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Development of a Scalable Synthesis of Oxadiazole Based $S1P_1$ Receptor Agonists

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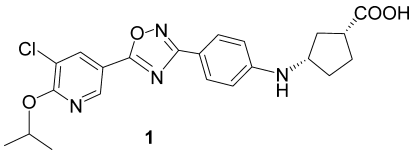
ABSTRACT: A robust and scalable synthesis was developed for the preparation of oxadiazole based $S1P_1$ inhibitors. A new method for the separation of triphenylphosphine oxide from reaction products and an improved method for the synthesis of oxadiazoles in the presence of DBU were incorporated into the process to achieve its scalability.

INTRODUCTION

Compounds targeting $S1P_1$ receptor have been actively pursued as a promising therapy for the treatment of multiple sclerosis.[1] One of these compounds—Gilenia (fingolimod)—has already achieved a marketed drug status.[2] Still more work is ongoing to identify follow-up candidates with improved safety profile.

In this manuscript we report a robust and scalable synthesis of two promising oxadiazole based $S1P_1$ agonists **1** and **2** which was developed to support their clinical evaluation.



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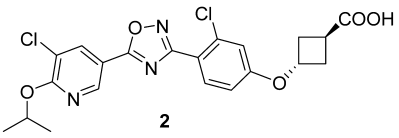


2

As shown in Scheme 1, we have envisioned that both compounds **1** and **2** could be synthesized in a convergent manner by combining nicotinic acid derivative **3** and respective amidoximes **4** or **5** with the formation of the oxadiazole core. Preparation of intermediates **4** and **5** could be accomplished via SN_{Ar} type arylation of fluoronitriles **6** or **8** with amino acid **7** or hydroxyester **9**, respectively.

Development of a robust process based on Scheme 1 chemistry is reported in the following parts of this manuscript with more detailed discussion focused on an improved synthesis of oxadiazoles and a new method for nonchromatographic separation of triphenylphosphine oxide from the process intermediates.

RESULTS AND DISCUSSION

Process Development for Compound 1. Scheme 2 outlines the process which was developed for the preparation of oxadiazole derivative **1**.

First, amidoxime **4** was prepared utilizing a three step sequence which included arylation of the available *R,S*-aminocyclopentanecarboxylic acid **7** with fluorobenzonitrile **6**, protection of the carboxylic acid functionality in **10** as ethyl ester, and hydroxylamine addition to the nitrile group in **11**. This process gave amidoxime **4** in 70% overall yield. Then, chloro(isopropoxy)nicotinic acid **3** was prepared according to a literature procedure[3] in 72% overall yield.

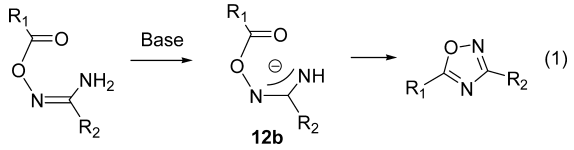
Combining building blocks **3** and **4** into the oxadiazole core was evaluated next. It should be noted that oxadiazole formation from amidoxime and carboxylic acid requires three chemical steps (acid activation, coupling, and cyclization, as shown in Scheme 3); however, the process is typically conducted in "one-pot" where a preformed activated acid is heated with amidoxime.[4]

Application of this protocol to acid **3**, which was activated with HOBT/EDAC reagent, and amidoxime **4** resulted (after heating in DMF at 100−110 °C) in the formation of numerous degradation products and low yield of desired **12** (~30%).

As it was previously reported that water—a byproduct from the condensation step (see Scheme 3)—could cleave the acylamidoxime intermediate, the reaction was repeated in the presence of molecular sieves[5] providing, however, only marginal yield improvement.

We felt that further optimization of oxadiazole **12** synthesis would require a separate evaluation of each reaction step shown in Scheme 3. First, we found that activation of acid **3** with either HOBT/EDAC or carbonyldiimidazole (CDI) provided highly reactive species capable of acylating amidoxime **4** in quantitative yield. The resulting acylamidoxime intermediate **12a** was then isolated and subjected to various cyclization conditions. Under thermal conditions (100−150 °C) oxadiazole **12** was produced in low yield due to the formation of previously observed degradation products.

As an alternative to the thermal process we decided to evaluate a base induced cyclization of **12a**, as the literature reported that strong bases, such as sodium hydride, could promote cyclization of acylamidoximes even at ambient temperature.[6] A different reaction mechanism which included the formation of reactive anion **12b** was proposed to explain the accelerated oxadiazole formation under the basic conditions, as shown in eq 1.[6]



12b (1)

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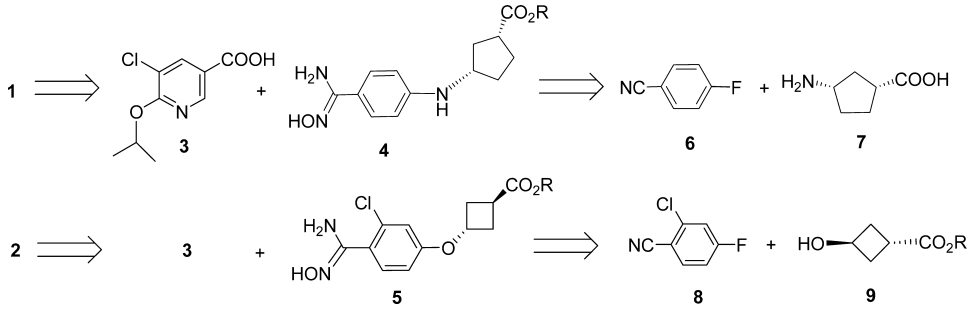
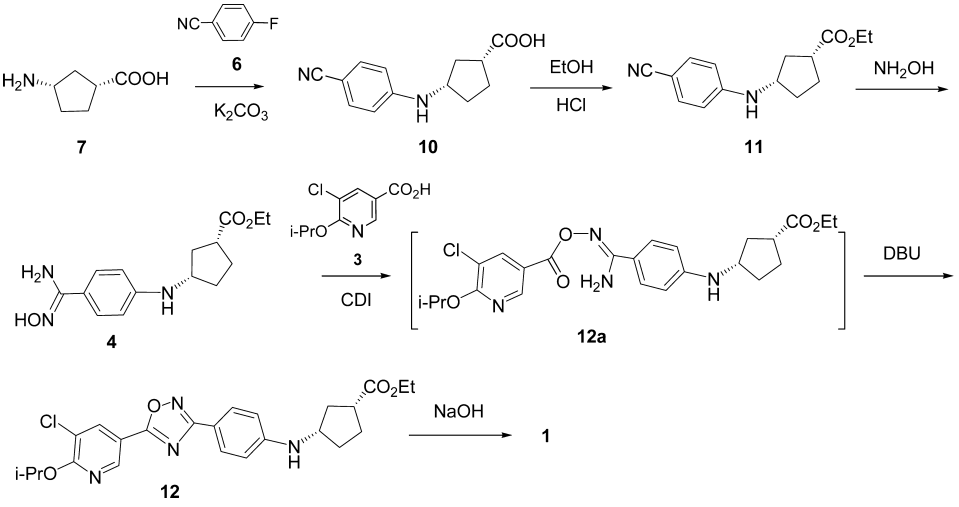
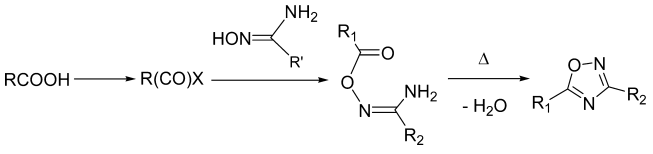
Scheme 1. Retrosynthetic Route to Compounds 1 and 2



Scheme 2. Synthesis of Oxadiazole Derivative 1



Scheme 3. General Synthesis of Oxadiazoles



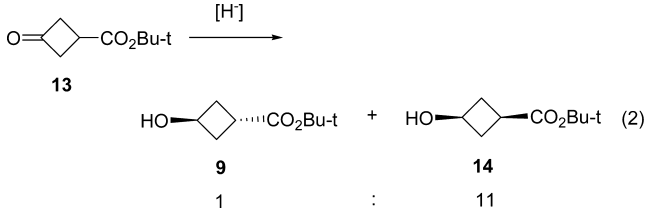
In an effort to identify a base suitable for the cyclization of intermediate **12a** we evaluated a series of amines as the reaction promoters. No oxadiazole formation from **12a** was observed in the presence of triethylamine or diisopropylethylamine after 1 h at 60 °C in THF. However, addition of a stronger base—DBU or TMG—provided remarkable reaction acceleration resulting in complete conversion of **12a** into the oxadiazole.[7]

Importantly, the formation of degradation related side-products was eliminated under the base induced cyclization conditions enabling isolation of high purity oxadizole **12** via a simple precipitation with water. As we found a solution to the problematic cyclization step, applicability of the new conditions to one-pot process was evaluated next. After some additional optimization we developed a highly efficient protocol for one-pot preparation of **12** which combined CDI induced activation[8] of acid **3**, acylation of amidoxime **4**, and DBU promoted cyclization of intermediate **12a**. Under the new conditions penultimate **12** was isolated in better than 90% yield (see Experimental section for additional details).

It was then found that subsequent hydrolysis of ester **12** (Scheme 2) under the standard conditions (sodium hydroxide in aqueous ethanol) was accompanied by epimerization of the stereocenter adjacent to the carboxyl group resulting in formation of the corresponding diastereomer of **1** (2.5%). While optimizing this reaction we noticed that the extent of epimerization depended on the type of the alcohol cosolvent. The highest level of the diastereomer (~6.0%) was observed when the reaction was conducted in aqueous methanol. At the same time, hydrolysis in *tert*-butanol resulted in no epimer formation. To explain this data we suggested that the degree of epimerization correlated with the concentration of highly basic sodium alkoxide in the system: as sodium *tert*-butoxide was practically nonexistent in the sodium hydroxide-water-*tert*-butanol mixture, no formation of the diastereomer was observed under these conditions.

Careful pH adjustment of the reaction mixture upon hydrolysis completion resulted in precipitation of compound **1** which was isolated in 89% yield. Overall, the synthesis of **1** from starting materials **3** and **7** was accomplished in 5 steps and 52% yield.

Process Development for Compound 2. Initially we thought that alcohol **9**—the starting material for the synthesis of amidoxime **5** (Scheme 1)—could be prepared via stereoselective reduction of the available ketoester **13**,[9] as shown in eq 2.



Unfortunately, regardless of variations in the reaction conditions or in the nature of the reducing agent (borohydrides,

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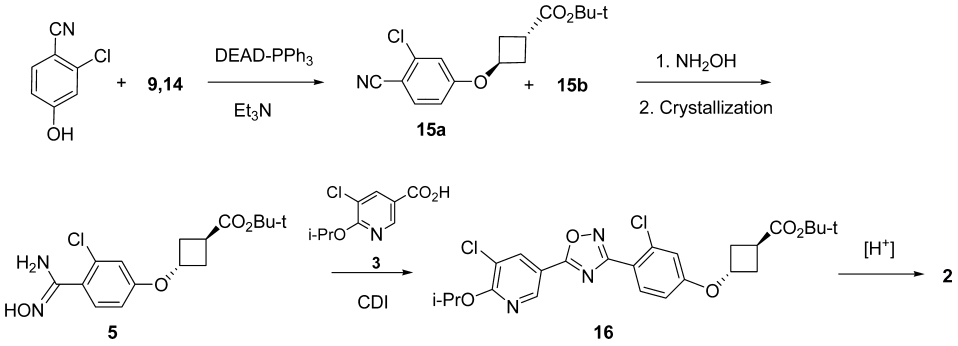
Scheme 4. Modified Synthetic Route to Compound 2



aminoboranes, etc.) we were able to obtain only mixtures of the corresponding *cis*- and *trans*-alcohols, where *cis*-isomer **14** was the major component (eq 2). The highest (~11:1) selectivity was achieved in the reduction of **13** with sodium borohydride in methanol.

Preferential formation of *cis*-isomer **14** required adjustment of our synthetic strategy. As shown in Scheme 4, it was decided to utilize Mitsunobu type epimerization to enable conversion of the major *cis*-isomer **14** into the desired nitrile **15a** with *trans*-configuration. We were also hoping that impurities originating from the minor hydroxyester **9** could be rejected via crystallization of one of the later stage intermediates.

As expected, under Mitsunobu reaction conditions (THF, 50 °C) a mixture of alcohols **9** and **14** was converted into nitriles **15a,b** in 11:1 *trans*-/*cis*- ratio and in good yield (80−85% by assay).

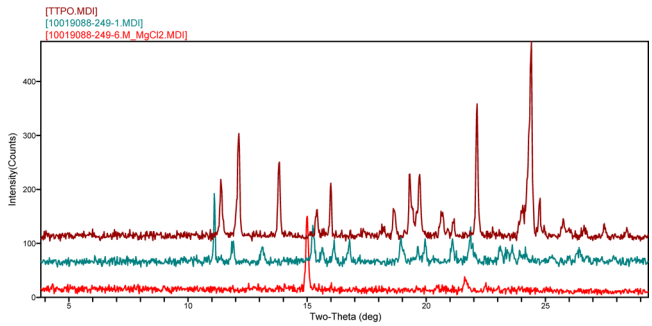
At the initial stage of process development separation of compounds **15a,b** from triphenylphosphine oxide (TPPO) byproduct could only be accomplished by chromatographic methods. However, we felt that development of a nonchromatographic method for the removal of TPPO from the Mitsunobu reaction mixture was necessary to achieve the process scalability.

The difficulty of TPPO separation from the Mitsunobu reaction products is a well-known complication that undermines utility of this important transformation. As a solution, polymer bound[10] and water-soluble[11] derivatives of triphenylphosphine were introduced into synthetic practice and successfully utilized in small scale preparations. However, large scale application of these reagents did not seem practical due to their cost and availability. Instead, we decided to evaluate a possibility of TPPO precipitation from the reaction mixture via a complex formation. The literature observation that TPPO could form stable complexes with some metal halides, in particular, magnesium chloride, was very encouraging.[12] Indeed, we found that addition of magnesium chloride to our Mitsunobu reaction mixture resulted in 20−30% reduction of TPPO concentration in the supernatant. However, it soon became clear that a better understanding of the complex properties was needed to improve the efficiency of TPPO removal. We thought that solvent could play a significant role in this process affecting the complex solubility. This was confirmed when we observed that magnesium chloride treatment resulted in better than 95% TPPO removal from its toluene solution, but only ~50% from dichloromethane (see Table 1 for additional details).

We were intrigued whether low efficiency in dichloromethane was due to the increased complex solubility or because of its dissociation in this solvent. To find the answer a dichloromethane solution, obtained after treatment of TPPO with excess

Table 1. Solvent Dependence of TPPO Removal Efficiency

solvent	dichloromethane	THF	toluene
TPPO removed (%)	45	80	>95
Complex Solubility (mg/mL)	57	5.2	2.1



a) TPPO – top, TPPO-$MgCl_2$ – middle, $MgCl_2$ - bottom

Figure 1. XRD diffraction patterns for TPPO, magnesium chloride, and TPPO-$MgCl_2$ Complex.

magnesium chloride, was concentrated and the precipitate was analyzed by XRD, NMR, and ICP methods.

The XRD confirmed the formation of a unique compound for which the diffraction pattern was different from either magnesium chloride or TPPO (see Figure 1). ^{1}H NMR of the complex showed a slight downshift of aromatic hydrogens vs TPPO reference, and ICP data for phosphorus and magnesium corresponded to 1:1 TPPO to magnesium chloride ratio (see Experimental section).

The isolated TPPO-$MgCl_2$ complex was then used to determine its solubility in the solvents commonly used in Mitsunobu reaction. The data from Table 1 show good correlation between the solubility and efficiency of TPPO removal, with toluene being the best solvent.

Taking into account that the rate of Mitsunobu reaction was reported to increase in nonpolar solvents,[13] and that reduced DEAD—another reaction byproduct—is also insoluble in toluene, the formation of compounds **15a,b** was reevaluated in this solvent. Under the optimized conditions the reaction went to completion in 20 h at 25−30 °C. After that, magnesium chloride (2 equiv) was added and the mixture was heated to 50−60 °C for 1−2 h. HPLC analysis of the supernatant indicated >95% reduction in TPPO concentration. While evaluating scalability of this process we noticed that the efficiency of TPPO removal was reduced when the magnetic stirring bar was replaced with an overhead stirrer, indicating that maintaining clean surface area of magnesium chloride was important for the complex formation. We have then found that with overhead mixing the desired level

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of TPPO removal could be reproducibly achieved either utilizing freshly milled magnesium chloride or by repeating the procedure twice with commercially available powder (325 mesh).

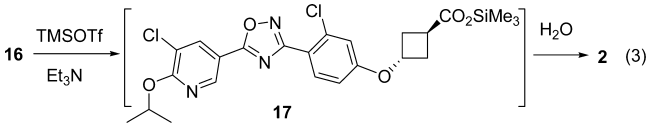
A toluene solution of **15a**,**b** which was obtained after filtration of excess magnesium chloride, TPPO complex, and reduced DEAD was suitable for use in the subsequent oximation step. Alternatively, a mixture of **15a** and **15b** could be isolated in 81% yield via crystallization from aqueous isopropanol. This crystallization also resulted in the reduction of undesired isomer **15b** from 8% to 4−6% level.[14]

Purified nitriles **15a**,**b** were then reacted with hydroxylamine to give the corresponding amidoximes. We were pleased to find that at this stage desired *trans*-amidoxime **5** could be isolated in better than 99% purity via efficient crystallization (see Experimental section).

Oxadiazole formation from acid **3** and amidoxime **5** was very efficient when conducted under the improved conditions reported above for the preparation of compound **1** and provided oxadiazole derivative **16** in 92% yield.

We were hoping that hydrolysis of penultimate intermediate **16** to the API (**2**) would proceed smoothly as the utilization of *tert*-butyl protection group (which could be removed under acidic conditions) obviated the epimerization issue observed during the preparation of compound **1**. However, it turned out that acidic hydrolysis of the ester group in **16** was accompanied by competitive cleavage of the isopropyl group in the pyridine fragment (4−90% depending on the reaction conditions).

We were able to completely suppress the ether cleavage only after neutral hydrolysis conditions employing (trimethylsilyl)-triflate-triethylamine reagent[15] were identified. This reaction initially results in the formation of intermediate silyl ester **17** which is then hydrolyzed with water to regenerate the acid (eq 3). During the silyl ester cleavage acid **2** directly precipitated from the reaction mixture and was isolated in an impressive 99% yield.



Overall, the synthesis of **2** from starting materials **3** and **13** was accomplished in 5 steps and 66% yield.

CONCLUSIONS

A robust and scalable synthesis was developed for the preparation of oxadiazole based $S1P_1$ inhibitors **1** and **2**. The process incorporates a new method for the separation of triphenylphosphine oxide from reaction products and an improved method for synthesis of oxadiazoles in the presence of DBU.

EXPERIMENTAL SECTION

General. HPLC conditions for reaction monitoring and intermediate purity control: Column Agilent Eclipse XDB-C18, 150 mm. Flow rate 1.5 mL/min, A = 0.1% perchloric acid, B = ACN. Gradient: 80% A to 100% B over 10 min, then 100% B for 5 min. UV detection at 205 nm.

All purity data are reported as wt% vs reference material.

*(1R,3S)-3-(4-Cyanophenylamino)cyclopentanecarboxylic acid (**10**).* A mixture of amino acid **7** (80 g, 0.62 mol), fluorobenzonitrile **6** (80 g, 0.66 mol), and potassium carbonate (milled ∼300 mesh, 171 g, 1.24 mol) in DMSO (500 mL) and water (10 mL) was heated to 105 °C with vigorous agitation until the reaction was complete (<10% of **6** by HPLC, typically 16−20 h). The reaction mixture was cooled to ambient temperature and diluted with MTBE (400 mL) and water (800 mL). The aqueous layer was separated, cooled to 10 °C, and pH was adjusted to 4−5 with conc. HCl. Precipitated product was filtered, washed with water (1 L), then with 1:2 ethanol−water (1 L) and dried under vacuum at 55 °C to yield **10** (118 g, 82%, 98% purity). ^{1}H NMR (DMSO-d_6): 1.50 (1H), 1.60 (1H), 1.84 (2H), 1.96 (1H), 2.30 (1H), 2.74 (1H), 3.77 (1H), 6.60 (2H), 6.72 (1H), 7.41 (2H), 12.08 (1H). ^{13}C NMR (DMSO-d_6): 27.3, 31.8, 35.7, 41.7, 53.0, 95.4, 112.1, 120.7, 133.3, 151.8, 176.6.

*Ethyl (1R,3S)-3-(4-cyanophenylamino)cyclopentanecarboxylate (**11**).* Hydrogen chloride (33g, 0.91 mol) was gassed into ethanol (800 mL) at <20 °C. The solution was then transferred onto the acid **10** (100 g, 0.43 mol) and the resulting solution was mixed until the reaction was complete (<1% s.m. by HPLC, typically 2 h). The reaction mixture was cooled to ∼10 °C and triethylamine was added to achieve pH 7−8. The product was then precipitated by addition of water (1 L). The product was filtered, washed with water (500 mL) ,and dried at 55 °C under vacuum to yield **11** (103 g, 91%, 99% purity). ^{1}H NMR (DMSO-d_6): 1.15 (3H), 1.51 (1H), 1.63 (1H), 1.86 (2H), 1.97 (1H), 2.30 (1H), 2.81 (1H), 3.77 (1H), 4.04 (2H), 6.60 (2H), 6.71 (1H), 7.41 (2H). ^{13}C NMR (DMSO-d_6): 14.2, 27.2, 31.7, 35.6, 41.5, 52.8, 59.8, 95.1, 111.7, 120.1, 132.7, 151.1, 174.2.

*Ethyl (1R,3S)-3-[4-(N′-hydroxycarbamimidoyl)phenylamino]cyclopentanecarboxyl-ate (**4**).* Hydroxylamine (50% in water, 55.0 g, 0.83 mol) was added to a solution of nitrile **11** (50 g, 0.19 mol) in DMSO (250 mL) at <20 °C. The solution was slowly heated to 50 °C and mixed at this temperature until the reaction was complete (<5% s.m. by HPLC, typically 6 h). Then the reaction mixture was cooled to ∼20 °C and transferred into a mixture of water (500 mL) and ethyl acetate (500 mL). The organic layer was separated and the aqueous was re-extracted with ethyl acetate (250 mL). Combined organic layers were filtered through a "FilterAid" cartridge to remove insoluble material and concentrated in vacuo. The residue was then chase-distilled with acetonitrile to ∼200 mL volume. The resulting solution of **4** was directly used in the following coupling step. Assay yield of **4** for this step was 52 g (94%). For the isolated **4**: ^{1}H NMR (DMSO-d_6): 1.16 (3H), 1.51 (1H), 1.60 (1H), 1.86 (2H), 1.97 (1H), 2.30 (1H), 2.81 (1H), 3.74 (1H), 4.04 (2H), 5.51 (2H), 5.82 (1H), 6.50 (2H), 7.36 (2H), 9.17 (1H). ^{13}C NMR (DMSO-d_6) 14.2, 27.2, 31.9, 36.0, 41.6, 53.2, 59.8, 111.1, 119.9, 125.7 148.4, 150.6, 174.4.

*Ethyl (1R,3S)-3-[4-{N′-(5-chloroisopropoxynicotinoyloxy)-hydroxycarbamimido-yl}phenylamino]cyclopentanecarboxylate (**12a**).* Nicotinic acid **3** (56 g, 0.26 mol) was slurried in acetonitrile (110 mL). In a separate vessel CDI (40g, 0.25 mol) was slurried in acetonitrile (400 mL). The CDI slurry was then transferred to the nicotinic acid slurry over 10−15 min to control evolution of carbon dioxide. The vessel used to prepare CDI slurry was rinsed with acetonitrile (40 mL) and the wash was transferred into the reaction mixture. After 0.5 h a solution of amidoxime **4** (70.0 g, 0.24 mol) in acetonitrile (200 mL) was added to the activated acid solution over 20−30 min. The mixing was continued until the reaction was complete (<3% s.m. by HPLC, typically 30 min). The product was then precipitated by addition of water (650 mL). The product was filtered, washed with water (150 mL), and dried under vacuum at no more than

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40 °C to yield **12a** (100 g, 85% for two steps: oximation and coupling, 99% purity). ^{1}H NMR (DMSO-d_6): 1.16 (3H), 1.36 (6H), 1.51 (1H), 1.60 (1H), 1.86 (2H), 1.96 (1H), 2.30 (1H), 2.82 (1H), 3.78 (1H), 4.04 (2H), 5.40 (1H), 6.10 (1H), 6.57 (2H), 6.72 (2H), 7.48 (2H), 8.54 (1H), 8.84 (1H). ^{13}C NMR (DMSO-d_6): 14.2, 21.7, 27.2, 31.9, 35.9, 41.6, 53.1, 59.8, 70.3, 111.1, 116.7, 117.2, 119.5, 127.3, 138.4, 146.7, 149.7, 156.5, 159.8, 160.8, 174.4.

*Ethyl (1R,3S)-3-[4-{5-(5-chloro-6-isopropoxypyridin-3-yl)-1,2,4-oxadiazol-3-yl}phenylamino]cyclopentanecarboxylate (**12**).* DBU (43.5 g, 0.28 mol) was charged to a mixture of **12a** (70 g, 0.14 mol) in THF (1 L). The solution was heated to 60 °C and mixed at this temperature until the reaction was complete (<2% s.m. by HPLC, typically 3 h). The reaction mixture was cooled to ∼20 °C and pH adjusted to 8−9 with aq. HCl (27 g conc. HCl in 1 L water). The precipitated product was filtered, washed with 1:2 THF−Water (300 mL), and dried under vacuum at 50 °C to yield **12** (61.7 g, 92% yield, 99.4% purity). ^{1}H NMR (DMSO-d_6): 1.16 (3H), 1.38 (6H), 1.51 (1H), 1.60 (1H), 1.88 (2H), 1.98 (1H), 2.33 (1H), 2.84 (1H), 3.81 (1H), 4.04 (2H), 5.43 (1H), 6.41 (1H), 6.68 (2H), 7.77 (2H), 8.47 (1H), 8.85 (1H). ^{13}C NMR ($CDCl_3$): 14.0, 21.7, 27.9, 32.4, 36.2, 42.0, 54.2, 60.6, 70.8, 112.00, 112.8, 114.6, 114.7, 118.9, 128.7, 136.8, 144.9, 149.4, 161.0, 168.7, 172.1, 176.7.

*(1R,3S)-3-[4-{5-(5-Chloro-6-isopropoxypyridin-3-yl)-1,2,4-oxadiazol-3-yl}phenylamino]cyclopentanecarboxylic acid (**1**).* A solution of sodium hydroxide (15 g, 0.37 mol) in water (220 mL) was charged to a slurry of **12** (44 g, 93 mmol) in THF (400 mL) and *tert*-butanol (130 mL). The solution was mixed at 20 °C until the reaction was complete (<0.5% s.m. by HPLC, typically 20−22 h). The reaction mixture was cooled to ∼10 °C and pH adjusted to 8−10 with conc. HCl. The mixture was concentrated in vacuo to ∼270 mL volume and chased with ethanol to ∼270 mL volume. The mixture was then diluted with ethanol (880 mL) and heated to 45 °C. Careful pH adjustment to 5−6 with 6 N HCl resulted in product precipitation. Agitation was continued at 50 °C for 1 h, then the internal temperature was slowly adjusted to 15 °C. The product was filtered off and washed with 1:1 ethanol−water, then with water. The product was dried under vacuum initially at 55 °C, then at 80 °C until the ethanol was reduced to less than 0.5 wt % to yield **1** (37 g, 89% yield, 99.7% purity). ^{1}H NMR (DMSO-d_6): 1.38 (6H), 1.52 (1H), 1.60 (1H), 1.86 (2H), 1.98 (1H), 2.31 (1H), 2.75 (1H), 3.76 (1H), 5.43 (1H), 6.45 (1H), 6.68 (2H), 7.76 (2H), 8.48 (1H), 8.85 (1H), 12.15 (1H). ^{13}C NMR (DMSO-d_6): 21.6, 27.2, 31.9, 35.9, 41.7, 53.2, 70.8, 112.00, 112.06, 114.6, 118.0, 128.4, 137.2, 145.2, 151.1, 160.4, 168.3, 171.8, 176.8.

*tert-Butyl 3-hydroxycyclobutanecarboxylate (mixture of cis- and trans-isomers **14**, **9**).* Ketone **13** (213 g, 1.25 mol) was diluted with THF (150 mL) and slowly added to a suspension of sodium borohydride (22 g, 0.58 mol) in THF−Methanol (10:1, 1.2 L) at <10 °C. Mixing was continued at this temperature until the reaction was complete (<2% s.m. by GC, typically 1 h). The reaction mixture was diluted with MTBE (1.9 L) followed by addition of potassium carbonate solution (20% in water; 1 L). The aqueous layer was separated and the organic was washed with monobasic potassium phosphate solution (10% in water, 1 L). The aqueous layer was separated and the organic was diluted with toluene (1 L). Additional aqueous layer was formed and separated. The mixture was concentrated in vacuo. The residue was chased with toluene to ∼0.5 L volume. The resulting solution of alcohols **9**, **14** was assayed and directly used in the following Mitsunobu step. The assay yield was 213 g (99%) for a 92:8 mixture of **14**:**9**. ^{1}H NMR was consistent with literature data.[16]

*tert-Butyl trans-3-(3-chloro-4-cyanophenoxy)cyclobutanecarboxylate (**15**).* A mixture of alcohols **9**, **14** (∼50% solution in toluene, 200 g, 0.58 mol), 2-chloro-4-hydroxynebzonitrile (84.5 g, 0.55 mol), and triphenylphosphine (175 g, 0.67 mol) in toluene (700 mL) was cooled to 0−5 °C and diethylazadicarboxilate (DEAD, 40% solution in toluene, 300 g, 0.69 mol) was added at <25 °C. The reaction mixture was then heated to 25−30 °C until the reaction was complete (<5% s.m. by HPLC, typically 20 h). Then magnesium chloride (325 mesh powder, 130 g, 1.34 mol) was charged and the mixture was heated to 60 °C. The mixture was diluted with heptanes (700 mL) and heating was continued until TPPO concentration in the supernatant was reduced below 5% versus original value (typically 2 h). The mixture was cooled to ambient temperature and filtered to remove the solids. The filter cake was washed with toluene−heptanes (700 mL) and the combined filtrate was concentrated in vacuo and chased with IPA to approximately 450 mL volume. The mixture was diluted with IPA to approximately 600 mL volume and cooled to below 10 °C. As product precipitation was observed the mixture was further diluted with 2:1 IPA−water (1.5 L) to precipitate the remaining product. The product was filtered, washed with IPA-water, and dried under vacuum at 50 °C to yield **15** (145 g, 81%). The material contains 4−5% of cis-isomer **15b**. ^{1}H NMR ($CDCl_3$): 1.48 (9H), 2.43 (2H), 2.68 (2H), 3.08 (1H), 4.90 (1H), 6.75 (1H), 6.88 (1H), 7.54 (1H). ^{13}C NMR ($CDCl_3$): 28.3, 33.2, 33.3, 71.0, 80.8, 104.9, 113.9, 116.0, 116.2, 134.7, 137.9, 160.6, 174.0.

*tert-Butyl trans-3-[3-chloro-4-(-N′-hydroxycarbamimidoyl)phenoxy]cyclobutane-carboxylate (**5**).* Hydroxylamine (50% in water, 58 g, 0.88 mol) was added to a solution of nitrile **15** (67.5 g, 0.22 mol) in DMSO (400 mL). The solution was slowly heated to 50 °C and mixed at this temperature until the reaction was complete (<1% s.m. by HPLC, typically 15 h). The reaction mixture was cooled to 20 °C and diluted with ethanol (250 mL) and water (350 mL) to precipitate the product. The mixture was agitated until the product concentration in the supernatant was reduced to less than 5 mg/mL. The product was filtered off and washed with ethanol−water (1:1.5). The product was dried under vacuum 50 °C until the residual water by Karl Fisher test was below 0.5%. The yield of amidoxime **5** was 67 g (90%, 99% purity, *cis*-isomer impurity <1%). ^{1}H NMR (DMSO-d_6): 1.43 (9H), 2.32 (2H), 2.62 (2H), 3.05 (1H), 4.85 (1H), 5.72 (2H), 6.80 (1H), 6.87 (1H), 7.28 (1H), 9.37 (1H). ^{13}C NMR (DMSO-d_6): 27.7, 32.29, 32.33, 70.0, 80.0, 113.3, 115.6, 126.3, 132.0, 133.0, 150.3, 157.4, 174.1.

*tert-Butyl trans-3-[3-chloro-4{5-(5-chloro-6-isopropoxypyridin-3-yl)-1,2,4-oxadiazol-3-yl}phenoxy]cyclobutanecarboxylate (**16**).* CDI (25 g, 154 mmol) was dissolved in acetonitrile (450 mL). The CDI solution in then transferred into a reactor containing nicotinic acid **3** (33 g, 154 mmol) over 5−10 min to control the carbon dioxide evolution. The vessel used to prepare the CDI solution was rinsed with acetonitrile (50 mL) and the rinse was added to the reaction mixture. After 0.5 h the solution of imidazolide was transferred into a reactor containing amidoxime **5** (50 g, 147 mmol). The mixture was agitated at ambient temperature until the acylation reaction was complete (<5% of **5** by HPLC, typically 30 min). Then DBU (44.7 g, 293 mmol) was added and the mixture was heated to 70 °C until the cyclization was complete (<2% of acyl amidoxime intermediate by HPLC, typically 1 h). The product precipitated upon cooling the mixture to 20 °C. It was then filtered, washed

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with 1:1 acetonitrile−water (200 mL), and dried under vacuum at 50 °C to yield oxadiazole **16** (70.4 g, 92%, 100% purity). ^{1}H NMR ($CDCl_3$): 1.44 (6H), 1.49 (9H), 2.45 (2H), 2.72 (2H), 3.09 (1H), 4.93 (1H), 5.47 (1H), 6.82 (1H), 6.92 (1H), 7.84 (1H), 8.36 (1H), 8.84 (1H). ^{13}C NMR ($CDCl_3$): 22.1, 28.3, 33.3, 33.4, 70.6, 71.2, 80.7, 113.6, 114.2, 117.0, 118.0, 119.0, 132.5, 134.2, 136.6, 144.9, 159.0, 160.9, 166.9, 171.7, 174.3.

*trans-3-[3-Chloro-4{5-(5-chloro-6-isopropoxypyridin-3-yl)-1,2,4-oxadiazol-3-yl}phenoxy]cyclobutanecarboxylic acid (**2**).* Triethylamine (11.6 g, 115 mmol) was added to a mixture of *tert*-butyl ester (**16**, 34.4 g, 66 mmol) in ethyl acetate (340 mL). Then trimethylsilyl triflate (24.0 g, 108 mmol) was added over 30 min The reaction mixture was heated to 70 °C and mixed at this temperature until the reaction was complete (<0.5% s.m. by HPLC, typically 2 h). The reaction mixture was cooled to 20 °C and water (34 g, 1.9 mol) was added. The batch was then concentrated under vacuum to ∼100 mL volume. A mixture of acetonitrile−water (1:2, 120 mL) was added and the batch was concentrated again to ∼100 mL volume. The residue was diluted with acetonitrile−water (1:2, 600 mL) and the slurry was mixed until the product concentration in the supernatant dropped to less than 0.5 mg/mL. The product was filtered and the cake was washed with acetonitrile−water (1:2, 120 mL). The product was dried under vacuum at 60 °C until the residual water was reduced to less than 0.5% (by Karl Fisher test) to yield **2** (15.2 g, 99%, 99.7% purity). ^{1}H NMR (THF-d_8): 1.42 (6H), 2.45 (2H), 2.75 (2H), 3.12 (1H), 4.98 (1H), 5.48 (1H), 6.91 (1H), 7.02 (1H), 7.97 (1H), 8.44 (1H), 8.85 (1H), 10.95 (1H). ^{13}C NMR (THF-d_8): 22.3, 32.7, 34.0, 71.6, 71.9, 80.7, 114.4, 115.5, 117.8, 119.1, 119.6, 133.3, 134.8, 137.5, 145.7, 160.2, 161.7, 167.7, 172.5, 175.9.

Preparation of Triphenylphosphine Oxide (TPPO)−Magnesium Chloride Complex. TPPO (2.0 g, 7.2 mmol) was dissolved in dichloromethane (20 mL) and magnesium chloride (1.37 g, 2 equiv) was added. Mixing was continued for 5 h at room temperature. The slurry was filtered and the filtrate was concentrated to ∼1/2 volume. The resulting solid was filtered off and dried at 50 °C in vacuo to 0.96 g (36%) of white solid. ^{1}H NMR ($CDCl_3$): 7.40 (m, 6H), 7.53 (m, 3H), 7.64 (m, 6H). ICP for Mg and P was consistent with 1:1 TPPO−$MgCl_2$ ratio.

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Notes

The authors declare no competing financial interest.

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