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An Efficient Process for the Manufacture of Carmegliptin§

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ABSTRACT: A short and high-yielding synthesis of carmegliptin (**1**) suitable for large-scale production is reported. The tricyclic core was assembled efficiently by a decarboxylative Mannich addition−Mannich cyclization sequence. Subsequent crystallization-induced dynamic resolution of enamine **7** using (*S*,*S*)-dibenzoyltartaric acid was followed by diastereoselective enamine reduction to give the fully functionalized tricyclic core with its three stereogenic centers. The C-3 nitrogen was introduced by Hofmann rearrangement of amide **28**, and the resulting amine **10** was coupled with (*S*)-fluoromethyl lactone **31**. Following cyclization to lactam **13** and amine deprotection, **1** was obtained in 27−31% overall yield with six isolated intermediates.

1. INTRODUCTION

Type 2 diabetes (T2D) is a disease characterized by high levels of blood glucose in the context of insulin resistance and relative insulin deficiency. The disease has been classified by the Center for Disease Control and Prevention (CDC) as an epidemic, with the prevalence rates doubling over the past 15 years and expected to increase significantly worldwide, even in developing countries, in the years to come.[1] It is estimated that worldwide 285 million people (6.6% of the population) suffer from diabetes.[2] Inhibition of dipeptidyl peptidase IV (DPP-IV) is a proven approach for the treatment of T2D.[3] DPP-IV is responsible for the degradation/deactivation of glucagon-like peptide 1 (GLP-1) by cleaving the N-terminal two amino acids, resulting in reduced insulin secretion.

Carmegliptin[4] (**1**) (Figure 1) is a new generation DPP-IV inhibitor developed at Roche, structurally distinct from earlier drug candidates.[5] The structure is characterized by a 2-amino-hexahydro-benzo[*a*]quinolizine core, featuring a densely functionalized six-membered azacycle with three stereogenic centers and all the substituents adopting an equatorial orientation.[6] The C-3 nitrogen is incorporated in a chiral lactam side chain possessing a fluoromethyl substituent in β-position which poses a significant synthetic challenge.

The Discovery Chemistry route (Scheme 1) consists of a 21-step synthesis with a 16-step longest linear sequence.[4b] The synthesis started with 2-(3,4-dimethoxyphenyl)ethylamine and its conversion to imine **3** by Bischler−Napieralski reaction. Decarboxylative malonate addition was followed by a 1,4-addition and a Dieckmann reaction[7] to give the tricyclic enol ester *rac*-**6**. The enamine formation, diastereoselective hydride reduction (establishing the relative configuration of all three stereocenters), and Curtius rearrangement (introducing the C-3 nitrogen functionality) provided the bis-protected diamine *rac*-**9**. Teoc (trimethylsilylethyl carbamate) cleavage and chiral HPLC separation afforded enantiopure amine **10** in ∼5% yield from amine **2**. The lactam moiety was introduced by coupling of amine **10** with acid chloride *rac*-**11** and cyclization. Boc deprotection and crystallization finally led to carmegliptin in about 2% overall yield. Besides the long linear sequence and the very low overall yield, several issues were identified in this synthesis: (i) selectivity in the Dieckmann cyclization (step 4); (ii) nonscalable hydride reduction (step 7); (iii) safety issues in the Curtius rearrangement (step 10); (iv) optical resolution by preparative HPLC on chiral stationary phase; (v) coupling of amine **10** with *rac*-**11** (step 10). This route was deemed unsuitable for large-scale supply since it did not meet our criteria for safety, robustness, and economical as well as ecological viability.

In this contribution, the efforts from Process Research and Process Development to devise a scalable route that addresses the aforementioned issues and would allow for the production of carmegliptin on ton scale are described.[8] Route exploration and a scalable synthesis of the optically active fluoromethyl lactone **31** needed for the lactam side chain are described elsewhere.[9]

2. RESULTS AND DISCUSSION

2.1. Decarboxylative Mannich Addition−Mannich Cyclization−Enamine Formation Sequence. In the Discovery Chemistry synthesis, the assembly of the tricyclic core was achieved by a Michael addition−Dieckmann cyclization sequence from *rac*-**4**. The Michael addition was found to exhibit a high potential for a runaway behavior as a result of ethyl acrylate (used in large excess) polymerization. For the first API delivery, the problem was solved by performing the Michael addition in acetonitrile under copper(I) catalysis.[10] Additionally, the Dieckmann cyclization suffered from poor regioselectivity (4:3 mixture of desired/undesired regioisomers) necessitating tedious isomer separation and resulted in moderate isolated yield. A more efficient access to (±)-enamine **7** was required.

The synthesis of the enaminoester *rac*-**7** by double Mannich reaction had already been reported starting from acetone dicarboxylic acid (Scheme 2).[11] This approach was briefly evaluated but not further pursued as the thermal stability of the amino acid

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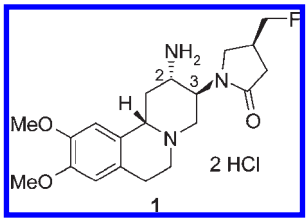

Figure 1. Structure of carmegliptin.

intermediate *rac*-**14** was questionable.[12] Control of double Mannich addition on acetone dicarboxylic acid was an additional liability.

The solution consisted in first reacting imine hydrochloride **3** with 3-oxo-glutaric acid mono ethyl ester (**16**) to afford ester *rac*-**15** (Scheme 3) and then perform a Mannich cyclization. These two steps could potentially be telescoped; however, ester *rac*-**15** offered itself as a stable crystalline intermediate allowing easy purification and was therefore isolated. On the other hand, the Mannich cyclization and enamine formation were best performed in a one-pot sequence.

Cyclic anhydride **18**[13] (Scheme 3) was prepared by addition of acetone dicarboxylic acid (**17**) to acetic anhydride in acetic acid[14] at 10−15 °C. The product crystallized from the reaction mixture and was isolated by filtration in ∼80% yield.

The 3-oxo-glutaric acid mono ethyl ester (**16**) was prepared by addition of ethanol to a suspension of cyclic anhydride **18** in heptane and was directly used in the next step. The solution of the monoethyl ester was slowly added to a turbid solution consisting of imine hydrochloride **3** and catalytic amounts of sodium acetate in an ethanol/water mixture. Water was added in order to solubilize imine hydrochloride **3** which otherwise gave an extremely thick suspension in ethanol. CO_2 release was controlled by the addition rate as well as the amount of NaOAc. A catalytic amount of base was required to trigger the reaction. The product was obtained in 81−86% yield (from imine hydrochloride **3**). The product crystallized spontaneously from the reaction mixture as the hydrochloride salt. Hydrochloric acid was added in order to compensate for the catalytic NaOAc and heptane was additionally added to ensure maximum recovery of the product.

The Mannich cyclization was subsequently performed in methanol by reacting hydrochloride *rac*-**15** with formaldehyde in the presence of NaOAc to buffer the reaction. The cyclic ester *rac*-**6** was not isolated and was directly reacted with ammonium acetate leading to enamine *rac*-**7** which was isolated in ∼70% yield (from ketoester **15**) after aqueous workup and crystallization from methanol.

2.2. Crystallization-Induced Dynamic Resolution. In the Discovery Chemistry synthesis, chirality was introduced as early as in the third step by nucleophilic addition to dihydroisoquinoline **3** to give *rac*-**4**. Optical resolution of amine **10** was performed only at step 12 by preparative HPLC on chiral stationary phase (Scheme 1). While this approach was viable for the production of initial amounts of drug substance, an alternative access to enantiomerically pure API avoiding preparative HPLC was sought. As a result of time pressure, classical resolution by diastereomeric salt formation was investigated first at the expense of an enantioselective synthesis which was anticipated to take much longer to develop.

Several intermediates deemed suitable for such a resolution process were submitted to a salt screening, and the most promising results were found with enamine *rac*-**7**. A screening of chiral acids revealed that dibenzoyltartaric acid (DBTA) and dibenzoyltartaric acid monodimethylamide give 1:1 salts of very high diastereomeric purity (dr > 99.5:0.5) from ethanol in reasonable yield. These hits could be reproduced and scaled without difficulty to multigram quantities to afford the desired salt in up to 45% yield after filtration.

Intriguingly, upon close inspection, these high yields were accompanied by virtually racemic mother liquors, hinting at a concomitant racemization process of the enamine under acidic conditions. Crystallization-induced dynamic resolutions[15] (CIDR) of related substrates with different electronic properties using camphorsulfonic acid have been reported previously.[16]

On the basis of these findings, a process was developed which utilizes the commercially available nonnatural enantiomer (*S*,*S*)-dibenzoyl-D-tartaric acid ((+)-DBTA) as preferred resolving agent[17] and relies upon the in situ racemization of the dissolved fraction of enamine and concomitant crystallization of the desired diastereomeric salt as thermodynamic sink. Since racemization turned out to be rather slow at ambient temperature, prolonged heating of the mixture was required to achieve good conversion. A reaction temperature of 60 °C in EtOH was found to be a good compromise between rate of racemization and yield.[18] Under optimized conditions, the dibenzoyltartaric acid salt of the enamine was obtained in 93% yield and diastereomeric excesses greater than 99.5% (Scheme 4). As the racemization−crystallization process went on, the mixture became very thick, making efficient stirring indispensable. Slight variation of various reaction parameters (e.g., temperature, concentration, extended reaction times, or cooling rate) did not reflect negatively on the chemical or optical purity of the product with diastereomeric excesses of all batches greater than 99%.

Up to 50 kg of (*S*)-**20** were produced in-house. For larger quantities, the synthesis of (*S*)-**20** was outsourced to contract manufacturers that were able to supply the material on ton scale.

In order to better understand the resolution process, the kinetics of the underlying racemization and its mechanism were investigated: (*S*)-Enamine **7** was submitted to acidic conditions, and the extent of racemization was followed as a function of time and temperature. A homogeneous reaction mixture was needed to guarantee reliable analytical sample preparation. This was achieved during the early phases of the reaction by using (*R*,*R*)-dibenzoyl-L-tartaric acid ((−)-DBTA), which gave the more soluble diastereomer of the salt. The temperature interval studied spanned from 40 to 70 °C, a range which could potentially be useful for the dynamic resolution process. The results are summarized in Figure 2.[19]

Under the optimized conditions used for CIDR (EtOH, 60 °C, DBTA), the rate constant of racemization was determined to be $k = 0.89\ s^{-1}$. As expected, k increased linearly with the temperature (Figure 2) and correlated well with the pK_a of the acid used ($k_{\text{sulfonic acids}} > k_{\text{TFA}} > k_{\text{carboxylic acids}}$).

Moreover, the racemization was studied in various solvents at 50 °C using (−)-DBTA. Figure 3 shows the extent of racemization as a function of time with the six solvents investigated.[20]

These results clearly indicated that the rate of racemization increases with polarity (MeOH > EtOH > 2-PrOH). Polar protic solvents seem favored over aprotic polar solvents (alcohols > DMSO ≈ 1,4-dioxane). Given the solvent dependency of the pK_a, these findings are in agreement with the observed increase in reaction rate with the pK_a of the acid used.

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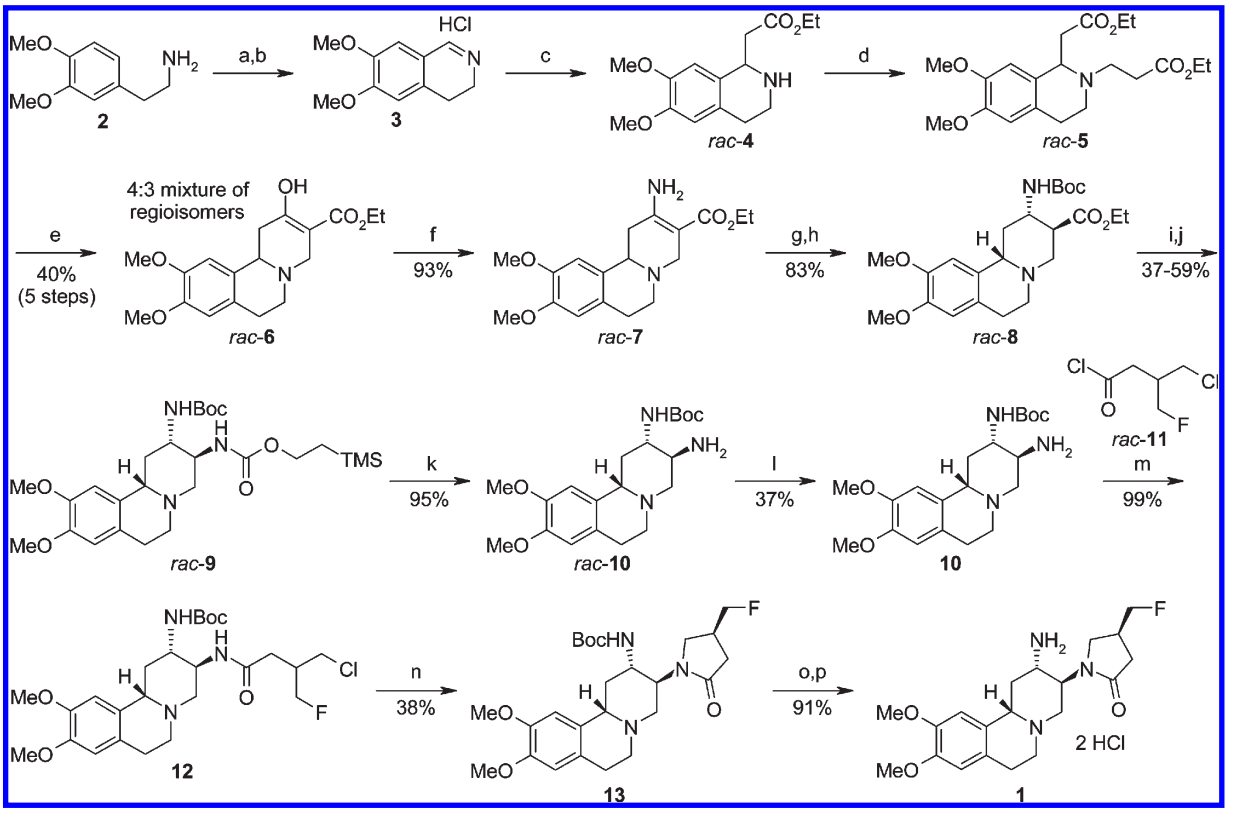
Scheme 1. Discovery Chemistry synthesis of carmegliptin[a]

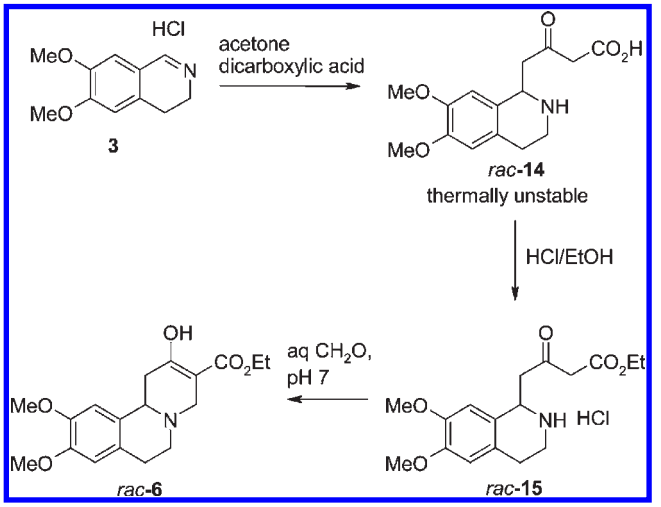


[a] Reagents and conditions: a) HCO_2Me, Δ; b) $POCl_3$, MeCN; c) $HO_2CCH_2CO_2Et$, neat, 120 °C; d) ethyl acrylate, neat; e) *t*-BuOK, neat (5 steps); f) NH_4OAc, MeOH; g) $NaBH_4$, TFA, THF; h) Boc_2O, CH_2Cl_2; i) KOH, aq THF; j) DPPA, Et_3N, $TMSCH_2CH_2OH$, PhMe, 80 °C; k) Et_4NF, MeCN; l) chiral HPLC; m) Et_3N, CH_2Cl_2; n) NaH, DMF; o) HCl, dioxane; p) HCl, 2-PrOH.

To investigate the mechanism of the underlying racemization process, trapping experiments were designed based on the hypothesis that ring-opened intermediates are involved and may be trapped using a suitable reducing agent. Indeed, earlier experiments showed a slight erosion of enantiomeric purity during the subsequent hydride-mediated reduction of enamine (*S*)-**7** to the corresponding amine, suggesting that scrambling of the stereogenic center is operative under these conditions. Thus, (*S*)-**7** was treated with trifluoroacetic acid (TFA) followed by addition of $NaBH_4$. The resulting mixture was treated with Boc_2O in dichloromethane to facilitate isolation of byproducts formed in trace amounts. The results of these experiments, which led to the isolation of ring-opened **22**, clearly favor the mechanisms depicted in Scheme 5.

2.3. Synthesis of Boc-Protected Amine 25. The subsequent reduction of the dibenzoyltartaric acid salt (*S*)-**20** with $NaBH_4$ and TFA establishes two additional stereogenic centers, making it one of the key transformations of the overall synthesis. The reaction conditions developed by Discovery Chemistry (TFA, THF, rt, then $NaBH_4$) led to **25** with good diastereoselectivity following Boc protection, and the undesired diastereomers were depleted by crystallization from heptane. However, these conditions prescribed the addition of $NaBH_4$ in one portion to a solution of the enamine and TFA (40 equiv) to avoid the formation of byproducts that were observed if the addition was performed portionwise. The resulting uncontrollable foaming and vigorous hydrogen evolution limited this procedure to laboratory scale.

Scheme 2. Initial double-Mannich route to enol ester *rac*-6



To avoid these drawbacks, a scalable protocol was devised for the first supply campaigns (up to several kg), which consisted in the preformation of a solution of enamine salt (*S*)-**20** and TFA (10 equiv) in THF followed by addition of this solution to a suspension of $NaBH_4$ in THF below −10 °C. It is worth noting that the reaction proceeded equally well using the dibenzoyltartaric acid salt (*S*)-**20** instead of the free base (*S*)-**7**. Excess TFA

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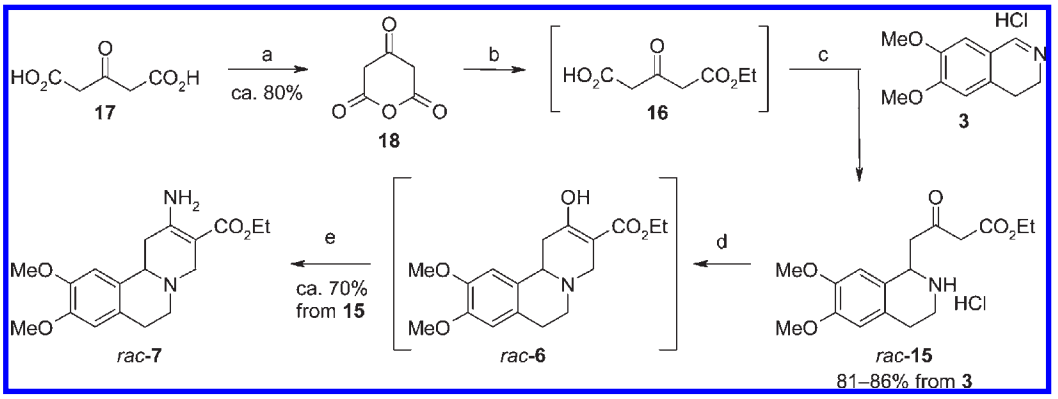
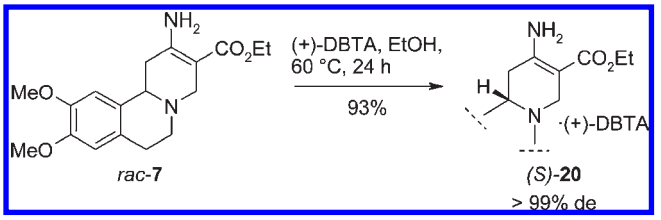
Scheme 3. Scale-up route to enaminoester *rac*-7[a]



[a] Reagents and conditions: a) Ac_2O, AcOH, 10−15 °C; b) EtOH, heptane, rt; c) NaOAc (0.1 equiv), $MeOH/H_2O$, rt; d) aq CH_2O, MeOH, rt; e) NH_4OAc, MeOH, 50 °C.

Scheme 4. Crystallization-induced dynamic resolution



was removed by concentration to dryness. Following basic aqueous workup, the crude mixture was treated with Boc_2O in dichloromethane to give ester **25** in yields of up to 70% after crystallization by solvent exchange to heptane. In this protocol the addition of TFA to enamine salt (*S*)-**20** and the subsequent dosing of this solution to $NaBH_4$ in THF were very exothermic, and hence both required cryogenic reactors. To overcome this drawback for subsequent larger campaigns, the reducing agent was preformed in THF by slow addition of TFA to $NaBH_4$ below −5 °C, followed by addition of enamine salt (*S*)-**20**. Optimized amounts for the formation of the trifluoroacetoxy borohydride reagent were found to be 5.0 equiv of TFA and 1.35 equiv of $NaBH_4$. Under such conditions, the formal reducing agent was determined to be $NaBH_{1.7}(O_2CCF_3)_{2.3}$ by measuring the amount of evolved hydrogen gas. This reagent, which has only limited stability at temperatures above −10 °C, was prepared just prior to use and directly combined with enamine salt (*S*)-**20**. After the addition the temperature was successively increased within 10 h to ambient temperature. The reaction mixture was quenched by the addition of water and the pH adjusted with 50% aq KOH to pH 11.0−11.5. The need for dichloromethane can be removed if the protection is carried out prior to extraction.[21] Thus, the quenched solution was treated at 5−10 °C with a solution of Boc_2O (1.25 equiv) in toluene, and the resulting mixture was allowed to warm up to room temperature. The pH had to be kept constant at approximately pH 10 to prevent ester hydrolysis during the entire reaction period. The crude Boc-protected ester **25** was extracted with toluene and processed further.

The reduction did not proceed with complete stereoselectivity. Besides the desired (2*S*,3*S*)-isomer **25**, two other diastereomers, i.e. **26** (2*S*,3*R*) and **27** (2*R*,3*S*), were formed in a typical ratio of approximately 13:1:1 (Scheme 6). The diastereomeric ratio was rather insensitive to the reaction temperature, the mode of addition, and the $NaBH_4$/TFA ratio.

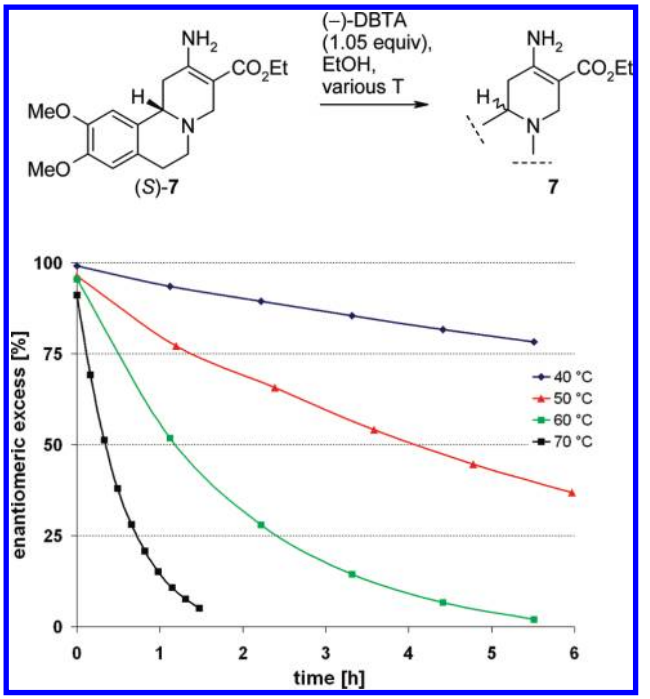


Figure 2. Extent of racemization as a function of temperature and time.

2.4. Introduction of the C-3 Nitrogen. In the Discovery Chemistry synthesis, the C-3 amine was introduced in a three-step sequence consisting of ester saponification, Curtius−Yamada rearrangement[22] mediated by diphenylphosphoryl azide (DPPA)[23] using 2-trimethylsilyl ethanol as nucleophile to give the Teoc-protected amine, and finally fluoride-induced deprotection. The upscaling of the Curtius rearrangement was not possible from a safety perspective, due to its requirement of using diphenylphosphoryl azide at a reaction temperature of 80 °C, significantly above the maximum permissible safe process temperature of 50 °C determined by in-depth studies in our safety laboratory. To circumvent this safety issue, a Hofmann rearrangement, a well-established alternative to the Curtius reaction, was envisaged.[24]

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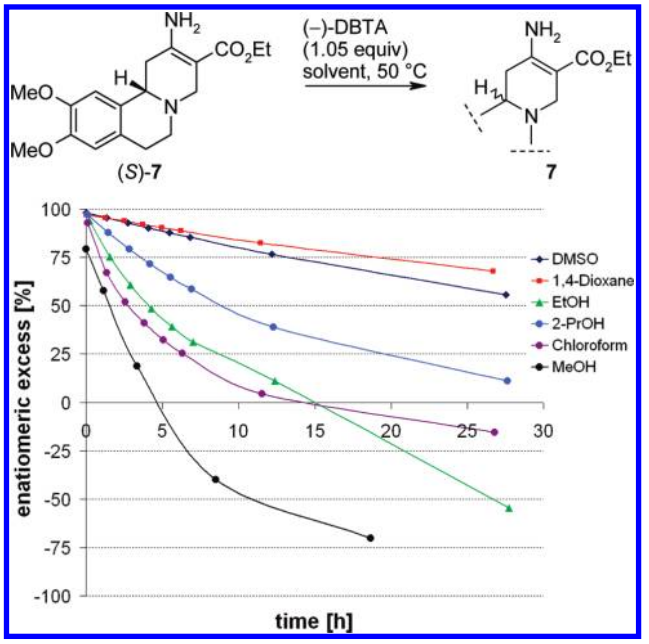


Figure 3. Extent of racemization as a function of solvent and time.

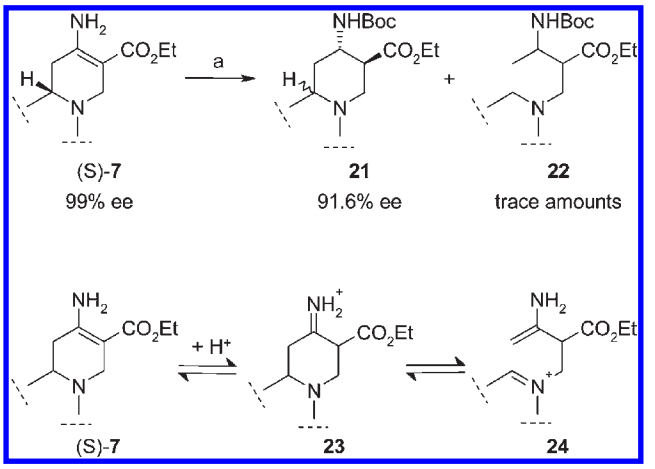
The requisite amide **28** was found to be easily accessible from ester **25** by a mild amidation reaction with formamide (10 equiv) and sodium methoxide (3 equiv) in THF.[25] This reaction presumably proceeds by nucleophilic attack of the formamide anion to the ester to give a mixed imide, which is cleaved by sodium methoxide to generate the desired amide **28**.

For large campaigns, isolation and purification of ester **25** was avoided by telescoping the reduction−protection−amidation sequence (Scheme 7): This required that residual water be azeotropically removed after Boc protection to avoid ester hydrolysis under the basic amidation conditions. Both undesired cis diastereomers **26** and **27** (which were the main contaminants present in crude ester **25**), partially epimerized to the thermodynamically more stable trans isomers under the basic amidation conditions, affording crude amide mixtures containing all three undesired amide stereoisomers in the range of 2−4% each.

Amide **28**, which precipitated from the reaction mixture, could conveniently be isolated by filtration on kilogram scale. However, scale-up of this protocol was thwarted by bad filtration properties of the crystals and hence associated long filtration times. The filterability of the crystals was improved by diluting the suspension with water followed by trituration at 60−65 °C for several hours. Moreover, this treatment dissolved all precipitated inorganic sodium salts. The impurity resulting from methoxide-induced transesterification of the ethyl ester **25** with methanol[26] was mostly hydrolyzed to the corresponding sodium carboxylate, which was completely removed in the mother liquor in the subsequent solid−liquid separation. Isolated yields of this telescoped three-step process were typically around 80%. All undesired isomers were completely separated into the mother liquor, yielding isolated amide **28** in purities of >99.6% (HPLC). The only organic byproduct present in >0.10% was the aforementioned methyl ester with ~0.2% by area (HPLC).

Many oxidizing agents have been reported for the Hofmann rearrangement, including hypochlorite, hypobromite, and NBS as the most prominent examples.[27] Modern variations based on iodosobenzene diacetate (PIDA)[28] or iodosobenzene bistrifluoroacetate (PIFA)[29] offer advantages with respect to selectivity and reaction rate.

Scheme 5. Isolation of ring-opened products from CIDR[a]



[a] Reagents and conditions: a) i. TFA, THF, rt; ii. $NaBH_4$, rt; iii. Boc_2O, CH_2Cl_2, rt.

Initial attempts using PIDA or PIFA failed using the standard conditions reported in the literature (1.2 equiv PIDA or PIFA, MeCN/H_2O, rt), giving practically no conversion. However, in the presence of sodium hydroxide, isolated yields of >50% were obtained with PIDA (Scheme 8), along with significant amounts of unsymmetrical urea **29**[30] and symmetrical urea **30** (up to 20% combined) (Figure 4). These byproducts were only sparingly soluble in organic solvents and turned out to be difficult to remove in the subsequent workup.

For the first supply campaigns, the importance of slow dosing of PIDA was recognized, resulting in decreased amounts of urea byproducts **29** and **30** (8−10% combined). After reaction completion, acetonitrile and iodobenzene were distilled off,[31] the pH of the aqueous residue was adjusted to pH 9−10, and the product was extracted with dichloromethane. Crystallization was achieved by solvent exchange to toluene. To remove **30** to acceptable levels,[32] a polishing filtration of both the dichloromethane and hot toluene product solutions was required.

An extensive screening of the relevant reaction parameters (amount of base, temperature, concentration, H_2O/MeCN ratio, and rate of addition) revealed that urea byproducts can be minimized to <2% by adding a solution of PIDA (1.15 equiv) in H_2O/MeCN within 3−4 h at 24−28 °C to a suspension of the amide and KOH (5 equiv) in water (8.3 kg/kg amide **28**) and acetonitrile (4.3 kg/kg amide **28**). The improved impurity profile allowed considerable simplification of the workup by using toluene/THF 5:1 (w/w) at 70−75 °C for the extraction instead of dichloromethane: This high temperature and the use of THF as cosolvent ensured a clear phase separation by completely dissolving amine **10** as well as urea **30**. Azeotropic removal of THF and water with toluene led to the precipitation of **30** which was filtered off at 70−80 °C. Crystallization of amine **10** from the filtrate occurred upon cooling to −10 °C. Using this optimized process, enantiomerically pure amine **10** (ee >99.8%) was obtained in isolated yields of 85−90% and purities >99% (w/w), while eliminating dichloromethane as solvent. The only organic byproduct present in >0.10% was the urea derivative **30** with 0.15−0.20% by area (HPLC).

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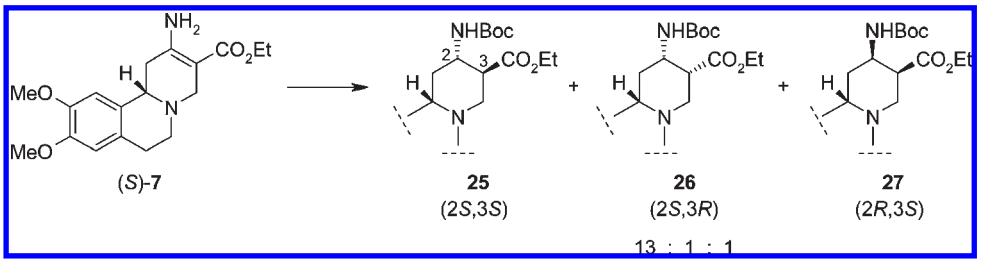
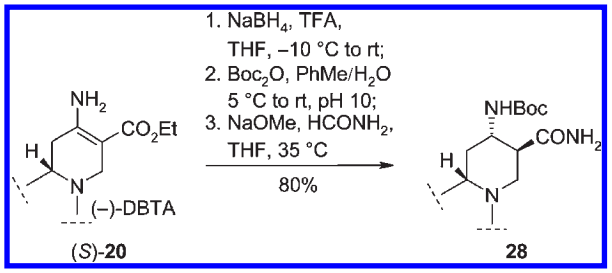
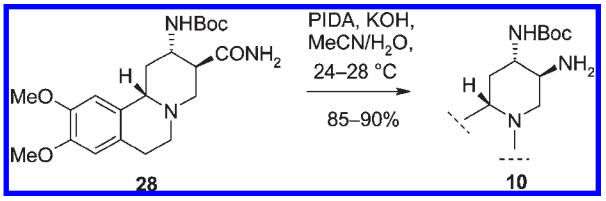
Scheme 6. Stereoisomers obtained by hydride-mediated enamine reduction following treatment with Boc_2O



Scheme 7. Telescoped three-step process to amide 28



Scheme 8. Hofmann rearrangement to amine 10



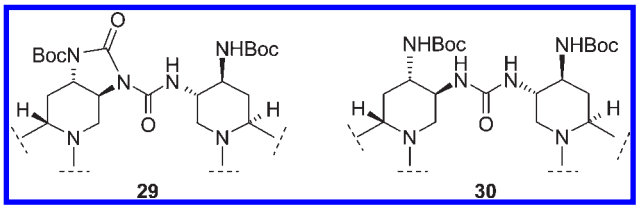
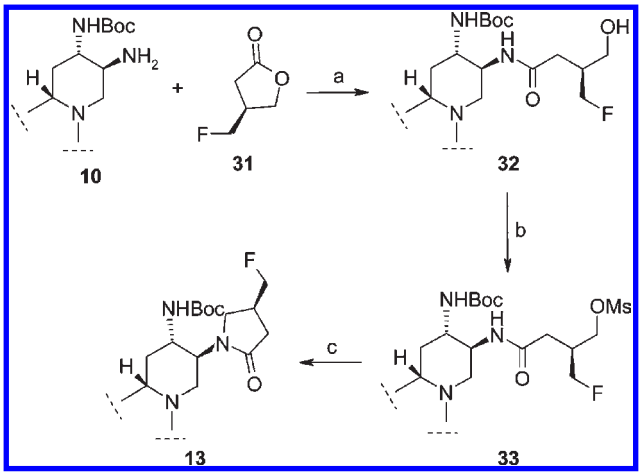


Figure 4. Byproducts obtained in the Hofmann rearrangement.

From a safety perspective, the reaction was unproblematic: The Hofmann rearrangement was dose-controlled with an enthalpy of $\Delta_r H = -415$ kJ mol^{-1} and an associated total adiabatic temperature rise ($\Delta_{adia}T_{max}$) of only 14 °C.

2.5. Formation of the Fluoromethyl Lactam. Originally, the lactam side chain was introduced by a two-step reaction sequence consisting of coupling amine **10** with acid chloride *rac*-**11**, followed by intramolecular chloride displacement under basic conditions (NaH, DMF, rt). Following workup, a 1:1 mixture of diastereomers was obtained which were separated by silica gel chromatography to give lactam **13** in 38% yield over two steps. The preparation of the acid chloride from the corresponding lactone ($SOCl_2$, $ZnCl_2$, 80 °C, 4 d) turned out to be very challenging, resulting in low yields (60%) and extensive byproduct formation, and was accompanied by a nauseating stench that discouraged us from scaling up this reaction.

Scheme 9. Telescoped three-step process to fluoromethyl lactam 13



Reagents and conditions: a) 0.10 equiv of 6-chloro-2-pyridinol, PhMe, 110−85 °C; b) MsCl, Et_3N, THF, 22−30 °C; c) *t*-BuOLi in THF, −10 to 0 °C, then aq workup and crystallization from MeOH (77−80% overall yield).

Alternatively, the direct coupling of amine **10** with (*S*)-fluoromethyl lactone **31**[33] to form the hydroxybutyramide **32** as a single diastereomer was investigated (Scheme 9). Subsequent activation of the primary alcohol was followed by treatment with a strong base to induce intramolecular cyclization to lactam **13**.

The coupling step could be performed in good yield in the presence of catalytic amounts of 2-hydroxypyridine (0.20 equiv) in refluxing toluene to provide hydroxybutyramide **32** in ~93% conversion.[34] Owing to its low solubility in many solvents, product isolation was effected by simple filtration of the precipitated hydroxybutyramide **32**. Subsequent activation of the primary alcohol as mesylate was carried out under standard conditions (MsCl, Et_3N, THF) to give **33**. Cyclization of the mesylate was achieved by treatment with LHMDS (3 equiv) at −10 to 0 °C.[35] To circumvent the drawbacks associated with the use of this silicon-containing base on large scale,[36] a screening was initiated with the aim of minimizing byproduct formation. With bases like sodium *tert*-butoxide, significant amounts (>10%) of the O-alkylated cyclized product were formed. Only lithium *tert*-butoxide[37] showed a performance similar to that of LHMDS (<2% O-alkylated byproduct) in the cyclization reaction and was therefore chosen as the preferred base on larger scale.

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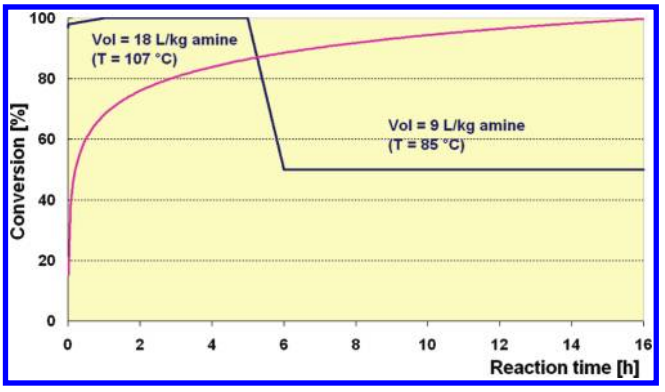


Figure 5. Conversion as a function of time, volume, and temperature in the formation of amide **32**.

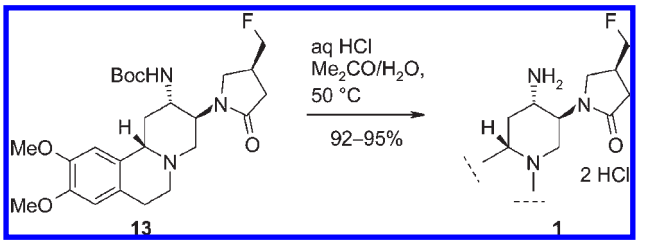
A limiting factor in this three-step sequence was the filtration of the hydroxybutyramide **32**, which turned out to be extremely slow and could not be improved despite extensive efforts. It became clear that isolation of this compound is very impractical on large scale and should be avoided. A precondition for a telescoped process was to achieve a higher conversion in the coupling step with lactone **31**, since residual amine **10** would be mesylated, leading to contamination of the API with the corresponding sulfonamide. The conversion in this equilibrium reaction[38] could be increased by ensuring as complete a precipitation of the hydroxybutyramide from the reaction mixture as possible. This was achieved by adhering to a strict concentration and temperature profile: The reaction was started by adding lactone **31** (1.3 equiv) to a solution of amine **10** and 6-chloro-2-hydroxypyridine[39] (0.1 equiv) in toluene (18 mL/g amine) at 105−110 °C. After 5−7 h, conversion levels of 80−85% were typically reached, whereupon 50% of the toluene was distilled off, and at the same time, the temperature was decreased (to 85 °C) to induce the further precipitation of the product (Figure 5).[40] The reaction was usually judged complete (<1.5% amine) after another 7−9 h at this temperature.

Upon complete conversion, toluene was partly distilled off and replaced by THF. Following mesylation and cyclization, aqueous work-up, solvent exchange to methanol and subsequent crystallization afforded fluoromethyl lactam **13** in 77−80% yield and purities of >99.5% by area (HPLC).

2.6. Deprotection and Salt Formation. Deprotection and hydrochloride formation was accomplished in a single step by treatment of fluoromethyl lactam **13** with hydrochloric acid in a mixture of water and a suitable organic solvent. The choice of the solvent proved to be crucial. With alcoholic solvents (MeOH, EtOH, or 2-PrOH), good yields of **1** were obtained; however, considerable amounts of the corresponding genotoxic alkyl chlorides were formed, which could not be removed to levels acceptable for chronic treatment. With THF, ring-opening to afford 4-chloro-1-butanol and 1,4-dichlorobutane was observed to some extent. Additionally ∼0.3% (w/w) of THF always remained in the isolated crystals, an amount which is far above our internal acceptable limit for THF in drug substances.

In order to obtain **1** devoid of genotoxic alkyl chlorides, two approaches have been evaluated. First, removal of alkyl chlorides and, second, avoiding their formation. Removal of the alkyl chlorides was successfully achieved by an additional recrystallization procedure from aqueous acetonitrile or aqueous acetone

Scheme 10. Deprotection and salt formation



(∼93% yield). However, this procedure requires an additional processing step with associated loss in overall yield.

The formation of alkyl chlorides was avoided by using acetone as organic solvent:[41] **13** was suspended in a water/acetone mixture, and concentrated aqueous hydrochloric acid (3.5 equiv) was added at ∼50 °C (Scheme 10). Gas evolution (isobutene and carbon dioxide) did not start until after dosing of the first equivalent of acid. The maximum rate of gas formation was observed just before the end of dosing. Subsequent dilution with acetone initiated the crystallization of carmegliptin (**1**), which was obtained in 92−95% yield and excellent quality with no impurities >0.15% by area (HPLC) present.

3. CONCLUSION

In summary, a safe and robust process for the synthesis of the DPP-IV inhibitor carmegliptin was developed (Scheme 11), which is suitable for large-scale production and uses readily available starting materials. The synthesis of dibenzoyltartaric acid salt (*S*)-**7** was successfully outsourced to several contract manufacturers, which were able to provide this building block in excellent quality on ton scale.

The salient features of our route include the efficient assembly of the tricyclic skeleton by double Mannich reaction to give *rac*-**7**, its high-yielding crystallization-induced dynamic resolution using a cheap, commercially available tartaric acid derivative as resolving agent, and a stereocontrolled reduction of the resolved enamine (*S*)-**7** to provide the core of carmegliptin with its three stereogenic centers in high yield and excellent control of absolute and relative configuration. Moreover, the lactam side chain was introduced by coupling amine **10** with fluoromethyl lactone **31**, followed by intramolecular cyclization.

Intensive process development (downstream from outsourced (*S*)-**7**) led to significant simplification and optimization of the overall process. The overall yield of this eight-step sequence could be increased to over 50% with only three isolated intermediates as a result of extensive telescoping. All undesired solvents (e.g., dichloromethane) and genotoxic impurities were eliminated in the final process, with less than 200 kg of solvent being needed to produce 1 kg of API.[42] Using the route outlined above, nearly 1000 kg of API have been produced thus far.

4. EXPERIMENTAL SECTION

4.1. General Remarks. Unless noted otherwise, reagents and solvents were used as received from commercial suppliers. Technical grade solvents were used for all experiments. All reactions were carried out under a positive pressure of either argon or nitrogen. Yields are weight-based and not corrected for assays unless otherwise noted. The chemical purity and

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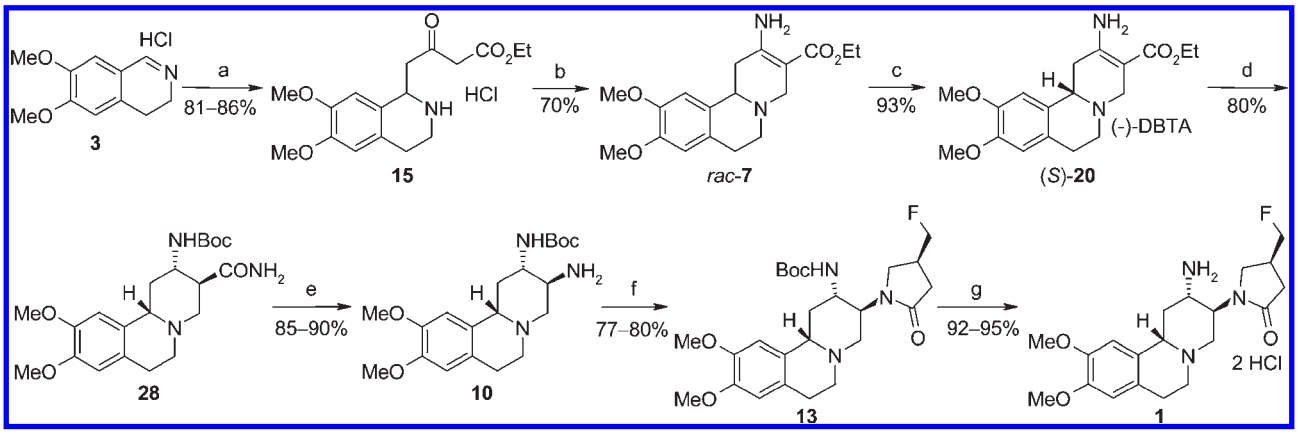
Scheme 11. Manufacturing process of carmegliptin



Reagents and conditions: a) **16**, NaOAc (0.1 equiv), MeOH, H_2O; b) aq CH_2O, MeOH rt then NH_4OAc, 50 °C; c) (+)-DBTA, EtOH, 60 °C, 15 h; d) i) $NaBH_4$, F_3CCO_2H, THF, −10 °C to rt; ii) Boc_2O, PhMe/H_2O, 5 °C to rt, (pH 10); iii) NaOMe, $HCONH_2$, THF, 35 °C, then crystallization from H_2O/MeOH; e) PIDA, KOH, MeCN/H_2O, 24−28 °C, then crystallization from PhMe; f) i) **31** (1.3 equiv), 6-chloro-2-pyridinol (0.1 equiv), PhMe, 110−85 °C; ii) MsCl, Et_3N, THF, 22−30 °C; iii) *t*-BuOLi, THF, −10 to 0 °C, then crystallization from MeOH; g) HCl, acetone/H_2O, 50 °C.

conversions were determined by HPLC (% by area). Enantiomeric excesses (ee) were determined by HPLC on chiral stationary phase using the indicated conditions. ^{1}H NMR spectra were recorded at 400 MHz using tetramethylsilane (TMS) as internal reference. Data are presented as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (J) in Hz, and integration. ^{13}C NMR spectra were recorded at 100 MHz. Absorptions in IR spectra are recorded in wavenumbers (cm^{-1}). Low-resolution mass spectra were obtained by positive or negative ion spray ionization (ESI). Data are reported in the form of m/z.

4.2. Preparation of Pyran-2,4,6-trione (18). Acetone dicarboxylic acid (32.5 kg, 222 mol, 1.00 equiv) was charged in the reactor followed by AcOH (46 L). The suspension was cooled to 15−20 °C, and Ac_2O (35 L) was added. The reaction mixture was stirred for 4−5 h at 8−10 °C. A solution was obtained during the course of the reaction after which the product started to crystallize. The resulting suspension was filtered, and the filter cake was washed with PhMe (65 L) and dried at 45 °C/30 mbar to give 22.5 kg of the title compound (79% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 2H), 5.23 (s, 1H), 12.5 (br s, 1H).

4.3. Preparation of (*Z*)-4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl)-3-hydroxy-but-2-enoic Acid Ethyl Ester Hydrochloride (15). Cyclic anhydride **18** (22.3 kg, 174 mol, 1.20 equiv) was suspended in heptane (83 L) at room temperature. EtOH (58 L) was added dropwise over 15−20 min while maintaining the temperature between 20−25 °C. After 1 h reaction, the resulting clear solution was transferred to a feed tank. The reactor and the lines were rinsed with EtOH. The resulting solution was added over 1.5 h to a turbid solution consisting of imine hydrochloride **3** (33.0 kg, 145 mol, 1.0 equiv), NaOAc (1.20 kg, 14.5 mol, 0.10 equiv), H_2O (8.5 L), and EtOH (250 L) while keeping the temperature between 20−25 °C. Crystallization of the product was usually observed during the reaction. After 1.5 h, 37% aq HCl (1.5 L, 17 mol, 0.12 equiv) was added to the resulting suspension. Heptane (240 L) was added over 30 min. The yellow suspension was cooled and stirred for 2 h at 0−5 °C. The suspension was filtered and washed with a cold (0 °C) mixture of EtOH (55 L) and heptane (110 L). The filter cake was dried at 45 °C/20−30 mbar until constant weight to give 42 kg of the title compound (81% yield, 96% by area (HPLC) and 0.2% (w/w) residual EtOH). The product may contain up to 1.8% (w/w) NaCl.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (t, J = 7.3 Hz, 3H), 2.83−3.01 (m, 2H), 3.18−3.35 (m, 2H), 3.34 (dd, J = 19 and 4 Hz, 1H), 3.46 (dd, J = 19 and 8 Hz, 1H), 3.68 (d, J = 19 Hz, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 3.77 (d, J = 19 Hz, 1H), 4.12 (t, J = 7 Hz, 2H), 4.76 (br dd, J = 8 and 4 Hz, 1H), 6.77 (s, 3H), 6.78 (s, 3H). MS ESI: m/z 322.2 ($[M + H]^+$)

4.4. Preparation of (±)-2-Amino-9,10-dimethoxy-1,6,7,11b-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylic Acid Ethyl Ester (*rac*-7). Ketoester hydrochloride **15** (2.60 kg, 7.19 mol, 1.00 equiv) was charged in the reactor and dissolved by addition of MeOH (15 L). A solution of NaOAc (0.590 kg, 7.19 mol, 1.00 equiv) in MeOH (6 L) was added. The addition system was rinsed with MeOH (3 L). The obtained solution was transferred in a feed tank, and the reactor and transfer lines were rinsed with MeOH (5 L). The resulting solution was added at 20−25 °C over 25−30 min to a solution of 37% aq CH_2O (0.58 L, 7.55 mol, 1.05 equiv) in MeOH (13 L). The feed tank and transfer lines were rinsed with MeOH (10 L). The reaction mixture was stirred for 4−5 h at 20−25 °C (IPC indicated conversion to intermediate *rac*-**6**), whereupon NH_4OAc (1.7 kg, 21.6 mol, 3.0 equiv) was added. The reaction mixture was heated to 45−50 °C overnight and then cooled to 20−25 °C. The resulting red reaction mixture was concentrated under pressure at ∼25−30 °C to an oily residue which was taken in CH_2Cl_2 (22 L) and H_2O (11 L). The resulting pH 5−6 was adjusted to pH > 7 by addition of aq $NaHCO_3$ (1.5 kg in 15 L water). The organic phase was separated and washed with aq NaCl (1.7 kg in 15 L water). The aqueous phases were re-extracted with CH_2Cl_2 (20 L). The organic phases were combined, and solvent was exchanged to MeOH (7 L final MeOH volume). The resulting suspension was dissolved at reflux. The solution was cooled over 15 h to −25 °C to −20 °C and stirred for 5 h. The suspension was filtered, and the filter cake was washed with cold (−25 °C) MeOH (4 L) and cold (−25 °C) heptane (1.6 L). The crystals were dried under reduced pressure at 35 °C to give 1.83 kg of the title compound (71%, 97% by area (HPLC), 7.4% (w/w) residual MeOH).

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^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.3 Hz, 3H), 2.40−2.72 (m, 4 H), 3.03−3.16 (m, 3 H), 3.43−3.52 (m, 3 H), 3.73 (d, J = 13.7 Hz, 1 H), 3.86 (s, 6 H), 4.18 (m, 2 H), 6.59 (s, 1 H), 6.60 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.56, 154.24, 147.68, 147.46, 128.68, 126.92, 111.47, 108.25, 91.05, 59.05, 58.04, 56.10, 55.86, 53.67, 50.99, 37.56, 28.94, 14.62. HRMS (ESI): m/z 333.1 ($[M + H]^+$); Expected mass: 332.1736; Found: 332.1734 (calculated for M).

4.5. Preparation of (*S*)-2-Amino-9,10-dimethoxy-1,6,7,11b-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylic Acid Ethyl Ester, (*S*,*S*)-2,3-Bisbenzoyloxy-succinic Acid Salt ((*S*)-20). A 160-L Hastelloy reactor was charged with enamine *rac*-7 (27.7 kg, 74.5 mol, containing ∼8% (w/w) MeOH and EtOH (97 L). (*S*,*S*)-(+)-Dibenzoyl-D-tartaric acid (28.5 kg, 79.5 mol, 1.06 equiv) was added under stirring followed by EtOH (41 L) to give an off-white suspension. The mixture was heated to 60 °C over 45 min and stirred at this temperature for 24 h. The thick yellowish suspension was cooled to ambient temperature over 8 h and filtered. The crystals obtained were washed with EtOH (82 L, 0 °C) and dried under reduced pressure at 45 °C for 24 h to give 48.1 kg (93%, ee >99.5%) of the title compound as white crystals.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (t, J = 7.2 Hz, 3H), 2.41−2.29 (m, 1H), 2.68−2.59 (m, 1H) 2.86−2.72 (m, 1H), 3.02−2.90 (m, 1H), 3.15−3.05 (m, 1H), 3.40−3.27 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.85−3.75 (m, 1H), 3.96−3.85 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 5.74 (s, 2H), 6.62 (s, 1H), 6.81 (s, 1H), 7.58−7.53 (m, 4H), 7.73−7.66 (m, 2H), 8.03−7.96 (m, 4H), 14.1 (br. s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.5, 26.8, 34.7, 49.5, 52.0, 55.4, 55.7, 57.1, 58.4, 71.7, 85.0, 109.0, 111.6, 125.1, 126.0, 128.8, 129.0, 129.3, 133.7, 147.4, 147.8, 155.6, 164.7, 167.0, 167.5. IR (cm^{-1}): 3440, 3320, 2924, 2854, 1734, 1618, 1376, 1260, 1237, 1129, 1027, 769, 714. MS (ESI): m/z 333.1 ($[M + H]^+$ free amine). Anal. Calcd for $C_{36}H_{38}N_2O_{12}$: C, 62.6; H, 5.55; N, 4.06. Found: C, 62.45; H, 5.82; N, 3.77. $[\alpha]^{20}_D$ = −133.7° (c 1.025, DMSO). Chiral HPLC: Chiralpak OD-RH column (5 μm, 250 × 4.6 mm), MeCN/H_2O: aq $NaClO_4$ (0.5 M) 0.714:0.026:0.26, flow rate: 1.0 mL min^{-1}, oven temperature: 40 °C, detection: 210 nm, R_t: 14.0 min (R), 15.6 min (S).

4.6. Preparation of (2*S*,3*S*,11*βS*)-3-(Carbamoyl-9,10-dimethoxy-1,3,4,6,7,11*β*-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl]-carbamic Acid *tert*-Butyl Ester (28). A 1000-L reactor was charged under a nitrogen atmosphere with $NaBH_4$ (14.8 kg, 391 mol, 1.35 equiv) and THF (550 kg). The suspension was treated at −17 to −10 °C within 4 h with TFA (162 kg, 1421 mol, 5.0 equiv). (*S*)-**20** (200 kg, 290 mol) was added as a solid to the suspension within 5 h at −15 to −10 °C. The starting material container and the transfer lines were rinsed with THF (100 kg). The reaction mixture was heated to 0 °C within 3 h and stirred at this temperature for 3 h. The reaction mixture was heated to 20 °C within 3 h and stirred at this temperature for 5 h. Upon complete conversion (<1.0% by area (HPLC) of starting material), the reaction was transferred in a 2500-L vessel and quenched by the addition of H_2O (658 kg). The mixture was stirred at 20−25 °C for 30 min and then cooled to 5−10 °C. The pH of the mixture was adjusted at this temperature from approximately 1.8 to 11.0−11.5 by the careful addition of 50% aq KOH (187 kg). The mixture was treated at 5−10 °C within 30 min with a solution of Boc_2O (80.5 kg, 369 mol, 1.27 equiv) in PhMe (40.0 kg). The receiver and the transfer lines were rinsed with PhMe (73 kg). The reaction mixture was allowed to warm to 20−25 °C within 30 min and stirred at this temperature for 100 min. During the entire reaction time the pH was kept constant at pH ∼10 by the careful addition of 50% aq KOH (16 kg in total). Upon complete conversion (<0.5% by area (HPLC) of free amine), the stirrer was stopped, and the biphasic mixture was allowed to separate for 20 min. The lower aqueous layer was separated and extracted with PhMe (240 kg). The combined organic layers were washed with H_2O (180 kg) and concentrated under reduced pressure at 30−50 °C to almost dryness. The residue was treated with THF (400 kg), and the resulting mixture was concentrated at 30−50 °C under reduced pressure to almost dryness. The residue was diluted with THF (1500 kg), and the mixture was concentrated at 30−50 °C under reduced pressure to a residual volume of 1400−1500 L. In the case of a complete solvent exchange (<0.10% (w/w) H_2O, <8.0% (w/w) PhMe) the residue was treated at 32−38 °C first within 10 min with formamide (131 kg, 2902 mol, 10.0 equiv) and subsequently within 1 h with 30% NaOMe in MeOH (156 kg, 868 mol, 3.0 equiv). The mixture was stirred at 35 °C for 12 h. Upon complete conversion (<0.5% by area (HPLC) of ethyl ester **25** and <3.0% of the corresponding methyl ester), the suspension was treated with H_2O (740 kg). The mixture was concentrated at 30−55 °C under reduced pressure to a residual volume of 1200−1250 L. The suspension was diluted with MeOH (550 kg), and the resulting mixture was heated at 60 °C for 10 h. The suspension was cooled to 30 °C and subsequently centrifuged immediately. The crystals were washed in two portions with a mixture of H_2O (86 kg) and THF (66 kg) and dried at 70 °C and <30 mbar for 10 h to afford 100.4 kg (85%) of the title amide **28** as colorless crystals with an assay (HPLC) of 97.8% (w/w).[43]

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17−1.25 (m, 1H), 1.38 (s, 9H), 2.30−2.49 (m, 4H), 2.52−2.62 (m, 1H), 2.76−2.97 (m, 3H), 3.07−3.12 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 3.65−3.75 (m, 1H), 6.61−6.71 (m, 3H), 6.84 (br s, 1H), 7.04 (br s, 1H). IR (cm^{-1}): 3446, 3346, 2923, 1684, 1663, 1535. MS (ESI): m/z 406.2 ($[M + H]^+$). Anal. Calcd for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36. Found: C, 62.09; H, 7.76; N, 10.39.

4.7. Preparation of (2*S*,3*S*,11*βS*)-3-(Amino-9,10-dimethoxy-1,3,4,6,7,11*β*-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl]-carbamic Acid *tert*-Butyl Ester (10). A suspension of amide **28** (120 kg, 296 mol) in a mixture of H_2O (1000 kg) and MeCN (522 kg) was treated within 30 min at 15−28 °C with 50% aq KOH (166.0 kg, 1479 mol, 5 equiv) and the resulting suspension stirred at 24−28 °C for 30 min. To the suspension was added within 3−4 h at 24−28 °C a solution of iodosobenzene diacetate (106 kg, 329 mol, 1.10 equiv) in a mixture of H_2O (270 kg) and MeCN (448 kg). After the addition, the suspension was stirred at 24−28 °C for 1 h. Upon complete conversion (<0.1% by area (HPLC) of starting material), the suspension was concentrated under reduced pressure and at a maximum internal temperature of 45 °C (70 °C jacket temperature) to a residual volume of approximately 1200 L. The pH of the mixture was adjusted to pH 9.5 by treatment with 37% aq HCl (33.8 kg) at 20−40 °C. THF (210 kg) and PhMe (1040 kg) were added at 20−40 °C, and the resulting mixture was heated to 70−75 °C and stirred at this temperature for 30−60 min. The agitator was stopped, and the biphasic mixture was allowed to separate for 30 min. The lower aqueous layer was discharged and the organic layer washed with H_2O (180 kg) at 70−75 °C. From the organic layer, THF and H_2O were removed by azeotropic distillation with PhMe at a maximum internal temperature of 70 °C. At the end of the distillation the THF content should be <0.5%, and the volume of

the mixture was adjusted to 1700−1800 L. The mixture was heated to 70−80 °C to obtain a dimmish solution. To remove the urea byproduct **30**, the solution was filtered at 70−80 °C. The first reactor, the filter, and the transfer lines were rinsed with hot PhMe (400 kg). The filtrate was concentrated at a maximum internal temperature of 80 °C under reduced pressure to a residual volume of 1000−1100 L, whereby the product partly precipitated. The suspension was heated to 90 °C to obtain a clear solution. The solution was cooled to −8 °C within 7 h and subsequently stirred at this temperature for 2 h. The crystals were filtered off using a centrifuge, washed in two portions with cooled PhMe (<0 °C; 300 L), and dried at 60 °C/<30 mbar for 7 h to afford 94.6 kg (85%) of amine **10** as slightly yellow crystals with an assay (HPLC) of 99.8% (w/w) with <0.10% of the corresponding enantiomer (by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (br s), 1.34 (q, J = 12 Hz, 1H), 1.49 (s, 9H), 2.19 (t, J = 12 Hz, 1H), 2.48−2.66 (m, 3H), 2.67−2.75 (m, 1H), 2.92−2.99 (m, 1H), 3.01−3.15 (m, 2H), 3.18−3.24 (m, 1H), 3.39−3.51 (m, 1H), 3.837 (s, 3H), 3.844 (s, 3H), 4.55 (br s), 6.57 (s, 1H), 6.66 (s, 1H). IR (cm^{-1}): 3355, 2923, 2854, 1679, 1523, 1463, 1251. MS (Ion Spray) m/z 378.4 (MH^+). Anal. Calcd for $C_{20}H_{31}N_3O_4$: C, 63.64; H, 8.28; N, 11.13. Found: C, 63.77; H, 7.97; N, 11.15. Chiral HPLC: Chiralpak AD-H column (5 μm, 250 × 4.6 mm), n-heptane/isopropanol (with 0.1% $NHEt_2$) 60:40, flow rate: 1.0 mL min^{-1}, oven temperature: 30 °C, pressure: 76 bar, detection: 210 nm, R_t: 4.8 min ((*R*)-**10**), 6.4 min ((*S*)-**10**).

4.8. Preparation of (2*S*,3*S*,11β*S*)-3-((4*S*)-Fluoromethyl-2-oxo-pyrrolidin-1-yl)-9,10-dimethoxy-1,3,4,6,7,11β-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl]-carbamic Acid *tert*-Butyl Ester (13). *4.8.1. Using LHMDS as Base for Cyclization.* A solution of amine **10** (90.0 kg, 238 mol) and 6-chloro-2-pyridinol (3.60 kg, 27.8 mol, 0.120 equiv) in anhydrous PhMe (1180 kg) was heated to 85−90 °C and treated at this temperature within 60 min with (*S*)-fluoromethyl lactone **31**[9] (36.6 kg, 310 mol, 1.30 equiv, 99.0−99.5% ee). After the addition, the mixture was heated to 105 °C and stirred at this temperature for 7 h. Approximately 570 kg of PhMe were distilled off at 70−90 °C under reduced pressure and the resulting suspension (800−850 L) was subsequently stirred at 85 °C for another 12 h. Upon complete conversion (<1.0% starting material) the reaction mixture is concentrated to a residual volume of ∼500 L. The residue is diluted with THF (1200 kg) and subsequently concentrated to a residual volume of ∼1600 L. The water-free suspension was cooled to 23−25 °C and treated at a maximum temperature of 30 °C with methanesulfonyl chloride (40.8 kg, 356.0 mol, 1.50 equiv) followed by Et_3N (41.0 kg, 405 mol, 1.70 equiv) within 45 min. The resulting thick suspension was stirred at 25−30 °C for 75 min. Upon complete mesylation (<1.5% hydroxybutyramide **32**), the reaction mixture was cooled to −10 to 0 °C and subsequently treated at this temperature within 2 h with LHMDS (23.8% in THF, 503 kg, 715 mol, 3.00 equiv). After complete addition, the resulting dimmish solution was stirred for additional 2 h at −5 °C. Upon reaction completion (<0.2% mesylate **33**) the reaction mixture was treated at −5 to 5 °C within 1 h with H_2O (220 kg). The layers were allowed to separate at 0−5 °C for 30 min and the aqueous layer was subsequently discharged. The organic layer was washed at 0−5 °C twice with 5% aq H_2SO_4 (2 × 240 kg). Both combined aqueous layers were back extracted with PhMe (195 kg). The combined organic layers were concentrated to a residual volume of 700−800 L and washed once with H_2O (95 kg). The organic layer was concentrated at <40 °C under reduced pressure to a residual volume of 150 L. MeOH (950 kg) was added and the mixture concentrated at <40 °C under reduced pressure to a residual volume of 500−530 L. The resulting suspension was heated to reflux temperature (∼65 °C) and stirred at this temperature for 30−60 min to obtain a clear (or dimmish) solution. The mixture was allowed to cool to −10 °C within 5 h and the resulting suspension stirred for 2 h at −10 °C. The crystals were centrifuged, subsequently washed in portions with a cooled mixture (−5 °C) of MeOH (81 kg) and H_2O (51 kg), and dried at 45−50 °C/< 30 mbar to afford 88.8 kg (78% yield) of the title compound as colorless to slightly yellow crystals with an assay (HPLC) of 99.1% (w/w). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H); 1.37−1.49 (m, 1H); 2.07−2.15 (m, 1H); 2.22−2.32 (m, 1H); 2.33−2.65 (m, 5H); 2.72−2.78 (m, 1H); 2.81−2.92 (m, 2H); 3.02−3.17 (m, 2H); 3.63−3.76 (m, 2H); 3.70 (s, 3H); 3.71 (s, 3H); 3.85−3.93 (m, 1H); 4.33−4.42 (m, 1H); 4.45−4.55 (m, 1H); 6.64 (s, 1H); 6.78 (s, 1H); 6.92 (d, J = 8 Hz, NH). IR (cm^{-1}): 3401, 2926, 2854, 1696, 1512, 1466, 1010, 982. MS (ESI): m/z 478.1 ($[M + H]^+$). Anal. Calcd for $C_{25}H_{36}FN_3O_5$: C, 62.87; H, 7.60; N, 8.80. Found: C, 62.49; H, 7.56; N, 8.67.

4.8.2. Using t-BuOLi as Base for Cyclization. A 1500-mL reactor equipped with a mechanical stirrer, a Pt-100 thermometer, a dropping funnel, and a nitrogen inlet was charged with amine **10** (30.0 g, 79.5 mmol) and 6-chloro-2-pyridinol (1.20 g, 9.10 mmol) in PhMe (480 g). The mixture was heated to 85−90 °C, and (*S*)-fluoromethyl lactone **31** (12.2 g, 103 mmol) was added within 60 min. After the addition, the mixture was heated to 105 °C and stirred at this temperature for 6 h. Approximately 300 mL of PhMe were distilled off, and the resulting thick suspension (250−300 mL) was stirred at 85 °C for another 13 h. One hundred milliliters of PhMe were distilled off and replaced by 400 g of THF. At the end of the distillation a reaction volume of 500 mL was adjusted. The mixture was cooled to 23 °C and treated at 23−30 °C with methanesulfonyl chloride (13.8 g, 0.120 mol) followed by Et_3N (14.0 g, 0.140 mol). The resulting thick suspension was allowed to stir at 25−30 °C for 75 min, cooled to −10 to 0 °C, and subsequently treated at this temperature within 2 h with *t*-BuOLi (20% in THF, 95.0 g, 0.240 mol). After addition completion, the suspension was stirred for 2 h at −5 °C. The mixture was treated at <0 °C within 30 min with H_2O (70 g). The layers were allowed to separate at 0−5 °C for 30 min, and the aqueous layer was subsequently discharged. The pH of the organic layer was adjusted to pH 10.2 with 3% aq H_2SO_4 (∼32 g). H_2O (38 g) was added, and the layers were allowed to separate at 0−5 °C for 20 min. The aqueous layer was removed, and the organic layer was washed at room temperature with H_2O (70 g). The two aqueous phases were combined and extracted with PhMe (65 g). From the combined organic layers THF and PhMe were completely distilled off and replaced by MeOH (300 g in total). At the end of the solvent exchange a volume of ∼200 mL was adjusted in the reactor. The resulting suspension was heated to reflux temperature and stirred at this temperature for 30−60 min to obtain a clear solution. The solution was allowed to cool to −10 °C within 5−7 h and the resulting suspension stirred for 2 h at −10 °C. The crystals were filtered off, washed with a cooled mixture (−5 °C) of MeOH (30 g) and H_2O (10 g) and dried at 45 °C/< 30 mbar to afford 30.0 g (79% yield) of the title product as colorless crystals with an assay (HPLC) of 99.2% (w/w).

4.9. Preparation of (2*S*,3*S*,11β*S*)-1-(2-Amino-9,10-dimethoxy-1,3,4,6,7,11β-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-3-yl)-(4*S*)-fluoromethyl-pyrrolidin-2-one Dihydrochloride (1). A suspension of carbamate **13** (136 kg, 285 mol) in a mixture of H_2O (112 kg) and acetone (122 kg) was treated at 50 °C within 60 min with 37% aq HCl (98.0 kg). After 90 min at 47−52 °C the solution was polish filtered through a 5 μm filter. The first reactor and the transfer lines were washed with a hot (47−52 °C) mixture of H_2O (13.0 kg) and acetone (116 kg). The filtrate was cooled to 25 °C and treated at this temperature within 80 min with acetone (1600 kg) whereupon the product crystallized out. The resulting suspension was stirred for 1 h at 25 °C and subsequently centrifuged. The crystals were washed in two portions with acetone (391 kg) and dried at 50 °C and <30 mbar until constant weight to afford 122.4 kg (95%) of the title compound as colorless crystals with an assay (HPLC) of 98.8% (w/w).

^{1}H NMR (400 MHz, D_2O) δ 2.11−2.22 (m, 1H); 2.45 (dd, *J* = 17.6 Hz, 6.7 Hz; 1H); 2.76 (dd, *J* = 17.6 Hz, 9.55 Hz, 1H); 2.90−3.05 (m, 1H); 3.08−3.19 (m, 2H); 3.24−3.36 (m, 1H); 3.43 (dd, *J* = 9.8 Hz, 5.75 Hz, 1H); 3.49−3.58 (m, 1H); 3.70−3.84 (m, 4H); 3.87 (s, 3H); 3.88 (s, 3H); 4.12 (td, *J* = 11.6 Hz, 4.5 Hz, 1H); 4.45−4.55 (m, 1H); 4.56−4.68 (m, 3H); 6.91 (s, 1H), 6.95 (s, 1H). IR (cm^{-1}): 3237, 2925, 1682, 496, 478. MS (ESI): *m*/*z* 378.3 ($[M + H]^+$ (free amine)). Anal. Calcd for $C_{20}H_{30}Cl_2FN_3O_3$: C, 53.34; H, 6.71; N, 9.33; Cl, 15.74; F 4.22; O, 10.66. Found: C, 53.04; H, 6.43; N, 9.45; Cl, 15.66; F, 4.29; O, 11.09.

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Notes

[§]See the accompanying paper in this issue by Adam et al. (DOI: 10.1021/op200019k).

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REFERENCES

(1) http://www.cdc.gov/chronicdisease/resources/publications/AAG/ddt.htm.

(2) http://www.diabetesatlas.org/content/diabetes-and-impaired-glucose-tolerance.

(3) Gupta, R.; Walunj, S. S.; Tokala, R. K.; Parsa, K. V. L.; Singh, S. K.; Pal, M. *Current Drug Targets* **2009**, *10*, 71.

(4) (a) Böhringer, M.; Fischer, H.; Hennig, M.; Hunziker, D.; Huwyler, J.; Kuhn, B.; Löffler, B. M.; Lübbers, T.; Mattei, P.; Narquizian, R.; Sebokova, E.; Sprecher, U.; Wessel, H. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1106. (b) Mattei, P.; Böhringer, M.; Di Giorgio, P.; Fischer, H.; Hennig, M.; Huwyler, J.; Kocer, B.; Kuhn, B.; Löffler, B. M.; MacDonald, A.; Narquizian, R.; Rauber, E.; Sebokova, E.; Sprecher, U. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1109.(c) Böhringer, M.; Kuhn, B.; Lübbers, T.; Mattei, P.; Narquizian, R.; Wessel, H. P. (F. Hoffmann-La Roche AG). U.S. Pat. Appl. 2004/0259902, 2004.

(5) For an overview on DPP-IV inhibitor syntheses, see: Mulakayala, N.; Reddy, C. H. U.; Iqbal, J.; Pal, M. *Tetrahedron* **2010**, *66*, 4919.

(6) The coupling constant between H_2 and H_3 is *J* = 11.5 Hz, which is typical for a diaxial orientation of these protons.

(7) Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119.

(8) Abrecht, S.; Adam, J.-M.; Fettes, A.; Hildbrand, S. (F. Hoffmann-La Roche AG). PCT Int. Appl. WO/2008/031749 A1, 2008. Bromberger, U.; Diodone, R.; Hildbrand, S.; Meier, R. (F. Hoffmann-La Roche AG). PCT Int. Appl. WO/2009/027276 A1, 2009.

(9) Details on the synthesis of the requisite (*S*)-fluoromethyl lactone **31** are described elsewhere: Adam, J.-M.; Foricher, J.; Hanlon, S.; Lohri, B.; Moine, G.; Schmid, R.; Stahr, H.; Weber, M.; Wirz, B.; Zutter, U. *Org. Process Res. Dev.* **2011**, *15*, DOI: 10.1021/op200019k.

(10) Xu, L. W.; Li, J.-W.; Xia, C.-G.; Hu, X.-X. *Synlett* **2003**, 2425.

(11) (a) Chapman, J. H.; Holton, P. G.; Ritchie, A. C.; Walker, T.; Webb, G. B.; Whiting, K. D. E. *J. Chem. Soc.* **1962**, 2471. (b) Schneider, W.; Kämmerer, E.; Schilken, K. *Pharmazie* **1966**, 26.(c) Walker T.; England W.; Frederick K.; Rhondda M.; Wales G.; Ritchie A. C. U.S. Patent 3,105,835, 1963.

(12) Decomposition was observed at room temperature as also previously observed in the literature; see reference 9.

(13) (a) The cyclic anhydride is mainly in the enol form in DMSO-d_6. For keto-enol form analytical data see also:Kiang, A. K.; Tan, S. F.; Wong, W. S. *J. Chem. Soc (C)* **1971**, 2721. (b) For earlier preparations see: Findlay, S. P. *J. Org. Chem.* **1957**, *22*, 1385–1394. Ray, J. A.; Harris, T. M. *Tetrahedron Lett.* **1982**, *23*, 1971. Kozikowski, A. P.; Schmiesing, R. *Tetrahedron Lett.* **1978**, *19*, 4241.Ruminski P. G.; Dhingra O. P. U.S. Patent 4,747,871. Sharma, V. K.; Shahriari-Zavareth, H.; Garratt, P. J.; Sondheimer, F. *J. Org. Chem.* **1983**, *48*, 2379. Meltzer, P. C.; Wang, B.; Chen, Z.; Blundell, P.; Jayaraman, M.; Gonzales, M. D.; George, C.; Madras, B. K. *J. Med. Chem.* **2001**, *44*, 2619 and references cited therein.

(14) Precharging of the diacid in acetic acid led to clump formation.

(15) For reviews on crystallization-induced dynamic transformations, see: (a) Brands, K. M. J.; Davies, A. *J. Chem. Rev.* **2006**, *106*, 2711. (b) Kolarovic, A.; Berkes, D. A.; Baran, P.; Povazanec, F. *Tetrahedron Lett.* **2005**, *46*, 975. (c) Berkes, D.; Jakubec, P.; Winklerova, D.; Povazanec, F.; Daich, A. *Org. Biomol. Chem.* **2007**, *5*, 121.

(16) (a) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1461. (b) Clark, R. D.; Kern, J. R.; Kurz, L. J.; Nelson, J. T. *Heterocycles* **1990**, *31*, 353.

(17) Dibenzoyltartaric acid was preferred over dibenzoyltartaric acid monodimethylamide for cost reasons.

(18) Temperatures higher than 60 °C for extended periods of time led to decomposition of the resolving agent.

(19) The kinetic studies were performed on a Multimax ART workstation (Mettler-Toledo) equipped with a 16 × 5 mL reactor block. Dosing of the solvents as well as sampling (quench and dilution) was fully automated. HPLC analyses were performed off-line (the quench and dilution protocol provided stable samples).

(20) Negative values of the enantiomeric excess indicate that crystallization of the (*R*)-enamine (−)-DBTA salt has started, in which case the (*R*)-enantiomer becomes predominant, and analytical sampling becomes difficult because of the heterogeneous reaction mixture.

(21) Dichloromethane is the only solvent which can be used to extract the relatively polar unprotected ester.

(22) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *102*, 6203. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(23) Liang, H. *Synlett* **2008**, 2554.

(24) Hofmann rearrangements can also be problematic upon scale-up because the reactions tend to be exothermic.

(25) Allred, E. L.; Hurwitz, M. D. *J. Org. Chem.* **1965**, *30*, 2376.

(26) Approximately 2% of the methyl ester (which is formed immediately when sodium methoxide is added to the reaction mixture) usually remained after the reaction.

(27) (a) Hofmann, A. W. v. *Chem. Ber.* **1881**, *14*, 2725. (b) Wallis, E. S.; Lane, J. F. *Org. React.* **1949**, *3*, 267.
(28) Zhang, L. H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. G. *J. Org. Chem.* **1997**, *62*, 6918.
(29) (a) Radhakrishna, A. S.; Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 1746. (b) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.
(30) This byproduct is presumably formed by intramolecular trapping of the intermediate isocyanate, followed by intermolecular addition to a second isocyanate.
(31) During this distillation **29** is quantitatively hydrolyzed to yield **30**.
(32) The urea byproduct **30** is carried through to the final step where it is deprotected. It could not be depleted by crystallization in any step and hence must be limited to max. 0.25% in isolated amine **10**.
(33) **31** was typically produced with 99.0−99.5% ee. See reference 8 for details.
(34) Openshaw, H. C.; Whittaker, N. *J. Chem. Soc. C* **1969**, 89.
(35) The cyclization was also performed under Mitsunobu conditions using diethyl azodicarboxylate (DEAD), di-*tert*-butyl azodicarboxylate (DTAD) or diisopropyl azodicarboxylate (DIAD) in combination with triphenylphosphine or tributylphosphine. However, the crude yield usually was below 70%, the separation from the phosphine oxides was difficult, and the cost of the reagents was an issue. This variant was therefore abandoned in favor of above cheap and effective mesylation−cyclization method. For related cyclizations under Mitsunobu conditions, see: Bell, I. M.; Beshore, D. C.; Gallicchio, S. N.; Williams, T. M. *Tetrahedron Lett.* **2000**, *41*, 1141.
(36) During workup, silicon-containing byproducts (e.g., hexamethyldisiloxane or trimethylsilanol) are formed, which are present in all organic and aqueous waste streams and which cause plugging of the pipes upon incineration if no appropriate incineration facilities are in place.
(37) Lithium *tert*-butoxide is commercially available as a 20% (w/w) solution in THF from e.g. Chemetall.
(38) If hydroxybutyramide **32** is heated over the weekend in toluene (10 mL/g hydroxybutyramide) at 105 °C in the presence of 2-hydroxypyridine, 20% by area (HPLC) of amine **10** are formed, showing that it is indeed a reversible reaction.
(39) This catalyst was found to be considerably more active than 2-hydroxypyridine.
(40) The reaction was originally conducted at higher concentration (10 L/kg amine) and in a full batch mode. However, under such conditions, the product crashed out already during the heating period, leading to an extremely thick suspension and crust formation on the reactor walls. Also, a constant reaction temperature of 85 °C was probed, leading to an overall considerably lower and incomplete conversion.
(41) The deprotection of **13** with HCl in acetone revealed only traces of the nongenotoxic aldol condensation products mesityloxide and isomesityloxide. For discussion, see: Coffey, D. S.; Hawk, M. K. N.; Pedersen, S. W.; Ghera, S. J.; Marler, P. G.; Dodson, P. N.; Lytle, M. L. *Org. Process Res. Dev.* **2004**, *8*, 945.
(42) Although all distillates are recyclable, recycling of the solvent was not taken into account.
(43) Typically, yields of 80% were obtained instead of the 85% in the experiment described herein. This high yield is due to holdup from the previous batches.