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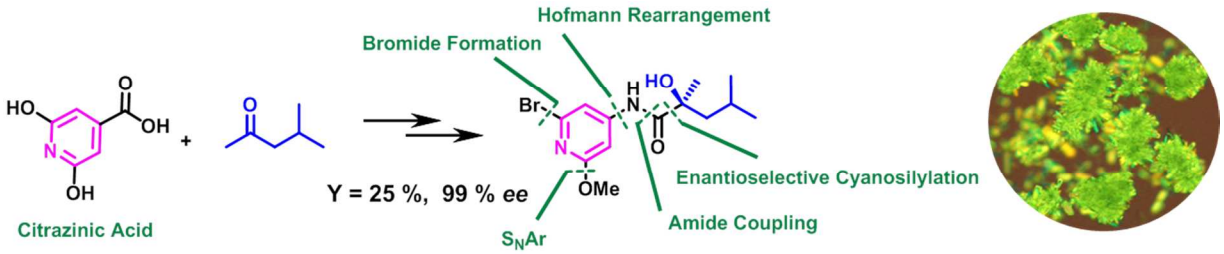
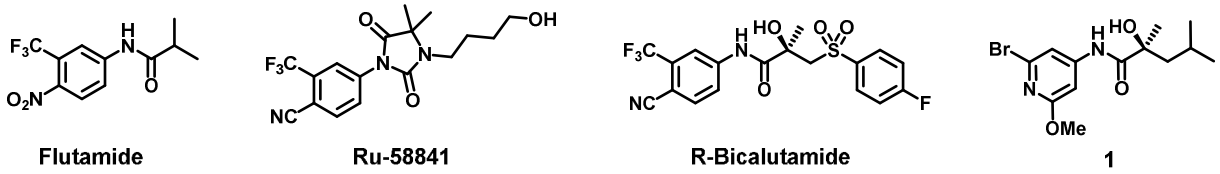


ABSTRACT : An efficient route to (*S*)-*N*-(2-bromo-6-methoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide **1**, a new topical antiandrogen, is described. The target compound has been manufactured on kilogram scale with an overall yield of 25 % (HPLC purity 98.8% and >99% *ee*) from citrazinic acid. The key amide coupling between aminopyridine **4** and *α*-hydroxy-acid **6** was performed using a temporary protecting group to facilitate the acyl chloride formation. Aminopyridine **4** was manufactured from commercially available citrazinic acid *via* dibromide formation using phosphorus(V) oxybromide followed by mono S_NAr reaction with sodium methoxide and a final Hofmann rearrangement. Enantiopure *α*-hydroxy-acid **6** was obtained using an enantioselective cyanosilylation followed by salt resolution with (*S*)-α-methyl benzylamine. The absolute configuration of compound **1** was determined with anomalous scattering and the final crystallization of API was performed after seeding a liquid-liquid mixture below the monotectic temperature and afforded a crystalline powder presenting a “desert rose” shape clusters.

KEY WORDS : Antiandrogen, oiling-out, monotectic, anomalous scattering, Hofmann rearrangement, enantioselective cyanosilylation, amide coupling.

INTRODUCTION : Hormones and androgens play an important role in skin disorders such as oily skin or acne.[1] Multiple hormonal modulators are available for the treatment of acne such as spironolactone, flutamide, cyproterone acetate and finasteride by oral route.[2] However, due to systemic side effects such as fetus feminization, they can only be used in females and contraception has to be set up. Oral antiandrogens have also been applied topically[3] to reduce systemic side effects and are promising agents to treat acne in females, nevertheless long term safety is an issue with these hepatic stable drugs. The design of a topical antiandrogen with a fast clearance and a fast metabolism is of great interest, because it could have a local anti-seboreic activity in skin without any systemic side-effects. Compound **1** is a potent androgen receptor antagonist in the nanomolar range that has been designed and developed for the treatment of both excess sebum and acne treatment.[4] Its structure shares some analogy with known nonsteroidal antiandrogens (Flutamide, RU-58841 or R-Bicalutamide) but displays an original pyridine core (Figure 1). Based on its interesting properties, compound **1** was selected as the clinical candidate and multi-kilogram batches of API were required to support preclinical and clinical studies.

Figure 1 : Non Steroidal Antiandrogens and Compound 1 Structure

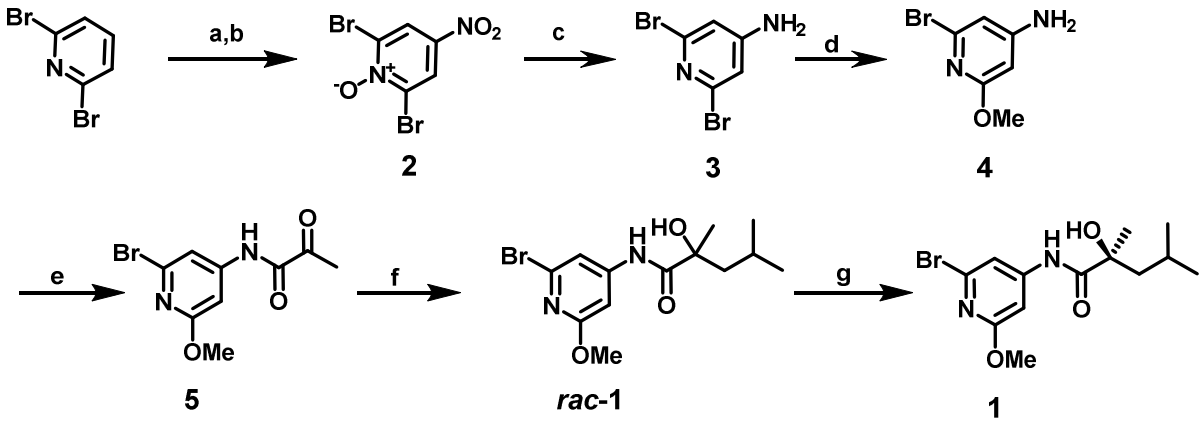


Background :

The discovery route to compound **1** is depicted in Scheme 1. Access to this tri-substituted pyridine is not trivial and the initial chemical pathway relied on oxidation of commercially available 2,6-dibromopyridine with hydrogen peroxide, followed by nitration at the 4 position to yield *N*-oxide **2**. Concomitant iron reduction of nitro group and *N*-oxide afforded the dibromo aminopyridine **3**. S_NAr of one bromine atom with a methoxy group was carried out with sodium

hydroxide in methanol under microwave irradiation at 120 °C and 7 bars of pressure to give aminopyridine **4**. Acylation of compound **4** with pyruvic acid and DCC followed by addition of *iso*-butyl magnesium chloride afforded the racemic compound ***rac*-1** which was engaged in a preparative chiral HPLC. Compound **1** was obtained with 99% *ee*, but as an oil, with an overall yield lower than 1% from 2,6-dibromopyridine and the absolute configuration of the stereogenic center was not determined at this stage of development.

Scheme 1 : Discovery Route to Compound 1.

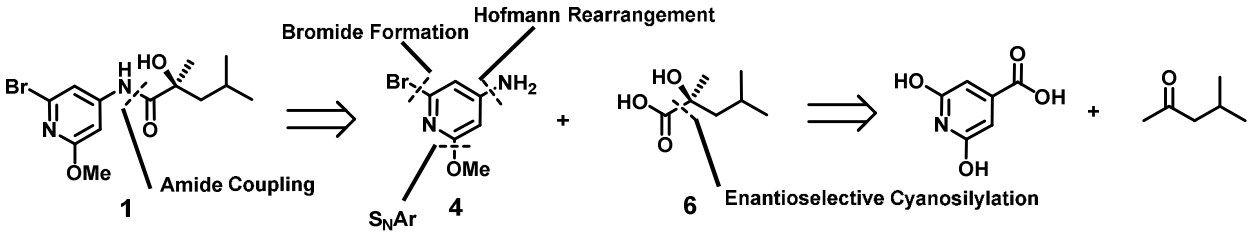


a) H_2O_2, TFA, 80%. b) H_2SO_4, HNO_3, 73%. c) Fe, NH_4Cl, EtOH, 51%. d) MeOH, NaOH, MW 120 °C, 7 bars 84%. e) DCC, pyruvic acid, NMP, 29%. f) *i*-BuMgCl, THF, 34% g) Chiral HPLC separation, 45%.

This chemical pathway based on a functionalization of key intermediate **5**, was appropriate to have fast access to libraries of compounds and build quickly structure-activity relationships; However considerable improvements needed to be performed in order to manufacture kilogram batches of drug substance to support preclinical and clinical trials. The major drawback of this approach was the final construction of racemic compound **1** that was subjected to chiral HPLC separation along with the use of energetic nitropyridine **2** as well as high pressure S_NAr reaction. The new synthetic route envisaged was based on an amide coupling of aminopyridine **4** with enantiopure α-hydroxy-acid **6** (Scheme 2). In order to realize this route, a scalable process to

make the aminopyridine **4** using a Hofmann rearrangement, as well as a simple manufacture of *α*-hydroxy-acid **6** *via* enantioselective cyanosilylation of MIBK were considered.

Scheme 2 : Retrosynthesis of Compound 1.



Characterization of API and absolute configuration determination:

In addition to the synthesis of compound **1**, effort was focused on the crystallization of this new API. This small molecule (Mw = 331 g/mol) was fairly soluble (>40 mg/mL) in 42 common solvents screened except in water and in alkanes (2 mg/mL), however crystals of racemic form (m.p. 106 °C, ΔH_R = 31264 J.mol^{-1}) were obtained after crystallization from *n*-heptane/diisopropyl ether 95/5 mixture. Crystallization of enantiopure **1** obtained from chiral HPLC separation was more troublesome than anticipated but was finally achieved from pure *n*-heptane. This first solid had a melting point of 52 °C, but DSC analysis showed a second fusion around 80 °C.[5] After recrystallization experiment from *n*-Heptane, this first solid phase turned to be a metastable solid form and a new crystalline phase was obtained with a melting point of 81 °C (ΔH_E = 20137 J.mol^{-1}). This 25 °C difference between enantiopure **1** and ***rac*-1** indicated that we might have an unfavorable racemic compound behavior system as depicted in Figure 2. An extensive polymorph screen was undertaken in order to identify other crystalline forms of enantiopure **1** being accessible under process-relevant conditions and only one solid phase was obtained. The construction of binary diagram using DSC measurement and calculated liquidus curves from simplified equations of Schröder-Van Laar and Prigogine-Defay (see experimental

support) was performed. The experimental data obtained were in accordance with the calculated ones, and confirmed our hypothesis of an eutectic with a value of about 95 mole percent.[6] In addition, superimposition of X-ray powder diffraction (XRPD) patterns solids with different molar fractions confirmed the racemic compound behavior system with two distinct patterns for the enantiopure **1** and the racemic solids (Figure 3).

Figure 2 : Binary Phase Diagram of Compound 1.

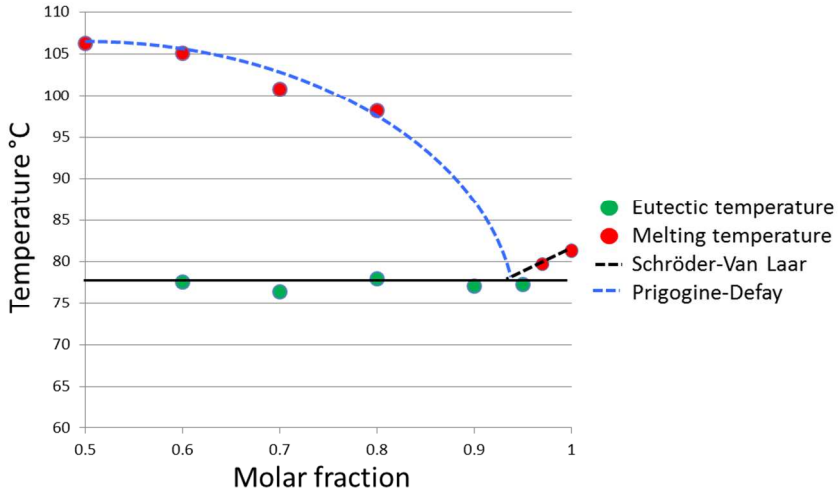
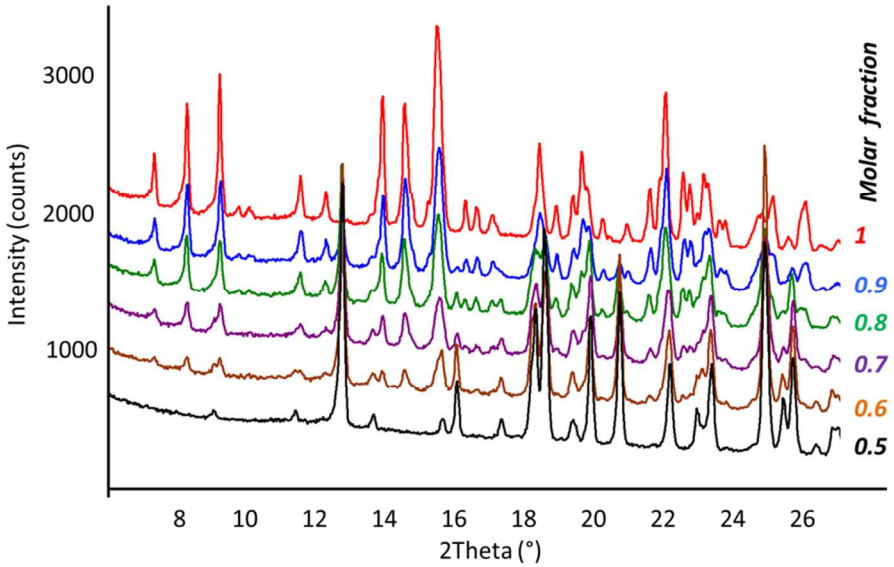
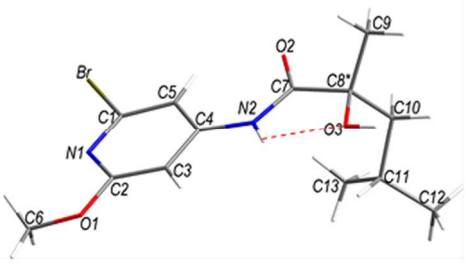


Figure 3 : XRPD Patterns of Solids with Different Molar Fractions.



Consequently, the control of the enantiopurity of *α*-hydroxy-acid **6** was mandatory because crystallization of enantio-enriched **1** below 95% *ee* would not be an option to provide enantiopure API. The other key was the determination of the absolute configuration of the quaternary center in compound **1**. The usual strategies to determine absolute configuration were investigated but as the pK_a of this substituted pyridine was predicted to be -0.4,[7] salt formation using chiral acids was unsuccessful, even attempted salt formation with camphor sulfonic acid gave poor results. In addition, attempts to derivatize the alcohol with chiral auxiliaries such as Mosher's ester failed as well, probably due to the steric hindrance and low reactivity of tertiary alcohol. The presence of a heavy bromine atom on the API structure was clearly an opportunity to perform an anomalous scattering experiment and access directly the absolute configuration without derivatization. Slow crystallization from *n*-heptane generated a single crystal that was subjected to anomalous scattering and we were able to establish the (*S*) absolute configuration of quaternary center (Figure 4).

Figure 4 : Absolute Configuration of Compound 1

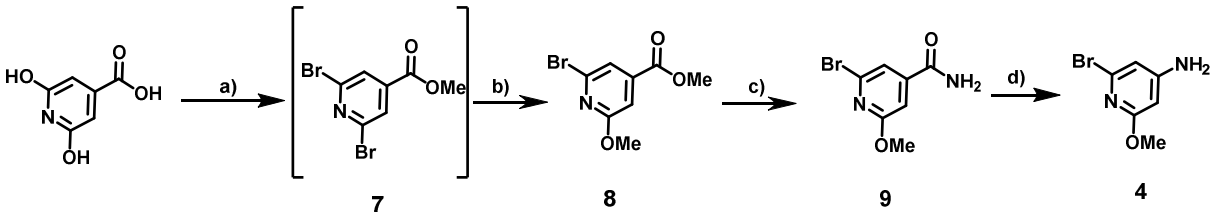


Synthesis of Aminopyridine 3 and Hydroxy-acid 6.

The synthesis of aminopyridine **4** was also revisited, and particularly the S_NAr of the methoxy group that was the key step. The substitution reaction with 2,6-dibromo-aminopyridine **3**, in the original route with sodium methoxide worked well in methanol in a sealed tube at 120 °C. However all experiments to realize the substitution reaction at lower temperature or in another

solvent afforded a complex mixture composed of self-reaction side-products of aminopyridine **4**. Attempts to perform the substitution, on the related electron deficient 2,6-dibromo 4-nitropyridine failed because the bromides substituents were this time too reactive, leading to mixtures of mono- and di-substituted products. Selective mono-substitution was rather difficult to achieve and the 2,6-dimethoxy-4-nitropyridine was always present in appreciable quantity even when sodium methoxide was used as the limiting reagent. Therefore, we completely changed the synthesis route to aminopyridine **4** and decided to introduce the amino group using a Hofmann rearrangement of the corresponding amide **9** (Scheme 3).

Scheme 3 : Manufacture of Aminopyridine 4

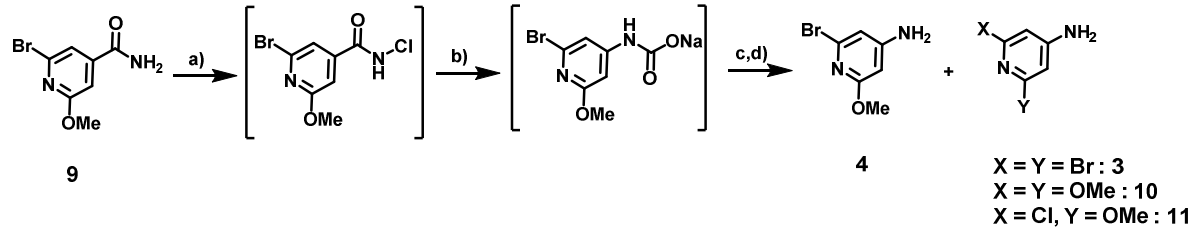


a) $POBr_3$, sulfolane, 125 °C then methanol b) MeONa, MeTHF, 44% over 2 steps. c) Aqueous NH_3 6.4 M, 25 °C, 87%. d) NaOCl 13.9% w/v, then NaOH 80 °C, 86%.

Synthesis of compound **7** was described in literature from commercially available citrazinic acid, but only on small scale, in neat phosphorus(V) oxybromide at 140-180 °C and with a chromatographic purification.[8] We investigated this reaction and during laboratory experiments, we noticed formation of sticky black syrup probably composed of polyphosphoric residues that were difficult to separate from reaction mixture. We found that the purity profile of this reaction was greatly improved when sulfolane (8 Vol) was used as a solvent with only 1.5 equivalents of phosphorus(V) oxybromide. To control the exothermic event, the brominating agent was added at 90 °C to the sulfolane solution of citrazinic acid and then heated to 125 °C for 2 hours. The mixture was quenched with methanol at 45 °C, diluted with MeTHF, treated with charcoal and

filtered through Clarcel®. Due to the difficult isolation of compound **7** the MeTHF solution was directly treated with sodium methoxide at 60 °C to afford compound **8**. During this step, the water content of the MeTHF solution was carefully controlled below 0.03% in order to avoid saponification of the methyl ester. The crude mixture was recrystallized from *iso*-propanol to afford compound **8** in 44% overall yield from citrazinic acid and in 99% purity on a kilogram scale. Methyl ester **8** was suspended in an aqueous solution of ammonia 6.4 M at 25 °C for 48 hours and afforded the corresponding amide **9** in 87% yield. The process safety for the Hofmann rearrangement was a concern that we wanted to investigate before starting kilogram manufacture.[9] During laboratory experiments on a 10 g scale, after the complete addition of bleach and heating of the chloramine crude mixture to 55 °C, we observed an exotherm rising the temperature up to 65 °C. To control this exothermic phenomenon the reaction was performed in two separated reactors. The formation of chloramine was realized at 20 °C with bleach and was slowly transferred into a second reactor containing a hot (80 °C) sodium hydroxide solution to effect the rearrangement. Under this process, the rearrangement was instantaneous without heat accumulation and the control of reaction was monitored by the addition rate of the chloramine solution. During the decarboxylation step with concentrated hydrochloric acid we also noticed foam formation due to CO_2 evolution and concomitant precipitation. Addition of one volume of ethanol to the reaction mixture reduced significantly the formation of foam, probably by reducing the surface tension of the aqueous solution. Compound **4** crystallized nicely after a basic work-up in 86% yield. Impurities **3** and **10** derived from unreacted material or double S_NAr with sodium methoxide were observed at 1.1%, and 0.1% respectively. Impurity **11** was obtained from an aromatic Finkelstein reaction[10] of residual chlorides during Hofmann rearrangement and was observed at around 0.3% (Scheme 4).

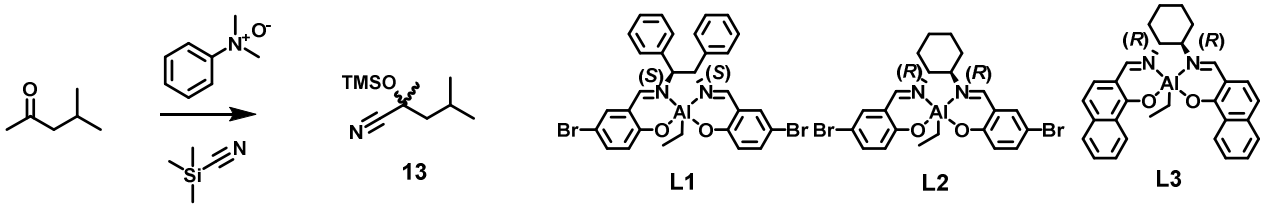
Scheme 4 : Hofmann Rearrangement Intermediates.



a) NaOCl 13.9% w/v, 25 °C. b) NaOH, 80 °C. c) HCl 36%, EtOH. d) NaOH, 86% from **9**

Access to enantiopure α-hydroxy-acid **6** was a key step for the manufacture of our API. Several routes have been described in the literature using Baeyer-Villiger oxidation of a ketoester,[11] or enantioselective 1,2-addition of *iso*-butyl magnesium bromide on a methyl vinyl ketone followed by ozonolysis,[12] but none of them was suitable for multi-kilogram production. Enantioselective cyanosilylation is a useful method to introduce quaternary centers on prochiral ketones,[13] nevertheless the chiral catalysts described are generally substrate dependent and enantiomeric excesses are in the 80% range. We applied the Feng *et al.* conditions on methyl *iso*-butyl ketone, with the catalyst system composed of an aluminum salen ligand and an *N*-oxide co-catalyst.[14] Results are summarized in Table 1.

Table 1 : Effect of Catalyst, Solvent and Temperature on Enantioselectivity



Entry[a]	catalyst	solvent	temperature	Yield [%]	*ee* [%][b]
1	**L1**	THF	25 °C	91	8 (*S*)
2	**L2**	THF	25 °C	90	68 (*S*)
3	**L3**	THF	25 °C	91	56 (*S*)

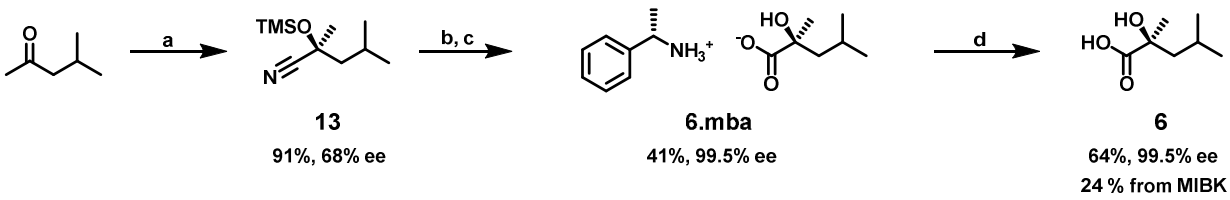
3	**L2**	THF	0 °C	<1%	ND
4	**L2**	DCM	25 °C	91	68 (*S*)

[a] All reactions were carried out with 0.4% of chiral Al-complex and 0.2% of *N*,*N*-dimethylaniline oxide over 18 h. [b] determined by chiral GC analysis on Astec Chiraldex B-DM column.

When catalyst **L1** was used, only a moderate 8% *ee* was obtained with MIBK in favor of the (*S*) enantiomer, whereas switching to catalyst **L2**, increased enantioselectivity to 68% *ee*. Bulky catalyst **L3** was also investigated but in this case the *ee* obtained was not improved compared to the previous result. Another option to increase the selectivity was to perform the reaction at a lower temperature, but interestingly this had a dramatic impact on the reaction rate as at 0 °C, only a very low conversion (<1%) was achieved after 18 h. During the work-up, solvents were removed under vacuum; the volatility of the O-TMS cyanohydrin **13** prompted us to evaluate a low boiling point solvent such as dichloromethane to replace THF. In dichloromethane, the reaction worked smoothly in 18 h and afforded the (*S*)-O-TMS cyanohydrin **13** in 91% yield with 68% *ee*. To avoid release of cyanhydric acid (HCN), TMSCN was always used as the limiting reagent compared to MIBK. As *α*-hydroxy-acid **6** was also fairly water soluble, the amount of water used in the hydrolysis step was decreased by using 36% HCl solution. The reaction mixture was heated under reflux for 1 hour, then the crude acid crystallized upon cooling at around 50 °C and afforded *α*-hydroxy-acid **6** in 77% yield and 68% *ee*. (Scheme 5). Since only a moderate enantiomeric excess was obtained from the cyanosilylation reaction, a further enantioselective crystallization step was necessary for the preparation of enantiopure **6**. The crude acid was crystallized with (*S*)-α-methyl benzylamine in ethyl acetate to give the ammonium salt **6.mba** that was filtered off and treated with 36% HCl to yield enantiopure acid **6** with an overall yield of 24% from MIBK. Direct crystallization of racemic *α*-hydroxy-acid **6**

with (*S*)-α-methyl benzylamine was also possible, however to obtain an enantiopure compound in one crystallization, a yield of 10% was the maximum we could achieve.

Scheme 5 : Developed Route to Enantiopure Hydroxy-Acid 6.



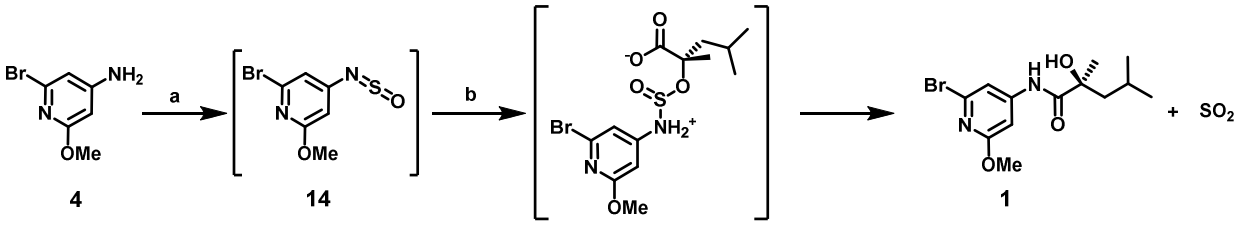
a) *N,N*-Dimethyl aniline oxide, TMSCN, DCM, 91%. b) HCl 36%, reflux, 77%. c) (*S*)-α-MBA, AcOEt 53% d) HCl 36%, 64%.

Development of final coupling step:

With the two key intermediates **4** and **6** in hand, we investigated the amide coupling in order to obtain the final API. Despite coupling of *α*-hydroxy-acids structurally related to our compound being described in literature,[15] in our case this amide bond proved to be very difficult to make. The steric hindrance of acid **6** and the weak nucleophilic behavior of aminopyridine **4** were suspected to be responsible for this lack of reactivity. Activation of acid **6** with common reagents such as thionyl chloride, oxalyl chloride, EDC/HOBT, T3P® or CDI were unsuccessful and no evidence of the expected coupled product was observed. An alternative coupling of *α*-hydroxy-acids with weakly nucleophilic amines has been described using thionyl chloride as an activator of the amino group. In this case, a *N*-sulfinyl amine intermediate is generated and reacts with the hydroxyl group to generate a cyclic intermediate that finally gives the amide bond with release of SO_2 (Scheme 6).[16] Activation of the aminopyridine **4** with thionyl chloride and imidazole in dichloromethane at -10 °C produced the *N*-sulfinyl amine **14**, that was used in the coupling reaction directly after a solvent switch from dichloromethane to acetonitrile. At room

temperature, no reaction occurred but when the mixture was heated under reflux, compound **1** was obtained with 50% conversion. This was a great improvement, but the conversion seemed to be blocked at 50% whatever the reaction conditions.

Scheme 6 : Coupling Reaction with *N*-Sulfinyl Amine

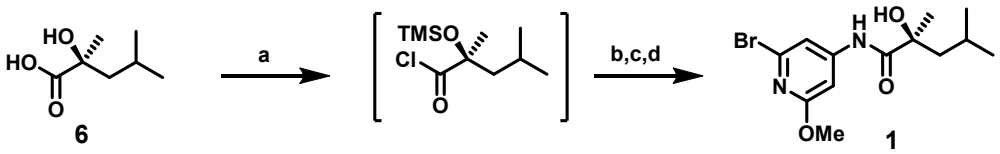


a) Imidazole, $SOCl_2$, DCM, -10 °C. b) **6**, ACN reflux, 18 h, 50% from **4**.

In order to improve yield and purity profile of this coupling reaction we came back to activation of the acid **6**. We demonstrated that the lack of reactivity was mainly due to the α-hydroxy function as the coupling reaction of aminopyridine **4** with 2,4-dimethylpentanoic acid activated with oxalyl chloride worked nicely. Early studies to temporary protect the free alcohol on *α*-hydroxy-acid **6**, using AcCl gave poor results but when we used TMS as a protecting group, we were able to generate the acyl chloride and then to add it to the aminopyridine **4** to provide the target compound in good yield[17] (Scheme 7). The protocol used was to protect both carboxylic acid and alcohol with two equivalents of TMSCl in pyridine at 10 °C. The water content of *α*-hydroxy-acid **6** was carefully monitored (< 1%) in order to achieve the desired protection. The acyl chloride was synthesized *in situ* with oxalyl chloride and a catalytic amount of DMF while maintaining the temperature below 5 °C. The crucial amide bond was realized by addition of a solution of aminopyridine **4** in dichloromethane at 25 °C and gave the targeted compound in 30 min. Final deprotection of the silyl group was achieved by adding a solution of

acetic acid in ethanol. The crude mixture was quenched with hydrochloric acid and extracted with dichloromethane, submitted to polish filtration and stored in solution.

Scheme 7 : Manufacture of Final API

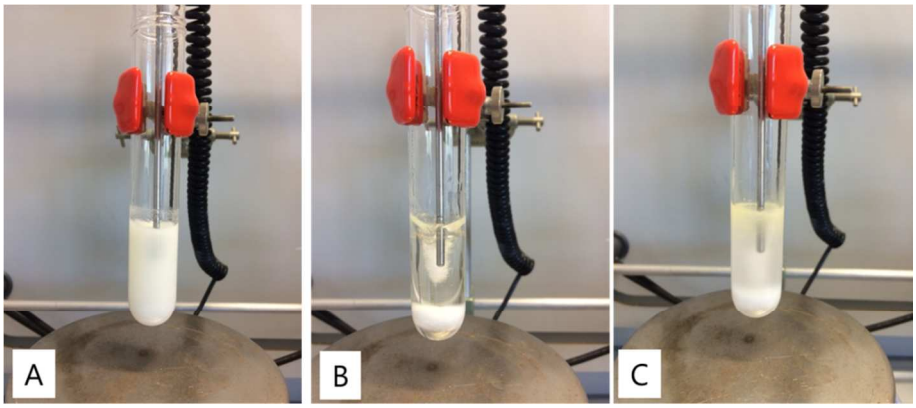


a) TMSCl, DMAP, pyridine, DCM, 10 °C then $(COCl)_2$, DMF b) **4**, pyridine, DCM. c) EtOH, AcOH. d) Cyclohexane, 5% compound **1** seeds, 74% from **6**

Crystallization in oiling-out system:

The main challenge of this synthesis resulted in the crystallization process of the final API, as this small molecule was highly soluble in every solvent tested except in alkanes or in water. Attempts to recrystallize compound **1** (m.p. = 81 °C) in water gave a liquid-liquid phase separation (LLPS) when the temperature reached 60 °C and this emulsion remained stable at 25 °C. At this temperature, seeds of crystalline material **1** were added and the oily phase slowly turned into a gummy solid. In *n*-heptane the behavior was slightly different as a clear solution was obtained when temperature reached 65 °C and oiling-out was observed upon cooling at around 60 °C (Figure 5). This oiling-out system was stirred at 25 °C for several days to perform a slurry ripening and submitted to heat cycles from 20 °C to 40 °C but no crystallization occurred.[18] This solubility gap (*e.g.* liquid-liquid phase separation) was indicative of a monotectic system, and in our case the observation of stable emulsions at room temperature indicated that the nucleation step was the limiting step.

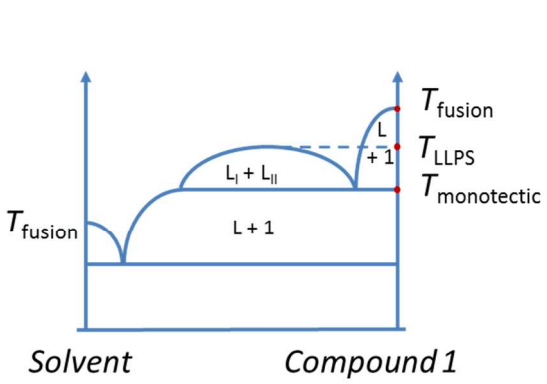
Figure 5 : Oiling-out Phenomenon in *n*-Heptane

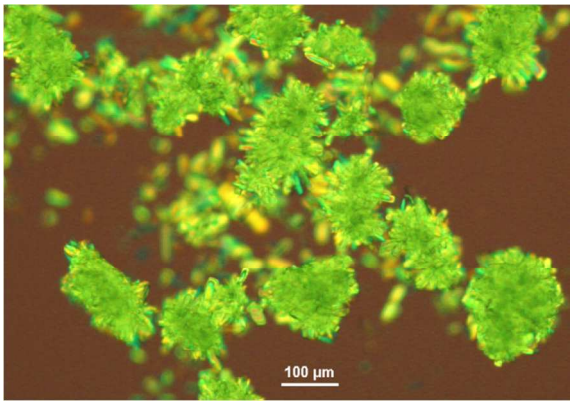


A) Suspension of pure **1** in *n*-Heptane (10 V/P) at 25 °C. B) Homogenous solution at 65 °C. C) Oiling-out at 60 °C.

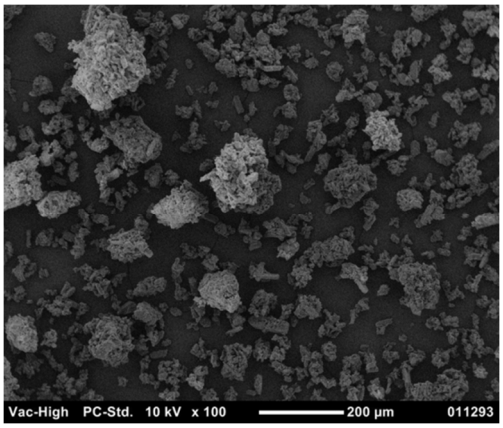
Oiling-out often occurs for small organic molecules with a low melting point and crystallization of such systems is generally unwanted as crystals obtained are usually impure and purging of impurities remains a challenge.[19] In such systems, a liquid-liquid phase separation occurs upon cooling, leading to two liquid phases: a solute lean phase (L_I) and a solute rich phase (L_{II}) (Figure 6a). The knowledge of the monotectic temperature is essential and seeding the liquid-liquid mixture to induce nucleation can only be performed below the monotectic temperature where crystals of compound **1** can thermodynamically exist.[20]

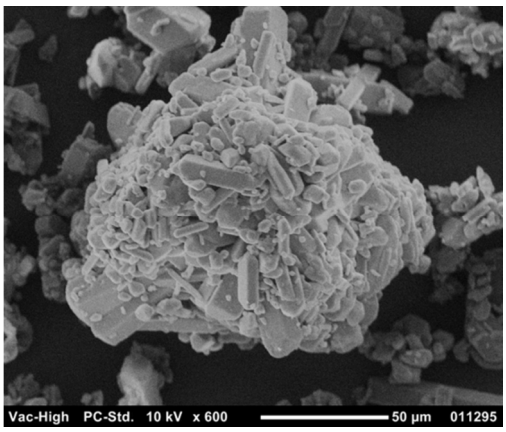
Figure 6 : Schematic Representation of a Monotectic System and Crystals of Compound 1 Obtained after Seeding





6a 6b





6c 6d

6a) Simplified representation of a monotectic system 6b) Microscopic observation of compound **1,** magnification 10X observed between crossed polarizing filters and a ¼ wavelength plate 6c) Scanning Electron Microscopy, magnification 100X 6d) Scanning Electron Microscopy, magnification 600X

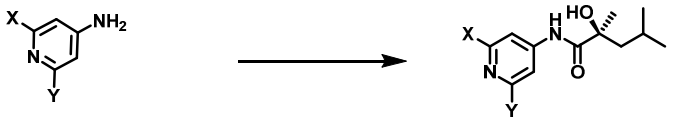
To approximate the monotectic temperature, we observed the LLPS temperature upon cooling homogenous solutions, and seeding with crystalline material was performed 5 °C below LLPS temperature. Several alkanes were tested and the LLPS temperature was recorded: *n*-hexane, (61 °C) *n*-heptane (60 °C), methylcyclohexane (36 °C), cyclohexane (33 °C).[21] Despite the fact that crystallization occurred in *n*-heptane and *n*-hexane, the solids obtained were greasy and mainly

stuck on the reactor glassware. The behavior observed in cyclohexane or methylcyclohexane was much better and afforded an even crystallization.

For our process, cyclohexane was chosen based on price and ICH solvent residual limits allowed in the API (cyclohexane 3800 ppm; methylcyclohexane : 1180 ppm). The scale up of the laboratory procedure was performed incrementally from a 0.1 L to 10 L reactor to ensure that the LLPS and the crystals shapes were not dependent of stirrer type and rotational speed.[22] This first study prompted us to perform the reaction in a 100 L reactor at kilogram scale, the crude dichloromethane solution of compound **1** was azeotroped with cyclohexane until temperature of condensates reached 75 °C, cyclohexane was added to the reactor to reach a final volume of about 10 V/P and cooled until oiling-out occurred at around 33 °C. At 28 °C seeds of compound **1** were added (5%) and the mixture was stirred gently for 16 hours at 28 °C. Microscopic observation of the powder displayed "desert rose" shape clusters of platelet crystals demonstrating that nucleation occurred in the solute-rich droplets of the emulsion (Figure 6b, 6c, 6d).[23] Compound **1** was obtained as a crystalline powder with 74% yield, an HPLC purity of 98.8% with less than 50 ppm of cyclohexane. The main impurities identified in compound **1** were the acylated compounds **14**, **15** and **16** arising from aminopyridines **3, 10** and **11**. (Scheme 8) During the crystallization process, the impurity **14** was efficiently purged, whereas levels of compounds **15** and **16** remained in the same range in compound **1** indicating that these two impurities have to be controlled in aminopyridine **4**. The purge of compound **14** was unexpected as crystallizations of systems exhibiting an oiling-out are usually not recommended for purification purpose. The conversion of coupling step was followed by TLC, thus the precise amount in crude mixture of impurity **14** was not determined. The coupling reaction conditions were applied to aminopyridine **3** with α-hydroxy-acid **6** and afforded compound **14** in a similar

yield (66% vs 74%) indicating that nucleophilicity of aminopyridines **3** and **4** were comparable and that compound **14** might be present in the crude mixture around 1%. The lack of incorporation of compound **14** in the compound **1** crystal lattice might be explained by the steric bulk of two bromines atoms on the structure or by a different solubility in cyclohexane.

Scheme 8 : Identified Impurities



X = Y = Br : 3
X = Y = OMe : 10
X = Cl, Y = OMe : 11

X = Y = Br : 14
X = Y = OMe : 15
X = Cl, Y = OMe : 16

Impurities in aminopyridine **4**	Related Impurities in compound **1**
3 : 1.1%	**14** : 0.1%
10 : 0.1%	**15** : 0.1%
11 : 0.3%	**16** : 0.3%

Conclusion :

In conclusion, we have developed a scalable process for the manufacture of compound **1** with an overall yield of 25% (HPLC purity 98.8% and > 99% *ee*) from citrazinic acid widely available commercially. A stable polymorphic form has been obtained and the absolute configuration has been established with anomalous scattering experiment thanks to the bromine atom on the structure. A new access to aminopyridine **4** has been developed through a dibromide formation of citrazinic acid followed by S_NAr reaction and Hofmann rearrangement. A simple synthesis of enantiopure α-hydroxy-acid **6** has been devised using an enantioselective cyanosilylation followed by (*S*)-α-methyl benzylamine salt resolution. The key amide coupling was achieved

with a TMS protection followed by acyl chloride formation and final crystallization was successfully achieved by seeding an oiling-out system in cyclohexane below the monotectic temperature. Our final API has been successfully manufactured several times at multi-kilogram scale to support preclinical and clinical studies.

General Information.

All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 MHz, 100 MHz. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks, and coupling constants are reported in hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet. X-ray powder diffraction (XRPD) analyses were performed by Holodiag using Panalytical X'Pert Pro MPD X-ray powder diffractometer. Differential scanning calorimetry (DSC) were performed using Perkin Elmer Diamond thermogravimetric analyzer, using 50 µL aluminum caps. Hold for 2.0 min at 20.0 °C, heat from 20.0 °C to 110.0 °C at 10.0 °C/min then hold for 2.0 min at 110.0 °C. Enantiomer ratios were determined by chiral GC analysis with Astec Chiraldex B-DM column, or by chiral HPLC analysis on Daicel Chiralpak ID or Chiralpack IC columns in comparison with racemates. The HRMS measurement was performed on a LCT (Time Of Flight) mass spectrometer from Waters in the positive-ion mode. Microscopic observation were performed with Zeiss AXIO microscope with 10X magnification and observed between crossed polarizing filters and ¼ wavelength plate. SEM observations were realized with a JEOL JCM 5000 Neoscope with an accelerating voltage of 10 kV.

Binary Phase Diagram. The binary phase diagram was constructed from DSC data's based on simplified Schröder-Van Laar equation for the portion of the liquidus curve between the eutectic

and the pure enantiomer and from Prigogine-Defay equation for the liquidus curve between the two eutectics. with x = mole fraction, R = gas constant ($J.mol^{-1}.K^{-1}$), T_E, T_R = melting temperature (°K) of enantiomer and racemic compounds, and ΔH_E, ΔH_R = enthalpy of fusion of enantiomer and racemic compounds ($J.mol^{-1}$) see also Supporting Information. The theoretical eutectic was obtained from the intersection of the two liquidus curves.

$Ln\ x = \frac{\Delta H_E}{R}\left(\frac{1}{T_E} - \frac{1}{T}\right)$: Schröder-Van Laar

$Ln\ 4x(1-x) = \frac{2\Delta H_R}{R}\left(\frac{1}{T_R} - \frac{1}{T}\right)$: Prigogine-Defay

Methyl 2-bromo-6-methoxyisonicotinate (8)

In a 20 L double jacketed reactor, citrazinic acid (1.0 kg, 6.4 mol, 1 eq.) and sulfolane (6.3 kg, 5 vol.) were charged. The reaction mixture was heated to 90 °C then a solution of phosphorus(V) oxybromide (2.77 kg, 9.7 mol, 1.5 eq.) in sulfolane (3.7 kg, 3 vol.) was added over 39 min. The reaction mixture was then heated to 125 °C and stirred to this temperature for 2 h. Consumption of citrazinic acid was monitored by HPLC. The reaction mixture was chilled to 40 °C, then methanol (2.6 L, 10 eq.) was introduced over 30 min and stirred at 45 °C for 30 min, methanol was distilled off under vacuum (V = 0.64 L). In a 20 L double jacketed reactor, water (8.0 kg, 8 vol.) was charged, then the previous reaction mixture was charged at 20 °C to allow precipitation. The reaction mixture was shilled to 0 °C then stirred at this temperature for 1 h. The solid was filtered off and washed with water (4 x 3 L.). The solid was re-charged into the reactor then MeTHF (4.30 kg, 5 vol.) was added with 0.68 kg of charcoal. The reaction mixture was heated at 50 °C and stirred at this temperature for 30 min. The reaction mixture was filtered on Clarcel®, and washed with dichloromethane (3 x 1 L) and with MeTHF (4 x 1.7 kg). The organic phase was washed with brine (1.0 L, 1 vol.) then azeotroped with MeTHF (8 L) until

water content reach 0.03%, to yield a methyl 2,6-dibromoisonicotinate solution (4.84 Kg). The previous solution was heated to 60 °C then a sodium methoxide solution 25%w/w in MeTHF (0.73 kg, 6.5 mol, 1 eq.) was added over 1 hour. The reaction mixture was shilled to 30 °C, then washed with saturated $NaHCO_3$ (8.0 L), and with another saturated $NaHCO_3$ (2.0 L), and finally with brine (3.0 L). The organic phase was concentrated and the residue (m = 0.90 kg) was recrystallized from isopropanol (5.0 L). The solid was filtered off, washed with isopropanol (1.2 L) and dried under vacuum at 45 °C. 691 g of methyl 2-bromo-6-methoxyisonicotinate were obtained. Overall yield = 44%.

NMR ^{1}H (400 MHz, $CDCl_3$): 7.54 (s, 1H); 7.22 (s, 1H); 3.91 (s, 3H); 3.89 (s, 3H). NMR ^{13}C (100 MHz, CDCl3) : 164.0, 163.6, 142.4, 138.7, 119.1, 109.5, 54.7, 53.1. ESI-HRMS(m/z) calcd for $C_8H_9BrNO_3^+$ $[M + H]^+$ 245.9760 found 245.9760

2-Bromo-6-methoxyisonicotinamide (9)

In a 10 L double jacketed reactor, methyl 2-bromo-6-methoxyisonicotinate **8** (450 g; 1.83 mol; 1.0 eq.) were charged followed with an ammonia solution 6.4 M (4 L). The suspension was stirred at 20 °C for 48 h, then the solid was filtered off, washed with water (7 x 900 mL) until pH of filtrate reached pH=8. The solid was dried under vacuum at 40 °C. 370 g de 2-bromo-6-methoxyisonicotinamide were obtained. Yield = 87%

NMR ^{1}H (400 MHz, DMSO-d_6): 8.23 (sl, 1H); 7.80 (sl, 1H); 7.57 (s, 1H); 7.23 (s, 1H); 3.88 (s, 3H). NMR ^{13}C (100 MHz, DMSO-d_6) : 164.5, 163.9, 147.2, 138.4, 118.5, 108.1, 54.5. ESI-HRMS(m/z) calcd for $C_7H_8BrN_2O_2^+$ $[M + H]^+$ 230.9764 found 230.9764

2-Bromo-6-methoxypyridin-4-amine (4)

In a 1L double jacketed reactor 2-bromo-6-methoxyisonicotinamide **9** (100 g; 0.44 mol; 1.00 eq.) and water (400 mL) were charged, and then the mixture was shilled to 10 °C. A sodium hydroxide solution was prepared from NaOH (21 g, 0.51mol) in 50 mL water, then this solution was added to the previous solution maintaining temperature below 10 °C. A bleach solution (279 mL; 139.50 g/L; 0.52 mol; 1.2 eq.) was added while keeping temperature below 10 °C, and then the reaction mixture was stirred at 20 °C for 2 h. In a 4 L double jacketed reactor NaOH (20.96 g; 0.51 mol; 1.16 eq.) were dissolved in 400 mL water, and heated to 80 °C. Onto this solution, the previous chloramine solution was added over 20 minutes (T = 77 °C) the mixture was stirred 2 hours at 80 °C then shilled to 25 °C. Water (700 mL) and ethanol (100 mL) were added and the reaction mixture was shilled to 10 °C. Hydrochloric acid 36% (140 mL; 12 M; 1.69 mol; 3.88 eq.) was added while keeping temperature below 6 °C then the reaction mixture was heated to 20 °C. Another Hydrochloric acid solution made from concentrated HCl 36% (36 mL; 12 M; 0.44 mol; 1.00 eq.) in 500 mL water was added and the suspension was filtered on dicalite® and finally recharged into the reactor. Sodium hydroxide (99.90 g; 2.42 mol; 5.55 eq.) was added portionwise while keeping temperature below 30 °C. The reaction mixture was stirred 1 hour at 25 °C and filtered off; the cake was washed with water (3 x 1L) and dried at 45 °C. 76 g of 2-bromo-6-methoxypyridin-4-amine were obtained. Yield = 86%.

RMN ^{1}H (400 MHz, DMSO-d_6): 6.38 (s, 1H); 6.26 (sl, 2H); 5.82 (s, 1H); 3.71 (s, 3H). RMN ^{13}C (100 MHz, DMSO-d_6): 164.2, 158.6, 138.4, 106.9, 90.7, 53.3. ESI-HRMS(m/z) calcd for $C_6H_8BrN_2O^+$ $[M + H]^+$ 202.9815 found 202.9816

(*S*)-1-Phenylethan-1-aminium (*S*)-2-hydroxy-2,4-dimethylpentanoate (6.mba)

In a 15 L double jacketed reactor trimethylsilyl cyanide (3 162 mL; 24.86 mol; 0.95 eq.) and *N*,*N*-dimethylaniline oxide (8.97 g; 65.42 mmol; 0.004 eq.)[14] were charged and this solution was stirred 1 hour at 23 °C. In a 10 L double jacketed reactor 2,2'-((1E,1'E)-(((1R,2R)-cyclohexane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis-4-bromophenolate ethylaluminium (55.92 g; 104.67 mmol; 0.006 eq.)[14] in MIBK (3 276 mL; 26.17 mol; 1.00 eq.) and DCM (7.86 L) was stirred 1 hour at 23 °C. This solution was added to the trimethylsilyl cyanide solution at 23 °C and the resulting reaction mixture was stirred 1 hour at this temperature. The mixture was concentrated until minimum volume then a mixture of *n*-heptane/ethyle acetate 80/20 with 1% of diisopropylethylamine (3 L) was added. This solution was filtered through a pad of silica and washed with a mixure *n*-heptane/ethyle acetate 80/20 with 1% of diisopropylethylamine (1 L). The filtrate was charged in the reactor and concentrated under reduced pressure to yield 2,4-dimethyl-2-((trimethylsilyl)oxy)pentanenitrile as a pale yellow oil (4 772 g) Yield = 91%, 68% *ee* (Chiral GC, Astec Chiraldex B-DM, 0.25 mm x 30 m, column temperature = 42 °C (isothermal), inject temperature = 105 °C, IonSource temperature = 150 °C, inlet pressure = 112.7 kPa) : t_r (minor) = 38.5 min, t_r (major) = 39.2 min.

In a 15 L double jacketed reactor, 2,4-dimethyl-2-((trimethylsilyl)oxy)pentanenitrile (2 406 g; 12.07 mol; 1.00 eq.) and concentrated HCl 36%. (6 L; 72 mol; 2.50 V) were charged, then the reaction mixture was stirred under reflux for 5 hours. Water (6 L) was added onto the reaction mixture to allow the temperature to reach 50 °C. Crystallization occurred and the mixture was allowed to cool to 23 °C. The solid was filtered off, washed with water and dried under vacuum at 45 °C. (*S*)-2-Hydroxy-2,4-dimethylpentanoic acid was obtained as a white crystalline powder. (1 368 g), Yield = 77%, 68% *ee*. HPLC (Daicel Chiralpak ID 250x4.6 mm, 5µm,

Water/MeOH/HCOOH 600:400:2, 0.7 mL.min^{-1}, 25 °C, UV 215 nm) : t_r (major) = 7.6 min, t_r (minor) = 9.4 min.

In a 15 L double jacketed reactor (*S*)-2-hydroxy-2,4-dimethyl-pentanoic acid (1 150 g; 7.87 mol; 1.00 eq.) and ethyle actate (11.5 L) were charged then (*S*)-1-phenylethylamine (912 mL; 7.08 mol; 0.90 eq.) was added while maintaining temperature below 30 °C. Crystallization was started with a seed of enantiopure (*S*)-1-phenylethan-1-aminium (*S*)-2-hydroxy-2,4-dimethylpentanoate (10 g) and the reaction mixture was stirred 3 hours at 20 °C, The solid was filtered off, washed with ethyl acetate (1 L) and dried under vacuum at 50 °C. (*S*)-1-Phenylethan-1-aminium (*S*)-2-hydroxy-2,4-dimethylpentanoate (1 122 g) was obtained as a white powder. Yield = 53%, 99.5% *ee*.

NMR ^{1}H (400 MHz, DMSO-d_6): 7.48 (m, 2H); 7.35 (m, 3H); 4.29 (q, J = 6.7 Hz, 1H); 1.71 (non, J = 6.7 Hz, 1H); 1.55 (dd, J = 13.4 & 6.6 Hz, 1H); 1.45 (d, J = 7 Hz, 3H); 1.33 (dd, J = 13.6 & 5.6 Hz, 1H); 1.12 (s, 3H); 0.87 (d, J = 6.6Hz, 3H); 0.81 (d, J = 6.6 Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6) : 180.1, 141.4, 128.5, 127.9, 126.7, 73.6, 49.9, 48.7, 28.3, 24.7, 24.3, 23.7, 21.8.

(*S*)-2-Hydroxy-2,4-dimethyl-pentanoic acid (6)

In a 15 L double jacketed reactor (*S*)-1-phenylethan-1-aminium (*S*)-2-hydroxy-2,4-dimethylpentanoate (3 081 g; 11.52 mol; 1.00 eq.) and water (3 L) were charged. Concentrated hydrochloric acid 36%. (7.7 L) was added while maintaining temperature below 40 °C. The reaction mixture was chilled to 10 °C, the solid was filtered off, washed with shilled water, and dried under vacuum at 45 °C. (*S*)-2-Hydroxy-2,4-dimethyl-pentanoic acid (1 078 g) was obtained as a white powder Yield = 64%, 99.5% *ee.*

NMR ^{1}H (400 MHz, DMSO-d_6): 12.36 (sl, 1H); 4.74 (sl, 1H); 1.74 (hept, J = 6.1 Hz, 1H); 1.74 (dd, J = 13.7 & 6.7 Hz, 1H); 1.46 (dd, J = 13.6 & 5.6 Hz, 1H); 1.25 (s, 3H); 0.88 (d, J = 6.6Hz, 3H); 0.83 (d, J = 6.6Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6): 178.2, 73.3, 48.5, 27.5, 24.4, 24.0, 23.4. ESI-HRMS(m/z) calcd for $C_7H_{13}O_3^-$ [M - H]$^-$ 145.0870 found 145.0856

(*S*)-*N*-(2-Bromo-6-methoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (1)

In a 100 L glass lined reactor (*S*)-2-hydroxy-2,4-dimethyl-pentanoic acid **6** (2019 g; 13.8 mol; 1.00 eq.), 4-dimethylaminopyridine (84.2 g; 0.69 mol; 0.05 eq.), dichloromethane (16 L) were charged. The mixture was shilled to 0 °C, and then pyridine (2.4 L) and dichloromethane (4 L) were added while maintaining temperature below 5 °C. Chlorotrimethylsilane (3.3 Kg; 30 mol; 2.20 eq.) was added while maintaining temperature below 5 °C and the reaction mixture was allowed to warm to 20 °C and then stirred at this temperature for 4 hours. The mixture was shilled to 0 °C and *N*,*N*-dimethylformamide (35 g; 0.17 mol; 0.03 eq.) was added followed by oxalyl chloride (1583 g; 12.5 mol; 0.90 eq.) keeping temperature below 5 °C. The reaction mixture was stirred 1 hour at 5 °C and another *N*,*N*-dimethylformamide (18 g; 0.09 mol; 0.02 eq.) was added. The mixture was allowed to warm to 20 °C and stirred 1 hour to this temperature. A solution of 2-Bromo-4-Amino-6-Methoxy-Pyridine **4** (2328 g; 11.4 mol; 0.83 eq.) in dichloromethane (18 L) and pyridine (1.2 L) was prepared and added onto the previous reaction mixture while keeping temperature below 25 °C. The mixture was stirred 30 min at this temperature and complete conversion was monitored TLC. A solution of acetic acid (1659 g; 2 eq.) in ethanol (13 L) was prepared and added onto the reaction mixture while keeping temperature below 25 °C and the reaction mixture was stirred 18 h. A solution of hydrochloric acid (1.6 L; 12.00 M) in water (18 L) was prepared and added to the reaction mixture, the aqueous phase was discarded and the organic phase was washed with water (20 L) then with a

solution of NaOH (773 g) in water (20 L) and finally with water (20 L). The organic phase was filtered through a filter packed with charcoal (600 g) and the filter was washed with dichloromethane (6 L). The resulting solution was charged into the reactor and concentrated, 20 L were removed and cyclohexane (28 L) was added and concentration was pursued until condensate temperature reached 75 °C. Extra cyclohexane (7 L) was added to reach a final volume of about 30 L and the reaction mixture was cooled to 28 °C. A seed of (*S*)-N-(2-bromo-6-methoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (99 g; 0.29 mol; 0.05 eq.) was added and the reaction mixture was shilled to 20 °C and stirred 16 hours at this temperature. The solid was filtered off, washed with cyclohexane (7 L) and dried under vacuum at 45 °C to yield (*S*)-N-(2-bromo-6-methoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (2.8 Kg). Yield = 74%, HPLC purity 98.8%, 99.5% *ee* HPLC (Daicel Chiralpak IC 250x4.6 mm, 5µm, *n*-Heptane/IPA/TFA 930:70:1, 1 mL.min^{-1}, 25 °C, UV 210 nm) : t_r (minor) = 5.1 min, t_r (major) = 5.9 min.

NMR ^{1}H (400 MHz, DMSO-d_6): 10.0 (sl, 1H); 7.73 (s, 1H); 7.33 (s, 1H); 5.70 (sl, 1H); 3.80 (s, 3H); 1.79-1.67 (m, 2H); 1.49 (dd, J = 13.6 & 5.2 Hz, 1H); 1.32 (s, 3H); 0.89 (d, J = 6.4 Hz, 3H); 0.78 (d, J = 6.4 Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6): 176.7, 164.0, 149.5, 138.1, 111.1, 74.9, 53.9, 48.6, 27.5, 24.3, 23.6, 23.2. ESI-HRMS(m/z) calcd for $C_{13}H_{20}BrN_2O_3^+$ $[M + H]^+$ 331.0652 found 331.0654

(*S*)-*N*-(2,6-Dibromopyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (14)

Using compound **1** procedure, but with 2,6-Dibromo-pyridin-4-ylamine (5.00 g; 19.85 mmol; 1.00 eq.), 5 g of (*S*)-N-(2,6-dibromopyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide were obtained. Yield = 66%

NMR ^{1}H (400 MHz, DMSO-d_6): 10.40 (sl, 1H); 8.17 (s, 2H); 5.77 (sl, 1H); 3.80 (s, 3H); 1.80-1.67 (m, 2H); 1.50 (dd, J = 13.6 & 5.0 Hz, 1H); 1.33 (s, 3H); 0.90 (d, J = 6.3 Hz, 3H); 0.78 (d, J = 6.3 Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6): 177.2, 149.3, 140.2, 116.4, 75.0, 48.7, 27.5, 24.3, 23.7, 23.3. ESI-HRMS(m/z) calcd for $C_{12}H_{17}Br_2N_2O_2^+$ $[M + H]^+$ 378.9651 found 378.9653

(*S*)-*N*-(2,6-Dimethoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (15)

Using compound **1** procedure, but with 2,6-Dimethoxy-pyridin-4-ylamine (2.5 g; 20 mmol; 1.00 eq.), 2.1 g of (*S*)-N-(2,6-dibromopyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide were obtained. Yield = 47%.

NMR ^{1}H (400 MHz, DMSO-d_6): 9.79 (sl, 1H); 6.87 (s, 2H); 5.62 (sl, 1H); 3.80 (s, 3H); 1.80-1.67 (m, 2H); 1.48 (dd, J = 14.0 & 5.0 Hz, 1H); 1.32 (s, 3H); 0.90 (d, J = 6.6 Hz, 3H); 0.78 (d, J = 6.6 Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6): 176.3, 163.1, 149.7, 91.3, 74.8, 53.1, 48.7, 27.5, 24.4, 23.6, 23.2. ESI-HRMS(m/z) calcd for $C_{14}H_{23}N_2O_4^+$ $[M + H]^+$ 283.1652 found 283.1650

(*S*)-*N*-(2-Chloro-6-methoxypyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide (16)

Using compound **1** procedure, but with 2-chloro-6-methoxypyridin-4-amine (5.00 g; 31 mmol; 1.00 eq.), 5 g of (*S*)-N-(2,6-dibromopyridin-4-yl)-2-hydroxy-2,4-dimethylpentanamide were obtained. Yield = 55%

NMR ^{1}H (400 MHz, DMSO-d_6): 10.1 (sl, 1H); 7.58 (s, 1H); 7.31 (s, 1H); 5.69 (sl, 1H); 3.82 (s, 3H); 1.81-1.67 (m, 2H); 1.49 (dd, J = 13.8 & 5.2 Hz, 1H); 1.33 (s, 3H); 0.90 (d, J = 6.6 Hz, 3H); 0.78 (d, J = 6.6 Hz, 3H). NMR ^{13}C (100 MHz, DMSO-d_6): 176.8, 164.2, 149.8, 147.7, 107.3,

97.6, 74.9, 53.9, 48.7, 27.5, 24.4, 23.6, 23.2. ESI-HRMS(m/z) calcd for $C_{13}H_{20}ClN_2O_3^+$ $[M + H]^+$ 287.1157 found 287.1157

ASSOCIATED CONTENT

SUPPORTING INFORMATION

^1H and ^{13}C NMR spectra of the compound **1**; procedures for synthesis, isolation and characterization data. This information is available free of charge *via* the Internet at http://pubs.acs.org/

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