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Practical and Scalable Synthesis of S1P$_1$ Receptor Agonist ACT-209905

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Supporting Information

ABSTRACT: A practical and scalable route for the fast delivery of 12 kg of S1P$_1$ agonist (ACT-209905) has been developed. ACT-209905 is composed of an amino pyridine group, an oxadiazole spacer, a 2-ethyl-5-methylphenol moiety and a chiral 1-amino-2-propanol side chain. The convergent synthesis consists of 16 steps with 9 isolated intermediates and is chromatography-free. Key building blocks are accessed from low-cost starting materials, such as acetone, diethyl oxalate, cyanoacetamide, and 2-ethyl-5-methyl aniline. A Negishi coupling that was troubled by the use of metal reagents and concomitant metal waste streams has been replaced by a less expensive Guareschi–Thorpe reaction to build up an amino isonicotinic acid. The chiral 1-amino-2-propanol moiety was secured by selective ring-opening of an epoxide with lithium hexamethyldisilazide as an ammonia surrogate, thus omitting the notorious double alkylated byproduct.

INTRODUCTION

The chiral amino pyridine derivative **1** (**ACT-209905**) is a S1P$_1$ receptor agonist with immunomodulating properties that could be of use in autoimmune diseases (Figure 1).[1,2] There was a need for a robust, safe, and scalable synthesis to enable a fast and reliable production of kilogram quantities of the active pharmaceutical ingredient (API) **1** for additional studies. This article deals with three major aspects that had to be addressed for a quick delivery of the requested amounts of **1**: (1) discussion of two alternative routes to synthesize amino isonicotinic acid **6** via a Guareschi–Thorpe reaction; (2) a new and inexpensive route for the preparation of hydroxy-benzamidine **11**, employing a high-yielding hydrolysis of a diazonium salt; and (3) improvements on the last stages to the API **1** circumventing serious issues for scale-up.

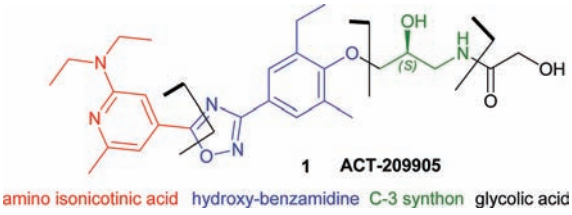

Figure 1. API **1** and retrosynthetic bond breaks revealing the key building blocks.

MEDICINAL CHEMISTRY ROUTE

The Medicinal Chemistry route required 12 stages, depicted in Schemes 1 to 3. Amino isonicotinic acid **6** was prepared in four steps starting from dichloro isonicotinic acid **2** (Scheme 1). Esterification of **2** with *N*,*N*-dimethylformamide di-*tert*-butylacetal produced ester **3**.[3] The first chloride was exchanged by diethylamine at 100 °C in an autoclave, while the second chloride was replaced by a methyl group employing a Negishi coupling. Finally, the *tert*-butylester **5** was cleaved under acidic conditions to form **6**. We intended to avoid the Negishi reaction, because of handling pyrophoric, expensive dimethyl zinc.[4]

Hydroxy-benzamidine **11** (Scheme 2) was constructed from 2-ethyl-6-methylphenol **7** that delivered benzaldehyde **8** via the Duff reaction,[5] followed by a Beckmann rearrangement to give amide **9**. Dehydration with diphosgene created nitrile **10** that was further elaborated with hydroxylamine to form the hydroxy-benzamidine **11**. Although this protocol was demonstrated on 15 g scale and a scalable route might have been easily developed, this path was abandoned due to the high cost of starting material **7**.[6] Hence, an alternative route was required as well for **11**.

The API **1** was assembled in four steps (Scheme 3). Building blocks **6** and **11** were coupled using (benzotriazol-1-yloxy)-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP) as coupling reagent. The intermediate underwent a thermal ring-closure reaction to oxadiazole **12**. Phenol **12** was alkylated with (*R*)-glycidol in a Mitsunobu reaction to yield **13**. Epoxide **13** was opened with excess NH_3 in MeOH at 65 °C in an autoclave to afford aminopropanol **14**. Finally, glycolic acid was coupled again with the help of PyBOP onto the free amino group to complete the polar side chain and the API **1**. The Mitsunobu reaction and the use of PyBOP was a concern in this sequence due to workup issues.

RESULTS AND DISCUSSION

Amino Isonicotinic Acid 6. We first focused on the process research and scale-up of the two key precursors **6** and **11**. In contrast to the original method for the construction of building block **6** we intended to introduce the diethylamino moiety to a 6-methyl isonicotinic acid derivative that could be conceivably derived from the Guareschi–Thorpe reaction.[7,8] Introduction of the diethyl amino moiety by refluxing

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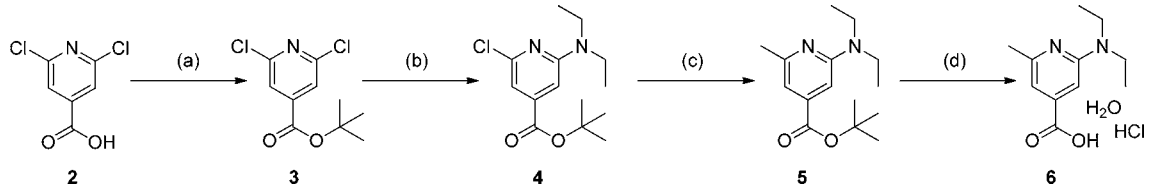
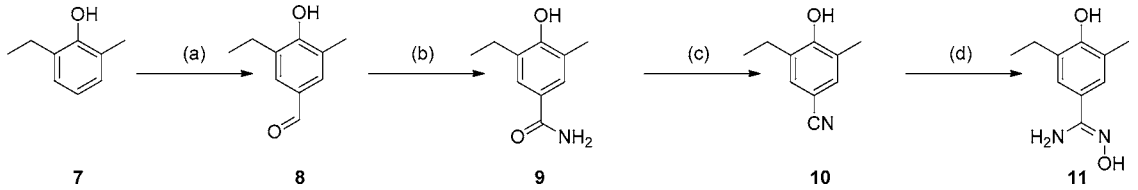
Scheme 1. [a]Route used by Medicinal Chemistry (amino isonicotinic acid 6)



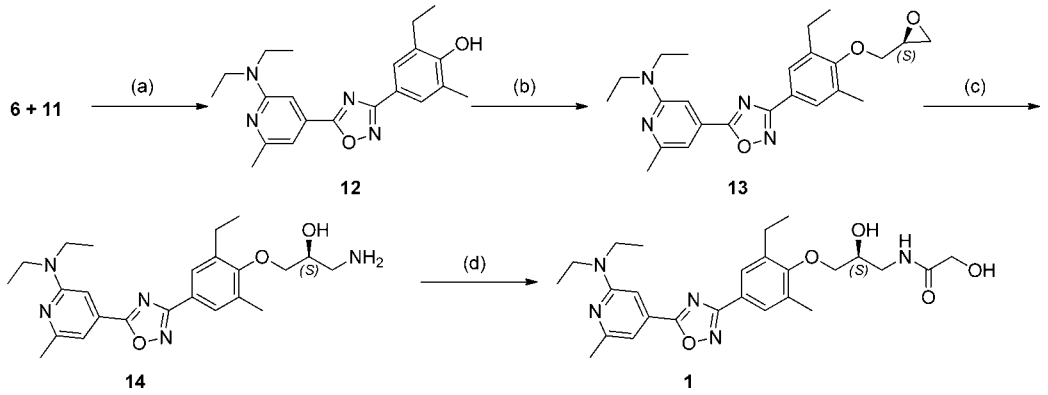
[a]Reagents and conditions: (a) **2** (1 equiv), *N,N*-dimethlyformamide di-*tert*-butylacetal (3.6 equiv), toluene, reflux, 93%; (b) diethylamine (1 equiv), 100 °C, autoclave, 103%; (c) dimethyl zinc in toluene (3 equiv), Pd(dppf) (0.01 equiv), dioxane, 75 °C, 41%; (d) 25% HCl, 80 °C, 97%.

Scheme 2. [a] Route used by Medicinal Chemistry (hydroxy-benzamidine 11)



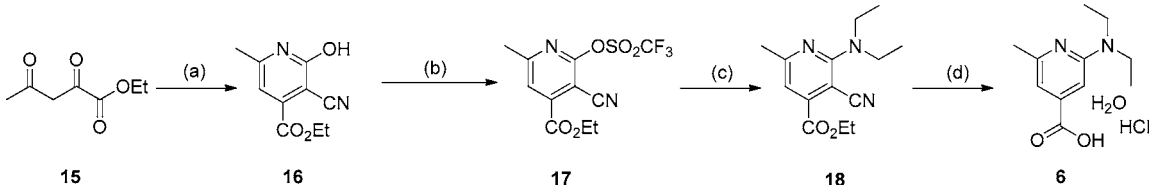
[a]Reagents and conditions: (a) **7** (1 equiv), hexamethylene tetramine (1 equiv), AcOH, H_2O, reflux, 80%; (b) $NH_2OH{\cdot}HCl$ (1.2 equiv), pyridine (1.8 equiv), MeOH, EtOH, reflux, 73%; (c) diphosgene (1.1 equiv), acetonitrile (ACN), reflux, 92%; (d) $NH_2OH{\cdot}HCl$ (2 equiv), $NaHCO_3$, MeOH, 60 °C, 105%.

Scheme 3. [a] Route used by Medicinal Chemistry (API 1)



[a]Reagents and conditions: (a) i) **6** (1 equiv), **11** (1 equiv), PyBOP (1.5 equiv), *N,N*-diisopropylethylamine (DIPEA), dichloromethane (DCM); ii) dioxane, reflux, 70% (two steps); (b) (*R*)-glycidol (1.2 equiv), PPh_3 (1.2 equiv), 40% diethyl azodicarboxylate (DEAD) in toluene (1.2 equiv), THF, 113%; (c) 7 N NH_3 in MeOH, 65 °C, autoclave, 53%; (d) glycolic acid (1.2 equiv), DIPEA (3 equiv), PyBOP (1.3 equiv), DCM, 95%.

Scheme 4. [a] Proof-of-concept of the Guareschi–Thorpe approach



[a]Reagents and conditions: (a) **15** (1 equiv), cyanoacetamide (1 equiv), diethylamine (0.32 equiv) EtOH, 60 °C, 66%; (b) $(CF_3SO_2)_2O$ (1.1 equiv), pyridine (1.2 equiv), DCM, 0 °C, 93%; (c) diethylamine (2 equiv), DMSO, 40 °C, 99%; (d) 32% HCl, reflux, 75%.

commercially available 2-chloro-6-methyl isonicotinic ester in diethylamine or employing Buchwald–Hartwig conditions gave no conversion.[9] Since the 2-chloro-6-methyl isonicotinic ester was not reactive enough, we turned to 3-cyano-2-*O*-tosyl, -trifluoromethylsulfonyl or -mesyl isonicotinic ester derivatives. The required substrate ethyl 3-cyano-2-hydroxy-6-methylisonicotinate **16** was obtained from condensation of acetopyruvate **15** with cyanoacetamide following literature protocols (Scheme 4).[10] The triflate **17** was prepared and subsequently treated with diethylamine in DMSO to cleanly yield **18**.[11] Hydrolysis and decarboxylation in refluxing concentrated aq HCl provided amino isonicotinic acid **6**. While the triflate **17** was a good substrate for the amination, the corresponding mesylate or tosylate reacted with diethylamine to give a mixture of product **18** and starting material **16** due to sulfur–oxygen bond scission.[12]

With this positive result in hand, we checked the practicability of this sequence on larger scale. Although

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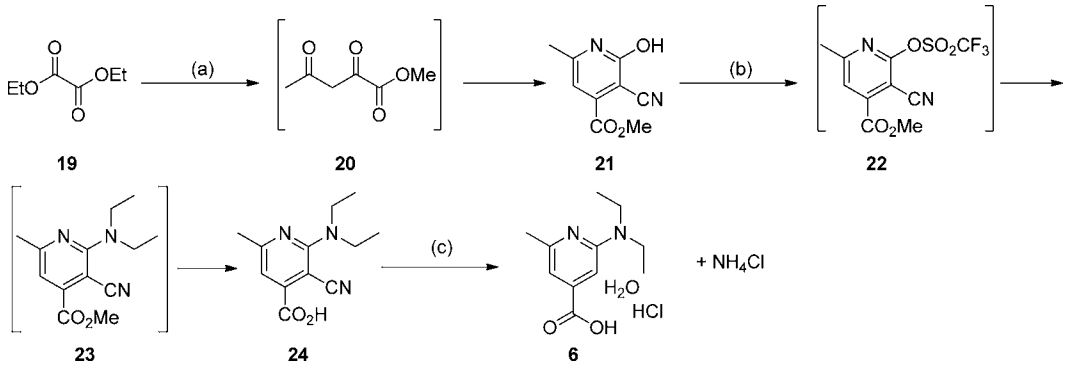
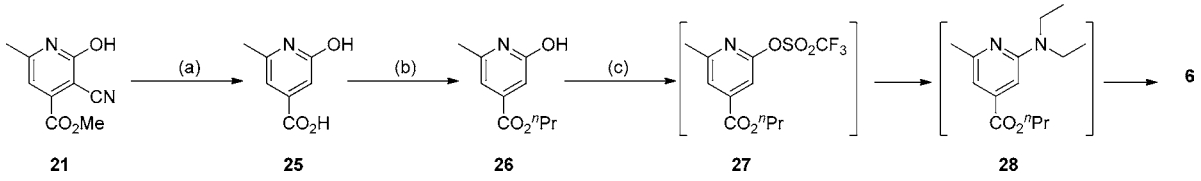
Scheme 5. [a] **First approach for the synthesis of amino isonicotinic acid 6**



[a]Reagents and conditions: (a) i) **19** (1 equiv), acetone (1 equiv), 5.4 M NaOMe (1 equiv), MeOH, 60 °C, ii) cyanoacetamide (1 equiv), 60 °C, iii) HOAc, 60 °C, 50%; (b) i) $(CF_3SO_2)_2O$ (1.1 equiv), pyridine (1.2 equiv), DCM, 0 °C, ii) diethylamine (4 equiv), 45 °C, iii) 30% NaOH, 80 °C, 92%; (c) 25% HCl, reflux, 2 d, 76%.

Scheme 6. [a] **Second approach for the synthesis of amino isonicotinic acid 6**



[a]Reagents and conditions: (a) 25% HCl, reflux, 15 h, 98%; (b) 1-propanol, H_2SO_4 (1.1 equiv), reflux, 91%; (c) i) $(CF_3SO_2)_2O$ (1.1 equiv), pyridine (1.1 equiv), DCM, 0 °C, ii) diethylamine (10 equiv), DMSO, 50 °C, iii) 25% HCl, reflux, 4 h, 87% (three steps).

acetopyruvate **15** was available for an acceptable price at this scale, the delivery time prompted us to prepare this starting material ourselves and introduce the product directly into the Guareschi–Thorpe reaction (see ref 10).[13] A protocol on 5 mol scale by Marvel et al. consists of the condensation of acetone and diethyloxalate **19** in the presence of equimolar amounts of NaOEt in EtOH.[14] This recipe proved difficult to scale because the intermediate suspension of the Na salt of **15** was difficult to stir. Marvel et al. recommended to prepare the *methyl* acetopyruvate **20** according to Freri, thus omitting this problem.[15] Indeed, the methyl ester was synthesized without issues in moderate yield (50%), when diethyl oxalate was reacted with acetone in MeOH and NaOMe (Scheme 5).[16] Since the Guareschi–Thorpe reaction required reaction conditions similar to those of the synthesis of pyruvate **20**, both steps could be easily combined. In practice, a solution of **19** and acetone was added to NaOMe in MeOH at 60 °C, followed by consecutive addition of cyanoacetamide and HOAc at 60 °C, leading to a reactive crystallization of **21** that was easily isolated by filtration. The product was isolated with excellent purity (96% a/a, LC–MS) in 50% yield. The water from the condensation was probably leading to saponification of **20** or **21**. Because all reagents are low-priced, this moderate yield seemed acceptable. Formation of triflate **22**, addition of diethylamine at 45 °C to form the amino isonicotinic ester **23**, and saponification with aqueous NaOH provided the acid **24** in an excellent yield of 92%. Isonicotinic acid **6** was generated by refluxing **24** in 25% HCl for two days. The desired acid **6** was isolated as a brownish solid after removal of most of the solvent and addition of acetone. The ^1H NMR spectrum of **6** recorded in d_6-DMSO showed a signal at 7.2 ppm, indicating the presence of NH_4Cl, stemming from nitrile hydrolysis prior to decarboxylation. Rework by dissolving contaminated **6** in 1-propanol at elevated temperatures, filtration of NH_4Cl, and workup of the mother liquor was tedious. Reaction of contaminated **6** with **11** in the coupling step showed that NH_4Cl was not interfering.

Although this route delivered **6** in good yield by operationally simple protocols, we had to improve the quality of amino isonicotinic acid **6**. A more efficient approach was desired. In order to obtain salt-free **6**, the reaction sequence was altered (Scheme 6): removal of the nitrile group was performed prior to amination. After the Guareschi–Thorpe product **21** was refluxed in 25% HCl for 15 h, isonicontinic acid **25** was isolated in a yield of 98% and high purity. The acid **25** had to be protected as an ester. Methyl or ethyl esters were not suitable because of their low solubility in organic solvents. The *n*-propyl ester **26** was soluble in DCM and was our preferred option. The esterification was performed in 1-propanol with 1.1 equiv of H_2SO_4 at reflux. Removal of solvent, aqueous workup, and crystallization from TBME afforded ester **26** in 91% yield. Formation of the triflate **27** in DCM with pyridine, aqueous workup, and solvent switch to DMSO prepared the solution for the next stage. Replacement of the triflate with diethylamine was not as simple as for the first approach. Triflate **27** was less reactive than the corresponding **22** bearing the nitrile group. The reaction required a polar solvent like DMSO, a large excess of diethylamine (10 equiv), a reaction temperature of 50 °C, and a longer reaction time of 15 h. We also observed that higher reaction temperatures were not appropriate, because more starting material **26** was generated due to the attack of diethylamine at the sulfur of the CF_3SO_2 group.[12] However, these conditions gave *n*- propyl amino isonicotinate **28** in a clean reaction. The workup was designed to remove the excess of diethylamine and to carry the intermediate to the final stage without isolation. Diethylamine was removed by distillation and aqueous extraction at pH 6. A solvent switch from TBME to conc. HCl telescoped to the final stage. Refluxing propylester

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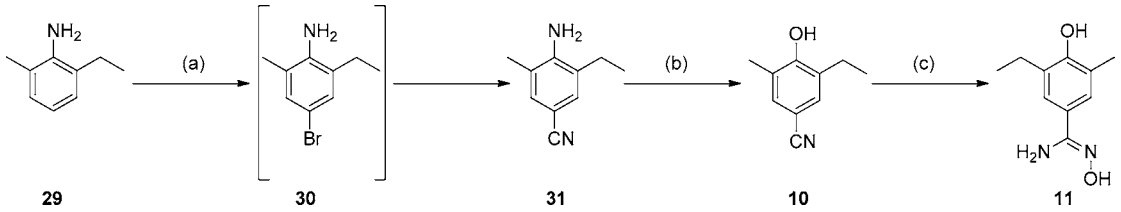
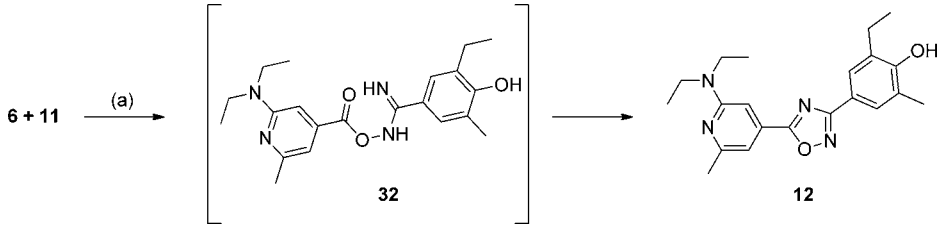
Scheme 7. [a] **Route used for the preparation of multigram and kilogram quantities of hydroxy-benzamidine 11**



[a]Reagents and conditions: (a) i) **29** (1 equiv), Br_2 (1.05 equiv), DCM, 0−20 °C, ii) NaCN (1.3 equiv), KI (0.2 equiv), Cu(I) (0.15 equiv), *N,N′*-dimethylethylenediamine 85% w/w (1.4 equiv) toluene, reflux, 67%; (b) 30% aq H_2SO_4, $NaNO_2$ (1.2 equiv), ACN, 53 °C, 81%; (c) $NH_2OH{\cdot}HCl$ (2.5 equiv), Et_3N (2.5 equiv), MeOH, reflux, 75%.

Scheme 8. [a] **Coupling of 6 and 11 and subsequent oxadiazole formation**



[a]Reagents and conditions: (a) i) **6** (1 equiv), **11** (1.2 equiv), DCC (1.1 equiv), $HOBt{\cdot}H_2O$ (0.1 equiv), Et_3N (1 equiv), THF, 0 °C; ii) reflux, 24 h, 73%.

28 in 25% HCl for two to four h generated amino isonicotinic acid **6**. Since the product was very soluble in water, it was necessary to concentrate the reaction mixture to approx 50% of its volume. On cooling to 50 °C the product started to crystallize. Acetone (10 vol.) was added to enhance the yield, and **6** was isolated in high yield (87%) and purity (100% a/a, LC−MS) over three steps.

A process to prepare building block **6** in excellent quality and good yield was found. The downside of the new sequence was the addition of two steps: the protection of the isonicotinic acid as an *n*-propyl ester and deprotection at the end of the sequence. The more facile decarboxylation step being completed in 20 h was beneficial, though. However, the introduction of the diethylamine moiety was less efficient, requiring more reagent, longer reaction time, and a narrow reaction temperature window. The overall yields for both approaches were similar (35% for the first, 39% for the second approach). The second approach was scaled up to 500 g, and later to 17 kg at an external supplier without issues.

Hydroxy-benzamidine 11. Since 2-ethyl-6-methylphenol **7** was too expensive for scale-up, we were looking for an inexpensive raw material for the construction of phenol **11** with the specific 2-ethyl-5-methyl substitution pattern. A viable commercially available precursor is 2-ethyl-6-methylaniline **29**, which could be further elaborated to the desired benzamidine **11** (Scheme 7). Aniline **29** is the starting material for the production of herbicide (*S*)-metolachlor.[17] The nitrile group was introduced in two steps. First, **29** was brominated in a high-yielding and operationally simple step with bromine in DCM. As neat **30** displayed an onset temperature of an exothermic decomposition (DSC) of 124 °C (−441 J/g), a telescoping strategy was mandated without isolation of **30**. A solvent switch from DCM to toluene was carried out. The nitrile group was installed following a protocol by Buchwald et al., who reported a Cu(I)-catalyzed domino halide-cyanation reaction using the system NaCN, catalytic CuI, and *N,N′*-dimethylethylene diamine as ligand.[18] Nitrile **31** was purified by crystallization from toluene to yield a grey solid with excellent purity (99% a/a, LC−MS). The envisioned hydrolytic decomposition of the diazonium salt derived from aniline **31** posed safety risks: the freshly prepared solution of the diazonium salt displayed a left limit of 26 °C with an exothermic decomposition of −92 J/g in the differential scanning calorimetry (DSC); major hazards of diazonium salts arise from their inherent instability and the release of one equivalent of nitrogen gas. Indeed, the aqueous diazonium salt solution was labile already at 0−4 °C. A classical transfer from one cooled reactor to a hot acid solution in a second reactor was therefore not considered. Instead, an in situ hydrolysis process was devised. To this end, aniline **31** was dissolved in aqueous H_2SO_4 and acetonitrile (ACN) at 45−55 °C. A solution of $NaNO_2$ in water was added over a period of 35 min. The decomposition of the diazonium salt and the gas release (practically no foaming) was controlled by the addition rate at 45−55 °C. The conversion was completed approx 10 min after end of dosage. The formation of byproducts was negligible as reflected by the high yield of 81% and high purity of 94% a/a (LC−MS). The final step was carried out similar to the procedure used by our Medicinal Chemists. Stress tests showed that the product **11** was stable under aqueous acidic conditions while it decomposed in aqueous basic media, and displayed a low onset temperature in DSC as neat substance.[19] Clearly, the standard isolation by evaporation of an organic phase containing **11** was not tolerated, and we aimed at a precipitation of **11** from water instead. A further safety issue was the use of excess hydroxylamine that had to be controlled. We were also concerned about the amphoteric character of **11** which could lead to difficulties during isolation. After converting nitrile **10** to hydroxy-benzamidine **11**, aqueous HCl was added to the reaction mixture to adjust the pH to below 2. MeOH was distilled off under reduced pressure, and **11** was precipitated by adjusting the pH to 7 with aqueous NaOH. At higher pH the Na phenolate was formed. The product was isolated in a yield of 75% and purity of 100% a/a (LC−MS). An inductively coupled plasma optical emission

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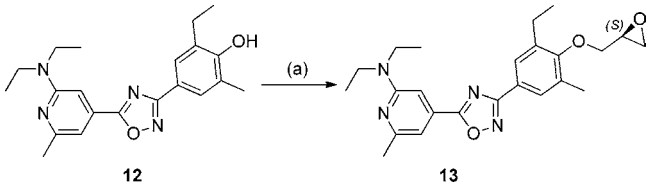
spectrometry (ICP-OES) analysis of **11** revealed a Na content of 844 ppm.

Coupling of 6 and 11 and Oxadiazole Formation. The coupling of the two building blocks **6** and **11** was investigated. The use of PyBOP was not an option for us due to the cost of the reagent and the difficulties to remove the tris-(pyrrolidinophosphine) oxide.[20] Formation of the acid chloride of **6** and reaction with hydroxy-amidine **11** provided "*O*-acyl hydroxamidine" **32** with byproduct. Peptide coupling conditions utilizing water-soluble *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole hydrate (HOBt hydrate) in THF or DMF resulted in incomplete conversion. When the reaction was performed with inexpensive dicyclohexyl carbodiimide (DCC) in THF and Et_3N as base, conversion to **32** was complete in 4 h at 0 °C (Scheme 8).[21] The mixture was heated to reflux, and the oxadiazole **12** was formed. After concentration and addition of TBME, the dicyclohexyl urea was filtered off. Aqueous workup and crystallization from ethanol delivered **12** as a yellow solid in a yield of 73% with excellent purity. The dicyclohexyl urea was detected by ^{1}H NMR at less than 1% w/w, and it was further purged away during the last stages.

The pH and stoichiometry played an important role in the sequence. If the pH was too acidic, **12** precipitated as insoluble HCl salt. The best pH was determined to be 6−7. If 1.1 equiv of **6** and 1 equiv of **11** were used, acylation of the phenol **32** by **6** was observed. In addition the reaction was performed successfully in aqueous phosphate buffer/THF mixtures. The oxadiazole **12** was obtained in a yield of 67% after similar workup.

Phenol Alkylation with a Chiral C_3 Building Block. Phenol **12** was alkylated with (*R*)-glycidol under Mitsunobu conditions in order to obtain **13** in a timely manner (Scheme 9).[22] This strategy was advisible to quickly investigate the downstream chemistry. The product was isolated after chromatography and crystallization from heptane or MeOH in a yield of 80% with excellent purity (100% a/a, LC−MS). The reaction proceeded without erosion of the optical purity since the enantiomeric purity of (*R*)-glycidol was similar to the enantiomeric purity of **13**.[23] With this protocol, 600 g of **13** were prepared, but the protocol was not deemed suitable for the next scale.

Scheme 9. [a] Alkylation of phenol 12 via a Mitsunobu reaction



[a]Reagents and conditions: (a) PPh_3 (1.2 equiv), (*R*)-glycidol (1.2 equiv), DEAD (1.2 equiv), THF, 0 °C, 80%.

Therefore, we looked for an alternative alkylation reaction. Literature study revealed that phenols could be alkylated with optically active epichlorohydrin in the presence of Me_4NCl and subsequent treatment with NaOH in MeOH to yield the desired oxiranes in high optical purity.[24−26] Treatment of phenol **12** with 10 equiv of (*R*)-epichlorohydrin and 0.33 equiv of Me_4NCl at 25 °C for two days afforded a mixture of oxirane **13** and chloropropanol **33** (Scheme 10). Oxirane **13** is formed from **33**, as confirmed by the ratio of **33**:**13** in the IPC that is approximately 70:30 at the start and approximately 40:60 at the end of the reaction. Addition of MeOH and aqueous NaOH led to full conversion of the chloro derivative **33** to epoxide **13**. The product was isolated by filtration in a yield of 98%. The enantiomeric ratio (er) was (*S*):(*R*) = 97.8:2.2.[27] At 20 °C the alkylation required a reaction time of 2 days, at 30 °C 1.5 days, while at 40 °C 15 h were sufficient. The er of the products obtained at 20 and 40 °C decreased from 98:2 to 97:3. Recrystallization of **13** from MeOH did not change the er. The protocol was smoothly scaled up to 17 kg.

An alkylating agent with the amino function already in place could be an efficient reagent for our synthesis. Two possible reagents are depicted in Figure 2. (*S*)-2,3-Epoxypropyl-phthalimide **I** could react with phenol **12** to form 3-aryl-1-amino-2-propanol.[28,29] The other reagent, oxazolidin-2-one **II**, described by Cardillo et al. and Ryono et al., was successfully used in phenol alkylations.[30] These approaches were not tested due to time constraints.

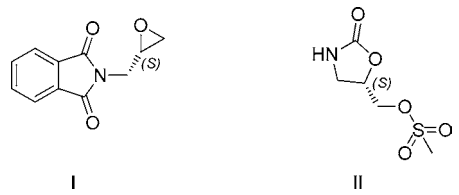
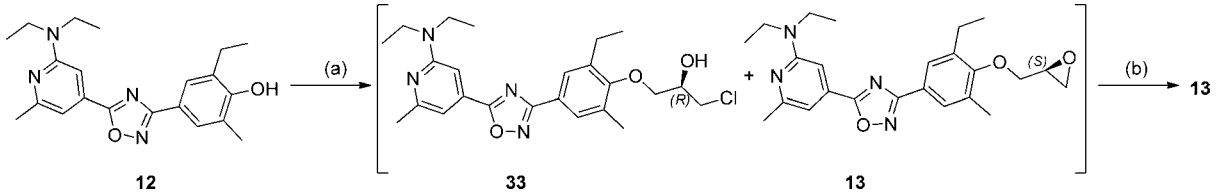


Figure 2. Potential protected 1-amino-2-propanol surrogates for phenol alkylation.

For the epoxide opening, the intermediate **13** was suspended in commercially available 7 N NH_3 in MeOH (14 equiv) and heated to 60 °C in an autoclave (Scheme 11). A large excess of NH_3 was used in order to suppress formation of bis-alkylated amine **34**.[31,32] Nevertheless, product **14** was contaminated with approximately 20% a/a (LC−MS) of secondary amine **34**. Purification of **14** was only successful by chromatography. Performing the reaction in aqueous NH_3 gave similar selectivity.

Scheme 10. [a] Alkylation of phenol 12 with (*R*)-epichlorohydrin



[a]Reagents and conditions: (a) (*R*)-epichlorohydrin (10 equiv), Me_4NCl (0.3 equiv), 25 °C, 2 d. (b) MeOH, NaOH, 0−20 °C, 1 h, 98%.

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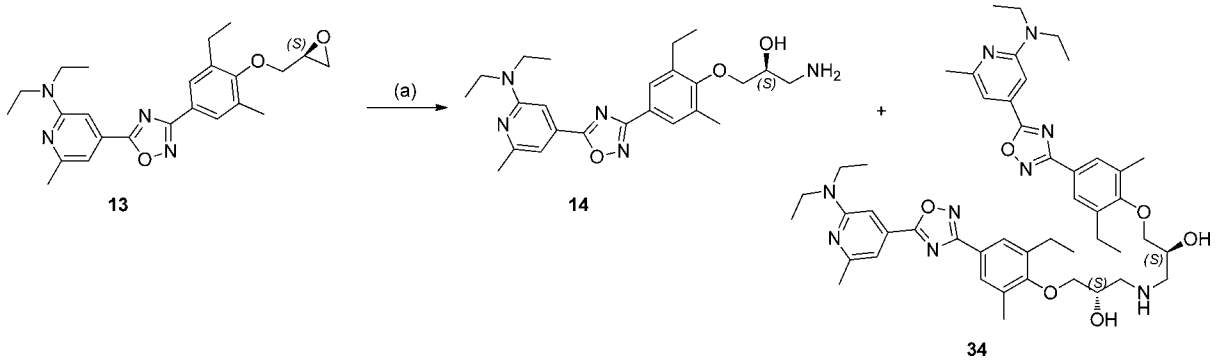
Scheme 11. [a] **Epoxide opening with NH_3**



[a]Reagents and conditions: (a) 7 N NH_3 in MeOH (14 equiv), 60 °C.

Since the side reaction could not be suppressed, we looked for an alternative amination reaction (Figure 3).

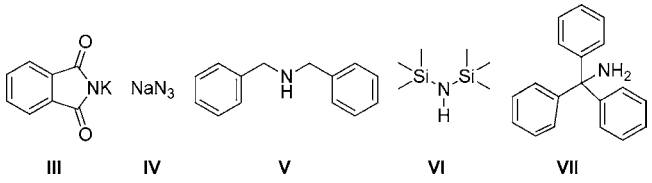


Figure 3. Possible protected NH_3 surrogates for epoxide opening.

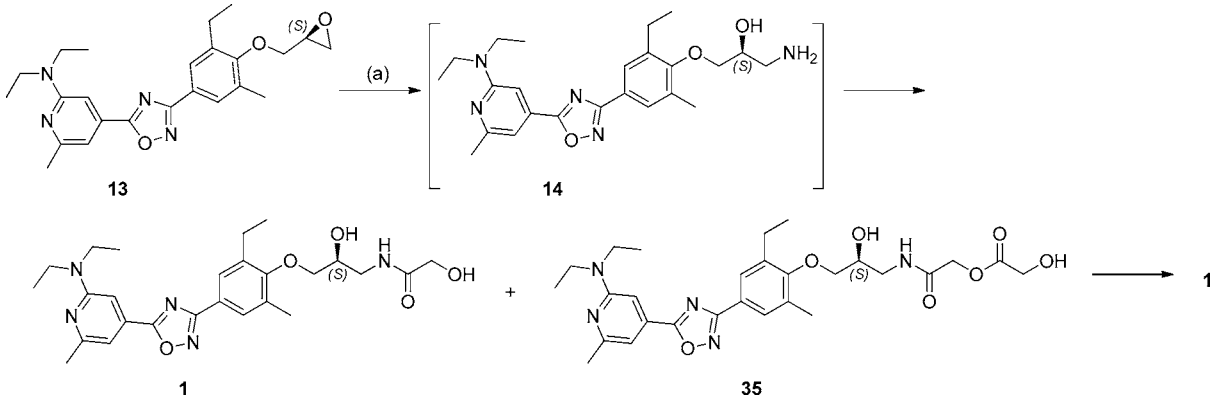
In our hands K-phthalimide **III** reacted sluggishly with **13** in DMF at elevated temperatures.[33] NaN_3 **IV** reacted cleanly with **13** in polyethylene glycol.[34] The azide was reduced with H_2 and Pd/C. Unfortunately, the oxadiazole spacer was not stable under these conditions. Reduction with PPh_3 was not checked due to a known side reaction (formation of aziridine).[35] Likewise, dibenzylamine **V** was not tested.[36] Hexamethyldisilazane **VI** was not reactive enough to open the oxirane. Tritylamine **VII** was successfully introduced as a masked amino equivalent by Desai, but it was not tested.[37]

Gratifyingly, LiHMDS, reacted cleanly and selectively with **13** in THF (Scheme 12). To our knowledge, this is the first successful application of an epoxide opening with LiHMDS as NH_3 surrogate on scale, omitting the formation of dialkylated byproduct.[38,39] This is a notorious problem in the synthesis of many β-blockers of the propanolol type and β-adrenoceptor agonists.[32b] The reaction reached full conversion at 20 °C after 24 h when 2 equiv of LiHMDS was used. The reaction mixture was washed with concentrated NH_4Cl solution and brine, but the crude product was contaminated with TMS-protected amino alcohol **14** as detected by LC–MS. The amino alcohol **14** was used in the next step without further purification, and 1.1 equiv glycolic acid, EDC·HCl, and HOBt·H_2O were added to the THF solution containing crude **14**. The conversion to **1** was 95%. A recharge of 25% of each reagent gave a conversion of 98%. LC–MS revealed that **1** was contaminated with the byproduct **35** containing two glycolic acid moieties **35**. The purity of the crude product was 89% a/a (LC–MS). Therefore, the crude product was treated with NaOH solution in MeOH to cleave the extraneous ester bond. After this treatment the purity increased to 95% a/a (HPLC). Single crystallization from EtOAc raised the purity to 98.6% a/a (HPLC). The er of **1** was (*S*):(*R*) = 98.4:1.6. The yield over two stages was 49%. The scale-up at a contract research organization (CRO) produced up to 12 kg with a similar result.

CONCLUSION

The original synthesis of $S1P_1$ receptor agonist **1** (**ACT-209905**) was not suitable for scale-up. The revised synthesis consists of 16 steps with 9 isolated intermediates and an overall yield of 14% from diethyl oxalate **19** (Scheme 13).[40] New routes for the two key building blocks amino isonicotinic acid **6**

Scheme 12. [a] **Epoxide opening with LiHMDS and formation of API 1**



[a]Reagents and conditions: (a) i) LiHMDS (2 equiv), THF, 20 °C, 15 h, ii) EDC·HCl (1.25 equiv), HOBt·H_2O (1.25 equiv), glycolic acid (1.3 equiv), THF, aqueous workup, iii) 1 N NaOH, MeOH, 60 °C, iv) crystallization from EtOAc, 49% (2 steps).

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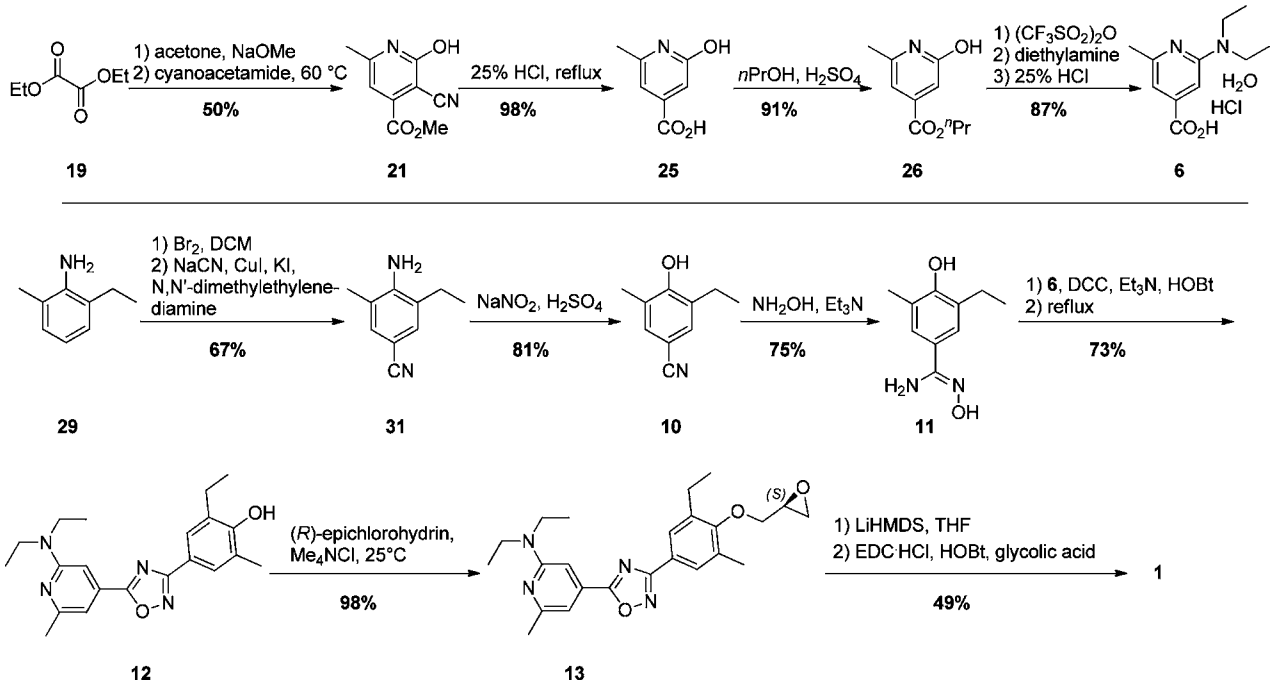
Scheme 13. Scale-up synthesis of 1



and hydroxy-benzamidine **11** were found and developed, starting from inexpensive diethyl oxalate **19** and 2-ethyl-6-methylaniline **29**, respectively. The final stages were revised, avoiding chromatography and the use of the unacceptable coupling reagent PyBOP. For the introduction of the chiral 1-amino-2-propanol moiety the Mitsunobu reaction was replaced by an operationally simple alkylation with (*R*)-epichlorohydrin, and the amino function was established by a selective and high-yielding epoxide opening employing LiHMDS as NH_3 surrogate. As a testimony to the robustness of the synthesis, the scale-up to 12 kg of **1** at a CRO proceeded with 12% overall yield (equivalents, volumes, temperature, and purities being similar as disclosed in the Experimental Section).[41]

EXPERIMENTAL SECTION

General. One vol or 1 wt means 1 L of solvent or 1 kg of reagent with respect to 1 kg of the reference starting material. Compounds are characterized by ^{1}H NMR (400 MHz, Bruker) or ^{13}C NMR (100 MHz, Bruker); internal standard for quantitative NMR was 1,4-dimethoxybenzene. Details for the HPLC and LC−MS methods are listed in the Supporting Information. Unless stated otherwise, yields are given as is.

Methyl 3-Cyano-2-hydroxy-6-methyl-isonicotinate (21). A solution of 5.4 M NaOMe in MeOH (507 mL, 1.0 equiv) and MeOH (3 L) were heated to 60 °C. A mixture of diethyl oxalate **19** (400 g, 2.737 mol, 1.0 equiv) and acetone (158.75 g, 1.0 equiv) was added to the solution in 25 min. The reaction mixture was stirred at 60 °C for 45 min. Cyanoacetamide (230 g, 1.0 equiv) was added in three portions over 15 min. The mixture was stirred at 60 °C for 60 min. Acetic acid (246 g, 1.5 equiv) was added to the suspension. The suspension was cooled to 5 °C and filtered. The cake was washed with TBME (250 mL). The solid was dried at 50 °C under reduced pressure on a rotary evaporator to obtain **21** as a yellow solid. Yield: 263 g (50%). Purity (LC−MS): 96% a/a, R_t 0.683 min; $[M + 1]^+$ = 193; assay by ^{1}H NMR (D_6 DMSO) with 1,4-dimethoxybenzene as internal standard: 95% w/w; ^{1}H NMR (D_6 DMSO): δ 13.06 (br, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 2.33 (s, 3H).

2-Hydroxy-6-methylisonicotinic Acid (25). A suspension of Guareschi−Thorpe product **21** (585 g, 1.04 mol, 1.0 equiv) in 25% HCl (4.5 L) was heated to reflux for 21 h. The suspension was cooled to 5 °C and stirred for 2 h. The mixture was filtered and washed with water (2 × 400 mL). The white solid **25** was dried at 75 °C and a pressure of 5 mbar. Yield: 455 g (98%). Purity (LC−MS): 99% a/a, R_t 0.470 min; $[M + 1]^+$ = 154; ^{1}H NMR (D_6 DMSO): δ 11.43 (br s, 2H), 6.73 (s, 1H), 6.49 (s, 1H), 2.26 (s, 3H).

Propyl 2-Hydroxy-6-methylisonicotinate (26). A suspension of **25** (169 g, 1.1 mol, 1.0 equiv) in 1-propanol (1500 mL) and conc. H_2SO_4 (78 mL, 1.3 equiv) was heated to reflux for 30 min. The mixture turned into a solution and 1-propanol (1.2 L) was removed via distillation at 115−140 °C external temperature. The reaction mixture was cooled to 20 °C, and DCM (1 L) was added. The solution was added to a mixture of water (1 L) and DCM (700 mL) at 5 °C. The organic layer was separated and washed with water (1 L) and sat. aq $NaHCO_3$ solution (500 mL). The organic layer was concentrated at 65 °C, and 1.4 L solvent was removed. A suspension was formed and diluted with TBME (0.5 L). The suspension was cooled to 20 °C and filtered. The white solid **26** was dried at 50 °C and 5 mbar. Yield: 197 g (91%). Purity (LC−MS): 100% a/a, R_t 0.740 min; $[M + 1]^+$ = 196; ^{1}H NMR (D_6 DMSO): δ 11.99 (br, 1H), 6.63 (s, 1H), 6.36 (s, 1H), 4.20 (t, J = 6.5 Hz, 2H), 2.23 (s, 3H), 1.70 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

2-(Diethylamino)-6-methylisonicotinic Acid Hydrochloride Hydrate (6). A mixture of propyl methylisonicotinate **26** (424 g, 2.12 mol, 1.0 equiv), pyridine (254 mL, 1.1 equiv), and DCM (3.1 L) was cooled to −5 °C. Triflic anhydride (384 mL, 1.1 equiv) was added in 60 min. The mixture was heated to 20 °C and stirred for 10 min. A further portion of triflic anhydride (34.9 mL, 0.1 equiv) was added at 20 °C. The reaction mixture was washed with water (2 L). The organic layer was concentrated to a minimum stirring volume at

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60−75 °C (3.1 L solvent removed). DMSO (2 L) and Et_2NH (2.198 L, 10 equiv) were added to the residue. The solution was heated to 50 °C for 16 h. The temperature was increased to 80−110 °C, and solvent and Et_2NH (1.02 L) were distilled off. The mixture was cooled to 30 °C and diluted with TBME (3 L). The solution was washed with water (3 L) and aqueous HCl (650 mL, consisting of 32% HCl [700 mL] and water [2.3 L]). The aqueous layer (pH = 6) was separated and extracted with TBME (1 L). The combined organic layers were washed with water (1 L). TBME (2.78 L) was distilled off at 75 °C. The mixture was treated with 25% HCl (1 L) at 20 °C and heated at 125−150 °C for ∼4 h, while 1-propanol and aqueous HCl were distilled off (∼730 mL solvents were removed). To the mixture was added water (0.5 L), and the distillation was continued to remove 0.5 L solvent. The jacket temperature was set to 40 °C. The product started to crystallize at 60 °C. To the suspension was added acetone (2 L) at 36 °C. The suspension was cooled to 20 °C and filtered. The yellow solid **6** was dried at 60 °C and 5 mbar. Yield: 481 g (87%). Purity (LC−MS): 99% a/a; R_t 0.686 min; $[M + 1]^+ = 209$; ^1H NMR (D_2O): δ 7.30 (s, 1H), 6.88 (s, 1H), 3.60 (q, J = 7.1 Hz, 4H), 2.46 (s, 3H), 1.19 (t, 6H). ^{13}C NMR (D_2O): δ 166.8, 151.9, 148.9, 144.2, 110.6, 109.5, 44.9, 19.1, 11.3.

4-Amino-3-ethyl-5-methylbenzonitrile (31). *Caution: cyanides are toxic and can release toxic HCN. All precautions for the work with cyanides have to be followed.* Bromine (43.384 kg, 1.05 equiv) was added to a solution of 2-ethyl-6-methyl aniline **29** (34.949 kg, 258.48 mol) in DCM (128 L) at 10 °C in 175 min. A solution of 30% NaOH (39 L) was added in 30 min. DCM (11 L) and water (15 L) were added and the phases separated. The aqueous phase was extracted with DCM (35 L). The combined organic layers were washed with water (43 L). A solvent switch to toluene (186 L) was performed at 52−95 °C and a pressure of 980 mbar to 500 mbar. A sample was concentrated to dryness, and ^1H NMR of 4-bromo-aniline **30** was performed: ^1H NMR ($CDCl_3$): δ 7.09 (s, 2 H), 3.61 (s, 2 H), 2.51 (q, J = 7.5 Hz, 2 H), 2.18 (s, 3 H), 1.27 (t, 3 H). DSC data: left limit of exothermic decomposition 124 °C, −441 J/g. NaCN (17.31 kg, 1.3 equiv), KI (8.571 kg, 0.2 equiv), CuI (4.930 kg, 0.1 equiv) and *N,N′*-dimethylethylenediamine (26.699 kg, 85% w/w, 1.0 equiv) were added at 20 °C. The mixture was heated to 115 °C and stirred at this temperature for 21 h. HPLC of a sample showed incomplete conversion. More CuI (2.46 kg, 0.05 equiv) and *N,N′*-dimethylethylenediamine (10.569 kg, 85% w/w, 0.4 equiv) were added at 25 °C. The mixture was heated to 110 °C and stirred at this temperature for 18 h. Water (168 L) and isopropyl acetate (258 L) were added at 70 °C. The layers were separated, and the organic layer was washed with water (141 L) at 40 °C. The organic layer was diluted with isopropyl acetate (56 L) and washed with a mixture of 10% citric acid solution (94 L) and brine (28 L) at 43 °C. The organic layer was washed twice with a solution of brine (28 L) in water (141 L). Solvent (370 L) was removed at 95−103 °C, while toluene (77 L) was added. The reaction mixture was cooled to 5 °C and filtered. The cake was washed with 5 °C cold toluene (52 L). The product was dried to obtain **31** as a grey solid. Yield: 27.893 kg (67%). Purity (LC−MS): 99% a/a, R_t 1.517 min, mass not detected; ^1H NMR (D_6 DMSO): δ 7.21 (s, 1H), 7.18 (s, 1H), 5.57 (s, 2H), 2.47 (m, 2H), 2.10 (s, 3H), 1.13 (t, J = 7.3 Hz, 3H). DSC data: left limit of exothermic decomposition 162 °C, −64 J/g.

3-Ethyl-4-hydroxy-5-methylbenzonitrile (10). A freshly prepared solution of $NaNO_2$ (137.5 g, 1.2 equiv) in water (270 mL) was added to a mixture of 30% H_2SO_4 (5 kg), aniline **31** (266.6 g, 1.66 mol, 1.0 equiv) and acetonitrile (270 mL) at 50−55 °C over 35 min. *[CAUTION: evolution of nitrogen gas!]*[42] The mixture was cooled to 20 °C and extracted with TBME (1.7 L). The aqueous layer was extracted with TBME (2 × 1 L). The combined organic layers were washed with water (1 L). The TBME layer was concentrated to dryness on a rotary evaporator at 70 °C and pressure of 900 to 5 mbar to obtain a solid (271 g), which was crystallized from EtOAc (120 mL) and methyl cyclohexane (1.2 L) to afford **10** as a beige solid. Yield: 218 g (81%). Purity (LC−MS): 94% a/a, R_t 1.526 min, mass not detected; ^1H NMR ($CDCl_3$): δ 7.31 (s, 2H), 5.37 (br, 1H), 2.65 (q, J = 7.5 Hz, 2H), 2.28 (s, 3H), 1.26 (t, 3H).

3-Ethyl-*N*,4-dihydroxy-5-methylbenzimidamide (11). A mixture of nitrile **10** (300 g, 1.86 mol, 1 equiv), $NH_2OH{\cdot}HCl$ (323 g, 2.5 equiv) and Et_3N (648 mL, 2.5 equiv) in MeOH (2.4 L) was heated to 70 °C for 6 h. The mixture was cooled to 20 °C and 2 N HCl (1.7 L) was added. The brown solution was concentrated at 55 °C and a pressure of approx 200 mbar to remove solvent (2.4 L). The residue was extracted with TBME (1.5 L). The organic layer was discarded. The pH of the aqueous layer was adjusted to 7 by addition of 32% NaOH (280 mL) in water (500 mL). The resulting suspension was cooled to 10 °C and filtered. The product was dried at 40 °C and 5 mbar to afford **11** as a beige solid. Yield: 272 g (75%). Purity (LC−MS): 99% a/a, R_t 0.846 min, $[M + 1]^+ = 195$; ^1H NMR (D_6 DMSO): δ 9.29 (s, 1H), 8.34 (s, 1H), 7.25 (m, 2H), 5.59 (m, 2H), 2.58 (q, J = 7.4 Hz, 2H), 2.18 (s, 3H), 1.14 (t, 3H). ^{13}C NMR (D_6 DMSO): δ 154.0, 151.6, 130.3, 126.0, 124.8, 124.4, 124.2, 23.5, 17.3, 14.8. DSC data: left limit of exothermic decomposition 98 °C, −741 J/g.

4-(5-(2-(Diethylamino)-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2-ethyl-6-methylphenol (12). *Caution: HOBt ·H_2O was reported by some groups to be shock sensitive.*[43] Isonicotinic acid **6** (50 g, 0.19 mol, 1 equiv), $HOBt{\cdot}H_2O$ (2.57 g, 0.1 equiv), hydroxy-benzamidine **11** (44.4 g, 1.2 equiv), and Et_3N (26.5 mL, 1 equiv) were dissolved in THF (700 mL), and the mixture was cooled to −5 °C. A solution of DCC (43.2 g, 1.1 equiv) in THF (150 mL) was added, and the mixture was stirred at 0 °C for 2 h. The suspension was heated to reflux for 30 h and then concentrated at 75 °C, whereby THF (210 mL) was removed. TBME (200 mL) was added to the residue, and the mixture was cooled to 10 °C. The urea was filtered off and washed with TBME (200 mL). The combined filtrates were washed with half sat. aq $NaHCO_3$ solution (500 mL). After removal of solvent, a yellow solid (82 g) was obtained. The crude product was heated to reflux in EtOH (750 mL). The resulting solution was cooled to 10 °C and filtered. After drying at 50 °C and reduced pressure **12** was isolated as a yellow solid. Yield: 51 g (73%). Purity (LC−MS): 100% a/a, R_t 1.717 min, $[M + 1]^+ = 367$; ^1H NMR (D_6 DMSO): δ 8.94 (s, 1H), 7.68 (m, 2H), 7.04 (s, 1H), 6.96 (s, 1H), 3.57 (q, J = 6.6 Hz, 4H), 2.68 (q, J = 7.3 Hz, 2H), 2.41 (s, 3H), 2.27 (s, 3H), 1.17 (m, 9H).

(*S*)-*N,N*-Diethyl-4-(3-(3-ethyl-5-methyl-4-(oxiran-2-ylmethoxy)phenyl)-1,2,4-oxadiazol-5-yl)-6-methylpyridin-2-amine (13). *Via Mitsunobu.* A solution of 40% diethylazodicarboxylate (DEAD) in toluene (246 mL, 1.2 equiv) was added to a solution of phenol **12** (164 g, 0.448 mol, 1.0 equiv), PPh_3 (145 g, 1.2 equiv), and (*R*)-glycidol (35.65 mL, 1.2 equiv) in THF (2 L) at <5 °C in 20 min. The mixture was concentrated and THF was replaced by TBME (1 L). The mixture was cooled to 0 °C and filtered. The cake was washed

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with TBME (0.5 L). The filtrate was concentrated to dryness to obtain 320 g of a crude oil. The product was purified by a filtration over silica (1.6 kg) using EtOAc/heptane 1:4 (v:v) as eluent to get an orange oil (200 g) which was crystallized from heptane (1.5 L). The product was dried at 50 °C and reduced pressure to obtain **13** as a yellow solid. Yield: 156 g (83%). Purity (LC−MS): 100% a/a, R_t 1.837 min, $[M + 1]^+$ = 423; er (HPLC method 2): (*S*):(*R*) = 98.6:1.4, R_t 5.801 min (*S*-isomer), 5.499 min (*R*-isomer); ^{1}H NMR (D_6 DMSO): δ 7.77 (s, 2H), 7.03 (s, 1H), 6.96 (s, 1H), 4.19 (d, J = 11.2 Hz, 1H), 3.68 (dd, J_1 = 11.1 Hz, J_2 = 6.8 Hz, 1H), 3.56 (q, J = 6.7 Hz, 4H), 3.38 (s, 1H), 2.85 (t, J = 4.5 Hz, 1H), 2.73 (m, 3H), 2.41 (s, 3H), 2.34 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 6.8 Hz, 6H).

Via (R)-Epichlorohydrin. A mixture of phenol **12** (10 g, 0.027 mol, 1.0 equiv), (*R*)-epichlorohydrin (25 g, 10 equiv, 99% ee by CoA), and Me_4NCl (1 g, 0.33 equiv) was stirred at 25 °C for 2 d. MeOH (40 mL) and 32% NaOH (5.8 mL, 1.7 equiv) were added to the suspension at 0 °C. The suspension was stirred at 20 °C for 60 min. The suspension was filtered and washed with MeOH (10 mL) to obtain **13** as a yellow solid after drying at 50 °C and reduced pressure. Yield: 11.25 g (98%). Purity (LC−MS): 100% a/a, R_t 1.837 min, $[M + 1]^+$ = 423; er (HPLC method 2): (*S*):(*R*) = 97.8:2.2, R_t 5.801 min (*S*-isomer), 5.499 min (*R*-isomer).

(*S*)-*N*-(3-(4-(5-(2-(Diethylamino)-6-methylpyridin-4-yl)-1,2,4-oxadiazol-3-yl)-2-ethyl-6-methylphenoxy)-2-hydroxypropyl)-2-hydroxyacetamide (1). 1M LiHMDS in THF (213 mL, 2 equiv) was added to a solution of epoxide **13** (45 g, 0.107 mol, 1.0 equiv) in THF (0.5 L) at 22 °C. The solution was stirred at 22 °C for 1 d. The reaction mixture was added to sat. aq NH_4Cl solution (0.75 L). The mixture was stirred for 1 h, and TBME (200 mL) was added. The aqueous layer was separated, and the organic layer was washed with brine (2 × 250 mL). After concentration to dryness, aminopropanol **14** was obtained as a brown oil which was used in the next step without purification. Yield: 54 g (115%). Purity (LC−MS): 92% a/a, R_t 1.339 min, $[M + 1]^+$ = 440; ^{1}H NMR (D_6 DMSO): δ 7.78 (m, 2H), 7.06 (s, 1H), 6.98 (s, 1H), 3.77 (m, 3H), 3.58 (q, J = 6.9 Hz, 4H), 3.18 (d, J = 2.9 Hz, 2H), 2.74 (m, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 1.32 (s, 1H), 1.23 (m, 3H), 1.16 (t, J = 7.0 Hz, 6H). EDC·HCl (22.6 g, 1.1 equiv) was added in portions to a solution of **14**, glycolic acid (8.95 g, 1.1 equiv), HOBt·H_2O (15.9 g, 1.1 equiv), and THF (500 mL) at 22 °C. The mixture was stirred at 20 °C for 3 h. Glycolic acid (1.6 g, 0.2 equiv), HOBt·H_2O (2.2 g, 0.15 equiv), and EDC·HCl (3.1 g, 0.15 equiv) were added, and stirring was continued for 15 h. THF was removed at 50 °C and reduced pressure. To the residue was added EtOAc (0.5 L). The solution was washed with water (0.5 L), half-sat. aq $NaHCO_3$ solution (2 × 0.5 L) and water (0.25 L). The organic layer was concentrated to dryness to obtain **1** as a yellow solid. Yield: 50 g (94%). Purity (HPLC method 1): 89% a/a. Purification: The crude material (50 g), MeOH (0.5 L), and 1 N NaOH (25 mL) were stirred for 45 min at 60 °C. MeOH was removed at 50 °C and reduced pressure. EtOAc (0.5 L) was added to the residue at 20 °C, and the resulting solution was extracted with water (2 × 250 mL). The organic layer was concentrated to dryness at 50 °C and reduced pressure. The crude solid was dissolved in EtOAc (0.5 L) at 70 °C, the solution was cooled to 20 °C, and the resulting suspension was filtered and dried to obtain **1** as a yellow solid. Yield: 26 g (49%). Purity (HPLC method 1): 98.6% a/a, R_t 7.6 min, er (HPLC method 2): (*S*):(*R*) = 98.4:1.6, R_t 12.3 min (*S*-isomer), 10.0 min (*R*-isomer); ^{1}H NMR (D_6 DMSO): δ 7.78 (s, 2H), 7.69 (m, 1H), 7.05 (s, 1H), 6.97 (s, 1H), 5.56 (t, J = 5.5 Hz, 1H), 5.31 (d, J = 5.0 Hz, 1H), 4.01 (m, 1H), 3.84 (d, J = 5.4 Hz, 2H), 3.75 (m, 2H), 3.57 (q, J = 6.7 Hz, 4H), 3.45 (m, 1H), 3.24 (m, 1H), 2.73 (q, J = 7.3 Hz, 2H), 2.42 (s, 3H), 2.34 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 175.4, 173.2, 168.7, 158.6, 157.7, 157.2, 137.6, 132.3, 131.5, 128.4, 126.7, 122.8, 107.5, 100.3, 74.1, 70.2, 62.2, 42.4, 42.3, 24.8, 22.9, 16.5, 14.8, 12.9.

■ ASSOCIATED CONTENT

Supporting Information

Analytical methods and characterization data of **1** and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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