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Process Development toward a Pro-Drug of *R*-Baclofen

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ABSTRACT: This paper describes the process development conducted toward the multi-kilogram synthesis of a novel transported pro-drug of *R*-baclofen. The key steps in the synthesis were the enzyme-catalyzed kinetic resolution of isopropyl-(methylthiocarbonyloxy)methyl-2-methylpropionate using *Candida antarctica* lipase A to provide the desired (*S*)-enantiomer. This was followed by the reaction with sulfuryl chloride and *N*-hydroxysuccinimide to produce (*S*) 1-(2,5-dioxoazolidinyloxycarbonyloxy)-2-methylpropyl 2-methylpropanate. The synthesis of (*S*) 1-(2,5-dioxoazolidinyloxycarbonyloxy)-2-methylpropyl 2-methylpropanate enabled the efficient use of *R*-baclofen in the final coupling stage of the synthesis. The new route reported here is more efficient and sustainable than those reported previously and had the potential to become the commercial route of manufacture.

KEYWORDS: *R-baclofen, pro-drug, process development, biocatalysis, C. antarctica lipase A, sulfuryl chloride*

DISCUSSION

In 2014, Indivior (formerly Reckitt Benckiser Pharmaceuticals) entered into a licensing agreement for arbaclofen placarbil **6** as a potential treatment of alcohol use disorders.[1] Arbaclofen placarbil **6** is a novel transported pro-drug of *R*-baclofen. Upon review of the data provided, it was apparent that two routes had been used been used for the synthesis of drug substance **6**. The original route is outlined in Scheme 1.[2]

In the original synthesis, the functionalized hydroxysuccinimide **2** was prepared in two steps from commercially available dibenzoyl-L-tartaric acid. This was then reacted with thiocarbonate **3** in the presence of peracetic acid to give compound **4** in high diastereomeric purity, following fractional crystallization. The reaction of compound **4** with *R*-baclofen **5** to produce drug substance **6** was high yielding; hence, this route was very efficient in terms of the usage of *R*-baclofen. However, as aqueous washes were not effective, chromatography was the only method that could successfully separate desired product **6** away from the byproduct **2**. This limitation meant that the route outlined in Scheme 1 was not amenable to the large-scale synthesis of drug substance **6**.

This then followed a second, chromatography-free route to the drug substance **6**, Scheme 2. Succinate ester **8** was produced in 3 steps from 1-chloro-2-methylpropyl chloroformate. In this second route, racemic succinate ester **8** was reacted with *R*-baclofen to produce essentially a 1:1 ratio of the desired compound **6** and the undesired (*R*, *R*) diastereoisomer **9**. Compound **6** could be isolated in high isomeric purity following the fractional crystallization of the hemihydrate form.[3] The hemihydrate was then dried under relatively mild conditions and recrystallized to provide the desired anhydrate form of the drug substance **6**. The separation of diastereoisomers by fractional crystallization only occurred when the hemihydrate was crystallized and was ineffective when the anhydrate was crystallized. The overall yield from *R*-baclofen **5** to the drug substance **6** was 30%. The *N*-hydroxysuccinimide byproduct produced in the coupling of succinate ester **8** with *R*-baclofen was readily removed during the aqueous workup that followed the reaction. The route outlined in Scheme 2 had been scaled up such that drug substance **6** could be manufactured in 50 kg batches.

The role of a process development chemist within the pharmaceutical industry extends beyond the supply of the drug substance for preclinical development, formulation development, and clinical development and also includes the development of a synthetic route capable of meeting the commercial demands for the product. Alcohol use disorder is a chronic disease with a large potential patient population and thus poses a significant burden upon society.[4] In the event of a successful development program, the potential commercial demand for the drug substance **6** was projected to be in the order of 20,000−30,000 kg per year. Based upon this assessment, a critical review of the drug substance manufacturing strategy was undertaken.

Multiple commercial manufacturers of *R*-baclofen **5** were identified, and from discussions with the suppliers, it was apparent that the long-term supply of large volumes of *R*-baclofen should not be overly problematic. It was noted that several different synthetic routes were being used across the potential supply base and that would need to be taken into account when setting the specification for *R*-baclofen.

The biggest challenge posed by the second-generation chromatography-free route was the inefficient use of the two key building blocks, *R*-baclofen **5** and succinate ester **8**. A 30% chemical yield for the final stages of the synthesis translates into the need for 1.9 kg of *R*-baclofen **5** and 2.5 kg of succinate ester **8** per kg of the drug substance produced. Late-stage

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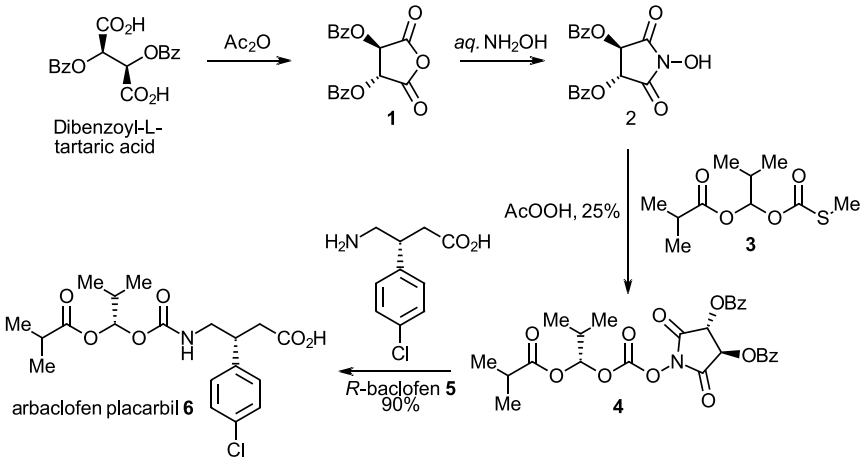
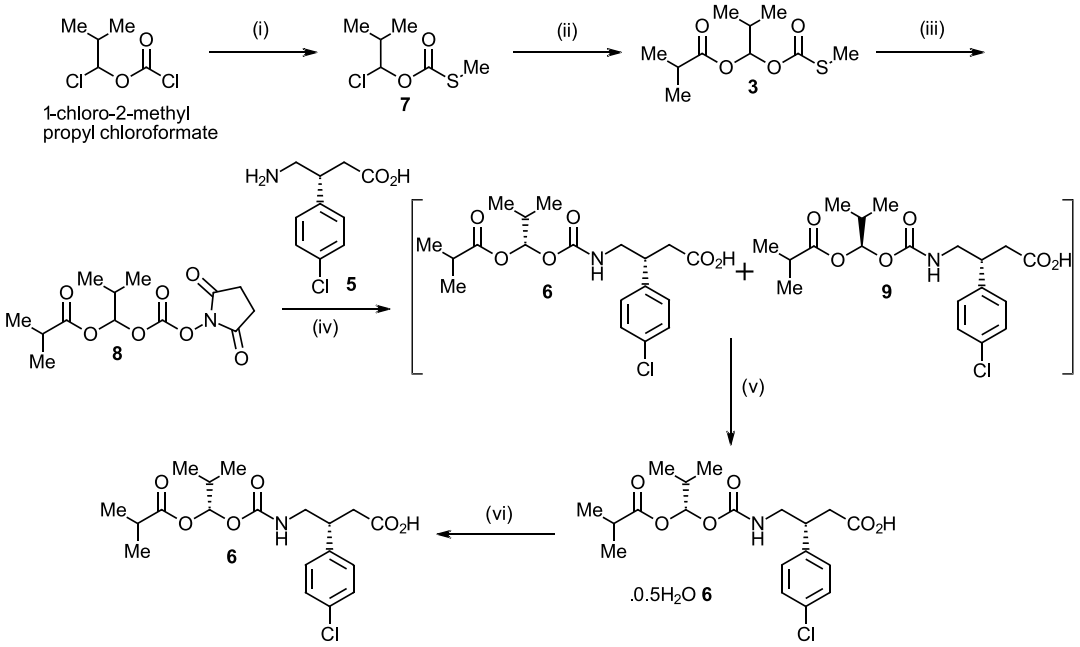
Scheme 1. Original Route to Arbaclofen Placarbil 6

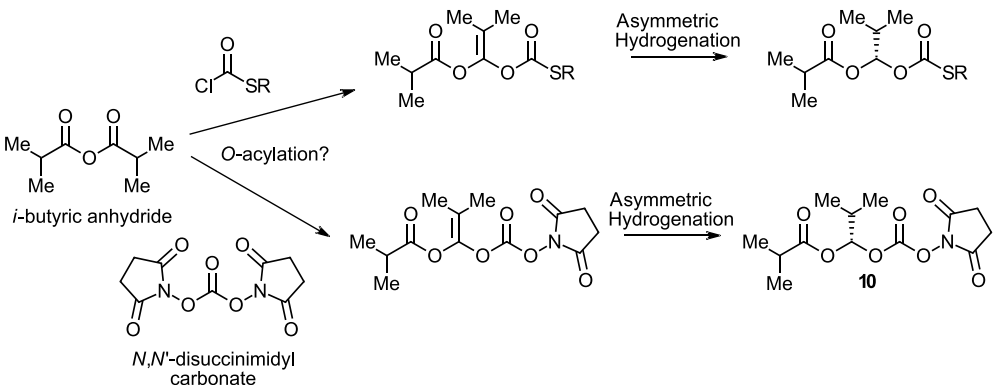


Scheme 2. Chromatography Free Route to Arbaclofen Placarbil 6[a]



[a]Reagents and conditions: (i) aq NaSMe, $Bu_4N{\cdot}HSO_4$, CH_2Cl_2, 95%; (ii) i-butyric acid, NEt_3, Δ, 79%; (iii) *N*-hydroxysuccinimide, AcOOH, AcOH, 5 °C, 56%; (iv) aq *t*-BME, **5**, 45 °C; (v) aq *t*-BME, methylcyclohexane, 33%; and (vi) drying at 70 °C, 30 mbar, then acetone, *n*-hexane recrystallization, 90%

Scheme 3. Potential Asymmetric Hydrogenation Route to Succinate Ester 10



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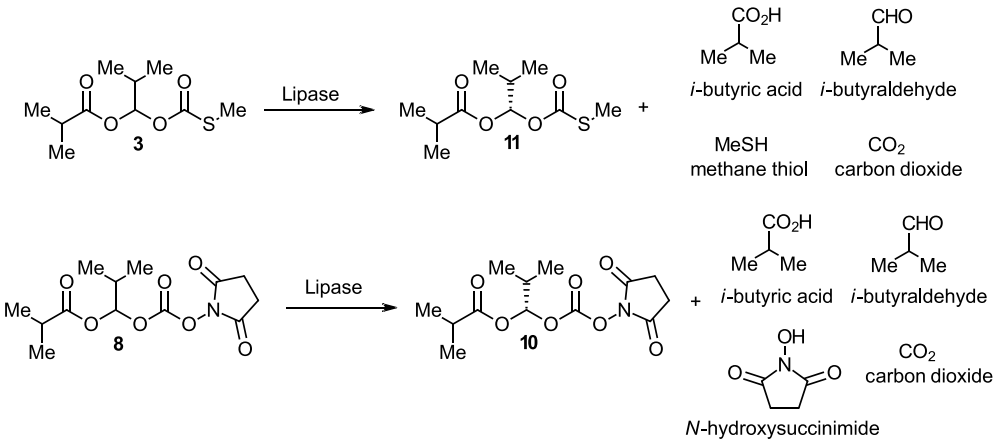
Scheme 4. Potential Enzymatic Resolution of Substrates 3 and 8



inefficiencies such as these are not appropriate for such a high-volume product. Although an option for recovering and recycling *R*-baclofen was available,[3] this would add further complexity to setting an appropriate specification for *R*-baclofen. All sources of *R*-baclofen, be they from different suppliers using different routes of synthesis or recovered a single time or multiple times from the process, would need to meet the same specification that controlled and guaranteed the drug substance's critical quality attributes. *R*-Baclofen was also a significant cost center in the manufacturing process, reducing the demand for *R*-baclofen would significantly reduce the cost of goods.

A potential solution to this late-stage inefficiency would be the use of the (*S*)-enantiomer of the succinate ester **8**. As per the original supply route (Scheme 1), the reaction between a single enantiomer of succinate ester **8** with *R*-baclofen **5** should give a high yield of drug substance **6**. As per the chromatography free route, the byproduct *N*-hydroxysuccinimde **2** would be readily removed during the aqueous workup following the coupling reaction. Without the need to generate the hemihydrate to conduct the fractional crystallization, the need for a formal recrystallization to set the polymorphic form could be eliminated. The goal therefore became the synthesis of the (*S*)-succinate ester **10**.

A potential asymmetric approach is outlined in Scheme 3. The approach called for the selective mono O-acylation of i-butyric anhydride with either *N*,*N*′-disuccinimidyl carbonate or a chlorothioformate followed by asymmetric hydrogenation of the resulting double bond. Although the precedent for either step was extremely limited, the brevity of the approach, coupled with the ready availability of the materials and the potential productivity gains, made the approach worth investigating. No O-acylation products were observed when i-butyric acid anhydride was treated with a variety of bases in the presence of either *N*,*N*′-disuccinimidyl carbonate or *S*-i-propyl chlorothioformate and the approach was discontinued.

Without any other clear alternatives for a concise asymmetric synthesis, focus reverted to the existing synthesis of succinate ester **8** (Scheme 2) with the view of improving the throughput and introducing a resolution step into the sequence. Two alternative strategies were investigated: (1) continuous chiral chromatography[5] and (2) enzymatic resolution. Two synthetic intermediates were investigated,[6] namely, the step 2 intermediate thiocarbonate **3** and the step 3 intermediate succinate ester **8**. Thiocarbonate **3** was liquid and was isolated in approximately 85% w/w purity following the step 2 process, whereas succinate ester **8** was a crystalline solid that could be isolated in >99% purity following crystallization.

Both substrates were screened against an extensive range of chiral stationary phases using a wide variety of solvent mobile phases to obtain the separation between the two enantiomers. It was noted during the screening phase that succinate ester **8** lacked stability in solvent systems containing alcohols, with *N*-hydroxysuccinimide being produced. The best separation for thiocarbonate **3** was achieved using a Chiralcel OZ stationary phase and a 80:20 v/v mixture of heptane/*t*-BME as the mobile phase. Although the separation selectivity of the two enantiomers would have been acceptable as an analytical method, it was insufficient to warrant further development toward an industrial process. Better separation selectivity of the two enantiomers was achieved for succinate ester **8** using the Chiralpak ID stationary phase and 100% *t*-BME as the mobile phase. Further evaluation was conducted on the separation of succinate ester **8**, looking at the effect of temperature and time on the stability on the feedstock and desired enantiomer of the product. No racemization of the desired (*S*) enantiomer **10** was observed. Simulations performed for a multicolumn continuous process gave a productivity of value of 1 kg of racemate per kg of stationary phase per day. In comparison to the enzymatic approach outlined below, the economics of the preparative chromatography were unlikely to be competitive and the approach was discontinued.[7]

The intent behind the enzymatic resolution approach was to screen commercially available enzymes for the selective hydrolysis of the undesired (*R*)-enantiomers of either substrates **3** and **8**, thus leaving the desired (*S*)-enantiomers **11** and **10** unreacted, as shown in Scheme 4. The initial goal was to achieve an isolated yield of the product in the order of 40% and with a chiral purity >98%.

Screening started with succinate ester **8**. Cognizant of the potential for compound **8** to undergo background hydrolysis, a stability study of the substrate in potential screening conditions was undertaken. Biphasic aqueous (0.25 M phosphate buffer pH 7.5)/organic (substrate = 1 mg/mL) systems were evaluated. Of the two best solvents (*t*-BME and toluene), toluene was shown to be superior and seemed to show good stability at 25 °C for 72 h. A total of 91 commercially available lipases were screened against substrate **8**[8] from which 5 hits were identified. All of the hits preferentially hydrolyzed the same enantiomer of substrate **8**. Three of the hits were lipases

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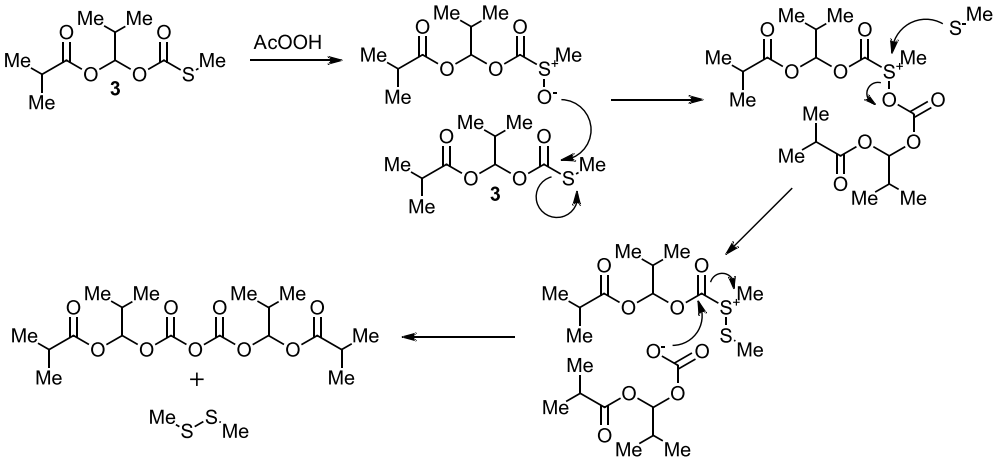
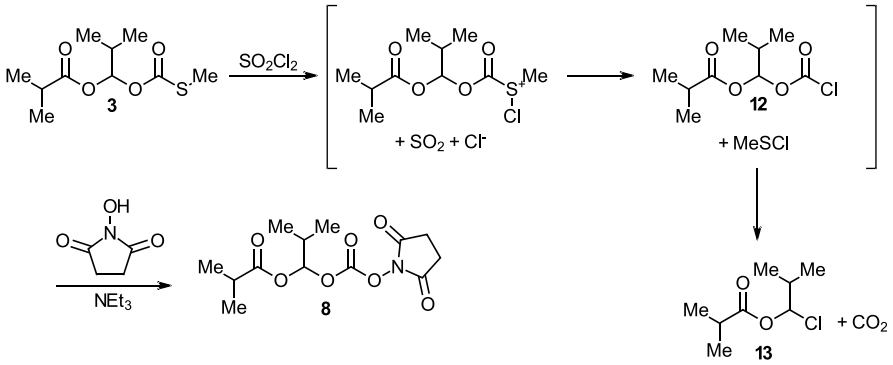
Scheme 5. Potential Disproportionation Pathway in the Conversion of Thiocarbonate 3 to Succinate Ester 8



Scheme 6. Conversion of Thiocarbonate 3 to Succinate Ester 8 Using SO_2Cl_2



from *Aspergillus niger* and two from *Candida antartica* A. The best hit in terms of chiral purity of product **10** (98.2%) and losses because of background hydrolysis (47%) was IMMCA-LA-T2-150 lipase (*C. antartica* A lipase immobilized on polymethacrylate). Before moving forward to try and optimize this hit, it was important to establish which enantiomer was being hydrolyzed. To this end, substrate **8** was reacted under the screening conditions to give 180 mg of product **10** and with a chiral purity of 89%. A portion of this material was then reacted with *R*-baclofen to produce drug substance **6**. Analysis by chiral high-performance liquid chromatography (HPLC) confirmed that the correct diastereoisomer of the drug substance was being produced and hence that the enzyme was indeed hydrolyzing the undesired (*R*)-enantiomer of **8**. The optimization of the hit had two goals: (1) increase the reaction concentration to 150 g/L as this would be the minimum concentration needed to make this a commercially viable process and (2) minimize the background hydrolysis to try and maximize yield.

Repeating the solution stability study at higher concentrations of substrate **8** (10 mg/mL) and higher temperature (30 °C) showed approximately 34% hydrolysis in 50:50 toluene/phosphate buffer compared to 6% in 100% toluene. The effect of the phosphate buffer concentration was investigated; running enzymatic reactions with a higher concentration of buffer (1 M) and maintaining the pH >7 gave a high chiral purity (98.5%) but also gave higher degradation (only 39% of desired enantiomer remaining), whereas running the reactions at a lower buffer concentration (0.05 M) resulted in the pH of the reaction dropping to pH = 5, giving a lower chiral purity (94%) but less degradation (66% of desired enantiomer remaining).

These results showed that by increasing the buffer capacity to reduce the pH drop during the reaction an undesired enzymatic hydrolysis of the desired (*S*)-enantiomer occurred because of increases in activity and/or a reduction in the selectivity of the enzyme at a pH close to the initial value (pH = 7.5). Follow on experiments all at high substrate concentration and looking at; enzyme loading, toluene/buffer ratio, buffer concentration, and temperature failed to establish any reaction conditions that could come close to the initial goal of yield in the order of 40% and a chiral purity >98%. It was only ever possible to get an acceptable chiral purity but with a very low yield or an acceptable yield but with modest chiral purity; therefore, this approach was discontinued.

Screening of thiocarbonate **3** against a panel of 60 commercially available enzymes was more straightforward as background hydrolysis was less of an issue. Multiple hits were found for the hydrolysis of the (*S*)-enantiomer, whereas a single hit, again using *C. antartica* A, was found for the desired transformation, hydrolysis of the (*R*)-enantiomer.[9] Again, the IMMCALA-T2-150 catalyst was the preferred option, probably because of an affinity of the substrate for the hydrophobic support. By maintaining the pH of the reaction at a constant pH = 7.5 by the addition of 20% aq NaOH, the rate of the reaction could be significantly improved. Once the reaction was complete, product **11** could be extracted into dichloromethane (DCM). Preliminary experiments gave an isolated yield of thiocarbonate **11** in the region of 35−40% and with a chiral purity >98%. Based on these observations, the enzymatic

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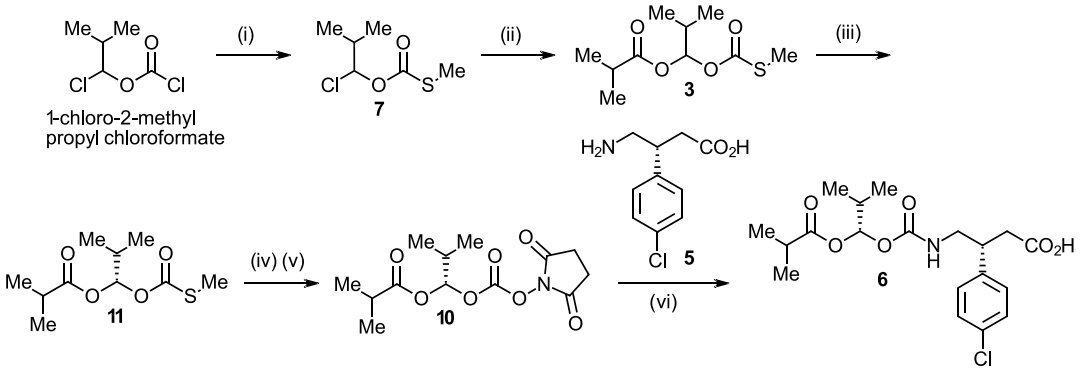
Scheme 7. Potential Manufacturing Route to Arbaclofen Placarbil 6[a]



[a]Reagents and conditions: (i) Stage 1 aq NaSMe, $Bu_4N{\cdot}HSO_4$, CH_2Cl_2, 92%; (ii) Stage 2 i-butyric acid, NEt_3, Δ, 81%; (iii) Stage 3 IMMCALA-T2-150, aq potassium phosphate buffer (0.96 M), pH = 7.5, aq NH_4OH, 35 °C, 36.5%; (iv) Stage 4 SO_2Cl_2, NEt_3, *N*-hydroxysuccinimide, CH_2Cl_2, −20 °C 65%; (v) Stage 4R IPA, heptane, 94%; and (vi) Stage 5 aq *t*-BME, **5**, 45 °C, 78%

hydrolysis of racemic thiocarbonate **3** to give (*S*)-enantiomer **11** appeared to give a viable route to the single enantiomer succinate ester **10**.

A second limitation of the chromatography-free route outlined in Scheme 2 was the poor throughput associated with step 3, the conversion of thiocarbonate **3** to succinate ester **8**. The peracetic acid solution needed to be added over approximately 12 h, this was then followed by a 12 h reaction period, thus leading to a long batch cycle time. Even following extensive investigation and optimization, the yield was never more than 56%, which combined with the long cycle time gave a poor space/time efficiency. A potential reason for the modest yield observed in step 3 may have been the disproportionation pathway outlined in Scheme 5.[10]

From an investigation into the use of alternative reagents for the transformation of thiocarbonate **3** into succinate ester **8,** the potential use of sulfuryl chloride (SO_2Cl_2) became apparent.[11,12] Although the conditions discovered would need to work on the conversion of the (*S*)-enantiomer **11** to succinate ester **10**, initial investigations were conducted on racemate **3** as it was more readily available and of higher purity, as shown in Scheme 6.

The complete consumption of thiocarbonate **3** was achieved using a minimum of 1.5 equiv of SO_2Cl_2 at −18 °C in DCM. By ReactIR, almost instantaneous conversion to chloroformate **12** was observed. Intermediate **12** had limited thermal stability, and by ReactIR, it was observed that decomposition to chloride **13** started around −9 °C. Once the intermediate chloroformate **12** had formed, *N*-hydroxysuccinimide could be added. Following the *N*-hydroxysuccinimide addition, triethylamine was added. The addition of triethylamine was highly exothermic and promoted the conversion of chloroformate **12** to succinate ester **8**. If the triethylamine was added prior to the *N*-hydroxysuccinimide, then very limited amounts of the desired product were produced. During these preliminary experiments, it was shown that the *N*-hydroxysuccinimide could be added to the reaction mix prior to the SO_2Cl_2 addition without adversely affecting the yield, a modification that was likely to be useful on scale up. The solution yields from these preliminary experiments were >80%, with the yields of the isolated product in the range 65−70%. When the SO_2Cl_2 conditions were applied to the single enantiomer thiocarbonate **11**, the corresponding succinate ester **10** was produced without any loss in stereochemical integrity.

Following the route evaluation process, there appeared to be a route to the desired (*S*)-enantiomer succinate ester **10**, as shown in Scheme 7. 1-Chloro-2-methylpropyl chloroformate was to be converted to racemic thiocarbonate **3**, *via* intermediate **7** using the pre-existing conditions. The enzymatic resolution of thiocarbonate **3** would give the desired (*S*)-enantiomer **11**, which could then be converted to (*S*)-enantiomer succinate ester **10**. The reaction of succinate ester **10** with *R*-baclofen would give a high yield of the desired drug substance **6**. It was also recognized that there would be many difficulties to overcome. Intermediates **7**, **3**, and **11** were all neutral molecules and liquids, so there were no opportunities to upgrade the purity of these compounds by liquid/liquid extractions or by crystallization of the parent compound or a salt. Intermediate **10** was the only crystalline intermediate in this portion of the synthesis and as the penultimate intermediate in the synthesis of drug substance **6**, control of the quality of intermediate **10** would be key to controlling the quality of the final drug substance. Because the quality of intermediate **11** was noticeably poorer than racemate **3** due to the complex mixture of byproducts produced by the hydrolysis process, it would therefore be challenging to obtain high purity succinate ester **10** *via* the enzyme resolution/SO_2Cl_2 process.

The pre-existing conditions were applied to Stage 1 without any modifications. The commercially available 1-chloro-2-methylpropyl chloroformate was reacted in a controlled fashion with aqueous sodium methanethiolate. Initially, 0.85 equiv. of thiolate were added, and the reaction progression checked by either ^{1}H NMR or gas chromatography (GC) analysis. A second charge of the thiolate was made to try and get complete consumption of the chloroformate (target >99% conversion), without forming dimethyldithiocarbonate **14** (Figure 1). Knowledge[13] from the chromatography-free synthesis (Scheme 2) indicated that dimethyldithiocarbonate **14** would undergo a reaction in step 3 to produce succinate

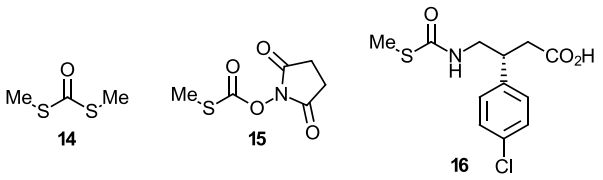


Figure 1. Structures of potential impurities **14**, **15**, and **16**.

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ester **15**, which in turn could react with *R*-baclofen to give thiocarbamate **16**. Following the reaction, it was important to remove as much of the DCM solvent as possible by distillation as it was known that residual DCM at levels as low as 3% w/w were detrimental to the subsequent Stage 2 chemistry. Likewise, the levels of residual water in product **7** needed to be controlled. On scale, a total of 870 kg of 1-chloro-2-methylpropyl chloroformate was processed across two batches to produce 857 kg of chlorothiocarbonate **7** in 92% yield and excellent purity. The levels of both unreacted 1-chloro-2-methylpropyl chloroformate and dimethyldithiocarbonate **14** were both <0.2%, and the levels of residual DCM and water were both suitably controlled.

The pre-existing conditions were applied to Stage 2 without any modifications. The chlorothiocarbomate **7** was added to a hot solution (108 °C) of NEt_3 in i-butyric acid. The target reaction endpoint of <5% unreacted chlorothiocarbonate **7** was achieved after 13 h at this temperature. Following aqueous workup and removal of the solvent, thiocarbonate **3** was isolated in 81% yield (corrected for purity) and with an assay purity of 89% w/w. In total, 856.5 kg of thiocarbonate **3** was produced across 2 batches. The principle impurities present in the isolated thiocarbonate **3** were unreacted chlorothiocarbonate **7** (2.3%), enol thiocarbamate **17** formed by the elimination of HCl from the starting material (2.8%), enol thiol **18** (1.0%), and thioester **19** (0.7%), as shown in Figure 2.

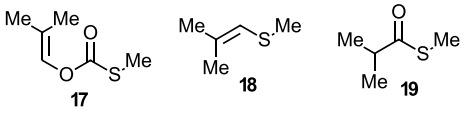

Figure 2. Structures of impurities **17**, **18**, and **19**.

No dimethyldithiocarbonate **14** was detected in the isolated thiocarbamate **3**; hence, the risk of forming compounds **15** and **16** later in the synthesis was potentially negated. Following the scale-up campaign, an investigation into distillation as a method to further purify thiocarbonate **3** was investigated. The use of flash distillation under vacuum in a thin-film evaporator was attempted on a laboratory scale. Removing the partially volatile components by setting the jacket temperature at 118 °C and applying a vacuum of 20 mbar gave a good recovery of the product, but only a slight upgrade in purity to 91% w/w. By decreasing the vacuum to 10 mbar, only a slight further improvement in purity to 94% w/w was observed; however, the recovery was greatly reduced as the product started to co-distill. Ultimately, distillation proved not to be a ready method to increase the purity of thiocarbonate **3**.[14]

From the preliminary stage 3 experiments into the enzymatic resolution of racemic thiocarbonate **3** to give the (*S*)-enantiomer **11**, it became clear that in addition to the temperature there were two other parameters that controlled the rate of the reaction, (1) control of pH at pH = 7.5 and (2) head space purging with N_2 to remove volatile byproducts. Hydrolysis of racemic thiocarbonate **3** generated an array of secondary byproducts arising from the recombination of the primary byproducts. Compound **20** (Figure 3), produced by the recombination of methylthiolate, i-butyraldehyde, and i-butyric acid, was formed in most early experiments. In an attempt to sequester i-butyraldehyde as the bisulfite adduct, the enzymatic resolution was carried out in the presence of 0.5 equiv of $NaHSO_3$. The enzymatic reaction was largely

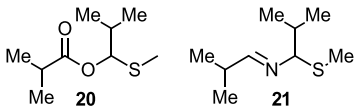

Figure 3. Structures of impurities **20** and **21**.

unaffected by this modification; however, the final product isolated from the reaction did not perform as well as others in the subsequent Stage 4 chemistry. For the control of pH, two alternative titrants were investigated, namely, 20% aq KOH and 24% aq ammonium hydroxide. When aq ammonium hydroxide was used as the titrant an alternative main byproduct **21** was produced. Reactions using aq ammonium hydroxide proceeded at a faster rate than those using aq KOH. Additionally, when the uptake of aq ammonium hydroxide ceased that was a good indicator that the reaction had reached the desired endpoint (chiral purity >99%). When aq KOH was used as the titrant, the uptake stopped prior to the reaction endpoint being achieved. The development of the Stage 3 reaction conditions was carried out hand-in-hand with the development of the SO_2Cl_2 chemistry at Stage 4. From the various options trialed, KOH versus ammonium hydroxide as the titrant and the reactions running in the presence or absence of $NaHSO_3$, it was found that the use of ammonium hydroxide in the absence of $NaHSO_3$ gave the best overall performance and hence were selected to move forward. Initial Stage 3 experiments had used a headspace sweep with N_2 to remove volatile components. As the scale of the reactions increased, it was found to be more effective if a sub-surface sparging with N_2 was used. By increasing the reaction temperature to 35 °C, the duration of the reaction decreased to 4−6 h. It was noted that upon achieving reaction completion, the hold time prior to workup should be minimized to avoid product degradation.

The workup solvent was changed from DCM to *t*-BME as having a product extraction layer with a density less than that of water would make the subsequent aqueous washes more process efficient. Once the enzyme resin had been removed from the reaction mixture by filtration, the resin was slurry washed with *t*-BME to try and maximize the recovery of the product. The *t*-BME extracts were then washed with aq K_2CO_3 to try and remove any i-butyric acid. Finally, (*S*)-enantiomer **11** was isolated as a liquid, following the removal of all the solvent by distillation. It was essential to remove as many of the volatile thiol byproducts as possible to enable the Stage 4 chemistry to be successfully executed, the theory being that excess thiols present in Stage 3 product **11** would consume SO_2Cl_2 during the Stage 4 reaction. Initially, there were concerns that the enzyme may have been leached off the resin support. These concerns were alleviated when it was shown that no further reaction progress was observed when the enzyme resin was removed from an incomplete reaction. Subsequently, the final drug substance **6** was tested for the residual enzyme (*vida infra*).

On both lab and kilo-lab scale (4 kg input of **3**), compound **11** was isolated with a purity in the order of 60% w/w, an assay corrected yield of 41%. The process was subsequently run in 2500 L equipment and 293.42 kg of compound **11** was produced across 3 batches. The purity of compound **11** was 60% w/w; however, the assay corrected yield had reduced slightly to 36.5%. A potential reason for the yield shortfall could have been the use of a sub-optimal filter for the isolation and washing of the enzyme resin. The filter used on scale had a surface area of 2 m^2 and a capacity of 1600 L, this may have

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been too large to effectively wash and deliquor only 28 kg of the enzyme resin. On a lab scale, the third *t*-BME wash was typically free of product **11**, whereas on scale, the third *t*-BME wash still contained detectable, but unquantified, levels of compound **11**. The chiral purity for the isolated compound **11** was 100% for each of the 3 batches. The principle impurity present was imine **21** at 16.5% w/w, other impurities included Stage 1 intermediate **7**, enol thiocarbonate **17**, and compound **20**, all at approximately 4−5% along with a significant number of low-level unidentified impurities. The consistency, or otherwise, of all the low-level impurities was not fully established at this time.

The previously discussed ReactIR experiments had shown that using purified racemic thiocarbonate **3** required 1.5 equiv of SO_2Cl_2 to achieve the complete consumption of the starting material. When unpurified racemic thiocarbonate **3,** direct from the Stage 2 process and with a purity of approximately 85% w/w, was used in the Stage 4 process, then 1.98 equiv of SO_2Cl_2 were needed. Applying these conditions to single enantiomer **11** with a purity of 60% w/w gave incomplete conversion to the corresponding chloroformate (cf. compound **12** in Scheme 6). To get a satisfactory isolated yield of product **10**, it was necessary to achieve as full a conversion as possible. However, if SO_2Cl_2 was overcharged then sticky low-purity product was isolated. In anticipation of obtaining a variable outcome upon scale up, it was decided to initially charge 2.50 equiv SO_2Cl_2 to achieve ca. 80−85% conversion, and then following sampling, make a second smaller charge to achieve complete conversion. Reactions were monitored using off-line ^{1}H NMR, the acetal methine proton of thiocarbonate **11** came at δ 6.72, whereas for the intermediate chloroformate the corresponding proton came at δ 6.58. Having achieved the complete conversion of thiocarbonate **11** to the intermediate chloroformate, NEt_3 was added to promote the addition of *N*-hydroxysuccinimide to form product **10**. The NEt_3 addition was highly exothermic and the temperature needed to be maintained at −20 °C to minimize decarboxylation and the formation of byproduct **13**. Once the NEt_3 addition was complete, the resulting very thick slurry could be warmed slightly and water was added. At this point, the phases separated readily and the aqueous phase with a pH = 2−3 could be discarded. During the development phase, as the amount of SO_2Cl_2 was increased, then the amount of NEt_3 charged was also increased and ultimately ca. 5.7 equiv was needed to ensure the pH of the aqueous was in a suitable range.

Developing a workup and isolation procedure was not without challenges, one of which was controlling the odor. The sulfur-containing byproducts from the reaction were not fully oxidized, and this led to strong smelling waste streams and potentially an odorous isolated intermediate **10**. The odor problem was overcome by passing a process stream through an activated charcoal filter unit. To affect an effective workup procedure, it was necessary to swap solvents from DCM to *t*-BME. Having removed the DCM by distillation, water was added to resolubilize all the salts present prior to the addition of *t*-BME. Once the *t*-BME had been added, aq potassium carbonate could be added and a clean phase split was achieved. The *t*-BME phase could then be passed through the activated charcoal filter. Finally, the crude intermediate **10** could be isolated by crystallization from a mixture of *t*-BME and heptane. On a lab scale, compound **10** could be isolated with an assay purity >95% w/w and with a yield in the range 60−65%. The process was subsequently run in 2500 L equipment, and 238 kg of compound **10** was produced across 3 batches. The purity of compound **10** for all 3 batches was 98% w/w, and the average yield across the batches was 65%. The HPLC impurity profile contained multiple low-level impurities of which succinate ester **15**[15] at 0.15% and the succinate ester of i-butyric acid at 0.4% in a single batch were identified. Although Stage 1 intermediate **7** and enol thiocarbonate **17** had been present at approximately 4.5% in the substrate, none of the corresponding succinate esters were observed in the product. The true fate of imine **21** was not determined. The chiral purity of crude **10** remained at 100%.

The time and resource available for the development of Stages 3 and 4 was limited. Given the high number of low-level impurities produced and limited opportunities to purge the impurities, it was thought unlikely that it would be possible to make "pass grade" intermediate **10** by the first intent, therefore a recrystallization procedure was built into the plan.

In the Stage 4R process, crude intermediate **10** was recrystallized from a mixture of i-propanol (IPA) and heptane. The 3 batches of crude intermediate **10** were individually recrystallized to give 215.6 kg of pure **10** in 94% average yield. All 3 batches of pure **10** had an assay purity = 100% w/w and the HPLC profile had no impurities >0.05%.

The final stage in the route, Stage 5, was the coupling of the single enantiomer succinate ester **10** with *R*-baclofen **5** to give drug substance **6**. The focus of the development work was to generate a process whereby the desired anhydrate form could be isolated in specification and by the first intent. The second objective was to replace the ICH Class 2 solvent *n*-hexane used in the final recrystallization with a Class 3 solvent.[16] Because of limitations on time and resource, it was decided to use the aq *t*-BME reaction and workup conditions from the chromatography-free route (Scheme 2). The two reactants were added to a 2:1 v/v ratio of *t*-BME/H_2O. Succinate ester **10** was freely soluble in *t*-BME (>50 g/L) and has only limited solubility in water (ca. 3 g/L). *R*-Baclofen **5** had poor solubility in *t*-BME (<0.5 g/L) and limited solubility in water (10 g/L). This meant that at the start of the reaction it was a tri-phasic mixture with significant amounts of *R*-baclofen out of the solution; however, by the end of the reaction, it was a bi-phasic mixture with all materials in solution. Despite the previously noted instability of succinate esters **8** and **10** toward hydrolysis, these conditions gave a solution yield of drug substance **6** in the range 90−95%. The bi-phasic aq *t*-BME system was shown to be superior to using just *t*-BME. The reaction endpoint was determined using off-line ^{1}H NMR analysis; essentially, once all the succinate ester **10** had been consumed, the reaction was at an endpoint.[17] Following reaction completion, the phases were split and the aqueous phase discarded. The *t*-BME phase-containing product **6** was then washed with aq HCl and then H_2O to remove the majority of the *N*-hydroxysuccinimide byproduct and the majority of the unreacted *R*-baclofen **5**.

The development of a crystallization and isolation procedure began with a review of the recrystallization conditions used in the chromatography-free route (Scheme 2). Here, drug substance **6** was recrystallized in 90% yield in a relatively dilute process that used 2.6 vol of acetone and 24.4 vol of *n*-hexane. For a potentially high-volume product, a more volume efficient process would be needed. Therefore, in addition to replacing *n*-hexane, it would be necessary to replace the acetone as well, as it was assumed that the high solubility of drug substance **6** in acetone was driving the need to add such a

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large volume of the antisolvent. As typical material from the route under development (Scheme 7) was in short supply, development of alternative crystallization conditions was initiated using high-quality drug substance generated by the chromatography-free conditions. The goal was to develop a seeded crystallization that was more volume efficient, target <20 vol and gave a recovery in the crystallization process >90% (therefore solubility < 5 mg/mL at the isolation temperature). Two options were developed, either *t*-BME and *n*-heptane or butanone and *n*-heptane. Initially, the *t*-BME-based option looked appealing as no solvent exchange would be required. However, when the material from the development route started becoming available, it was clear that the *t*-BME-based option was less well able to reject low-level impurities when compared to the butanone option. Hence, the butanone option was preferred and developed. A supersaturated solution of drug substance **6** in 12.5 vol of 1:3 v/v butanone/*n*-heptane could be established at 55 °C. Upon seeding, crystallization was initiated. Following further antisolvent addition (7.5 vol *n*-heptane) and cooling to 20 °C, drug substance **6** could be isolated in 92% yield. The key to generating the desired anhydrate form was to control the levels of residual water in the system prior to the crystallization, as any water present would lead to the formation of the undesired hemi-hydrate. This was readily achieved as part of the distillation process to switch from the reaction solvent *t*-BME to the crystallization solvent butanone. Following the aqueous workup, the *t*-BME solution was diluted with butanone (15 vol). The solution was then concentrated by distillation at atmospheric pressure and 15 vol of the distillate removed. The concentrate was then sampled, and the water content determined (target <0.20% w/w) along with the relative concentration of prodrug **6** (typically in the range 30−35% w/w). *n*-Heptane could then be added, the resulting solution cooled and seeded to induce crystallization. During the development phase, it was noted that any *R*-baclofen **5** remaining in the *t*-BME solution was dehydrated to give lactam **22** (Figure 4) during the distillation

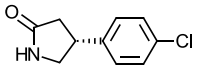

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Figure 4. Structures of impurity **22**.

process, and then rejected during the crystallization. A simplification to the Stage 5 process that was never investigated would have been to replace *t*-BME with butanone as the co-solvent for the coupling reaction, thus removing a solvent from the stage.

When all the separate aspects of the Stage 5 process were combined and applied to typical succinate ester **10** produced by the newly developed process (Scheme 7), drug substance **6** was isolated in 85−87% yield. However, a new low-level unidentified impurity (range detected 0.05−0.17%) with a relative retention time (RRT) = 0.75 was observed by HPLC in the analysis of the isolated product. The specification limit for any unknown impurity was ≤0.1% w/w. HPLC analysis at the end of a reaction showed that the unknown RRT = 0.75 impurity was being produced during the reaction, rather than being produced as a degradant during the workup and distillation stages and that relatively little was rejected during the crystallization. It was also concluded that the source of the unknown impurity was likely to be the succinate ester **10** rather than *R*-baclofen **5**. To try and control the level of the unknown RRT = 0.75 impurity below the specification limit, the amount of the *n*-heptane antisolvent added to the crystallization was reduced slightly. This modification did sufficiently reduce the level of the RRT = 0.75 impurity in the isolated product; however, at the expense ca. 5% of the yield. As all 3 scale-up batches of recrystallized succinate ester **10** appeared to have comparable HPLC profiles and assay values, a user test experiment of a single batch was conducted. This user test experiment, using the modified crystallization process was successful. The largest unspecified impurity in the isolated product was <0.04% w/w. This gave confidence that a workable procedure to control the unknown RRT = 0.75 impurity was in place.

The process was then run on a 2500 L scale. Three batches were performed, each using 48.89 kg of *R*-baclofen **5** and 67.00 kg of succinate ester **10** and produced >150 kg of drug substance **6** in 78% yield. The modifications to the solvent composition to try and control the unknown impurity worked in two out of the three batches. In the third batch, the impurity was found to be at 0.16% w/w, this was above the specification limit for any unknown impurity that was set at ≤0.1% w/w, and this batch was recrystallized to bring it into specification. Analysis by X-ray powder diffraction (XRPD) showed that all batches were the desired anhydrate form and chiral HPLC showed that drug substance **6** had been produced with 100% diastereoisomeric purity. Testing for the residual enzyme was also undertaken.[18,19] Using sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis, a limit test of <1500 ppm (<0.15%) was established. The three batches produced from this campaign (Scheme 7) were tested alongside a control batch produced by the chromatography-free route (Scheme 2) and all batches were shown to be below the 1500 ppm limit.

A possible reason for the failure of one of the batches because of the unknown RRT = 0.75 impurity may have been because of poor deliquoring of the filter cake and subsequent precipitation of the impurity by the wash. The crystallization process did produce relatively small particles, for the batch with the elevated levels of impurity, the D90 of the undried filter cake was <20 μm. The addition of pure *n*-heptane onto a poorly deliquored filter cake containing a mix of butanone/*n*-heptane may have caused more unknown impurity previously in the liquors to co-precipitate alongside the product. Attempts were made to try and identify the RRT = 0.75 impurity. Nominal weight mass spectrometry gave $[M + H]^+ = 568$ and an isotope pattern consistent with the molecule containing 2× Cl. A molecular weight = 567 would imply an odd number of nitrogen atoms. If the unknown contained two molecules of baclofen (contributing 2× Cl and 2× N), then a third nitrogen atom would be needed. Based upon these observations, a tentative molecular formula of $C_{28}H_{39}Cl_2N_3O_5$ was assigned and two possible structures generated. The generation of accurate mass data gave $[M + H]^+ = 568.1251$, a difference of 191.6 ppm from the value calculated for $C_{28}H_{39}Cl_2N_3O_5$, hence making this molecular formula unlikely. The closest predicted molecular formula for compounds containing just carbon, hydrogen, 2× chlorine, either 1, 3 or 5× nitrogen, and oxygen was $C_{25}H_{27}Cl_2N_3O_8$ (difference of 0.5 ppm), unfortunately no plausible structures incorporating two intact baclofen units could be generated and the structure of the unknown impurity remained unresolved. The lack of control over the RRT = 0.75 unknown impurity highlighted an area for

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future development. Although the recrystallized succinate ester **10** had a high assay purity, there was potentially a low-level, undetected impurity present within the material that was ultimately giving rise to the RRT = 0.75 impurity in the final drug substance. This unknown in succinate ester **10** would need to be detected, identified, and controlled.

Abatement of the noxious sulfur-containing off-gases was a concern prior to scaling the Stage 1−4 processes to 2500−3000 L equipment. For Stages 1 and 2, the off-gases were passed through a scrubber containing 5% aq hydrogen peroxide. For Stage 3, the off-gases from the N_2 sparge were passed through a 10% aq sodium hydroxide scrubber and then sent to an incinerator. The N_2 flow rate for the sparging was 30 m^3/h against a capacity of 40 m^3/h for the incinerator. For Stage 4, the off-gases were passed through a 10% aq sodium hydroxide scrubber. In all cases, the abatement was successful and no noxious odors detected.

In summary, a new route to drug substance **6** was developed and the processes successfully run on a 2500 L scale, thus demonstrating a proof of principle. The new route (Scheme 7), which had the potential to become a commercial manufacturing route, overcame all the shortcomings identified with the previously used chromatography-free route (Scheme 2). The chemical efficiency from racemic thiocarbonate **3** to the drug substance **6** was 17% for both routes. However, even with an unoptimized yield of 78% for the final coupling, the new route required only 0.7 kg of *R*-baclofen **5** per kg of drug substance **6** compared with 1.9 kg for the previous route. If production of the drug substance had reached 20,000 kg per year, this would have equated to a saving of 24,000 kg of *R*-baclofen per year. This example clearly shows the benefits of introducing any resolution stage as early as possible in the synthetic sequence to maximize gains.[20] The new route was successfully demonstrated at a large scale and accomplished one of the primary design goals of reducing the use of *R*-baclofen. As with almost any new route of synthesis, advances come with costs. The one cost that was apparent was the difficulty in controlling impurities when opportunities to reject impurities by liquid−liquid extraction or crystallization are limited. The enzyme-catalyzed kinetic resolution of racemic thiocarbonate **3** generated a multitude of impurities/byproducts, which further propagated in the Stage 4 process. This made the understanding of the impurity profile of succinate ester **10** difficult and the isolation of high-quality materials challenging.

EXPERIMENTAL SECTION

Stage 1—Manufacture of *O*-(1-Chloroisobutoxy)-*S*-methyl Thiocarbonate 7. To a 3000 L reactor was charged DCM (636 L, 843 kg, 1.46 vol) followed by 1-chloro-2-methylpropyl chloroformate (435 kg, 2.54 kmol, 1.0 equiv), and the resulting solution cooled to 0 ± 5 °C. An aq solution of tetrabutylammonium bisulfate (26.7 kg, 76 mol, 0.03 equiv) in water (53 L, 53 kg) was prepared and then added to the reactor followed by a line wash with water (30 L, 30 kg). Aq sodium methanethioate (20.9% w/w, 722 kg, 2.15 kmol, 0.85 equiv) was added over 8 h 30 min while maintaining the temperature in the range 0−10 °C (target = 4 °C) and then stirred for 10 min prior to sampling. NMR analysis showed 82% conversion to product. Additional aq sodium methanethioate (20.9% w/w, 161.6 kg, 482 mol, 0.19 equiv) was added over 85 min while maintaining the temperature in the range 0−10 °C (target = 4 °C) and stirred for 10 min prior to sampling. NMR analysis showed >99% conversion to product. The stirring was stopped, and the phases separated. The DCM phase was washed with water (2 × 848 L, 2 × 848 kg, 2 × 1.95 vol). The DCM solution was diluted with fresh DCM (83 L, 110 kg, 0.19 vol) and then concentrated by distillation under reduced pressure. Approximately 700 L of the distillate was removed with a vacuum of 500 mbar and jacket temperature <60 °C and then a further 300 L removed until no more distillate was observed with a vacuum <30 mbar and jacket temperature = 68 °C. At the distillation endpoint, residual DCM was determined by GC analysis, which showed 0.25% w/w DCM and water determination by Karl Fischer titration which showed residual water <0.05% w/w. The product was cooled to 20 °C and discharged from the reactor into a lined drum *via* a 10 μm filter. Mass of product **7** = 432.93 kg. Assay = 99% w/w. Corrected yield = 428.60 kg (92.2%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.05 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.6 Hz), 2.18 (1H, m), 2.38 (3H, s), 6.35 (1H, d, J = 4.47 Hz); ^{13}C NMR{^{1}H} (125 MHz, $CDCl_3$) 13.4, 17.3, 17.4, 35.3, 90.5, 170.5.

Stage 2—Manufacture of Isopropyl-(methylthiocarbonyloxy)methyl-2-methylpropionate 3. To a 3000 L reactor was charged i-butyric acid (478 kg, 505 L, 5.41 kmol, 2.25 equiv). Triethylamine (269 kg, 369 L, 2.65 kmol, 1.10 equiv) was added maintaining the temperature in the range 10−70 °C (exothermic addition). The resulting solution was then heated to 108 °C (range = 105−113 °C) and thiocarbonate **7** (444 kg, 2.406 kmol, 1.0 equiv) was added over 2 h maintaining temperature in the range 105−113 °C (target = 108 °C). Once the addition was complete, the reaction was maintained at the temperature for 13 h prior to sampling for HPLC analysis (target endpoint, unreacted thiocarbonate **7** <5%). The reaction mixture was cooled to 60 °C and water (904 kg, 904 L, 2.06 vol) added. The reaction mixture was further cooled to 20 °C and DCM (181 L, 239 kg, 0.41 vol) added, and the reaction mixture was stirred for 30 min. The stirrer was stopped, and the phases separated. The DCM phase was diluted with further DCM (181 L, 239 kg, 0.41 vol) and then washed with 15% aq potassium carbonate (1139 kg, 1169 L, 2.66 vol) (exothermic, CO_2 released), the target pH for the reaction mixture was pH 8. The DCM phase was diluted with further DCM (181 L, 239 kg, 0.41 vol). The DCM phase was then washed with water (398 kg, 398 L, 0.9 vol). The DCM solution was diluted with fresh DCM (81 L, 107 kg, 0.18 vol) and then concentrated by distillation under reduced pressure. Approximately 440 L of the distillate was removed with a vacuum of 500 mbar and jacket temperature <60 °C until no more distillate was observed and then a further 660 L removed with a vacuum <70 mbar and jacket temperature <100 °C, again until no more distillate was observed. Product **3** was cooled to 20 °C and discharged from the reactor into a lined drum *via* a 10 μm filter. Mass of product **3** = 515.58 kg. Assay = 89% w/w. Corrected yield = 458.87 kg (81.4%).

A purer sample of product **3** was obtained following flash chromatography (heptane and EtOAc as the eluent) for characterization purposes.

δ_H ($CDCl_3$, 400 MHz) 0.97 (6H, d, J = 6.9 Hz), 1.18 (3H, d, J = 7.0 Hz), 1.19 (3H, d, J = 7.0 Hz), 1.99−2.11 (1H, m), 2.34 (3H, s), 2.58 (1H, sept, J = 7.0 Hz), 6.70 (1H, d, J = 5.2 Hz); δ_C{^{1}H} ($CDCl_3$, 100 MHz) 13.4, 16.3, 16.4, 18.6, 18.8, 31.7, 33.9, 94.5, 170.4, 175.0; IR ν: 1754, 1722, 1080, 951 cm^{-1}.

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Stage 3—Manufacture of (*S*)-Isopropyl-(methylthiocarbonyloxy)methyl-2-methylpropionate 11. To a 2500 L reactor was charged aq potassium phosphate buffer (0.96 M, pH = 7.5, 564 kg, 2 vol) and then thiocarbonate **3** (317 kg, assay = 89% w/w, corrected mass = 282.13 kg, 1.204 kmol, 1.0 equiv). If required, the pH was adjusted to pH = 7.5 by the addition of aq ammonium hydroxide (24.9% w/w). The IMMCALA-T2-150 enzyme resin (28.2 kg, 10% by wt) was added, sub-surface sparging with N_2 started (30 m^3/h) and the mixture heated to 35 °C. The pH was maintained at a constant pH = 7.5 by the addition of aq ammonium hydroxide (24% w/w, 66 kg). The reaction completion was checked by chiral HPLC analysis, target >99% chiral purity. After 4 h, the chiral purity was 98.7%; after 5 h 30 min, the chiral purity was 99.6%. Having achieved the reaction endpoint, the sub-surface sparging with N_2 was stopped. While still hot, the enzyme resin was removed by filtration and then the residual enzyme was slurry washed in the filter with *t*-BME (3 × 423 L, 3 × 313 kg, 3 × 1.5 vol). The filtrates were combined, the phases allowed to separate, and the aqueous phase discarded. The *t*-BME solution was washed with 10% aq potassium carbonate (2 × 175 kg, 2 × 175 L, 2 × 0.62 vol) and then water (176 kg, 176 L, 0.62 vol). The *t*-BME solution was then concentrated by distillation at atmospheric pressure and a jacket temperature = 80 °C until no more distillate was observed. Vacuum was applied and the distillation continued with a jacket temperature = 50 °C until a vacuum of 10−20 mbar achieved. The distillation endpoint was determined by GC analysis (target residual *t*-BME <5% w/w, target residual DCM <1.0% w/w) and HPLC assay determination (target compound **11** assay >57.0% w/w). The product was cooled to 20 °C and discharged from the reactor into a lined drum *via* a 10 μm filter. Mass of product **11** = 171.50 kg. Assay = 60% w/w. Corrected yield = 102.90 kg (36.5%).

Stage 4—Manufacture of (*S*)-1-(2,5-Dioxoazolidinyloxycarbonyloxy)-2-methylpropyl 2-Methylpropanate 10. To a 2500 L reactor was charged; thiocarbonate **11** (164 kg, assay = 60% w/w, corrected mass = 98.4 kg, 0.420 kmol, 1.0 equiv), *N*-hydroxysuccinimide (189.1 kg, 1.643 kmol, 3.91 equiv), and DCM (532 L, 708 kg, 5.41 vol), and the resulting slurry cooled to −20 °C. SO_2Cl_2 (83.9 L, 140.1 kg, 1.038 kmol, 2.47 equiv) was added over 1 h while maintaining the temperature in the range −15 to −25 °C (exothermic addition, target = −20 °C) and stirred for 1 h prior to sampling. ^{1}H NMR analysis showed 89% conversion to product. Additional SO_2Cl_2 (7.9 L, 13.2 kg, 0.097 kmol, 0.23 equiv) was added while maintaining the temperature in the range −15 to −25 °C (target = −20 °C) and stirred for 30 min prior to sampling. ^{1}H NMR analysis showed 100% conversion. NEt_3 (353 L, 256.6 kg, 2.54 kmol, 6.04 equiv) was added while maintaining the temperature in the range −15 to −25 °C (exothermic addition, target = −20 °C) and then stirred for 1 h prior to warming to 0 °C. H_2O (547 L, 547 kg, 5.61 vol) was added while maintaining the temperature in the range 0−10 °C (exothermic addition, target = 5 °C). The layers were separated, and the aqueous phase discarded. The DCM phase was concentrated to dryness by distillation, jacket temperature = 30 °C, and vacuum applied until the pressure <50 mbar and no more distillate was observed. H_2O (552 L, 552 kg, 5.61 vol) was added and the mixture stirred for 10 min. *t*-BME (549 L, 406 kg, 5.58 vol) was added and the mixture stirred for 10 min before being cooled to 5 °C. 10% aq potassium carbonate (573 kg, 573 L, 5.82 vol) was added and the mixture stirred for 10 min. The layers were separated, and the aqueous phase discarded. The organic layer was washed with H_2O (552 L, 552 kg, 5.61 vol). The organic layer was then passed through a filter-containing activated charcoal cartridges (2.8 kg charcoal). The charcoal cartridges were then rinsed with *t*-BME (302 L, 223.5 kg, 3.07 vol). The filtrates were combined and then concentrated to dryness by distillation, jacket temperature = 30 °C, and vacuum applied until the pressure <50 mbar and no more distillate was observed. *t*-BME (115 L, 85.1 kg, 1.17 vol) was added followed by heptane (53 L, 36.3 kg, 0.54 vol) and the solution aged at 30 °C for 15 min. The resulting solution was cooled to 8 °C for over 1 h. If crystallization did not occur spontaneously, then a seed was added. The resulting slurry was aged at 8 °C for 1 h. Further heptane (73 L, 49.6 kg, 0.74 vol) was added over 1 h and then the slurry cooled to −10 °C for over 4 h. The slurry was filtered and then the filter cake was washed with heptane (547 L, 372 kg, 5.56 vol). The filter cake was deliquored and then dried under vacuum at 30 °C. Target LOD <0.5% w/w. Mass of product **10** = 93.95 kg. Assay = 98% w/w. Corrected yield = 92.07 kg (73%).

Stage 4R—Recrystallization of (*S*)-1-(2,5-Dioxoazolidinyloxycarbonyloxy)-2-methylpropyl 2-Methylpropanate 10. To a 2500 L reactor was charged crude **10** (67.0 kg, assay = 98%, 0.218 kmol, 1.0 equiv) followed by IPA (205 L, 161 kg, 3.06 vol) and heptane (169 L, 115.5 kg, 2.52 vol), and the resulting suspension was heated to 30 °C to generate a clear solution. The solution was then cooled to 20 °C and aged for 1 h. If spontaneous nucleation does not occur, then a seed can be added. The resulting slurry was cooled to −10 °C for over 4 h and then aged at −10 °C for at least 1 h. The slurry was filtered, and the filter cake washed with cold heptane (360 L, 246 kg, 5.37 vol). The filter cake was deliquored and then dried under vacuum at 30 °C. Mass of product **10** = 61.72 kg. Assay = 100% w/w. Yield = 94%. mp 66.1 °C (DSC); δ_H ($CDCl_3$, 400 MHz) 1.02 (6H, d, J = 6.9 Hz), 1.19 (3H, d, J = 7.0 Hz), 1.20 (3H, d, J = 7.0, 2.0 Hz), 2.11−2.19 (1H, m), 2.62 (1H, sept, J = 7.0 Hz), 2.84 (4H, s), 6.58 (1H, d, J = 5.0 Hz); δ_C {1H} ($CDCl_3$, 100 MHz) 16.0, 16.2, 18.6, 18.6, 25.5, 31.7, 33.9, 98.1, 150.3, 168.4, 174.7; IR ν: 1825, 1787, 1735, 1201, 953 cm^{-1}; $[\alpha]_D^{26}$ +1.0° (c 1.02, $CHCl_3$); mass spectrometry (MS) electrospray ionization (ESI^+) m/z: 324.2 $[M + Na]^+$.

Stage 5—Manufacture of (*R*)-3-(4-Chlorophenyl)-4-[(*S*)-2-methyl-1-(2-methylpropanoyloxy)-propoxycarbonylamino]-butyric Acid 6. To a 2500 L reactor was charged; *t*-BME (226 L, 167.4 kg, 3.37 vol), H_2O (112 L, 112 kg, 1.67 vol), *R*-baclofen **5** (49.89 kg, 0.233 kmol, 1.05 equiv), and succinate ester **10** (67.00 kg, 0.222 kmol, 1.0 equiv), and the resulting mixture heated to 45 °C. After 6 h, the reaction was sampled for ^{1}H NMR analysis and then cooled to 20 °C. The stirrer was stopped and the phases separated. The aqueous phase was discarded. The organic phase was washed with 1 M aq HCl (113 L, 113 kg, 1.67 vol), then H_2O (2 × 112 L, 2 × 112 kg, 2 × 1.67 vol). The organic phase was transferred to a clean reactor *via* an in-line filter. Butanone (1003 L, 807.4 kg, 15 vol) was added *via* an in-line filter and the resulting solution concentrated by distillation at atmospheric pressure to collect a total of 1000 L of distillate. For the first 2 h of the distillation, the jacket temperature was set at 75 °C. For the remainder of the distillation, the jacket temperature was set at 100 °C. Once the distillation was complete, the solution was sampled for water determination by Karl Fischer titration, which showed residual water = 0.08% w/w (target <0.20% w/w), and assay determination by ^{1}H NMR, which showed compound **6** =

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30.6% w/w. The solution was cooled to 65 °C and *n*-heptane (475 L, 323 kg, 7.09 vol) added *via* an in-line filter and the resulting solution cooled to 55 °C. A seed of compound **6** (desired anhydrate form, 400 g) was added and the resulting slurry stirred at 55 °C for 1 h. *n*-Heptane (352 L, 241 kg, 5.25 vol) was added *via* an in-line filter over 2 h. The resulting slurry was cooled to 20 °C over 7 h and then aged at 20 °C for 4 h. The slurry was filtered and the filter cake washed with *n*-heptane (266 L, 182 kg, 3.97 vol). The filter cake was deliquored and then dried under vacuum at 75 °C. Mass of product **10** = 69.00 kg. Assay = 99.8% w/w. Yield = 78%. mp 127 °C (DSC); δ_H ($CDCl_3$, 400 MHz) 0.83 (3H, d, J = 6.4 Hz), 0.84 (3H, d, J = 6.4 Hz), 1.07 (3H, d, J = 6.4 Hz), 1.09 (3H, d, J = 6.4 Hz), 1.88 (1H, m), 2.50−2.74 (3H, m), 3.18 (3H, m), 6.38 (1H, d, J = 5.2 Hz), 7.24 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.46 (1H, t, J = 6.0 Hz), 12.08 (1H, br s); $\delta_C\{^1H\}$ ($(CD_3)_2SO$, 100 MHz) 17.2, 17.3, 19.5, 19.6, 32.3, 34.2, 38.5, 42.1, 46.3, 93.8, 129.0, 130.7, 132.1, 141.9, 155.2, 173.8, 175.4; IR ν: 3391, 2973, 1735, 1698 cm^{-1}; $[\alpha]_D^{25}$ 29.1° (c 1.10, $CHCl_3$); mass spectrometry (MS) electrospray ionization (ESI^+) m/z: 399.9 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00491.

^1H and ^{13}C NMR spectra for compounds **3**, **6**, **7**, **10**, and **11** (PDF)

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Notes

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■ ABBREVIATIONS

aq, aqueous; Bz, benzoyl; *t*-BME, *tert*-butyl methyl ether; ca., circa; cf., confer/conferatur; DCM, dichloromethane; DSC, differential scanning calorimetry; equiv, equivalents; GC, gas chromatography; HPLC, high performance liquid chromatography; h(s), hour(s); IPA, i-propanol; ICH, International Conference on Harmonization; LOD, loss on drying; min(s), minute(s); NMR, nuclear magnetic resonance spectroscopy; RRT, relative retention time; SDS-PAGE, sodium dodecylsulfate-polyacrylamide gel electrophoresis; vol(s), volume(s); v/v, volume for volume; w/w, weight for weight; XRPD, X-ray powder diffraction

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(14) One potential future option was to propose thiocarbonate **3** as the registered starting material for the GMP stages of the synthesis.

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To strengthen this position an upgrade in purity may have been adventitious.
(15) Although no dimethyldithiocarbonate **14** was present in the Stage 2 intermediate it's not inconceivable that low levels *S*-methyl chlorothioformate were formed during the Stage 4 reaction and thus produced succinate ester 15.
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