Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

Process Development of a Potent Glucosylceramide Synthase Inhibitor

Christopher G.F. Cooper,* Edward R. Lee, Richard A. Silva, André J. Bourque, Scott Clark, Sanjeev Katti, and Vitaly Nivorozhkin

Genzyme Corporation, 153 Second Avenue, Waltham, Massachusetts 02451, United States

Supporting Information

ABSTRACT: An economic, scalable process for the production of glucosylceramide synthase (GCS) inhibitor **7** has been developed. Herein we report a three-step synthesis to aldehyde **4** with high yield and purity that employs the selective cleavage of an endocyclic C−O bond of a THP ether using borane/THF as the key step. This particular methodology has not been used previously from a development standpoint and offers an attractive way towards introducing pentanol side chains. Aldehyde **4** is then coupled with deoxynojirimycin *via* flow hydrogenation using an H-Cube to safely produce the free base of **7**, which is isolated as an MSA salt in 50% overall yield. Herein we discuss the evolution of this process from its original form and the thermodynamics of its associated chemistry.

INTRODUCTION

Compounds that inhibit GCS have been of pharmacologic interest for many years due to their potential utility in lowering glycosphingolipid (GSL) levels. Elevated GSL levels have been implicated in numerous disorders, including Type II Diabetes, Gaucher, Sandhoff, Tay−Sachs, Niemann−Pick C, and Fabry diseases, and therefore GCS inhibitors have been investigated as treatments for enzyme deficiencies.[1−7] Iminosugars have been under increased investigation due to their potential utility for these conditions, and both Zavesca and Miglitol are currently marketed therapies which make use of such a core.[8] The potent GCS inhibitor **7** was first reported by Aerts et al. in 1998, where it was reported to be 100-fold better in inhibiting GCS than *n*-butyldeoxynojirimycin.[9] Since its discovery, **7** has been shown to have potential applications in Gaucher's Disease, Type II Diabetes, Niemann−Pick C, ulcerative colitis, and cystic fibrosis.[8]

While a great amount of literature is available on the potential applications of **7**, there are relatively few economically practical ways to produce it.[4−6] Of the methods that have been previously published, none seemed to be immediately amenable to scale-up by conventional economically viable methods. Our goals on this project were to first establish an economically viable route to aldehyde **4** and then to optimize the coupling conditions to form alkylated aza-sugar **6**. The aldehyde synthesis was approached from many angles, first using literature procedures (Schemes 2 and 3), followed by a route employing a ketal intermediate (Scheme 4). These routes failed due to purity, robustness, and yield concerns but led us to our final route (Scheme 1) where the aldehyde is constructed via a selective borane cleavage of a THP ether followed by catalytic TEMPO oxidation.

The reductive amination of aldehyde **4** had historically been done using a tetrabenzylated aminosugar and catalytic hydrogenation over Pd on C.[4] We felt that this process could be improved by direct coupling of the aldehyde to the unprotected sugar and also by switching from batch hydrogenation to flow hydrogenation.[10] This change has allowed us to shorten our synthetic route and substantially decrease processing times and increase throughput. More importantly, it has provided us with a safe, scalable route for future campaigns. Through these modifications, we are able to synthesize **7** through a 5-step process. The synthesis is conveniently carried out in one vessel and affords high purity material in a 52% overall yield.

RESULTS AND DISCUSSION

The synthetic strategy to constructing **7** is to assemble it *via* reductive amination from its two building blocks, 5-adamantylmethoxy-1-pentanal (**4**) and 1-deoxynojirimycin (**5**). Groups have previously carried out this transformation by coupling **4** with tetrabenzylated **5** through reductive amination, followed by deprotection.[4] While some elegant process work was performed to carry this out at scale, the route is costly and not particularly atom efficient. Aminosugars, such as **5**, are now made via biotransformation[11] which has recently allowed them to become economically viable starting materials at scale. Our process purchases **5** from Bayer AG and permitted us to concentrate on optimizing the rest of the process.

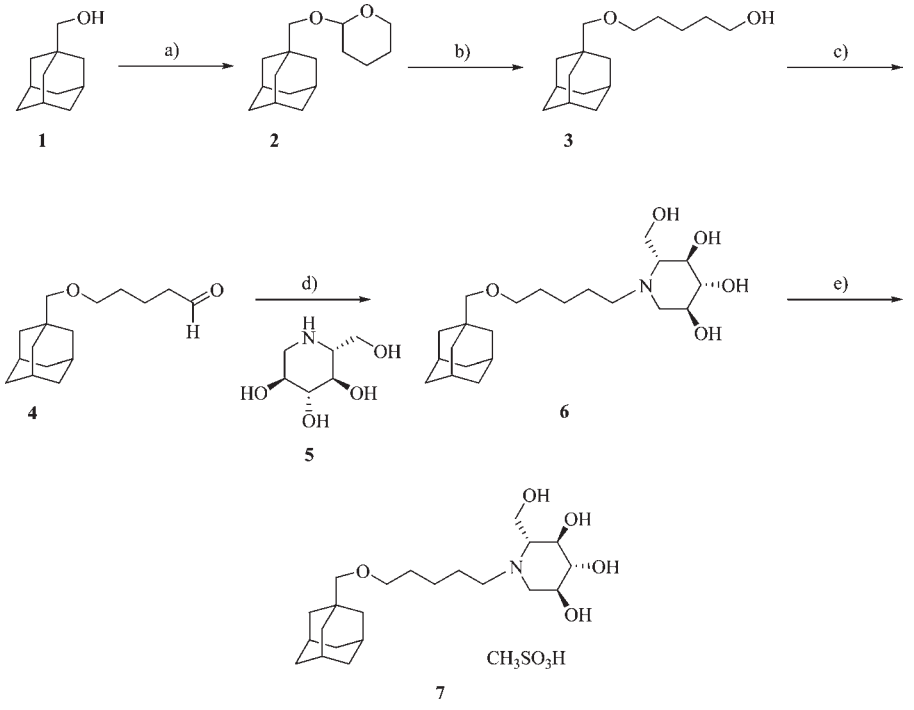
The second component necessary for the production of **7** is the aldehyde coupling partner, **4**. The original route (Scheme 2) employs 1,5-pentanediol as a starting material and produces aldehyde **4** in five steps with an overall yield of 47%.[4]

There are some issues with running this process at scale. Formation of tosylate **9** gives a statistical mixture of the desired product and ditosylated product even when using a limiting amount of tosyl chloride. This impurity is difficult to remove. Additionally, tosylate displacement is carried out in DMF using

Special Issue: Continuous Processing 2012

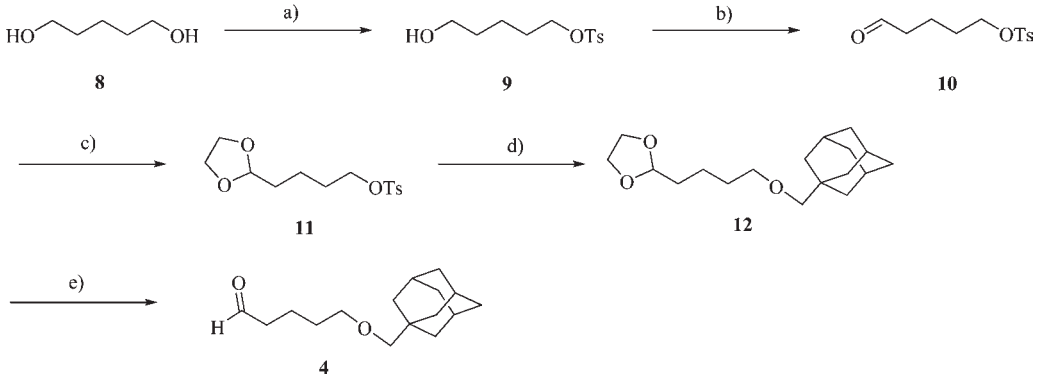
Received: May 4, 2011
Published: June 26, 2011

Scheme 1. Synthetic route to GCS inhibitor 1[a]



[a] Reagents and conditions: (a) 3,4-Dihydro-2*H*-pyran, cat. TsOH, THF, 50 °C, 1 h, used crude. (b) 1 M BH_3 in THF, 40 °C, 24 h, used crude. (c) TEMPO, NaOCl, DCM, aq. $NaHCO_3$, 0−10 °C, 1 h, used crude. (d) THF/H_2O, hydrogenated over $Pd(OH)_2$ in a flow reactor. (e) ACN/MeOH, MSA, then IPA recrystallization; 52% yield over 5 steps.

Scheme 2. Initial route to aldehyde 4[a]



[a] Reagents and conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 16 h, 73%. (b) TEMPO, NaOCl, KBr, CH_2Cl_2, 9% aq $NaHCO_3$, 5 °C, 2.5 h 91%. (c) Ethylene glycol, pTsOH, TBME, reflux, 3 h 96.5%. (d) NaH, DMF, 1-adamantanemethanol, 40 °C, 4 h. Product distilled, 80.5%. (e) 6 M HCl, Acetone, 91%.

sodium hydride, a safety concern given the possibility of a self-accelerating reaction.[12,13] Purification of **12** was necessary; however distillation was problematic as 1-adamantanemethanol sublimed and caused blockages during the distillation.

In response to some of the issues associated with the process outlined above for the manufacture of the aldehyde, an alternative route was developed in our laboratories (Scheme 3).[6]

This route afforded the desired aldehyde in 55% yield over three steps. This route represents a more expedient way to get the desired aldehyde but required optimization before large scale work. Alkylation of 1-adamantanemethanol to afford **13** gave inconsistent results. Under these reaction conditions, the predominant reaction taking place is elimination of the 5-bromo-1-pentene, thus requiring large excesses of the bromide to react all the alcohol. Phase transfer conditions produced similar results. Several other protocols were attempted for this substitution; both strong and weak bases were tried, as well as low and high temperatures. The problem with the reaction is that 1-adamantanemethanol is a neopentyl system and is therefore a poor nucleophile for an S_N2 reaction: the product is kinetically

dx.doi.org/10.1021/op2001222 |*Org. Process Res. Dev.* 2012, 16, 1090–1097

unfavored. Furthermore, column purification was necessary for **13** to achieve acceptable purity of aldehyde **4**.

Our initial attempts at a new route for aldehyde **4** were focused on eliminating the ditosylated impurity in the original synthesis, using cost-effective reagents, altering the tosylate displacement conditions to remove DMF, and developing a procedure for purifying the aldehyde without distillation, which resulted in a new route (Scheme 4).

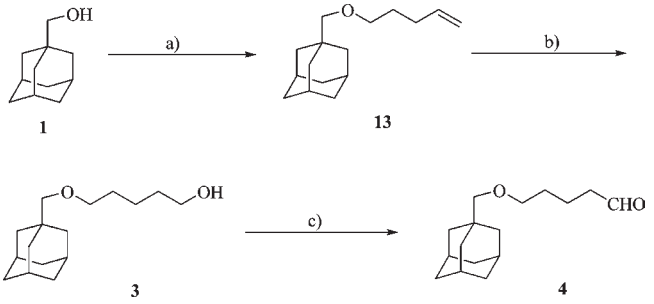
Formation of **14** went in modest yield (40−50%) when using sulfonic acid catalysts and organic media, due to the equilibrium between the desired ketal and THP ether in the initial step.[14] By running the reaction in aqueous acid, we favor the formation of the desired ketal as a 2:1 mixture, vs a 1:1 mixture seen in organic systems. While this has been previously observed for tetrahydrofuranyl reactions,[15] it was previously unreported for these ketalizations. Although the yield was low, **14** could be isolated in >98% purity *via* crystallization from aqueous IPA. This crystallization solvent offered the additional advantage of destroying unreacted TsCl. The alkylation of this product went in high yield in THF, giving **15** in yields of 98% or greater. Problems arose when we attempted to deprotect the ketal to form **4**. The use of very strong acids (e.g., sulfuric acid, triflic acid) was successful in removing the protecting group but also began to promote aldol side reactions and discolored the reaction mixture immediately upon addition. After an extensive screen, formic acid offered the most economical solution to the problem, as well as producing the highest yields of the desired aldehyde. While aldol side products were still possible, they could be minimized by running the reaction at temperatures under 50 °C and by monitoring reaction progress via HPLC. This route was used to make 500 g of crude aldehyde. This material could be used crude to form the desired API in acceptable purity or could be isolated as a pure solid via formation of its bisulfite adduct in aqueous IPA. While this route was capable of producing high purity material, the overall yield was low (29%) and the product made *via* this route contained aldol impurities that differed from those seen in the toxological material. As this would have required a bridging study to validate the new impurities, the route was abandoned. A key feature of this route was that it introduced the alkyl chain onto adamantly alcohol in an atom efficient manner. If possible, we wanted to incorporate this feature into any new route.

One way we thought we might accomplish this was by the reductive cleavage of a tetrahydropyranyl (THP) ether intermediate. THP ethers are popular protecting groups for primary alcohols as they are easily installed, stable to most nonacidic conditions, and easily removed *via* mild acids. From the literature, these ethers are more or less inert towards catalytic hydrogenation and are stable to treatment with both aluminum hydride and borohydride reagents. Hence, we required precedent for cleaving the endocyclic bond of a THP ether selectively in order for this route to be successful (Scheme 5).

Few papers have been published on the regiospecific cleavage of THP ethers, although Lewis acids have been shown to effect cleavage with varying degrees of endo vs exo selectivity.[16,17] The first to report selective reductive ring cleavage was Cossy.[18] Based on this literature, we decided to develop a route to **7** based on a borane ring opening of a THP ether as shown in Scheme 1. THP ether **2** was formed by reacting 1-adamantanemethanol with a slight excess of dihydropyran in THF with catalytic tosic acid. The reaction proceeds cleanly and can be used for the subsequent step without purification and proceeds quantitatively based on in-process NMR analysis.

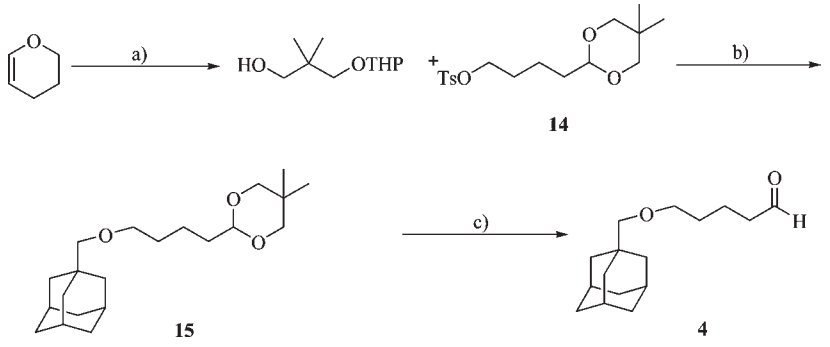
Reduction of ether **2** to alcohol **3** *via* reaction with a borane/THF complex was successful but required safety investigation prior to scaleup. The dangers of working with borane/THF complexes have been well documented.[19] While the problems with this reagent typically occur with storage of the raw material, the fact that it is a highly reactive substance that can become unstable upon prolonged heating led to several precautions. The borane/THF complex used was stabilized with

Scheme 3. First generation process for aldehyde 4[a]



[a] Reagents and conditions: (a) 5-bromo-1-pentene, NaOH, DMSO, 70 °C, 16 h, 65.4%. (b) (1) 9-BBN, diethyl ether, THF, rt, 16 h. (2) aq NaOH, 30% H_2O_2, rt, 3 h, 89%. (c) (1) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, 30 min. (2) Et_3N, warm to rt, 95%.

Scheme 4. Synthesis of 4 via dihydropyran[a]

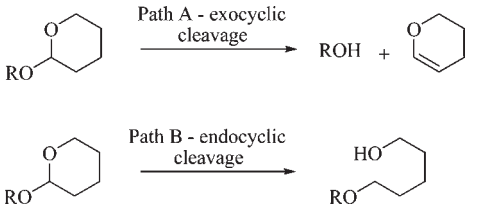


[a] Reagents and conditions: (a) (1) neopentyl glycol, 1 M HCl, 50 °C, 2 h. (2) CH_2Cl_2, Et_3N, TsCl, 0 °C to rt, 2 h, 50% over 2 steps. (b) 1-Adamantanemethanol, NaH, THF, reflux, 16 h, 98%. (c) Formic acid, 45 °C, 3 h, 60%.

N-isopropyl-*N*-methyl-*tert*-butylamine, which has been shown to be much more stable than either unstabilized borane/THF or borane/THF stabilized with sodium borohydride.[20] Of particular importance to us was that the stabilized borane/THF has a reported self-accelerated decomposition temperature (SADT) threshold of >50 °C.[20] This is a measure of the lowest temperature at which a self-accelerating reaction can begin to occur by itself. Unstabilized borane/THF solutions or solutions stabilized with $NaBH_4$ have SADT thresholds at or just above 40 °C.[20]

Our initial efforts focused on the kinetics of this reaction. Based on the reaction mechanism, we reasoned that given enough time, the reaction would proceed to completion if 0.33 equiv of borane/THF complex was charged. When the reaction was run with this many equivalents at 40 °C, we observed a kinetic trace that was reminiscent of second-order kinetics. We reason that, after a relatively fast formation of an initial alkoxyborane species, subsequent reactions are slower due to the decreased Lewis acidity of the borane center—as we have previously seen, coordination is essential to this ring-opening process. While the reaction would run to completion with as few as 0.7 equiv of borane/THF complex, we were interested in having the reaction complete within a 24 h period, to minimize borane degradation. Although the borane is stabilized, it undergoes ∼10% degradation after 48 h at 48 °C.[20] While complete conversion was observed for all amounts of borane/THF ≥ 0.7 equiv, 2 equiv of the borane/THF complex at 40 °C for 16 h gave complete conversion of THP ether **2** to alcohol **3**. The use of 2 equiv of borane was chosen because the reaction was consistently complete in 16 h, whereas lower amounts had greater variation in reaction time.

Scheme 5. THP ether reactivity



A series of calorimetric experiments were run using a Mettler Toledo RC-1 Reaction Calorimeter to quantify the process safety parameters. The experiments were used to investigate three operations within the reaction:

1 The heat rise and thermal behavior of borane being dosed into the reaction
2 The heat flow during the reaction, with attention being paid to any thermal accumulation
3 The heat rise, thermal behavior, and gas evolution during the reaction quench.

While addition of borane to the reaction mixture was an exothermic process, the heat generated was dosing controlled.

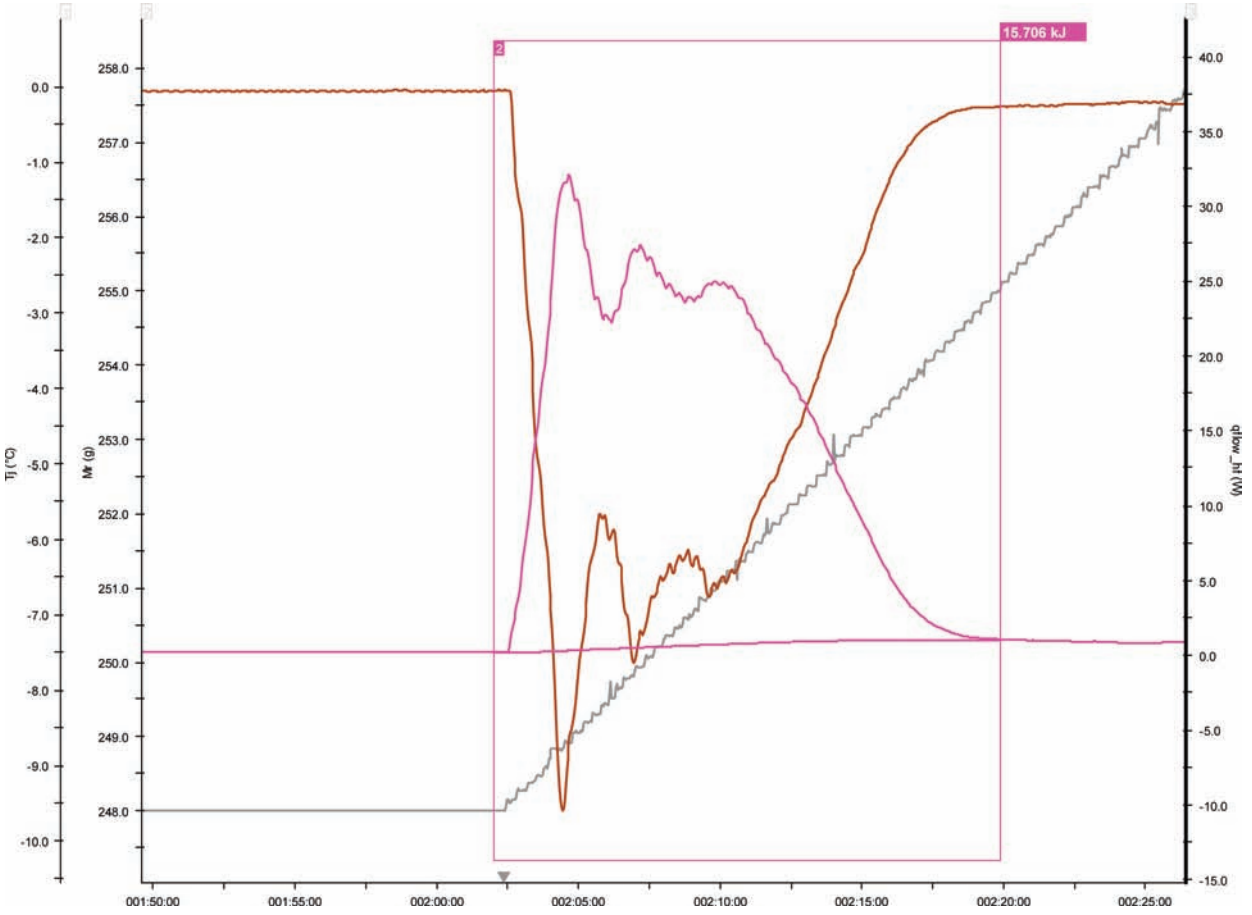


Figure 1. Calorimetric data for the borane quench. The heat flow is shown in pink, the jacket temperature in brown, and the mass of reaction in gray. Based on these data, the adiabatic temperature rise for the operation was 32.24 °C.

dx.doi.org/10.1021/op2001222 |*Org. Process Res. Dev.* 2012, 16, 1090–1097

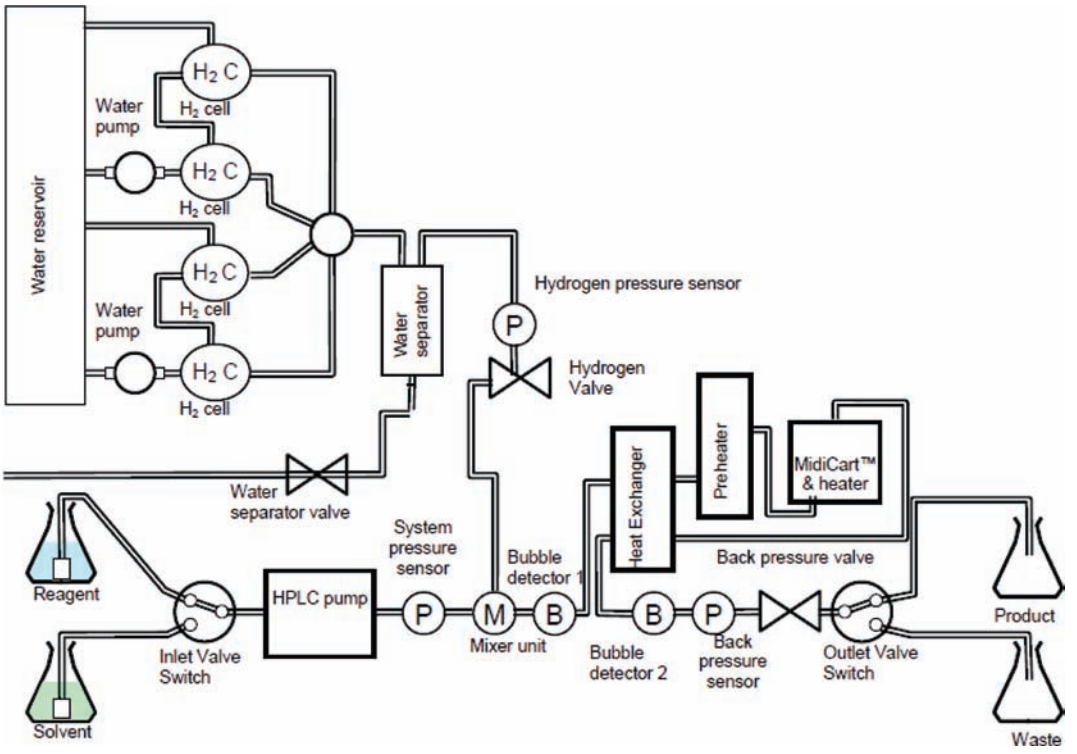


Figure 2. H-Cube MIDI flow hydrogenator.

Because of this, the reaction was dosed at 0 °C, followed by ramping the temperature over 2 h to 40 °C, where it was held for 16 h. During the hold point, there was no noticeable thermal accumulation taking place during the reduction. Once the reaction was deemed complete by either HPLC or NMR analysis, it was cooled to 0 °C and quenched with 1 M HCl. While the quench of the reaction was exothermic (adiabatic temperature rise of 32.24 °C), the heat rise was dosing controlled (see Figure 1). Furthermore, while off-gassing was observed, it was also dosing controlled and did not lead to foaming or bumping. With these data in hand, we felt confident that the reaction could be safely scaled.

Once a safe process for producing **3** was developed, we could easily convert it to aldehyde **4** *via* a TEMPO oxidation.[21] The resultant aldehyde was isolated crude after a solvent extraction workup and could be used "as is" for the final reductive amination. Overall, the yield for aldehyde production has been almost doubled from previous attempts to an average yield of 85% and now uses inexpensive materials throughout. The process to make the aldehyde has been run on multiple occasions with consistent yields and purity from batch to batch, signifying process robustness.

Developing a route to couple **4** with DNJ (**5**) through reductive amination proved to be surprisingly difficult. Due to the water solubility of penultimate product **6**, reductive aminations using borohydrides or transfer hydrogenation conditions were not suitable. Catalytic hydrogenation of the imine seemed promising and worked well at small scale. However, the throughput of this reaction was limited by the pressure vessels on hand.

Flow hydrogenation addressed the issue. From a safety standpoint, the reaction volume in a flow system at any moment in time is very small (~ 8 mL in our system) and minimizes the danger from any unexpected event. From a throughput standpoint, we are no longer limited by batch size, as batches can be continuously processed in a flow system. Additionally, flow hydrogenation eliminates mass transfer limitations, which can cause reactions to run slowly at increasing scale, and can also lead to the formation of side products due to increased reaction time.

While there were several options available for kilo-lab scale flow systems, the H-Cube MIDI[22] worked well for us and addressed our safety concerns. The apparatus is fully explosion proof, could integrate into our kilo-lab facilities without issue, and generates hydrogen in situ via the electrolysis of water eliminating the need for high pressure hydrogen tanks. It is also capable of flow rates between 3 and 25 mL/min, using temperatures between ambient and 150 °C, and generating up to 100 bar of hydrogen pressure (1450 psi) (Figure 2).

A particular challenge to running this reaction under flow conditions was the selection of an appropriate solvent. Initially, we were running these aminations in batch mode using IPA as a solvent, as the final salt could be isolated directly once amination was complete. Flow chemistry holds many advantages over batch chemistry but cannot work unless all the materials in the reaction are completely soluble. DNJ has only moderate solubility in IPA, and while DNJ exhibited high solubility in water, aldehyde **4** was not miscible with the resultant solution. Acetic acid initially offered itself as a replacement, as it is widely used in processes; both DNJ and the aldehyde were readily soluble in it, and the reaction ran very nicely in it (the reaction ran to full conversion at lower temperatures and pressures than the solvent system ultimately selected). However, the issue with acetic acid was that the resultant acetate salt was difficult to free base and isolate in order to convert to the MSA salt. Additionally, attempting a salt exchange failed to give crystalline material. Based on these concerns, we switched to a mixed solvent system

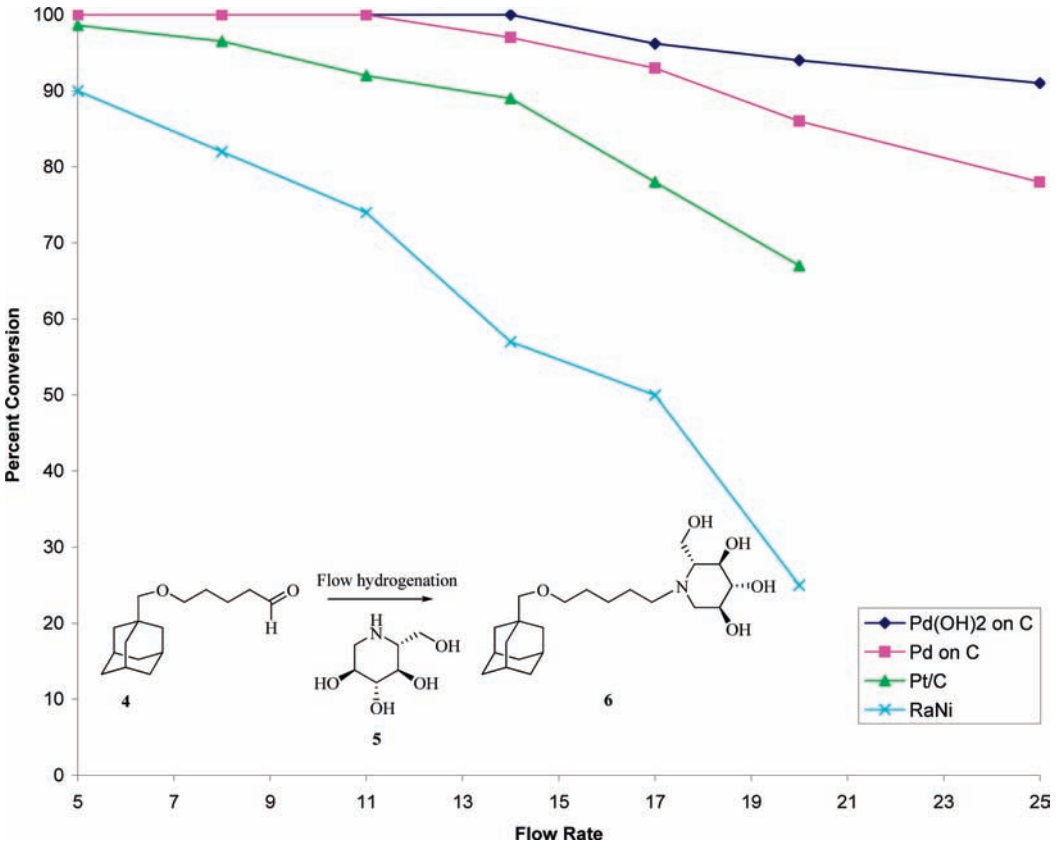


Figure 3. Percent conversion of starting material to product vs flow rate: The reductive amination was run at 150 °C, under 100 bar of H_2 using a 600 mmol/L reaction solution.

of 2:2:1 MeOH/THF/H_2O. This system was capable of keeping all the reagents in solution at rt at a concentration of 600 mmol/L DNJ. More concentrated solutions would result in crystallization of the starting materials during the flow reaction. Adding more water to the mixture to increase DNJ solubility was not an option, as it caused the aldehyde to become immiscible.

Once the solubility issues of the starting materials was solved, we focused on developing flow conditions that would maximize our throughput for a single pass hydrogenation. For a given catalyst, many reaction conditions can be screened quickly by varying flow rate and temperature. We undertook a catalyst screen to determine which catalysts were best suited for this chemistry, with a particular focus on reaction throughput. A plot of reaction conversion vs flow rate is shown in Figure 3.

From Figure 3, it is clear that the Pd based catalysts perform the best with increasing flow rate leading to the decision to use $Pd(OH)_2$ on C as our catalyst. It is interesting to note that when the above experiments were done in AcOH, conversion was consistently higher at lower pressures and higher flow rates. The stoichiometry of the reaction turned out to be critical for our final impurity profile. While the reaction would run to >98% conversion using equimolar amounts of aldehyde and iminosugar, it turned out to be more or less impossible to remove unreacted DNJ from our reaction mixture. Despite being more hydrophobic than DNJ, free base **6** was still very water-soluble, making washing out residual DNJ through solvent extraction unachievable. Additionally, forming MSA salt **7** did nothing to lower residual amounts of DNJ. Initially, experiments were performed using purified aldehyde and DNJ to determine the amount of aldehyde needed to consume >99.8% of DNJ during a single pass. These experiments showed that 1.6 equiv of aldehyde would consistently reach this level. Based on an 85% yield of aldehyde **4** from the starting material, 0.53 equiv of DNJ could be used relative to the amount of 1-adamantanemethanol started with.

The optimized conditions were to dissolve **4** and **5** in a mixture of THF/MeOH/H_2O and then to hydrogenate at 100 bar and 150 °C, at a flow rate of 15 mL/min. The reaction was complete in a single pass at this rate. Based on the flow rate and the molarity of the solution, 1 kg of this material per day could be processed. To date, we have piloted this chemistry several times on 100 g scale with consistent results but have no plans to scale it larger due to a change in project focus. We routinely employ flow methodologies on scale, not only for reductive aminations but also for the reduction of other moieties.

The crude reaction mixture containing **6** was solvent swapped into a mixture of MeOH and ACN, and the mesic acid salt formed *via* addition of MSA. This salt was recrystallized from IPA to give the final material, in 99.4% purity.

■ CONCLUSION

A scalable, economic, and novel route to GCS inhibitor **7** was developed. The key step in the current route is a borane mediated endocyclic C−O bond cleavage of a THP ether. Because of this step, we were able to increase the yield of building block **4** substantially and were able to use it to make suitable material for clinical studies. Reaction calorimetry was used to confirm the safety and scalability of all steps, but particularly of the borane

dx.doi.org/10.1021/op2001222 |*Org. Process Res. Dev.* 2012, 16, 1090–1097

reduction. The use of flow hydrogenation was key for preparing **7** in a rapid manner, which increased both throughput and safety.

EXPERIMENTAL SECTION

General. 1-adamantanemethanol was obtained from Carbosynth Ltd. (Berkshire, UK), and deoxynojirimycin was obtained from Bayer AG (Leverkusen, Germany). Borane/THF complex (1.0 M) stabilized with *N*-isopropyl-*N*-methyl-*tert*-butylamine was purchased from Aldrich and used fresh. Due to the weak absorbing nature of the compound, LC purity determination was performed using an Agilent 1100 HPLC equipped with a Corona CAD detector. All reactions were carried out in an inert atmosphere using nitrogen as the blanket gas.

1-Adamantanemethanol Tetrahydropyranyl Ether (2). A solution of 1-adamantane methanol (**1**, 132.8 g, 0.8 mol) and tosic acid (3.04 g, 0.016 mol) in THF (400 mL) was heated to 45 °C under nitrogen. Once at temperature, 3,4-dihydro-2*H*-pyran (73.4 mL, 0.8 mol) was added *via* addition funnel at a rate such that the temperature was maintained within 0.5 °C of the set point. Once addition was complete, the reaction was heated to 55 °C for 2 h. The reaction was cooled to rt and sampled for analysis. The starting material was converted to product in excess of 95% by NMR analysis and was used for subsequent steps without further purification. A 2 mL sample was concentrated under reduced pressure for analysis. ^{1}H NMR (400 MHz, $CDCl_3$) 4.52 (t, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.45 (m, 1H), 3.38 (d, 1H), 2.90 (d, 1H), 1.4−2.0 (m, 20 H). ^{13}C (100 MHz, $CDCl_3$) 98.99, 78.18, 61.75, 39.71, 37.26, 33.72, 30.60, 33.72, 28.31, 25.61, 19.45.

5-(Adamant-1-yl-methoxy)-1-pentanol (3). The solution of **2** isolated in the previous step was cooled to 5 °C, and 1.6 L of 1 M borane/THF complex in THF (1.6 mol) were slowly added to the solution *via* addition funnel over 1 h. Addition was performed slowly in order to prevent any thermal accumulation and also control the amount of off-gassing observed. Once addition was complete, the reaction was warmed to rt over 1 h and then heated at 45 °C for 18 h. The reaction progress was checked *via* ^{1}H NMR and was found to be complete. The reaction mixture was cooled to 5 °C and was quenched by 300 mL of 1 M HCl *via* addition funnel over 1 h. Once addition was complete, the reaction was warmed to 55 °C for 1 h, to ensure destruction of any borane complexes, and was cooled to rt. The reaction mixture was diluted with 500 mL of brine, and the organic layer was isolated. The organic layer was charged to a clean reaction flask, and 1.8 L of solvent were distilled off. Methylene chloride was charged to the flask (2 L), and 1 L of solvent was distilled off. The reaction was filtered to remove a small amount of precipitated boric acid, and the filtrate was charged to a clean flask for the subsequent step. A 2 mL sample was taken and concentrated under reduced pressure for analysis. ^{1}H NMR (400 MHz, $CDCl_3$) 3.63 (t, 2H), 3.40 (t, 2H), 2.95 (s, 2 H), 1.98 (m, 3 H), 1.4−1.8 (m, 19 H). ^{13}C NMR (100 MHz, $CDCl_3$) 81.89, 71.57, 62.77, 39.74, 37.25, 34.09, 32.48, 29.29, 28.30, 22.42.

5-(Adamant-1-yl-methoxy)-1-pentanal (4). The solution of alcohol **3** from the previous step was cooled to 5 °C, and a solution of K_2CO_3 (14.4 g, 0.104 mol), $NaHCO_s$ (87.3 g, 1.04 mol), and KBr (0.95 g, 0.08 mol) in 1.6 L of H_2O was charged. TEMPO (2.5 g, 0.16 mol) was charged to the stirred reaction mixture. The reaction was then dosed with 10% sodium hypochlorite solution (600 mL) over 2 h. The reaction was dosed at a rate such that the reaction temperature did not rise above 10 °C at any point. Once dosing was complete, reaction completion was confirmed with NMR analysis. Excess oxidant was destroyed by addition of 10% aq sodium thiosulfate (600 mL), and the organic layer was isolated. The organic layer was washed with 1 M HCl (500 mL), sat. brine (500 mL), and water (500 mL). A 10 mL sample was taken and concentrated to dryness to get an estimated yield and an analysis. Based on the results, approximately 170 g (85% yield over three steps) of aldehyde were formed over the three-step synthesis. The aldehyde was left in solution in order to do the final coupling. ^{1}H NMR (400 MHz, $CDCl_3$) 9.78 (s, 1H), 3.41 (t, 2 H), 2.98 (s, 2H), 2.44 (t, 2H), 1.98 (m, 3H), 1.45−1.80 (m, 16 H). ^{13}C NMR (100 MHz, $CDCl_3$) 202.88, 82.11, 71.09, 43.88, 39.89, 37.40, 34.18, 29.18, 28.43, 19.19.

***N*-[5-(Adamantan-1-yl-methoxy)pentyl]-1-deoxynojirimycin Methanesulfonic Acid Salt (7).** The aldehyde solution from the previous step was concentrated to a minimum stir volume (120 mL), and 140 mL of THF and 280 mL of MeOH were added. In a separate flask, 70 g of deoxynojirimycin (0.428 mol) were dissolved in 280 mL of DI H_2O and added to the aldehyde solution. The solution was briefly stirred to ensure dissolution and then polish filtered through a 0.22 μm filter. The reaction solution was then passed through the H-Cube MIDI flow hydrogenator at a flow rate of 15 mL/min, over a 20% $Pd(OH)_2$ on a C catalyst bed, at 145 °C under 95 bar of hydrogen pressure. The reaction was complete after a single pass through the apparatus. After hydrogenation, the reaction mixture was charged to a 5 L three-neck round-bottom flask, equipped with an overhead stirrer, nitrogen line, and thermocouple. The reaction mixture was distilled to a minimum stir volume (200 mL), and toluene (1 L) was charged. The reaction was again distilled to a minimum stir volume (200 mL). The reaction mixture was dissolved in 1.5 L of 30% methanol in ACN and was brought to rt. Methanesulfonic acid (28 mL) was added to the reaction mixture over 1 h. The reaction mixture was heated to 50 °C and allowed to cool to rt over 1 h. The reaction was cooled to 0 °C, stirred for 1 h, and filtered. The filtered solids were suspended in 700 mL of isopropanol and dissolved at 50 °C. The reaction was allowed to cool to rt and stir for 2 h. Filtration followed by drying under vacuum at 60 °C to a constant weight afforded 130.7 g of the desired compound as a white solid (Yield 61.5%). ^{1}H NMR (400 MHz, DMSO-d_6) 9.26 (s, 1H, from MSA), 5.51 (m, 4H from OH groups), 3.92 (m, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 3.32−2.92 (m, 11H), 2.39 (s, 3H from mesic acid), 1.91 (m, 3H), 1.68−1.30 (m, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 81.01, 76.38, 70.38, 67.19, 66.03, 65.36, 53.96, 53.33, 51.99, 39.63 (under DMSO peak, resolves w/APT), 39.23 (under DMSO peak, resolves with APT), 36.71, 33.60, 38.54, 37.59, 22.92, 21.96. DSC, 182.58 °C, 95.86 J/g (melting point). TGA, 0% LOD up to 191.3 °C, at which point decomposition occurs. AUC Purity (HPLC, Corona CAD Detector) 99.4%. This material contained 740 ppm of residual isopropanol, which meets ICH guidelines. No other solvents were observed via GC headspace analysis. Less than 1 ppm of residual Pd was detected via ICP MS.

ASSOCIATED CONTENT

Supporting Information. ^{1}H, ^{13}C, APT NMR spectra, HPLC data, DSC and TGA data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: christopher.cooper@genzyme.com.

REFERENCES

(1) Wennekes, T.; Lang, B.; Leeman, M.; van der Marel, G. A.; Weber, M.; van Wiltenburg, J.; Wolberg, M.; Aerts, J. M.; Overkleeft, H. S. *Org. Proc. Res. Dev.* **2008**, *12*, 414.
(2) Aerts, J. M.; Ottenhoff, R.; Powlson, S.; Grefhorst, A.; van Eijk, M.; Dubbelhuis, P. F.; Aten, J.; Kuipers, F.; Serlie, M. J.; Wennekes, T.; Sethi, J. K.; O'Rahilly, S.; Overkleeft, H. S. *Diabetes* **2007**, *55*, 1341.
(3) Hirth, B.; Rennie, G. *PCT Int. Appl.* **2005**, WO 2005063706.
(4) Jeyakumar, M.; Norflus, F.; Tifft, C. J.; Cortina-Borja, M.; Butters, T. D. *Blood* **2001**, *97*, 327.
(5) Moran, M. T.; Schofield, J. P.; Hayman, A. R.; Gou-Ping, S.; Young, E.; Cox, T. M. *Blood* **2000**, *96*, 1969.
(6) Zhao, H.; Przybylska, M.; Wu, I. H.; Zhang, J.; Siegel, C.; Komarnitsky, S.; Yew, N. S.; Cheng, S. H. *Diabetes* **2007**, *56*, 1210.
(7) Shayman, J. A.; Radin, N. S. Amino Ceramide-Like Compounds and Methods of Use. US Patent 6,255,336, July 9, 1999.
(8) Cox, T.; Platt, F.; Aerts, J. *Iminosugars* **2007**, 295.
(9) Overkleeft, H.; Renkama, G.; Neele, J.; Vianello, P.; Hung, I.; Strijland, A.; van der Burg, A.; Koomen, G.; Pandit, U.; Aerts, J. *J. Biol. Chem.* **1998**, *273*, 26522.
(10) Ley, S. V.; Knudson, K. R.; Ladlow, M.; Saaby, S. *Chem. Commun.* **2005**, 2909.
(11) Kinast, G.; Schedel, M. (Bayer AG). 6-Amino-6-deoxy-L-sorbose. Ger Offen. DE 2834122, February 14, 1980.
(12) Buckley, J. *Chem. Eng. News* **1982**, *60* (28), 5.
(13) De Wall, G. *Chem. Eng. News* **1982**, *60* (37), 43.
(14) Bartels, G. (Hoechst AG). Simplified preparation of 2-(3-bromopropyl)- and 2-(4-bromobutyl)-5,5-dimethyl-1,3-dioxane Ger. Offen. DE 3537289, February 23, 1987.
(15) Stowell, J.; Polito, M. *J. Org. Chem.* **1992**, *57*, 2195.
(16) Eliel, E.; Nowak, B.; Daignault, R. *J. Org. Chem.* **1965**, *30*, 2448.
(17) Guindon, Y.; Bernstein, M.; Anderson, P. *Tetrahedron Lett.* **1987**, *28*, 2225.
(18) Cossy, J.; Bellosta, V.; Muller, M. C. *Tetrahedron Lett.* **1992**, *33*, 5045.
(19) Urben, P. G., Ed. *Brethericks's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth Heinemann: Boston, 1999.
(20) See Aldrich Technical Bulletin AL-218, available online at http://www.sigmaaldrich.com.
(21) For a review, see: Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245.
(22) Information and schematics available through http://www.thalenano.com/products/h-cube-midi.

NOTE ADDED AFTER ASAP PUBLICATION

This article was published on the Web on July 5, 2011. Omitted references have been added and a misspelling of an author's name has been updated. The corrected version was reposted on August 22, 2011. An additional reference was added; the corrected version was reposted on December 16, 2011.