: Anal. Calcd for $C_{49}H_{50}O_5$: C, 80.08; H, 6.85. Fd. C, 79.89; H, 6.61. HRMS: Calcd for M − H_2O + H = 719.3737 Da, Measured 719.3729 Da. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 7.5 Hz), 2.57−2.63 (q, 2H, J = 7.5 Hz), 3.53 (t, 1H, J = 4.4 Hz), 3.57−3.62 (m, 1H), 3.74−3.83 (m, 5H), 3.90 (s, 2H), 4.23 (d, 1H, J = 9.3 Hz), 4.35 (d, 1H, J = 10.2 Hz), 4.57 (d, 1H, J = 12.3 Hz), 4.64−4.68 (dd, 2H, J = 2.6 and 10.9 Hz), 4.87−4.97 (m, 3H), 6.89 (d, 2H, J = 7.4 Hz), 7.17−7.37 (m, 26H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.54, 28.37, 41.48, 69.05, 73.43, 74.86, 75.10, 75.63, 76.84, 78.31, 79.38, 81.76, 84.4, 86.64, 125.33, 127.49, 127.55, 127.59, 127.69, 127.91, 127.99, 128.15, 128.19, 128.31, 128.40, 128.50, 128.76, 128.88, 137.69, 138.16, 138.20, 138.36, 138.70, 138.31, 141.37, 141.89.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-Ethylbenzyl)-(phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol (1). *Hydogenolysis of **6a**.* A hydrogenation vessel was charged with peroxide-free THF (200 mL) and purged with N_2 gas for 20 min. The catalyst 10% Pd/C (4.0 g, 50% wet with water, Heraeus-type K-02105) and compound **6a** (20.0 g) were added, and the mixture was purged with N_2 gas for 10 min. Hydrogen gas was sparged through the mixture at 20−25 °C (cooling required) until the H_2 uptake ceased. After 4 h completion of reduction was confirmed by HPLC (IPC: **6a** should be ≤0.1 HPLC A%). The mixture was sparged with N_2 for 10 min and then stirred with charcoal (6.0 g) for 18 h to remove color. The mixture was filtered over a pad of filter aid (1.0 g), and the filter was washed with THF (40 mL). The filtrate was evaporated in vacuum to give 10.3 g (103%, >97 A %) of crude compound **1** as a colorless foam . The product was slightly hygroscopic and therefore was stored under a N_2 atmosphere: HRMS Calcd for $C_{21}H_{27}O_5$: M + H = 359.1859 Da, Measured = 359.1863 Da. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, 3H, J = 7.4 Hz), 2.51−2.56 (q, 2H, J = 7.4 Hz), 3.11−3.29 (m, 4H), 3.30 (s, 1H), 3.33 (br s, 6H), 3.40−3.45 (m, 1H), 3.66−3.70 (m, 1H), 3.87 (s, 2H), 3.95 (d, 1H, J = 9.3 Hz), 7.07−7.22 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.58, 28.35, 41.32, 61.87, 70.02, 74.68, 77.2, 77.97, 79.44, 81.82, 125.07, 127.93, 128.58, 128.82, 129.0, 137.88, 138.40, 141.53, 141.97.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-Ethylbenzyl)-(phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol:2 L-Phenylalanine:H_2O Complex (12). A slurry of *C*-arylglucoside **1** (5.10 g) in EtOH (30.0 mL), water (32.0 mL) and L-phenylalanine (4.2 g) was heated at 80 °C to obtain a clear solution and then cooled to 20 °C over 2 h. The complex starts to crystallize ~40−45 °C. The temperature was held at 20 °C for 6 h. The crystals were filtered and washed with 0 °C water (20 mL) followed by MTBE (20 mL). The product was dried under vacuum at 40 °C to constant weight to give 7.1 g (70.5%, 99 A%) of the complex **12**: Anal. Calcd for $C_{39}H_{50}N_2O_{10}$: C, 66.27; H, 7.13; N, 3.96. Fd. C, 66.22; H, 7.15; N, 3.93. ^{1}H NMR (400 MHz, CD_3OD/D_2O) δ 1.16 (t, 3H, J = 7.6 Hz, CH_3), 2.56 (q, 4H, J = 7.5 Hz, CH_2), 3.06 (dd, 1H, J = 8.5 Hz, J = 14.4 Hz, PhAl-CH_2), 3.30 (m, 1H, PhAl-CH_2), 3.46 (m, 3H, H-2, H-3, H-4), 3.53 (q, 1H, J = 8.8 Hz, H-5), 3.69 (dd, 1H, 11.8 Hz, 5.6 Hz, H-6a), 3.85 (m, 2H, H-6b, PhAl-HCOOH), 3.92 (s, 2H, Ph-CH_2-Ph), 4.15 (d, 1H, 9.4 Hz, H-1), 4.71 (MeOH), 5.0 (1H, HOH), 7.10 (m, 4H, Ar-H), 7.3 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, CD_3OD/D_2O) δ 16.37, 29.34, 37.93, 42.27, 57.48, 62.77, 71.60, 75.98, 79.31, 81.81, 83.50, 126.75, 128.65, 129.01, 129.59, 129.92, 130.16, 130.54, 136.84, 139.82, 140.26, 143.09, 143.39, 174.29.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-Ethylbenzyl)-(phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol:L-Phenylalanine Complex (13). A slurry of *C*-arylglucoside **1** (10.0 g) in EtOH (14.0 mL) was heated to 60 °C to obtain a clear solution. This solution was added to a suspension of L-phenylalanine (4.6 g) in water (180 mL). EtOH (3.6 mL) was used as a rinse to transfer the residual solution of compound **1**. The mixture was heated to 83 °C and then cooled slowly to 52 − 54 °C over 10 to 15 min and seeds (~1%) of complex **13**

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were added. (**Note:** The seeding process was repeated at this temperature if the original seed crystals had dissolved). The mixture was cooled to 40−42 °C and stirred for 4 h. The temperature was lowered to 22−25 °C over 2−4 h, and stirring was continued for 2 h. Finally, the mixture was cooled to 18 °C and stirred for 2 h. The crystals were filtered and washed with ice-cold water (25 mL) and MTBE (2 × 5 mL). The product was dried under vacuum at 40 °C to constant weight to give 12.0 g (82%, 99 A%) of the complex **13**. (Full characterization data for **13** is given at the end of final process.)

a). 2,3,4,6-Tetra-*O*-acetyl-*β*-*D*-glucopyranosyl-1-C-(4′-ethyldiphenyl-methane-3-yl) (11). *Synthesis of 7a.* D-Glucono-1,5-lactone (**7**) (35 kg) and THF (344.8 kg) was treated with 4-methylmorpholine (146.5 kg, ∼8 equiv), and the slurry was cooled to 5 °C. Trimethylsilylchloride (110.9 kg, 6 equiv) was introduced, the slurry was stirred for 15 min and then warmed to 30−35 °C over 0.5 h. After 5 h the reaction was complete by GC analysis. The reaction mixture was cooled to 0−5 °C. Toluene (454.1 kg) was charged and then the reaction was quenched with water (700 kg). The mixture was stirred for 10−15 min, and then the phases were separated. The bottom aqueous layer was removed, and a solution of NaH_2PO_4 (13.0 kg) in water (260 kg) was added. The mixture was agitated for 10 min, and then the phases were separated. The bottom aqueous layer was removed, and water (273 kg) was charged. The mixture was agitated for 10 min, and the aqueous layer was separated. The organic solution was distilled at 40−60 °C under reduced pressure (23−25 in. Hg), while adding toluene until the solution was <0.05% water by KF analysis. The concentration of the silylated product solution was adjusted to ∼0.1 g/mL by adding anhydrous toluene or distillation, as necessary. The solution yield of 2,3,4,6-tetra-*O*-trimethylsilyl-D-gluconolactone (**7a**)[9,10] ranged from 91 to 98%, which is measured by a GC assay based on the standard GC curve of the product or by weighing after removal of the solvent.

Conversion of 7a to 11. 5-Bromo-4′ethyldiphenylmethane (**4**) (44.8 kg), anhydrous THF (78.8 kg) and toluene (281 kg) at < −70 °C was treated with *n*-BuLi (48.9 kg, 2.5 M in hexanes) at < −70 °C. The mixture was stirred until the lithiation was complete by HPLC analysis (when compound **4** is ≤1% relative to the hydrocarbon). This lithiated anion solution derived was added to the cooled 2,3,4,6-tetra-*O*-trimethylsilyl-D-gluconolactone solution prepared above at ← 70 °C. The mixture was agitated at ←70 °C for one to two hours.. A solution of CH_3SO_3H (22.2 kg, 1.4 equiv) in 334 kg MeOH was charged while maintaining the temperature of the reaction mixture ←60 °C. After completion of the methyl glycosidation reaction (by HPLC) an aqueous sodium bicarbonate solution (11 kg of $NaHCO_3$ in 220 kg water) was added. The organic layer was washed with water (220 kg), and the aqueous phase was removed. The combined aqueous layers were extracted with ethyl acetate (223 kg). The organic layers were combined, and the solvent was distilled at 35−60 °C under reduced pressure (∼25 in. Hg) until the KF of the solution was <0.07% and the amount of EtOAc was <1% relative to toluene by GC analysis. The solution yield of the product from the coupling ranged from 72 to 89%.

DMAP (0.11 kg), diisopropylethyl amine (64.33 kg) and acetic anhydride (45.56 kg) were charged to the solution of methylglucoside **9** above. The solution was stirred at ≤35 °C until the combined area percent of the intermediate acetylated species was ≤2% of the area of the tetra-acetylated product **10**. Typical reaction times were 4−7 h. A solution of H_3PO_4 (48.44 kg) in water (528 kg) was charged. If necessary, additional H_3PO_4 was added until at pH ≤3. The mixture was stirred for 10 min and then the bottom aqueous phase was separated. The organic phase was washed by water (245.54 kg). The organic solution containing the acetylated product **10** was concentrated at atmospheric pressure to a volume of 4−6 L/kg of methyl-1-C-(4′-ethyldiphenylmethane-3-yl)-*α*-D-glucopyranoside (**9**), this solution was directly used for the next telescopic process.

***α*-D-Glucopyranoside, methyl 1-C-[3-[(4-ethylphenyl)-methyl]phenyl] (9).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, 3H, J = 7.5 Hz), 2.52−2.58 (q, 2H, J = 7.5 Hz), 2.84 (m, 5H), 3.01 (br s, 1H), 3.24 (d, 1H, J = 9.3 Hz), 3.55−3.65 (m, 2H), 3.81−3.95 (m, 6H), 4.01 (br s, 1H), 5.01−5.22 (m, 1H), 7.01−7.06 (m, 4H), 7.15 (t, 1H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.9 Hz), 7.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.58, 28.37, 41.46, 49.16, 62.11, 70.22, 74.44, 74.68, 77.22, 101.33, 125.03, 127.71, 127.87, 128.11, 128.76, 128.88, 137.92, 138.16, 141.04, 141.89.

***α*-D-Glucopyranoside, Methyl 1-C-[3-[(4-ethylphenyl)-methyl]phenyl]-2,3,4,6-tetraacetate (10).** Anal. Calcd for $C_{30}H_{36}O_{10}$: C, 64.73; H, 6.51. Fd. C, 64.55; H, 6.46. HRMS: Calcd for M − MeOH + H = 525.2125 Da, Measured 525.2124 Da. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.5 Hz), 1.71 (s, 3H), 1.94 (s, 3H), 2.05 (bt, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.6 (q, 2H, J = 7.5 Hz), 3.1 (s, 3H), 3.9 (s, 2H), 4.02−4.06 (m, 1H), 4.21−4.24 (dd, 1H, J = 2.2 and 12.3 Hz), 4.33−4.37 (dd, 1H, J = 4.8 and 12.3 Hz), 4.94 (d, 1H, J = 10.1 Hz), 5.22 (t, 1H, J = 9.7 Hz), 5.57 (t, 1H, J = 9.7 Hz), 7.04 (d, 2H, J = 7.4 Hz), 7.10 (d, 2H, J = 7.4 Hz), 7.16 (m, 1H), 7.23−7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.60, 20.20, 20.60, 20.64, 20.74, 28.39, 41.50, 49.49, 62.22, 68.73, 68.85, 71.41, 73.99, 100.36, 124.44, 127.19, 127.99, 128.62, 128.74, 129.68, 135.96, 138.02, 141.22, 142.05, 168.94, 169.56, 170.13, 170.71.

The reactor containing the acetylated intermediate **10** was charged with acetonitrile (174.8 kg) and water (0.6 kg, 1 equiv with respect to acetylated intermediate). The mixture was cooled to ≤15 °C, and Et_3SiH (30.3 kg) was added. $BF_3{\cdot}Et_2O$ (24.5 kg, 2.1 equiv) was charged over >20 min, maintaining temperature at <15 °C. The reaction mixture was stirred for 4−7 h until complete by HPLC analysis. The mixture was cooled to ∼15 °C and then charged the required amount of 2,2-dimethoxypropane based on GC assay to determine the remaining amount of Et_3SiH, and KF to determine the remaining amount of H_2O. The reaction mixture was stirred until the complete disappearance of Et_3SiH was established by GC analysis. The Et_3SiH quench was judged to be complete when a neat sample was assayed to have an undetectable amount of Et_3SiH in the GC assay. The minimum quantifiable amount for this GC assay is ∼0.2 ppm. An aqueous solution of $NaHCO_3$ (120.02 kg $NaHCO_3$ in 120.17 kg water) was charged at room temperature (22−25 °C) until the pH of the aqueous phase was ≥6. The mixture was agitated for ≥10 min, and the phases were split. The lower aqueous phase was removed, and a 20% solution of NaCl (24.03 kg salt in 120.17 kg water) was used to wash the organic layer. The aq phase was separated, and the product-rich organic phase was concentrated at atmospheric pressure until most of the acetonitrile was removed (∼230 L of distillate was collected). Toluene (223.49 kg) was added, and the distillation was continued until the pot temperature reached at least 112 °C and a volume of 4−6 L/kg of methyl-1-C-(4′-ethyldiphenylmethane-3-yl)-*α*-D-glucopyranoside (**9**) input was reached. Heptane (240 kg) was charged

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while maintaining the temperature at >70 °C. The solution was cooled to ~60 °C over ≥1 h, and the slurry was held at 60 ± 10 °C for ≥1 h. The slurry was cooled to 20 ± 10 °C over ≥1 h. The slurry was filtered in a centrifuge, and the cake was washed with ≥2 cake volumes of heptanes (58 kg). The wet cake was dried under vacuum at ≤60 °C to an LOD of ≤0.2% to give ≥40 kg of the tetraacetate **11** (overall yield 86%, 99 A% purity): Anal. Calcd for $C_{29}H_{34}O_9$: C, 66.14; H, 6.50. Fd. C, 66.26; H, 6.50. HRMS: Calcd for M + H = 527.2281 Da, Measured 527.2278 Da. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.5 Hz), 1.65 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.57−2.62 (q, 2H, J = 7.5 Hz), 3.79−3.83 (m, 1H), 3.93 (s, 1H), 4.13−4.17 (dd, 1H, J = 2.3 and 12.3 Hz), 4.25−4.29 (dd, 1H, J = 4.8 and 12.3 Hz), 4.35 (d, 1H, J = 10.1 Hz), 5.09 (t, 1H, J = 9.6 Hz), 5.22 (t, 1H, J = 9.7 Hz), 5.30 (t, 1H, J = 9.2 Hz), 7.05 (d, 2H, J = 6.2 Hz), 7.10 (d, 2H, J = 7.9 Hz), 7.13−7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.62, 20.12, 20.52, 20.76, 28.38, 41.40, 62.35, 68.59, 72.64, 74.25, 76.09, 80.18, 124.56, 127.95, 128.75, 129.48, 136.40, 141.32, 142.03, 150.12, 168.81, 169.50, 170.39, 170.75.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-Ethylbenzyl)-(phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol/L-phenylalanine Complex/Water (13). Water (68.70 kg), 2,3,4,6-tetra-*O*-acetyl-1-C- (4′-ethyldiphenyl-methane-3-yl)-β-D-glucopyranose (11, 64.40 kg), and EtOH (62.44 kg, SDA-3A, 190 proof) were stirred with minimum agitation at 20 °C. NaOH (57.02 kg, 0.1 N) was introduced, and the mixture was heated slowly to 40−50 °C. After 1−2 h, the in-process HPLC (excluding the solvent front and system peaks) of the deacetylated product **1** in the solution was >97%. The solution was cooled to 20 °C, water (154.56 kg) was charged, and the solution temperature was adjusted to 18−25 °C. The mixture was stirred for 1 h. Concentrated HCl (37%, ~123.44 kg) was added to adjust the pH to 6.3. L-Phenylalanine (20.20 kg) and water (141.68 kg) were added, the slurry was heated to 75 °C, and the clear solution was passed through a polish filter. Deionized water at 75 °C (51.52 kg) was used to rinse the filtering flask and then added to the mixture to adjust the composition of the solvent to ~2 vol % EtOH in solution. The slurry was heated at 75 °C, and then the clear solution was cooled to 55−60 °C, typically maintained at ~57 °C. Seed crystals of the complex **13** (322 g) were added, the slurry was cooled to 40 °C over 1 h, and the pot temperature was maintained at 40 °C for 4 h. The slurry was cooled further to 18−25 °C over 2 h and stirred at this temperature for 12−16 h. The slurry was collected on a Robatel centrifuge filter. The filter cake was washed with 10 °C water (322 kg) to remove the inorganics, NaCl and NaOAc. The water wash was continued until the conductivity of the wash was <0.001 σ siemens. The filter cake was washed further with EtOAc (290 kg) to remove any excess compound **1**. The wet cake was dried under vacuum at 18−25 °C for at least 4 h and then at 40 °C for at least 12 h. The drying was stopped at KF reading = 2.8−3.6% (water that corresponds to monohydrate). Complex **13** was obtained as a white solid (54−58 kg, yield 80−88%, >99.90 A% purity): Anal. Calcd for $C_{30}H_{39}NO_8$: C, 66.52; H, 7.25; N, 2.58. Fd. C, 66.37; H, 7.37; N, 2.66. ^{1}H NMR (400 MHz, CD_3OD/D_2O) δ 1.16 (t, 3H, J = 7.6 Hz, CH_3), 2.57 (q, 4H, J = 7.5 Hz, CH_2), 3.06 (dd, 1H, J = 8.5 Hz, J = 14.4 Hz, PhAl-CH_2), 3.30 (m, 1H, PhAl-CH_2), 3.46 (m, 3H, H-2, H-3, H-4), 3.53 (q, 1H, J = 8.8 Hz, H-5), 3.69 (dd, 1H, 11.8 Hz, 5.6 Hz, H-6a), 3.85 (m, 2H, H-6b, PhAl-HCOOH), 3.92 (s, 2H, Ph-CH_2-Ph), 4.15 (d, 1H, 9.4 Hz, H-1), 4.71 (MeOH), 5.0 (1H, HOH), 7.10 (m, 4H, Ar-H), 7.3 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, CD_3OD/D_2O) δ 16.1, 29.2, 37.8, 42.1, 57.4, 62.7, 71.5, 75.8, 79.2, 81.7, 83.3, 126.5, 128.5, 128.8, 129.4, 129.5, 129.7, 130.0, 130.4 136.8, 139.6, 140.1, 142.9, 143.2, 174.1.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This manuscript is dedicated to the memory of John Dimarco, a colleague and friend.

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(6) Crystallographic coordinates and unit cell data (excluding structure factors) for **5**, **6a**, **11**, **12**, **13**, and L-proline forms **1**-P1, **1**-P2, **1**-P3, **1**-TP have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 756030−756038. These data can be obtained free of charge via www.ccdc.cam.ac.uk/const/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB21EZ,U.K. Fax + 44 1223 336033. E-mail deposit@ccdc.cam.ac.uk).

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