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An Efficient Large-Scale Process for the Human Leukocyte Elastase Inhibitor, DMP 777[1]

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Abstract:

This report describes a *new* convergent, selective, and economical synthesis of DMP 777,[1] ending with the coupling of the chiral *β*-lactam half of the molecule (1) to the chiral amine as the isocyanate (2). Other steps involve the coupling of the *β*-lactam 3 to the phenolic moiety under phase-transfer conditions, followed by resolution of the resulting piperazine derivative using a chiral acid, and recycling of the undesired enantiomer also under phase-transfer conditions. The chiral amine 4 was produced efficiently starting from (*R*)-α-methylbenzylamine and the corresponding butyrophenone.

Contemporary pharmaceuticals often contain multiple chiral centers which provide a significant challenge to the process chemist. Fortunately, an array of tools is now available to address absolute stereochemistry, including classical resolution, chiral auxiliaries, asymmetric catalysis, and enzyme resolution. It is increasingly evident that no single method is consistently superior. A thorough approach to process development requires the consideration of all available chiral technologies to provide the most efficient route to a given drug candidate.

DMP 777, an inhibitor of leukocyte elastase, could prevent degradation of the structural proteins elastin and collagen, a process implicated in cystic fibrosis and rheumatoid arthritis.[2]

Retrosynthetic analysis indicates that **DMP 777** should be accessible by coupling two enantiopure fragments, *β*-lactam **1** and isocyanate **2** (Figure 1). Potentially, *β*-lactam **1** may derive from the commercially available racemic lactam **3**.[3] Consequently route-development efforts focused on identifying efficient conditions for elaboration of **3** into racemic **1**, and its subsequent resolution. The precursor to isocyanate **2**, amine **4**, is not an article of commerce; therefore, a process from simple materials had to be devised. We will discuss in turn the synthesis of fragments **1** and **2** and conclude by describing a procedure for their efficient coupling.

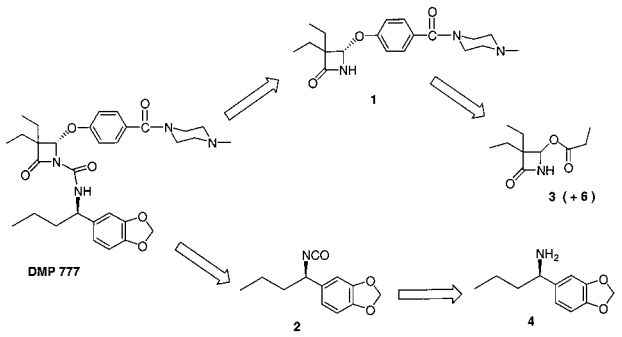

Figure 1. **Retrosynthetic analysis of DMP 777**

A short convergent process required a practical synthesis and resolution of the *β*-lactam portion (Scheme 1). The reaction conditions had to be balanced to provide the requisite basic elimination of propionic acid from **3** to give the reactive 3,3-diethylazetin-2-one, **5**, without hydrolysis of lactam. Phase-transfer catalytic conditions using a tetrabutylammonium salt gave the most efficient reaction, with an isolated yield of 88%.[4] About 25 chiral acids were screened for utility in the resolution. Diacetoneketogulonic acid (DAG) gave by far the best resolution, with the *R*-enantiomer DAG salt crystallizing out in high ee and thus overcoming a 10-bond separation between amine group and the chiral center. The *S*-isomer was then easily precipitated, DAG was recovered, and the *R*-isomer was racemized under phase-transfer conditions similar to those for its original synthesis (conversion of **3** to **1**-racemate). DAG is an intermediate in an industrial-scale ascorbic

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(1) Sheeran, P. J.; Anzalone, L.; Li, H.-Y.; Fortunak, J. M.; Storace, L. U.S. Patent 6,194,569, 2001. This work was presented at the 220th American Chemical Society National Meeting, August 21, 2000.

(2) Macdonald, S. J. F.; Clarke, G. D. E.; Dowle, M. D.; Harrison, L. A.; Hodgson, S. T.; Inglis, G. G. A.; Johnson, M. R.; Shah, P.; Upton, R. J.; Walls, S. B. *J. Org. Chem.* **1999**, *64*, 5166−5175 and references therein.

(3) Reference to previous process: Cvetovich, R. J.; Chartrain, M.; Hartner, F. W., Jr.; Roberge, C.; Amato, J. S.; and Grabowski, E. J. J. *J. Org. Chem.* **1996**, *61*, 6575−6580.

(4) A reference for use of PTC in synthesis of *β*-lactam derivatives: Murakami, M.; Aoki, T.; Nagata, W. *Heterocycles* **1990**, *30*, 567−581. DAG reference: Mohasci, E.; Leimgruber, W. *Organic Syntheses*; John Wiley & Sons: New York, 1988; Collected Vol. 6, pp 826−829.

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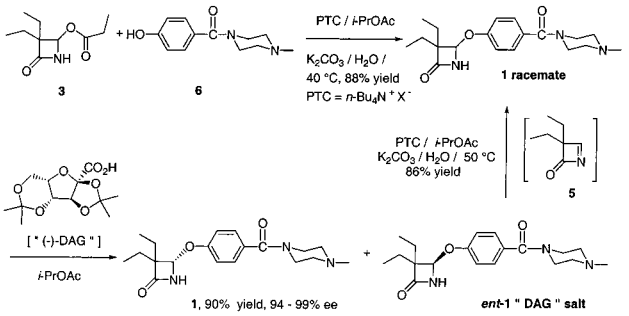
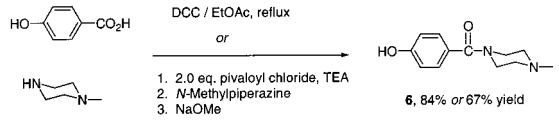
acid process and so was available in bulk. For an alternative synthesis of **1**, see ref 5.

Scheme 1. **Chiral lactam**



The starting propionyloxylactam **3** and the benzoylpiperazide **6** were obtained from commercial sources. Initially, **6** was synthesized by the two methods indicated (Scheme 2). The convenient one-step DCC coupling was unusual because it had to be heated to reflux to obtain a clean high-yield reaction. DCC couplings are typically carried out at 0−25 °C. In this case, the bifunctional nature of the acid caused some reaction of DCC at the phenol end. However, on heating, equilibria favored formation of the desired product. Some pilot-plant facilities avoid the use of DCC because it is a skin sensitizer. The three-step pivaloyl chloride route to the benzoylpiperazide avoids DCC and is also efficient since none of the intermediates need to be isolated.

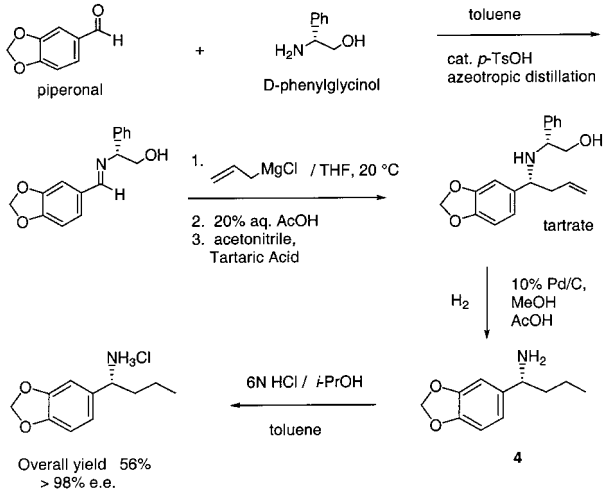
Scheme 2. **Benzoylpiperazide**



A number of routes to the chiral amine **4** were considered, including the published routes and an aminotransferase enzymatic resolution of the racemic amine. Five different enantioselective routes were successfully demonstrated as summarized in Schemes 3−7. The fifth route, clearly the most efficient from a raw material and operational cost basis, was ultimately selected for scale up. The enantioselective processes include routes based on chiral auxiliaries as well as asymmetric catalysis and provided reaction enantioselectivities ranging from 86 to 96% ee. Formation and isolation of the hydrochoride salt of **4** upgraded the ee to about 99%. The hydrochoride salt of **4** was needed for conversion to isocyanate in the next step.

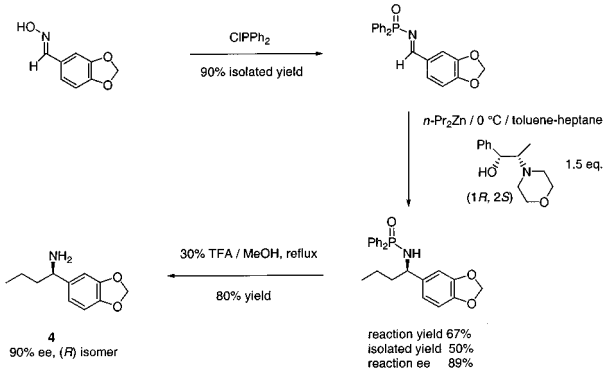
The D-phenylglycinol approach[6,7] (Scheme 3) worked well using allylmagnesium chloride as nucleophile, giving addition in 89% de. The allyl group could be reduced and the chiral auxiliary hydrogenolyzed in one step. Use of propylmagnesium chloride provided a slow reaction rate, byproducts, and poor yield. Propylcerium dichloride[7] gave addition in 94% de, and 70% isolated yield, but was relatively impractical from a production perspective when compared to a simple Grignard reagent.

Scheme 3. **Chiral amine, D-phenylglycinol approach**



One underutilized method of enantioselective synthesis of amines involves the use of phosphinylimines.[8] Phosphinylimines are readily made from arylaldoximes and chlorophosphines, or from aldehydes and phosphinamides. Typically, reaction of phosphinylimines with a dialkylzinc reagent in the presence of a chiral moderator provides phosphinamides in high ee and moderate yields. One of the main advantages of this route is that chromatography is not necessary. Phosphinamides are easily isolated, purified, and crystallized. The best ligand is the morpholine derivative of norephedrine, as reported by Soai. The reaction (Scheme 4) is slow, requiring 16 h at 0 °C followed by completion at room temperature for several hours, which allows time for a variety of byproducts to form. The main byproducts were derived from reduction: simple reduction of phosphinylimine to an *N*-benzylphosphinamide, and reductive formation of diphenylphosphine oxide which adds to phosphinylimine in conjugate fashion. Other ligands including quinines, prolinol derivatives, and other norephedrine derivatives (all vicinal amino alcohols) mediated the reaction but gave inferior results. *In general the phosphinylimine route gives acceptable selectivity only with aromatic phosphinylaldimines, and not with ketimines*.

Scheme 4. **Chiral amine, phosphinylimine−alkylzinc route**

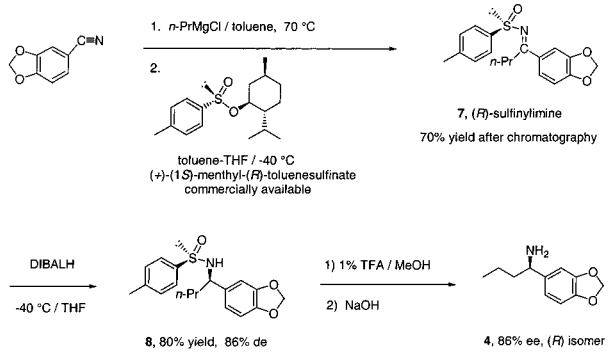


Another method for the synthesis of chiral amines uses a chiral sulfur atom as an auxiliary.[9] Sulfinylimine **7** was synthesized using a commercially available menthyl sulfinate

(5) Lipase route: Roberge, C.; Cvetovich, R. J.; Amato, J. S.; Pecore, V.; Hartner, F. W., Jr.; Greasham, R.; Chartrain, M. *J. Ferment. Bioeng.* **1997**, *83*(1), 48−53.
(6) Li, H.-Y.; Anzalone, L.; Ma, P. U.S. Patent 5,932,749, 1999.
(7) Wu, M. J.; Pridgen, L. *J. Org. Chem.* **1991**, *56*, 1340−1344.

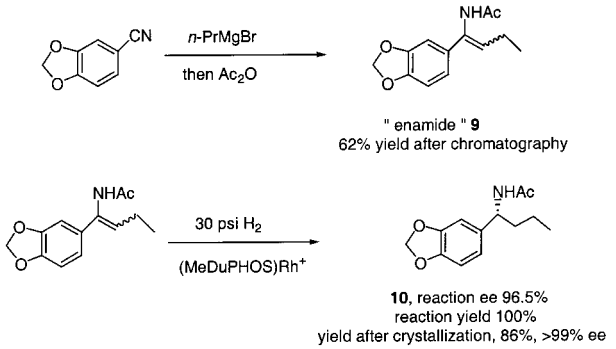
(Scheme 5). It was purified by silica gel chromatography. Diastereoselective reduction of the imine gave the desired sulfinamide **8**, which could be readily isolated and purified. Deprotection under mild acidic conditions gave **4**. This was the only route in which the chiral auxiliary was recoverable. The need for chromatography of **7** inhibited further development of this route.

Scheme 5. **Chiral amine, sulfinylimine route**



A catalytic asymmetric hydrogenation route using a DuPhos catalyst[10] (Scheme 6) was also demonstrated. The required enamide **9** was prepared by addition of propylmagnesium bromide to piperonylonitrile followed by acylation with acetic anhydride. The crude enamide was purified by flash chromatography. Asymmetric hydrogenation of the enamide was carried out using (MeDuPHOS)Rh(COD)$^+$ as catalyst in methanol solvent. The hydrogenation proceeded at an 1800:1 substrate-to-catalyst ratio (0.05 mol % catalyst) under mild conditions (30 psi hydrogen, room temperature). The desired amide **10** was produced quantitatively in 96.5% enantiomeric excess. A single crystallization afforded pure **10** in 86% yield and >99% enantiomeric excess. The apparent need for chromatography after the first step could possibly be overcome with further research, but scale-up of this route was inhibited.

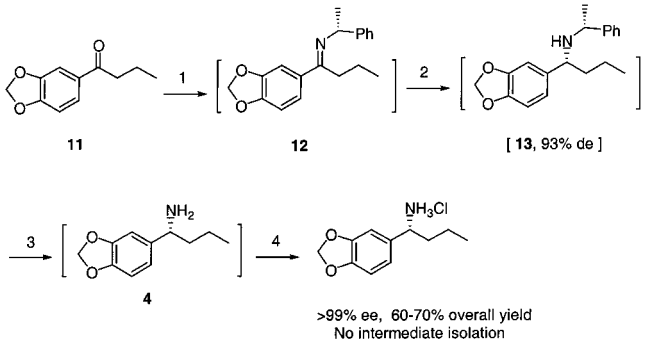
Scheme 6. **Chiral amine, DuPHOS route**[a]



[a] (MeDuPHOS)Rh$^+$:1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene−(cyclooctadiene)rhodium (I) tetrafluoroborate.

The (*R*)-phenylethylamine route (Scheme 7) was determined to be the most efficient, due to yield, low cost of starting materials and reagents, and operational efficiency.[6] Starting from butyrophenone derivative **11**, the imine was produced as a 2:1 *E*/*Z* mixture (The isomer ratio was conveniently monitored by HPLC and NMR). Success of this route was dependent on a number of factors. The *E*-imine **12** reduces selectively, using Raney nickel, to the required diastereomer of **13**. Under optimum reaction conditions, the *Z*-imine is reduced very slowly to the undesired diastereomer but isomerizes more rapidly to the *E*-isomer. Finally, under optimum palladium-catalyzed reduction conditions, the benzyl group containing the less substituted aromatic ring is highly selectively cleaved. Similar steric-controlled selective reductions have been reported.[11]

Scheme 7. **Chiral amine, method of choice**[a]



[a] 1. $TiCl_4$ (0.55 equiv), (*R*)-PEA (1.2 equiv), Et_3N (2 equiv), toluene. 2. Ra-Ni, H_2, toluene−EtOH, 150 psi, 25 °C, 4 h, then 70 °C, 2 h. 3. 10%Pd/C (10 wt %), H_2, AcOH, toluene−EtOH. 4. HCl in *i*-PrOH−toluene; *i*-PrOH−*n*-heptane.

Even though the efficient synthesis of isocyanates from amine HCl salts and phosgene in refluxing toluene (Scheme 8) has been known for many decades, a surprise awaited us. Small amounts of iron dissolved in liquid phosgene (from a steel cylinder) induced racemization of the isocyanate! Transfer of phosgene as a gas avoided this problem, leaving iron behind in the cylinder. In control experiments, it was also found that pyridine inhibits the effect of iron (probably through coordination with iron) and that ferric chloride racemizes the isocyanate at reflux in toluene. The mechanism of racemization has not been investigated but may involve formation of a π complex between the electron-rich aromatic ring of **2** and an iron cation, or by a mechanism similar to that of the known racemization of α-methylbenzylamine by Pd.[12] Phosgene equivalents such as diphosgene, triphosgene, and so forth were shown to be useful

(8) Soai, K. J.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097−1098. Stec, W. J. *Synthesis* **1978**, 521−3, and **1982**, 270−272. Hutchins, R. O.; Abdel-Magid, A.; Stercho, Y. P.; Wambsgan, A. *J. Org. Chem.* **1987**, *52*, 704−706. Brown, C.; Hudson, R. F.; Maron, A.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1976**, 663−664.

(9) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4−6 and references therein. Davis, F. A.; Reddy R. E.; Portonovo, P. S. *Tetrahedron Lett.* **1994**, *35*, 9351−9354.

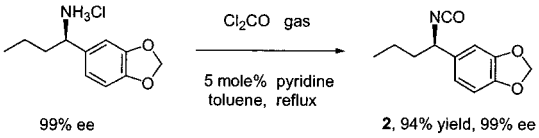
(10) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084; Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590; Zhang, F.-Y.; Pai, C.-C.; Chan A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. Review of DuPHOS ligands and their uses see: Burk, M. J. *Chemtracts: Org. Chem.* **1998**, *11*, 787.

(11) Bringmann, G.; Geisler, J.-P.; Geuder, T.; Kunkel, G.; Kinzinger, L. *Liebigs Ann. Chem.* **1990**, 795−805.

(12) Murahashi, S.-I.; Noriaki, Y.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002−5011.

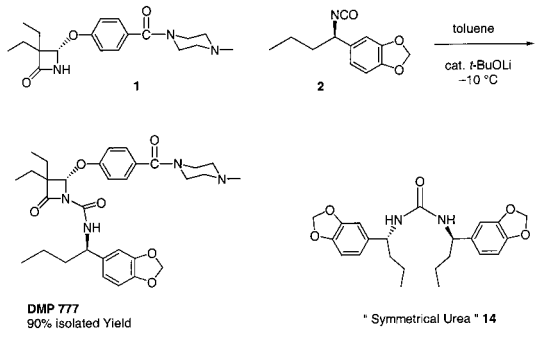
but were considered to be less practical or efficient than the phosgene method.

Scheme 8. **Chiral isocyanate**



In preparation for pilot-plant-scale reactions of the final, convergent step (Scheme 9) a number of solvents and catalysts (including DBU) were evaluated. These reactions were sometimes complicated by formation of variable amounts of symmetrical urea **14**, which required extra purification procedures and lowered isolated yields to 70−80%. Furthermore, there was mass spectroscopic evidence for a 1:2 adduct between DBU and the isocyanate,[13] which was proposed to form "symmetrical urea" during aqueous workup. The working hypothesis used in development of an efficient coupling process was that the catalyst needs to be of sufficient basicity to deprotonate the lactam while having poor nucleophilicity, and that the resulting anion needs to react with isocyanate much faster than it would decompose by elimination of phenolate. Base, cation, solvent, and temperature were the relevant variables examined. It was found that the reaction required a base with conjugate acid pK_a of >20. The more strongly *N*-coordinating lithium cation provided the necessary lactam anion stability. Only trace levels of symmetrical urea are formed when lithium *tert*-butoxide (5 mol %) is used as catalyst and the stoichiometry carefully controlled. This catalyst offered the most robust process and allowed optimization of volume, solvent, temperature, and so forth. A clean reaction made it possible to crystallize the coupled product directly out of the quenched and washed reaction solution in high yield and purity.

Scheme 9. **Final, convergent, step; coupling to produce DMP 777**



This entire synthesis has been carried out safely, reliably, and volume efficiently on pilot-plant scale. A total of 190 kg of **DMP 777** were prepared by this process.

(13) DBU−isocyanate 1:2 adducts: Oediger, H.; Moeller, F. Ger. Offen. 2640964, Bayer A-G, 1978; *Chem. Abstr.* **1978**, *88*, 190910.

Experimental Section

For characterization of known compounds **1**−**4**, and **DMP 777** see ref 3.

3,3-Diethyl-4-{4-[(4-methylpiperazinyl)carbonyl]phenoxy}azetidin-2-one (Racemic 1). Water (219 L) was charged to a 300-gal vessel, followed by potassium carbonate (137 kg, 993 mol), tetrabutylammonium hydrogen sulfate (415 g, 1.2 mol; about 4.8 mol % relative to **3**), **6** (56 kg, 244 mol; 0.97 mol equiv relative to **3**), and isopropyl acetate (330 L). The mixture was warmed to 45 °C, and a solution of 3,3-diethyl-4-oxoazetidin-2-yl propanoate **3** (59 kg, 85% w/w content, 251 mol; health caution: compound **3** is a mutagen) in isopropyl acetate (56 L) added over 1.2 h. The **6** dissolves as reaction proceeds. After being held at 45 °C for 1 h, the reaction was observed to be complete by HPLC (<0.2% of total area remaining for **6** versus the completion criterion of less than 5% of **6**). The lower (aqueous) layer was separated, and the organic phase was concentrated under reduced pressure (100 mm/40 °C) to about 250 L. Methyl *tert*-butyl ether (250 L) was added, and the mixture was stirred for 10 h at 15 °C while the product slowly crystallized. After cooling to −10 °C over 2 h, the mixture was filtered, and then the wet cake was returned to the vessel and slurried in 290 L of methyl *tert*-butyl ether at 20 °C. The slurry was cooled to −5 °C and filtered (2% yield loss in the filtrate). After drying at 50 °C and 50 mm in a vacuum oven to constant weight, 75.6 kg of product was obtained as a white solid, 98.0% w/w purity, 88% yield (corrected for purity of both starting material and product). A sample was purified for use as analytical reference material by dissolving it in warm toluene, washing the solution thoroughly with water, drying, and then crystallizing the product by addition of *tert*-butyl methyl ether. mp 105−107 °C.

Resolution. (4*S*)-3,3-Diethyl-4-{4-[(4-methylpiperazinyl)-carbonyl]phenoxy}azetidin-2-one 1. 2,3:4,6-Di-*O*-diisopropylidene-2-keto-L-gulonic acid (DAG, 28.3 kg, 96.5 mol) was slurried in 266 L of isopropyl acetate and heated with stirring to 70 °C in a 200-gal, glass-lined vessel. This gave a pale-yellow, slightly hazy solution. A 300-gal, glass-lined vessel was charged with 532 L of isopropyl acetate followed by a small DAG charge (5.7 kg, 19.3 mol, to ensure that no chemical degradation of the racemic amine occurs with heating.). The racemic amine (66.8 kg, 193 mol) was then charged and the resulting slurry heated to 70 °C to give a clear solution. The DAG solution was then added, at a constant rate to the racemic amine solution over 2.5 h. The suspension was cooled to 20 °C over 3 h and held with stirring for an additional 11 h. A stir time of >5 h is required to reach the maximum ee possible for **1** in the liquors. The salt was filtered by centrifugation and the wet cake washed with 25 kg of isopropyl acetate. This solid was later dried to give 62.9 kg of **1-enantiomer** DAG salt (92% ee). The ee of the combined liquors and wash was 93% for **1**. The liquors were transferred back to the 300-gal vessel (which had been cleaned with water and then a methanol boil-out) and washed with 20% aqueous potassium bicarbonate solution. The layers were separated, and the organic layer

was washed with 188 kg of 15% aqueous sodium chloride solution. The isopropyl acetate solution was concentrated by distillation at about 100 mmHg/40 °C. A total of 460 L of isopropyl acetate was collected out of a total of approximately 1000 L. Vacuum was released, and 235 kg of heptanes was charged to the vessel. Vacuum, heating, and distillation were resumed until a final volume of approximately 110 L was reached. GC analysis showed the composition of the solvent to be 60:40 isopropyl acetate−heptanes with the target being 25−40% isopropyl acetate. After cooling to 20 °C and stirring for 9 h, an additional 60 kg of heptanes was added and the mixture stirred at 20 °C for 2 h. Analysis of a sample showed the liquors to be about 79% ee **1**. Quantitative HPLC showed the liquors contained only about 350 g of **1** (0.19 wt % **1** in 207 kg of liquors). The precipitated **1** was filtered and then washed with 100 kg of heptanes. After drying to a constant weight, 31.0 kg of material was obtained. The dried product had an assay of 100%. KF determination showed 0.29% water by weight, and the ee was 94%. The yield, corrected for assay of both starting material and product, was 91.6%. This material was useable for the next step. A sample was recrystallized from toluene and then again from chlorobutane; it was then slurried in 20 °C *tert*-butyl methyl ether to >99% ee, mp 121−123 °C. Chiral HPLC method: column, Chiracel OD 4.6 mm × 25 cm, 10 μm; detector: 240 nm; 40 °C; flow rate 1.0 mL/min; mobile phase: A, hexane; B, ethanol; C, 2-propanol; linear gradient ratio of A:B:C: 90:10:0 at $t = 0$; to 80:20:0 at 10 min; to 75:20:5 at 15 min; to 65:20:15 at 20 min; to 60:20:20 at 25 min; stop time 35 min; post-time 5 min. Retention times: toluene 2.9 min; **1**, 13.0 min; ***ent*-1**, 18.4 min.

Racemization of *ent*-1-DAG to *rac*-1. Water (290 L) was charged to a 300-gallon vessel, followed by potassium carbonate (64 kg, 464 mol) and 34 kg of sodium chloride. ***ent*-1-DAG** (72.5 kg, 117 mol) was added and then isopropyl acetate (442 kg). The mixture was agitated for 15 min, and then the aqueous layer was withdrawn and charged to a 200-gal reactor for later DAG recovery. This solution was extracted with 316 kg of isopropyl acetate, and the extract was combined with the organic solution in the 300-gal reactor, whereupon 2.6 kg of **6** (10 mol %; added to inhibit decomposition), tetrabutylammonium bromide (188 g), and aqueous potassium carbonate (64 kg in 103 L water) were also added to the 300-gal vessel. The mixture was then heated to 60 °C until the ee of the mixture was <5% or the impurity levels began to rise (typically 2−3 h). If the total area % response for ***rac*-1** reaches 90% or less, then racemization should be stopped to avoid material loss due to poor crystallization efficiency. The mixture was then cooled to 20−25 °C, and the phases were separated. The isopropyl acetate layer was washed with 60 L of 25% aqueous potassium carbonate solution and then with 75 kg of 20% aqueous sodium chloride solution. The isopropyl acetate layer was concentrated at 40−50 °C/40−50 mm to about one-third to one-fourth of its original volume. To this solution at 30 °C was added 87 kg of *tert*-butyl methyl ether. The solution was cooled to 20 °C over 1 h and then held for 2 h. The suspension was then cooled to −10 °C over 1 h and held at −10 °C for 2 h. The crystallization was complete when the solution contained ≤3% w/w content of ***rac*-1**. The ***rac*-1** was isolated by centrifugation with recycling of the mother liquors, and the cake was then washed with 15 kg of *tert*-butyl methyl ether. The ***rac*-1** was dried (40 °C/50 mm) to constant weight, 34 kg (99 area %, 99 wt %, 3.7% ee, 86% yield).

Synthesis of 1-(4-Hydroxybenzoyl)-4-methylpiperazine, 6, using DCC. *N*-methylpiperazine (226 mL, 2.0 mol) was added slowly (15 min) to a slurry of 4-hydroxybenzoic acid (229 g, 2.0 mol) in 2 L of ethyl acetate at 50−70 °C. A solution of dicyclohexylcarbodiimide (438 g, 2.1mol) in 0.4 L of ethyl acetate was added over 1.5 h to the salt slurry at 70−78 °C. The mixture was refluxed 1 h and followed by gradient HPLC: C18, 20−95% acetonitrile−H_2O−0.05% TFA, 250 nm; product at 2.6 min, starting acid at 4.5 min, DCC adduct at 9.7 min. The mixture was cooled, 1.1 L of 2 M aqueous HCl was added, and the mixture was stirred 1.5 h. It was then filtered and the DCU cake rinsed thoroughly with water (3 × 250 mL). The layers were separated. The pH of the water layer (pH 1) was then adjusted to 13 with NaOH and heated to hydrolyze any ester by-products (2 area %) and then readjusted to pH 9. *n*-Butyl alcohol (2 L) was added. The layers were separated at 75 °C (4% yield loss to aqueous layer). The organic layer was azeotropically dried by distillation of butyl alcohol (1 L). It was then filtered hot to remove salt (2 wt %). The filtrate was concentrated by distillation to half its starting volume. The product crystallized as the concentrate was cooled to 0 °C. The product was collected by filtration, rinsed with butyl alcohol, and dried in a vacuum oven at 95 °C. Yield 380 g, 84% (97 wt % pure; 100 area %). About 4% yield remained in the filtrate. mp 184−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.17 (s, 3H), 2.28 (br, 4H), 3.46 (br, 4H), 6.79 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H), 9.83 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 45.6 (CH_3), 44.4 (very broad, CH_2 × 2), 54.5 (CH_2 × 2), 114.8 (CH × 2), 126.0 (C), 129.1 (CH × 2), 158.7 (C−O), 169.2 (C═O). CIMS $(M + H)^+$, 221.

Preparation of 1-(4-Hydroxybenzoyl)-4-methylpiperazine, 6, Using Pivaloyl Chloride. Isopropyl acetate (120 kg), was charged to a 100-gal reactor, followed by triethylamine (29 kg, 287 mol). The solution was cooled to 10 °C and *p*-hydroxybenzoic acid (18.0 kg, 130 mol) added in portions. The resulting salt slurry was warmed to 30 °C, held for 0.75 h, then cooled to 0−5 °C. Pivaloyl chloride (34.6 kg, 287 mol), was added over 1.0−2.0 h while controlling the temperature at 0−5 °C. The reaction was held at 0−10 °C until complete (about 3 h). Reaction progress was followed by HPLC until the ratio of ester/mixed anhydride to 4-hydroxybenzoic acid was >30/1. The reaction mass at 8−12 °C was washed twice with 65 L of water. The solution of ester/mixed anhydride (4-[(2,2-dimethylpropanoyl)oxycarbonyl]phenyl 2,2-dimethylpropanoate), at 0−5 °C was treated with *N*-methylpiperazine (10.8 kg, 106 mol) while maintaining at 0−10 °C. The reaction was warmed to 20−25 °C and held until complete (ester/amide to ester/

anhydride ratio >90/1 by HPLC). Water (65 L) was then added and the pH adjusted to 8.4−8.6 with 30% sodium hydroxide. The contents of the reactor were warmed to 40 °C, and the lower aqueous phase was separated. The organic phase was washed with 68 kg of 7% aqueous sodium bicarbonate at 40 °C, followed by 65 L of water and then 65 L of 30% aqueous sodium chloride (all at 40 °C). The organic solution of the ester/amide (4-[(4-methylpiperazinyl)-carbonyl]phenyl 2,2-dimethylpropanoate) was cooled to 20−25 °C, and sodium methoxide (25 kg of 25% solution of in methanol, 116 mol) was added, while the temperature was maintained at 25−35 °C. The reaction was held at 35−40 °C until complete (<1 area % of ester/amide) by HPLC. It was then cooled to 20−25 °C, 24 L of water added, and the pH adjusted to 8.4−8.6 with 37% HCl. After aging at 20−25 °C for 0.5 h and then at 5−10 °C for 1.0 h, the reaction was filtered and the wet cake washed with 39 kg of *i*-PrOAc. The solvent-wet solid was slurried in 58 L of water. After filtration it was dried in a vacuum tray drier at 45 °C/50 mmHg to constant weight of 19.5 kg **6** (98 wt %), 67% yield. HPLC method: column, Zorbax SB-Phenyl, 4.6 mm × 15 cm, 5 μm; flow rate, 1.0 mL/min; 20 °C; 240 nm; mobile phase 0.1% TFA/water and acetonitrile; linear gradient; initial 5% CH_3CN, hold 5 min, then to 25% CH_3CN at 10 min, hold 5 min, then to 50% CH_3CN at 20 min, then to 100% CH_3CN at 25 min; stop time 35 min; post time 5 min. Retention times: **6**, 5.2 min; *p*-hydroxybenzoic acid, 11.6 min; ester/amide, 17.2 min; ester/anhydride, 26.3 min. Ester/mixed anhydride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.37 (s, 9H), 7.17 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9 (CH_3), 27.0 (CH_3), 38.6 (C), 39.2 (C), 121.7 (CH), 126.6 (C), 131.8 (CH), 155.5 (C−O), 171.7 (C═O), 176.5 (C═O), 185.8 (C═O). Ester/amide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (s, 9H), 2.3 (s, 3H), 2.4 (br, CH_2 × 2), 3.6 (br, CH_2 × 2), 7.1 (d, J = 8.6 Hz, 2H), 7.4 (d, J = 8.6 Hz, 2H).

Chiral Amine, D-Phenylglycinol Approach. (3*E*)-4-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)-3-aza-2-phenyl(2*R*)but-3-en-1-ol. A solution of piperonal (2.3 kg), D-phenylglycinol (2.1 kg), and *p*-toluenesulfonic acid (2.3 g) in toluene (12 L) was heated to reflux. Once the theoretical amount of water had distilled (3−4 h; a Dean−Stark trap was used), the reaction was analyzed (<5% piperonal as determined by ^{1}H NMR). The solution was cooled to 80−85 °C. Heptane (7 L) was added slowly, and the resulting solution was cooled further to 5−10 °C, and aged for 1 h. Product precipitation begins at about 60 °C. The product was isolated by filtration and dried under vacuum at 50−55 °C to give 3.85 kg of imine (95.4% yield of 100% purity). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (br, 1H, OH), 3.86 (dd, J = 11 and 4.4 Hz, 1H), 3.95 (dd, J = 11 and 8.4 Hz, 1H), 4.45 (dd, J = 8.4 and 4.4 Hz, 1H), 6.00 (s, 2H), 6.81 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.20−7.45 (m, 6H) 8.24 (s, 1H, N═CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.8 (OCH_2), 76.0 (NCH), 101.5 (CH_2), 106.8 (CH), 108.1 (CH), 124.9 (CH), 127.4 (CH × 2), 127.5 (CH), 128.6 (CH × 2), 130.8 (C), 140.8 (C), 148.3 (C−O), 150.1 (C−O), 161.9 (N═CH).

2-[(1-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)but-3-enyl)-amino]-2-phenyl(2*R*)ethan-1-ol. A 2 M solution of allylmagnesium chloride in THF (9.4 L) was added to a cold solution (10−15 °C) of the imine (2.02 kg) in THF (9.0 L) over a period of about 2 h. The rate of addition was controlled to maintain the temperature below 30 °C. The resulting mixture was aged for 1 h (<5 area % of imine, by HPLC), cooled to 5−10 °C, and quenched by adding it slowly to a 30% aqueous acetic acid solution (13 L) while keeping the temperature below 30 °C. The organic phase was separated and treated with 20% aqueous NaOH solution to pH 8−10. The layers were separated, and the organic solution was washed with 10% aqueous NaCl and then concentrated to an oil under reduced pressure. Acetonitrile (15 L) was added followed by tartaric acid (1 equiv, 1.1 kg). The mixture was warmed to 50 °C, aged for 1 h, and then cooled to 20 °C over 2−4 h. After 1−2 h at this temperature, the product was filtered, washed with acetonitrile (10 L), and dried to constant weight under vacuum at 45−50 °C to give the benzyl glycinol tartrate salt, 2.57 kg, 96 wt %, 81% yield as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (m, 1H), 2.58 (m, 1H), 3.57 (m, 2H), 3.77 (m, 2H), 4.23 (s, OCH × 2, tartrate), 4.96 (m, 2H), 5.55 (m, 1H), 5.96 (s, 2H), 6.72 (dd, J = 8.0 and 1.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 1.4 Hz, 1H), 7.19−7.29 (m, 5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 40.0 (CH_2), 60.0 (NCH), 62.0 (NCH), 64.8 (OCH_2), 72.5 (OCH × 2, tartrate), 101.2 (CH_2), 108.0 (CH), 108.2 (CH), 117.9 (CH_2), 121.4 (CH), 127.6 (CH), 128.1 (CH × 2), 128.5 (CH × 2), 135.2 (CH), 136.3 (C), 141.1 (C), 146.6 (C−O), 147.6 (C−O), 174.0 (CO_2 × 2, tartrate).

1-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)(1*R*)butylamine 4. A nitrogen-sparged and vacuum-degassed solution of the benzyl glycinol tartrate (2.5 kg) in methanol (9 L) and acetic acid (4 L) was pressure-transferred to a slurry of "wet" 10% palladium on carbon (~50% water content, 0.8 kg) in methanol (8 L) and acetic acid (4.0 L). The resulting slurry was hydrogenated at ambient pressure and 20−25 °C for 24−48 h. Progress of the reaction was followed by HPLC. The propenyl side chain reduces rapidly, followed by "debenzylation". Once the reaction was complete, the catalyst was removed by filtration and washed with methanol. The combined filtrates were then concentrated under reduced pressure to a residue, which was partitioned between toluene (3 L) and 1 N aqueous HCl (5 L). The aqueous phase was separated and basified to pH 12−13 with 30% aqueous NaOH solution in the presence of toluene (6 L). The layers were separated, and the aqueous layer was extracted with toluene (4 L). The combined organic solutions were washed with 20% aqueous NaCl, clarified through a Celite pad, and analyzed for product content. The toluene solution was cooled to 10−15 °C and treated with 1 equiv 6 N HCl in isopropyl alcohol while maintaining a temperature below 20 °C. The slurry was aged 1 h at 20−25 °C and then filtered. The solid was washed with toluene and dried to give **4** HCl salt, 2.05 kg, 100 wt %, 99.9% ee, 82% yield.

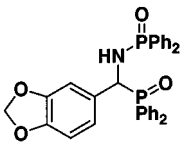
Phosphinylimine Route. Piperonaldoxime (66 g, 0.40 mol) was dissolved in methylene chloride (660 mL) and then

triethylamine (0.41 mol) and heptane (200 mL) were added; the solution was cooled to −45 °C. Chlorodiphenylphosphine (79 mL, 0.40 mol) in 100 mL methylene chloride was added dropwise over 25 min while maintaining the above temperature. Hexanes (500 mL) was added while warming the mixture to room temperature. The TEA−HCl was filtered off. The filtrate was concentrated on a rotary evaporator, the residue dissolved in 1.5 L of hot toluene, and 3 g of Darco added. After filtration, the filtrate was concentrated by rotary evaporation (distilled off 1 L of toluene). Heptane (800 mL) was added, and *N*-(diphenylphosphinyl)piperonaldimine (128 g, 90% yield) was collected as a yellow powder, mp 138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 2H), 6.90 (d, J = 7 Hz, 1H), 7.45 (m, 7H), 7.60 (s, 1H), 7.92 (m, 4H), 9.15 (d, J = 30 Hz, 1H, PN═CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.9 (CH_2), 107.3 (CH), 108.3 (CH), 128.4 (d, J = 13 Hz, CH × 4), 128.8 (CH), 131.5 (d, J = 10 Hz, CH × 4), 131.6 (d, J = 3 Hz, CH × 2), 148.6 (C−O), 152.5 (C−O), 172.3 (d, J = 7 Hz, C═NP), several peaks were not resolved. CIMS $(M + H)^+$, 350.

The phosphinylimine (11.0 g, 90%, 30 mmol) and the morpholine derivative of (1*R*, 2*S*)-norephedrine (10 g, 45 mmol) were added to a mixture of dry toluene (100 mL) and heptane (100 mL); the mixture was cooled to −15 °C, and dipropylzinc (13 mL, 94 mmol) was added via syringe while maintaining −15 °C. The mixture was stirred 15 h at 0 °C and then 24 h at 19 °C. Quantitative HPLC showed 67% reaction yield of the desired phosphinamide [HPLC method: C18, 25 cm, 60% acetonitrile−water (0.05% TFA), 225 nm] with 69 area % product (6.5 min), 3% starting material (5.5 min), 3% reduction product (4.0 min), and 8% of the phosphine oxide addition product (4.3 min, see below). The mixture was poured into cold 5% citric acid (500 mL) and the solid phosphine oxide addition product collected by filtration. The layers were separated (the chiral moderator can be recovered from the aqueous layer), and the organic phase was shaken with 5% citric acid and then 5% $NaHCO_3$, dried (Na_2SO_4), stirred with 12 g of silica gel, filtered, and rotovapped to give 10 g of residue. A sample of the product was purified by preparatory TLC for chiral HPLC analysis: Chiralcel OD, 15% ethanol/hexanes, flow rate 0.7 mL/min, (*R*)-enantiomer at 7.6 min, (*S*)- at 9.2 min, which showed 89% ee (*R*)-isomer. The product was dissolved in hot toluene (50 mL) and heptane added (50 mL). The product crystallized slowly with cooling to 0 °C and was collected by filtration to give the phosphinamide (6.0 g, 90 area %, 89% ee, 46% yield). The reaction times and isolation were not optimized. A product sample was purified for characterization by flash chromatography (5% *i*-PrOH/30% ether/hexanes) followed by recrystallizations from 1-chlorobutane and then toluene/hexanes, mp 140 °C. IR 3436, 3190. NMR shows the phenyl rings are diastereotopic. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 7 Hz, 3H), 1.20 (m, 2H), 1.70 (m, 1H), 1.90 (m, 1H), 3.22 (dd, J = 6 and 10 Hz, 1H, NH), 4.07 (m, 1H, NCH), 5.94 (s, 2H), 6.55 (d, J = 8 Hz, 1H), 6.67 (s, 1H), 6.68 (d, J = 8 Hz, 1H), 7.34 (td, J = 7 and 3 Hz, 2H), 7.4−7.5 (m, 4H), 7.76 (dd, J = 7 and 12 Hz, 2H), 7.86 (dd, J = 7 and 12 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (CH_3), 19.4 (CH_2), 41.9 (d, J = 4 Hz CH_2), 55.4 (d, J = 1 Hz NCH), 100.9 (OCH_2), 106.6 (CH), 108.0 (CH), 119.9 (CH), 128.2 (d, J = 13 Hz, CH × 2), 128.4 (d, J = 13 Hz, CH × 2), 131.6 (d, J = 3 Hz, CH), 131.7 (d, J = 3 Hz, CH), 131.8 (d, J = 85 Hz, C−P), 131.8 (d, J = 10 Hz, CH × 2), 132.5 (d, J = 10 Hz, CH × 2), 133.5 (d, J = 82 Hz, C−P), 137.9 (d, J = 5 Hz, C), 146.4 (C−O), 147.6 (C−O). ^{31}P NMR (162 MHz, $CDCl_3$, H_3PO_4 external) δ 23.5. ESMS $(M + H)^+$, 394.

4. The phosphinamide (1.0 g), was dissolved in methanol (4 mL) and 2.0 mL of TFA added. The solution was heated to reflux until completion (3 h). The solution was concentrated on a rotovap and the residue partitioned with water and toluene. The toluene layer was discarded. The pH of the water layer was adjusted to 12 with NaOH and the product extracted with *i*-PrOAc to give the (*R*)-amine, **4** (0.34 g, 80% yield, 90% ee).

Byproduct of the Propylzinc Reaction, the Phosphine Oxide Addition Product.



IR 3425. NMR shows the phenyl rings are diastereotopic (four different rings). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.5 (br, 1H, NH), 5.13 (q, J = 11 Hz, 1H, NCH), 5.82 (s, 2H, OCH_2), 6.40 (dd, J = 8 and 2 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 6.76 (s, 1H), 7.17−7.43 (m, 13H), 7.55 (m, 5H, ortho to P), 8.06 (dd, J = 10 and 7 Hz, 2H, ortho to P). ^{13}C NMR (not all peaks were resolved; 75 MHz, $CDCl_3$) δ 53.4 (d, J = 39 Hz, PCH), 100.9 (OCH_2), 107.7 (CH), 109.3 (CH), 122.7 (CH), 127.6−129.0 (m), 131.0−132.5 (m).^{31}P NMR (162 MHz, $CDCl_3$) δ 26.2 (d, J_{PP} = 27 Hz), 34.0 (d, J = 27 Hz). CIMS $(M + H)^+$, 552.

Chiral Amine: Sulfinylimine Route. (1*E*)-2-(2*H*-Benzo[*d*]1,3-dioxolen-5-yl)-1-aza-1-[(4-methylphenyl)(*R*)sulfinyl]pent-1-ene, 7. Piperonylonitrile (25 g, 0.17 mol) was dissolved in toluene (100 mL) and reacted with *n*-propylmagnesium chloride (0.18 mol) at 70 °C/30 min. After cooling and addition of THF (75 mL), (+)-menthyl *p*-toluenesulfinate solid (25 g, 0.085 mol) was added at −50 °C. The mixture was slowly warmed to 15 °C and then quenched with cold 5% citric acid. After thorough washing, the toluene solution was concentrated on a rotovap to give 54 g of oil containing the desired sulfinylimine **7**, menthol, piperonal, and so forth. The reactions were followed by HPLC [C18, 80% acetonitrile−H_2O (0.05% TFA), flow rate 1 mL/min, 225 nm; sulfinylimine at 4.0 min]. The product was purified by flash chromatography (silica gel, 20−50% *t*-BME−hexanes and then again with chloroform) and yielded 20 g (70% yield). The product was a 1:1 mixture of two geometric isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 1.63 (m, 2H), 2.40 (s, 3H), 3.13 (br, 2H), 6.00 (s, 2H), 6.80 (d, J = 7 Hz, 1H), 7.32 (d, J = 7 Hz, 2H), 7.38 (br d, 1H), 7.42 (br, 1H), 7.75 (d, J = 7 Hz, 2H). ^{13}C NMR (due to configurational mobility, not all peaks

resolved; 75 MHz, $CDCl_3$) δ 14.1 (CH_3), 21.4 ($ArCH_3$), 22.1 (CH_2), 35.1 (br, CH_2), 101.7 (CH_2), 107.8 (CH), 107.9 (CH), 123.1 (CH), 125.3 (CH × 2), 129.7 (CH × 2), 131.7, 141.6, 144.0, 148.1. CIMS $(M + H)^+$, 330.

(2*H*-Benzo[*d*]1,3-dioxolen-5-yl)(1*R*)butyl)[(4-methylphenyl)(*R*)sulfinyl]amine 8. Diastereoselective reduction of the chiral su1finylimine **7** (1.8 mmol, 0.6 g) in THF at −40 °C using DIBAlH (3.2 mmol) gave, after workup with citric acid and toluene extraction, 0.52 g of sulfinamide **8** (90 area % by HPLC, retention time 3.8 min; see above for method). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7 Hz, 3H), 1.23 (m, 2H), 1.74 (m, 1H), 1.99 (m, 1H), 2.38 (s, 3H), 4.15 (d, 1H, J = 6 Hz, NH), 4.31 (m, 1H, NCH), 5.92 (s, 2H), 6.6 (m, 3H), 7.19 (d, J = 7 Hz, 2H), 7.51 (d, J = 7 Hz, 2H). CIMS $(M + H)^+$, 332. The chiral auxiliary was removed in warm 1% TFA/MeOH to give the desired amine **4** in 86% ee, (*R*) (chiral HPLC).

DuPhos Route. *N*-(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl-(*R*)butyl)acetamide 10 by asymmetric hydrogenation of enamide **9**, that is, *N*-(1-(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl)-but-1-enyl)acetamide. A Fisher−Porter tube was charged with **9** (13.0 g, 61.5 mmol), 1,2-bis-((2*R*,5*R*)-2,5-dimethylphospholano)benzene (cyclooctadiene)−rhodium (I) tetrafluoroborate (20.0 mg, 0.033 mmol), and methanol (75 mL) under nitrogen. The system was flushed with hydrogen, pressured to 30 psig H_2, and stirred for 68 h at room temperature. The solution was filtered though a pad of silica, and the solvent was removed at reduced pressure. The enantiomeric excess of the crude product was determined to be 96.5% by chiral GC analysis (L-Val, 160 °C, isothermal). The product was crystallized from ether/heptane at 3 °C to afford pure acetamide **10** (11.26 g, 86% yield) as a white crystalline solid, $[\alpha]_D^{25} = +134.6$ (c = 1, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.28 (m, 2H), 1.91 (m, 2H), 1.93 (s, 3H), 4.80 (m, 1H), 5.65 (br d, 1H), 5.90 (s, 2H), 6.74 (s, 3H). Upon chiral GC analysis as above, we were unable to observe the minor enantiomer under conditions where 0.5% was readily observable, indicating that enantiomeric excess was >99%.

Chiral Amine: (*R*)-(+)-Phenylethylamine Route. 1-(2*H*-Benzo[3,4-*d*]1,3-dioxolen-5-yl)butan-1-one 11. A 12-L reaction flask was charged with 1,2-methylenedioxybenzene (1.50 kg, 12.3 mol), dichloroethane (5 L), and *n*-butyric anhydride (2.43 kg, 15.3 mol); the resulting mixture was cooled to −15 °C. Boron trifluoride (1.15 kg, 17 mol) was then charged slowly during 1−2 h, while maintaining the temperature at or below −5 °C. After addition was complete, the mixture was stirred at −5 to −10 °C for 3 h. The reaction was then quenched into a sodium acetate solution (9.1 kg sodium acetate trihydrate in 11 L of water). The bottom, organic layer was washed with 5% NaOH (5 L) and then water (2 × 2.5 L). The organic phase was concentrated to an oil (~3 L) which was crystallized from cold heptane (3.5 L). The solid was filtered and washed with cold heptane (2 L) to give **11** (2.03 kg, 100 wt %, 86% yield). mp 52−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3H), 1.75 (h, J = 7.4 Hz, 2H), 2.86 (t, J = 7.4 Hz, 2H), 6.03 (s, 2H), 6.84 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.56 (dd, J = 1.7 and 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 17.9 (CH_2), 40.2 (CH_2), 101.7 (OCH_2), 107.7 (CH), 107.8 (CH), 124.1 (CH), 131.8 (C), 148.0 (C−O), 151.4 (C−O), 198.4 (C=O).

5-((1*E*)(3*R*)-2-Aza-3-phenyl-1-propylbut-1-enyl)-2*H*-benzo[*d*]1,3-dioxolene 12. A 100-gal, glass-lined reactor was charged sequentially with toluene (144 kg), (*R*)-(+)-α-methylbenzylamine (12.9 kg, 106 mol, 1.25 equiv), triethylamine (22.2 kg, 219 mol, 2.5 equiv), and **11** (16.6 kg, 86.4 mol, 1 equiv) and then cooled to 0 °C. Titanium (IV) chloride (10.0 kg, 52.7 mol, 1.2 equiv) was charged subsurface over 1−2 h with vigorous stirring, while maintaining the temperature at less than 20 °C. After addition was complete, the reaction mass was heated to a gentle reflux (111 °C) with continued stirring for 6 h. After the reaction was complete, (2.8 area % of **11** relative to both isomers of **12**) it was cooled to 20−25 °C and filtered to remove precipitated triethylamine hydrochloride and titanium dioxide. The filter cake was washed with 58 kg of toluene. The combined toluene solutions were washed at 5−10 °C with 10% aqueous sodium hydroxide solution (55 kg) and twice with 50-L portions of water. The solution was passed through a cartridge filter and then concentrated at atmospheric pressure (110 °C) to approximately one-fourth volume to afford a solution of **12** in toluene (52.6 kg, 48.3 wt %; solution yield of 83.6%, corrected for the purity of starting **11** of 98 wt %). All lots were >99 area % by HPLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.45 (m, 2H), 1.50 (d, J = 7 Hz, 3H), 2.67 (t, J = 7 Hz, 2H), 4.85 (q, J = 7 Hz, 1H), 5.99 (s, 2H), 6.80 (d, J = 8.7 Hz, 1H), 7.30 (m, 5H) 7.45 (s, 1H), 7.47 (d, J = 8.7 Hz, 1H).

(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl(1*R*)butyl)((1*R*)-1-phenylethyl)amine 13. A slurry of **12** (34.3 kg of a 50.3 w/w % solution in toluene; 17.25 kg, 58.4 mol content) and Raney nickel (2 kg of type 2800, in 88.5 kg of ethanol) was hydrogenated at 150 psi hydrogen pressure at 25 °C for 4 h to completely reduce the **12**. The temperature was then increased to 70 °C to increase the rate of isomerization of the ketimine geometric isomer of **12**, and the hydrogenation was continued at 75 psi for another 2.5 h. After the reaction was complete by HPLC analysis, the catalyst was filtered and washed with 10 kg of ethanol. The ethanol wash was combined with the reaction solution to give **13** in toluene−ethanol (132.7 kg, 12.1 wt %, 89% de, for a calculated yield of 16.1 kg, or 92%). A sample of **13** was isolated as the mandelic acid salt for use as analytical reference material: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.72 (t, J = 7.4 Hz, 3H), 1.01 (m, 1H), 1.14 (m, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.45 (m, 1H), 1.63 (m, 1H), 3.19 (t, J = 7.2 Hz, 1H, NCH), 3.49 (q, J = 6.6 Hz, 1H, NCH), 4.93 (s, 1H, OCH), 6.00 (s, 2H, O_2CH_2), 6.50 (dd, J = 7.7 and 1.5 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 6.91 (s, 1H), 7.2−7.5 (m, 10H). HPLC method: column, Waters Symmetry-C18, 150 × 3.9 mm, 5 μm; 40 °C; detection, 285 nm; flow rate: 0.8 mL/min; mobile phase: acetonitrile and 0.05 M aqueous KH_2PO_4, pH adjusted to 6.0 with sodium hydroxide; linear gradient: initial composition 65:35 buffer−acetonitrile, to 30:70 at 10 min; retention times: **11**, 3.0 min; toluene, 4.0 min; *Z*-isomer of **12**, 6.5 min; **12,** 9.2 min; **13**, 7.2 min; **13**-diastereomer, 5.5 min.

(*R*)-α-Propylpiperonylamine Hydrochloride (4·HCl). A 50-gal, stainless steel reactor was charged sequentially with

13 solution (132.7 kg with a content of 16.1 kg), acetic acid (10 kg) and 50% water-wet 10% palladium-on-carbon (5.3 kg). The stirred suspension was hydrogenated at 150 psi at a temperature of 20−25 °C for 8 h. After reaction was complete, the catalyst was filtered and washed with 10 kg of ethanol to give a solution of **4** (152 kg). The filtrate was combined with another batch to give 301 kg of solution with an assayed w/w content of 6.97% (21.0 kg) **4**. This solution was concentrated in a 100-gal, glass-lined vessel to a volume of about 40−50 L and diluted with ethanol (17 kg) and toluene (170 kg). This solution was washed twice with 90 kg of 10% aqueous sodium hydroxide solution, followed by 2 × 55 L of water. After charging 24 kg of isopropyl alcohol, HCl gas (5.5 kg, 150 mol) was sparged below the surface of the stirred solution at 20 °C, and a slurry formed. After stirring at 20 °C for 1 h, the precipitated solid was filtered and the filter cake washed with isopropyl alcohol−heptane (66 kg:86 kg) to give crude **4·HCl** (96% ee). The wet cake was then slurried in 157 kg of isopropyl alcohol−heptane (99 kg/58 kg). Filtration at 15 °C and drying to a constant weight gave 16.4 kg of **4·HCl** (99.9% purity by HPLC area, 99.0% ee). mp 239−240 °C. HPLC method: as above but initial composition of 90:10 buffer−acetonitrile, with gradient to 30:70 at 10 min; flow rate: 1.0 mL/min; retention times: **13**, 14 min; **4**, 5.7 min. Chiral HPLC method: column, CrownPak CR+, 4.0 mm × 15 cm, 5 μm; detection: 285 nm; flow rate: 1.3 mL/min; 50 °C; mobile phase: 84:15:1 water:methanol:70% perchloric acid (premixed); retention times: **4**, 16.4 min; (*S*)-enantiomer, 13.0 min.

1-(2*H*-Benzo[*d*]1,3-dioxolen-5-yl)(*R*)butanisocyanate 2. In 77 L of toluene was slurried 33.6 mol (7.7 kg) of the above HCl salt, and 136 mL (1.7 mol, 5 mol %) of pyridine added. The solution was heated to 100−110 °C. Phosgene (4.0 kg, 40 mol) was introduced as a gas (from the vapor space of the phosgene cylinder) below the surface of the toluene. The slurry temperature was kept at 100−110 °C during the transfer. The reaction mass was held at reflux (typically 106−109 °C) for an additional 30 min and then cooled to 90 °C. The solution was sparged at this temperature with subsurface nitrogen to purge remaining unreacted phosgene (a packed column, counter-current scrubber containing 5% NaOH was used). In all batches the reaction was complete, and no additional charge of phosgene was required. The solution was then cooled to 0−10 °C and transferred to a stirred solution of cold aqueous 5% sodium bicarbonate in a 100-gal glass-lined vessel while maintaining 0−10 °C. The toluene layer was washed with water at 5−10 °C and then distilled at 45−50 °C reduced pressure to a water content of <50 ppm (determined by Karl−Fischer titration). The solution yield of **2** was 95.4%. For characterization, the product was isolated in pure form by distillation, bp 90−92 °C/0.1 mmHg. HPLC method: column, Zorbax SB-Phenyl, 4.6 mm × 15 cm, 5 μm; flow rate, 1.0 mL/min; 40 °C; 235 nm; mobile phase: buffer solution: 0.05 M aqueous ammonium acetate, methanol, and acetonitrile; a linear gradient was applied over 25 min by varying the amounts of aqueous buffer and acetonitrile, while holding the amount of methanol constant at 20%; initial 50% buffer, 30% CH_3CN to 60% CH_3CN at 25 min; stop time 25 min; post time 5 min. Retention times: **6**, 2.6 min; **4**, 3.6 min; toluene, 4.8 min; **1**, 5.9 min; olefinic byproduct, 8.9 min; **2**, 10.1 min; symmetrical urea, 11.0 min. HPLC chiral method: column, Chiralpak AD, 4.6 mm × 25 cm, 10 μm; 10 °C; 245 nm; mobile phase: hexane−methanol 98:2; flow rate, 1.0 mL/min; stop time, 10 min; retention times: toluene, 3.5 min; **2** ((*S*)-enantiomer), 6.2 min; **2** ((*R*)-enantiomer), 6.9 min.

***N*-(1-(2*H*-Benzo[*d*]1,3-dioxolen-5-yl)(1*R*)butyl)((4*S*)-3,3-diethyl-4-{4-[(4-methylpiperazinyl)carbonyl]phenoxy}-2-oxoazetidinyl)carboxamide DMP 777.** Toluene (210 kg) was charged to a reaction vessel followed by 40 kg of **1** (113.0 mol), and the stirred mixture was chilled to about 5 °C. A Karl−Fischer determination of the supernatant solution showed a water content of 140 ppm. Azeotropic distillation can be done if necessary at 45 °C/55−60 mmHg to reduce the water level below the designated acceptable limit of 350 ppm. A toluene solution of **2** (153 kg of a 17.1% w/w solution, 119 mol) was added, and the reaction slurry was cooled to −10 °C. The catalyst (4.0 kg, 1 M lithium *tert*-butoxide in hexanes, 5.7 mol, 5.0 mol % relative to **1**) was added. A modest exotherm was observed which caused the temperature of the reaction mass to go up to −5 °C over 6 min. The jacket temperature was held constant at −15 °C. All of the **1** dissolved within 30 min to give a light-yellow solution. HPLC analysis showed the reaction was complete (completion criteria: <0.1 area % **2** and 0.1−1.2% remaining unreacted **1**). The reaction was quenched with 0.35 kg of glacial acetic acid (5.7 mol) and washed with 43 kg of 2% aqueous sodium chloride solution while warming to 20 °C. After separation of the aqueous layer, the organic layer was concentrated to slightly less than one-half the original volume by distilling at 40 °C/60 mmHg to approximately 200 L. Analysis of the toluene solution by HPLC showed (by area) <0.1% **2**, 0.3% **1**, 0.06% symmetrical urea **14**, 0.3% **4**, 0.1% **6**, 0.4% of the methyl carbamate derived from reaction of traces of residual methanol in the apparatus with **2**, 0.2% *tert*-butyl carbamate derived from reaction of *tert*-butyl alcohol with **2**, 0.15% of olefinic elimination byproduct of **2**, and 3.3% of diastereomer derived from reaction of ***ent*-1** (carried along as an impurity in **1**) with **2**. The warm (40−45 °C) toluene solution was filtered through a 0.5 μm, in-line cartridge filter into a 200-gal, glass-lined vessel. After warming the product solution to 50 °C, *tert*-butyl methyl ether (58 kg) was added, followed by heptanes (119 kg, added over 1 h) while keeping the temperature at about 50 °C. The product precipitated during the heptanes addition. The mixture was held at 45 °C for 1 h. After cooling at a steady rate to −15 °C over 7 h, the mixture was centrifuged, and the cake was washed with a solution of 33 kg of toluene in 61 kg of heptanes which had been precooled to −20 °C. The wet cake was dried to constant weight in a vacuum oven at 40 °C/50 mmHg to yield 59.6 kg **DMP 777**, 93% yield. The filtrate and washes were combined (365 kg) and assayed by HPLC to determine the overall mass balance of the reaction. It contained 4.5% yield of **DMP 777** (2.6 kg), 2.0 kg of its diastereomer (*R*,*R* and *S*,*S*), 20 g of **6**, 210 g of **4**, 210 g of **14**, 40 g of **1**, 470 g of methyl carbamate, 250 g of *tert*-butyl carbamate, and 50 g of the olefin byproduct carried through from the **2** solution. HPLC method: column, Zorbax SB-C18, 25 cm × 4.6 mm, 5 μm; 50 °C; detector, 235 nm; flow: 1.1 mL/min; mobile phase: A = 30% methanol/water

(0.02 M trifluoroacetic acid and triethylamine, pH 7.4), B = acetonitrile; linear gradient, 30% B to 70% B at 15 min; then, flow rate 1.5 mL/min and linear gradient to 95% B at 19 min; stop time, 20 min; retention times: **6**, 2.6 min; **4**, 4.4 min; **1**, 5.2 min; methyl carbamate, 6.7 min; toluene, 8.1 min; symmetrical urea, 10.6 min; *tert*-butyl carbamate, 11.0 min; olefin, 11.6 min; **2**, 11.7 min; diastereomer of **DMP 777**, 14.5 min; **DMP 777**, 14.9 min. For published chiral HPLC methods see ref 14.

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