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The development of a practical synthesis of the potent and selective somatostatin sst_3 receptor antagonist [4-(3,4-difluoro-phenyl)-piperazine-1-yl]-{(4*S*,4a*S*,8a*R*)-2[(*S*)-3-(6-methoxy-pyridin-3-yl)-2-methyl-propyl]-decahydroisoquinoline-4-yl}-methanone (NVP-ACQ090)

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Abstract—The decahydroisoquinoline derivative NVP-ACQ090 is a potent and selective antagonist at the somatostatin sst_3 receptor. The original research synthesis of NVP-ACQ090 comprises a main chain of nine linear steps and two side chains of three and steps, respectively. This synthesis is highly convergent, but very complex and expensive, and involves several reagents that are not acceptable for a large scale synthesis. In chemical development, all the unacceptables could be replaced, and the overall efficiency of the synthesis was much improved.

1. Introduction

Somatostatin (somatotropin-release-inhibiting factor, SRIF) is a widely distributed peptide hormone originally isolated from the hypothalamus as an inhibitor of growth hormone release.[1] It occurs in two biologically active forms, a tetradecapeptide $SRIF_{14}$ and a 28-residue peptide $SRIF_{28}$, and is widely distributed in the central nervous system, endocrine and peripheral tissues. Multiple biological effects are attributed to SRIF, which include the inhibition of processes like the pancreatic secretion of insulin and glucagon, the release of gastrin by the gut, and cell proliferation.[2] In the CNS, SRIF acts as neurotransmitter or neuromodulator, having effects on locomotor activity, cognitive function and the release of other neurotransmitters.[3] To date, five somatostatin receptor subtypes (sst_1 to sst_5) have been cloned and characterized, all belonging to the G-protein-coupled receptor superfamily.[4] So far, only sst_2 and sst_5 have been linked to specific physiological functions, namely inhibition of growth hormone release, glucagons release and gastrin secretion for sst_2,[5] and insulin release inhibition for sst_5.[6]

In order to elucidate further the function of the different SRIF receptor subtypes, and to evaluate the potential of somatostatin receptor ligands as therapeutic agents, there is a clear need for non-peptidic, metabolically stable, potent and subtype selective SRIF receptor agonists and antagonists.[7] First non-peptidic structures with micromolar affinity for SRIF receptors used sugar or benzodiazepine cores to align the crucial functionalities of the Phe, Trp and Lys side chains appropriately.[8] In the meantime, more selective non-peptidic agonists for all five receptor subtypes with nanomolar affinity have been published.[9] The only non-peptidic and potent antagonists reported so far are sst_2 selective derivatives of the dipeptide d-Trp-Lys[10] and sst_3 selective d-Trp derived imidazoles.[11]

In the course of a program directed towards the identification of non-peptidic and subtype selective SRIF

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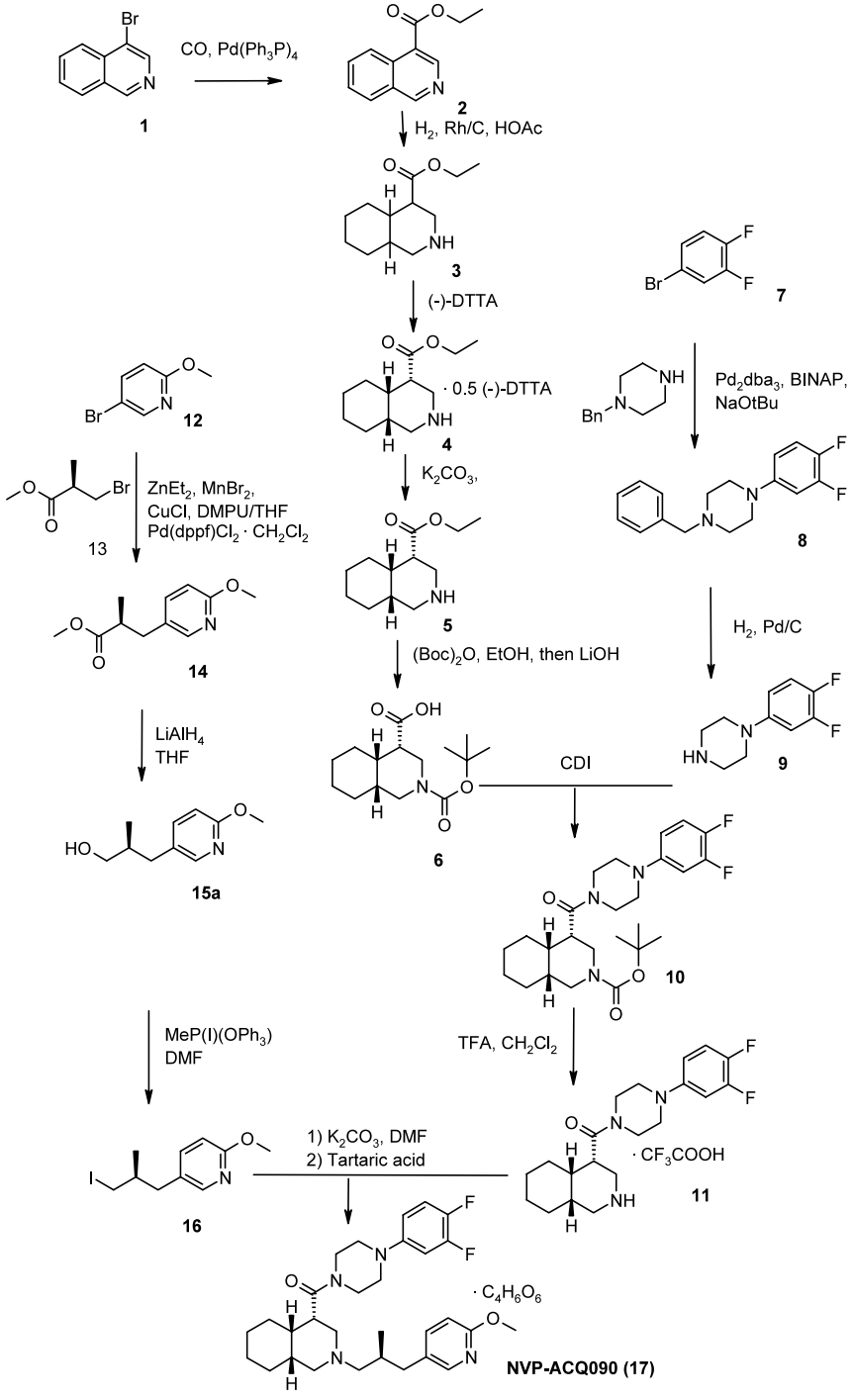
agonists and antagonists, we identified the highly potent and selective sst_3 antagonist NVP-ACQ090. The SAR around this novel structure, as well as its in vitro and in vivo properties, were extensively evaluated; the results of these studies will be reported elsewhere in due course. Herein, we present the research synthesis of this relatively complex molecule, and in particular we describe an improved procedure appropriate for larger scale production, considering economical and safety criteria.

2. Results and discussions

The main chain of the research synthesis (Scheme 1) started from 4-bromoisoquinoline **1**. The first step was a Pd-catalyzed carbonylation[12] to isoquinoline-4-carboxylic acid ethyl ester **2**, followed by a Rh-catalyzed high pressure hydrogenation which led to a mixture of isomers containing around 80% of the desired diastereomer. After crystallization from ethanol/MTBE the racemic decahydroisoquinoline ester **3** could be



Scheme 1. Research synthesis of NVP-ACQ090 (**17**).

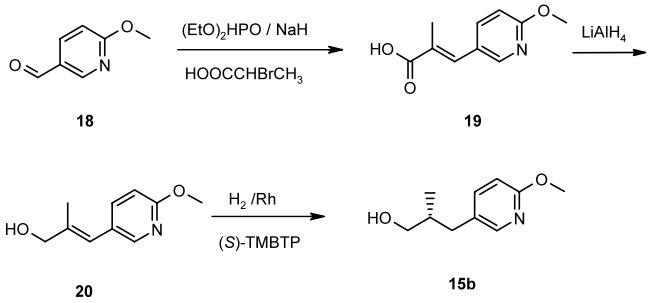
isolated in 53% yield. In the following step a resolution of the racemate **3** via diastereomeric salt formation was performed with *p*-toluoyl tartaric acid. The intermediate salt **4** could be isolated in 17% yield and an ee of 97% as the hemi-*p*-toluoyltartrate salt. The free base **5** was then liberated in 90% yield. The absolute configuration of **5** was determined by X-ray analysis of the corresponding Mosher's acid amide. Boc protection and ester hydrolysis yielded the Boc-protected free acid **6**. Intermediate **9** was prepared in two steps starting from *N*-benzylpiperazine and 3,4-difluoro bromobenzene **7**. A Pd-catalyzed Buchwald-type arylation of benzylpiperazine[13] followed by *N*-debenzylation led to the piperazine derivative **9** in 93% overall yield. Coupling of the acid **6** with the piperazine derivative **9** was achieved via the acid chloride prepared in situ with hexachloroacetone/Diphos.[14] Cleavage of the Boc protecting group finally afforded the key intermediate **11**. For the methoxypyridine bearing side chain, the research synthesis started from 5-bromo-2-methoxypyridine **12**. In a Knochel type Pd-catalysed coupling[15] with (*S*)-3-bromo-2-methyl propionic acid methyl ester **13** the intermediate **14** was obtained in 56% yield. However, in an upscale experiment this yield dropped to 43%. The ester **14** was reduced to the alcohol **15a** with $LiAlH_4$ in 82% yield. At this stage the enantiomeric purity was confirmed to be >99%. Initially, the coupling of the main chain intermediate **11** with the pyridine side chain was achieved via reductive amination[16] of the aldehyde obtained by oxidation of the alcohol **15a**. However, partial racemisation of the α-center of the aldehyde occurred and lead to the formation of an undesired diastereomer of the drug substance **17**, which could, if present in quantities above 3%, only be removed via crystallization with substantially reduced yield. Therefore, alcohol **15a** was transformed to the iodo compound **16** in good yield (89%). The assembly of the product **17** was finally achieved by direct alkylation[17] of the amine **11** with iodide **16** in 85% yield (tartrate salt).

In chemical development, the overall strategy of the research synthesis was retained due to its highly convergent nature. However, the efficiency of individual steps had to be improved, and several unacceptables had to be replaced, especially in the side chain leading to intermediate **16**. A supplier of isoquinoline-4-carboxylic acid ethyl ester **2** was found. In the main chain, several improvements could be realized: The pressure of the hydrogenation could be reduced from 150 bar to 6 bar by changing the catalyst system from Rh/C to the Nishimura catalyst.[18] With 2% M/M of Nishimura catalyst the isoquinoline-4-carboxylic acid ethyl ester **2** could be hydrogenated in acetic acid at 70°C and 6 bar within 10 h providing **3** in an isolated yield of 64%. The yield for the resolution of the racemate **3** could be improved from 17 to 27% by changing the solvent system from ethanol to isopropanol. For the piperazine derivative **9**, a commercial source was identified. The initial acid chloride coupling procedure was replaced by a safer and more convenient protocol using carbonyldiimidazole[19] as the coupling agent.

Our development activities mainly focused on the synthesis of the side chain leading to the intermediate **16**. The major disadvantage of the research synthesis of this side chain is the use of hazardous diethyl zinc in the Pd catalysed coupling step to intermediate **14**, and the relatively expensive starting materials **12** and **13**. For the starting 5-bromo-2-methoxypyridine **12**, a supplier for bulk quantities could not be identified. We therefore envisaged a new strategy utilizing an asymmetric hydrogenation of either the unsaturated acid **19** or the allylic alcohol **20** as key step. Both unsaturated compounds can be prepared conveniently from commercially available 6-methoxy nicotinic aldehyde **18** via Wittig–Horner olefination (Scheme 2).

Broger et al. showed that a catalyst derived from $[Rh(nbd)Cl]_2$ and BINAP hydrogenates (*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-en-1-ol to yield 4-*tert*-butylphenyl-2-methylpropanol with an enantiomeric purity of up to 96%.[20] Pfaltz et al. developed an iridium catalyst consisting of an oxazoline phosphine ligand, which is capable of hydrogenating a similar substrate—(*E*)-3-phenyl-2-methylprop-2-en-1-ol—with 95% yield and an enantioselectivity of 96%.[21] Furthermore, we have developed a rhodium catalyst with a walphos type ligand, which allows the hydrogenation of 2-alkyl substituted cinnamic acid derivatives with up to 95% ee.[22]

An exploratory catalyst screening for the enantioselective hydrogenation of the unsaturated acid **19** (see Table 1) revealed that high enantioselectivities of 85–88% ee were obtained with two different catalysts: Ruthenium catalysts formed from $[RuI_2(p\text{-cymene})]_2$ and ligands of the MeObiphep family (see Fig. 1), and rhodium catalysts generated *in situ* from $[Rh(nbd)_2]BF_4$ and walphos type ligands, respectively. In particular, the catalysts Ru/(*R*)-3,4,5-TriMeO-(TriMeObiphep) afforded the saturated acid at 50 bar H_2/60°C with 88% ee (*S*). Using identical reaction conditions, Ru/3,5-*t*Bu-4-MeObiphep hydrogenated **19** with 88% ee. With a rhodium catalyst formed in situ from $[Rh(nbd)_2]BF_4$ and the walphos ligand W001-1 at 1 mol%, the desired product could be isolated with 87% ee (*S*), and at 0.1 mol% catalyst with 85% ee. These enantioselectivities are significantly lower than those found for a structurally similar substrate.[22] When a different walphos ligand derivative with a $(p\text{-}CF_3Ph)_2P$ at the stereogenic C atom of the ferrocene scaffold was used, only 77.4% ee were obtained.



Scheme 2. Route to **15** via enantioselective hydrogenation.

Table 1. Enantioselective hydrogenation of **19** and **20**. Screening of catalysts

Entry	Substrate	Catalyst	*s*/*c*	Solvent (ml)	p(H_2) (bar)	*T*. (°C)	*t* (h)	Conv. (%)	Ee (%)	Config.
1	**19**	**C**/(*R*)-3,4,5-TriMeO-(TriMeO)biphep (**L1**)	200	MeOH (10)	50	60	67	100	88	*S*
2	**19**	C/(*R*)-3,5-*t*-Bu-4-MeO-MeObiphep (**L2**)	200	MeOH (10)	50	60	16.5	100	88	*S*
3	**19**	**B**/(*R*,*R*)-Ph_2PPhFcCHCH_3P(3,5-CF_3Ph)$_2$ (**W001-1**)	100	MeOH (10)	100	20	20	100	87	*S*
4 [a]	**19**	**B**/(*R*,*R*)-Ph_2PPhFcCHCH_3P(3,5-CF_3Ph)$_2$ (**W001-1**)	1000	MeOH (25)	100	20	20	84.1	85	*S*
5	**19**	**B**/(*R*,*R*)-(3,5-Me-4-MeOPh)$_2$PPhFcCHCH_3P(3,5-CF_3Ph)$_2$ (**W005-1**)	100	MeOH (10)	100	20	21	100	85	*S*
6	**19**	**B**/(*R*,*R*)-Ph_2PPhFcCHCH_3P(4-CF_3Ph)$_2$ (**W021-1**)	100	MeOH (10)	100	20	21	100	77	*S*
7	**19**	**B**/(*R*,*R*)-bicp	100	MeOH (10)	100	20	19	19	3	*R*
8	**20**	**A**/(*S*)-TMBTP	1000	Toluene (20)	80	60	19.5	100	97.5	*R*
9 [a]	**20**	**A**/(*S*)-TMBTP	2000	Toluene (20)	80	60	19	100	94	*R*
10	**20**	**A**/(*R*)-*p*-DMA-MeObiphep (L3)	100	Toluene (10)	80	60	17	100	92	*S*
11	**20**	**A**/(*R*)-cyb$_4$-MeObiphep (L4)	100	Toluene (10)	80	60	17	100	90	*S*
12	**20**	**A**/(*R*)-MeObiphep	100	Toluene (10)	50	80	17	100	89	*S*
13	**20**	**A**/(*R*,*R*)-bicp	100	Toluene (10)	50	80	17	100	79	*S*
14	**20**	**B**/(*R*,*R*)-Me-duphos	100	MeOH (10)	50	30	16.5	75	6	*R*
15	**20**	**B**/(*R*)-MeObiphep	100	MeOH (10)	50	30	16.5	5	1	*R*

Reaction conditions: substrate **19**: 1 mmol ([a] 10 mmol), substrate **20**: 1.67 mmol ([b] 16.7 mmol); catalyst precursor A = [Rh(nbd)Cl]$_2$; B = [Rh(nbd)$_2$]BF_4; C = [RuI_2(*p*-cymene)]$_2$; ee values determined by HPLC (Chiralcel OD-H), sat. acid as methyl ester

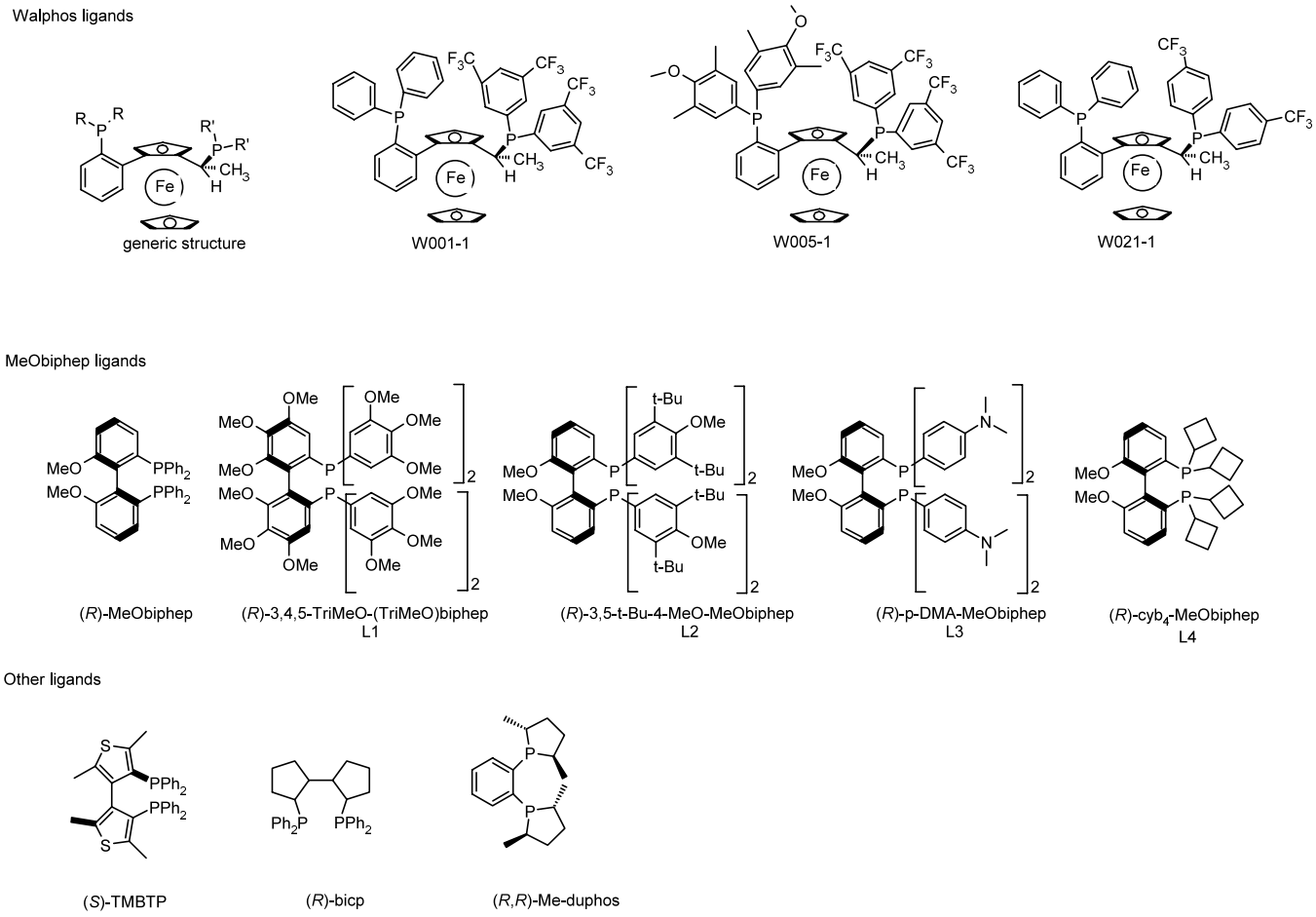


Figure 1. Structures of chiral diphosphine ligands.

In contrast to the unsaturated acid **19**, the asymmetric hydrogenation of the allylic alcohol 20 was shown to be more stereoselective. The catalyst derived from $[Rh(nbd)Cl]_2$ and (*S*)-TMBTP[23] yielded at 80 bar H_2/60°C and a catalyst load of 0.1 mol% the saturated alcohol **15b** with up to 97.5% ee. When the *s*/*c* ratio was doubled to 2'000, the enantiomeric purity of crude **15b** decreased slightly to 94%. Among the ligands of the MeObiphep family, *p*-DMA-MeObiphep and cyb_4-MeObiphep gave the best results, with 92 and 90% ee, respectively. The choice of the precursor type and the solvent influenced both activity and enantioselectivity, as demonstrated with Rh/MeObiphep. Whereas the neutral Rh catalyst in toluene afforded **15a** with 89% ee (complete conversion), the cationic catalyst in methanol hydrogenated **20** practically racemic (only 5% conversion within 16.5 h; entries 12 and 15).

In this feasibility study it could be shown that the enantioselective hydrogenation of allylic alcohol **20** is indeed a practical and convenient route to highly enantiomerically enriched alcohol **15**.

The starting allylic alcohol **20** was prepared from the commercially available 6-methoxy nicotinic aldehyde **18** via Wittig–Horner olefination on in situ generated 2-(diethylphosphinoyl) propionic acid, followed by a reduction with $LiAlH_4$. An enantiomeric excess of 97% as it is achieved in the hydrogenation of the allylic alcohol **20** is sufficient to achieve the specifications of the final drug substance, whereas 89% ee in the hydrogenation of **19** is too low to meet the specifications for the final drug substance, without having a big loss in the yield due to several recrystallisations of **17**.

Another route to enantiomerically enriched alcohol **15** that was investigated was an enzyme catalyzed kinetic resolution of the corresponding racemic alcohol *rac*-**15**. Reaction of *rac*-**15** with vinyl acetate in *tert*.-butyl methyl ether in the presence of lipase Amano PS, followed by silica gel chromatography, yielded the desired (*S*)-isomer of **15** as the acetic acid ester in 49.3% yield and an ee of 92.5%, along with the unwanted (*R*)-**15b** in 47.8% yield and an ee of 98.6%. Hydrolysis of the ester finally afforded the desired alcohol **15a**. This approach was not further pursued due to the relatively modest ee that was achieved, the chromatographic separation that was necessary, and the loss of half of the material that is inherent to the resolution of a racemate.

The enantiomerically enriched alcohol **15** (prepared via the Knochel-type coupling) was then transformed to the iodo compound **16** by the same method as in the research synthesis in 89% yield. After the final alkylation and salt formation step (85%), the drug substance could be isolated in an overall yield of 8.5% based on isoquinoline-4-carboxylic acid ethylester **2**.

In conclusion, a highly efficient and convergent synthesis to the enantiomerically pure decahydroisoquinoline derivative NVP-ACQ090 was identified. Since all unacceptables of the initial research synthesis could be eliminated, this process is suitable for large scale production.

3. Experimental

Experimental work is described for the final process, which was developed and manufactured on kilogram scale. The starting materials, solvents and reagents were of technical grade and available in bulk. All reactions were carried out under an atmosphere of nitrogen. The NMR spectra were measured on a Bruker Avance 400 MHz and a Bruker Drx 500 MHz spectrometer, the chemical shifts are given in δ (ppm) relative to TMS (0 ppm).

3.1. *rac*-(4*S*,4a*S*,8a*R*)-Decahydro-isoquinoline-4-carboxylic acid ethyl ester 3

A mixture of isoquinoline-4-carboxylic acid ethyl ester **2** (404 g; 2 mol), 8.08 g Nishimura catalyst (Rh(III) oxide/Pt(IV) oxide; 46% Rh; 20% Pt, Degussa) in 3600 ml acetic acid was hydrogenated at 6 bar and 70°C. After 10 h the theoretical amount of hydrogen has been taken up. The mixture was filtered through Celite, washed with 200 ml acetic acid, and the acetic acid was distilled off in vacuo at 50°C. The evaporation residue was redissolved in ethanol:toluene (1:1), and the solvent removed in vacuo again. The residue was dissolved in ethanol (1.33 l) at 50°C and MTBE (8 l) was added. The solution was cooled to 40°C and then seeded with 0.7 g of the acetate salt of **3**. After 15 min MTBE (5.3 l) was added within 30 min. The suspension was then cooled within 1 h to 0–5°C, stirred for another 1h, then filtered and washed with MTBE (3.3 l). The product was dried at 35°C for 20 h to yield 347.9 g (64%) of the diastereomerically pure **3** as the acetate salt. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.12–1.22 (m, 6H), 1.32–1.49 (m, 2H), 1.52–1.56 (m, 2H), 1.68–1.81 (m, 1 H), 1.92 (s, 3H), 2.16–2.29 (m, 2H), 2.81–3.02 (m, 4 H), 3.16–3.23 (m, 1H), 4.02–4.16 (m, 2H), 9.38 br. s (2H). MS: 212 ($M+1^+$), 182; 136; 119. Anal. calcd for $C_{12}H_{21}NO_2 \cdot CH_3COOH$: C, 61.97; H, 9.29; N, 5.16; O, 23.58. Found: C, 61.9; H, 9.4; N, 4.9; O, 23.4.

3.2. (4*S*,4a*S*,8a*R*)-Decahydro-isoquinoline-4-carboxylic acid ethyl ester 5

The free base **3** (liberated from the corresponding acetate salt in toluene/Na_2CO_3) (7.14 kg; 33.79 mol) was dissolved in isopropanol (66.6 l) and heated to 31°C. To this solution di-*p*-toluoyl-l-tartaric acid (4.617 kg; 11.95 mol) was added. The temperature is raised to 38°C and the solution was seeded with the desired diastereomer. The mixture was slowly cooled to 20°C, stirred for 3 h at 20°C, then filtered and washed twice with 4.5 l of isopropanol. This salt was dried at 45°C in vacuo overnight, to yield 4.66 kg of crude 4 di-*p*-toluoyl tartrate hemi salt. This crude product (enantiomeric ratio of 85:15) was dissolved in 74.3 l isopropanol at reflux, cooled to 70°C, seeded with the desired diastereomer 4 (di-*p*-toluoyl-l-tartrate hemi salt), cooled to rt again and stirred for another 3 h at 20°C. The

product was filtered, washed with isopropanol (9 l) and dried in vacuo at 45°C and 10 mbar over night, to yield 3.65 kg (27%) of the intermediate di-*p*-toluoyl-l-tartrate hemi salt **4** (ee 96.2%). 3.6 kg of the above tartrate salt **4** were added to 19.2 l of H_2O. Then 2 M NaOH (5 l) was added, followed by MTBE (11 l). The phases were separated and the aqueous layer was reextracted twice with MTBE (5.5 l). The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated to dryness to yield 1.7 kg (90% based on the di-*p*-toluoyl-l-tartrate salt) of crystalline **5** (ee 96.8%).

3.3. (4*S*,4a*S*,8a*R*)-Octahydro-isoquinoline-2,4-dicarboxylic acid-2-t-butyl ester 6

Intermediate **5** (133.4 g; 631 mmol) was dissolved in 1267 ml ethanol. A solution of Boc_2O (151.6 g; 695 mmol) in 303 ml ethanol was added within 30 min at rt. After stirring for 90 minutes at rt, 850 ml of ethanol were distilled off, and then a 1 M solution of 883 ml of LiOH was added at rt. This mixture was stirred for 72 h, then MTBE (630 ml) and saturated aqueous NaCl solution (1580 ml) were added. To the aqueous phase, which contained the product, CH_2Cl_2 (1500 ml) and 2 M acetic acid (700 ml) were added. The layers were separated, the aqueous phase was reextracted twice with CH_2Cl_2 (300 ml each), filtered and evaporated to dryness. The residue was crystallized by adding hexane (500 ml). After cooling the suspension at 0–5°C over night and further cooling to −20°C for 5 h, the product was filtered and dried at 45°C to yield 154.3 g (86%) of white crystalline product **6** with 99% chemical purity according to HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.16–1.32 (m, 3H), 1.35–1.63 (m, 13 H), 1.71–1.85 (m, 2H), 2.15–2.23 (m, 1H), 2.54–2.61 (m, 1H), 2.83–2.92 (m, 2H), 3.65–3.73 (m, 1H), 3.98–4.06 (m, 1H). MS: 284 ($M+1^+$), 266; 250; 228; 212; 203; 184; 166; 138.

3.4. 1-Benzyl-4-(3,4-difluorophenyl)-piperazine 8

A mixture of $Pd_2dba_3{\cdot}CHCl_3$ (2.4 g; 2.32 mmol), (*R*)-(+)-BINAP (4.9 g; 7.87 mmol), 1-bromo-3,4-difluorobenzene (198.8 g; 1.03 mol), *N*-benzylpiperazine (219.0 g; 1.24 mol), sodium *t*-butoxide (140 g; 1.46 mol) in toluene (500 ml) was heated to 80–85°C under an Ar atmosphere for 2.5 h. After TLC showed complete conversion the reaction mixture was cooled to rt and MTBE (2 l) were added. The whole reaction mixture was washed 6 times with H_2O (1 l). The combined water phases were reextracted twice with MTBE (1 l). The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography (MTBE/hexane = 1:1; 1.1 kg silica gel) to yield 295 g **8** (99%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.62 (s, 4H), 3.10 (s, 4H), 3.58 (s, 2H), 6.52–6.60 (m, 1H), 6.64–6.74 (m, 1H), 6.96–7.08 (m, 1H), 7.20–7.44 (m, 5H). MS: 288 (M^+), 197; 119; 91.

3.5. 4-(3,4-Difluorophenyl)-piperazine 9

A mixture of intermediate **8** (572 g; 1.98 mol), Pd/C (10%; 28.6 g) in ethanol (5.5 l) and 4 M HCl (0.5 l; 2 mol) was hydrogenated at rt and atmospheric pressure. After 17.5 h additional Pd/C (10%; 28.6 g) was added. After 47 h the hydrogenolysis of the benzyl group was complete. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was dissolved in H_2O (3 l) and the aqueous phase was extracted with ethyl acetate (1 l). Then the pH of the aqueous phase was adjusted to a pH of ca. 9 by addition of Na_2CO_3. The aqueous phase was extracted with ethyl acetate (5 l). This organic phase was washed with brine (1 l), dried over Na_2SO_4, filtered and evaporated to dryness to yield the first crop of crude **9** (360 g). An additional crop (36 g) was isolated after reextraction of the aqueous phase with ethylacetate (4 l). The two crops were dissolved in ethyl acetate (3 l) and washed with 0.5 M NaOH (4×500 ml). After drying the organic phase over Na_2SO_4, the suspension was filtered and the solvent removed in vacuo, to yield 387 g of product **9** (99%), which crystallized upon standing. ^{1}H NMR of the dihydrochloride (DMSO/D_2O, 400 MHz): 3.16–3.24 (m, 4H), 3.28–3.36 (m, 4H), 6.72–6.84 (m, 1H), 7.00–7.08 (m, 1H), 7.22–7.34 (m, 1H). MS: 199 ($M+1^+$); 156. Anal. calcd for $C_{10}H_{12}F_2N_2$: C, 60.60; H, 6.10; N, 14.13. Found: C, 60.44; H, 6.29; N, 14.06.

3.6. (4*S*,4a*S*,8a*R*)-Decahydro-isoquinoline-4-yl-[4-(3,4-difluorophenyl)-piperazine-1-yl]-methanone 11

To a solution of **6** (3.14 kg; 11.08 mol) in toluene (31 l), carbonyldiimidazole (1.98 kg; 12.21 mol) was added within 10 min. This mixture was stirred for 2 h at rt. Then a solution of triethylamine (2.21 kg; 21.8 mol) in toluene (7 l) was added within 10 min. To this suspension, a suspension of 1-(3,4-difluorophenyl)-piperazin dihydrochloride **9** (3.0 kg; 11.06 mol) in 12 l of toluene was added immediately. This mixture was stirred at rt for 112 h. H_2O (50 l) was added and an aqueous workup was done. The solvent of the organic phase was removed under reduced pressure and the residue was dried at 45°C in vacuo to yield 5.14 kg of the product **10** (quantitative yield) of a purity of 97.3% (HPLC), but still containing 7.8% toluene. The above intermediate (5.14 kg) was suspended in toluene (21 l) and 6.9 l (90 mol) of trifluoroacetic acid were added at rt. The addition was exothermic and gas evolution occurred. The mixture was stirred for 3 h at rt, evaporated to dryness under reduced pressure, and MTBE (22.5 l) was added to the residue. The mixture was stirred at rt over night, then at 0–5°C for 2 h. The product **11** as the trifluoroacetate salt was filtered, washed with MTBE (6 l) and dried in vacuo at 40°C to yield 4.34 kg **11** as the trifluoracetate salt (82% based on 6). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.06–1.29 (m, 3H), 1.36–1.64 (m, 4H), 1.70–1.85 (m, 1H), 1.94 (dd, $J=4.2$; 8.6; 1H), 2.25–2.40 (m, 1H), 2.87–3.17 (m, 7H), 3.20–3.32 (m, 1H), 3.36–3.46 (m, 1H), 3.53–3.74 (m, 4H), 6.49–6.59 (m, 1H), 6.61–6.72 (m, 1H), 6.91–7.10 (m, 1H), 8.97–9.17 (m, 1H), 9.47–9.62 (m, 1H). MS: 364 ($M+1^+$). $[\alpha]_D^{25} = +20.8$ (*c* 1.0, MeOH) (free base) mp: 140–143°C (free base) Anal. calcd for $C_{20}H_{27}F_2N_3O$: C, 66.09; H, 7.49; N, 11.56. Found: C, 65.79; H, 7.57; N, 11.67.

3.7. (*S*)-3-(6-Methoxy-pyridin-3-yl)-2-methylpropionic acid methylester 14

$MnBr_2$ (9.1 g; 42.4 mmol), CuCl (2.5 g; 25.3 mmol) and DMPU (700 ml) were placed under Ar atmosphere in a round bottomed flask. Methyl (*R*)-(+)-3-bromo-2-methylpropionate **13** (154 g; 851 mmol) was added slowly during 30 min. The mixture was cooled in an ice bath, and diethylzinc (80 ml; 781 mmol) was added at 0°C within 20 min. The cooling bath was removed and the mixture was stirred for additional 4 h at rt. The reaction mixture was cooled to −35°C and then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (20.9 g; 25.6 mmol) and a solution of 5-bromo-2-methoxy pyridine **12** (134 g; 713 mmol) in THF (340 ml) were added within 40 minutes. After 1 h at rt, the mixture was heated to 60°C for 16 h. The mixture was cooled to 0°C and within 10 min a 25% aq. NH_4Cl soln. (2.1 l) was added, followed by MTBE (1.5 l). The whole reaction mixture was filtered through Hyflo and the phases were separated. The aqueous layer was reextracted with MTBE (0.5 l) and the organic layers were washed with brine and concentrated in vacuo. The crude product was purified by column chromatography (3.7 kg silica gel; hexane:ethyl acetate = 5:1) to give **14** (64.7 g; 43% yield based on **12**). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.09 (d, J = 6.8; 1H), 2.51–2.67 (m, 2H), 2.85 (dd, J = 13.1; 6.6), 3.57 (s, 3H), 3.84 (s, 3H), 6.61 (d, J = 8.5, 1H), 7.32 (dd, J = 8.4; 2.5; 1H), 7.88 (d, J = 2.1; 1H). MS: 210 ($M+1^+$).

3.8. (*S*)-3-(6-Methoxy-pyridin-3-yl)-2-methylpropan-1-ol 15

To a suspension of $LiAlH_4$ (500 g; 13.3mol) in THF (30 l) a solution of intermediate 14 (1.749 kg; 8.36 mol) in THF (10 l) was added at 0–5°C within 0.75 h. The reaction was stirred for another 1 h at 0–5°C, then 50% K_2CO_3 aq (4 l) were carefully added. The suspension was filtered over a filteraid and evaporated to dryness. The crude product **15a** (1.443 kg) was purified by column chromatography (50 kg silica gel; ethyl acetate:heptane fraction = 1:2) to yield the alcohol **15a** (1.243 kg; 82%) with a purity of 99.5% and an ee of 99.8% according to HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz): 0.83 (d, J = 6.8; 1H), 1.76–1.88 (m, 1H), 2.29 (dd, J = 13.8; 8.1; 1H), 2.64 (dd, J = 13.8; 6.0; 1H), 3.42 (d, J = 5.8; 1H), 3.87 (s, 3H), 6.64 (d, J = 8.5; 1H), 7.37 (dd, J = 8.4; 2.4; 1H), 7.90 (d, J = 2.1; 1H). MS: 182 ($M+1^+$).

3.9. (*E*)-3-(6-Methoxy-pyridin-3-yl)-2-methyl-acrylic acid 19

To a mixture of 60% sodium hydride (60% in mineral oil; 5.50 g; 138 mmol) in MTBE (130 ml) diethylphosphite (6.25 g; 45 mmol) was added, followed by a solution of 2-bromopropionic acid (6.85 g; 45 mmol) in MTBE (50 ml), which was added within 30 min. This mixture was stirred for 30 min at rt until hydrogen gas evolution ceased. Then a solution of 6-methoxypyridine-3-carbaldehyde **18** (5.75 g; 42 mmol) in MTBE (20 ml) was added. This reaction mixture was stirred for 2 h and then poured into 300 ml of H_2O. The layers were separated and the pH of the aqueous phase was adjusted to pH 4. The aqueous phase was extracted with 200 ml of MTBE. The organic phase was dried over $MgSO_4$ and evaporated to a volume of 50 ml. Heptane fraction (100 ml) was added and the mixture was evaporated to a volume of 100 ml. The thick suspension was cooled in the ice bath and filtered. After drying in vacuo at 40°C, 6.3 g (78%) of pure **19** were obtained. ^{1}H NMR (D_6-DMSO; 400 MHz): 2.02 (s, 3H), 3.87 (s, 3H), 6.84 (d, J = 8.8; 1H), 7.52 (s, 1H), 7.82 (dd, J = 8.6; 2.5; 1H), 8.28 (d, J = 2.3; 1H), 12.46 (br. s, 1H). MS: 194 (M^++1), 176, 148.

3.10. (*E*)-3-(6-Methoxy-pyridin-3-yl)-2-methyl-prop-2-en-1-ol 20

To a solution of **19** (4.25 g, 22 mmol) in THF (60 ml) a 1 M solution of $LiAlH_4$ in THF (22 ml; 22 mmol) was added dropwise at 0°C. This reaction mixture was stirred for 3 h at 0°C, and then quenched by addition of 3 ml acetic acid. 80 ml of a saturated aqueous solution of potassium sodium tartrate were added and the phases were separated. The aqueous phase was reextracted with 80 ml of MTBE, the combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product **20** was purified by flash chromatography to yield 3.5 g (89%) of the allylic alcohol **20** as an oil. ^{1}H NMR (D_6-DMSO, 400 MHz): 1.77 (s, 3H), 3.83 (s, 3H), 3.97 (d, J = 5.3; 2H), 4.99 (t, J = 5.7; 1H), 6.38 (s, 1H), 6.76 (d, J = 8.3; 1H), 7.60 (dd, J = 8.6; 2.5; 1H), 8.06 (d, J = 2.3; 1H). MS: 179 (M^+), 164; 136; 122.

3.11. (*R*)-3-(6-Methoxy-pyridin-3-yl)-2-methylpropan-1-ol 15b

A mixture of the allylic alcohol **20** (3 g; 16.7 mmol) in 20 ml toluene and 3.85 mg 2,5-norbornadien-rhodium(I)chloride dimer and 4.93 mg of (*S*)-TMBTP ligand (Rh:ligand = 1:1.05; substrate/catalyst = 2000) was hydrogenated at 60°C and 80 bar for 19 h. The conversion was complete and the crude product was purified by column chromatography (0.1 kg silica gel; ethylacetate:hexane = 1:1) to yield **15b** (2.9 g; 96.5%) with an enantiomeric purity of 94% according to HPLC. A smaller scale experiment with 1.67 mmol of **20** and a substrate: catalyst ratio of 1000:1 gave an ee of 97.5% for **15b**. NMR and MS correspond to **15a**.

3.12. Enzymatic resolution of (±)-3-(6-Methoxy-pyridin-3-yl)-2-methylpropan-1-ol *rac*-15

To a solution of rac-**15** (2.78 g, 15.3 mmol) in MTBE (10 ml) and vinyl acetate (10 ml, 9.3 g, 108 mmol), lipase Amano PS (20mg LPSAX 07509) was added and the mixture was stirred at rt. After 24 h the mixture was filtered to remove the enzyme, and the filtrate was evaporated under reduced pressure. The obtained acetate/alcohol mixture was separated by column chromatography (toluene/ethyl acetate 9:1→ether) yielding (*R*)-**15b** (1.33 g, 7.34 mmol, 47.8%, 98.60% ee) and (*S*)-**15a** as acetate (1.69 g, 7.57 mmol, 49.3%, 92.5% ee). HPLC determination of optical purities: acetate of **15**: CHIRALPAK AD(1117) 250×4.6 mm hexane/ethanol 95:5. 15: CHIRALCEL OD-H (1108) 250×4.6 mm hexane/ethanol 95:5.

3.13. 5-((*S*)-3-Iodo-2-methyl-propyl)-2-methoxy-pyridine 16

To a solution of alcohol **15a** (12.8 g; 70.6 mmol) in DMF (260 ml), methyltriphenoxyphosphoniumiodide (45.5 g; 100.6 mmol) was added portionwise at 0°C. After stirring for 1.5 h at 0°C, ice cold H_2O (1 l), followed by a 1:1 mixture of MTBE/hexane (300 ml) was added. The phases were separated and the aqueous layer was reextracted three times with 150 ml MTBE:hexane = 1:1. The combined organic phases were washed with brine containing 2% sodium thiosulfate. The solvent was evaporated in vacuo and the residue was chromatographed on 490 g silica gel to yield 18.3 g (89%) of iodide **16**. ^{1}H NMR ($CDCl_3$, 400 MHz): 0.93 (d, J = 6.5; 3H), 1.48–1.61 (m, 1H), 2.21 (dd, J = 14.2; 6.9; 1H), 2.36 (dd, J = 14.1; 7.2; 1H), 3.05 (dd, J = 9.9; 4.9), 3.13 (dd, J = 9.9; 4.9; 1H), 3.49 (s, 3H), 6.56 (d, J = 9.3, 1H), 7.10 (d, J = 2.5; 1H), 7.18 (dd, J = 9.3; 2.5; 1H). MS: 291 (M^+); 122; 94. $[\alpha]_D^{25}$ = +25.4 (*c* 1.0, MeOH). Anal. calcd for $C_{10}H_{14}INO$: C, 41.26; H, 4.85; N, 4.81; I, 43.59. Found: C, 41.68; H, 4.92; N, 4.78; I, 43.43.

3.14. [4-(3,4-Difluoro-phenyl)-piperazine-1-yl]-{(4*S*,4a*S*,8a*R*)-2[(*S*)-3-(6-methoxy-pyridin-3-yl)2-methyl-propyl]-decahydro-isoquinoline-4-yl}-methanone 17

To a solution of **11** (361 g; 756 mmol) and **16** (201 g; 690 mmol) in DMF (1800 ml), anh. K_2CO_3 (281 g, 2.03 mol) was added. This suspension was stirred for 24 h at rt. The reaction mixture was poured on a mixture of ice water (25 l) and isopropyl acetate (5 l). The phases were separated and the aqueous layer was reextracted twice with isopropyl acetate (2 l). The combined organic phases were washed with brine and evaporated to dryness. The residue was chromatographed over silica gel (9 kg; MTBE:NH_3 (aq) = 99.1:0.9) to yield 358 g of product **17** (98.5% based on **16**; HPLC purity 99%; assay titration 93.2%), which contained some residual solvent.

3.15. Tartrate salt of 17

The free base **17** (358 g; 679 mmol; 634 mmol (based on the assay) was dissolved in acetone (10 l) and heated to 50°C. To this solution, l-(+)-tartaric acid (93.8 g; 625 mmol) followed by 2 l of acetone was added to yield a clear solution. After a few minutes the crystallisation started. The mixture was evaporated to a volume of 2–2.5 l and cooled in an ice bath for 1.5 h. The product was filtered, washed with ice cold acetone (1.5 l) and dried in vacuo at 50°C to yield 399 g of the tartrate salt of **17** (85% based on **16**) with a purity of 99.8% (HPLC), an assay of the antipode <0.1% (HPLC) and an assay of 99.1% ($HClO_4$). Mp: 189–191°C: $[\alpha]_D^{25}$ = +15 (*c* 1, EtOH). Anal. calcd for $C_{34}H_{46}F_2N_4O_8$: C, 60.34; H, 6.85; N, 8.28; F, 5.61. Found: C, 59.96; H, 6.69; N, 8.18; F, 5.56. ^{1}H NMR (DMSO-D_6, 500 MHz): 0.80 (d, J = 6.7, 3H), 1.02 (m, 1H), 1.15 (m, 1H), 1.22 (m, 1H), 1.38 (d, J = 12.2, 1H), 1.50 (m, 3H), 1.68 (d, J = 11.8, 1H), 1.91 (m, 1H), 2.04 (m, 1H), 2.17 (m, 1H), 2.31 (dd, J = 13.7; 8.2, 1H), 2.43 (m, 2H), 2.53 (m, 2H), 2.64 (dd, J = 13.7; 5.4, 1H), 2.71 (t, J = 11.5, 2H), 2.98 (m, 2H), 3.15 (m, 2H), 3.23 (m, 1H), 3.47 (m, 1H), 3.58 (m, 1H), 3.67 (m, 2H), 3.81 (m, 3H), 4.16 (s, 2H), 6.76 (m, 2H), 7.03 (m, 2H), 7.27 (m, 1H), 7.55 (dd, J = 8.6, 2.4, 1H), 7.96 (d, J = 2.0, 1H), 8.74 (s, 4H). MS: 527 ($M+1^+$), 365; 364.

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