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Large-Scale Synthesis of a Substituted D-Phenylalanine Using Asymmetric Hydrogenation

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Supporting Information

ABSTRACT: A synthetic route to an *N*-BOC D-phenylalanine pharmaceutical intermediate suitable for rapid scale-up to 150-kg scale was required. A seven-step route based on asymmetric hydrogenation of an *N*-acetyl dehydroamino-acid was developed. Starting with terephthalic dialdehyde, monoreduction of one aldehyde group, Erlenmeyer condensation, and ring-opening/*O*-deacetylation with methanol provided the 4-(hydroxymethyl)-substituted dehydrophenylalanine hydrogenation substrate. Asymmetric hydrogenation of this enamide using [((*R*,*R*)-Ethyl-DuPhos)Rh(COD)]BF_4 proceeded in high enantiomeric excess. Subsequently, the *cis*-2,6-piperidyl group was introduced by mesylation/displacement, the BOC group was introduced, and acetyl and methyl ester groups were removed by basic hydrolysis. This route was used to manufacture 150 kg of the BOC amino acid **1**.

INTRODUCTION

An unnatural D-phenylalanine intermediate in the form of the *N*-BOC acid **1** was required as part of a development program for a novel therapeutic agent (see Figure 1). A rapid scale-up to 150 kg was required, and thus, it was necessary to use an approach to amino acid synthesis that we were confident from the outset could be reliably used on this scale. Therefore, we were attracted to asymmetric hydrogenation, which we expected could be used with relatively little development and for which suitably active and selective catalyst systems were readily available on the scale required, as an approach to this amino acid derivative.[1,2]

Potential dehydroamino acid hydrogenation substrates are shown in Scheme 1. The piperidyl group could be introduced at a late stage by coupling to a (4-(hydroxymethyl)phenyl)alanine derivative **2**, hence requiring a 4-hydroxymethyl or protected 4-hydroxymethyl substituted 2-acetamidocinnamate substrate **3**. Alternatively, the piperidyl group could be introduced before the asymmetric hydrogenation, employing the more advanced substrate **4**. Placing the asymmetric hydrogenation step early in the synthesis would minimise the issue of removal of residual metal from the product. In addition, we anticipated that coupling of the piperidyl group to **2** should be a relatively clean, high-yielding reaction, and that synthesis, isolation, and purification of the piperidyl-containing substrate **4** could be more difficult than the simple hydroxymethyl enamide **3**. Therefore, we chose to carry out the asymmetric hydrogenation of a hydroxymethyl enamide **3** and introduce the piperidyl group at a later stage. The key starting material for synthesis of the enamide by condensation chemistry by either approach was 4-(hydroxymethyl)benzaldehyde **5**. Syntheses of single isomer (4-(hydroxymethyl)phenyl)alanines **2** had previously been achieved from tyrosine by cyanation[3] or carbonylation,[4] resolution using an amino acid acylase,[5] from 4-(hydroxymethyl)phenyl hydantoin using a hydantoinase[6] and asymmetric phase-transfer catalysed alkylation.[7] As a D-amino-acid, the chiral pool routes were not attractive compared to asymmetric synthesis, and the resolution-based routes were likely to be more wasteful and expensive, while being no more easily scaled up than asymmetric synthesis using asymmetric hydrogenation.

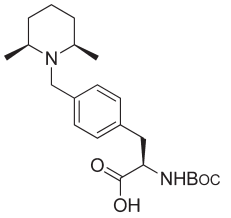

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Figure 1. Unnatural D-phenylalanine derivative **1**.

RESULTS AND DISCUSSION

The route selection work carried out on laboratory scale is described in three sections covering substrate synthesis, the asymmetric hydrogenation step and downstream chemistry and is followed by an account of the development on 100-g scale and implementation of the chosen route in the pilot plant.

Synthesis of Enamides. 4-(Hydroxymethyl)benzaldehyde **5** was prepared by sodium borohydride reduction of readily available, inexpensive terephthalic dialdehyde (Scheme 2).[9] In alcoholic solvents, a complex mixture of products was obtained, but in THF—water, a roughly 70:30 mixture of **5** and diol **6** with around 1% remaining dialdehyde was obtained in a clean reaction. The product mixture was isolated by aqueous workup

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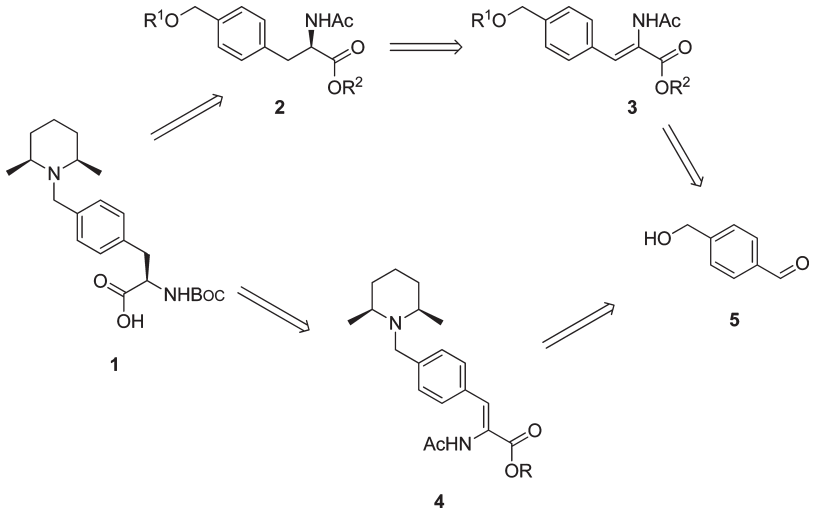
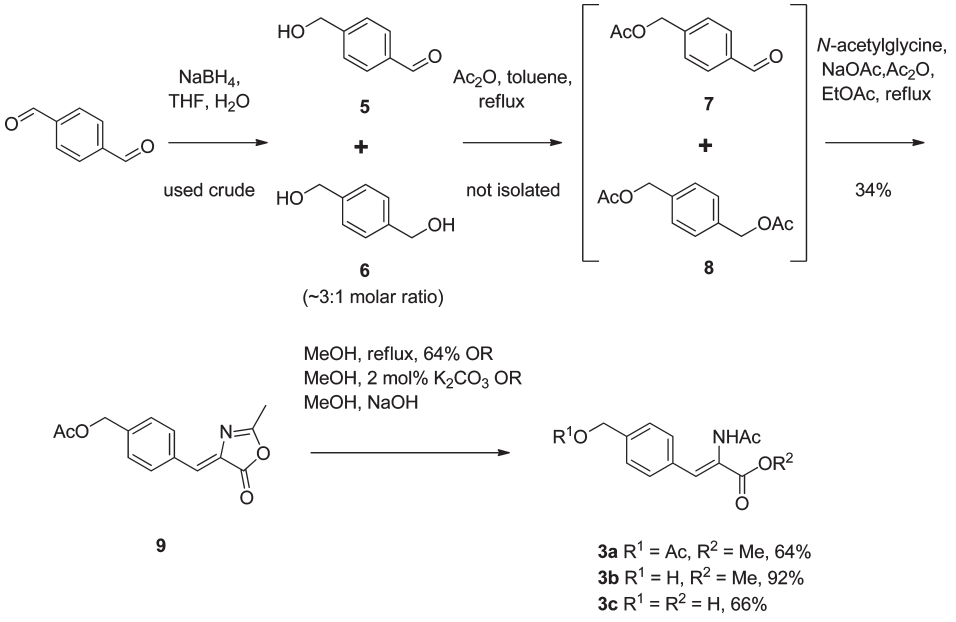
Scheme 1. Retrosynthetic analysis



Scheme 2. Synthesis of enamides



and extraction with toluene, followed by precipitation of a mixture of aldehyde **5** and diol **6** by addition of hexane. The aldehyde **5** could be obtained nearly free of diol **6** by suspension of the diol/aldehyde mixture in toluene and filtration of the insoluble diol **6**.

The most inexpensive method for synthesis of enamides from aromatic aldehdyes is the Erlenmeyer condensation reaction,[10] which has the advantage of providing these compounds exclusively as the (*Z*)-geometric isomer. When **5** was subjected to standard Erlenmeyer condensation conditions (*N*-acetylglycine, acetic anhydride, sodium acetate, ethyl acetate, reflux), both acetylation of the hydroxyl group and condensation took place to give azlactone **9** in 57% yield. Better yields of around 64% in 96% purity by GC were obtained if the reaction was carried out stepwise. Thus, esterification of hydroxyaldehyde **5** to acetate **7** with acetic anhydride was carried out first, then acetylglycine was added to the reaction. Purification of the aldehyde **5** was undesirable on large scale, and unnecessary; the crude approximately 3:1 hydroxyaldehyde **5**/diol **6** mixture obtained in the sodium borohydride reduction could be used directly in the Erlenmeyer condensation. Noncrystalline diacetate **8** arising from diol **6** was removed in the crystallization of azlactone **9**, which crystallized from the reaction on cooling to about 60 °C. After addition of water, further azlactone **9** was precipitated, after which this was isolated by filtration. On a 50-g scale, hydrolysis of the azlactone **9** to acid **3d** was not a significant problem. Although the overall yield from dialdehyde was modest at around 30%, this route provided rapid assembly of the carbon framework of the amino

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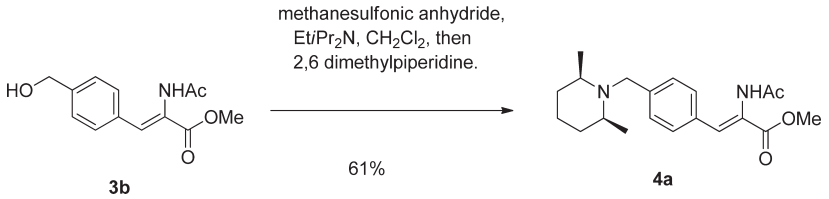
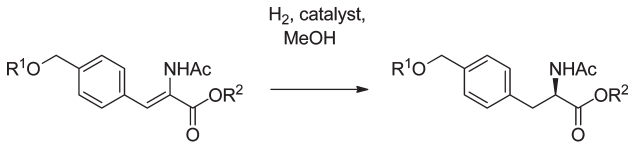
Scheme 3. Introduction of piperidyl group to enamide 3b



3b 4a

Scheme 4. Asymmetric hydrogenation step.[a]



3a R^1 = Ac, R^2 = Me
3b R^1 = H, R^2 = Me
3c R^1 = R^2 = H
3d R^1 = Ac, R^2 = H

2a R^1 = Ac, R^2 = Me
2b R^1 = H, R^2 = Me
2c R^1 = R^2 = H

[a] Reagents and conditions: see Tables 1 and 2.

acid from inexpensive, readily available materials, and the chemistry appeared to be readily scalable. Enamides **3** differing in their protection at the alcohol and carboxylate functionalies could be obtained by employing different conditions in opening of **9**. Thus, by reaction with methanol under neutral conditions or by direct addition of methanol to the Erlenmeyer condensation reaction before product isolation, azlactone **9** was opened *in situ* to methyl ester **3a**. Although, this had the attraction of allowing isolation of a more hydrolytically stable material than azlactone **9**, this reaction was found to be unreliable and often to give incomplete conversion; thus, isolation of azlactone **9** was preferred for scale-up. Treatment of **9** with methanol and 2 mol % potassium carbonate at ambient temperature both opened the azlactone and cleaved the *O*-acetyl group to give the hydroxymethyl enamide **3b**. By treatment with methanol and stoichiometric sodium hydroxide, acid **3c** was obtained.

Introduction of the piperidyl group prior to hydrogenation by conversion of enamide **3b** to **4a** was a further possibility outlined in Scheme 1. Under the conditions described below for coupling of the piperidyl group to the post-asymmetric hydrogenation compound **2b**, reaction of **3b** was possible (Scheme 3) but lower yielding, and the mesylate intermediate appeared to be less stable. Therefore, we were satisfied that, of the possible orders of steps shown in Scheme 1, our choice of carrying out the asymmetric hydrogenation before introduction of the piperidyl group was preferable.

Selection of Substrate and Catalyst. An initial catalyst screen was carried out with **3a** using a range of cationic rhodium complexes of commercially available ligands at a relatively high catalyst loading (Scheme 4, Table 1) using an Argonaut Endeavor catalyst screening system. The highest enantioselectivity was achieved with Ph-BPE,[11] but high enantioselectivities (>90%) were also achieved with Me-, Et-, and *i*Pr-DuPhos. However, Me- and Et-DuPhos were available at lower cost than Ph-BPE and *i*PrDuPhos, and at the time, more readily available on the scale required. Therefore, catalysts derived from these ligands were preferred for scale-up and provided sufficiently high enantioselectivities, and sufficiently low catalyst loadings could be achieved.

Further small-scale studies with all three substrates were carried out with the Me- and Et-DuPhos rhodium catalysts to

Table 1. Asymmetric hydrogenation of 3a with [(Ligand)Rh(COD)]BF_4.[a]

entry	ligand	conversion %[b]	ee (%)[c]
1	(*R*,*R*)-Me-DuPhos	>98	91.3 (*R*)
2	(*R*,*R*)-Et-DuPhos	>98	96.2 (*R*)
3	(*S*,*S*)-*i*Pr-DuPhos	>98	93.6 (*R*)
4	(*R*,*R*)-Me-FerroTANE	>98	85.9 (*R*)
5	(*R*,*R*)-Et-FerroTANE	>98	80.1 (*R*)
6	(*R*,*R*)-Me-BPE	>98	71.6 (*R*)
7	(*R*,*R*)-Ph-BPE	>98	98.2 (*S*)
8	(*S*)-PhanePhos	>98	42.9 (*S*)
9	(*S*)-Tol-BINAP	>98	4.0 (*R*)
10	(*R*)-(*S*)-JosiPhos	>98	15.3 (*R*)
11	(*S*,*S*,*R*,*R*)-TangPhos	>98	69.3 (*R*)
12	(*R*,*R*)-DIPAMP	>98	74.2 (*S*)
13	(*S*,*S*)-BPPM	0	–
14	(*R*)-$MonoPhos_2$	>98	23.3 (*R*)
15	(*R*,*R*)-Me-5-Fc	>98	28.3 (*R*)
16	(*S*,*S*)-*t*BuP*	>98	92.5 (*R*)

[a] Reaction conditions 2 mmol substrate, *s*/*c* 250:1, MeOH, 25 °C, 7 bar H_2. [b] Determined by ^{1}H NMR. [c] Determined by Chiral HPLC, conditions see Experimental.

Table 2. Asymmetric hydrogenation of substrates 3 with [(DuPhos)Rh(COD)]BF_4.[a,b]

entry	substrate	ligand	catalyst[c] loading	reaction time (min)	ee (%)
1	**3a**	(*R*,*R*)-Et-DuPhos	1000:1	6	97.6
2	**3a**	(*R*,*R*)-Et-DuPhos	2500:1	20	97.8
3	**3b**	(*R*,*R*)-Me-DuPhos	1000:1	5	97.6
4	**3b**	(*R*,*R*)-Me-DuPhos	2500:1	35	95.1
5	**3b**	(*R*,*R*)-Et-DuPhos	1000:1	12	99.7
6	**3b**	(*R*,*R*)-Et-DuPhos	2500:1	45	99.6
7	**3c**	(*R*,*R*)-Et-DuPhos	250:1	15	99.0

[a] Reaction conditions: 2 mmol substrate, *s*/*c* 1000−2500:1, MeOH, 40 °C, 7 bar H_2. [b] Full conversion achieved for all entries (determined by ^{1}H NMR). [c] Estimated from mass of substrate and catalyst used.

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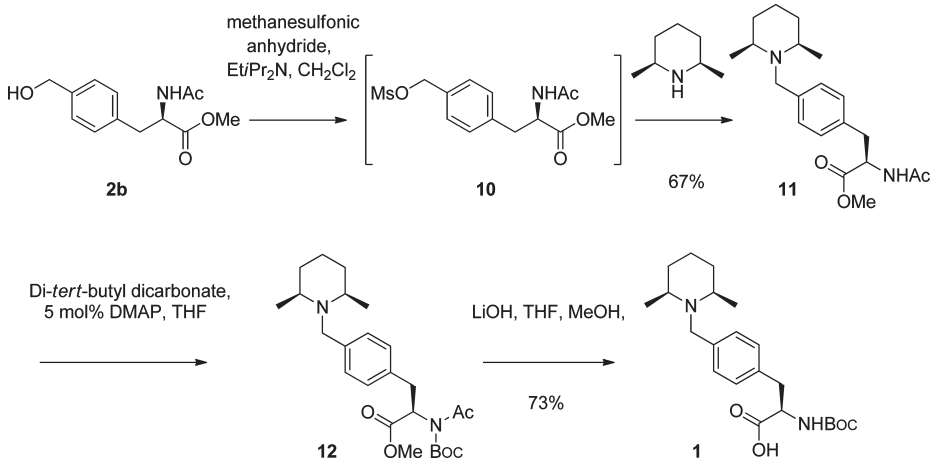
Scheme 5. Downstream steps after asymmetric hydrogenation



determine the most favorable substrate/ligand combination for scale-up (Table 2). The results were inconsistent, because the effect of substrate purity on both reactivity and selectivity was not initially recognised. Higher enantioselectivities than in the initial screen were achieved with all three substrates. The acetoxy-protected substrate **3a** was more reactive than the hydroxy substrate **3b**, but higher enantiomeric excess was achieved with **3b**. With the hydroxy substrate **3b**, higher reactivity but lower selectivity was achieved with Me- than with Et-DuPhos. Full conversion was not achieved with either **3a** or **3b** at molar *s*/*c* > 2500:1. High selectivity was also achieved with hydroxy acid **3c**, but this required a higher catalyst loading than the other substrates to achieve full conversion. When less pure samples of **3a** and **3b** from pilot-plant batches were used, selectivities and reaction rates were much lower. This dependence of enantiomeric excess on substrate purity could also account for the differences seen between the selectivities found in the initial catalyst screen and these studies. The lower reactivity of **3c** can also be ascribed to the greater difficulty in isolation and purification of this compound. Subsequently, in the asymmetric hydrogenation of **3c** with [((*R*,*R*)-Ethyl-DuPhos)Rh(COD)]BF_4 on a larger (10 g) scale using substrate purified by crystal digestion, a catalyst loading of 5000:1 was achieved.

While all three substrates could potentially be used in the synthesis of **1**, the shortest overall synthetic scheme (Scheme 6) employed hydroxyester **3b**. In addition, the hydrogenation product **2b** crystallized readily, which was advantageous for isolation on large scale at this stage of the synthesis. With the highest enantioselectivity and highest rate with this substrate being achieved with different catalysts, compromise was required in selecting a catalyst for scale-up; however, with the need for rapid scale-up, the higher selectivity with this substrate achieved with Et-DuPhos was the most important criterion, so hydrogenation of **3b** with [((*R*,*R*)-Ethyl-DuPhos)Rh(COD)]BF_4 was selected for scale-up.

Downstream Steps to Amino Acid 1. The remaining steps of the synthesis from ((4-hydroxymethyl)phenyl)alanine **2b** are shown in Scheme 5. Introduction of the benzylic *cis*-2,6-dimethylpiperidyl group could be achieved by oxidation of the alcohol to the aldehyde and reductive amination[12] or by activation as a leaving group and *N*-alkylation. We found the hindered *cis*-2,6-dimethylpiperidine to be a generally unreactive amine. Reductive amination using either palladium on carbon and hydrogen or sodium triacetoxyborohydride was sluggish, and aldehyde reduction predominated; thus, we favored the alcohol activation/alkylation approach. Alkylation of *cis*-2,6-dimethylpiperidine with mesylate **10** occurred under mild conditions. Activation was carried out by mesylation of **2b** in dichloromethane with methanesulfonic anhydride, after which *in situ* reaction with *cis*-2,6-dimethylpiperidine to give *N*-acetyl piperidinyl amino acid methyl ester **11** proceeded cleanly at room temperature. Methanesulfonyl anhydride rather than methanesulfonyl chloride was used to avoid formation of the unreactive chloride, and the hindered base, ethyldiisopropylamine, was used to avoid quaternisation of the base. The additional cost and lead-time of methanesulfonic anhydride were offset by the higher degree of confidence in scale-up with this reagent. The non-crystalline **11** could be purified to remove nonbasic impurities by extraction into mild aqueous acid such as citric acid, basification, and re-extraction into dichloromethane. After introduction of the piperidyl group, completion of the synthesis required adjustment of the amino and carboxylate protecting groups. The *N*-BOC group was introduced with di-*tert*-butyl dicarbonate and catalytic 4-(dimethylamino)pyridine in THF. Finally, both the *N*-acetyl group and methyl ester of imide **12**[13] were cleaved with lithium hydroxide, which could be achieved without racemisation provided the base was added slowly to control both the reaction exotherm and pH. While the final product **1** is an amino acid, it was sufficiently lipophilic to extract the neutral form into organic solvents from weakly acidic solutions. Thus, isolation was achieved by acidification to pH close to 5.5 and extraction into dichloromethane. However, the presence of residual inorganics made crystallization difficult, and it was necessary to remove these by an ion-exchange resin treatment in aqueous solution. Subsequent removal of water by distillation, addition of ethanol, removal of ethanol by distillation, and final crystallization from ethyl acetate−MTBE gave **1**[12] in an acceptable crystalline form. The final crystallization did not provide a sufficient upgrade of enantiomeric excess, so high enantiomeric excess in the asymmetric hydrogenation and careful control of the temperature and addition of base in the final deprotection reaction were essential to obtaining **1** within the specification of >98.5% enantiomeric excess, >98% purity. The overall yield from terephthalic dialdehyde was 15% in seven steps, but the nonselective monoreduction

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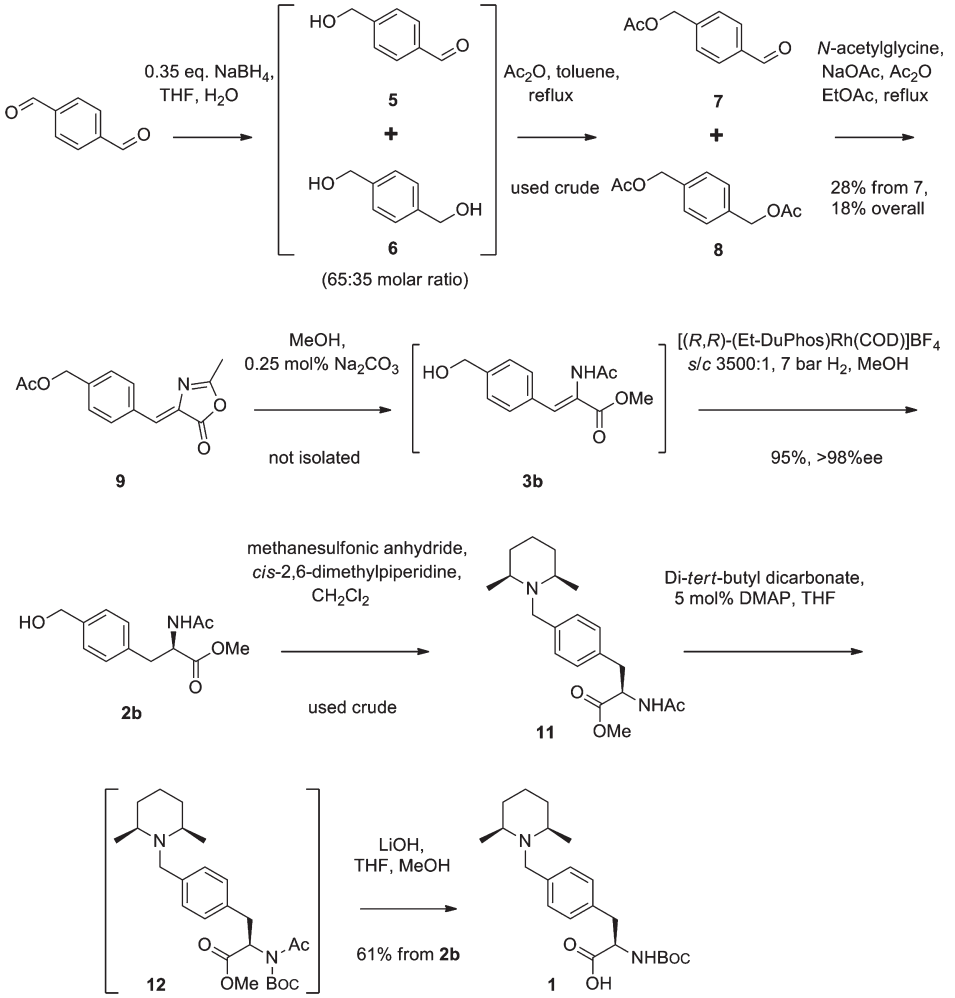
Scheme 6. Overall route used on 100 g to 30 kg scale



in the first step was responsible for a large proportion of the loss in yield, which was about 45% from azlactone **9**. The chemistry appeared to be scalable, and we were confident of the ability of this route to deliver the product on the 100 kg+ scale required for the pilot-plant campaigns.

Laboratory Scale-Up to 100 g. Scale-up from the small-scale initial studies was carried out in three stages, laboratory synthesis of a 100-g sample, followed by 30- and 150-kg campaigns (Scheme 6). The 100-g sample preparation allowed development in readiness for transfer to the pilot plant. In the reduction of terephthalic dialdehyde to aldehyde **5** with sodium borohydride, purification by precipitation of diol **6** was found to be unnecessary. After workup of the reaction and distillation of most of the solvent from the toluene/THF solution, the ~3:1 aldehyde **5**/diol **6** mixture remained liquid and could be used directly in the next step, provided the solution was kept hot at about 70 °C. The method of conversion of 4-(hydroxymethyl)benzaldehyde **5** to azlactone **9** used on small scale had been by reaction of the aldehyde with the full 2.5 equiv of acetic anhydride required for both *O*-acetylation and Erlenmeyer condensation, then addition of solid *N*-acetylglycine to the reaction. This was not possible on the plant due to the need for addition of a solid reagent to the reaction. Therefore, this procedure was modified, and the acetylation was carried out with 1.5 equiv of acetic anhydride, after which the solvent was removed by distillation and the crude aldehyde (~3:1 **7**/**8**) was drained from the reactor. This allowed the solid reagents for the Erlenmeyer condensation to be charged to an empty reactor. After charging the ethyl acetate solvent and 2 equiv of acetic anhydride and heating the reaction, aldehyde **7** was charged, thus avoiding any potential runaway exotherm. Difficulty was encountered with both solidification of the reaction on cool-down and hydrolysis of azlactone **9** to **3d** if water was added at too high a temperature. Slow cooling to 20−25 °C followed by addition of water at this temperature minimized both these problems. Isolation of azlactone **9** at this stage gave sufficiently pure material to allow the azlactone opening and asymmetric hydrogenation to be telescoped while maintaining a catalyst loading of molar *s/c* 1500−2500:1. The azlactone opening was carried out using sodium carbonate rather than potassium carbonate, and the methanolic solution of enamide **3b** was carried forward and used directly in the asymmetric hydrogenation without isolation. It was later recognized that isolation and purification of this intermediate could be desirable to permit a lower catalyst loading to be used in the asymmetric hydrogenation reaction. After the asymmetric hydrogenation, MTBE antisolvent was added, and crystalline **2b** was isolated in 80% yield from azlactone **9**.

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In the coupling with *cis*-2,6-dimethylpiperidine, the piperidine was found to be suitable as both base and reagent, and the coupling procedure could be simplified by carrying out the reaction by addition of a 4-fold excess of *cis*-2,6-dimethylpiperidine to a solution of **2b** and 1.6 equiv of methanesulfonic anhydride in dichloromethane. While methanesulfonic anhydride and 2,6-dimethylpiperidine do react, this is slower than the alcohol mesylation reaction due to the hindered nature of 2,6-dimethylpiperidine. However, this change had unforeseen consequences as described below. Purification of **11** by extraction into aqueous citric acid, basification, and re-extraction into dichloromethane to remove nonbasic impurities such as *cis*-2,6-dimethylpiperidine methanesulfonamide arising from the coupling step was retained. No significant changes to the reactions in the final stages of the synthesis were made, other than a reduction in the relative quantities of solvents required and the previous yields were maintained. A minor change to the final isolation was required. After extraction of the product **1** into dichloromethane, rather than evaporation to dryness, the solvent exchange back to water was carried out by addition of water, after which resin was charged. Finally, the dichloromethane was removed by distillation. The final drying of the amino acid **1** had previously proved problematic. The product readily formed stable solvates with common solvents which required heating to nearly 100 °C (close to the melting point of the compound) to break down; this tended to change the form of the product from a crystalline solid to a foam. Careful control of the drying by carrying it out slowly at 70 °C eliminated this problem. Removal of ethanol was particularly difficult, and a more careful choice of solvent for the final isolation would be desirable.

Scale-Up to Pilot Plant. The process modified as described for the 100 g sample preparation was used for the 30 kg pilot campaign. For steps as far as the asymmetric hydrogenation, little further modification was required. Two 30 kg asymmetric hydrogenation reactions were carried out in this campaign. A molar catalyst loading of *s*/*c* 3500:1 was used. The crystallization of **2b** was carried out using toluene, rather than MTBE as the antisolvent. In the coupling of *cis*-2,6-dimethylpiperidine to **2b**, difficulty was encountered in achieving high conversion to **11**. In a separate observation, which proved to be connected, final analysis of the product **1** showed one previously minor impurity to be present at a much higher level of 0.52%, and at close to 10% in the filtrates of the final crystallization. LC/MS analysis showed a molecular weight of 364, lower than the mass of **1** by 14, corresponding to a difference of one methyl group. A known impurity in the *cis*-2,6-dimethylpiperidine was 2-methylpiperidine, present at a level of 0.25%. Therefore, the corresponding 2-methylpiperidyl compound **13** (Figure 2) was a reasonable candidate for this impurity. The much higher level of this impurity in **1** compared to the level of 2-methylpiperidine in the *cis*-2,6-dimethylpiperidine can be explained by the combination of use of a large excess of *cis*-2,6-dimethylpiperidine in the coupling with **2b** and higher reactivity of the less hindered impurity, resulting in concentration of the impurity in the product. The need for a large excess was partly due to reaction between methanesulfonic anhydride and *cis*-2,6-dimethylpiperidine consuming a substantial quantity of both reagents when the reagents were charged to the reaction in the manner described above. While using a lower stoichiometry of 2,6-dimethylpiperidine and an external base (as in the initial route selection work) could offer a solution to this process-related impurity issue, insufficient time was available to investigate this option.

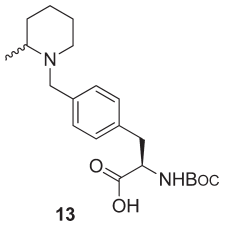

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Figure 2. Process-related impurity **13**.

It was recognized that the BOC protection step and final deprotection and isolation, which required multiple solvent exchanges, could be streamlined, but insufficient time was available to develop a more concise alternative procedure.

For the 150 kg campaign, difficulties were encountered when moving to a larger scale for the first two steps. The conversion in the sodium borohydride reduction was lower due to inefficient mixing in the reactor used. Variable levels of hydrolysis of the azlactone **9** during isolation was again apparent. A short-term remedy available was to dehydrate partially hydrolysed material with acetic anhydride. These difficulties led to a lower yield over the first two steps to about 19% from terephthalic dialdehyde. The asymmetric hydrogenation reaction was not scaled up further due to the limit placed by the size of the largest available reactor, and material was processed in eight batches. The mesylation/piperidine introduction was carried out in two batches. The use of *cis*-2,6-dimethylpiperidine as both base and reagent was maintained in this campaign, but a change was made to the method of addition of the reagents. Instead of addition of the full quantity of methanesulfonic anhydride at the beginning of the reaction followed by the *cis*-2,6-dimethylpiperidine, the methanesulfonic anhydride was added in four separate portions, and after each, one-quarter of the 2,6-dimethylpiperidine required was added in four aliquots. This led to an improvement in the conversion in this reaction due to a reduction in the side reaction of the *cis*-2,6-dimethylpiperidine and methanesulfonic anhydride, and an improvement in the purity of the final product. With this improvement in purity, the final treatment with resin was found to be unnecessary, and the product crystallized directly. The BOC protection and final deprotection and isolation was carried out as a single batch. The overall yield from azlactone **9** was 85%. The difficulties encountered on the 150-kg campaign were largely due to the need for rapid scale-up, and with a relatively small amount of development these difficulties could be reduced or eliminated. The key issues are the following: achieving better control over the product quality in the terepthalic dialdehyde reduction step, achieving a higher and consistent yield in the azlactone formation, for which the former would be critical, better control of the purity of enamide **3b**, allowing a consistently lower catalyst loading to be achieved in the asymmetric hydrogenation step, a more robust procedure for the piperidine introduction step in which the number of equivalents of 2,6-dimethylpiperidine is reduced, for example by employing an external base, and a more streamlined isolation process for the final product **1** with careful attention to choice of solvent, especially with regard to the difficulty of drying this material.

Overall, the seven-step asymmetric hydrogenation-based route was well suited to rapid scale-up for the production of amino acid derivative (**1**). The asymmetric hydrogenation step was readily integrated into the overall synthetic route, and the material was produced on time and in specification using this chemistry.

EXPERIMENTAL SECTION

General. Melting points were recorded using a Perkin-Elmer DSC6 digital scanning calorimeter. Optical rotations were determined using a Perkin-Elmer 341 polarimeter in units of 10^{-1} deg cm^2 g^{-1} (c in g/100 mL). Proton and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer using Me_4Si or residual $CHCl_3$ as an internal reference. Mass spectra were recorded using a ThermoFinnigan LCQ Advantage using APCI. GC methods were run using a Perkin-Elmer Autosytem XL gas chromatograph. HPLC methods were run using a Gilson modular system or a TSP modular system.

Preparation of 4-(Hydroxymethyl)benzaldehyde ***5***.[9] To a 2-L three-neck flask, fitted with an overhead agitator, thermometer and condenser, terephthalaldehyde (85.8 g, 0.640 mol) and THF (500 mL) were charged to give a pale yellow solution. Sodium borohydride (8.75 g, 0.231 mol) was dissolved in water (35 mL), and the resultant solution was charged to the three neck flask over 20 min maintaining the internal temperature below 30 °C. The reaction mixture was stirred for a further 2 h; reaction was complete by GC (dialdehyde 0.5%, monoaldehyde **5** 58.9%, diol **6** 36.0%). Water (500 mL) and toluene (500 mL) were charged with stirring, and then the layers were separated. The aqueous layer was further extracted with toluene, and then the combined organics were backwashed with water. The organic layer was distilled at ambient pressure until the internal temperature reached 105 °C; approximately 600 mL of distillates were collected. The mixture was cooled to below 30 °C, and then hexane (500 mL) was charged before cooling to 0−5 °C in order to precipitate the product from solution. The solid product was isolated by vacuum filtration, and the solid cake was washed with a 50/50 mixture of toluene and hexane (200 mL total) and then dried at 40−45 °C under vacuum to give 69.0 g of **5** (∼53%). The solid melted in the vacuum oven. The product purity by GC was 66.2% with 27.9% of the diol **6** present. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 4.80 (s, 2H), and 2.1 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 148.4, 135.9, 130.4, 127.0, and 64.8.

Preparation of 4-[(Z)-(2-Methyl-5-oxo-1,3-oxazol-4(5H)-ylidene)methyl]benzyl Acetate ***9***. To a 2-L three-neck flask, fitted with an overhead agitator, thermometer, and condenser were charged sodium acetate (59.2 g, 0.722 mol), crude 4-(hydroxymethyl)benzaldehyde **2** (69.0 g, ∼0.33 mol), ethyl acetate (100 mL) and acetic anhydride (120 mL, 1.27 mol). The slurry was heated to reflux (104−106 °C) and maintained at reflux for 15 min before cooling to below 40 °C. *N*-acetylglycine (42.2 g, 0.360 mol) and ethyl acetate (100 mL) were charged, and the resultant mixture was heated to reflux (93−95 °C) and maintained for 18 h. The batch was cooled to below 60 °C at which point it solidified; and water (400 mL) was added, and the resultant solid was isolated by vacuum filtration, the slurry washed in water (300 mL), then washed in MTBE (300 mL), and then displacement washed with MTBE (100 mL). The yellow solids were dried under vacuum at 45 °C to give 56.2 g of azlactone **9** (65%); purity by GC was 96.1%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.13 (s, 1H), 5.14 (s, 2H), 2.41 (s, 3H), and 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 168.1, 166.7, 139.4, 133.4, 133.2, 132.7, 131.1, 128.7, 66.1, 21.4, and 16.1.

Preparation of Methyl (Z)-2-(Acetylamino)-3-[4-(acetoxymethyl)phenyl]propenoate) ***3a***. A suspension of azlactone **9** (10.0 g, 38.6 mmol) in methanol (100 mL) was heated at reflux for 5 h to provide a clear solution. A portion of this solution (50 mL, ∼5.60 g) was concentrated *in vacuo*. Methanol (11 mL) and toluene (11 mL) were added, and the suspension was heated to 80 °C to give a clear solution, which was slowly cooled to room temperature before placing in an ice−water bath. Filtration followed by washing with methanol−toluene (1:1, 5 mL) provided enamide **3a** as a very pale, yellow solid (3.60 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7 Hz, 2H), 7.38−7.34 (m, 3H), 7.12 (br s, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 2.13 (s, 3H), and 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 169.6, 166.1, 137.5, 134.0, 132.1, 130.2, 128.5, 124.9, 66.1, 53.1, 23.7, and 21.3.

Preparation of Methyl (Z)-2-(Acetylamino)-3-[4-(hydroxymethyl)phenyl]propenoate ***3b***. Potassium carbonate (89 mg, 0.64 mmol) was suspended in methanol (12 mL). The azlactone **9** (3.40 g, 13.1 mmol) was added in portions over 45 min, then the brown solution was stirred for another 1 h. The solution was neutralized from pH 12.3 to pH 6−7 with Dowex 50WX-8-200 ion-exchange resin; then the resin was removed by filtration. The solvent was evaporated, and the compound was purified by recrystallization from ethyl acetate (about 20 mL) to give the enamide **3b** as a yellow, granular solid (3.03 g, 91.8%). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.7 (br s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 4.65 (s, 2H), 4.4 (br s, 1H), 3.75 (s, 3H), and 2.09 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 170.2, 170.1, 166.9, 145.1, 133.7, 132.6, 131.0, 127.8, 127.6, 127.4, 64.6, 52.8, 23.2. m/z (APCI) 267, (M + NH_4^+, 78%) and 250 (MH^+, 100%).

Preparation of (Z)-2-(Acetylamino)-3-[4-(hydroxymethyl)-phenyl]propenoic Acid ***3c***. Sodium hydroxide (16.9 g, 422 mmol) was dissolved in methanol (200 mL). Azlactone **9** (36.5 g, 141 mmol) was added over 1 h, the dark-brown solution was heated to reflux for 1 h, then allowed to cool to room temperature. Water (200 mL) was added, then most of the solvent was evaporated to about 150 mL. The solution was extracted with MTBE (100 mL), then acidified from pH (13.5 to 2.5 with 2 M sulfuric acid (about 100 mL). The suspension was stirred for 1 h, then filtered. The collected solid was washed with water (4 × 50 mL), then dried to give a green solid (23.5 g). This was suspended in isopropyl alcohol (80 mL), heated to reflux for 30 min, then allowed to cool to room temperature, stirred for 2 h, then filtered, washed with isopropyl alcohol (2 × 30 mL), and dried to give the acid **3c** as a pale-green solid (21.8 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.65 (br s, 1H), 9.46 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.15 (s, 1H), 5.27 (br s, 1H), 4.51 (s, 2H), and 1.98 (s, 3H); ^{1}H NMR (100 MHz, DMSO-d_6): δ 169.5, 166.8, 144.2, 132.4, 131.6, 129.9, 127.1, 126.8, 62.9, and 22.9. m/z (APCI) 253, (M + NH_4^+, 100%) and 250 (MH^+, 73%).

Preparation of Methyl (2R)-2-(Acetylamino)-3-[4-(acetoxymethyl)phenyl]propanoate ***2a***. A glass linear was charged with **3a** (500 mg, 2.01 mmol) and methanol (4 mL) and then was secured in the Argonaut Endeavor. The manifold was flushed with nitrogen, and the vessel was charged with nitrogen to a pressure of ∼5.7 bar, the contents were stirred (250 rpm) for 5 min, and the vessel was vented. This charge/stir/vent cycle was repeated four times. The vessel was heated to 40 °C while stirring at 250 rpm for 20 min under 0.35 bar of nitrogen and then vented. A Schlenk flask was charged with [((*R*,*R*)-Me-DuPhos)Rh(COD)]BF_4 (5.7 mg, 0.0094 mmol) and evacuated/refilled with nitrogen three times prior to adding deoxygenated methanol (11.6 mL). An aliquot of the catalyst solution

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(1 mL, 0.000804 mmol, *s/c* 2500) was added to the pressure vessel. The manifold was flushed with hydrogen, and the vessel was charged with hydrogen to ~5.7 bar without stirring. This charge/vent cycle was repeated twice. The vessel was charged to ~5.7 of hydrogen, and an automated program which maintained a constant hydrogen pressure of 100 psi, stirring at 1000 rpm, and heating to 40 °C was executed for 16 h. The vessel was vented, and the contents were diluted with methanol (7 mL) and dichloromethane (3 mL) to obtain a clear solution. An aliquot was concentrated *in vacuo* to provide **2a** as a white solid. ^{1}H NMR and HPLC analysis indicated >98% conversion and 95.1% ee, respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8 Hz, 2H), 7.08 (d, J = 2 Hz, 2H), 5.90 (d, J = 8 Hz, 1H), 5.08 (s, 2H), 4.92−4.87 (m, 1H), 3.74 (s, 3H), 3.17 (dd, J = 14, 6 Hz, 1H), 3.10 (dd, J = 14, 5 Hz, 1H), 2.11 (s, 3H), 2.00 (s, 3H).

Preparation of Methyl (2R)-2-(Acetylamino)-3-[4-(hydroxymethyl)phenyl]propanoate ***2b***. To a 50-mL Parr hydrogenation vessel were charged **3b** (1.25 g, 5.01 mmol) and methanol (20 mL), and the vessel was sealed and purged. The catalyst [((*R*,*R*)-Ethyl-DuPhos)Rh(COD)]BF_4 (50 mg, 0.08 mmol) was charged, and after resealing and purging the vessel the mixture hydrogenated at 7.1 bar until uptake of hydrogen gas ceased. The clear yellow solution was concentrated under vacuum at 40 °C to give a suspension of a pale-yellow solid in methanol, toluene (50 mL) was charged, and the remainder of the methanol was removed at 40 °C. The solid was isolated by vacuum filtration, washed with toluene (20 mL), and dried to 45 °C to give 1.1 g of **2b** (88%). The enantiomeric excess of the product was greater than 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.88 (d, J = 6.8 Hz, 1H), 4.92−4.86 (m, 1H), 4.68 (s, 2H), 3.75 (s, 3H), 3.17 (dd, J = 13.6, 5.6 Hz, 1H), 3.10 (dd, J = 13.6, 5.4 Hz, 1H) and 2.00 (d, 3H); ^{1}H NMR (400 MHz, acetone-d_6) δ ppm 7.40 (d, J = 6.4 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 4.71−4.65 (m, 1H), 4.60 (s, 2H), 3.10 (dd, J = 13.2, 5.2 Hz, 1H), 2.95 (dd, J = 13.2, 8.2 Hz, 1H), 2.9 (br s, 1H) and 1.88 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 173.3, 170.5, 142.2, 136.9, 130.2, 127.8, 64.7, 54.9, 52.6, 38.4, and 23.0. m/z (APCI) 269, ($M + NH_4^+$, 100%) 252 (MH^+, 42%), and 234 (17).

Preparation of (2R)-2-(Acetylamino)-3-[4-(hydroxymethyl)-phenyl]propanoic Acid ***2c***. The enamide-acid **3c** (10.5 g, 44.6 mmol) was suspended in methanol (80 mL) in a 300-mL pressure vessel linear. The vessel was assembled, then purged with nitrogen (3 × 3.6 bar); then a solution of [((*R*,*R*)-Et-DuPhos)Rh COD]BF_4 (59 mg, 0.09 mmol) in degassed methanol (1.0 mL) was added. The vessel was purged with hydrogen (2 × 3.6 bar), then charged to 7.1 bar with hydrogen. The reaction was stirred for 120 min, repressurising to 7.1 bar psi at intervals. A total of 5.6 psi hydrogen was consumed. The pressure was released, then the vessel was purged with nitrogen (3.6 bar). The solvent was evaporated to give the (*R*)-*N*-acetyl (4-(hydroxymethyl)phenyl)-alanine **2c** as an orange foam (11.0 g, 104%); enantiomeric excess >98%. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.42 (d, 1H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 4.74−4.68 (1H, m), 4.60 (s, 2H), 3.19 (dd, J = 13.8, 5.4 Hz, 1H), 2.98 (dd, J = 13.8, 8.0 Hz, 1H,) and 1.90 (s, 3H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, J = 8.0 Hz, 1H,), 7.01 (d, J = 8.4 Hz, 2H,), 6.96 (d, J = 8.4 Hz, 2H), 4.25 (s, 2H), 4.19−4.13 (m, 1H), 2.81 (dd, J = 13.8, 5.0 Hz, 1H), 2.60 (dd, J = 13.8, 9.6 Hz, 1H), and 1.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.6, 169.5, 140.9, 136.4, 129.1, 126.7, 63.0, 54.0, 48.9, 36.9, and 22.7. m/z (APCI) 255, ($M + NH_4^+$, 100%), 238, (MH^+, 100%) and 220 (11).

Preparation of Methyl (2R)-2-acetylamino-3-(4-{[(2R,6S)-2,6-dimethylpiperidin-1-yl]methyl}phenyl)propanoate ***11***. To a 250-mL three-neck flask, fitted with an overhead agitator, thermometer, and addition funnel, **2b** (20.0 g), were charged diisopropylethylamine (16.3 g, 126 mmol) and dichloromethane (80 mL). Methanesulfonic anhydride (18.6 g, 107 mmol) was dissolved in dichloromethane (70 mL) and charged to the addition funnel, then charged to the batch over 20 min, maintaining the temperature below 25 °C. The resultant orange solution, containing *O*-mesylate **10** was stirred for 3 h, and then *cis*-2,6-dimethylpiperidine (18.6 g, 164 mmol) was charged; the mixture was stirred at ambient temperature for 5 h, and then further methanesulfonic anhydride (4.5 g, 2.6 mmol) and *cis*-2,6-dimethylpiperidine (9.0 g, 8.0 mmol) were charged. The dark-orange solution was stirred overnight at ambient temperature. The product was extracted into 20% w/w aqueous citric acid (120 g), washed with dichloromethane (70 mL), then basified with 50% aqueous potassium carbonate solution (100 g). The product oil was extracted into dichloromethane (2 × 100 mL) and then distilled at 40 °C to give 18.5 g of **11**, a pale-orange viscous oil (67%). Purity by HPLC was 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 5.97 (d, J = 8.0 Hz, 1H), 4.89−4.84 (m, 1H), 3.77 (s, 2H), 3.71 (s, 3H), 3.14−3.04 (m, 2H), 2.46−2.44 (m, 2H), 1.98 (s, 3H), 1.67−1.62 (m, 1H), 1.57−1.55 (m, 2H), 1.32−1.28 (m, 3H), and 1.05 (d, J = 5.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 170.0, 141.3, 133.8, 129.2, 128.7, 57.7, 53.7, 53.5, 52.7, 37.9, 35.0, 24.7, 23.6, and 22.6. m/z (APCI) 347 (MH^+, 100%).

Preparation of Methyl 2(R)-Acetyl-(tert-butoxycarbonyl)-amino-3-(4-{[(2R,6S)-2,6-dimethylpiperidin-1-yl]-methyl}-phenyl)propanoate ***12***. The *N*-acetyl-amino acid methyl ester **11** (6.07 g, 17.5 mmol) was dissolved in THF (15 mL) under nitrogen. A solution of di-*tert*-butyl-dicarbonate (5.73 g, 26.3 mmol, 1.5 equiv) in THF (10 mL) was added, and then 4-dimethylaminopyridine (115 mg, 1.02 mmol, 5 mol %) was added. The solution was heated at 40 °C under nitrogen for 16 h. Water (2.5 mL) was added, and the solution was stirred for 30 min whilst allowing to cool to room temperature (this treatment helps the following partition). The mixture was partitioned between toluene (40 mL) and water (25 mL). The aqueous phase was separated, and the organic phase was washed with water (10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to give mixed acetyl/BOC imide **12** as a brown oil (7.73 g, 17.3 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 5.47 (dd, J = 10.2, 6.0 Hz, 1H), 3.76 (s, 2H,), 3.73 (s, 3H), 3.40 (dd, J = 14.0, 6.0 Hz, 1H), 3.14 (dd, J = 14.0, 10.2 Hz, 1H), 2.45−2.42 (m, 2H), 2.28 (s, 3H), 1.64−1.62 (m, 1H), 1.57−1.54 (m, 2H), 1.43 (s, 9H), 1.31−1.26 (m, 3H), and 1.05 (d, J = 5.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.3, 152.4, 140.6, 135.4, 129.4, 128.4, 84.2, 57.6, 57.5, 57.4, 53.7, 52.7, 35.7, 35.1, 35.1, 28.3, 26.7, 24.7, and 22.6. m/z (APCI) 447 (MH^+, 100%) and 347 (27).

Preparation of 2(R)-(tert-Butoxycarbonyl-amino)-3-(4-(2R,6S)-2,6-dimethylpiperidine-1-yl)-methyl-phenyl)-propionic Acid 1.[12]. The mixed imide **12** (7.70 g, 17.2 mmol) was dissolved in THF (25 mL). Methanol (8 mL) was added, and the solution was cooled to 2 °C. A solution of $LiOH \cdot H_2O$ (1.45 g, 34.5 mmol, 2 equiv) in water (35 mL) was added over 75 min. [Temperature was maintained at 2−5 °C and pH at start of LiOH addition = 10.2. This quickly rose to 13.7 with the first two drops of LiOH.] Addition rate was adjusted such that pH remained below 13.7; pH upon completion of addition = 13.3. [Care needs to be taken

at the start of the addition since pH and temperature can rise rapidly at this point.] The reaction was stirred for a further 75 min at 3−5 °C (final pH 13.05). TLC (silica plate, DCM/MeOH, 9:1, visualised with $KMnO_4$) showed reaction to be complete. The mixture was acidified with 10% $KHSO_4$ (33 mL) [final pH 6.2, temperature rises from 5 to 15 °C, addition of $KHSO_4$ was then stopped since pH was changing very slowly and pH paper indicated a pH of 5−6 had been reached]. The solution was concentrated under reduced pressure (final pressure 50 mbar, 30 °C) to remove THF/MeOH. Some insoluble material separated. This was removed by extraction with MTBE (25 mL), and the MTBE phase was discarded. The aqueous phase (pH = 5.4) was saturated with NaCl and extracted with DCM (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and filtered. A sample was removed for analysis (ee 97.8%). The bulk was concentrated under reduced pressure (300 mbar, 30 °C). At the first sign of foaming, evaporation was stopped (residual solution 17 g), and water (50 mL) was added. Evaporation was continued (final conditions 70 mbar, 30 °C) to give a clear aqueous solution (traces of insoluble particles, pH of solution = 3.5). Amberlite IRA-67 (Merck, cat. no. 1.15959.0500, weakly basic ion-exchange resin, 2.25 g, prewashed with water) was added in portions, and the solution was stirred until pH 6.0 was reached (approximately 1 h). The solution was filtered through a pad of Celite, and the Celite was washed with water (10 mL). The solution was evaporated (final conditions 50 mbar, 50 °C). The residue was evaporated from ethanol (10 mL) and then from ethyl acetate (10 mL) (final conditions 20 mbar, 40 °C). The residue was dissolved in ethyl acetate (10 mL) (warming at 40 °C required). Heating was then stopped, and MTBE (20 mL) was added whilst stirring the solution. [After a few minutes precipitation was observed. Usually on smaller scale it has been necessary to seed the mixture.] The mixture was stirred at room temperature overnight. The precipitate was filtered, washed with EtOAc/MTBE (1:1, 2 × 5 mL), and dried under high vacuum (warm water bath, approximately 40−50 °C required) to give **1** as an off-white solid, (4.90 g, 73%), ee 98.6%, mp 105−110 °C. $[\alpha]_D^{25}$ −53.9 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 6.63 and 6.21 (d, J = 7.6 Hz and d, J = 6.0 Hz, 1H), 4.00−3.94 (m, 1H), 3.67 (s, 2H), 3.00 (dd, J = 13.2, 4.4 Hz, 1H), 2.78 (dd, J = 13.2, 9.4 Hz), 2.55−2.35 (m, 2H), 1.63−1.48 (m, 3H), 1.31 (s, 9H), 1.27−1.14 (m, 3H), and 0.96 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.3 (s), 172.6 (s), 155.4 (s), 139.5 (s), 136.6 (s), 129.2 (d), 127.6 (d), 77.9 (s), 57.5 (d), 56.0 (d), 53.4 (t), 37.0 (t), 34.2 (t), 28.5 (q), 23.9 (t), and 21.7 (q). m/z (APCI) 391 (MH^+, 100%), 335 (6).

HPLC method for chiral analysis of N-acetyl-4-(acetoxymethyl)-phenylalanine methyl ester 2a and N-acetyl-4-(hydroxmethyl)-phenylalanine methyl ester ***2b****:* column: Chiracel OD (250 mm × 4.6 mm, 10 μm); flow rate: 1.0 mL min^{-1}; mobile phase: heptane/propan-2-ol isocratic (80:20); detector: UV/vis 254 nm; retention times: (*R*)-**2a**, 7.08 min; (*S*)-**2a**, 8.71 min; (*R*)-**2b**, 8.57; (*S*)-**2b**, 10.06 min.

HPLC method for chiral analysis of N-acetyl-4-(hydroxmethyl)-phenylalanine methyl ester ***2b****:* column: Chiracel OJ (250 mm × 4.6 mm); flow rate: 1.0 mL min^{-1}; mobile phase: heptane/propan-2-ol isocratic (85:15); detector: UV/vis 214 nm; temperature: 40 °C; retention times: **3b**, 24.7 min; (*R*)-**2b**, 15.4; (*S*)-**2b**, 18.2 min.

HPLC method for chiral analysis of methyl (2R)-2-(acetylamino)-3-[4-(hydroxymethyl) phenyl]propanoic acid ***2c****:* column: Chirobiotic T (250 mm × 4.6 mm, 5 μm); flow rate: 1 mL/min; detector: UV/vis 210 nm, mobile phase: methanol/TEA/Acetic Acid (100:0.1:0.1); retention times: (*S*), 5.80 min; (*R*), 10.78 min.

HPLC method for chiral analysis of 2(R)-(tert-butoxycarbonyl-amino)-3-(4-(2R,6S)-2,6-dimethylpiperidine-1-yl)-methyl-phenyl)-propionic acid 1: column: Chirobiotic T (250 mm × 4.6 mm, 5 μm); flow rate: 0.8 mL min^{-1}; detector: UV/vis 210 nm; mobile phase: 0.1% triethylammonium acetate (pH 4.5)/methanol isocratic (62:38); retention times: (*S*), 10.77 min; (*R*), 14.68 min.

■ ASSOCIATED CONTENT

Supporting Information. Chromatographic methods for analysis of compounds **1**, **2a**, **2b**, **2c**, **3b**, **5**, **6**, **7**, **8**, **9**, **11**, and **12**. Pilot-plant procedures for 30-kg manufacture of **1**. ^{1}H NMR spectra of compounds **1**, **2a**−**c**, **3a**−**c**, **9**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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