Organic Process Research & Development

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Enzymatic Desymmetrization Route to Ethyl [3-(2-Amino-2-methylpropyl)phenyl]acetate

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ABSTRACT: An efficient process to ethyl [3-(2-amino-2-methylpropyl)phenyl]acetate **6** has been developed. Key steps include a novel enzymatic desymmetrization of diester **2** and a Ritter reaction between alcohol **4** and chloroacetonitrile, followed by chemoselective deprotection with thiourea.

INTRODUCTION

During the development of PF-00610355 (Figure 1), a novel once-daily inhaled β_2-adrenoreceptor agonist for the treatment of asthma and COPD,[1] we required significant quantities of methyl [3-(2-amino-2-methylpropyl)phenyl]acetate **6a**. Due to the short timelines, we decided to use the Medicinal Chemistry route (Scheme 1, steps a, c, and e−g) to meet this initial demand; however, for convenience we decided to prepare the ethyl ester **6** rather than the methyl ester **6a** as the preceding step is conducted in ethanol.[1]

RESULTS AND DISCUSSION

Prior to scaling up, we examined the route in the lab, which highlighted some key concerns, the low-yielding (27%) and laborious sequence used to access monoester **3** via equilibration of the diester **2** with diacid **1** in acidic ethanol and the Ritter reaction between chloroacetonitrile and alcohol **4**, followed by deprotection with thiourea.[2] However, small-scale laboratory runs and process safety testing indicated that these steps were safe to operate and provided an acceptable quality product.

Although diacid **1** is commercially available, we chose to prepare this through hydrolysis of the readily available dinitrile **7** (Scheme 1, step b). Treatment of the diacid **1** with 1.2 equiv of ethanol in acidic THF (Scheme 1, step d) afforded an equilibrium mixture of diacid **1**, monoester **3**, and diester **2** similar to that obtained using the original process, thus removing the need to prepare the diester **2** and then equilibrate it with diacid **1** (Scheme 1, steps a and c). This modified process afforded an improved 39% yield of the monoester **3**; however, the product purity was moderate (typically 90%, the remainder being mainly a mixture of diacid **1** and diester **2**).

Selective conversion of monoester **3** to the desired tertiary alcohol **4** was achieved by reaction with 3 equiv of methyl magnesium chloride in high yield (93%) but low purity (64% by HPLC analysis). Due to this low purity, crystallization of the alcohol **4** was not possible, and the crude product was taken directly to the Ritter step. Slow addition of concentrated sulfuric acid to a mixture of alcohol **4** and chloroacetonitrile in acetic acid provided the desired chloroacetamide **5** in moderate yield (63%)

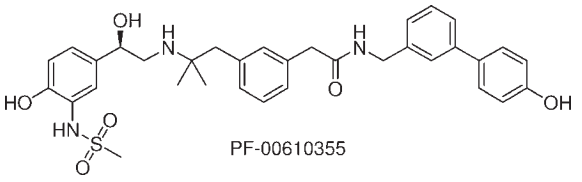


Figure 1. Structure of PF-00610355, a novel once-daily β_2-adrenoreceptor agonist.

and purity (84%) after crystallization from toluene/heptane. Deprotection of chloroacetamide **5** with thiourea in a mixture of acetic acid and ethanol afforded a solution of the intermediate amino acid **6b**, after filtration of the byproduct **8**.[3] Finally, **6b** was converted to the ethyl ester **6** by addition of concentrated sulfuric acid to the ethanolic solution obtained after filtration.

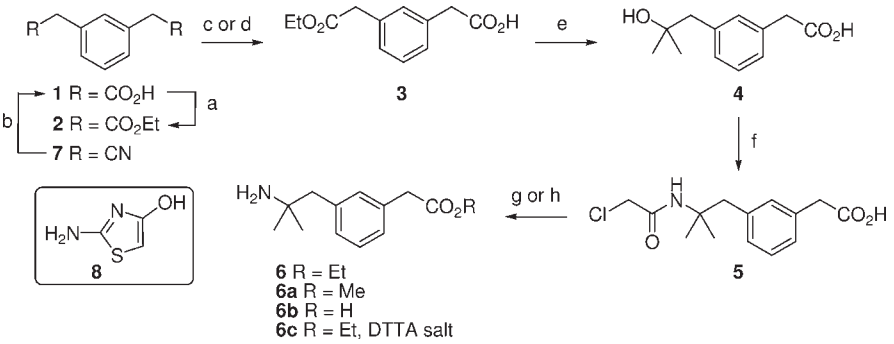
While this process worked reasonably well on lab scale (up to ∼150 g, ∼70% yield), it performed poorly on kilogram scale, and isolation of **6** of suitable purity proved impossible due to the high impurity burden. To recover as much material as possible from the crude product, a salt screen was conducted, and fortuitously di-*p*-toluoyl-(L)-tartaric acid (DTTA) in acetonitrile (MeCN) was found to provide a crystalline salt **6c** that afforded an excellent purge of impurities. Importantly, given the variable purity of the in-going **6**, the process was tolerant of a wide variation in acid−base stoichiometry, consistently providing the 1:1 salt **6c**. The yield was usually around 70%, but this was highly dependent on the quality of the in-going material, and in some cases only 35−40% yield could be achieved. This enabled us to recover sufficient **6** (as the DTTA salt **6c**) from the crude reaction mixtures to advance the development of PF-00610355; however, this process was clearly not acceptable for future material demands.

After a careful analysis of the campaign, the following areas were identified for further investigation.

1. The sequence used to prepare monoester **3**. While this process worked, it was low yielding and labor intensive, and the moderate purity **3** obtained had a significant impact on

Received: April 20, 2011
Published: June 24, 2011

Scheme 1[a] Initial Route to **6**



[a] Reagents and Conditions. (a) EtOH, H_2SO_4, reflux; (b) 6 M HCl, reflux; (c) **1** + **2**, EtOH, 1,4-dioxane, HCl, reflux; (d) **1**, EtOH (1.2 equiv), HCl, THF, 50 °C; (e) MeMgCl, THF; (f) chloroacetonitrile, H_2SO_4, AcOH; (g) (i) thiourea, AcOH, EtOH, reflux; (ii) HCl, MeOH, reflux (to **6a**); (h) (i) thiourea, AcOH, EtOH, reflux (to **6b**); (ii) H_2SO_4, EtOH, reflux (to **6**); (iii) DTTA, MeCN (to **6c**).

the downstream steps as the impurities and their fate products were difficult to purge.

2. The lack of purification points in the sequence resulted in an unacceptably high impurity burden being carried into the latter steps.
3. The deprotection—esterification sequence generated significant quantities of highly colored impurities and provided poor quality material with inconsistent yield, necessitating purification via crystallization of the DTTA salt **6c**.

From an examination of the literature, it was evident that enzymatic hydrolysis potentially offered a highly selective route to the desired monoester **3**.[4] Hydrolase enzymes, in particular, pig liver esterase, have found extensive use in the desymmetrization of prochiral diesters to produce chiral monoesters; however, only a few examples of their use for the selective monohydrolysis of achiral diesters have been published.[5]

A wide range of readily available hydrolase enzymes were screened[6] for the chemoselective monohydrolysis of diester **2**, and the best hits from this screen are summarized in Table 1. Immediately apparent was that there were several enzymes that appeared to offer significant selectivity for the desired monoester **3**.

From this initial screen, *Thermomuces lanoginosus* lipase was selected for further development as it was highly selective, in addition to being cheap and readily available as a 100 KLU/g solution (Lipolase 100 L). Furthermore, we had significant internal experience with the use of this enzyme and how best to optimize the reaction conditions.[7] Since this ultimately provided a successful, cost-effective route to prepare monoester **3**, none of the other enzymes were investigated further.

These initial screening conditions were then scaled up to ~1 g input, and the concentration was increased to a more practical 250 g/L. Under these conditions, the reaction proceeded extremely slowly (50% conversion in 4 days); however, upon examination of a range of different buffers, calcium acetate was found to be extremely beneficial. Using a pH 7 calcium acetate buffer on a 1 g scale, full conversion to monoester **3** was achieved in ~16 h at a concentration of 250 g/L.

After further process development, the optimal reaction conditions were to suspend diester **2** in a mixture of Lipolase (0.32 mL/g; approx 32 KLU/g **2**) and 0.2 M $Ca(OAc)_2$ buffer (4 mL/g) at ambient temperature (around 20 °C) and then to maintain the pH between 5.5 and 6.8 through addition of 1 M sodium hydroxide until reaction completion (usually around 16 h on lab scale, up to 48 h on larger scale).

Table 1. [a]Enzymes Showing Selectivity Towards Formation of Monoester 3

enzyme	diacid **1** (%)	monoester **3** (%)	diester **2** (%)
Mucor miehei Esterase	0	100	0
Rhizomucor miehei Lipase	0	60	40
Thermomuces lanoginosus Lipase	0	50	50
Penicillin G Acylase	0	20	80
Candida antarctica Lipase B	54	16	30

[a] Reactions screened at 10 g/L in pH 7.5 potassium phosphate buffer with 10 wt % enzyme. Conversion was measured after 16 h.

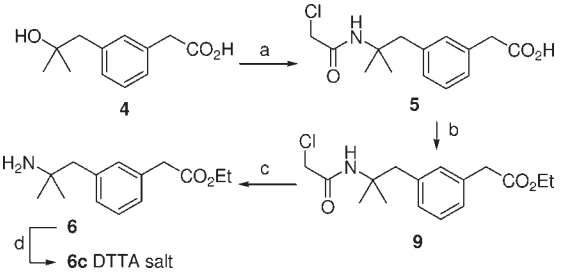
Since chemical hydrolysis to the diacid **1** occurs at higher pH, careful pH control is required. Similarly, using more concentrated solutions of sodium hydroxide results in higher levels of diacid **1**, presumably resulting from chemical hydrolysis in localized high pH areas during the addition of hydroxide to the reaction mixture. As it proved simpler to separate residual diester **2** from monoester **3** (rather than diacid **1**), the reaction was stopped at ~95% conversion to minimize the levels of diacid **1** present.

Once the reaction was complete, the pH was adjusted to ~4, and the monoester **3** was extracted into ethyl acetate. Removal of the enzyme debris was required at this stage; otherwise, subsequent separations were extremely slow. On large scale, this was achieved by filtration through a Gauthier filter (while successful on lab scale, filtration through a Celite pad was not effective on pilot plant scale). Purification of crude **3** was achieved through an acid—base cycle (mainly to remove diester **2**), and the product was isolated as a toluene concentrate for use in the next step. The yield was generally high on lab scale (around 80%), but initial scale-up attempts were less successful, with only ~60% yield of lower purity product obtained (up to 10% diacid **1** was the main impurity). This was largely due to pH overshoots during the reaction resulting in chemical hydrolysis to diacid **1** and ineffective removal of enzyme debris resulting in poor phase separations and significant material losses. Once these problems had been identified and resolved, we were able to consistently obtain good quality monoester **3** in around 80% yield.

To identify suitable purification points, all the intermediates in the process were evaluated in both crystallization and salt

dx.doi.org/10.1021/op200108k |*Org. Process Res. Dev.* 2011, 15, 871–875

Scheme 2[a] Optimized Route to **6**



[a] Reagents and Conditions. (a) Chloroacetonitrile, H_2SO_4, AcOH, DCM; (b) H_2SO_4, EtOH, reflux; (c) (i) thiourea, AcOH, EtOH, reflux; (ii) aq Na_2CO_3, DCM; (d) DTTA, MeCN.

screens. From these screens, crystallization of alcohol **4** was found to be an important purification point. Crystallization from toluene afforded a reasonable purge of impurities (purity increased from ~65% to ~85%), as long as care was taken to remove any residual THF and acetic acid, arising from hydrolysis of isopropyl acetate, from the mixture. Fortunately, this was readily accomplished by azeotropic distillation from the extraction solvent (isopropyl acetate, containing some THF) to toluene. On scale-up, this modified isolation process delivered crystalline alcohol **4** in an acceptable 68% yield, although still of relatively low purity (around 85%).

Having developed a reliable process to prepare sufficiently pure alcohol **4**, the focus then shifted to the conversion of alcohol **4** to amine **6**. The Ritter−deprotection−esterification sequence was identified as one of the main sources of product degradation and impurity generation in the initial synthesis.

As a result of the high concentration of the Ritter reaction (2 mL/g AcOH), there was a considerable scope for the generation of localized "hot spots" during the very exothermic addition of concentrated sulfuric acid to the reaction mixture; this was thought to be one source of impurity generation. The subsequent thiourea-mediated deprotection (in acetic acid/ethanol) gave amino acid **6b** that proved challenging to isolate and purify and so was telescoped crude into the esterification, resulting in significant impurity generation from thiourea-related residues, a problem that was exacerbated on scale.

To reduce the amount of acid used in the Ritter reaction and allow for better temperature control, the use of an inert cosolvent, dichloromethane (DCM), was examined. Conducting the reaction in 5 mL/g of DCM proved successful and enabled the quantities of acid to be significantly reduced (3 equiv of AcOH and 2 equiv of H_2SO_4 instead of 2 mL/g and 1.5 mL/g, respectively). This reduction in acid level greatly simplified the workup, and reasonable quality **5** (85−90% pure) was isolated in 65−70% yield after crystallization from toluene/heptane.

Recognizing that separating the deprotection and esterification steps, preferably by isolating and purifying an intermediate, might reduce the high impurity burden, the step-reordered sequence (esterification, then deprotection) was examined (Scheme 2), as purification of the intermediate protected amino ester **9** was likely to be more facile than purification of amino acid **6b**. In addition, a range of alternative bidentate reagents (for example, guanidine and 1,2-ethylenediamine) were screened as thiourea[8] replacements in the deprotection step; however, none of these offered a viable alternative and were not pursued.[9]

Esterification of chloroacetamide **5** in acidic ethanol afforded the desired protected amino ester **9**, which was isolated in excellent purity (>95%) by crystallization from toluene/heptane. Subsequent deprotection of **9** with thiourea in a mixture of ethanol and acetic acid proceeded smoothly, and after filtration to remove the precipitated byproduct **8**, concentration afforded crude **6** (as the acetate salt). Analysis of this indicated that the crude material was virtually pure (in contrast to that prepared by the previous route), and after partitioning between 2 M aq Na_2CO_3 and DCM and concentration of the organic phase, pure **6** was obtained in 73% yield. While suitable quality **6** could be obtained from this process, it was considered advantageous to isolate a solid, so the di-*p*-toluoyl tartrate salt **6c** identified previously was prepared. This optimized procedure was then scaled-up in our kilo-lab, delivering over 10 kg of tartrate salt **6c** in an excellent and reproducible (two batches) 64% overall yield from **4** (Scheme 2).

In conclusion, a significantly improved process to monoester **3** has been developed through a novel enzymatic desymmetrization route. In addition, through a combination of step-reordering and process development, an effective route to amino ester **6** has been demonstrated on kilogram scale.

EXPERIMENTAL SECTION

Reactions Were Monitored by HPLC as Follows.

Column	Phenomenex Luna 3μ Phenyl-hexyl 50×2.0 mm
Injection	2 μL
Flowrate	0.8 mL/*min*
Solvents	Solvent A-H_2O : MeCN : TFA 1000 : 25 : 1
	Solvent B-H_2O : MeCN : TFA 25 : 1000 : 1
Detection	Diode array at 210, 225, and 254 nm

1,3-Benzenediacetic Acid 1. 1,3-Phenylenediacetonitrile **7** (40 kg; 256.1 mol) was added to a mixture of 37% hydrochloric acid (160 L) and water (160 L), and the resulting suspension was heated to 100 °C. After 19 h, HPLC analysis indicated that the reaction was complete. The reaction mixture was cooled to 20 °C, and the solid was isolated by filtration, washed with water (2 × 80 L), and dried under vacuum at 50 °C to give the diacid **1** as a fine white solid (45.55 kg; 92%), identical to commercially available material.

1,3-Benzenediacetic Acid, 1,3-Diethyl Ester 2[1]**.** Concentrated sulfuric acid (1.82 L) was charged to a suspension of **1** (45.55 kg; 234.6 mol) in EtOH (455.5 L), and the resulting mixture was heated to reflux. After 20 h, HPLC analysis showed complete reaction. The mixture was concentrated by distillation under vacuum to remove ethanol, and then toluene (136.5 L) was added. The toluene solution was washed with 5% aqueous sodium hydrogen carbonate (91 L) to remove any residual **1** and was then concentrated down to ~100 L (roughly 1 mL/g toluene) and was used directly in the next step. An aliquot was concentrated to dryness to give **2** as a viscous liquid, and analytical data were identical to that published in the literature (ref 1).

1,3-Benzenediacetic Acid, 1-Ethyl Ester 3[1]**.** Lipolase (9.4 L; 100 KLU/g solution) was added to a stirred solution of 0.2 M calcium acetate (117.5 L), and the homogeneous solution was stirred at room temperature for 30 min before diester **2** (~1 mL/g toluene solution; 29.35 kg of **2**; 117.3 mol) was added. The

dx.doi.org/10.1021/op200108k |*Org. Process Res. Dev.* 2011, 15, 871–875

Table 2. Solvent Timetable

time (mins)	solvent A (%)	solvent B (%)
0.00	100.0	0.00
0.50	100.0	0.00
8.00	25.4	74.6
12.50	100.0	0.00

mixture was stirred at ambient temperature for 48 h, at which point HPLC analysis indicated ~95% conversion of diester **2** to monoester **3** and minimal levels of diacid **1**. During this time, the pH was checked regularly and maintained between 5.5 and 6.8 (target 6.5) by addition of 1 M sodium hydroxide aliquots (approx 5 L). Upon reaction completion, the pH was adjusted to 3.5 with 1 M hydrochloric acid, and EtOAc was added (117 L). The biphasic mixture was then filtered through a Gauthier filter and separated. The aqueous layer was extracted with EtOAc (2 × 117 L). The combined organic phase was extracted with saturated aqueous sodium hydrogen carbonate (3 × 150 L) (**CAUTION** − significant effervescence and foaming, particularly with first extraction). The combined aqueous extracts were adjusted to pH 2 by addition of 2 M hydrochloric acid (**CAUTION** − effervescence and foaming), and the resulting mixture was extracted with toluene (2 × 147 L). The toluene extract was then concentrated to ~40 L (about 1 mL/g toluene) and was used directly in the next step. Estimated yield from HPLC assay was 19.7 kg (76%). A sample was concentrated to dryness to give **3** as an oil, and the analytical data were identical to that in the literature (ref 1).

1,3-Benzenediacetic Acid, 1-Ethyl Ester 3 (Alternative Procedure). Ethanol (85.4 g; 1.85 mol; 1.2 equiv) and 37% hydrochloric acid (30 mL) were added to a solution of **1** (300 g; 1.54 mol) in THF (3.0 L), and the resulting thin suspension was heated to 50 °C. Once the equilibrium mixture of diacid **1**, diester **2**, and monoester **3** had been reached (around 5−6 h), the solvent was exchanged to toluene (1.5 L) by distillation. The resulting suspension was stirred for 15 min, and then the solid (diacid **1**) was removed by filtration and washing with toluene (300 mL). The combined filtrate and washes were extracted with saturated sodium hydrogen carbonate (1.35 L, then 2 × 300 mL) (**CAUTION** − effervescence, particularly with first extraction). The combined aqueous phase was adjusted to pH 6 with 2 M hydrochloric acid (**CAUTION** − effervescence), and the resulting slightly milky solution was extracted with *tert*-butyl methyl ether (1.2 L, 2 × 600 mL). The combined organic extracts were washed with water (600 mL), dried over magnesium sulfate, and concentrated to dryness under vacuum to give the product **3** as a pale straw-colored oil (134 g; 39%).

[3-(2-Hydroxy-2-methylpropyl)phenyl]acetic Acid 4[1]. A solution of monoester **3** (3.59 kg; 16.15 mol) in dry THF (36 L) was prepared in a clean, dry, and nitrogen-inerted reactor. The solution was cooled to 0−5 °C, and a solution of 1 M MeMgBr in THF (56.53 L; 56.53 mol; 3.5 equiv) was added at such a rate as to keep the temperature below 15 °C. (**CAUTION** − Exothermic reaction and methane evolution.) On completion of addition (between 1 and 2 h), the cooling was removed, and the gray suspension was warmed to 20 °C and held for 1 h, at which point HPLC analysis indicated complete reaction. The slurry was cooled to 0−5 °C, and then water (17.95 L) was added at such a rate as to keep the temperature below 20 °C. The pH was adjusted to ~2 by addition of 5 M hydrochloric acid, and the mixture was extracted with iPrOAc (2 × 18 L). The combined iPrOAc extracts were washed with water (3 × 18 L), after which the solvent was exchanged to toluene by vacuum distillation. The volume was adjusted to ~20 L toluene by distillation; the solution was cooled to 5 °C; and the resulting slurry was granulated for 2 h. The solid was isolated by filtration, washing with toluene (3.59 L), and dried under vacuum at 50 °C to give **4** as a white solid (2.29 kg; 68% uncorrected). HPLC analysis indicated approximately 85% purity. Mp 58 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (6H, s), 2.64 (2H, s), 3.52 (2H, s), 4.28 (1H, s), 7.09 (3H, m), 7.20 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.1, 40.8, 49.4, 69.3, 126.7, 127.4, 128.7, 131.3, 134.1, 138.9, 172.7. MS: m/z 209 $[M + H]^+$.

{3-[2-(2-Chloroacetylamino)-2-methylpropyl]phenyl}acetic Acid 5[1]. Chloroacetonitrile (1.63 kg, 21.62 mol) was added to a slurry of alcohol **4** (3.00 kg, 14.41 mol) in DCM (15 L). Acetic acid (2.6 kg, 43.23 mol) was added, maintaining the temperature between 5 and 10 °C. The resulting solution was treated with concentrated sulfuric acid (2.83 kg, 28.82 mol), maintaining the temperature between 5 and 10 °C. The mixture was warmed to 20 °C, and after 90 min the reaction mixture was added to cold water (30 L), maintaining the temperature below 10 °C. The mixture was stirred for 30 min at 5−10 °C and then at 20 °C for 30 min. The layers were separated, and the aqueous layer was extracted with further DCM (15 L). The combined DCM layers were distilled down to 8 L volume at atmospheric pressure. The concentrate was treated with *n*-heptane (27 L) and toluene (3 L) and concentrated in vacuo to remove residual DCM. The resulting slurry was granulated at 20 °C for 2 h, and then the solid precipitate was isolated by filtration, washed with *n*-heptane (2 × 3 L), and dried under vacuum at 40 °C to give **5** as an off-white solid (3.76 kg; 92%). Mp 92 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.22 (s, 6H), 2.97 (s, 2H), 3.53 (s, 2H), 3.97 (s, 2H), 7.01 (m, 2H), 7.11 (m, 1H), 7.21 (m, 1H), 7.62 (s, 1H), 12.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.7, 40.7, 43.1, 43.4, 53.5, 127.1, 127.6, 128.6, 131.4, 134.4, 137.9, 165.4, 172.6. MS: m/z 284/286 $[M + H]^+$. Anal. Calcd for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.39; Cl, 12.49; N, 4.94. Found: C, 59.60; H, 6.36; Cl, 11.94; N, 4.51.

Ethyl 2-{3-[2-(2-Chloroacetamido)-2-methylpropyl]phenyl}acetate 9. A solution of chloroacetamide **5** (3.76 kg, 13.24 mol) in ethanol (30.1 L) was treated with concentrated sulfuric acid (130 g, 1.31 mol) and heated at reflux for 90 min. The cooled solution was adjusted to ~pH 5 using 1.0 M aqueous sodium hydrogen carbonate solution (2.0 kg). The mixture was concentrated down to 8 L volume in vacuo, diluted with toluene (11.7 L), and concentrated down to 12 L volume in vacuo. The concentrate was diluted with toluene (25.8 L) and washed with water (22.6 L), and the aqueous layer was re-extracted with further toluene (15.0 L). The combined toluene layers were concentrated down to 8 L in vacuo. The concentrate was held at 35 °C, and *n*-heptane (15.0 L) was added, maintaining the temperature above 30 °C. The mixture was cooled, and the resulting slurry was granulated at 20 °C for 2 h. The solid precipitate was isolated by filtration, washed with *n*-heptane (2 × 3.76 L), and dried in a vacuum oven at 40 °C to give ethyl ester **9** as a white solid (3.15 kg; 76%). Mp 52 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, J = 7.0 Hz, 3H), 1.22 (s, 6H), 2.95 (s, 2H), 3.59 (s, 2H), 3.94 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 7.00 (m, 2H), 7.09 (d, J = 7.6 Hz 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.1, 26.6, 40.3, 43.2, 43.4, 53.5, 60.2, 127.1, 127.7, 128.8, 131.3, 133.8, 138.0, 165.4, 171.1. MS: m/z 312/314 $[M + H]^+$. Anal. Calcd for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; Cl, 11.37; N, 4.49. Found: C, 61.79; H, 7.03; Cl, 11.04; N, 4.30.

dx.doi.org/10.1021/op200108k |*Org. Process Res. Dev.* 2011, 15, 871–875

Ethyl 2-[3-(2-Amino-2-methylpropyl)phenyl]acetate Hydrogen (2*R*,3*R*)-2,3-Bis[(4-methylbenzoyl)oxy]succinate 6c. A solution of the chloroacetamide **9** (3.10 kg, 9.95 mol) in ethanol (34.1 L) was treated with thiourea (0.91 kg, 11.93 mol) and acetic acid (6.2 L), and the resulting mixture was heated at reflux for 4 h. The mixture was cooled, and the precipitated solid was removed by filtration and washed with ethanol (3.1 L). The combined filtrate and wash were concentrated down to 8 L volume in vacuo; toluene (31 L) was added; and the solution was concentrated to 8 L in vacuo. This process was repeated with toluene (24.8 L). The resulting mixture was treated with water (9.3 L) and 2 M aqueous sodium carbonate solution (7.5 L), and the product was extracted into DCM (31.0 and 15.5 L). The combined DCM extracts were concentrated down to 8 L volume at atmospheric pressure; MeCN (12.4 L) was added; and the mixture was concentrated down to 8 L volume in vacuo. The concentrate was diluted with MeCN (24.8 L) and adjusted to 20 °C before a solution of di-*p*-toluoyl-L-tartaric acid (3.65 kg, 9.45 mol) in MeCN (18.6 L) was added. The resulting slurry was stirred for 15 h at 20 °C, and then the solid precipitate was isolated by filtration, washed with MeCN (2 × 6.2 L), and dried in a vacuum oven at 50 °C to give tartrate salt **6c** as a white solid (5.72 kg; 93%). Mp 158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H), 2.34 (s, 6H), 2.78 (s, 2H), 3.63 (s, 2H), 4.06 (q, J = 7.0 Hz, 2H), 5.61 (s, 2H), 7.03 (m, 2H), 7.15 (br. d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.2 Hz, 4H), 7.80 (d, J = 8.2 Hz, 4H), 8.30 (br s., 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 21.1, 24.6, 24.6, 45.0, 53.4, 60.2, 72.4, 127.0, 127.7, 128.1, 128.9, 129.1, 129.3, 131.5, 134.2, 135.6, 143.6, 164.9, 168.2, 171.0. MS: m/z 236 $[M + H]^+$. Anal. Calcd For $C_{34}H_{39}NO_{10}$: C, 65.69; H, 6.32; N, 2.25. Found: C, 65.71; H, 6.32; N, 2.36.

Ethyl [3-(2-Amino-2-methylpropyl)phenyl]acetate 6[1] (Alternative Procedure). A mixture of chloroacetamide **5** (151.4 g, 534 mmol), thiourea (48.7 g, 640 mmol), and acetic acid (303 mL) in ethanol (1.5 L) was heated to reflux under a nitrogen atmosphere. After 5 h the reaction mixture was cooled to 25 °C, and the resulting suspension was concentrated to dryness in vacuo. Toluene (900 mL) was added to the residue, and the resulting suspension was concentrated to dryness. This process was repeated with fresh toluene (900 mL). The residue was then suspended in ethanol (1.5 L), stirred for 1 h, and then filtered. The filtrate was cooled in an ice bath (temp 0−5 °C), and concentrated sulfuric acid (227 mL) was added at such a rate as to keep the temperature below 15 °C. Once the addition was complete, the mixture was stirred for 1 h at 20 °C. The resulting solution was concentrated in vacuo to remove most of the ethanol, and then aqueous sodium hydrogen carbonate was added to adjust the pH to around 9. The mixture was filtered, and the solid residue was washed with water (300 mL) and EtOAc (1.0 L). The combined biphasic filtrate and washes were separated, and the aqueous layer was extracted with EtOAc (1.0 L and 500 mL). The combined EtOAc phase was dried over magnesium sulfate, filtered, and concentrated in vacuo to give amino ester **6** as a brown oil (89.5 g; 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.01 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H), 2.64 (s, 2H), 3.62 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 7.06 (m, 3H), 7.21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0, 28.2, 40.7, 48.7, 50.7, 60.1, 127.0, 127.7, 128.9, 131.5, 133.8, 138.0, 171.0.

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ACKNOWLEDGMENT

We thank Stuart Field, Steve Fussell, Neal Sach, and Imelda McCarthy for reaction screening; Watcharee Cooper, Isabelle Lemaitre, and Guy Mathews for analytical support; Carlos Martinez and Junhua Tao for their advice on screening and optimization of enzymatic processes; Rob Bright and Fabrice Salingue for their expertise and supervision during the transfer to scale-up facilities; and David Entwistle for numerous fruitful scientific discussions.

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(8) A recent MSDS lists the following hazards for thiourea: H302 Harmful if swallowed, H351 Suspected of causing cancer, H411 Toxic to aquatic life with long lasting effects, H361d Suspected of damaging the unborn child. While the reagent can be used with appropriate precautions, an alternative, safer, reagent would be preferable.

(9) The best alternative was ethylenediamine which afforded ~30% deprotection, along with significant degradation.