JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Scalable Asymmetric Syntheses of Foslevodopa and Foscarbidopa Drug Substances for the Treatment of Parkinson's Disease

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Cite This: https://doi.org/10.1021/acs.joc.1c00905 Read Online

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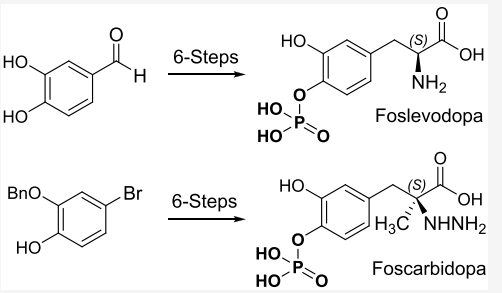
ABSTRACT: Foslevodopa (FLD, levodopa 4′-monophosphate, **3**) and foscarbidopa (FCD, carbidopa 4′-monophosphate, **4**) were identified as water-soluble prodrugs of levodopa (LD, **1**) and carbidopa (CD, **2**), respectively, which are useful for the treatment of Parkinson's disease. Herein, we describe asymmetric syntheses of FLD (**3**) and FCD (**4**) drug substances and their manufacture at pilot scale. The synthesis of FLD (**3**) employs a Horner−Wadsworth−Emmons olefination reaction followed by enantioselective hydrogenation of the double bond as key steps to introduce the α-amino acid moiety with the desired stereochemistry. The synthesis of FCD (**4**) features a Mizoroki−Heck reaction followed by enantioselective hydrazination to install the quaternary chiral center bearing a hydrazine moiety.



INTRODUCTION

Parkinson's disease (PD) is a progressive and debilitating neurodegenerative disorder which is characterized by decreased dopaminergic activity in the brain and affects over six million people worldwide.[1] One of the standard treatments for early Parkinson's disease involves oral administration of levodopa (Figure 1, LD, **1**) as a dopamine replacement therapy. Levodopa (**1**) is converted in vivo to dopamine by DOPA decarboxylase. The active metabolite of LD (**1**), dopamine, controls the symptoms of Parkinson's disease, and unlike LD (**1**), dopamine does not cross the blood-brain barrier. However, LD (**1**) is rapidly decarboxylated to dopamine in extracerebral tissues, especially in the gastrointestinal tract, and activates peripheral dopamine receptors and often causes severe side effects, such as nausea, vomiting, and dyskinesia.[2] Therefore, levodopa (**1**) is often administered in combination with carbidopa (Figure 1, CD, **2**), an inhibitor of DOPA decarboxylase enzyme. Carbidopa (**2**) does not effectively cross the blood−brain barrier and therefore selectively inhibits the conversion of LD (**1**) to dopamine outside of the brain, which increases the LD (**1**) half-life and uptake in the brain while reducing its dosage and side effects.[3]

One challenge with LD (**1**) treatments is the relatively short half-life in plasma, even with the coadministration of CD (**2**), which makes it difficult for patients to achieve and maintain optimal levels of dopamine in the brain.[1] Moreover, upon progression of Parkinson's disease, gastric motility is typically impaired, which makes the absorption of LD (**1**) from tablet form unpredictable. To circumvent these issues, a novel formulation of LD (**1**) and CD (**2**) (Duopa) was developed as a gel that enables continuous administration of the drug via direct infusion into the intestine through a jejunal tube.[4]

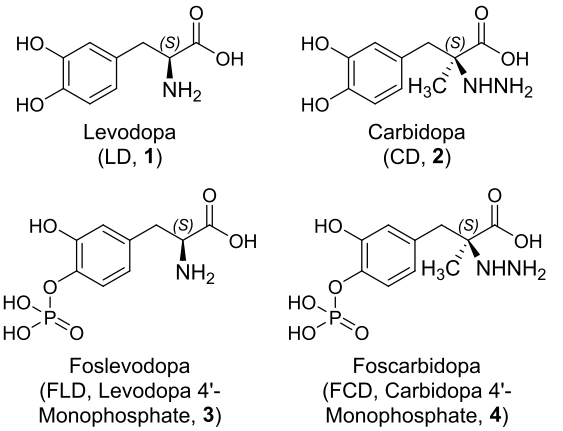


Figure 1. Levodopa and carbidopa and their phosphate prodrugs.

Special Issue: Excellence in Industrial Organic Synthesis 2021

Received: April 19, 2021

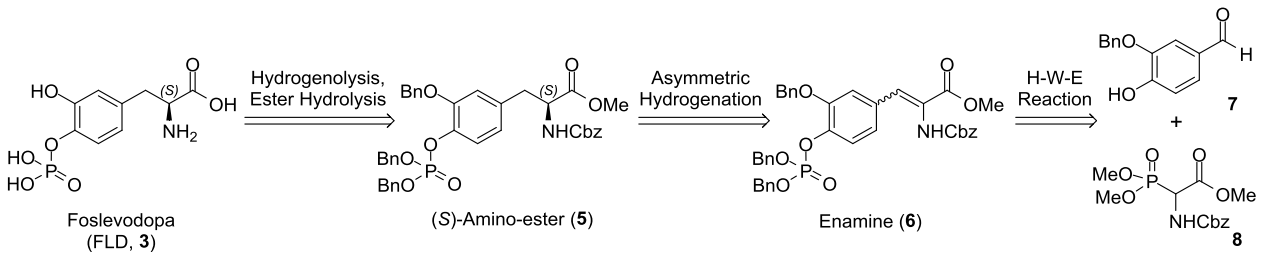


Figure 2. Retrosynthesis of foslevodopa.

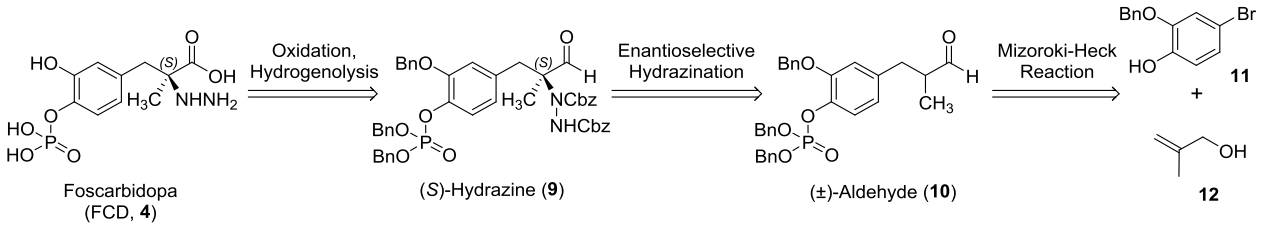
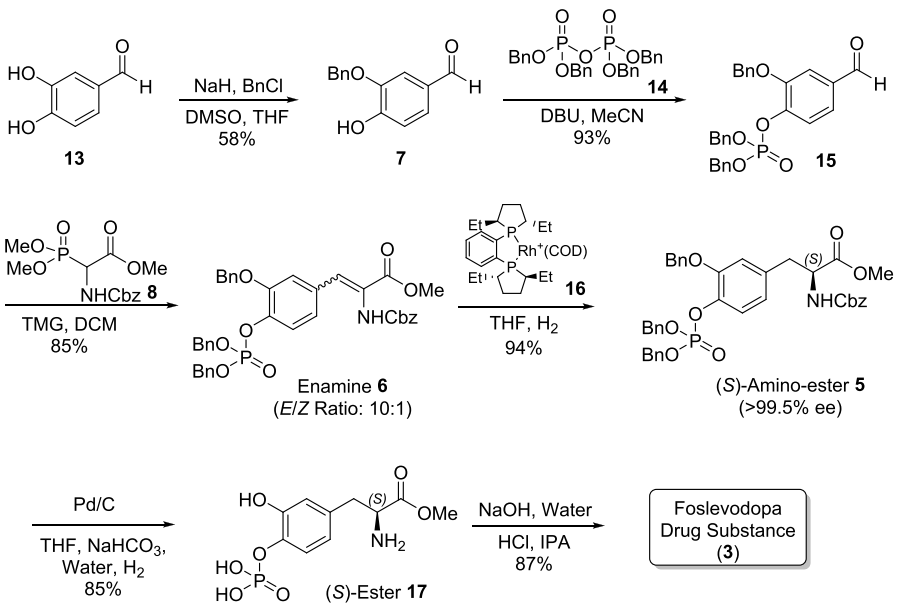


Figure 3. Retrosynthesis of foscarbidopa.

Scheme 1. Synthesis of Foslevodopa (3)



Duopa gel formulation allows continuous dosing of LD (**1**) and CD (**2**) with aid of a pump to prevent the peaks and troughs associated with traditional LD (**1**) and CD (**2**) tablet therapy. Despite the multiple benefits of Duopa, drug administration requires surgery at the beginning of the therapy to install the jejunal tube.[4]

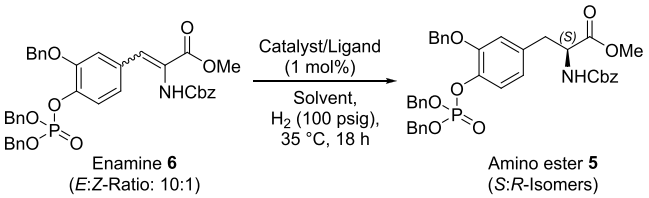
With the goal of overcoming the challenges associated with LD (**1**) and CD (**2**) existing therapies, a prodrug strategy was envisioned for the treatment of Parkinson's disease. Prodrug strategies can enable drug development endeavors when an active ingredient presents challenges, such as poor solubility, inadequate pharmacokinetic profile, undesirable pill burden or high injection volume, formulation difficulties, etc., and they have been successfully applied to bring novel drugs to market in scenarios where the parent compound would have likely failed during clinical development.[5] A prodrug is generally described as a weakly active or inactive chemical entity capable of converting to the parent drug, which achieves the desired physicochemical properties and undergoes an in vivo chemical or enzymatic transformation to deliver the active molecule at efficacious levels.[5]

Levodopa (**1**) and carbidopa (**2**) have poor aqueous solubility, approximately 4−5 mg/mL at physiological pH (7.4), which limits options for solution dosage forms. Our investigations found that phosphate derivatives of LD (**1**) and CD (**2**) imparted higher aqueous solubility and enabled subcutaneous delivery of drug at adequate dosages.[6] Foslevodopa (**3**) and foscarbidopa (**4**) were identified as phosphate prodrugs of levodopa (**1**) and carbidopa (**2**), respectively, for treatment of Parkinson's disease via continuous subcutaneous infusion.[7]

No selective LD monophosphate synthesis has been reported previously, and there was no precedent for CD phosphates;[7] therefore, synthetic routes to access foslevodopa and foscarbidopa were developed. Here, we describe the asymmetric synthesis of FLD (**3**) which employs a Horner−

https://doi.org/10.1021/acs.joc.1c00905
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Catalysts and Ligand Screening for Enantioselective Enamine (6) Reduction



Entry	Catalyst	Ligand	% Conversion	% ee (5)
1	[((*R*,*R*)-Et-DuPhos)Rh(cod)BF_4]	–	>99	95.6[a]
2	[((*S*,*S*)-Et-DuPhos)Rh(cod)BF_4] (**16**)	–	>99	97.8
3	[Rh(nbd)$_2$]BF_4	Josiphos J001-2	>99	68.8
4	((*S*)-Segphos)Ru(OAc_2)	–	10	31.0
5	[Ir(cod)Cl]$_2$	(*R*)-Monophos	<5	Not Determined
6	[Ir(cod)Cl]$_2$	(*R*)-BINAP	<6	Not Determined
7	((*R*)-BINAP)Ru($OAc)_2$	–	<10	46.0
8	[((*S*)-BINAP)$RuCl_2$]*p*-cymene	–	<1	Not Determined
9	[((*R*)-Segphos)$RuCl_2$]*p*-cymene	–	0	Not Applicable
10	[Rh(nbd)$_2$]BF_4	(*R*)-BINAP	>99[b]	Not Determined
11	[Rh(nbd)$_2$]BF_4	(*S*,*S*)-*i*Pr-DuPhos	67	Not Determined
12	[((*S*,*S*)-Et-DuPhos)Rh(cod)BF_4] (**16**)	–	97[b]	97.0[c]
13	[((*S*,*S*)-Et-DuPhos)Rh(cod)OTf]	–	80	Not Determined
14	[((*S*,*S*)-Et-DuPhos)Rh(cod)BF_4] (**16**)	–	>99[d]	94.3[d]
15	[((*S*,*S*)-Me-DuPhos)Rh(cod)BF_4]	–	80	95.1
16	[((*S*,*S*)-Et-DuPhos)Rh(cod)BF_4] (**16**)	–	>99[e]	>99.5%[e,f]

Notes: [a]*R*-isomer. [b]Reaction led to significant debenzylation. [c]Reaction run using 50 psig H_2. [d]Reaction run at 30 °C. [e]All reactions run in dichloromethane except for Entry 16, which was run in THF. [f]It was not clear if both *E*- and *Z*-isomers of **6** were directly reduced to the desired (*S*)-**5** or if one of the isomers of **6** was selectively reduced to (*S*)-**5** and the other olefin isomer of **6** was concurrently isomerized/equilibrated and was then reduced to (*S*)-**5**.

Wadsworth–Emmons olefination followed by enantioselective hydrogenation as key steps to introduce the α-amino acid moiety. Also reported is the synthesis of FCD (**4**), which employs a Mizoroki–Heck reaction, followed by enantioselective hydrazination, for installation of the quaternary center with the desired stereochemistry. In addition, optimization of the FLD (**3**) and FCD (**4**) processes and manufacture of both drug substances (**3** and **4**) on kilogram scale is reported.

RESULTS AND DISCUSSION

Retrosynthesis of Foslevodopa (3) and Foscarbidopa (4). The foslevodopa (**3**) retrosynthetic analysis is shown in Figure 2. We envisioned that FLD (**3**) could arise from (*S*)-amino-ester **5**, which could be accessed through an enantioselective reduction of enamine **6** as the key step.[8] The enamine **6** could be derived by Horner–Wadsworth–Emmons olefination[9] of 3-(benzyloxy)-4-hydroxybenzaldehyde (**7**) and commercially available phosphonate ester **8**. The retrosynthetic analysis of foscarbidopa (**4**) is shown in Figure 3, and it was envisioned from (*S*)-hydrazine derivative **9** via oxidation of the aldehyde to a carboxylic acid and cleavage of protective groups. The (*S*)-hydrazine **9** would be obtained from racemic aldehyde **10** using an enantioselective α-hydrazination to install the quaternary chiral center.[10] Finally, the (±)-aldehyde **10** would arise from 2-(benzyloxy)-4-bromophenol (**11**) and 2-methylprop-2-en-1-ol (**12**) through a Mizoroki–Heck coupling reaction.[11]

Synthesis of Foslevodopa (3). The synthesis of foslevodopa (**3**) began with selective protection of 3,4-dihydroxybenzaldehyde (**13**) via alkylation of the more nucleophilic alkoxide. This was performed with benzyl chloride using 2.2 equiv of sodium hydride, in a mixture of DMSO and THF, to provide 3′-protected benzyl ether **7** in 58% yield and 98.5% purity (Scheme 1).[12] Under these conditions, the corresponding 4′-isomer and 3′/4′-dibenzyl impurities were also observed. These were rejected through recrystallization. Use of THF as a cosolvent was necessary to avoid the potential safety hazards of sodium hydride in DMSO, especially during scale-up.[13] The 4′-phenolic group in 3-(benzyloxy)-4-hydroxybenzaldehyde (**7**) was then converted to the corresponding dibenzyl phosphate **15**, in excellent yield (93%), by reaction with tetrabenzyl pyrophosphate (**14**, TBPP, 1.05 equiv)[14] and DBU (1.15 equiv) in acetonitrile. These conditions had not been previously reported and were found to be uniquely effective and convenient for the preparation of sterically hindered phenol phosphates.[15] The remaining carbon framework of foslevodopa (**3**) was installed through a Horner–Wadsworth–Emmons olefination. Accordingly, the phosphate **15** was treated with 1.1 equiv of (±)-benzyloxycarbonyl-α-phosphonoglycine-trimethyl ester (**8**), in the presence of tetramethylguanidine (TMG), to furnish enamine **6** in 85% yield, as a 10:1 mixture of *E*/*Z* isomers.[16]

With enamine **6** in hand, our efforts then turned toward finding the best conditions for an enantioselective hydrogenation to provide (*S*)-amino-ester **5**. These efforts are summarized in Table 1. Use of 1 mol % rhodium catalyst **16** containing the Et-DuPhos ligand was shown to give excellent conversion (>99%) and 97.8% ee (entry 2). A variety of catalysts known for enantioselective reduction of enamines were examined but gave poor reactivity and/or selectivity (entries 3–10).[17] Use of *i*-Pr-DuPhos or Me-DuPhos ligands led to lower reactivity (entries 11 and 15). The counterion was also shown to be critical for optimal reactivity (entry 13), with triflate providing inferior results to those with tetrafluorobo-

https://doi.org/10.1021/acs.joc.1c00905
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 2. Synthesis of Foscarbidopa (6)

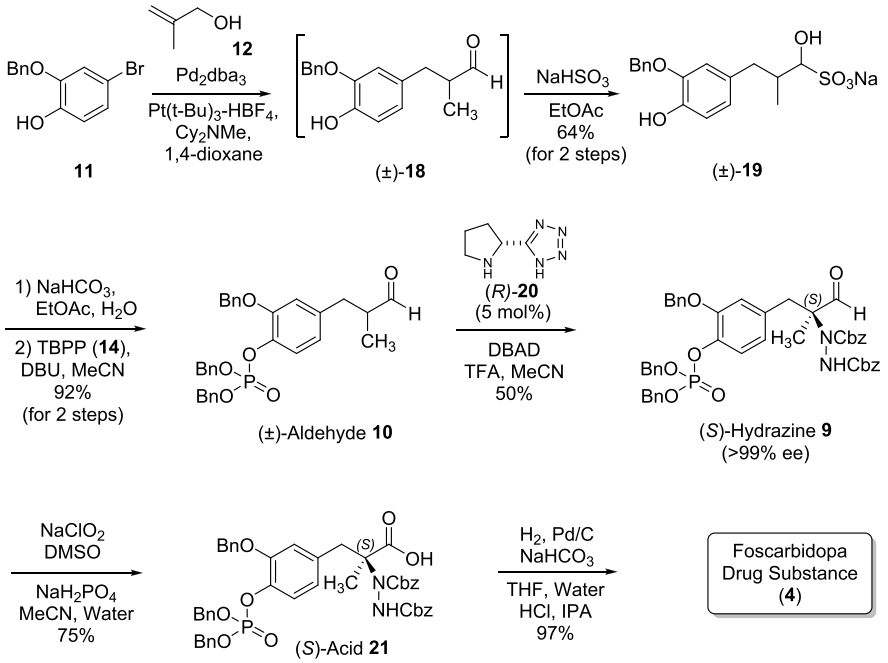
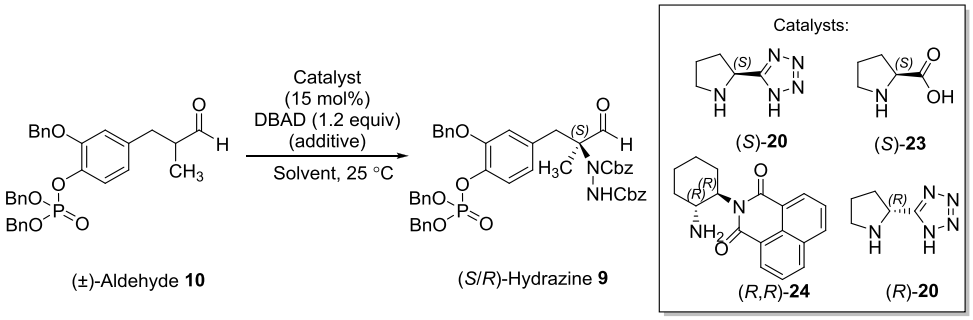


Table 2. Optimization of α-Hydrazination of (±)-Aldehyde 10 to (S)-Hydrazine 9



Entry	Catalyst	Additive	Solvent	Time (h)	Conversion (%)	(S)-9 ee (%)
1	(S)-**20**	None	MeCN	23	41	−51
2	(S)-**20**	None	CH_2Cl_2	18	45	−45
3	(S)-**20**	None	PhMe	18	38	−46
4	(S)-**20**	None	THF	18	51	−50
5	(S)-**20**	None	EtOAc	18	67	−46
6	(S)-**20**	None	MTBE	18	64	−40
7	(S)-**23**	None	MeCN	15	33	−40
8	(R,R)-**24**[a]	TFA (20 mol %)	MeCN	14	97	−50
9	(S)-**20**	TCA (15 mol %)	MeCN	18	62	−60
10	(S)-**20**	TFA (15 mol %)	MeCN	18	93	−60
11	(R)-**20**	TFA (15 mol %)	MeCN	16	99	60
12	(R)-**20**[b]	TFA (5 mol %)	MeCN	16	98	60

Notes: [a]20 mol % catalyst used. [b]5 mol % catalyst used.

rate. A decrease of hydrogen pressure or temperature gave slightly diminished enantioselectivity (entries 12 and 14). A change to THF from dichloromethane as solvent allowed for enamine **6** to be reduced to the (S)-amino-ester **5** in 94% yield and >99.5% ee (entry 16). It was gratifying to note that both E/Z-enamine isomers **6** converted to the desired product (S)-**5**. Further studies would be warranted to evaluate the hydrogenation reaction mechanism. Thus, under optimized conditions (entry 16), the enamine **6** was selectively reduced in the presence of 1 mol % (0.01 equiv) of rhodium catalyst (2*S*,5*S*)-**16** and hydrogen at 100 psig to give the (S)-amino-ester **5** in 94% yield and >99.5% ee.

Finally, to complete the synthesis of foslevodopa (**3**), the (S)-amino ester **5** was subjected to hydrogenolysis using Pd/C to remove the benzyl and Cbz groups. This was accomplished in THF and water in the presence of sodium bicarbonate. After the reaction was complete, pH adjustment with hydrochloric acid followed by crystallization gave (S)-ester **17** in 85% yield and 98.7% ee. The debenzylated product, (S)-ester **17**, was subjected to hydrolysis using sodium hydroxide. The resulting

https://doi.org/10.1021/acs.joc.1c00905
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mixture was treated with hydrochloric acid to afford foslevodopa (**3**) in 87% yield and 99.6% ee. Thus, starting from 3,4-dihydroxybenzaldehyde (**13**), the overall yield of foslevodopa (**3**) drug substance was 31% for six steps, at lab scale. This six-step synthesis was executed on pilot scale to obtain 29.3 kg of foslevodopa (**3**) drug substance for clinical studies, with the overall yield and quality comparable to those of lab scale batches (99.7 area% purity and 99.2% ee).

Synthesis of Foscarbidopa (4). The synthesis of foscarbidopa (**4**, Scheme 2) began with a Mizoroki−Heck coupling of 2-(benzyloxy)-4-bromophenol (**11**) with 2-methylprop-2-en-1-ol (**12**). The coupling reaction was catalyzed by $Pd_2(dba)_3$/*t*-Bu_3P-HBF_4 (1.5/3.0 mol %) in 1,4-dioxane in the presence of *N*-cyclohexyl-*N*-methlcyclohexanamine (Cy_2NMe) at 100 °C.[11] After the reaction was complete, purification of the expected (±)-aldehyde product (**18**) via crystallization was complicated by the low melting point of this intermediate. For this reason, the (±)-aldehyde (**18**) was derivatized as its bisulfite adduct (±)-**19** and isolated in a 2-step yield of 64%, without the need for chromatography.[18] In the next step, the bisulfite adduct (**19**) was cleaved in situ with sodium bicarbonate, and the aldehyde intermediate (**18**) was phosphorylated using tetrabenzyl pyrophosphate (**14**, TBPP)[14] and DBU (1.15 equiv) in acetonitrile,[15] to provide 4′-phosphorylated (±)-aldehyde **10** in 92% yield over the two steps.

With (±)-aldehyde **10** in hand, our focus turned to exploration of the key enantioselective α-hydrazination to install the desired quaternary chiral center (Table 2). Following literature precedent on a related substrate,[10] initial data showed that (±)-aldehyde **10** was converted preferentially to the undesired (*R*)-enantiomer of hydrazine **9**, when catalyzed by (*S*)-tetrazole **20** in the presence of dibenzyl azodicarboxylate (DBAD), albeit with low conversion and moderate enantiomeric excess (entry 1). A solvent screening study showed no improvement to the enantioselectivity and only a moderate increase in the conversion of **10** to **9** (entries 2−6). Use of L-proline (*S*)-**23** as a catalyst gave lower conversion and enantioselectivity (entry 7). Diamine catalyst (*R*,*R*)-**24** with trifluoroacetic acid (TFA) as an additive provided excellent conversion albeit with no improvement to the enantioselectivy.[10] Performing the reaction with (*S*)-tetrazole **20**, in the presence of the additive trichloroacetic acid (TCA), provided product in 62% conversion and 60% ee (entry 9). Switching to trifluoroacetic acid (TFA) as an additive with (*S*)-tetrazole **20** increased the conversion to 93% with 60% ee (entry 10). The use of (*R*)-tetrazole **20** with TFA as an additive provided excellent conversion of **10** with 60% ee favoring the desired enantiomer (*S*)-**9** (entry 11). Adequate catalyst activity and conversion were retained upon lowering the catalyst and additive loading to 5 mol % (entry 12).

With the optimized conditions in hand, the α-hydrazination of (±)-aldehyde **10** provided (*S*)-hydrazine **9** in 84% assay yield (57% ee). Addition of water allowed crystallization of (S)-**9** directly from the crude reaction mixture in 50% yield. Following the installation of the quaternary chiral center, the (*S*)-hydrazine **9** was oxidized under Lindgren conditions using sodium chlorite[19] for conversion of the aldehyde to the carboxylic acid (*S*)-**21** in 75% yield. Finally, hydrogenolysis of (*S*)-acid **21** was performed using Pd/C as catalyst in aqueous THF. The resulting mixture was treated with hydrochloric acid and isopropanol to enable isolation of foscarbidopa (**4**) in 97% yield and >99% ee. Thus, starting from commercially available 2-(benzyloxy)-4-bromophenol (**11**), the overall yield of foscarbidopa (**4**) drug substance was 25% over six steps. The foscarbidopa (**4**) process, which consists of six steps starting from 2-(benzyloxy)-4-bromophenol (**11**), was optimized and several scale-up batches were manufactured on pilot scale to obtain 14.3 kg of foscarbidopa (**4**) drug substance, with overall yield and quality comparable to that of lab scale batches (99.7 area% purity and 99.9% ee).

CONCLUSION

Synthetic routes were developed for foslevodopa (FLD, **3**) and foscarbidopa (FCD, **4**), which are phosphate prodrugs of levodopa (LD, **1**) and carbidopa (CD, **2**) drug substances. The synthesis of FLD (**3**) featured an enantioselective hydrogenation of enamine (**6**) in excellent selectivity as the key step. The synthesis of FCD (**4**) employed an enantioselective α-hydrazination of (±)-aldehyde (**10**) as the key step to install the quaternary chiral center. The syntheses of FLD (**3**) and FCD (**4**) were optimized to enable manufacturing at multikilogram scale.

EXPERIMENTAL SECTION

General Procedure. Unless otherwise noted, all solvents and reagents were purchased from commercial sources and used without additional purification. The temperature listed for each experiment refers to the internal reaction vessel temperature. Small-scale reactions were performed using a heating mantle with a thermocouple/temperature probe. Large scale reactions were performed using a jacketed reactor using ethylene glycol-water as the heating media. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were measured with either a Varian 400 MHz or Varian Inova 500 MHz spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane ($CHCl_3$ standardized at 7.26 ppm). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (central peak of $CHCl_3$ standardized at 77.0 ppm). ^{31}P NMR chemical shifts are expressed in parts per million using the unified chemical shift scale (Xi: 40.480742), with H_3PO_4 as external reference. Progress of reactions were monitored using either HPLC or LC-MS. Analytical LC-MS was performed on a Thermo MSQ-Plus mass spectrometer and Agilent 1100/1200 HPLC system running Xcalibur 2.0.7, Open-Access 1.4, and custom login software. The mass spectrometer was operated under positive APCI or ESI ionization conditions dependent on the system used. High resolution mass spectra were acquired using time-of-flight (TOF MS ES$^+$). The HPLC system comprised an Agilent Binary pump, degasser, column compartment, autosampler, and diode-array detector, with a Polymer Laboratories ELS-2100 evaporative light-scattering detector. The column used was a Phenomenex Kinetex C8, 2.6 μm 100 Å (2.1 mm × 30 mm) at a temperature of 65 °C. Purification of the crude reaction products, when performed, was accomplished on a Grace Reveleris X2 normal-phase chromatography system using silica gel cartridges purchased from Grace or Silicycle. Specific parameters used in the separation of individual compounds are detailed under each entry. Unless otherwise noted, reactions were carried out under an atmosphere of nitrogen and yields refer to isolated yields of analytically pure (>95%) material. Chiral purities were determined by HPLC using a Chiralpak IC column (4.6 mm × 250 mm, 5 μm) with mobile phase 90:10 hexane/4:1 MeOH:EtOH + 0.1% H_3PO_4 at 25 °C and a flow rate of 1.8 mL/min with detection at 210 nM.

3-(Benzyloxy)-4-hydroxybenzaldehyde (7). In a dry reactor equipped with a temperature probe, 3,4-dihydroxybenzaldehyde (**13**, 1.2 kg, 8.68 mol, 1.0 equiv) was dissolved in DMSO (2.4 L) and THF (1.2 L) under nitrogen. The resulting solution was slowly added to a stirred mixture of sodium hydride (60% w/w, 0.768 kg, 19.08 mol, 2.2 equiv) in DMSO (6 L) and THF (2.4L) at 25−30 °C over a period of 1 h. The reaction mixture was stirred for 1 h. Benzyl chloride (1.20 kg,

https://doi.org/10.1021/acs.joc.1c00905
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9.55 mol, 1.1 equiv) was slowly added to the reaction mixture at 25−30 °C over a period of 1 h. The resulting mixture was stirred, and the progress of the reaction was monitored by HPLC. After about 30 min, the reaction mixture was slowly quenched into precooled water (5−10 °C) under a steady flow of nitrogen, and the mixture was stirred for an additional 10 min. The pH of the reaction mixture was adjusted to 3−4 using 6 N HCl solution and extracted 3 times with ethyl acetate (2 × 12 L, 1 × 6 L). The combined ethyl acetate solution was washed 3 times with purified water (3 × 12 L) and aqueous sodium chloride solution (3.6 L). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was cooled to 25−30 °C, MTBE (0.96 L) and THF (0.3 L) were added, and the mixture was stirred for 10 min. The resulting slurry was heated to 40 °C, mixed for 1 h, cooled to 10−15 °C, and stirred for additional 30 min. The resulting slurry was filtered to collect the solid, and the wet cake was washed with MTBE (0.3 L). The solid was dried under reduced pressure at 45−50 °C for 6 h to give 1.15 kg of 3-(benzyloxy)-4-hydroxybenzaldehyde (**7**) as a pale brown solid in 58% yield.[20] By following this lab scale procedure, a pilot scale batch of **7** (17.7 kg) was manufactured starting from 20.0 kg of 3,4-dihydroxybenzaldehyde (**13**) in 53% yield. Purity by HPLC: 98.5 area%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 1H), 9.74 (1 H), 7.50−7.31 (m, 7H), 7.01−6.99 (m, 1 H), 5.19 (s, 2 H); 4′-Regioisomer of **7** by GC: 0.08%, Loss on Drying: 0.4%.

Dibenzyl (2-(Benzyloxy)-4-formylphenyl)phosphate (15). To a solution of 3-(benzyloxy)-4-hydroxybenzaldehyde (**7**, 10.0 g, 43.8 mmol, 1.0 equiv) in acetonitrile (100 mL), tetrabenzyl pyrophosphate (**14**, TBPP, 24.8 g, 46.0 mmol, 1.05 equiv) was added at room temperature under nitrogen. The mixture was cooled to about 4 °C and treated with 1,8-diazabicyclo(5,4,0)undec-7-ene (DBU, 7.67 g, 50.4 mmol, 1.15 equiv). After the addition was complete, the reaction mixture was warmed to room temperature and mixed for 1 h. The mixture was quenched with water (400 mL) and extracted with MTBE (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (150 mL), water (150 mL), and saturated aqueous NaCl solution (150 mL). The organic phase was concentrated to afford 20.7 g of dibenzyl (2-(benzyloxy)-4-formylphenyl)phosphate (**15**) in 93% yield as a pale-yellow oil. By following this lab scale procedure, a pilot scale batch of **15** (49.1 kg) was manufactured starting from 25.6 kg of 3-(benzyloxy)-4-hydroxybenzaldehyde (**7**) in 89.6% yield. Purity by HPLC: 97.0 area%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 7.69 (dd, J = 1.8, 0.9 Hz, 1H), 7.56 (dd, J = 8.1, 1.8 Hz, 1H), 7.49−7.41 (m, 3H), 7.38−7.24 (m, 13H), 5.22 (s, 2H), 5.11 (dd, J = 8.2, 2.1 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 192.3, 150.6, 150.5, 144.5, 144.4, 136.5, 136.0, 135.9, 134.6, 129.0, 128.9, 128.9, 128.8, 128.6, 128.4, 128.3, 124.5, 124.5, 122.2, 122.2, 113.9, 70.8, 70.1, 70.0, 69.1, 69.0; ^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ −6.63; LC-MS (ESI) m/z: [M + H]$^+$ 489.0; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{26}O_6P$ 489.1467; found 489.1481.

Methyl (*Z*)-3-(3-(Benzyloxy)-4-((bis(benzyloxy)phosphoryl)-oxy)phenyl)-2-(((benzyloxy)carbon-yl)amino)acrylate (6). To a cooled solution of (±)-benzyloxycarbonyl-α-phosphonoglycine-trimethyl ester (**8**, 31.1 g, 94 mmol, 1.1 equiv) and dibenzyl (2-(benzyloxy)-4-formylphenyl)phosphate (**15**, 44.3 g, 85 mmol, 1.0 equiv) in dichloromethane (443 mL) was added 1,1,3,3-tetramethyl-guanidine (TMG, 11.78 g, 102 mmol, 1.2 equiv) at about 2 °C under nitrogen. The reaction mixture was allowed to warm to room temperature. After stirring overnight, the mixture was washed with water (3 × 222 mL), and the organic phase was concentrated to afford 68.9 g of crude product **6**. The residue was stirred with 40.5 g of silica gel 60 in 689 mL of ethyl acetate for 1 h and filtered to remove polar impurities. The filtrate was concentrated and suspended in MTBE (350 mL) at 4 °C and stirred for 1 h. The resulting slurry was filtered, and the wet cake was washed with cold MTBE. The solid was dried in the vacuum oven at 40 °C overnight to afford 50.4 g (85% yield) of enamine (**6**, *E*/*Z* Ratio: 10:1) as a white solid. By following this lab scale procedure, the pilot scale batch of enamine **6** (49.92 kg) was manufactured starting from 48.0 kg of phosphate ester **15** in 63.0% yield. Purity by HPLC: 98.0 area%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.0 (bs), 7.62 (t, J = 1.4 Hz, 1H), 7.50−7.18 (m, 23H), 5.25−5.02 (m, 8H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 166.1, 155.1, 149.7 (d, J_{CP} = 5.2 Hz), 140.4 (d, J_{CP} = 7.3 Hz), 137.1, 136.6, 136.1 (d, J_{CP} = 7.1 Hz), 131.61, 131.60 (d, J_{CP} = 1.7 Hz), 131.9, 131.63, 131.62, 128.90, 128.88, 128.8, 128.5, 128.39, 128.35, 128.2, 128.1, 126.3, 123.6 (d, J_{CP} = 1.6 Hz), 121.7 (d, J_{CP} = 3.0 Hz), 116.3, 70.6, 69.8 (d, J_{CP} = 5.9 Hz), 66.5, 60.2, 52.7; ^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6): δ −6.17; LC-MS (APCI) m/z: [M + H]$^+$ 694.2; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{39}H_{37}NO_9P$ 694.2206; found 694.2205.

Methyl (*S*)-2-Amino-3-(3-hydroxy-4-(phosphonooxy)-phenyl)propanoate (17). The enamine (**6**, E/Z Ratio: 10:1, 446.31 g, 521 mmol, 1.0 equiv) and 3.6 L of THF were charged to a 7.5 L reactor, and the solution was sparged with nitrogen. To another 7.5 L reactor, 1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene-(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate (**16**, 3.44 g, 5.21 mmol, 0.01 equiv) was charged, and the system was purged with nitrogen. THF (about 0.4 L) was charged, and the catalyst solution was sparged with nitrogen. To this catalyst solution, the THF solution of **6** was charged, and the reactor (including transfer lines) was purged with hydrogen. The reaction was stirred at 35 °C under 100 psig of hydrogen. After 20 h, HPLC revealed complete consumption of starting material **6**. The reaction mixture was transferred into a 12 L extractor, and 3.6 L of ethyl acetate were added. The solution was washed with aqueous 5 wt % cysteine/8 wt % $NaHCO_3$ solution (2 × 3.7 L) followed by 3.6 L of 5 wt % aqueous NaCl solution. The organic layer was separated and stirred overnight with 43.4 g of ENO-PC activated carbon at room temperature under nitrogen. The mixture was filtered, and the filtrate was concentrated to afford methyl (*S*)-3-(3-(benzyloxy)-4-((bis(benzyl-oxy)phosphoryl)oxy)phenyl)-2-(((benzyloxy)-carbonyl)-amino) propanoate (**5**, 420.1 g, 94% yield and >99.5% ee) as an oil, which was used directly in the next step.

To a 150 mL Parr hydrogenator were added 10 wt % (on a dry basis) of 5% Pd/C (1.33 g, catalyst contains 63.6% H_2O) and a 2.9 wt % aqueous $NaHCO_3$ solution (20.7 g). A portion of the above prepared (*S*)-amine **5** (5.70 g) was dissolved in THF (48.5 mL) and transferred to the reactor. The hydrogenator was pressurized with argon to 60 psig, and then the pressure was vented to 10 psig (× 6). In a similar fashion, the hydrogenator was then pressure purged with hydrogen (× 3) and a final fill of hydrogen to 50 psig followed by agitation at rt for at least 2 h. Following the completion of reaction as determined by HPLC, the mixture was filtered to remove the catalyst. The wet cake was rinsed with water (4.1 mL, 2 mL/g relative to theoretical yield of product). The biphasic reaction mixture was washed with MTBE (2 × 16 mL; discarded), and the aqueous layer was treated with 6 M HCl to adjust the pH to 1.8. To this slurry, *i*-PrOH (73 mL) was added to bring the final solvent composition to 3:1 *i*-PrOH/H_2O and stirring was continued overnight. The crystallization slurry was filtered, and the wet cake solids were washed with *i*-PrOH. The white solid was dried in the vacuum oven at 50 °C to afford 1.72 g of methyl (*S*)-2-amino-3-(3-hydroxy-4-(phosphono-oxy)phenyl)propanoate (**17**) in 85% yield and 98.7% ee. By following this lab procedure, a pilot scale batch of (*S*)-ester **17** (23.5 kg) was manufactured starting from 40.0 kg of enamine **6** in 74.3% yield for two steps. Purity by HPLC: 99.7 area%; Assay: 87.7% (w/w); Residual Solvents: 0.5% (w/w); Mp = 210.4 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ 7.23 (dd, J = 8.2, 1.3 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 6.78 (dd, J = 8.3, 2.2 Hz, 1H), 4.39 (dd, J = 7.9, 5.5 Hz, 1H), 3.85 (s, 3H), 3.28 (dd, J = 14.7, 5.5 Hz, 1H), 3.13 (dd, J = 14.6, 7.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ 170.0, 147.2 (d, J_{CP} = 5.5 Hz), 139.7 (d, J_{CP} = 6.6 Hz), 130.3 (d, J_{CP} = 1.6 Hz), 121.6 (d, J_{CP} = 7.5 Hz), 121.5 (d, J_{CP} = 3.3 Hz), 117.7 (d, J_{CP} = 0.8 Hz), 53.9, 53.5, 34.9; ^{31}P{^{1}H} NMR (162 MHz, D_2O) δ −2.95; LC-MS (ESI) m/z: [M + H]$^+$ 292.00. Anal. Calcd for $C_{10}H_{14}NO_7P$·1.0 HCl·1.0 H_2O: C, 34.93; H, 4.92; N, 4.07. Found: C, 34.93; H, 4.75; N, 4.21.

Foslevodopa (3). To a solution of (*S*)-methyl 2-amino-3-(3-hydroxy-4-(phosphonooxy)phenyl)-propanoate (**17**, 10.0 g, 34.3 mmol) in 40 mL of water was added 22.9 mL (4.0 equiv) of 6 N NaOH solution at 15−20 °C. When the pH reached 7−8, the solution was passed through a filter for clarification, and the remaining

https://doi.org/10.1021/acs.joc.1c00905
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NaOH solution was added. After the addition was complete, the reaction mixture was stirred at rt for 60 min (pH = 12.06). The mixture was acidified with 6 N HCl (137 mmol, 22.89 mL) to a final pH of 1.8. After 10 min, the reaction mixture became cloudy and 200 mL of *i*-PrOH were added. The resulting slurry was stirred for 30 min, and the solid was filtered and washed with *i*-PrOH. The wet cake was dried under vacuum at 40 °C overnight to afford foslevodopa [(*S*)-2-amino-3-(3-hydroxy-4-(phosphonooxy)phenyl)propanoic acid] (**3**. 7.85 g) in 87% yield. By following this procedure, a pilot scale batch of FLD drug substance (**3**, 29.3 kg) was manufactured starting from 39.9 kg of (*S*)-ester **17** in 77.3% yield. Chiral purity: 99.6% ee; Mp = 215.5 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ 7.23 (dd, J = 8.3, 1.3 Hz, 1H), 6.90 (dd, J = 2.3, 0.8 Hz, 1H), 6.82 (dd, J = 8.3, 2.2 Hz, 1H), 4.23 (dd, J = 8.3, 5.3 Hz, 1H), 3.28 (dd, J = 14.7, 5.2 Hz, 1H), 3.10 (dd, J = 14.6, 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ 171.9, 147.2, 139.5 (d, J_{CP} = 6.7 Hz), 130.9 (d, J_{CP} = 1.5 Hz), 121.56 (d, J_{CP} = 1.1 Hz), 121.53 (d, J_{CP} = 5.2 Hz), 117.8 (d, J_{CP} = 1.0 Hz), 54.4, 35.1; ^{31}P{^{1}H} NMR (162 MHz, D_2O): δ − 3.10; LC-MS (APCI) m/z: $[M + H]^+$ 278.04, $[M + H - H_2O]^+$ 260.10; Anal. Calcd for $C_9H_{12}NO_7P$·0.4 H_2O: C, 37.89; H, 4.56; N, 4.91. Found: C, 37.77; H, 4.29; N, 4.63.

3-(3-(Benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (18). A 500 mL three-neck round-bottom flask equipped with a thermocouple, stir bar, and reflux condenser was charged with 2-(benzyloxy)-4-bromophenol (**11**, 25.04 g, 89.71 mmol, 1.0 equiv), tris(dibenzylideneacetone) palladium (1.23 g, 1.34 mmol, 1.5 mol %), and tri-*tert*-butylphosphonium tetrafluoroborate (0.88 g, 3.02 mmol, 3.36 mol %). The flask was purged with nitrogen for 1 h. During this time, a second flask was charged with 1,4-dioxane (200.0 mL), 2-methylprop-2-en-1-ol (**12**, 6.95g, 8.30 mL, 96.34 mmol, 1.1 equiv), and *N*-cyclohexyl-*N*-methylcyclohexanamine (Cy_2NMe, 30.0 mL, 140 mmol, 1.55 equiv), and the solution was sparged with nitrogen for 1 h. The dioxane solution was transferred via cannula to the flask containing bromide **11**, palladium catalyst, and ligand, and the reaction mixture was heated at 100 °C for 1 h. The reaction mixture was cooled to 35 °C and diluted with ethyl acetate (250 mL) and 1.0 M HCl (250 mL). The biphasic mixture was stirred for 10 min, and the layers were separated. The organic phase was removed from the reactor, and the aqueous phase was returned. Ethyl acetate (150 mL) was added to the aqueous phase, and the mixture was agitated for 10 min. The aqueous layer was drained, and the combined organic phases were washed with a 5% *N*-acetylcysteine/8% $NaHCO_3$ mixture (250 g). The organic solution was filtered through Celite, and the solution containing 3-(3-(benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (**18**) was used directly in the next reaction. A small portion of this solution was dried to afford **18** as an off-white solid. By following this lab scale procedure, a pilot scale batch starting from 75.1 kg of 2-(benzyloxy)-4-bromophenol (**11**) was performed and the 3-(3-(benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (**18**) solution was directly used in the next step pilot scale batch. Residual Water by Karl Fischer: 3.3 wt %. Mp 45.0−47.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (d, J = 1.5 Hz, 1H), 8.79 (s, 1H), 7.47−7.39 (m, 2H), 7.38−7.22 (m, 3H), 6.80 (d, J = 2.1 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.55 (dd, J = 8.0, 2.0 Hz, 1H), 5.03 (s, 2H), 2.85 (dd, J = 13.7, 6.1 Hz, 1H), 2.64−2.53 (m, 1H), 2.41 (dd, J = 13.7, 8.0 Hz, 1H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 205.7, 146.8, 145.8, 137.8, 130.1, 128.7, 128.14, 128.09, 122.1, 116.1, 115.7, 70.4, 47.7, 35.9, 13.2; LC-MS (APCI) m/z: $[M + H - H_2O]^+$ 253.0. Anal. Calcd for $C_{17}H_{18}O_3$·0.15 H_2O: C, 74.79; H, 6.76. Found: C, 74.82; H, 6.68.

Sodium 3-(3-(Benzyloxy)-4-hydroxyphenyl)-1-hydroxy-2-methylpropane-1-sulfonate (19). To the solution of crude (3-(benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (**18**) prepared above sodium bisulfite (18.7 g, 179 mmol) was added, and the mixture was heated to 40 °C for 13 h. The resulting precipitate was filtered, and the solid was washed with ethyl acetate (3 × 100 mL) to give 36.0 g (64%) of sodium 3-(3-(benzyloxy)-4-hydroxyphenyl)-1-hydroxy-2-methylpropane-1-sulfonate (**19**) as a colorless solid as a 65:35 mixture of diastereomers (A and B), assigned based on ^{13}C NMR chemical shifts. (The relative stereochemistry of each diastereomer was not determined.) By following this lab scale procedure, the pilot scale batch was manufactured using the 3-(3-(benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (**18**) solution prepared from 75.1 kg of 2-(benzyloxy)-4-bromophenol (**11**), and 103.1 kg of adduct **19** was obtained in 64% yield. Potency: 60.0% by Q-NMR; Mp > 166 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ 7.50−7.34 (m, 5H; A/B), 6.92 (m, 1H; A/B), 6.86 (dd, J = 8.0, 4.0 Hz, 1H; A/B), 6.76 (dd, J = 8.0, 4.0 Hz, 1H; A/B), 5.20 (s, 0.67H; B), 5.19 (s, 1.33H; A), 4.29−4.24 (m, 1H; A/B), 3.11−3.05 (m, 0.33H; B), 2.70−2.62 (m, 0.67H; A), 2.54−2.46 (m, 0.67H; A), 2.40−2.24 (m, 1H; A/B), 2.24−2.12 (m, 0.33H; B), 0.95 (d, J = 8.0 Hz, 2H; A), 0.85 (d, J = 8.0 Hz, 1H; B); ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ 145.5, 145.3, 143.6, 143.5, 136.5, 133.1, 132.8, 128.7, 128.6, 128.3, 128.2, 128.1, 122.8, 122.7, 116.5, 116.1, 115.6, 115.5, 87.6, 85.7, 71.0, 70.9, 39.3, 37.1, 36.2, 36.0, 15.4, 12.3; LC-MS (APCI) m/z: $[M + H - SO_3Na - H_2O]$ 253.0. Anal. Calcd for $C_{17}H_{19}NaO_6S$·1.5 $NaHSO_3$: C, 38.49; H, 3.90. Found: C, 38.27; H, 3.50.

Dibenzyl (2-(Benzyloxy)-4-(2-methyl-3-oxopropyl)phenyl)-phosphate (10). A 500 mL three-neck round-bottom flask equipped with a thermocouple and an overhead stirrer was charged with sodium 3-(3-(benzyloxy)-4-hydroxyphenyl)-1-hydroxy-2-methylpropane-1-sulfonate solution (**19**, 15.1 g, 63.3 w/w%, 23.2 mol, 1.0 equiv), $NaHCO_3$ (16.97 g, 202 mmol, 8.70 equiv), water (155 mL), and ethyl acetate (140 mL). The resulting biphasic suspension was stirred vigorously at room temperature. After the complete consumption of starting material, the reaction was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with brine (75 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo* to provide 6.29 g of 3-(3-(benzyloxy)-4-hydroxyphenyl)-2-methylpropanal (**18**). This intermediate (**18**) was taken into a 250 mL three-neck flask, equipped with a thermocouple and an overhead stirrer, acetonitrile (63 mL) and tetrabenzyl pyrophosphate (**14**, 13.54 g, 24.38 mmol) were added, and the mixture was cooled to about 2 °C. To this mixture, DBU (4.55 mL, 30.2 mmol) was added dropwise, and the resulting solution was stirred for 1 h. The reaction was diluted with water (65 mL) and extracted twice with MTBE (130 mL). The combined organic layers were washed with water (65 mL), 5% NaCl solution (30 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo* to provide crude dibenzyl (2-(benzyloxy)-4-(2-methyl-3-oxopropyl)phenyl)phosphate (**10**, 11.38 g) in 92% yield as yellow oil. By following this lab scale procedure, a large pilot scale batch was manufactured starting from 97.3 kg of bisulfite adduct **19**, and dibenzyl (2-(benzyloxy)-4-(2-methyl-3-oxopropyl)phenyl)phosphate (**10**) was obtained as a solution in acetonitrile (HPLC assay: 22 wt % and 85.3% yield), which was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (d, J = 1.2 Hz, 1H), 7.43−7.38 (m, 2H), 7.34−7.19 (m, 13H), 7.14 (dd, J = 8.0, 1.2 Hz, 1H), 6.78 (dd, J = 2.0, 1.2 Hz, 1H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 5.08 (s, 2H), 5.06 (s, 2H), 5.03 (s, 2H), 3.02 (dd, J = 13.6, 5.6, Hz, 1H), 2.65−2.55 (m, 1H), 2.53 (dd, J = 13.6, 8.0 Hz, 1H), 1.06 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 204.1, 148.80, 149.75, 138.7, 136.9, 136.8, 136.4, 135.8, 135.7, 128.57, 128.55, 128.52, 128.50, 128.4, 128.1, 128.0, 127.81, 127.77, 121.59, 121.57, 115.22, 115.21, 71.0, 69.84, 69.78, 47.97, 47.96, 36.3, 13.3; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −5.88; LC-MS (APCI) m/z: $[M + H]^+$ 531.2. Anal. Calcd for $C_{31}H_{31}O_6P$·1.0 H_2O: C, 67.87; H, 6.06 Found: C, 67.68; H, 5.75.

Dibenzyl (*S*)-1-(1-(3-(Benzyloxy)-4-((bis(benzyloxy)-phosphoryl)oxy)phenyl)-2-methyl-3-oxo-propan-2-yl)-hydrazine-1,2-dicarboxylate (9). A 500 mL three-neck round-bottom flask equipped with a thermocouple were charged with (*R*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**20**, 0.15 g, 1.07 mmol, 4.97 mol %), acetonitrile (40 mL), and trifluoroacetic acid (0.084 mL, 1.07 mmol) at room temperature under nitrogen. To this mixture was added (*E*)-dibenzyl diazene-1,2-dicarboxylate (8.25 g, 27.7 mmol, 1.29 equiv) followed by a solution of dibenzyl (2-(benzyloxy)-4-(2-methyl-3-oxopropyl)phenyl) phosphate (**10**, 11.4 g, 21.49 mmol, 1.0 equiv) in acetonitrile (70 mL) added via cannula. The resulting solution was stirred at room temperature for 15 h. After the complete consumption of starting material, the reaction mixture was diluted with acetonitrile (88 mL), and water (58 mL) was added to precipitate the product;

https://doi.org/10.1021/acs.joc.1c00905
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the resulting slurry was stirred overnight at room temperature. The solid was collected by filtration, and the wet cake was washed with 28 wt % water in acetonitrile (30 mL) to provide dibenzyl (*S*)-1-(1-(3-(benzyloxy)-4-((bis(benzyloxy)-phosphoryl)oxy)phenyl)-2-methyl-3-oxopropan-2-yl)hydrazine-1,2-dicarboxylate (**9**, 8.9 g, 50% yield, >99% ee) as a white solid. By following this lab scale procedure, a large pilot scale batch was manufactured by using the acetonitrile solution of dibenzyl (2-(benzyloxy)-4-(2-methyl-3-oxopropyl)phenyl) phosphate (**10**, HPLC assay: 22 wt %) and 63.0 kg of (*S*)-hydrazine (**9**) was obtained in 29.2% overall yield for two steps. Mp: 114.0−114.6 °C; $[\alpha]_D^{23}$ −71.7° (c, 1.0; $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 9.55 (s, 1H), 7.46−7.22 (m, 25H), 7.11−6.95 (m, 2H), 6.76−6.67 (m, 1H), 5.27−4.96 (m, 10H), 3.20−2.87 (m, 2H), 1.14−0.98 (br s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 198.7, 157.5, 149.43, 149.38, 138.5, 138.4, 137.0, 136.7, 136.6, 136.2, 136.1, 128.87, 128.86, 128.81, 128.79, 128.78, 128.54, 128.46, 128.4, 128.3, 128.23, 128.21, 128.17, 128.16, 128.1, 123.5, 121.1, 117.3, 70.5, 70.4, 69.67, 69.65, 69.64, 69.61, 69.59, 67.02, 66.95; ^{31}P{^{1}H} NMR (162 MHz, DMSO-d_6) δ −5.98, −6.04 (2.6:1.0 mixture of rotamers); LC-MS (ESI negative mode) m/z: $[M - H]^-$ 827.0. Anal. Calcd for $C_{47}H_{45}N_2O_{10}P{\cdot}3.3\ H_2O$: C, 63.55; H, 5.85; N, 3.15. Found: C, 63.34; H, 5.61; N, 3.22.

(*S*)-3-(3-(Benzyloxy)-4-((bis(benzyloxy)phosphoryl)oxy)-phenyl)-2-(1,2-bis((benzyloxy)carbon-yl)-hydrazinyl)-2-methylpropanoic Acid (21). A 100 mL three-neck round-bottom flask equipped with a thermocouple was charged with dibenzyl (*S*)-1-(1-(3-(benzyloxy)-4-((bis(benzyloxy)-phosphoryl)oxy)phenyl)-2-methyl-3-oxopropan-2-yl)hydrazine-1,2-dicarboxylate (**9**, 5.10 g, 6.15 mmol, 1.0 equiv), acetonitrile (50 mL), and dimethyl sulfoxide (DMSO, 1.00 mL, 14.1 mmol, 2.29 equiv) under nitrogen. The white suspension was stirred, and a mixture of water (2.0 mL) and sodium dihydrogen phosphate monohydrate (1.78 g, 12.90 mmol, 2.09 equiv) was added to the reaction. Following this addition, a solution of sodium chlorite (2.88 g (80 wt %), 25.5 mmol, 4.15 equiv) in water (2.0 mL) was added dropwise. The resulting cloudy reaction turned yellow and became clearer as the reaction proceeded. After 90 min, the reaction was quenched with a solution of sodium sulfite (1.60 g, 12.7 mmol) in water (6.0 mL). The reaction was stirred for 20 min and transferred into a separatory funnel with isopropyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (70 mL) and concentrated to a volume of about 10 mL. The reaction flask was held at 2−8 °C for 16 h. The solid that formed was collected, washed with 20 mL of isopropyl acetate, and dried *in vacuo* to give 3.92 g of (*S*)-acid (**21**) in 75% yield as white solid. By following this lab scale procedure, a large pilot scale batch was manufactured by using dibenzyl (S)-1-(1-(3-(benzyloxy)-4-((bis(benzyloxy)-phosphoryl)oxy)phenyl)-2-methyl-3-oxopropan-2-yl)hydrazine-1,2-dicarboxylate (**9**, 49.0 kg) and 42.8 kg of (*S*)-acid (**21**) was obtained in 85.7% yield. Mp 120.3 °C−120.9 °C; $[\alpha]_D^{23}$ −84.5° (*c*, 1.0; $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43−7.21 (m, 25H), 7.11−6.90 (m, 2H), 6.80−6.64 (m, 1H), 5.18−4.99 (m, 10H), 3.28−2.92 (m, 2H), 1.26 (br s, 3 H); ^{13}C{^{1}H} NMR (175 MHz, DMSO-d_6): δ 175.8, 160.2, 159.8, 158.2, 157.7, 152.1, 152.0, 151.9, 141.5, 141.4, 141.3, 141.2, 139.8, 139.7, 139.5, 139.0, 138.96, 138.94, 138.92, 136.8, 131.7, 131.63, 131.61, 131.59, 131.58, 131.53, 131.3, 131.17, 131.15, 131.1, 131.0, 130.98, 130.97, 130.96, 130.8, 130.5, 126.4, 126.0, 123.8, 123.6, 120.3, 119.9, 73.3, 73.2, 72.43, 72.42, 72.40, 72.39, 72.37, 70.4, 70.2, 69.9, 69.3, 24.8; LC-MS (ESI) m/z: $[M + H]^+$ 845.1, $[M + NH_4]^+$ 862.0. Anal. Calcd for $C_{47}H_{45}N_2O_{11}P{\cdot}0.9\ H_2O$: C, 65.56; H, 5.48; N, 3.25. Found: C, 65.57; H, 5.42; N, 3.11.

Foscarbidopa (4). A 3.7 L Parr reactor was charged with 5 wt % (dry basis) of 5% Pd/C (63.6% H_2O, 15.0 g), water (182 mL), and 5 wt % aqueous $NaHCO_3$ (215 mL). To this catalyst slurry was added a THF solution (1090 mL) of (*S*)-acid **21** (109 g, 129.1 mmol, 1.0 equiv, Potency: 85%), and the reactor was purged with nitrogen followed by hydrogen. The reactor was then repressurized to 30 psig with hydrogen and agitated at room temperature for 1 h. Upon completion of the reaction, hydrogen was vented, and the reactor was purged with nitrogen. The biphasic reaction mixture was filtered to remove the catalyst, followed by rinsing with water (93 mL). The biphasic filtrate was diluted with MTBE (370 mL) and stirred for 10 min. The layers were separated (organic discarded), and the aqueous layer was washed with MTBE (370 mL) in portions. The pH of the aqueous layer was adjusted with 6 M HCl to 1.9, followed by seeding with 0.1 wt % of foscarbidopa (**4**) to induce nucleation. Isopropanol (1326 mL) was added to the slurry and mixed for 5 h at room temperature. The slurry was filtered, and the wet cake was washed with isopropanol (370 mL) followed by air-drying on the funnel for 2 h to provide 38.5 g (97%) of foscarbidopa (**4**, (*S*)-2-hydrazinyl-3-(3-hydroxy-4-(phosphonooxy)phenyl)-2-methylpropanoic acid) as a trihydrate and white solid. By following this lab scale procedure, a pilot scale batch was manufactured starting with 40.0 kg of (*S*)-acid (**21**), and 14.3 kg of FCD (**4**) were obtained in 86% yield as the trihydrate. Purity by HPLC: 99.7 area%; Assay: 99.6 wt %; ee > 99.9%; Mp 167.2 °C (dec); ^{1}H NMR (400 MHz, D_2O): δ 7.21 (d, J = 8.0 Hz), 6.84 (d, J = 2.0 Hz, 1H), 6.77 (dd, J = 8.0, 2.0 Hz, 1H), 3.18 (d, J = 16.0 Hz, 1H), 3.00 (d, J = 16.0 Hz, 1H), 1.53 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ 175.1, 146.8 (d, J_{CP} = 5.2 Hz), 139.5 (d, J_{CP} = 6.7 Hz), 130.4 (d, J_{CP} = 1.2 Hz), 122.3 (d, J_{CP} = 1.5 Hz), 121.2 (d, J_{CP} = 3.0 Hz), 118.5, 66.3, 41.3, 18.9; ^{31}P{^{1}H} NMR (162 MHz, D_2O): δ −3.13; LC-MS (APCI) m/z: $[M + H]^+$ 307.1. Anal. Calcd for $C_{10}H_{15}N_2O_7P{\cdot}3.2\ H_2O$: C, 33.01; H, 5.93; N, 7.70. Found: C, 33.38; H, 5.68; N, 7.33.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00905.

Copies of NMR spectra, HPLC and MS data descriptions (PDF)

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Notes

The authors declare the following competing financial interest(s): AbbVie sponsored and funded the study, contributed to the design, participated in collection, analysis, and interpretation of data, as well as in writing, reviewing, and approval of the final publication. A.D.H., J.S., R.C.K., M.A.M., V.S.C., J.S., D.R.H., R.E.R., T.B.T., J.R.B., B.J.K., B.C.D., J.J., E.V., and M.S. are, or were, employees of AbbVie and may own AbbVie stock. V.S.C. is currently an employee of Merck and had no additional conflicts to disclose. S.B., A.A., and S.G. are employees of Anthem Biosciences and have no additional conflicts to disclose.

■ ACKNOWLEDGMENTS

The authors wish to acknowledge and thank Jeffrey Bien (AbbVie, Process R&D) for excellent support in procuring materials and valuable suggestions.

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https://doi.org/10.1021/acs.joc.1c00905
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