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# Telescoped Process to Manufacture 6,6,6-Trifluorofucose via Diastereoselective Transfer Hydrogenation: Scalable Access to an Inhibitor of Fucosylation Utilized in Monoclonal Antibody Production

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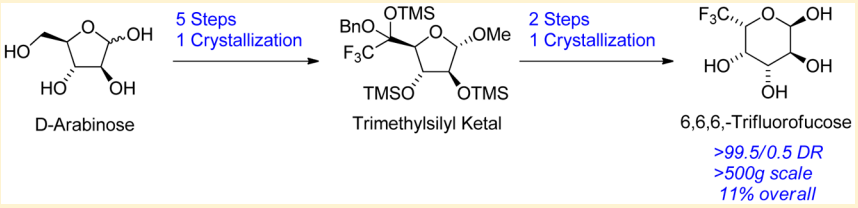
Supporting Information




**ABSTRACT:** IgG1 monoclonal antibodies with reduced glycan fucosylation have been shown to improve antibody-dependent cellular cytotoxicity (ADCC) by allowing more effective binding of the Fc region of these proteins to T cells receptors. Increased in vivo efficacy in animal models and oncology clinical trials has been associated with the enhanced ADCC provided by these engineered mAbs. 6,6,6-Trifluorofucose (**1**) is a new inhibitor of fucosylation that has been demonstrated to allow the preparation of IgG1 monoclonal antibodies with lower fucosylation levels and thus improve the ADCC of these proteins. A new process has been developed to support the preparation of **1** on large-scale for wide mAb manufacture applications. The target fucosylation inhibitor (**1**) was synthesized from readily available D-arabinose in 11% overall yield and >99.5/0.5 dr (diastereomeric ratio). The heavily telescoped process includes seven steps, two crystallizations as purification handles, and no chromatography. The key transformation of the sequence involves the diastereoselective preparation of the desired trifluoromethyl-bearing alcohol in >9/1 dr from a trimethylsilylketal intermediate via a ruthenium-catalyzed tandem ketal hydrolysis−transfer hydrogenation process.

## INTRODUCTION

Improved antibody-dependent cellular cytotoxicity (ADCC) has been observed using IgG1 antibodies having reduced levels of Asn297 glycan fucosylation due to more effective binding of the Fc region of these proteins to the Fc$\gamma$RIIIa receptors of effector T cells. Increased in vivo efficacy in animal models and oncology clinical trials has been associated with improved ADCC.[1,2] Protein fucosylation can be decreased by various means including (i) manipulation of cell growth and production conditions, (ii) use of engineered cell lines in which a key enzyme involved in protein fucosylation has been knocked out, and (iii) addition of chemical inhibitors of one or more of these enzymes.[3,4] Chemical inhibition is an attractive approach to reduce fucosylation during antibody manufacture as other protein or cell growth attributes remain undisturbed. Additionally, this method allows fucose levels to be controlled based on inhibitor dosage using already optimized cell lines.

6,6,6-Trifluorofucose (**1**) was found to impede fucosylation of both cell surfaces (FACS-based assay) and IgG1 monoclonal antibodies ($EC_{50}$ of ~4 $\mu$M).[5] The synthetic sugar analogue (**1**) was demonstrated to be an inhibitor of GDP-mannose 4,6-dehydratase (GMD) ($K_D$ = 11 $\mu$M by SPR), a key enzyme in the de novo pathway generating GDP-fucose and fucosylated glocoproteins from D-glucose. Both GDP-fucose and GDP-**1** were cocrystallized with GMD and shown to occupy nearly identical conformations within the allosteric pocket.[5]

A clear correlation was established between the levels of **1** utilized in CHO cell expression of anti-mesothelin[6] IgG1 monoclonal antibodies and the calcein cell lysis activity of these mAbs. For example, upon dosage of antibodies generated in the presence of 2 $\mu$M of **1** (~25% afucosylated), N87 gastric

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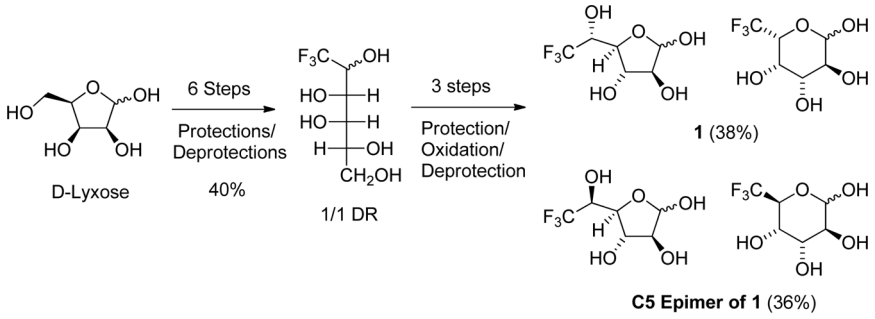
**Scheme 1. Tokokuni Route to 6,6,6-Trifluorofucose (1)**



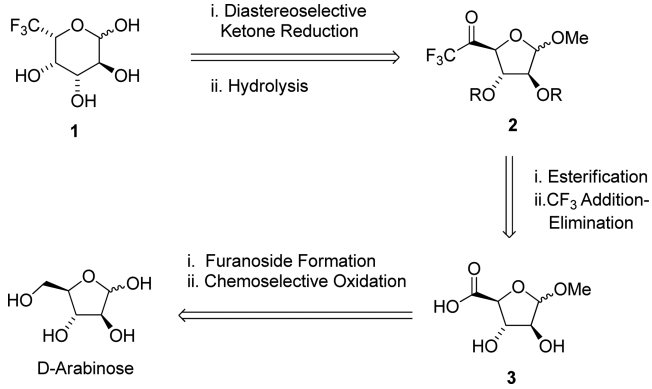

*Original Anomeric Carbon Not Preserved in 1*
*Non-Crystalline Intermediates/Multiple Chromatographies*
*Nine Protecting Groups /Non-Stereoselective*

carcinoma and CAPAN2 pancreatic adenocarcinoma cells were efficiently ($EC_{50}$ < 0.1 $\mu$g/mL) lysed by effector T cells from all healthy human donor populations.[1]

Considering the increased demand for **1** as a reagent to be utilized in large-scale mAb production, the development of an efficient manufacturing process to prepare the fucosylation inhibitor (**1**) on large-scale was mandated. The target material had previously been synthesized by Tokokuni and co-workers;[7] however, the published route to the molecule did not meet our manufacturing needs. The synthetic approach reported included nine steps from exotic raw material D-lyxose[8] (Scheme 1) and the stoichiometric use of toxic mercury and chromium reagents. The anomeric carbon in **1** was located on the opposite side of the sugar relative to its location in D-lyxose, leading to processing via open-chain non-crystalline intermediates, multiple silica gel chromatographies, and the use of nine protecting groups. Additionally, the formation of the trifluoromethyl-bearing alcohol at C6 was non-stereoselective, affording a 1/1 mixture of the corresponding epimers. We aimed to develop a route to 6,6,6-trifluorofucose (**1**) that would (i) preserve the anomeric carbon of the starting material in **1**, (ii) utilize telescoped reaction sequences and crystalline synthetic intermediates acting as purification handles, (iii) avoid chromatographic separations, (iv) include minimal utilization of protecting groups, and (v) be diastereoselective.

We selected D-(−)-arabinose as synthetic feedstock for our novel process to manufacture **1** considering that the former raw material is inexpensive[9] and readily available on kilogram scale. We planned to employ a methyl furanoside ring formation as the first step of the new approach and hydrolysis of the methyl furanoside ring as the last step of the sequence. Using such a strategy, all other chemical transformations would be performed on rigid five-membered rings, thus providing improved chances of uncovering stereoselective transformations and crystalline intermediates. Available precedents for enantioselective hydrogenation of trifluoromethyl ketones, either using positive pressure of hydrogen[10] or via transfer hydrogenation,[11] persuaded us that the hydrogenation of ketone **2** could be performed in a diastereoselective manner (Scheme 2). The diastereoselective reduction sought would be achieved by substrate control or brought about by the use of chiral catalyst. Esterification of known carboxylic acid **3**[12] followed by addition−elimination[13] of a trifluoromethyl group would yield ketone **2**. Methyl furanoside formation followed by chemoselective oxidation using platinum black had previously been reported to prepare intermediate **3** from D-(−)-arabinose;[12] however, this process would need to be developed to allow for multikilogram manufacture of **3**.

**Scheme 2. Retrosynthetic Analysis for Novel Approach to 1**




## RESULTS AND DISCUSSION

Although offering a moderate overall yield, the published route to synthesize **3** from D-(−)-arabinose yields the target material in high crude purity as an aqueous solution.[12] The first step of the process, leading to the formation of methyl furanoside intermediates **4a**/**4b**, must be limited to approximately 4 h at 20 °C. If the acid-catalyzed transformation is conducted for an extended period of time, significant quantities of the kinetic products **4a**/**4b** are converted to the thermodynamic products **4c**/**4d**[14] with one of the pyranoside anomers (**4d**) crystallizing from the reaction medium (Scheme 3).[15]

The second step of the preparation of **3** involves a Heyns oxidation,[16] a selective oxidation of the primary alcohol group in the presence of secondary alcohols by treatment with platinum black and oxygen. Platinum black is used in catalytic amounts (20 wt %) for this protocol and recycled via reduction with hydrogen. The oxidation is performed at elevated temperature in water using oxygen or air. Sodium bicarbonate ($NaHCO_3$) is utilized to maintain the pH of the reaction mixture between 8 and 9. The rate of oxidation has been observed to be higher within this pH range, and addition of the base in portion throughout the process is most effective to preserve ideal pH.

At this juncture in the preparation of **1**, a crystalline intermediate that could be utilized as purification handle was sought in order to provide material of reproducible purity profile. Benzyl ester **5a** offered this coveted feature as it could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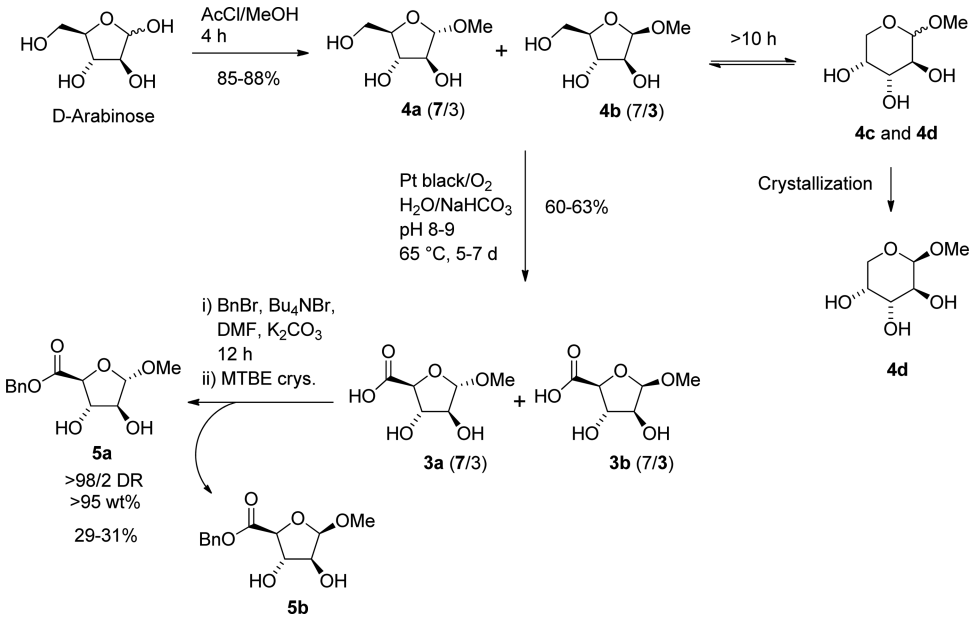
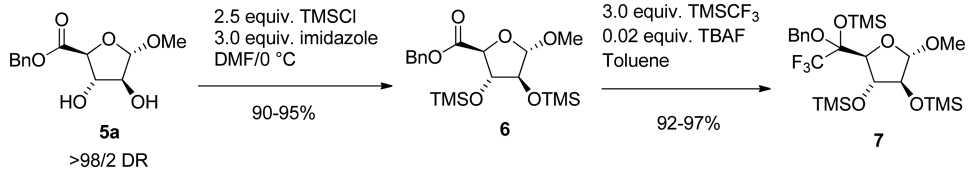
**Scheme 3. Preparation of Benzyl Ester 5a**




**Scheme 4. Preparation of Trifluoromethyl Furanoside 7**




be crystallized as a single diastereomer (>98/2 dr). The ester (**5a**) was prepared from crude **3** by treatment with benzyl bromide in *N*,*N*-dimethylformamide (DMF) in the presence of tetrabutyammonium bromide as phase transfer catalyst. The crude material was crystallized from *tert*-butylmethyl ether (MTBE), resulting in almost complete rejection of one of the two diastereomeric esters (**5b**) in the mother liquors. Material **5a** was isolated from inexpensive D-(−)-arabinose in a 16% overall yield.[17]

In consideration of the propensity of trifluoromethyl ketones to form hydrates, their availability as discrete species for processing is unreliable and their purification can be challenging.[18] We therefore contemplated a strategy involving the preparation and isolation of trimethylsilyl ketal **7** from ester **5a**.[19] Hydrolysis of ketal **7** would then be conducted in situ under reaction conditions promoting the desired diastereoselective ketone hydrogenation. Considering that the two hydroxyl groups of **5a** could not be expected to remain untouched during the formation of the trimethylsilyl ketal group from the ester, we elected to transiently protect them as trimethylsilyl ethers. Facile acid-catalyzed cleavage of the trimethylsilyl ether groups would subsequently be conducted during the isolation of the transfer hydrogenation product.

The alcohol groups of **5a** were protected using a standard protocol (TMSCl, imidazole, DMF, 0 °C, Scheme 4) and crude ester **6** utilized in the next step. Treatment of **6** with $TMSCF_3$ in the presence of catalytic tetrabutylammonium fluoride in toluene afforded ketal **7** in 85−90% yield from **5a**. It is important to note that crude **7** was not submitted to an aqueous treatment.[20] In this case, silica gel was added directly to the reaction mixture in order to quench the excess fluorinating agent. After filtration the product solution contained stable intermediate **7**, which was used without further purification in the subsequent diastereoselective hydrogenation step.

Potassium hydroxide was employed as part of the transfer hydrogenation reaction mixture in order to affect two purposes. First, the use of this hydroxide base results in the in situ formation of the trifluoromethylketone hydrogenation substrate. Additionally, the transfer hydrogenation catalyst, isolated and purchased as its hydrochloric acid salt, necessitates freebasing to be released in its active form. These two processes occur readily in isopropanol, a suitable solvent to conduct the transfer hydrogenation reaction.

A desilylation cascade occurs upon treatment of **7** with potassium hydroxide and prior to the transfer hydrogenation step under the reaction conditions. A proposed mechanism for this desilylation cascade is presented in Scheme 5. The cascade begins with the hydrolysis of the trimethylsilyl ketal group of **7** to afford ketone **8**, which exists in equilibrium with the corresponding ketone hydrate (**9**). Spatial proximity allows for one of the two hydroxyl groups of the ketone hydrate intermediate to act as a nucleophile in the base-catalyzed transfer of a trimethylsilyl group from the silyl ether function at C2 (**9**) to a newly formed trimethylsilyl hemiketal. The hemiketal thus formed is subsequently hydrolyzed to afford ketone **10**. The observation that alcohol **11** is the product of the hydrogenation process[21] prior to the acidic quench (vide infra) is consistent with the latter mechanistic proposal. In the absence of transfer hydrogenation catalyst or for a case scenario in which the amount[22] and/or the turnover rate of the catalyst utilized are insufficient to cause formation of alcohol **11**[23] to be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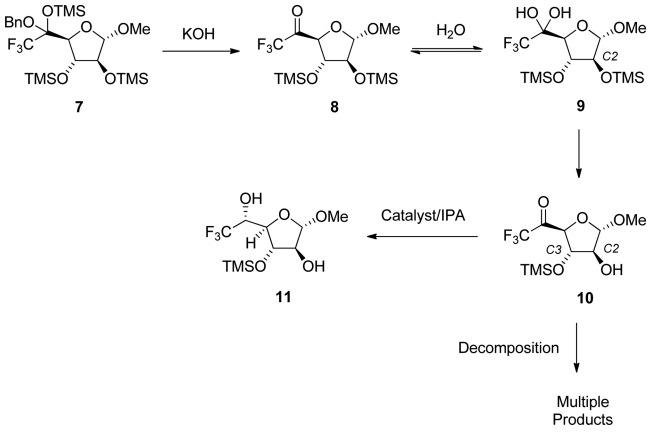
**Scheme 5. Proposed Base-Catalyzed Desilylation Cascade**




the only operative reaction pathway, decomposition on **10** leads to the formation of multiple products as observed upon treatment of **7** with potassium hydroxide in isopropanol.

We started our investigation of the planned ketone transfer hydrogenation with the experimental conditions reported by Noyori and co-workers in their seminal report.[24] Using the conditions reported in entry 1 in Table 1, the transformation was complete in 2 h at 20 °C and upward of 90% assay yield of desired alcohol **12** was obtained after hydrochloric acid quench. Noteworthy is the fact that we did not observe erosion of the diastereomeric ratio (dr) of alcohols (**12**/**13**) upon prolonged reaction times (14 h). Moreover, the use of triethylamine−formic acid as reductant, designed to offer a kinetically controlled[25] mixture of products irrespective of the structure of the starting material ketone, afforded alcohols **12** and **13** in only marginally superior dr (entry 2) relative to using isopropyl alcohol (IPA) as reductant (entry 1). We elected to prioritize process simplicity and continue using IPA as hydrogen source.

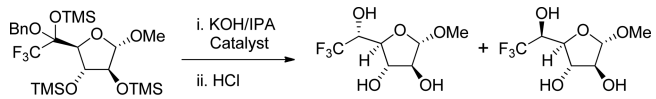
Employing <0.3 equiv of potassium hydroxide for the transformation led to >24 h reaction times (entry 3) due to sluggish formation of ketone **10**. *R,R*-TsDPEN RuCl (mes) was shown to be the enantiomer of the catalyst affording the matched case for stereoselectivity as can be visualized by examination of the observed diastereomeric ratio upon use of *S,S*-TsDPEN RuCl (mes) (entry 4). A catalyst of the $R_2NSO_2$DPEN RuCl (p-cym) series, which had been reported[26] to be effective for hydrogenation of trifluoromethyl and other fluororinated ketones, was tested (entry 5) and did not offer superior results when compared to *R,R*-TsDPEN RuCl (mes).

The transformation was evaluated using <2 mol % of catalyst (entry 6) or the more sterically encumbered catalysts *R,R*-2,4,6-$Me_3PhSO_2$DPEN RuCl (p-cym) (entry 7) and *R,R*-2,4,6-$iPr_3PhSO_2$DPEN RuCl (p-cym) (entry 8). In these cases, the ketone hydrogenation necessitated more than 4 h to reach completion and the observed yields of **12** were significantly reduced. The reason for these low yields is that the decomposition of ketone **10** becomes operative at low catalyst levels (entry 6) or in the presence of less reactive catalysts (entries 7 and 8). The experimental conditions reported in entry 1 (Table 1) were utilized for subsequent manufacturing activities.

Upon completion of the transfer hydrogenation, the hydrolysis of **11** to afford **12** was performed by addition of concentrated aqueous hydrochloric acid and the insoluble side products generated (including trimethylsilanol) were removed by filtration over Celite. Considering that the presence of benzyl alcohol in the product phase is detrimental to the subsequent acid-catalyzed furanoside hydrolysis, the aqueous solution was washed with dichloromethane to effect its removal. The ruthenium levels of the solution were reduced from 35−45 ppm to <1.5 ppm using the metal-scavenging resin Quadrapure BZA.[28] The resin was removed by filtration to afford the aqueous product solution containing alcohol **12** (>85% assay yield) and its diastereomer **13** (>7% assay yield). The crude material was used directly in the last step of the preparation of **1**. Purification of **12** by distillation was considered but determined to be unsafe due to the significant exothermic decomposition of **12** (549 J/g) observed at an onset temperature of 160 °C.[29,30]

We developed a straightforward hydrolysis procedure to prepare **1** from alcohol **12**, depicted in Scheme 6. The aqueous solution of crude methyl furanoside **12** was treated with 2 equiv of concentrated aqueous hydrochloric acid at 50 °C for 20 h. During this process, a subsurface nitrogen sparge was used to

**Table 1. Optimization of Diastereoselective Hydrogenation of Ketal 7**




| entry[a] | catalyst | catalyst loading (equiv) | KOH equiv | temp. (°C) | time (h) to completion | diastereo ratio (dr) **12**/**13** | yield (%) (**12**/**13**) |
|---|---|---|---|---|---|---|---|
| 1 | *R,R*-TsDPEN RuCl (mes) | 0.02 | 0.3 | 20 | 2.0 | 93/7 | 95 |
| 2[b] | *R,R*-TsDPEN RuCl (mes) | 0.02 | 0.3 | 20 | 2.0 | 96/4 | 55 |
| 3 | *R,R*-TsDPEN RuCl (mes) | 0.02 | 0.15 | 20 | >24 | 91/9 | 79 |
| 4 | *S,S*-TsDPEN RuCl (mes) | 0.02 | 0.15 | 20 | >24 | 65/35 | 72 |
| 5 | *R,R*-$Me_2NSO_2$DPEN RuCl (p-cym) | 0.05 | 0.45 | 20 | 2.0 | 83/17 | 86 |
| 6 | *R,R*-TsDPEN RuCl (mes) | 0.01 | 0.3 | 20 | 4.0−5.0 | 92/8 | 65 |
| 7 | *R,R*-2,4,6-$Me_3PhSO_2$DPEN RuCl (p-cym) | 0.02−0.1 | 0.3 | 20 | >8.0 | 94/6 | <20 |
| 8 | *R,R*-2,4,6-$iPr_3PhSO_2$DPEN RuCl (p-cym) | 0.02−0.1 | 0.3 | 20 | >8.0 | 97/3 | <20 |

[a]Assay yields of **12** and **13** were obtained using gas chromatography analysis and calibrated product standards.[27] [b]Experiment run using 10 equiv of $Et_3N$ and 25 equiv of $HCO_2H$ in 40 mL/g of EtOAc (no IPA).



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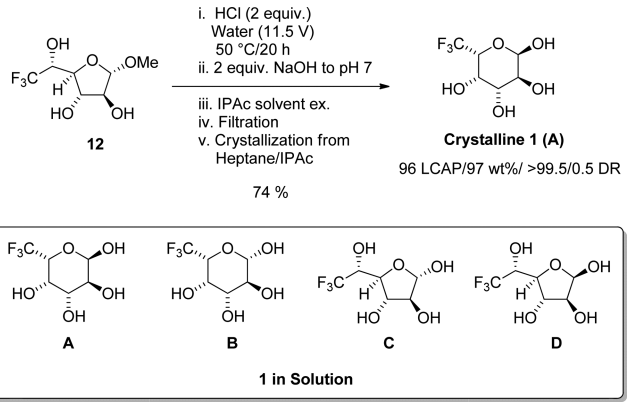
**Scheme 6. Preparation of 1 from Alcohol 12**




remove methanol from the reaction mixture and thus drive the equilibrium toward the product. Upon cooling the reaction mixture to 20 °C, the acid was neutralized with sodium hydroxide and the pH was adjusted to approximately 7. After solvent exchange from water to isopropyl acetate, the resultant dry suspension was filtered to eliminate sodium chloride. The material was crystallized[31] by seeding with crystalline **1** at 40 °C, cooling to 20 °C, and reducing the supernatant concentration of **1** by heptane addition. After filtration, cake wash, and drying of the solids, **1** was isolated as a crystalline solid in 73.8% corrected yield from ketal **7**. The anomer of **1** at C5 (see Scheme 1) was largely rejected in the crystallization, and the isolated solids contained <0.5% of this isomer.

The NMR signals corresponding to the four isomers of **1** present in solution were identified using detailed studies ($^1$H, $^{13}$C, $^{19}$F, 2D $^1$H−$^1$H TOCSY, 2D $^1$H−$^{13}$C HSQC, and 2D $^1$H−$^{13}$C HMBC). Dissolution of crystalline **1** in DMSO-$d_6$ and rapid collection (<30 min) of the $^1$H and $^{19}$F NMR spectra for the solution showed almost exclusively isomer **A**, providing strong evidence that the material crystallizes as the latter isomer. This evidence is corroborated by the results of density functional theory calculations at the M06-2X/6-31+G(d,p) level[32] on species **A**−**D** in the absence of solvent. On the basis of the computed free energy differences, it was predicted that form **A** should represent >80% of the isomeric mixture.[33] After dissolution of the material in DMSO-$d_6$ and standing for multiple hours, a mixture of isomers **A**−**D** is observed by NMR. This observation is in accord with IEFPCM implicit solvent calculations at the same level of theory, which predict a decrease in the amount of **A** (to ∼50%) with corresponding increases (to 12−19% each) in **B**−**D** at equilibrium in DMSO.[34,35]

## CONCLUSION

In summary, a new process has been developed to prepare 6,6,6-trifluorofucose (**1**), an inhibitor of fucosylation utilized in the production of mAbs. The heavily telescoped process includes seven steps, two crystallizations used as purification handles, and no chromatography. The synthetic sugar (**1**) was manufactured using this synthetic route in 11% overall yield and >99.5/0.5 dr from readily available D-arabinone. The key transformation of the sequence involves the diastereoselective preparation of the desired trifluoromethyl-bearing alcohol in >9/1 dr from a trimethylsilylketal intermediate via a ruthenium-catalyzed tandem ketal hydrolysis−transfer hydrogenation step. This process to prepare 6,6,6-trifluorofucose (**1**) enables the large-scale manufacture of mAbs displaying improved ADCC and in vivo efficacy.

## EXPERIMENTAL SECTION

**(2*R*/*S*,3*S*,4*S*,5*S*)-2-(Hydroxymethyl)-5-methoxytetrahydrofuran-3,4-diol (4a/4b).** To a solution of acetyl chloride (527 mL, 7.38 mol, 0.79 equiv) in methanol (14 L) was added D-arabinose (1400 g, 9.33 mol, 1 equiv) as a solid over the course of 15 min. The reaction mixture was agitated for 4 h and cooled to 0 °C (longer reaction times resulted in the formation of >10% of pyranoside side products). $NH_4HCO_3$ (832 g, 10.5 mol, 1.13 equiv) was added as a solid over the course of 15 min. The mixture was warmed to 20 °C and agitated for 4 h. Methanol (13 L) was evaporated (40 °C, 300 Torr), and the resultant mixture was filtered. The solids were rinsed with methanol (1 L). The combined filtrate was concentrated to a dry oil (1652 g, 79.6 wt % of isomers **4a**/**4b** by QNMR, 86% combined furanoside yield) and used in the next step without further purification. The furanoside anomeric methine signals in the $^1$H NMR spectrum observed at 4.7−4.75 ppm were utilized to quantify products **4a** and **4b** in the crude material.

**(2*R*/*S*,3*S*,4*S*,5*S*)-3,4-Dihydroxy-5-methoxytetrahydrofuran-2-carboxylic Acid (3a/3b).** $PtO_2$ (400 g, 1.76 mol, 0.22 equiv) was suspended in water (1.6 L) and reduced under $H_2$ (5 bar) for 12 h. The resultant Pt(0) catalyst was filtered. Crude **4a**/**4b** (1650 g, 79.6 wt %, 1313 g corrected mass, 8.00 mol) was dissolved in water (34 L), and the filtered Pt(0) catalyst (480 g wet, ∼0.22 equiv) was added. $NaHCO_3$ (470 g, 5.6 mol, 0.6 equiv) was added, thus resulting in a reaction mixture pH of 8−9. The mixture was heated to 60 °C, and subsurface bubbling of $O_2$ was performed for 6 days via a Teflon line. During this time $NaHCO_3$ was added to the reaction in order to maintain the reaction mixture pH between 8 and 9. The mixture was cooled to 20 °C, and the Pt(0) catalyst was filtered.[36] Water was evaporated under reduced pressure (50−100 Torr) to afford products **3a**/**3b** as a mixture of oils (1435 g, 61.3 wt % of isomers **3a** and **3b** by QNMR, 61.8% combined furanosides yield) used in the next step without further purification. The furanoside methine signals in the $^1$H NMR spectrum observed at 3.96−4.04 ppm were utilized to quantify products **3a** and **3b** in the crude material.

**(2*S*,3*S*,4*S*,5*S*)-Benzyl 3,4-Dihydroxy-5-methoxytetrahydrofuran-2-carboxylate (5a).** To crude **3a**/**3b** (1435 g, 61.3 wt %, 880 g corrected mass, 4.95 mol) were added *N*,*N*-dimethylformamide (24 L), potassium carbonate (1416 g, 10.26 mol, 2.08 equiv), and tetrabutylammonium bromide (90 g, 0.28 mol, 0.056 equiv). Benzyl bromide (1594 g, 9.32 mol, 1.89 equiv) was added over the course of 15 min while maintaining the reaction mixture temperature below 25 °C. The mixture was agitated for 14 h at 20 °C. The reaction mixture was poured on isopropylacetate (52 L), and the resultant suspension was agitated for 30 min. The mixture was filtered, and the filter cake was washed with isopropyl acetate (4 L). The filtrate was concentrated to dryness (65 °C, <0.1 Torr), and 76 L of distillate were collected. The residue was dissolved in isopropylacetate (20 L), and the solution was washed with water (2.4 L). The organic phase was filtered over a silica pad (1 kg), and the silica pad was washed with isopropylacetate (4 L). The solution was concentrated under reduced pressure, and 23.6 L of distillate were collected. The residue was suspended in *tert*-butylmethyl ether (6 L), and the mixture was agitated at 20 °C for 14 h. The suspension was filtered, and the solids were washed with *tert*-butyl methyl ether (1.6 L). The solids were dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 2 days to afford product **5a** (435 g, 1.62 mol, 91/9 diastereomeric ratio) in 32.7% corrected yield. The material (**5a**) was reprocessed according to the following procedure in order to upgrade the diastereomeric ratio. Crude ester **5a** (435 g, 1.62 mol, 91/9 diastereomeric ratio) was dissolved in dichloromethane (7 L). The mixture was warmed to 35 °C. Charcoal (Norit SX4, 25 g) was added, and the mixture was agitated at 35 °C for 1 h. The mixture was cooled to 30 °C and filtered over Celite. The Celite cake was rinsed with dichloromethane (2.5 L). The clear filtrate was evaporated to dryness under reduced pressure (9.2 L of distillate were collected). *tert*-Butylmethyl ether (0.9 L) was added to the residue, and the suspension was agitated for 12 h and filtered. The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solids were washed with *tert*-butylmethyl ether (0.25 L). The solids were dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 1 day to afford product **5a**[37] (394 g, 1.46 mol, 99/1 diastereomeric ratio, 99.5 wt % for **5a**/**5b**) in 29.7% corrected yield from **3a**/**3b**. HPLC analysis: XBridge BEH C18 XP column, 50 mm × 2.1 mm, 2.5 μm, 1200 bar; isocratic 95% water/5% acetonitrile for 5.5 min, 0.6 mL/min; 215 nm, **5a** at 3.72 min, **5b** at 3.94 min. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.30−7.42 (m, 5 H), 5.59 (d, $J$ = 6 H, 1 H), 5.47 (d, $J$ = 4 Hz, 1 H), 5.18 (s, 2 H), 4.82−4.83 (d, $J$ = 1.6 Hz, 1 H), 4.35 (d, $J$ = 6 Hz, 1 H), 4.02−4.07 (m, 1 H), 3.81−3.85 (m, 1 H), 3.29 (s, 3 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 170.3, 136.0, 128.6, 128.0, 110.2, 82.1, 81.0, 80.1, 66.1, 55.0. HRMS (ESI/Orbitrap) $m/z$: [M + Na]$^+$ calcd for $C_{13}H_{16}O_6$ 291.0845; found 291.0839; mp 115−117 °C.

**(2*S*,3*R*,4*S*,5*S*)-Benzyl 5-Methoxy-3,4-bis((trimethylsilyl)oxy)-tetrahydrofuran-2-carboxylate (6).** To a solution of **5a** (1.3 kg, 4.85 mol) and 1H-imidazole (0.99 kg, 14.6 mol, 3.0 equiv) in *N*,*N*-dimethylformamide (6.5 L, 5 V) at 0 °C was added chlorotrimethylsilane (1.54 L, 12.1 mol, 2.5 equiv) over the course of 1 h while maintaining the reaction mixture temperature below 10 °C. The mixture was warmed to 20 °C and agitated for an additional 1 h. Toluene (6.5 L, 5 V) was added. The mixture was washed three times with water (3 × 3.9 L) and azeotropically dried at reduced pressure (batch temperature did not exceed 40 °C) to generate a distillate volume of 16.1 L while simultaneously adding toluene (15.9 L). **6** was obtained as a solution in toluene (1.8 kg of product, 6 kg of solution, 30 wt %, < 500 ppm water) in 90% corrected yield: The solution was used in the subsequent step without further purification. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.31−7.41 (m, 5 H), 5.17−5.28 (m, 4 H), 4.88 (d, $J$ = 2 Hz, 1 H), 4.44 (d, $J$ = 6 Hz, 1 H), 4.19 (dd, $J$ = 6 and 8 Hz, 1 H), 3.97 (dd, $J$ = 2 and 4 Hz, 1 H), 3.24 (s, 3 H), 0.12 (s, 9 H), 0.08 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.2, 135.3, 128.5, 128.4, 109.9, 82.9, 81.4, 81.2, 66.8, 55.9, −0.05, −0.14. HRMS (ESI/Orbitrap) $m/z$: [M + H]$^+$ calcd for $C_{19}H_{32}O_6Si_2$ 413.1816; found 413.1810.

**(((2*S*,3*R*,4*S*,5*S*)-2-(1-(Benzyloxy)-2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-5-methoxytetrahydrofuran-3,4-diyl)bis(oxy))bis(trimethylsilane) (7).** To a solution of **6** (1.8 kg, 4.4 mol) in toluene (6 kg total weight) under a sweep of nitrogen was added additional toluene (7.2 L, 4 V) and a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 87 mL, 87 mmol, 0.02 equiv).[38] Trimethyl(trifluoromethyl)silane (1.94 L, 13.1 mol, 3 equiv) was added while maintaining the temperature of the mixture at 20 ± 5 °C (<30 min addition time), and the reaction mixture was agitated for an additional 2.5 h at that temperature. $SiO_2$ (1.8 kg) was charged to the solution, and the resultant mixture was agitated for 1 h. The mixture was filtered, and the solids were washed with toluene (3.6 L, 2 V). The toluene solution was concentrated under reduced pressure (batch temperature did not exceed 40 °C) to afford **7** in 93.0% corrected yield (2.28 kg, 98.8 wt %) as a 2/1 mixture of diastereomers. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.25−7.40 (m, 5 H), 4.73−4.85 (m, 3 H), 4.37−4.44 (m, 1 H), 4.34 (d, $J$ = 6 Hz, 0.33 H), 4.23 (d, $J$ = 6, 0.67 H), 3.44 (s, 1 H), 3.42 (s, 2 H), 0.23 (s, 6 H), 0.15−0.17 (m, 6 H), 0.14 (s, 6 H), 0.13 (s, 3 H), 0.10 (s, 6 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.8, 128.2, 128.1, 127.8, 127.5, 127.3, 127.2, 123.0 (q, $J$ = 291 Hz), 122.9 (q, $J$ = 291 Hz), 97.2 (q, $J$ = 30 Hz), 96.8 (q, $J$ = 30 Hz), 83.9, 83.8, 82.2, 79.2, 78.8, 66.7, 65.3, 56.0, 55.9, 1.5, 1.4, 0.3, 0.2, 0.1. $^{19}$F NMR (375 MHz, $CDCl_3$): δ −77.2, −77.6. HRMS (ESI/Orbitrap) $m/z$: [M + Na]$^+$ calcd for $C_{23}H_{41}F_3O_6Si_3$ 577.2061; found 577.2055.

**(2*S*,3*S*,4*S*,5*S*)-2-Methoxy-5-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)tetrahydrofuran-3,4-diol (12).** To a solution of **7** (2.26 kg, 4.08 mol) in isopropanol (9.5 L, 4.2 V) under a nitrogen sweep was added a potassium hydroxide solution in isopropanol (0.1 M, 12.2 L, 1.22 mol, 0.3 equiv)[39] and *R*,*R*-TsDPEN RuCl (mes) (50.7 g, 81.6 mmol, 0.02 equiv). The reaction mixture was agitated at 20 °C for 3 h. Aqueous concentrated hydrochloric acid (131 mL, 1.59 mol, 0.39 equiv) was added, and the mixture was agitated for 1 h. The mixture was filtered through a Celite pad (2.3 kg), and the filter pad was rinsed using isopropanol (3 L). Water (6.8 L, 3 V) was added, and the pH of the solution was adjusted to 7 ± 0.5 using 1 N aqueous sodium hydroxide (366 mL, 366 mmol, 0.09 equiv). The mixture was concentrated under reduced pressure and at a batch temperature of ≤40 °C to generate a distillate volume of 25 L. Water (6.8 L, 3 V) was added to the crude residue. The resultant mixture was agitated for 15 min and filtered over a glass frit.[40] The aqueous solution was washed three times with dichloromethane (23 L, 10 V), and the benzyl alcohol levels in the aqueous product phase were measured to be ≤3 mg/g. Quadrapure BZA resin (40 wt %, 900 g) was added to the solution, and the suspension was agitated at 20 °C for 15 h. The ruthenium levels of the mixture were measured to be ≤1.5 ppm. The mixture was filtered, and the scavenger cake was rinsed with water (2.3 L, 1 V). The process afforded an aqueous solution that contained a 11.8/1 mixture of desired isomer **12** and undesired isomer **13** in 93% corrected yield (0.88 kg of combined products, 16.8 kg of product solution, 5.2 wt % combined products, 1.1 ppm Ru) used in the next step without further purification. GC FID analysis: Rtx-5 Amine, 30 m × 0.32 mm ID, 1.0 μm df; inlet 10/1 split ratio, 300 °C; oven 120 °C for 2 min, 15 °C/min to 240 °C for 8 min; **12** at 6.98 min, **13** at 7.35 min. Representative data for the mixture of **12** and **13**: $^1$H NMR (400 MHz, DMSO-$d_6$, major isomer) δ 6.23 (d, $J$ = 10 Hz, 1 H), 5.44 (d, $J$ = 4 Hz, 1 H), 5.36 (d, $J$ = 8 Hz, 1 H), 4.66 (d, $J$ = 2.9 Hz, 1 H), 3.95−4.05 (m, 1 H), 3.75−3.91 (m, 3 H), 3.24 (s, 3 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 125.4 (q, $J$ = 280 Hz), 109.2, 81.4, 79.0, 76.4, 67.3 (q, $J$ = 28 Hz), 54.6. $^{19}$F NMR (375 MHz, DMSO-$d_6$) δ −74.8. HRMS (ESI/Orbitrap) $m/z$: [M + Na]$^+$ calcd for $C_7H_{11}F_3O_5$ 255.0456; found 255.0451.

**6,6,6-Trifluorofucose 1.** To an agitated aqueous solution of desired isomer **12** and undesired isomer **13** (0.88 kg of combined products, 16.8 kg of product solution, 5.2 wt % combined products) was added hydrochloric acid (37% w/w, ACS reagent, 3.79 mol, 1.0 equiv, 374 mL). A Teflon tube was submerged into the homogeneous reaction solution, and the mixture was purged with nitrogen using a moderate gas flow throughout the course of the reaction. The solution was heated to 50 °C and agitated for 14 h. The solution was cooled to 20 °C, and the purge was discontinued. Aqueous sodium hydroxide (5.0 N, 3.79 mol, 1.0 equiv, 758 mL) was charged to the solution to achieve a pH of 7 ± 0.5. The mixture was concentrated under reduced pressure and at a batch temperature of ≤60 °C to generate a distillate volume of 16 L. The distillation was continued under reduced pressure and at a batch temperature of ≤60 °C to generate a distillate volume of 12 L while simultaneously adding isopropyl acetate (IPAc, 56 L). The water content of the reaction by KF was measured to be ≤800 ppm. The mixture was filtered to remove NaCl, and the solids were rinsed with IPAc (3 L). The filtrate was concentrated under reduced pressure and at a batch temperature of ≤60 °C to generate a distillate volume of 39.5 L. The mixture was warmed to 60 °C, and water (1 equiv, 3.79 mol, 68 mL) was added. The solution was cooled to 40 °C and seeded with **1** (100 g, 0.44 mol, 0.12 equiv). The suspension was cooled to 20 °C over the course of 4 h (linear cooling gradient). Heptane (7.5 L, 9 V) was added to the suspension over the course of 1 h. The mixture was agitated for 30 min, and the supernatant content of **1** in the mixture was verified to be ≤10 mg/g. The slurry was filtered, and the white solids were washed with 50% v/v heptane/isopropyl acetate (1.5 L, 2 V). The solids were dried on a frit using a nitrogen sweep for 48 h to afford **1** in 73% corrected yield (573 g, 2.55 mol, 97.1 wt %, 96.3 LCAP, >99.5/0.5 dr, 8.5 ppm, 1.7% water, 1.5 wt % IPAc). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.66 (d, $J$ = 5 Hz, 1 H), 4.93−5.19 (m, 1 H), 4.81 (d, $J$ = 5 Hz, 1 H), 4.50 (d, $J$ = 6 Hz, 1 H), 3.77−4.03 (m, 1 H), 3.50−3.69 (m, 2 H), 2.50 (br s, 1 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 128.6, 125.8, 123.0, 120.2, 93.0, 68.6, 68.3, 67.8, 67.4. $^{19}$F NMR (375 MHz, DMSO-$d_6$): δ −71.4. HRMS (ESI/Orbitrap) $m/z$: [M + Na]$^+$ calcd for $C_6H_9F_3O_5$ 241.0300; found 241.0294; melting point =123−125 °C.[41]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00646.



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J. Org. Chem. 2016, 81, 4736−4743

$^{1}$H, $^{13}$C, $^{19}$F, 2D COSY, and NOESY NMR spectra and LCMS and GC spectra; comparison table for the $^{1}$H NMR signals of a sample of **1** prepared via the synthetic route reported by Toyokuni et al. and a sample of **1** prepared via the synthetic route reported herein; calculated Gibbs free energies, Boltzmann populations, and total energies for pyranoside and furanoside forms of **1** (PDF)

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### Notes

The authors declare no competing financial interest.

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(22) Use of <0.02 equiv of catalyst causes significant lowering in hydrogenation yield.
(23) Data for **11**: $^{1}$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 6.40 (d, $J$ = 8.1 Hz, 1 H), 5.56 (d, $J$ = 5.7 Hz, 1 H), 4.68 (d, $J$ = 2.4 Hz, 1 H), 4.02 (dd, $J$ = 8.0, 5.0 Hz, 1 H), 3.91 (td, $J$ = 8.1, 2.0 Hz, 1 H), 3.80 (dd, $J$ = 8.0, 2.0 Hz, 1 H), 3.75 (ddd, $J$ = 5.7, 5.0, 2.4 Hz 1 H), 3.24 (s, 3 H), 0.12 (s, 9 H). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 125.1, 108.9, 81.4, 78.6, 77.3, 66.9, 54.4, 0.1. The 2D $^{1}$H−$^{1}$H COSY spectrum of **11** showed that C-2 and C-5 bear hydroxyl groups (H-2 and C2-OH correlation and H-5 and C5-OH correlation) and that C-4 thus not bear a hydroxyl group, thus confirming the structure of **11**.
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(28) The rejection of ruthenium via the crystallization of **1** was not surveyed; however, it was considered unlikely that levels of metal of 35−45 ppm in solution of **7** would result in amounts of Ru in crystalline **1** of <100 ppm.
(29) The boiling point of **12** at a pressure of 2 Torr is 160 °C.
(30) DSC and ARC data for compound **12** supported this analysis.
(31) A low crystallization rate has been observed for 6,6,6-trifluorofucose (**1**) in the absence of water (the crystallization was observed to take >24 h in the absence of water), presumably due to a correspondingly low rate of equilibration of the four isomeric species of **1** in the absence of water, causing the concentration of the crystalline species **A** (vide infra) in solution to be low at any point during the designed process. One equivalent of water was thus added in order to allow for productive crystallization kinetics.
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(37) $^{1}$H NMR spectral analysis of **5a** and **5b** led to identification of these isomers. The coupling constant between H-1 and H-2 in **5a** is 1.6 Hz, showing unambiguously that these 2 protons are trans to each other. The coupling constant between H-1 and H-2 in **5b** is 4.3 Hz, consistent with a cis relationship.




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J. Org. Chem. 2016, 81, 4736−4743

(38) The addition of trimethyl(trifluoromethyl)silane should be performed as quickly as possible after the addition of tetrabutylammonium fluoride to avoid starting material decomposition (30% decomposition in 2 h).
(39) The addition of *R,R*-TsDPEN RuCl (mes) should be performed as quickly as possible after the addition of potassium hydroxide to avoid starting material decomposition.
(40) A ruthenium-rich black oil, not soluble in water, stuck to the walls of the reactor and was thus separated from aqueous product solution.
(41) $^{1}$H NMR data in $D_2O$ for manufactured **1** were compared with the $^{1}$H NMR data of **1** and **C5-epi-1** in $D_2O$ prepared by Toyokuni et al. Toyokuni et al. utilized coupling constant analysis to distinguish between **1** and **C5-epi-1**. The absolute configuration of **1** at C-5 was also confirmed by a separate method. The 2D $^{1}$H−$^{1}$H NOESY NMR spectrum of **1** ($\alpha$-pyranose) in *d*-DMSO showed that irradiation of H-1 resulted in a positive NOE effect at H-5, thus confirming the absolute configuration at C-5. The 2D $^{1}$H−$^{1}$H NOESY NMR spectrum of **1** ($\beta$-pyranose) in *d*-DMSO showed that irradiation of H-1 did not result in a positive NOE effect at H-5, thus corroborating this evidence. Bansal, R. C.; Dean, B.; Hakomori, S.; Toyokuni, T. *J. Chem. Soc., Chem. Commun.* **1991**, 796−798.



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