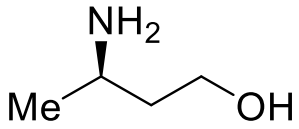
PROCESS DEVELOPMENT REPORT

The Medicines for All Initiative

Synthesis of (*R*)-3-aminobutan-1-ol



November 18th, 2019

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Executive Summary

We present a one-step synthesis of optically active (*R*)-3-aminobutan-1-ol from commercially available starting materials. This product is a key raw material used in the production of dolutegravir. Our process reduces (*R*)-3-aminobutanoic acid using the low-cost reducing agent sodium aluminum hydride. The approach provides isolated yields ranging from 61-67% with purity ranging from 96-99% and optical purity at 100% based on three 20 gram scale runs.

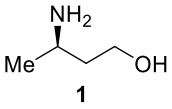
Introduction

The fixed dose combination therapy of tenofovir, lamivudine and dolutegravir is becoming first-line therapy for HIV patients in more than 50 low- to middle-income countries. Reducing the productions costs associated with this suite of medicines will increase the number of patients who have access to these medicines. Dolutegravir is a newer medicine and has received less attention from a synthetic standpoint relative to tenofovir and lamivudine. We previously reported a continuous process for producing the pyridone starting, and we now disclose a low cost route to the optically active amino alcohol raw material.

The four carbon (*R*)-3-aminobutan-1-ol is a major cost driver for dolutegravir production - nearly 30% of the overall cost. The synthesis of small chiral alcohols is challenging for many reasons including purification complications because of their low boiling points. A market price of (*R*)-3-aminobutan-1-ol is difficult to establish, as only low volume transactions with a wide range of prices are available. A recent sizeable purchase of 400 kg by a major Indian API manufacturer recorded in the India Import/Export database identifies a price of $345/kg. Anecdotal evidence from other manufacturers suggests that purchases are being made in the $150-200/kg range.

Prior Art

M4ALL has evaluated several routes reported in the patent and academic literature regarding the synthesis of (*R*)-3-aminobutan-1-ol (**1**).



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Each of the approaches can be categorized into one of four categories (Figure 1): 1) chemoenzymatic approaches 2) asymmetric catalysis 3) chiral resolutions 4) chiral auxiliaries/chiral pool. Representative examples for each approach will be discussed to highlight advantages and disadvantages.

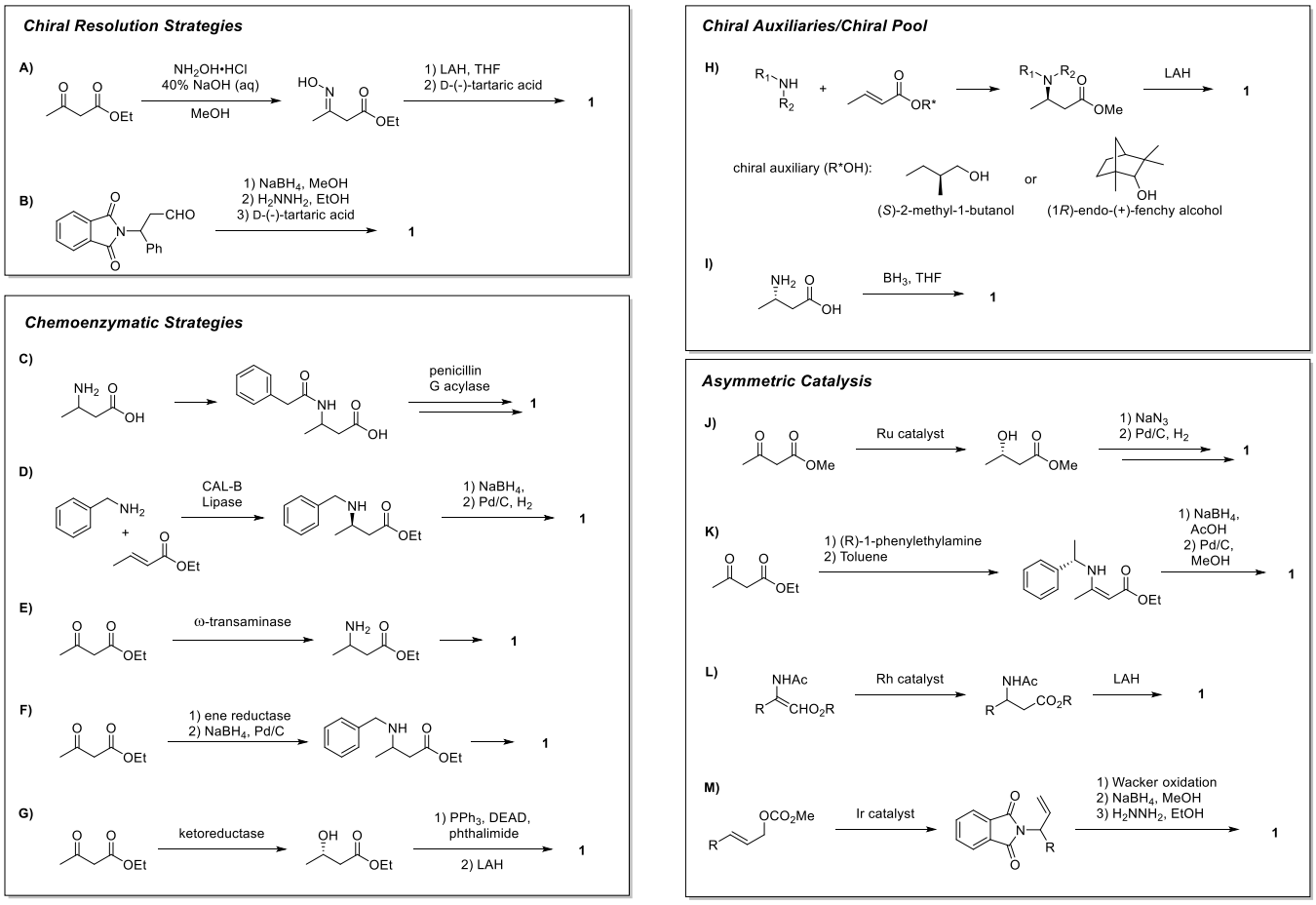


Figure 1. Summary of Synthetic Strategies to Access (*R*)-3-aminobutan-1-ol.

Chemoenzymatic approaches offer several advantages compared to traditional organic synthesis. Enzymatic transformations are facilitated by readily available materials (D-glucose, NADH/NADPH, etc.), inexpensive first-row transition metals, if a metal is required at all, and do not rely on the use of expensive chiral ligands. In each of the cases highlighted in Figure 1, multiple unit operations (up to 3 synthetic steps) are required to access **1**, making these strategies expensive.[1–4]

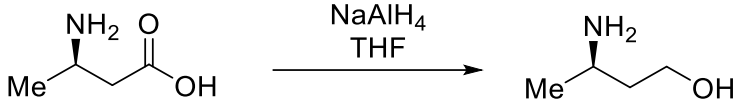
An alternative method for the preparation of enantiopure **1** utilizes asymmetric methodologies.[5] In one example, the stereocenter is installed via a Noyori hydrogenation of methyl acetoacetate using a ruthenium-BINAP catalytic system.[6] The resulting alcohol is subjected to a Mitsunobu transformation with sodium azide, which is reduced over Pd/C under hydrogen to yield the desired 1,3-aminoalcohol. This particular approach has several drawbacks. The Mitsunobu transformation is wasteful; stoichiometric reagents are required and stoichiometric byproducts are generated. Additionally, sodium azide and the alkyl azide intermediates can be shock and temperature sensitive. The other known approaches use ligands or organocatalysts that are either prohibitively expensive or require multistep syntheses. These known asymmetric methodologies are unattractive for large-scale, low-cost syntheses of **1**.

Chiral resolution strategies are also known but like the other approaches, have liabilities. Starting with racemic **1**, enantiopure acids D-tartaric acid, (*R*)-mandelic acid can be used to generate diastereomeric salts of **1**, where the undesired enantiomer can be preferentially removed.[7,8] Unfortunately, the highest yield that can be achieved is 50% as a result of half of the material being the undesired enantiomer. In reality, the yield would likely be much lower than 50% as multiple synthetic steps are required to access the racemic aminoalcohol prior to the chiral resolution step.

The final strategy makes use of either chiral auxiliaries or utilizes the stock of readily available enantiopure materials. In one example where a chiral auxiliary was used, an enantioselective conjugate addition of benzylamine to (*E*)-but-2-enoate esters derived from either (*S*)-2-methyl-1-butanol or fenchyl alcohol exhibited good stereoselectivities (78% *ee*).[9] This approach comes with a couple of drawbacks: 1) stoichiometric amounts of chiral auxiliary are required and 2) it requires a minimum of three synthetic steps, creating opportunities for material loss. While the chiral auxiliary could be recovered, the number of recycles necessary to create a low cost route is unrealistic. Thus, M4ALL determined this approach to be less promising than one where the chiral pool is utilized. For example, **1** can be accessed directly in one-step from the commercially available (*R*)-3-aminobutanoic acid.[10–13] The reduction of the amino acid to the corresponding aminoalcohol has been achieved in numerous ways; however, this strategy generally suffers from expensive reagents ($NaBH_4$, I_2, $LiAlH_4$, BH_3). Despite these minor drawbacks, a one-step process where the starting materials are low cost prompted us to survey alternative reducing agents.

Medicines for All specializes in defining lower costs processes and we sought to find an alternative route to dolutegravir, examining several possible routes including enzymatic, asymmetric reduction, classic resolution and reduction of chiral pool materials. Market intelligence indicated that (*R*)-3-aminobutanoic acid could be available for <$100/kg leading to the decision to optimize a reduction process using hydride-based reagents. While lithium aluminum hydride (LAH) reductions of aminobutanoic acid are well-known, the cost of LAH is prohibitive. Sodium aluminum hydride (NAH) is used as a reversible storage medium for hydrogen gas because it is safe and denser relative to compressed hydrogen gas. The large scale production/use of NAH results in a lower price per kilogram relative to other reducing agents. While LAH and NAH are similar, their differences are significant enough to require optimization. Herein, we report our reduction process of (R)-3-aminobutanoic acid using NAH.

Experimental Procedures



Material	Mol. Wt. (g/mol)	mmol	Eq.	Amount	Density
(*R*)-3-aminobutanoic acid	103.12	242	1.0	25.0 g	-
Sodium Aluminum Hydride	54.00	484	2.0	26.1 g	-
Tetrahydrofuran, anhydrous	72.11	---	---	200 mL	0.89

Table 1: Reagents and quantities for the synthesis of (R)-3-aminobutanol

Safety Precautions

1. Sodium Aluminum Hydride reacts violently with water.

Step I: Procedure for Homo-Beta-Alanine Reduction

1. A 1000 mL, three-neck, round bottom flask equipped with a temperature probe, reflux condenser, and stir bar was flushed with N_2. Anhydrous THF (200 mL) was then added under positive N_2 pressure. The system was then placed into an ice/NaCl bath to cool to -8 °C (Internal temperature: 10 °C).
2. Sodium aluminum hydride (26.1 g, 484 mmol, 2.0 equiv) was then added to the cooled THF solution using a solid addition funnel and the mixture allowed to stir for 1hr. [CAUTION: ADDITION OF POWDERED METAL HYDRIDES TO ORGANIC SOLUTIONS CAN BE EXPLOSIVE].
3. Once the sodium aluminum hydride addition was complete, (*R*)-3-aminobutanoic acid (25.0 g, 242 mmol, 1.0 equiv) was added over 25 minutes so as to maintain an internal temperature no greater than 5.2 °C.[1] [2]
4. After stirring for 1 hour, the flask was removed from the ice bath and allowed to warm to room temperature with continued mixing (internal temperature: 20.5 °C).
5. The reaction was refluxed for 16h and then placed in an ice/NaCl bath to cool to -8 °C (Internal Temperature: 2.4 °C). Generally, assays indicated that the reaction was complete sooner but the 16h time was selected to ensure complete consumption of starting material.

[1] Pre-cooling was necessary because addition of the aminobutanoic acid resulting in rapid rise in temperature. We cooled as a precaution.

[2] We added the solid aminobutanoic acid for convenience but found that addition the material as a solution in THF provided similar outcomes.

6. To the cooled system, 10% NaOH in water (50 mL) was added dropwise to quench excess sodium aluminum hydride. Internal temperature was kept between 3-10 °C by adding the NaOH over a period of 1.5-2.5 hr.[3]
7. An additional portion of 10% NaOH in water (200 mL) was added to dissolve the remaining aluminum salts, and the reaction was stirred for 30 min.
8. The reaction mixture was transferred to a separatory funnel, and the organic and aqueous layers were separated.[4] The basic aqueous layer (pH ~11) was extracted twice more with recycled THF (200 mL each, 400 mL total).
9. The organic layers (600 mL) were combined and distilled using a Pope Scientific wiped-film evaporator (Temperature: 140 °C, Pressure: 10 torr, Speed: 30%). The solution was added dropwise to the distillation zone over a period of 2.5 to 3 hr. After completion, an additional 200 mL of THF was passed through the evaporator to ensure complete collection of amino alcohol.[5] 18.1 g of (*R*)-3-aminobutan-1-ol (84% purity, 0.170 mol, 70%) was collected as a pale-yellow oil (bp 65-70 °C at 9 mbar).[6]

Sensitivity Assessment

We performed a sensitivity assessment of the reaction variables as a function of conversion to better understand what factors might alter the process:

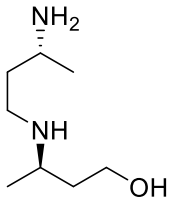
Sodium aluminum hydride: We screened equivalents between 1.0 and 3.0 and found that the completion conversion of the starting material occurred above 1.8 equivalents (relative to moles of sodium aluminum hydride – not relative to hydride equivalents). Under 1.8 equivalents and the conversion dropped.

Solvents: We performed the reaction with tetrahydrofuran (THF), 2-methyl-tetrahydrofuran (2-MeTHF), methyl tert-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and toluene. We observed little reaction for MTBE, CPME, and toluene. Both 2-MeTHF and THF showed significant reaction progress, however we observed complete conversion of starting material when using THF and only ~80% conversion when using 2-Me THF.

[3] Gelation of the aluminum salts was observed.
[4] Water/THF separations can be improved at high temperatures (35-40 °C).
[5] We recommend adding a stabilizer to the collected THF if recycling is intended.
[6] Use of a high boiling hydrocarbon "chaser" should improve the distillation yield without reducing the volume to unsafe levels.

Results

The reaction was performed repeatedly and by three separate researchers so as to demonstrate the reproducibility of this synthesis. Throughout the trials there was an observed isolated yield between ~65%-70%. The first six trials were distilled using a wipe-film evaporator which yielded a larger amount of lower purity (~85% purity by NMR) (*R*)-3-aminobutan-1-ol (Table 2.). Trials seven through ten were distilled by vacuum distillation with a short-path distillation head (bp 65-70 ˚C, 9 mbar). The first fractions were collected leaving byproduct (major byproduct observed was the dimer resulting from reductive amination – shown right) in the distillation pot and yielded slightly less material at higher purity (~98% purity by NMR) (Table 3).



Batch	1	2	3	4
Scale	25 g	25 g	25.4 g	19.5 g
Operator	John	John	Vijay	Vijay
Amount obtained	18.5 g	18.1 g	16.1 g	12.3 g
% Purity by NMR	80 %	84 %	85 %	83 %
% Isolated Yield (Corrected for purity)	69 %	70 %	62 %	58 %

Table 2: Process Snapshot of Runs 1-4

Batch	5	6	7	8	9	10
Scale	9.6 g	10.7 g	9.6 g	9.8 g	9.58 g	9.6 g
Operator	John		Vijay		Kashi	
Crude mass obtained	7.57 g	9.61 g	7.1 g	8.3 g	7.05 g	7.55 g
% Purity by NMR	73%	69%	76%	76%	85%	75%
Crude Yield (Adjusted for purity)	**67%**	**71%**	**65%**	**75%**	**72.5%**	**68.5%**
Distillation input	16.39 g		13.8 g		13.5 g	
Mass recovered (Adjusted for NMR purity)	10.46 g (10.25 g)		10.0 g (9.90 g)		10.80 g (10.31 g)	
Mass remaining in distillation pot (% Purity, % Yield)	5.83 g (15%, 5.0%)		3.8 g (4.0%, 1.0%)		2.4 g (2.9%, 0.63%)	
Mass discarded in heads (% Purity, % Yield)	0.300 g (68%, 1.2%)		--		--	
Adjusted amount for crude mass	10.74 g		11.05 g		11.15 g	
% Purity by NMR	98%		99%		95.5%	
Isolated Yield (Distillation, Receiver)	**61.2%**		**65.9%**		**67.2%**	

Table 3: Process Snapshot of Runs 5-10

Assay by GC using a commercial sample of the alcohol as a reference material showed agreement with NMR results. Chiral analysis was not performed for all batches but had consistently showed 100% chiral purity.

Conclusions

The market for dolutegravir is still evolving and many factors impact market prices. There are few shipments of the API at sufficient volumes to assess actual production costs. Extrapolation from market tenders for drug products containing dolutegravir suggests that manufacturers are using a $1300/kg price for the API, but this figure must include manufacturers' need to recoup their investment in research and development. These prices are expected to decline. Cost models based on current input costs, scale and published technology give an $800/kg figure. M4All cost models give a similar figure when $345/kg for the (*R*)-3-aminobutan-1-ol is combined with $10/kg conversion costs and yields in the 70-80% range. If the price of (*R*)-3-aminobutan-1-ol is reduced to around $100/kg based on the reported chemistry, the cost of dolutegravir can be expected to drop significantly.

References

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Product characterization

NMR

Purity was analyzed using quantitative NMR. Quantitative NMR was performed by integrating product signal and comparing against 1,3,5-trimethoxybenzene as standard (Figure 2 and Figure 3). A known amount of both product and standard were added to a vial and dissolved in $CDCl_3$. The following formula was used to assess purity:

$$P_x = I_x/I_{cal} \times N_{cal}/N_x \times M_x/M_{cal} \times W_{cal}/W_x \times P_{cal}$$

where I, N, M, W and P are the integrated area, number of nuclei, molecular mass, gravimetric weight and purity of the compound of interest (**1**) and the calibration compound (cal), respectively. ^{1}H NMR was run on a Bruker Avance 600 MHz with delay times (D1) of 15 second for the sake of quantitation.

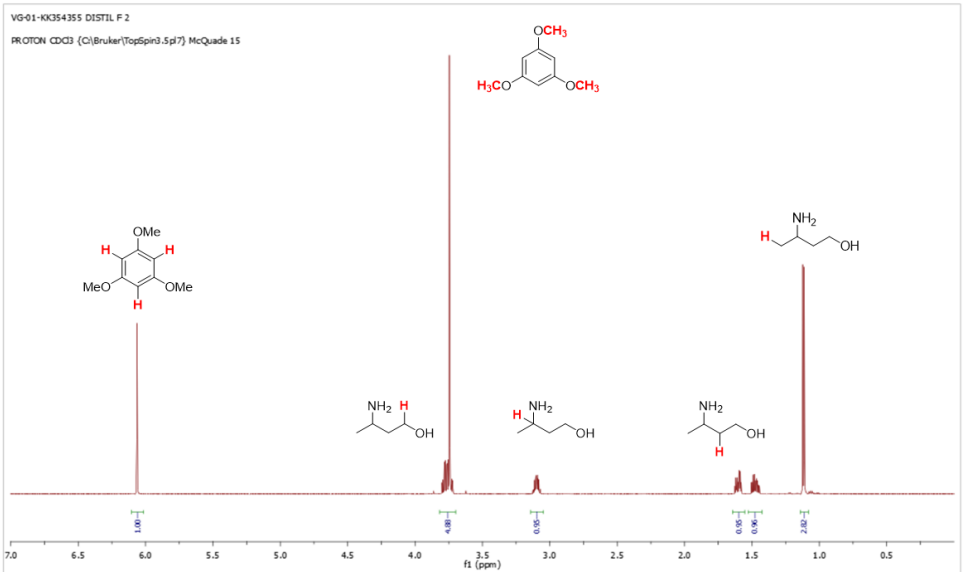

Figure 2. Quantitative NMR using trimethoxybenzene as a standard.

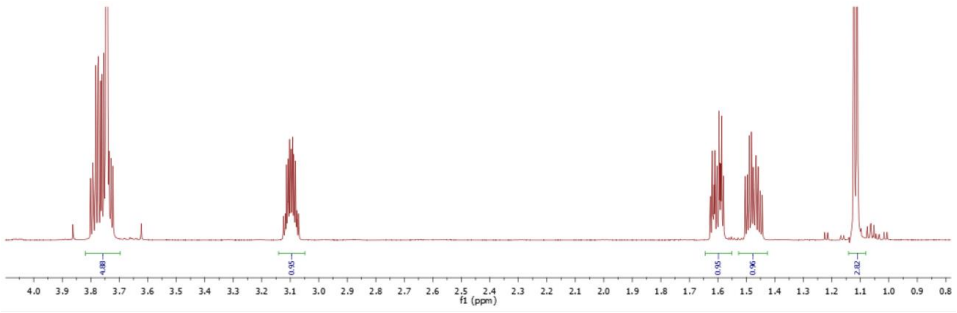

Figure 3. Quantitative NMR using trimethoxybenzene as a standard – expansion of the window featuring the aminobutanol peaks.

GC-MS Analysis

GC-MS analysis was accomplished using the GC method described below. Isolated (*R*)-3-aminobutan-1-ol showed no other compounds present (Figure 4). This method does not include solvents in the analysis. The mass spectrum is consistent with literature and reference material, showing a dominant [M-H_2O] fragment at m/z = 90.1.

Chromatogram of (R)-3-aminobutan-1-ol Product

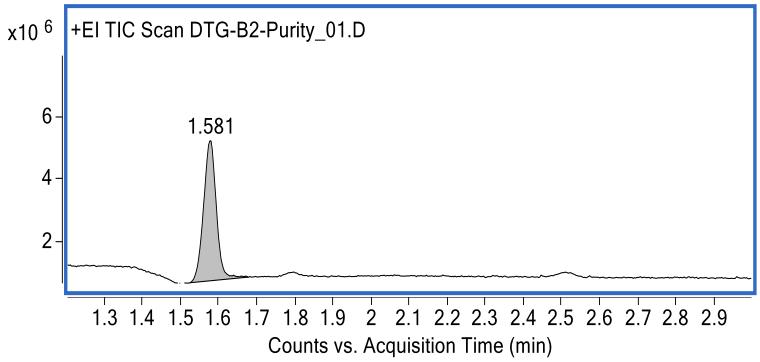

Figure 4. GC-MS Chromatogram of aminobutanol product

Mass Spectrum of (R)-3-aminobutan-1-ol Peak (Figure 5).

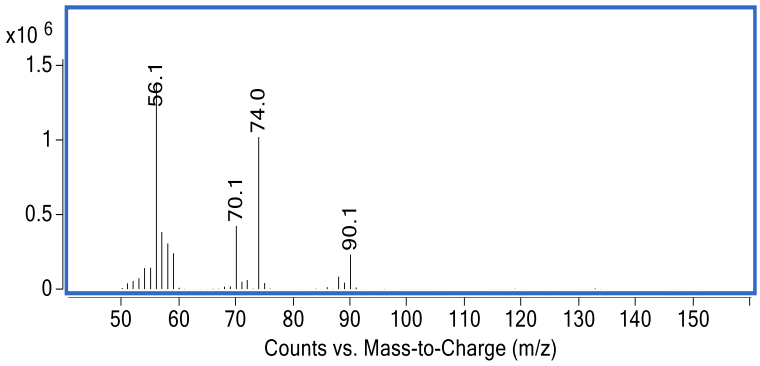

Figure 5. Mass spectrum of the aminobutanol product peak

Chiral Analysis

Chiral analysis was accomplished using the chiral SFC method described below. Isolated (*R*)-3-aminobutan-1-ol showed no (*S*) isomer present.

Chromatogram of CBZ-(*R*)-3-aminobutan-1-ol Product

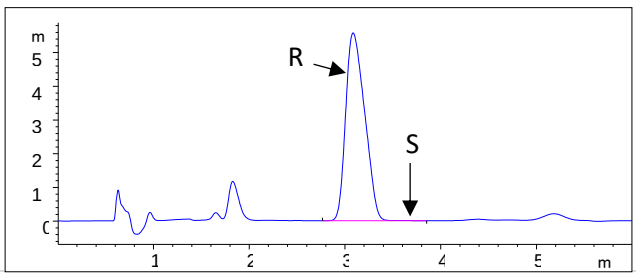

Figure 6. Chiral SFC chromatogram of the aminobutanol product

Analytical Methods

The desired product lacks a chromophore which precludes the use of HPLC methods making process monitoring difficult. In addition, the starting material behaves poorly on GC. Attempts were made to develop derivatization method for the starting material but when applied to in-process tests complex mixtures resulted making interpretation difficult. The acid can be observed by GC when new injection liners are used but performance deteriorates quickly when reaction samples are injected. The reaction also appears to proceed through an undetected intermediate – we speculate an aluminum chelated species. Reaction completion is thus determined by assay of the concentration of the (*R*)-3-aminobutan-1-ol, rather than loss of the starting material. The process has proven to be sufficiently robust that it may not be necessary to perform the in-process test in routine use.

GCMS Method

Assays were performed at time points during the reaction as well as during the THF extraction step. Samples were analyzed via either GC-FID or GC-MS using the methods described in Table 4. For reaction progress samples, samples were prepared by pipetting 200 µL or 100 µL of reaction mixture for GC-FID or GC-MS, respectively, into a 10 mL volumetric flask. A 10% NaOH solution was added at twice the aliquot volume to quench the $NaAlH_4$ before dilution with MeOH. The samples were sonicated for a minimum of 5 min before filtering through a 0.2 µm syringe filter for analysis. Samples from the THF extraction step extraction samples were prepared in an identical manor exclusive of the NaOH quenching step.

	GC-FID	GC-MS
Column	HP-1 (30 m x 0.32 mm x 5 µm)	
Injection volume	1 µL	
Split ratio	25:1	50:1
Gas flow rate	0.8 mL/min	
Oven Temperature	200°C	
Average Retention Time 3-aminobutanol	1.73 min	1.58 min

Table 4. Gas chromatography method parameters for 3-aminobutanol assay

Chromatogram of (R)-3-aminobutan-1-ol on GC-FID

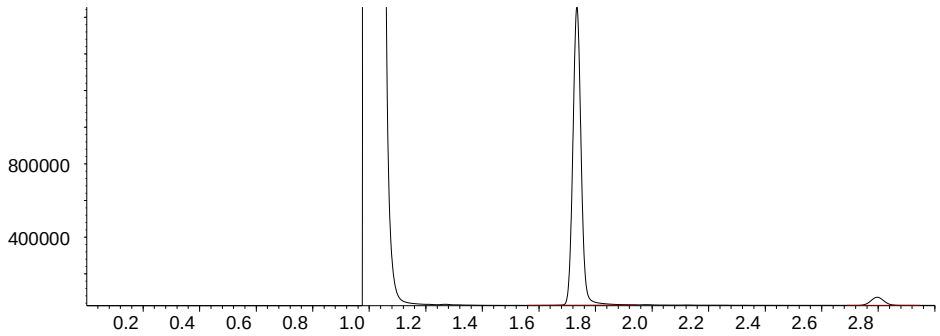

Figure 7. GC-FID Chromatogram of the aminobutanol product

Chiral Analysis

As expected, chiral analysis of the (*R*)-3-aminobutan-1-ol also proved difficult. In addition to the lack of a suitable chromophore required for HPLC, there are few chiral columns capable of enantioselective interactions with such a small, featureless molecule. A chiral GC cyclodextrin column was tested in hopes that it might form a discerning inclusion complex. This proved futile forcing derivatization. The ideal derivatization reaction would provide a single UV detectable product which would interact with a typical chiral column. A consideration was the potential to react with both the alcohol and amine moiety resulting in a mixture of products. Carbobenzyloxy (CBZ) derivatization answers these requirements and has been used to enable chiral separation of amines.[14] Alcohols also react with benzyl chloroformate but the products decompose on work-up, thus providing simple CBZ-amine products. A simple *in situ* derivatization could not be developed and the approach below was used.

(*R*)-3-aminobutanol (500 mg, 1 eq.), sodium carbonate (1.78 g, 3 eq.), and 20 mL of a 1:1 dioxane:H_2O mixture are stirred at 25 ^oC. Benzyl chloroformate (881 µL, 1.1 eq.) was added and the reaction stirred for 12 h. The reaction mixture was concentrated and then partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted twice with ethyl acetate (50 mL each, 100 mL total). The organics were dried over sodium sulfate, filtered and concentrated. Upon concentration the viscous oil solidified into a single mass. This material was dissolved in ethanol for analysis.

The CBZ-derivatized (*R*)-3-aminobutan-1-ol sample is dissolved in ethanol and analyzed by chiral SFC. A ChiralPak IB-N5 column (4.6 X 100mm; 5uM, Chiral Technologies, Inc.) was used with a 10% isopropanol (90% CO2) mobile phase at 3 mL/min. Under these conditions the desired (R) enantiomer elutes at 3.1 minutes while the undesired enantiomer elutes at 3.6 minutes (Figure 8).

Overlaid Chromatograms of CBZ-(R)-3-aminobutan-1-ol Product (A) and Racemate (B)

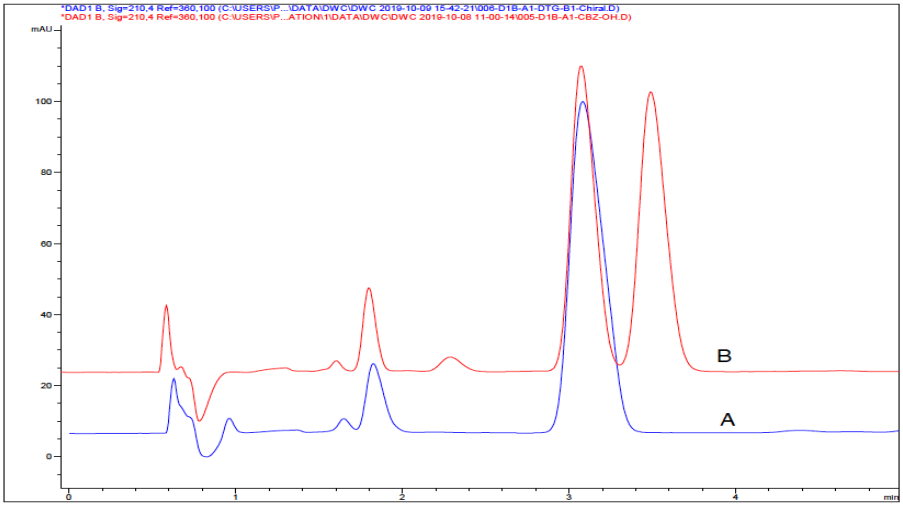

Figure 8. Chromatograms of the desired product and the racemic mixture.

Economic Analysis

The economic analysis of (*R*)-3-aminobutan-1-ol is shown in Table 5. Chemical input costs are based on the amount of material required to produce 1 kg of product. The analysis starts with 1 mole of starting material along with the stoichiometric ratios of other materials, factors in the percent yield obtained and the cost per kilogram of materials. This generates an overall raw material cost that is converted back to a per kilogram basis. It is also assumed that the THF solvent is recycled at 90% recovery. The price for THF does not refer to the use of anhydrous material as it is expected that THF can be dried sufficiently for use. Conversion costs can vary between manufacturing facilities so a rough approximation of $10/kg is added. This cost is a reasonable assumption for processes run at the expected 50MT/year scale.

Raw materials	M.Wt.	Amount /mole alanine	Amount /kg product	Equivalents	RM Price $/Kg	RM Cost $/batch	RM Cost $/Kg Product
(R)-3-aminobutanoic acid	103.12	103.12	1.78	1	$ 50.00	$ 5,156.00	$ 88.99
Sodium aluminium Hydride	54	108.00	1.86	2	$ 5.00	$ 540.00	$ 9.32
Tetrahydrofuran	72.11	73.42	12.7	8V	$ 1.40	$ 102.79	$ 1.77
Tetrahydrofuran	72.11	146.84	25.3	16V	$ 1.40	$ 205.58	$ 3.55
Sodium Hydroxide (10%)	40	40.00	0.69	1	$ 0.30	$ 12.00	$ 0.21
Water	18	1031.20	17.80	10V	$ 0.01	$ 6.19	$ 0.11
Product: R-3-amino-butanol-1	89.14	62.40	1			$ 6,022.56	$ 103.94
Yield = 70%						Conversion Cost =	$ 10.00
Recycle Solvent = 90%						Total Cost =	$ 113.94

Table 5. Cost Model for the Production of (*R*)-3-aminobutan-1-ol

While this model makes some reasonable assumptions, the resulting cost estimates carry 10-15% variation and they do not account for market effects which translate cost to market price. The model easily allows the variation of different parameters allowing us to perform sensitivity analysis, thus guiding research focus. The input price for the homo-beta-alanine is not established as it is not currently an article of open commerce – we have identified two producers who sell to specific customers. Our market intelligence indicates that this material is a fermentation byproduct with a price ranging from $40/kg to $100/kg. Work reported here was based on commercially available material and it is unclear whether fermentation material would give rise to quality issues.

The plot below shows the relationship between homo-beta-alanine price and predicted (*R*)-3-aminobutan-1-ol cost. The model shows a linear relationship with slopes varying depending on reaction yield (Figure 9). At a 65% yield, the relationship is (*R*)-3-aminobutan-1-ol cost = 1.65 X (homoalanine price) + $24.95. In this case $24.95 represents to cost of other raw materials and the $10/kg conversion cost. At different yields this intercept value varies only slightly while the slope is given by 1.15/yield, 1.15 being the ratio of the molecular weights of the product and starting material.

Even with a high price for the starting material and a suboptimal 60% yield, this process is expected to produce (*R*)-3-aminobutan-1-ol at a considerably lower price than what is currently available in the market. At an achievable 70% yield starting from $45/kg starting material we

expect the product to cost $106/kg. The use of NAH in place of the LAH typically used for such reductions has a dramatic impact on this result. With a current $180/kg LAH price, use of LAH would triple this cost to $317/kg.

Table 6. Estimated (*R*)-3-aminobutan-1-ol Cost ($/kg) as a Function of Homo Alanine Price

Homo Alanine $/kg	60% Yield	70% Yield	80% Yield
40	$103.32	$90.00	$80.00
45	$112.96	$98.26	$ 87.22
50	$122.60	$106.52	$94.45
55	$132.25	$114.78	$101.68
60	$141.89	$123.04	$108.91
65	$151.53	$131.31	$116.14
70	$161.17	$139.57	$123.37
75	$ 170.81	$147.83	$130.60
80	$180.45	$156.10	$137.83
85	$190.09	$164.36	$145.07
90	$199.73	$172.62	$152.30
95	$209.37	$180.89	$159.53
100	$219.01	$189.15	$166.76

Figure 9. Plot of (*R*)-3-aminobutan-1-ol $/kg as a function of Homoalanine price