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Development of an Asymmetric Hydrogenation Route to (*S*)-*N*-Boc-2,6-dimethyltyrosine

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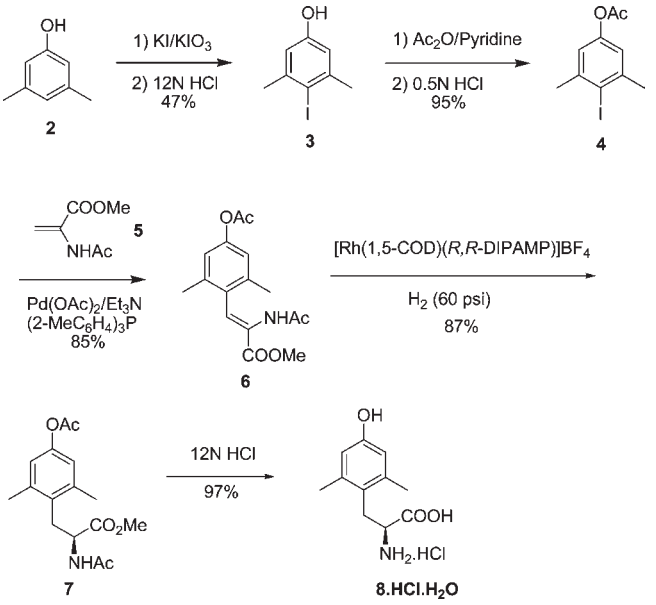
Supporting Information

ABSTRACT: An improved, simpler and potentially more economical route to (*S*)-*N*-Boc-2,6-dimethyltyrosine **1**, based on a previously published route, is presented. Key modifications were to prepare the dehydroaminoacid hydrogenation substrate **6** in a one-pot process directly from serine methyl ester and 4-iodo-3,5-dimethylphenyl acetate **4** and to identify a significantly more active asymmetric hydrogenation catalyst that allowed a 5-fold reduction in catalyst loading.

INTRODUCTION

During a recent development program we were required to prepare a significant quantity of (*S*)-*N*-Boc-2,6-dimethyltyrosine **1**, and, in order to meet the project timelines, rapid delivery of material was critical. Several routes to this amino acid have been published;[1] however, most have only been run on moderate scale. We selected the asymmetric hydrogenation route shown in Scheme 1 for further investigation as it had been previously demonstrated on kilogram scale.[1a,b] In this process, the key step is an enantioselective hydrogenation of methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-prop-2-enoate **6** with the chiral catalyst, [Rh(1,5-COD)(*R*,*R*-DIPAMP)]BF_4 under relatively forcing conditions (60 °C, 60 psi) and high catalyst loading (1 mol %). The hydrogenation substrate was prepared via Heck coupling between 4-iodo-3,5-dimethylphenyl acetate **4** and methyl 2-acetamidoacrylate **5**. Iodide **4** was synthesized in two steps from readily available 3,5-dimethylphenol **2**,[2] and acrylate **5** is commercially available.

Scheme 1. Published route to (*S*)-2,6-dimethyl-tyrosine 8[1a,b]



RESULTS AND DISCUSSION

Whilst this route had been demonstrated on kilogram scale, we still had some concerns as to whether it would be capable of delivering sufficient material within the required time frame. Specifically, were we to use the current catalyst loading (1 mol %), the cost of the catalyst would be prohibitive. It was therefore imperative for us to identify conditions that would allow for a significant reduction in catalyst usage. In addition, while acrylate **5** is commercially available, we could only source small quantities (the largest pack size was 5 g) in the time available and we were then faced with having to make significant quantities of this starting material internally.

Synthesis of Dehydroaminoacid 6. The published procedure[1a,b] for the preparation of **4** from 3,5-dimethylphenol was repeated. Unfortunately, however, in our hands the product failed to crystallize upon quenching the reaction with 0.5 N HCl, as published. Instead, an oily layer separated from the mixture that, after seeding, converted to a crystalline mass. However, the solid form was poorly controlled, and residual solvent and impurities were entrained. In order to overcome this, we modified the published workup and extracted the product into ethyl acetate following the acid quench. Further washing with dilute acid removed any residual pyridine, and the crude product was concentrated to a thick oil that was then used directly in the Heck coupling.

Since acrylate **5** was only commercially available in small quantities, we made the decision to prepare this, since a review of the literature indicated that it should be readily prepared from serine methyl ester.[3] The key step in many of the published processes was thermal elimination of acetic acid from *N*,*O*-diacetyl-serine methyl ester **9** in the presence of a base. However, upon attempting to reproduce these conditions, we found

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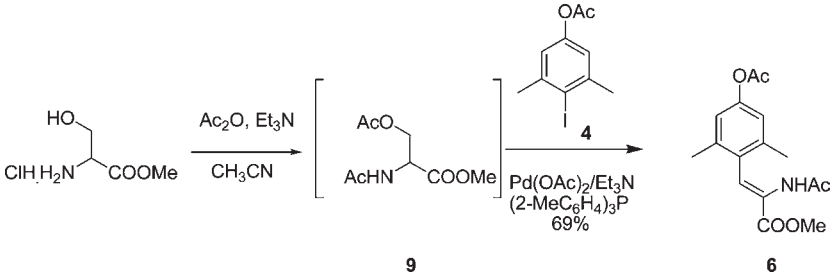
Scheme 2. Telescoped synthesis of dehydroamino acid 6 from serine methyl ester



isolation of the desired compound **5** to be rather challenging. In particular the product was prone to polymerization under the reaction conditions and was also rather water-soluble, resulting in significant yield losses during the workup.

Given the difficulties encountered with isolation of acrylate **5** and our desire to reduce the number of processing steps, we considered the possibility of telescoping the acrylate formation and Heck coupling steps. Since the Heck coupling is done under basic conditions using triethylamine in hot acetonitrile, it seemed plausible that elimination of acetic acid from *N*,*O*-diacetyl serine methyl ester **9** would occur under these conditions to generate the desired acrylate **5** in situ, thus avoiding the need to prepare and isolate this material in a separate step. In addition, since the isolation of *N*,*O*-diacetyl serine methyl ester **9** is also challenging, with significant degradation occurring during water washes to remove triethylammonium salts (as well as product losses to the aqueous phase), we decided to extend the reaction telescope to incorporate this step, as shown in Scheme 2.

To our delight, this telescoped one-pot, three-stage process worked extremely well. Readily available serine methyl ester hydrochloride was treated with acetic anhydride and triethylamine in acetonitrile at ambient temperature, generating a solution of diacetate **9**. Next, iodide **4**, palladium(II) acetate, tri-*o*-tolylphosphine, and further triethylamine were added; the mixture was heated to reflux, whereupon the desired tandem elimination—Heck coupling sequence occurred smoothly. The process afforded the desired dehydroaminoacid **6** in 69% yield after an extended workup required to remove potential catalyst poisons (see Experimental Section for more details). At this stage, given the time constraints and the need to deliver material quickly, we simply used the previously published reaction conditions for the Heck coupling (2 mol % Pd, 5 mol % phosphine) without optimization. We hope that further development might increase our yield to match that of the published process with acrylate **5** (69% vs 85%), as well as potentially delivering a reduction in catalyst loading. While we have not been able to test the generality of this telescoped process, it only requires cheap and readily available starting materials, and we would expect it to provide a practical route to a wide range of aromatic dehydroamino acids.

Enantioselective Hydrogenation of 6. The published procedure for the asymmetric hydrogenation of **6** using [Rh-(1,5-COD)(*R*,*R*-DIPAMP)]BF_4 was run at a substrate to catalyst ratio (S/C) of 100:1 (1 mol %).[1a,b] Given the catalyst cost,[4] conducting the hydrogenation at this catalyst loading was deemed prohibitively expensive. Furthermore, our initial studies with this catalyst indicated that we would not be able to significantly reduce the loading, as the reaction rate and ee dropped precipitously as the catalyst level was reduced. A small screen of catalysts that were readily available in sufficient quantity in-house was quickly conducted,[5] and from this we identified [Rh-(1,5-COD)(*S*,*S*-Et-FerroTANE)]BF_4[6] as a potential alternative. Under screening conditions the reaction employing this catalyst proceeded to completion (unlike many of the other catalysts screened) and gave the product in >90% ee. In addition, the S/C could be lowered to 500:1 with reaction completion still observed within an acceptable time and without any reduction of the ee. Longer term, the cost of using of this proprietary catalyst (at lower catalyst levels) instead of the more readily available Rh-DIPAMP would need to be carefully evaluated; however, at this stage it was suitable for our purposes.

During our initial development work, we were plagued with inconsistent conversion under nominally identical conditions. After some investigation we discovered that this process is particularly oxygen-sensitive (in comparison to the hydrogenation of less hindered dehydroamino acids), and careful application of the thorough oxygen-removal protocol described in the published process[1a] was essential to ensure reproducibility.

Our initial studies were performed in a hydrogenation vessel, employing disposable glass inserts. However, as we were required to use a multipurpose stainless steel reactor for our large-scale processing, we conducted a series of experiments in an intermediate-scale reactor to test the robustness of the process and the effectiveness of our cleaning protocol. On the basis of previous experience, the stainless steel reactor was fully dismantled and cleaned with acetic acid, followed by multiple water and ethyl acetate boil-outs prior to use. A series of experiments were carried out which demonstrated that robust and reproducible conversion and ee could be achieved at S/C 500:1. When lower catalyst levels were examined, a slight erosion of ee was noted, 88—90% at S/C 750:1. At S/C 1000:1 this became significant (68—76%), and quite variable. Therefore, we chose to conduct our scale-up experiments at S/C 500:1 to ensure acceptable quality was achieved. Further optimization of this step should hopefully allow for reduction in the catalyst loading.

Using these conditions, multiple scale-up runs of the hydrogenation step (from 130 g to a maximum of 800 g) were carried out without incident. In addition, we were also able to reduce the hydrogen pressure from 10 to 5 bar.

Preparation of (*S*)-*N*-Boc-2,6-dimethyltyrosine 1. The published procedure for deprotection of *N*-acetyl amino acid **7** using refluxing concentrated (12 M) HCl at relatively high concentration (4.3 mL/g) was deemed unsuitable for scale-up in our facility. At this high HCl concentration a significant amount of hydrogen chloride gas is evolved at reflux, requiring scrubbing. In addition, upon cooling the product **8** (hydrochloride salt) crystallizes from the reaction mixture as an unstirrable solid mass. To minimize HCl off-gassing, less concentrated (6 M) HCl was used, and the reaction temperature was held at just below the

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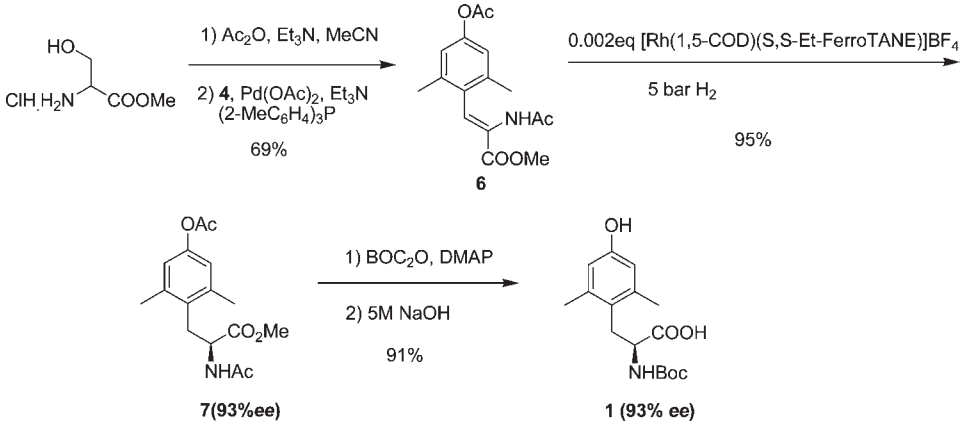
Scheme 3. Optimized route to (*S*)-*N*-Boc-2,6-dimethyltyrosine 1 (Method B in the Experimental Section)



boiling point (90−95 °C). Neither of these changes had any impact on the reaction time. Furthermore, in order to overcome the problem of uncontrolled precipitation of the hydrochloride salt upon cooling, the reaction mixture was cooled to 40 °C and then sodium hydroxide was added to adjust the pH to 4. At this pH, 2,6-dimethyltyrosine **8** precipitates, which is much easier to handle than its hydrochloride salt. For process simplicity, the pH was then adjusted to pH 9−10, and Boc anhydride was added. As the Boc protection proceeded, additional sodium hydroxide was added to keep the pH above 8 until the reaction was complete. Upon completion the pH of the reaction mixture was lowered to 4, and the desired product (*S*)-*N*-Boc-2,6-dimethyltyrosine **1** was extracted into ethyl acetate. This solution was then concentrated to low volume, and the residue was slurried in a mixture of ethyl acetate and heptane to give pure product **1** (Method A in the Experimental Section).

To further improve the synthesis and to avoid handling refluxing hydrochloric acid and the laborious pH adjustments of the reaction mixture in the workup, we decided to investigate the method described by Burk[7] for the direct conversion of *N*-acetyl amino ester **7** to the *N*-Boc amino acid **1** (Scheme 3). Treatment of *N*-acetyl amino ester **7** with Boc anhydride in presence of a catalytic amount of DMAP gave the expected *N*(Ac)Boc amino ester, and, upon treatment with 5 M NaOH, chemoselective hydrolysis of the acetamide occurred in addition to hydrolysis of the methyl ester and phenolic acetate. The sequence afforded *N*-Boc amino acid **1** in an excellent 91% yield after isolation and purification (Method B in Experiment Section).

Since our asymmetric hydrogenation process provided material of acceptable optical purity (the internal target was >90% ee), no work was done to investigate the possibility of upgrading the chiral purity (for example, via crystallization of a salt). It was noted, however, that no enhancement of chiral purity was observed during the crystallization of either *N*-acetyl amino ester **7** or *N*-Boc amino acid **1**.

In parallel to the asymmetric hydrogenation route described in Scheme 3, we also investigated whether the (*S*)-amino acid **8** could be accessed via an enzyme catalyzed hydrolytic resolution of racemic *N*-acetyl-2,6-dimethyltyrosine (see Supporting Information for full details). In summary, after an extensive screen, only one commercially available enzyme (porcine kidney acylase) was identified as being able to hydrolyze the acetamide with high enantioselectivity; however, this required extended reaction times (3 days), the presence of cobalt chloride, and a high enzyme loading (40 wt %). Fortunately, since the asymmetric hydrogenation route afforded suitable quality **1**, this process was not required. A single gram-scale experiment was conducted to provide an initial proof-of-concept for an enzymatic hydrolysis process using optically enriched material (Method C in the Experimental Section).

CONCLUSION

In summary, we have modified the published route towards (*S*)-*N*-Boc-2,6-dimethyltyrosine **1** to make it more practical to operate. Key changes to the published process were (1) the discovery and implementation of a novel one-pot process to the dehydroamino acid **6** from readily available serine methyl ester and (2) the identification of an alternative, more active catalyst for the asymmetric hydrogenation step.[5]

Although the overall yield of the revised process is slightly lower than that of the method previously published,[1a,b] we feel that it offers significant potential for further improvement. The modified Heck protocol removes the need to prepare methyl 2-acetamidoacrylate **5**, and the reduced catalyst loading in the asymmetric hydrogenation step has the potential to minimize catalyst costs. Future development of the enzymatic deacylation offers scope for upgrading the chiral purity as well as providing milder deprotection conditions.

EXPERIMENTAL SECTION

Most of the intermediates have been previously described,[1a] and in-house characterization data matched the published data.

All reagents were obtained commercially and used as received unless otherwise noted.

Most of the reactions were monitored by HPLC analysis using an Agilent 1100 series using an Agilent Zorbax SB C18 column, 3.0 mm × 50 mm × 1.8 μm, at 50 °C. UV detection was set at 210 nm with a rate of <0.01 min. The mobile phases used were water with 0.05% trifluoroacetic acid and acetonitrile at a flow rate of 1.2 mL/min. Two methods were used. A short method (starting level of acetonitrile at 5% increased to 100% in 3.5 min, maintained at 100% for 1 min then decreased to 5% in 0.1 min and finally maintained at 5% for 0.4 min) and a long method (starting level of acetonitrile maintained at 5% for 1 min, increased to 100% in 8 min, maintained at 100% for 2.5 min,

then decreased to 5% in 0.1 min, and finally maintained at 5% for 0.4 min).

Retention times for the short method: 3,5-dimethylphenol **2**, 2.4 min; 4-iodo-3,5-dimethylphenol **3**, 2.8 min; 4-iodo-3,5-dimethylphenyl acetate **4**, 3.4 min; methyl-2-acetamido acrylate **5**, 1.15 min; methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate **6**, 2.4 min; 4-acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **7**, 2.3 min; *N*-acetyl-2,6-dimethyltyrosine **10**, 1.6 min; 2,6-dimethyltyrosine methyl ester, 0.2−0.6 min; *N*-Boc-2,6-dimethyltyrosine **1**, 2.4 min.

Retention times for long method (used only for hydrogenation step): Methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate **6**: 4.5 min, 4-acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **7**: 4.4 min.

The conversions for the enzymatic deacetylation were followed by HPLC analysis using an Agilent 1200 series using agilent Zorbax SB C18 column, 3.0 mm × 50 mm × 1.8 μm, at 70 °C. UV detection was set at 204 nm with a rate of <0.0025 min (or 0.02 s). The mobile phases used were (A) 95% water/5% acetonitrile/0.1% trifluoroacetic acid and (B) 95% acetonitrile/5% water/0.1% trifluoroacetic acid at a flow rate of 1.8 mL/min. The method consisted of a gradient from 5% to 100% B over 3 min and 100% B maintained for 0.5 min. The mobile phase was then switched back to the 5% B over 0.1 min and held to reach a total run time of 4 min.

Retention times: 4-acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **7**, 1.31 min; intermediates in the in situ chemical hydrolysis, 0.89 and 1.07 min; *N*-acetyl-2,6-dimethyltyrosine **10**, 0.6 min; 2,6-dimethyltyrosine **8**, 0.27 min.

The conversion of serine methyl ester to methyl-2-acetamido acrylate was followed by GC/MS using an Agilent GC system 6890N with MS model 5975. An HP-5MSi column, 30 m × 0.250 mm × 0.25 μm, was used at a constant flow of 0.9 mL/min. The inlet temperature was set at 250 °C, and the oven was warmed from 50 to 280 °C at a rate of 20 °C/min and maintained at 280 °C for 1 min. Helium was used as carrier gas with hydrogen used for FID detection at 300 °C.

Retention times: serine methyl ester, 5.8 min; *N*,*O*-diacetylserine methyl ester **9**, 8.8 min; methyl-2-acetamido acrylate **5**, 6.8 min.

Chiral analysis by HPLC using an Agilent 1100 system. Two methods were used.

Chiralpak AD-H column, 4.6 mm × 100 mm × 5 μm, was used at 25 °C with UV detection set at 210 nm. The mobile phases used were heptane and a 50:50 mixture of methanol/ethanol at a flow rate of 2.5 mL/min. Starting level of heptane of 98% decreased to 30% in 5 min, increased to 98% in 0.1 min, and was maintained at that level for 2 min.

4-Acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **7**: (*R*), 1.8 min; (*S*), 1.9 min

N-Boc-2,6-dimethyltyrosine **1**: (*R*), 1.8 min; (*S*), 2.2 min

Chiralcel QN-AX column, 4.6 mm × 100 mm × 5 μm, was used at 25 °C with UV detection at 210 or 254 nm . The mobile phase used was a mixture of methanol/acetic acid/ammonium acetate 98/2/0.5 (v/v/w) at a flow rate of 1.5 mL/min.

N-acetyl-2,6-dimethyltyrosine **11**: (*R*), 6.5 min; (*S*), 8.7 min

4-Iodo-3,5-dimethylphenol 3[2]**.** 3,5-Dimethylphenol (1000.9 g, 8.19 mol) was added to a 30-L jacketed reactor containing methanol (10 L) to give a clear orange solution that was cooled down to 10 °C (external temperature). Hydrochloric acid solution (36.5% w/w, 5 L, 50.5 mol) was added portionwise at such a rate that the internal temperature was kept below 20 °C. The resulting solution was stirred at 5 °C (external) for 1 h. Separately, a slurry of potassium iodide (925.6 g, 5.58 mol) and potassium iodate (562.4 g, 2.63 mol) in water (7.5 L) was prepared. The phenol solution was further cooled to 0 °C (external) before the oxidant mixture was slowly added at such a rate that the internal temperature was kept below 15 °C. Upon contacting the acidic methanol, the iodate solution turned dark red, and over the course of the addition some precipitation occurred. The vessel used for preparing the oxidant solution was washed twice with water (500 mL), and the washes were transferred into the main vessel. After the addition of the oxidant, the reaction mixture was stirred at 0 °C (external) for 30 min, at 10 °C (external) for 2 h, and then at 20 °C overnight. The reaction mixture consisted of an off-white precipitate in a dark-orange solution. Sodium metabisulfite (74 g, 0.39 mol) was added, resulting in the solution turning pale yellow (no oxidant remained as determined by testing with an indicator strip). The reaction mixture was stirred at room temperature for 30 min before being filtered. The solid was washed with a solution of sodium metabisulfite (54 g, 0.28 mol) in water (500 mL), then with water (500 mL) followed by further washing with a mixture of water (1.5 L) and methanol (1.5 L) and finally with water (1 L). The resulting powder was dried in a vacuum oven at 50 °C overnight to give the title compound **3** (1190.2 g, 4.8 mol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H), 4.57 (s, 1H), 6.60 (s, 2H).

4-Iodo-3,5-dimethylphenyl Acetate 4[1a]**.** 4-Iodo-3,5-dimethylphenol **3** (2310.4 g, 9.3 mol) was charged to a jacketed 30-L reactor containing pyridine (2.3 L, 28.44 mol) to give a pale-orange solution that was cooled to 10 °C (external). Acetic anhydride (1.2 L, 12.7 mol) was added portionwise at such a rate that the internal temperature was kept below 39 °C. The reaction mixture was warmed to 55 °C and stirred at this temperature, with further charges of acetic anhydride (120 mL, 1.7 mol) and acetic anhydride (120 mL, 1.7 mol) and pyridine (200 mL, 2.4 mol) being added after 100 and 170 min, respectively. After a further 75 min at 55 °C the reaction was cooled to 25 °C and stirred for 72 h. Ethyl acetate (17.5 L) was added to the reaction mixture, and the organic layer was washed with 0.5 N HCl (10 L) until the pH of the aqueous layer was 1 (four washes were needed), followed by a water wash (10 L). The organic layer was dried with magnesium sulfate and then concentrated to dryness on a rotary evaporator to give the title compound **4** as a yellow oil that solidified on standing (2644 g, 9.1 mol, 98% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.36 (s, 6H), 6.90 (s, 2H).

Methyl (*Z*)-2-Acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate 6[1a]**.** DL-Serine methyl ester hydrochloride (1477 g, 9.49 mol) was added to a 30-L jacketed reactor containing acetonitrile (12.5 L) to give a white slurry. Triethylamine (5.3 L, 38.0 mol) was added to the reaction mixture and the slurry cooled to 0 °C. Acetic anhydride (2.26 L, 23.9 mol) was then added slowly, at such a rate that the internal temperature stayed below 15 °C. At the end of the addition, the reaction mixture was warmed to 20 °C and stirred for 30 min. Iodide **4** (2.5 kg, 8.62 mol), triethylamine (2.65 L, 19.0 mol), tri-*o*-tolylphosphine (131.8 g, 0.43 mol), and palladium acetate (38.9 g, 0.17 mol) were then added. The mixture was heated to 73 °C and stirred for 13 h. The reaction mixture was cooled to room temperature and filtered through a bed of Arbocel, washing with acetonitrile (7.5 L). The filtrate was concentrated on a rotary evaporator to remove approximately 20 L of solvent. The

residue was carefully diluted with a mixture of ethyl acetate (25 L) and saturated sodium bicarbonate (10 L). The layers were separated, and the organic solution was diluted with further ethyl acetate (2.5 L) before being washed with saturated sodium bicarbonate (10 L) followed by water (10 L). The organic solution was treated with magnesium sulfate (2 kg), filtered (washing with 5 L of ethyl acetate), and held for 72 h. During this time a small amount of precipitate formed, which was isolated by filtration and washed with ethyl acetate (2.5 L) to give dehydroamino acid **6** (112.2 g, 0.4 mol, 4% yield) of excellent purity. The filtrate was stirred with Carbon Darko KB wet powder 100 mesh (1 kg) for 2.5 h at room temperature and then filtered through a filter pad consisting of Arbocel and silica, washing with ethyl acetate (5 L). The filtrate was separated into two roughly equal portions that were concentrated to dryness on a rotary evaporator. The resulting yellow solid was slurried in a mixture of ethyl acetate (6.5 L) and heptane (13 L) for 2 h at reflux and then for 16 h at 20 °C. The precipitate was isolated by filtration, washed with a mixture of ethyl acetate (800 mL) and heptane (1.6 L) and then with heptane (1.4 L) to give the title product **6** as a white solid in two crops (848.7 g, 2.7 mol, 32% yield and 873.1 g, 2.8 mol, 33% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84 (s, 3H), 2.12 (s, 6H), 2.25 (s, 3H), 3.70 (s, 3H), 6.85(s, 2H), 6.91 (s, 1H), 9.30 (s,1H).

(*S*)-4-Acetoxy-*N*-acetyl-2,6-dimethyltyrosine Methyl Ester 7[1a]**.** Dehydroamino acid **6** (130 g, 425 mmol) and [Rh-(1,5-COD)(*S*,*S*-Et-FerroTANE)]BF_4 (0.63 g, 0.85 mmol, 0.002 equiv) were added to a 5-L hydrogenation vessel containing ethyl acetate (1.95 L) to give a slurry. The vessel was purged three times with nitrogen (5 bar) without stirring. The vessel was then pressurized with nitrogen (5 bar) and stirred for 10 min before the pressure was released; this was repeated twice. The vessel was pressurized with nitrogen (5 bar) and warmed to 60 °C with stirring. The pressure was released. The vessel was pressurized again with nitrogen (5 bar), stirred at 60 °C for 10 min, and then vented. This process was repeated twice. The vessel was then purged with hydrogen (5 bar, three times) without stirring, followed by pressurization with hydrogen (5 bar) and stirring at 60 °C for 16 h. The vessel was cooled to 20 °C and was purged three times with nitrogen (5 bar) with stirring. SiliaBond thiol (Silicycle Inc., 39 g) was added to the reaction mixture and the slurry stirred at 20 °C for 2 h. The mixture was filtered and washed with ethyl acetate (2 × 200 mL), and the filtrate was concentrated under reduced pressure to give an off-white solid. Ethyl acetate (130 mL) and heptane (650 mL) were added to the residue, and the slurry was warmed to reflux. Upon cooling, a precipitate formed that was stirred at room temperature overnight. The precipitate was isolated by filtration and washed with heptane (2 × 130 mL) to give the title compound **7** as a white solid (125.2 g, 407 mmol, 95% yield, 93% ee) after drying.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (s, 3H), 2.22 (s, 3H), 2.26 (s, 6H), 2.93 (dd, J = 16 and 8 Hz), 3.05 (dd, J = 16 and 8 Hz), 3.51 (s, 3H), 4.44 (q, J = 8 Hz), 6.75 (s, 2H), 8.84 (d, J = 4 Hz, 1H).

(*S*)-*N*-Boc-2,6-dimethyltyrosine 1. *Method A.* (*S*)-4-Acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **7** (975.8 g, 3.1 mol, 95% ee) was added to a 30-L jacketed reactor containing water (4.4 L) to give a slurry. Hydrochloric acid (36.5% w/w; 4.3 L, 50.0 mol) was slowly added at such a rate that the internal temperature was kept below 30 °C. The reaction mixture was heated to 90 °C and held for 6.5 h before cooling to 40 °C. The jacket temperature was then set at 10 °C, and 40% NaOH (3.6 L) was added slowly until the mixture reached pH 4, maintaining the internal temperature between 40 and 47 °C. The resulting slurry was stirred at 20 °C overnight. NaOH (40%, 200 mL) was added to adjust the pH to 10, followed by di-*tert*-butyldicarbonate (752 g, 3.45 mol). The reaction mixture was stirred at 20 °C for 72 h, maintaining the pH between 8 and 10 by regular addition of 40% NaOH (700 mL used in total). Hydrochloric acid (36.5% w/w; 1.15 L) was added (to adjust to pH 4), followed by ethyl acetate (10 L). After stirring for 10 min, the phases were separated. The organic layer was dried with magnesium sulfate and then concentrated to dryness to give a beige solid. This residue was stirred in a mixture of ethyl acetate (4 L) and heptane (8 L) for 16 h, isolated by filtration, and washed with a mixture of ethyl acetate (500 mL) and heptane (1 L), followed by heptane (600 mL), to give the title product **1** (689 g, 2.2 mol 70% yield, 95% ee) as an off-white powder after drying in a vacuum oven at 50 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (s, 2H), 1.29 (s, 7H), 2.14 (s, 6H), 2.73 (dd, J = 12 and 8 Hz, 1H), 2.91 (dd, J = 12 and 8 Hz, 1H), 3.95 (m, 1H), 6.33 (s, 2H), 7.00 (d, J = 8 Hz, 1H), 8.85 (s,1H).

Method B. To a slurry of (*S*)-4-acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester (120 g, 390 mmol, 93% ee) in THF (400 mL) was added di-*tert*-butyldicarbonate (170.8 g, 782 mmol) and THF (200 mL) followed by DMAP (9.5 g, 77 mmol) and THF (200 mL). The clear solution was stirred at 20 °C for 16 h, and then sodium hydroxide solution (5 M; 460 mL, 2.30 mol) was added. After stirring at 20 °C for 5 h, the phases were separated. The aqueous phase was diluted with water (150 mL) The pH was then adjusted to 4 with HCl (36.5%; 190 mL, 2.21 mol), keeping the reaction temperature below 30 °C. Ethyl acetate (500 mL) was added, and the phases were separated. The organic layer was dried with magnesium sulfate and then concentrated to dryness to give an orange oil that was refluxed in ethyl acetate (180 mL) for 1 h to give a white slurry. Heptane (480 mL) was added and the reaction mixture left under reflux for a further 2.5 h. The mixture was then cooled to 20 °C and held for 16 h. The solid was isolated by filtration, washed with heptane (120 mL) and dried to give the title product **1** (110.2 g, 356 mmol 91% yield, 93.4% ee).

Method C. (*S*)-4-Acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester **6** (1.0 g, 3.25 mmol, 94.6% ee) was added to phosphate buffer (0.1 M, pH 8.0) containing 1 mM cobalt chloride (40 mL) and stirred at 35 °C. Sodium hydroxide (5 M, 1.478 mL) was autotitrated to the slurry to maintain the reaction at pH 10. The addition stopped once the starting material's ester groups had hydrolyzed. Hydrochloric acid (6 N, 0.235 mL) was then charged to adjust the reaction mixture to pH 8 and porcine kidney acylase (Sigma A8376; 408.8 mg) added. The reaction was stirred at 35 °C for three days. Sodium hydroxide solution (10 M, 0.5 mL) was added to adjust to pH 10, followed by the addition of di-*tert*-butyldicarbonate (0.79 g, 3.62 mmol). The reaction mixture was stirred at 20 °C for 21 h, holding the pH between 8 and 10 by regular addition of 10 M NaOH (1 mL charged in total). HCl (36.5%, 1.1 mL) was added to adjust to pH 4 (some off-gassing noted), followed by addition of ethyl acetate (10 mL). The resultant biphasic mixture was filtered to remove enzyme residues which were further washed with ethyl acetate (10 mL). The organic phase was separated and dried over anhydrous magnesium sulfate before being concentrated under reduced pressure to give a dark foam. This residue was dissolved in ethyl acetate (5 mL) before heptane (10 mL) was slowly added to effect precipitation. The slurry was stirred at 20 °C for 16 h; then the

solid was isolated by filtration and washed with a mixture of ethyl acetate/heptane (1:1, 5 mL) to give the title product **1** (0.55 g, 54% yield, >99% ee, (*R*)-enantiomer not detected) as an off-white powder after drying in a vacuum oven at 50 °C.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) From a range of catalogue companies, the price quoted varied from £600/g to £900/g.

(5) A selection of hydrogenation catalysts were screened under 20 bar hydrogen at 60 °C in ethyl acetate for 20 h. Either 10 wt % of a preformed metal−ligand complex (Method A), or 4 wt % $Rh(COD)_2$-$(acac)_2$ and 6 wt % ligand (Method B) were used. No conversion was observed with the following: [(*R*)-TCFP-Rh-COD]BF_4 (Method A) or Josiphos SL-J001-1; Josiphos SL-J002-1; Mandyphos SL-M001-1; Mandyphos SL-M002-1; (*R*,*R*)-Norphos; Solphos SL-A00101; (*R*,*R*)-MeDuPHOS; (*S*,*S*,*R*,*R*)-Duanphos and (*R*)-Xylylphanephos (Method B). Partial conversion was observed with the following: Walphos SL-W001-1 (58% conversion); Walphos SL-W002-1 (25% conversion); Walphos SL-W003-1 (26% conversion); Mandyphos SL-M002-1 (14% conversion) (all Method B) and complete conversion was obtained with [(*R*,*R*)-MeBPE-Rh-COD]BF_4 (9% ee, (*R*)) and [(*S*,*S*)-Et-Ferrotane-Rh-COD]BF_4 (93% ee, (*S*)) (all Method A).

(6) This catalyst currently costs £394/500 mg from Strem (catalogue number 45-0155). As we had sufficient quantities of this catalyst in-house and a quick turnaround was required, no consideration was given to the long-term supply of this catalyst.

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