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Diastereospecific Enolate Addition and Atom-Efficient Benzimidazole Synthesis for the Production of L/T Calcium Channel Blocker ACT-280778

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Supporting Information

ABSTRACT: A scalable access to **1** (**ACT-280778**), a potent L/T calcium channel blocker, has been developed. The synthesis, amenable to kilogram manufacturing, comprises 10 chemical steps from enantiomerically pure 5-phenylbicyclo[2.2.2]oct-5-en-2-one (**3**) and 1,4-dimethoxybenzene with a longest linear sequence of 7 steps. Key to the success of this fit-for-purpose approach are a robust and atom-efficient access to benzimidazole **4**, the substrate-controlled diastereoselective enolate addition toward carboxylic acid **2** that was isolated by simple crystallization with high dr (>99:1), the convenient selective *N*-deacylation of intermediate **10**, and the identification of a suitable solid form of **1** as the bis-maleate salt (**1**·2 $C_4H_4O_4$). As an illustration of the robustness of this process, 14 kg of drug substance, suitable for human use, was produced with an overall yield of 38% over the longest linear sequence (7 steps).

INTRODUCTION

Chiral bicyclic benzimidazole **1** (**ACT-280778**) is a L/T calcium channel blocker potentially indicated for the treatment of hypertension and angina pectoris (Scheme 1). There was a need at Actelion for a robust, safe and scalable production of the active pharmaceutical ingredient (API) **1** to supply material for preclinical and clinical studies.

In this account,[1] we report a fit-for-purpose approach towards **1** that went through two optimization cycles in two production campaigns, starting with the route implemented in Discovery Chemistry (Schemes 2 and 3).[2] Two practical syntheses of **3** on multikilogram scale have already been reported by our laboratories for both racemic[3,4] and enantiomerically pure[5,6] forms. Discovery Chemistry designed an 8-step sequence to free base API **1** from bicyclic ketone **3** starting with the addition of the lithium enolate of *tert*-butylacetate onto *rac*-**3** (Scheme 2). It afforded mixtures of diastereoisomers (**6** and **7**) with an average ratio of 3.5−4:1 which were separated by chromatography. The enantiopure adduct **6** was subsequently separated from its undesired enantiomer via preparative HPLC in 31% overall yield. After saponification of **6** (98% yield), the optically pure acid **2** was coupled with the benzimidazole building block **4**, prepared in six steps from 1,4-dimethoxybenzene (Scheme 4), to yield amide **8** (79%). Product **8** was reduced (76%) with sodium bis(2-methoxyethoxy)aluminium (RedAl) followed by acylation with an excess of isobutyroyl chloride to yield **10**. Selective *N*-deacylation of **10** was accomplished by treatment with silica gel for a period of one week (81%). The amorphous API was isolated as the *bis*-HCl salt (**1**·2HCl) after treatment with a solution of HCl in AcOEt followed by concentration to dryness (90%).

At the outset of this project, a number of aspects had to be considered to enable the large scale production of **1**: (1) development of a shorter and scalable way to produce benzimidazole **4**, (2) identification of a chromatography-free access to carboxylic acid **2**, (3) improvement of the efficiency of the introduction of the isobutyroyl ester moiety in the last stage toward free base API **1**, (4) identification of a suitable solid form of **1**. A maximum of 5 g of API as HCl salt was prepared in multiple batches with 14% overall yield from **3**. This was sufficient to profile **1** until its selection for further development; however, the throughput was too low to consider the synthesis of multikilogram amounts of this substance.

RESULTS AND DISCUSSION

Synthesis of Benzimidazole 4. The benzimidazole **4** was first synthesized following the Discovery Chemistry route (Scheme 4).[2b] This sequence did not meet our requirements for scale-up due to the high costs of some raw materials and reagents[7] and the need for chromatography (phenylenediamine **12a**) to obtain pure **4**.

Still, the first two steps, i.e. the dinitration of readily available 1,4-dimethoxybenzene (**5**) and the subsequent reduction to the phenylenediamine **12a** as substrate for the benzimidazole formation were attractive. Three major challenges remained to be addressed for scale up: (1) the dinitrobenzene derivatives

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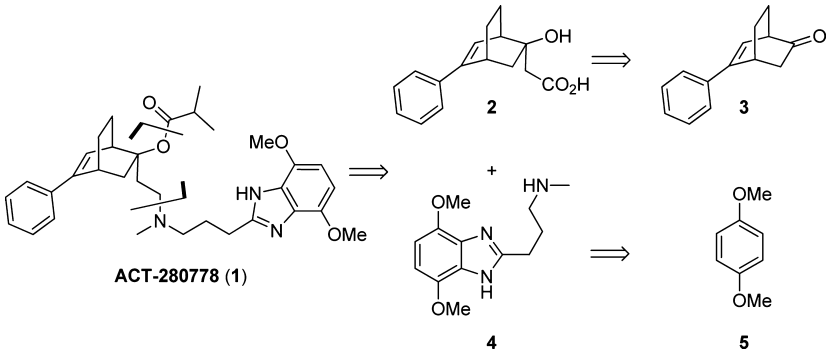
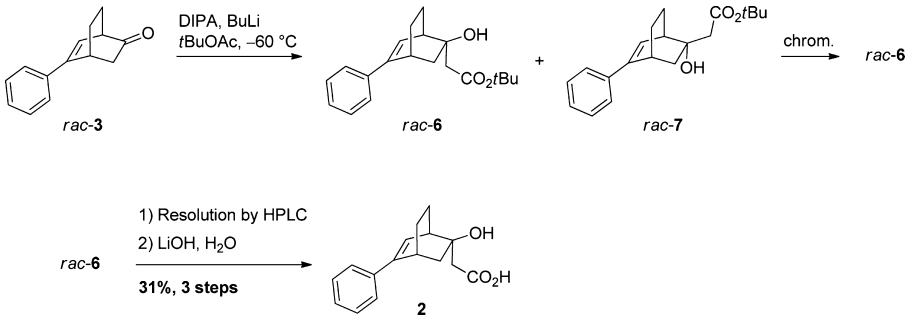
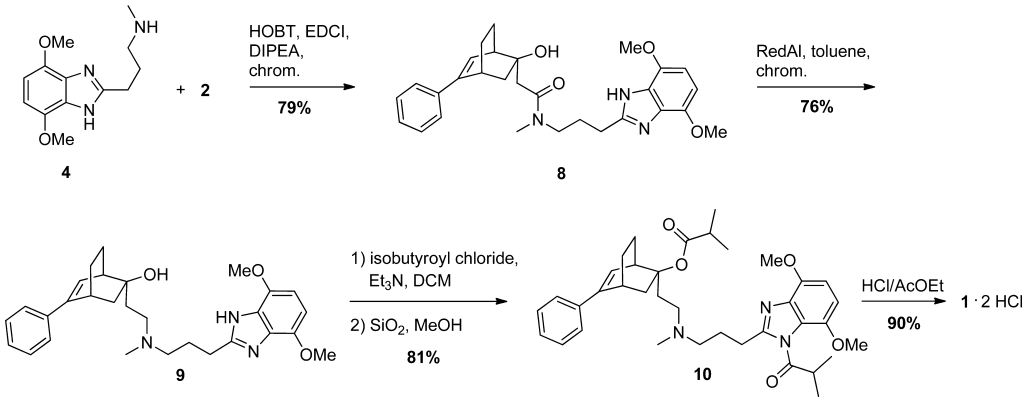
Scheme 1. Retrosynthesis of 1



Scheme 2. Discovery Chemistry synthesis of 2 (part 1 of 2)



Scheme 3. Discovery Chemistry synthesis of 1 (part 2 of 2)



(**11a**, **11b**) have a high decomposition energy (see Experimental Section),[8] (2) both phenylenediamine **12a** and benzimidazole **4** are highly water-soluble rendering an isolation very difficult, and (3) the phenylenediamine **12a** was obtained as deeply colored (black) substance that decomposed to a tarry black mass when exposed to air.

Several methods are known for the synthesis of benzimidazoles carrying a polar side chain at C2. The Phillips reaction,[9] i.e. the condensation of *o*-phenylenediamines with carboxylic acids in the presence of diluted mineral acids had been used with various amino acid derivatives.[10] We quickly focused on the unprecedented Phillips reaction with *N*-methyl pyrrolidinone (NMP) as condensation reagent. This strategy has the advantage of using a readily available solvent as reagent containing all required atoms for the targeted benzimidazole. Herein, we report the optimization of the process from the first kilograms in campaign 1 (15 kg) to 141 kg of **4** produced in campaign 2, describing how the issues encountered during the development have been solved. The chosen synthetic scheme for the production of **4** is short, comprising three synthetic steps (Scheme 5) and uses readily available raw materials. The benzimidazole **4** was built up in one step from the phenylenediamine intermediate **12a** by condensation with NMP in aqueous HCl.

Nitration. The dinitration of 1,4-dimethoxybenzene **5** with conc. HNO_3 (70%) is known to give a mixture of regioisomers.[11] Efficient stirring was crucial. The reaction rate correlated with the dissolution rate that increased with the stirrer speed: after addition of a portion of **5**, a brown spot[12] was visible that disappeared within seconds, and the product **11** was formed and precipitated within minutes even at 0 °C.[13] As suggested by the literature precedence, the reaction was aged at 50 °C for 1 h. However, this had no beneficial effect on yield, purity, or selectivity. The regioisomeric ratio (HPLC) was 4.8:1 and >7:1 at 20−25 and 0 °C, respectively. At −10 °C, approximately 35% accumulation was observed, mainly due to solubility issues of the starting material. Crystallization of the crude product from alcohols, toluene, and acetic acid were

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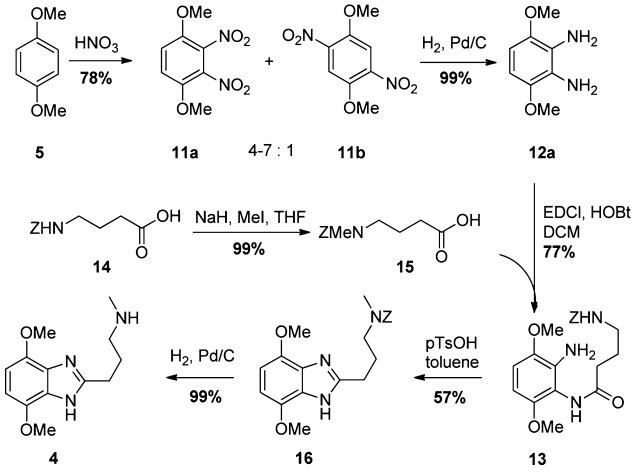
Scheme 4. Discovery Chemistry synthesis of 4 (Z = benzyloxycarbonyl)



found to enhance the regioisomeric ratio.[14] Regioisomerically pure **11a** thus obtained (**11a**:**11b** = 29:1) led to approximately 10% higher yield in the next step. However, the overall yield of steps 1 and 2 was not higher due to the yield loss in the crystallization. Therefore, **11** was processed as regioisomeric mixtures of 6−8:1. The process was scaled up uneventfully from 5- to 2 × 400-L scale: 1,4-dimethoxybenzene (**5**, 64 kg) was added in portions to 70% HNO_3 at 0−6 °C, followed by an aging period at 20 °C for 1−2 h. The suspension was quenched onto water,[15] followed by filtration and washing of the filter cake with water. The yield for both isomers **11** (99 kg) was 91−94% with a regioisomeric ratio of approximately 7:1. In total, 235 kg of **11** were produced.

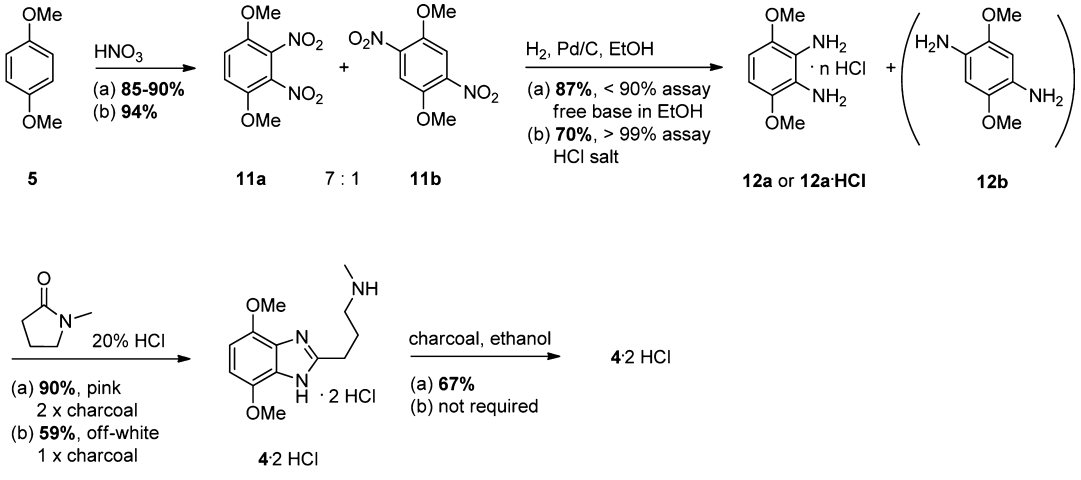
Hydrogenation. The 7:1 mixture of dinitro compound **11** was carried forward as such into the highly exothermic hydrogenation.[16] As the intermediate hydroxylamines are notoriously highly energetic compounds that could be explosive, they should not accumulate during the hydrogenation.[17] The main intermediates in the hydrogenation of **11** have been identified by LC−MS (Figure 1). With 1% catalyst loading, the reaction stalled at the hydroxylamine stage whereas a 10% load led to full conversion to the phenylenediamine within several hours. Amongst two appropriate Pd and Pt catalysts, we chose Pd as it led to a faster decay of the hydroxylamine **I** as compared to Pt/V.

The sticky phenylenediamine **12** obtained after filtration over Celite immediately turned black after contact with air.[18] To our surprise and delight, the undesired 2,5-regioisomer **12b** was not detected in the crude product (see ^{1}H NMR spectra in the Supporting Information [SI]). We speculate that this regioisomer was forming−probably via para-chinoid intermediates−oligomeric side products or was giving oxidation products that partially remained on the filter cake.[19] The first option was to process **12a** as a solution in EtOH without isolation.[20] To this end, on 11-kg scale, a 7:1 regioisomeric mixture of **11a**/**11b** (11.5 kg, 20% loss on drying (LOD)) was hydrogenated on 10% Pd/C (10% w/w) in EtOH at 20−30 °C and 1−2 bar hydrogen within 10 h. Crude **12a** was obtained as a solution in ethanol in yields of 88−92% (95% a/a HPLC). Typical NMR assays of aliquots of this solution after evaporation to dryness were 88−90% w/w with no individual byproducts present, indicating the presence of (polymeric) impurities not detected by UV or by NMR. This solution was carried through to the cyclization with NMP. However, the above-mentioned black impurities severely hampered workup and necessitated several charcoal treatments (vide infra). Therefore, the removal of the tar in **12a** was mandatory for the next scales. To this end, different types of charcoal were tested but no decoloration was obtained and the assay (weight of free base relative to the total weight as determined by HPLC with a reference standard) only slightly increased from 90% to maximum 94% w/w. Gratifyingly, the HCl salt synthesized by adding either aqueous (47%) or gaseous HCl (66% yield) to the EtOH solution of crude **12** gave an off-white (sometimes slightly pink) HCl salt **12a**·HCl with an assay of 82% w/w which corresponds to 100%, based on the mono-HCl salt.[21]

In campaign 2, a 7:1 regioisomeric mixture of dry **11a**/**11b** (194 kg) was hydrogenated on 10% Pd/C (5 wt %) in EtOH at 20−30 °C and 1−1.5 bar hydrogen within 12 h. After filtration of the mixture, HCl (1.5 equiv) was introduced as gas to precipitate **12a**·HCl in a good yield of 70% with an excellent assay (82% w/w, 100% a/a).[22]

Cyclization. Initially, the EtOH solution of free base **12a** was telescoped into the next step. Gratifyingly, the trans-

Scheme 5. Synthetic scheme used for (a) campaign 1 (15 kg 4·2HCl) and (b) campaign 2 (141 kg 4·2HCl)[a]



[a]See detailed process description in the text.

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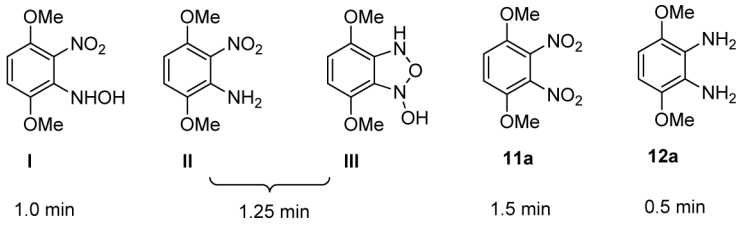

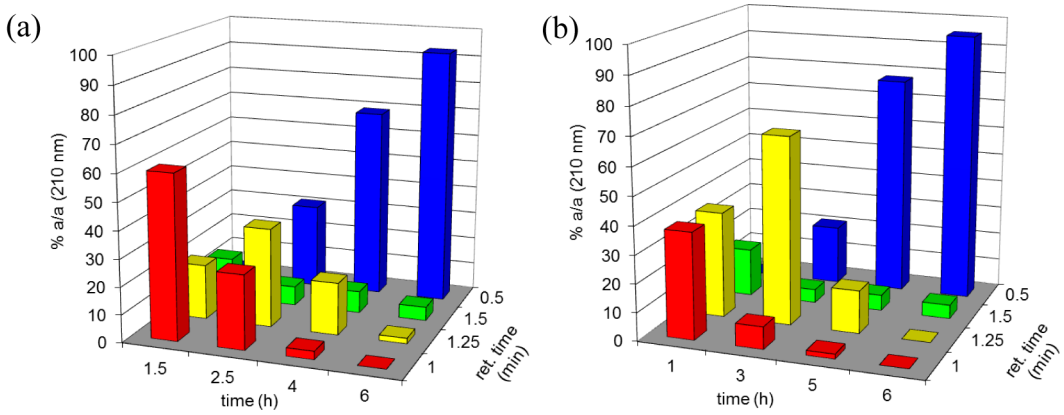

Figure 1. Monitoring of intermediates **I**, **II**/**III**, and of **11a** and **12a** during the hydrogenation of **11a** by LC−MS. (a) 3% Pt/2.5% V (Degussa CF 1082 RV/W) (b) 10% Pd/C (Engelhard ESCAT 163). Reaction in EtOH, H_2 (1 bar), 10% w/w catalyst loading. [LC−MS conditions: Eclipse Plus C18, 1.8 μm, 2.1 mm × 50 mm, 1 mL/min, 50 °C, eluent A: water, 0.04% TFA, eluent B: acetonitrile, 0.006% TFA, gradient: 2 min 95% B, 2.8 min 95% B, 3.0 min 5% B.]

formation of the free base **12a** to the benzimidazole proceeded well with 2 equiv NMP and 20% HCl[23] at 102−104 °C (reflux); the reaction started as soon as EtOH was removed by distillation, and the reaction took 1−2 days for completion. The major issues were the workup and the isolation: benzimidazole **4** is water-soluble, and it is insoluble in 2-methyl-THF, EtOAc, *i*PrOAc, MIBK, TBME, or toluene at pH 9. It is sparingly soluble in dichloromethane and acetone. However, an acceptable solubility was measured in *n*-butanol (4 vol at rt) that allowed for an aqueous workup at both pH 13−14 and at pH 1. *n*-Butanol was chosen as solvent for both extractions and for the salt formation: the HCl salt **4**·2 HCl was formed by addition of the *n*-butanol solution to HCl in AcOEt at 10 °C. Another challenge consisted of poor phase separation of the two black layers that were facilitated on scale by a conductivity meter. The crude free base obtained in first batches contained 10−30% of undetectable (by HPLC, ^{1}H NMR) impurities which were neither NaCl nor solvents, as indicated by sulphated ash, GC-headspace, chloride-titration and ICP-OES (Na). We assume that these impurities are tarry byproducts derived from oxidation of the phenylenediamines or demethylation products.[25] Stress tests with benzimidazole **4** showed that it was not stable in 32 and 20% HCl in a closed vial at 95 °C for 16 h, leading to 44 and 15% demethylated product according to LC−MS.[26] On the basis of these results, nonacidic benzimidazole syntheses should be preferred. However, no viable alternative was found.[27] To remove these tarry byproducts, two charcoal treatments[28] were included in the workup of campaign 1, and the bis HCl monohydrate salt of **4** (four 6-kg batches) was formed in *n*-butanol/AcOEt as pink crystals in 77% yield with 97−99% a/a purity. Although these batches met the current specifications, a user test with **4**·2 HCl in the amide bond formation failed.[29] This required a rework consisting of a third charcoal treatment of **4**·2 HCl in refluxing EtOH, affording **4**·2 HCl as off-white solid in 67% yield (15 kg).

The major change in campaign 2 was the use of the stable HCl salt of **12a** as starting material instead of the corresponding free base. Two out of three charcoal treatments (being associated with a lot of waste) could be skipped. Careful monitoring of the assay in weight % (in contrast to the area % purity by HPLC) in all unit operations was crucial. In order to suppress oxidative decomposition, all solvents and reagents were degassed prior to use, and sodium sulfite[30] was added to the cyclization mixture. The batches of campaign 1 contained 1−2% of salts according to sulphated ash. An extractive wash of the *n*-butanol layer after basification with 30% NaOH was investigated. Whereas a brine wash did not decrease the sulphated ash, a water wash reduced it to 0.5% with an associated slight loss of yield due to the water solubility of **4**·2 HCl. The water content turned out to be crucial for the crystallization. A water content of <0.5% led to very small crystals which were difficult to filter, whereas a water content of 3−8% gave larger crystals and hence faster filtration but with a yield reduced by 8%. A solubility study of **4**·2 HCl showed a minimal solubility at approximately 2% water in *n*-butanol. As a compromise between yield and quality, a water content of 3% was chosen as specification. In practice, 32% HCl and charcoal were added to the *n*-butanol phase after the basic extraction, and this suspension was filtered over Celite. The filtrate was concentrated to both azeotropically remove water and to trigger crystallization. At approximately 3.3 vol, the water content was adjusted to 3% based on the analysis of an aliquot. In campaign 2, seven batches of **4**·2 HCl (141 kg) were produced from the HCl salt **12a**·2 HCl with high assay (72% w/w) and purity (100% a/a HPLC). The water content was 5.3% (correspond-

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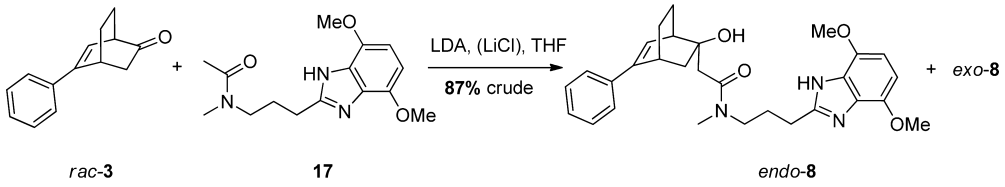
Scheme 6. Alternative synthesis of 8 by addition of the enolate of acetamide 17



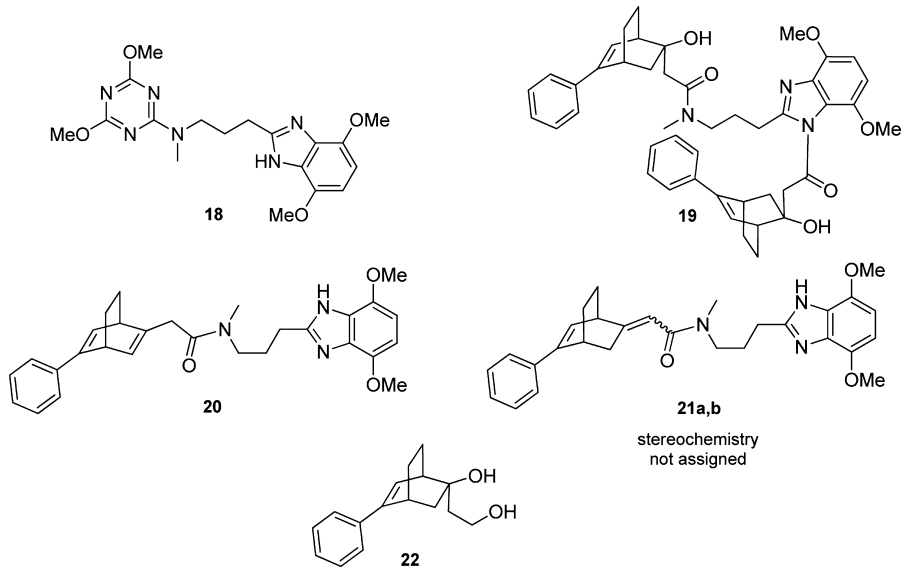


Figure 2. Impurities derived from CDMT-mediated coupling of **2** and **4**.

ing to the monohydrate), the chloride content was 21−22% (corresponding to the dihydrochloride), and the average yield was 59% (39% overall from **5**). In order to assess the impurities that have not been covered by the standard analytical methods, the color of a solution of **4**·2 HCl (2% w/w solution in water/acetonitrile 1:1) was compared with color reference solutions according to the *European Pharmacopoeia* 5.0.[31] This allowed for a qualitative determination of the colored impurities.

Diastereospecific Synthesis of Carboxylic Acid 2. With benzimidazole **4** now at hand, another line of attack consisted of reinvestigating the addition of the lithium enolate of *tert*-butylacetate onto optically pure phenyl ketone **3** obtained by resolution of *rac*-**3** with HPLC (Scheme 2). This reaction was originally performed in THF at −60 °C to yield a mixture of diastereoisomer (**6** and **7**) with a dr of 2.2 to 3.3:1. By lowering the temperature to −80 °C, together with the use of toluene as solvent instead of a mixture of THF and toluene, an improved dr of 4.5 to 5:1 was obtained. This *endo* selectivity is only driven by the difference in steric bulk of the CH_2−CH_2 bridge and the CH═CPh bridge.[32] The presence of the *tert*-butyl ester moiety as chelating group might stabilize in a solvent-dependent manner the 6-membered Li complex of the *endo* intermediate leading to *endo* adduct **6**. Secondary orbital overlaps may account for this selectivity as well.

For safety and environmental reasons, BuLi was substituted by HexLi.[33] Other bases such as LiHMDS or NaHMDS were tested, but none of them led to an improvement in terms of conversion or selectivity.[34] The crude mixture of diastereoisomers was not purified but rather directly used in the next saponification step after aqueous quench with citric acid. EtOH was added followed by aqueous KOH to trigger the hydrolysis of the mixture of *tert*-butyl esters. 2-Methyl-THF was found to be the optimal solvent to extract the desired mixture of acids with a minimal loss of product. After a solvent switch to AcOEt[35] followed by slow cooling, the desired acid **2** crystallized and was isolated with a yield of 55−60% over two steps (dr > 99:1, er > 98:2) starting from bicyclic ketone **3** with 98:2 er. A similar high level of enantiomeric purity (er > 98:2) was reached when the same sequence was conducted with **3** but with only 95:5 er. The absolute configuration of **3** was unambiguously proven by X-ray crystal structure analysis of two distinct derivatives [SI].

In order to satisfy the need for development, 90 kg of optically pure ketone **3** were manufactured. Diels−Alder cycloaddition on large scale[36] and highly productive resolution with preparative HPLC[37] are two key features of the bulk synthesis of **3**. The latter was obtained in several batches of high optical purity (er > 98:2) but with a maximal chemical purity of 80% w/w (NMR assay). Fortunately, this variability had no impact on the quality of the isolated acid **2**. It only affected the throughput at this stage. This protocol was successfully scaled up. A freshly prepared solution of LDA was added to a solution of ketone **3** in toluene at −80 °C. *tert*-Butyl acetate was added dropwise to afford a mixture of diastereoisomers that was subsequently saponified. After extraction with 2-methyl-THF and solvent exchange, the desired diastereoisomer was isolated by crystallization. On 8-kg scale, the dr of the acid **2** (isolated in 60% yield with 98% purity HPLC) slightly dropped to 98.3:1.7. The ratio was improved to >99.9:0.1 by recrystallization from AcOEt (90% recovery, 54% overall from **3**). Later, it turned out that **2** was the only solid intermediate isolated by crystallization until **1**. Indeed, all downstream intermediates (notably **8**, **9**, and **1** as free base) were foamy materials or viscous oils. The successful

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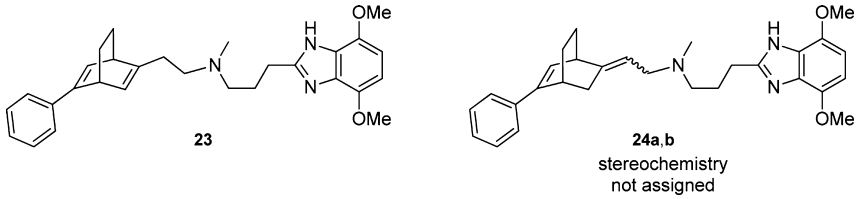
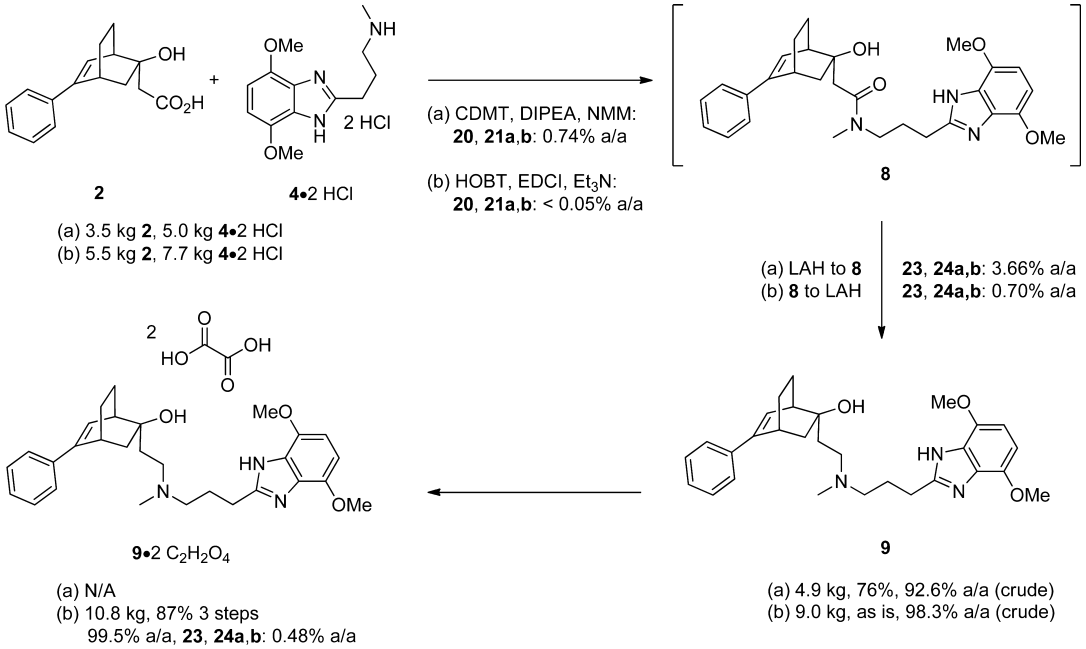


Figure 3. Impurities **23**, **24a,b**.

Scheme 7. Synthesis of 9: (a) campaign 1 (4.9 kg 9) and (b) campaign 2 (10.8 kg 9·2$C_2H_2O_4$)



isolation of pure bicyclic carboxylic acid **2** was, hence, crucial for the development of a practical route to **1**.

In an attempt to further improve the diastereoselectivity of this transformation, based on related precedents at Hoffmann-La Roche,[38] we envisioned that the use of functionalized acetamide **17** may increase the convergency of the sequence. Acetamide **17** was prepared from benzimidazole **4** using isopropenyl acetate [SI]. Initial experiments to add **17** to **3** showed that the corresponding adducts were obtained in a 7:1 ratio in favor of the desired amide *endo*-**8** (Scheme 6). By using LiCl as additive, this ratio increased to 9:1. Nevertheless, this approach was set aside since the undesired diastereoisomer could not be rejected below an acceptable limit without a significant loss of yield after formation of the corresponding oxalate salt of **9** in the next step.

Coupling of 2 and 4. With such well-defined solid building blocks at hand, the next step toward amide **8** was investigated (Scheme 3). The amide coupling of **2** and **4** was originally performed using HOBT/1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide·HCl (EDCI·HCl). In some reactions, incomplete conversion (90−95%) was observed. A rapid and complete conversion to the expected amide **8** was observed with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and propane phosphonic acid anhydride (T3P), whereas degradation was observed with isobutylchloroformate, pivaloyl chloride, and oxalyl chloride. When T3P was used, the bad smell arising after LAH reduction in the next stage was a concern. CDMT was hence selected for the first kg-campaign that afforded the amide **8** as a foam that was not isolated and engaged as such in the next step to yield amine **9**. A side reaction of CDMT with the benzimidazole side chain **4** giving **18** (Figure 2) required a slight overcharge of reagent. Under the reaction conditions,[39] acylation of the nitrogen atom of the benzimidazole ring was observed to yield impurity **19**. Three side products (*endo*-methylene **20**, *exo*-methylene, *cis*- and *trans*-**21a,b**, Figure 2) derived from dehydration of **8** were identified by LC−MS. Several acidic and basic washings did not fully remove (below 0.2% a/a) the series of dehydrated products (**20**, **21a,b**) that were carried through to the final product with minimal purging options in the absence of solid intermediates.[40]

The requirement to tightly control impurities in order to reproducibly deliver high-purity material triggered additional investigations in the preparation of the second kg-campaign. The use of EDCI/HOBT led to less dehydrated amide impurities (0.1% a/a vs 1% a/a with CDMT). The fact that incomplete conversion was observed during the first familiarization experiments using HOBT/EDCI was retrospectively assigned to the low assay of early batches of benzimidazole side chain **4**. With upgraded quality of this material, full conversion was observed so that CDMT could eventually be replaced. On the occasion of a 5.5-kg batch using EDCI, only traces of dehydrated impurities (less than 0.05% a/a) were formed. The use of EDCI, however, led to the formation of up to 3% a/a of the urea obtained by addition of the tertiary hydroxyl group onto the carbodiimide. This side product was partially removed by acidic washings (down to 1% a/a) and subsequently removed as alcohol **22** in the next reduction step. The desired

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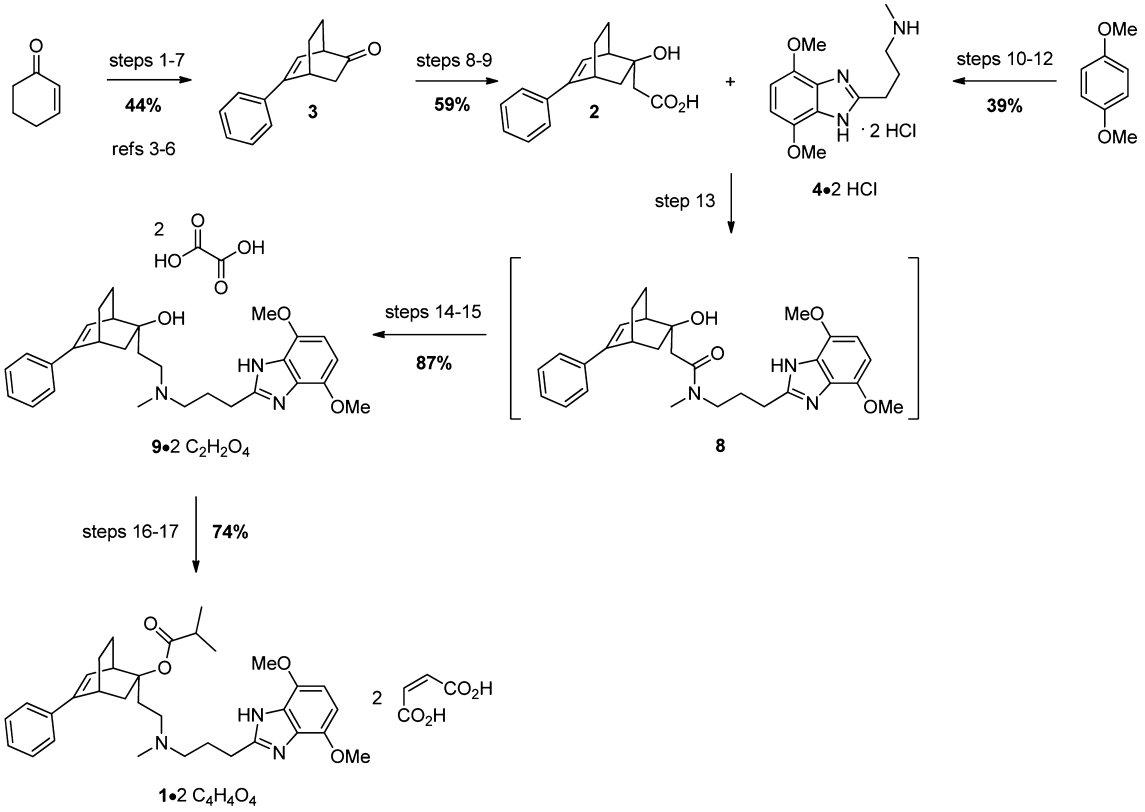
Scheme 8. Overall synthesis of 1·bis maleate salt (17% overall yield) from cyclohexenone



amide **8** (10.2 kg) was obtained with a purity of 97.4% a/a (HPLC) and was engaged as such in the next step.

Reduction of Amide 8. Amide **8** was initially reduced by addition of a 65% solution of RedAl in toluene (Scheme 3). Even though the conversion was satisfactory, the reaction mixture in toluene was heterogeneous and difficult to stir, and RedAl was replaced by LAH in THF. During the workup of the preceding amide coupling, a final wash with diluted acid was implemented after treatment with aqueous base. This led to residual HCl in **8** which was isolated in 76% yield on 7-kg scale (92.6% a/a HPLC). In this case, 2.3 equiv of LAH was necessary to observe complete conversion to amine **9**. Under these conditions, the reaction mixture typically contained 3–6% a/a (HPLC) of the mixture of dehydrated products (**23**, **24a**, **24b**, Figure 3). By adding the amide **8** *to* the LAH in THF, complete reduction of the amide (used as free base) was observed with only 2 equiv of LAH, as demonstrated during the second production campaign. After hydrolysis of the aluminum salts using aqueous KOH,[41] the crude mixture was filtered over Celite and stored as a solution in THF or 2-methyl-THF.

Despite extensive investigations, the unwanted dehydration reaction could not be suppressed below 0.5% a/a. To bypass this problem, the formation of the oxalate salt was envisioned. Upon treatment with oxalic acid of the crude solution of **9** in *i*PrOH, the oxalate salt crystallized out with an improved purity (from 98.3% a/a with 0.70% a/a of **23**, **24a**,**b** to 99.5% a/a with 0.48% a/a of **23**, **24a**,**b**). The filtration and drying of the very fine suspension in *i*PrOH, however, proved troublesome and took 3 days to be completed on a 9-kg scale.[42]

Using HOBT/EDCI instead of CDMT on the one hand and inverting the order of addition of LAH on the other hand allowed significant improvement of the overall purity of amine **9** (Scheme 7). The introduction of an additional purification step with the isolation of the oxalate salt of **9** helped to further increase the robustness of this process.

Scalable Preparation of 1 (As Free Base). In order to complete the synthesis of **1**, the tertiary alcohol had to be esterified to the isobutyroyl ester. To this end, the acylation of **9** was conducted in the presence of excess of isobutyroyl chloride (2.5 equiv) to observe complete consumption of starting material. However, the formation of **1** was accompanied by the simultaneous generation of compound **10** derived from overacylation on the nitrogen of the benzimidazole **4** (Scheme 3). Trials to tune the regioselectivity of this transformation using other solvents, bases or reagents (isobutyroyl anhydride) proved to be unsuccessful. In an attempt to purify **10** over silica gel, partial cleavage to **1** occurred. This observation led to a preparative isolation of the API by Discovery Chemistry. Nevertheless, this process could not be reliably reproduced.[43]

We hypothesized that selective hydrolysis of the *N*-isobutyroyl moiety over the tertiary ester function may be possible in the presence of a mild nucleophilic base. In a first trial, we were pleased to find that treatment of the crude reaction mixture with NaOMe in MeOH led to a rapid, mild, and selective cleavage of the *N*-acyl group, leaving the tertiary ester unaffected. Only under stress conditions with excess NaOMe under reflux, transesterification (up to 30%) was observed. This pivotal finding secured a practical access to larger quantities of **1**. Nevertheless, the identification of a suitable salt form of **1** remained a major challenge.

Preparation of the *bis*-maleate salt of 1. Before the isolation of the oxalate salt of amino alcohol **9**, all intermediates derived from **2** and the API itself as free base were isolated as oils or foams. Under these circumstances, the need for a well-defined solid form became pressing. When first treated with

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anhydrous HCl, the API was isolated as an amorphous material. Attempts to crystallize the free base were all unsuccessful; thus, a salt screening using a concise set of pharmaceutically acceptable acids in various solvent systems was performed. The key discriminating factors were good filterability and ease of drying. The *bis*-maleate salt (Scheme 8) turned out to be a breakthrough.[44] Indeed, a subsequent in-depth screening confirmed that this salt was the only form suitable for a clinical formulation. It showed the largest stability range among other candidates and exhibited good physicochemical properties. Most significantly, this salt was readily isolated by filtration after slow crystallization in contrast to other salts that formed thick and fine suspensions causing lengthy filtrations and drying. The same polymorphic form was consistently obtained. These favorable properties supported the selection of the *bis*-maleate salt for long-term development.

The crude API as a solution in AcOEt was therefore treated with a solution of maleic acid in MeOH under reflux. Upon cooling, the corresponding *bis*-maleate salt (**1**·2 $C_4H_4O_4$) was isolated with good yield (74% over two steps) and excellent chemical purity (99.7% a/a), suitable for human use. The identification of this salt turned out to be the cornerstone of this through process since it allowed for an efficient and robust purification that delivered material within specifications after three telescoped steps. Overall, this synthetic sequence delivered 14 kg of **1** with a yield of 38% (seven linear steps) from chiral bicyclic ketone **3**, and 17% yield (14 linear steps) from cyclohexenone (Scheme 8).

■ CONCLUSION

A practical synthesis of **ACT-280778** (**1**, as the *bis*-maleate salt) was developed and demonstrated on kilogram scale. Using the present process, 14 kg of drug substance was prepared, enough to complete phase II clinical trials. This became only possible after the manufacturing of large amounts of chiral bicyclic ketone **3** had been secured. A first achievement was the scalable synthesis of the benzimidazole side chain **4** based on a solvent (NMP) as atom-efficient reagent, and on the stable phenylenediamine hydrochloride **12a**. The development of a convenient way to isolate carboxylic acid **2** in diastereoisomerically pure form was crucial for purging impurities from the preceding steps. The use of sodium methoxide to selectively afford **1** from *bis*-acylated byproduct **10** and the identification of a convenient access to *bis*-maleate salt of **1** were the two other salient features. This route consists of a total of 7 + 3 steps from optically pure ketone **3** with 38% yield for the longest linear sequence. Notably, no chromatographic purification was required despite most of the intermediates being oils. Although further investigations will be required before larger scale campaigns may be undertaken, the work presented herein resulted in a rapid progression of this candidate into early clinical trials.

■ EXPERIMENTAL SECTION

General Remarks. Respectively, 1 vol or 1 wt means 1 L of solvent or 1 kg of reagent, with respect to the reference starting material; er (enantiomeric ratio), dr (diastereomeric ratio); er and dr reported in this paper have not been validated by calibration. Compounds are characterized by ^{1}H NMR (400 MHz, Bruker) or ^{13}C NMR (100 MHz, Bruker); internal standard for quantitative NMR was 1,4-dimethoxybenzene affording the assay data (in % w/w) in this paper. Details for the HPLC/MS and DSC methods are listed in the Supporting Information. All temperatures are internal temperatures and yields are presented as is, unless otherwise stated.

1,4-Dimethoxy-2,3-dinitrobenzene (5). (***Caution**: highly energetic substance!*[8] ***5** was not shock sensitive (falling hammer test according to Lütolf). However, a detonation was observed in the falling hammer test once the powder was wrapped in aluminium foil*). In a 600-L inox reactor, 1,4-dimethoxybenzene (**5**, 32 kg, white crystalline chips) was charged in 5 portions to 70% HNO_3 (482 kg, 10 vol, 23 equiv) at 0−6 °C within 50 min with good stirring (475 rpm, ***Caution**: exothermic addition!*). After stirring at 0−5 °C for 30 min, the mixture was warmed to 20 °C and stirred at 20 °C for 1 h. IPC (TLC) indicated full conversion. A second nitration batch (32 kg **5**) was produced in a second 600-L inox reactor. The suspensions of both 600-L reactors were added to water (1500 L) in a 4300-L SS reactor at 9−18 °C within 35 min. The suspension was filtered, washed with water (3 × 500 L, pH of filtrates: 1.4, 3.5, and 4.0), and dried in a tray dryer at 70 °C, 100 mbar for approximately 40 h to afford **11** as a yellow crystalline solid. Yield: 99.2 kg (94%). Purity (HPLC method 2): 98.9% a/a sum of **11a** and **11b**, ratio **11a**:**11b** = 7.6:1, **11a** t_R = 11.2 min, **11b** t_R = 10.8 min; ^{1}H NMR and ^{13}C NMR data in accordance with literature data.[11a]

3,6-Dimethoxybenzene-1,2-diamine hydrochloride (12a·HCl). Pd/C (9.8 kg, 10% Pd/C, type E 101 R/W, 5% w/w) and **11** (195.5 kg, regioisomeric mixture 7.6:1, **11a**:**11b**) were charged into an inerted 4300-L glass-lined reactor, followed by EtOH (1080 kg). The vessel was inerted. After purging three times with hydrogen, the stirrer was started, and the mixture was hydrogenated at 20−30 °C for 12 h at 1.5 bar. (***Caution**: exothermic dinitro hydrogenation, cooling with brine!*) IPC (HPLC) showed approximately 3% intermediates left. After inertization, the mixture was circulated through a cartridge filter. The filter was washed with EtOH (386 kg). The combined filtrates were charged into the vessel and HCl gas (45.7 kg, 1.5 equiv) was added at 15−23 °C within 1 h 45 min to reach pH < 0.5. (***Caution**: exothermic addition!*). The suspension was cooled to 10 °C, stirred at 10 °C for 30 min and filtered. The filter cake was washed with EtOH (540 kg) and dried in a tray dryer at 50−60 °C, 100 mbar for 16 h to afford **12a**·HCl as an off-white solid. Yield: 123.4 kg (70%). Mp 217 °C; assay (HPLC, free base): 82.2% (theoretical maximum 82% w/w for mono-HCl salt); purity (HPLC method 2): 99.0% a/a, t_R = 3.9 min; ^{1}H NMR (D_6-DMSO): δ 6.99−8.96 (br s, 4 H), 6.56 (s, 2 H), 3.77 (s, 6 H); Anal. Calcd. For $C_8H_{12}N_2O_2$·HCl: C: 46.95; H: 6.40; N: 13.69; Cl: 17.32. Found: C: 46.74; H: 6.41; N: 13.54; Cl: 17.05.

3-(4,7-Dimethoxy-1*H*-benzo[*d*]imidazol-2-yl)-*N*-methylpropan-1-amine dihydrochloride (4·2 HCl). A 64-L glass-lined reactor was charged with 21.5% HCl (41.4 kg, 4.1 equiv) and NMP (14.9 kg, 2.54 equiv). After degassing with N_2 at 20 °C for 15 min, sodium sulfite (350 g, 0.05 equiv) and **12a**·HCl (12.1 kg, assay 82.2% w/w) were added, and the mixture was stirred at 107−109 °C for 19 h. IPC (HPLC) indicated less than 0.1% **12a**·HCl. In a 400-L stainless-steel reactor, *n*-butanol (109 kg), 30% NaOH (52.4 kg) and water (20 kg) were added, followed by degassing with N_2 at 20 °C for 15 min. The black mixture from the 64-L reactor was added to the 400-L reactor at 20−30 °C. (***Caution**: exothermic quench!*) The pH was >12. After phase separation the organic phase was washed with water (2 × 33 kg) and transferred into a 200-L glass-lined reactor. 37% HCl (10.4 kg, 1.8 equiv) was added at 20−30 °C to adjust the pH to <3. After addition of activated charcoal (10.0 kg, 1

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wt), the mixture was stirred at 60−80 °C for 2 h. After cooling to 20 °C, Celite (7.0 kg) was added, and the mixture was stirred at 20−25 °C for 30 min. The following filtration (200-L reactor) and distillation (in the cleaned 64-L reactor) were run in parallel. The mixture was pumped over a filter nutsche and circulated back into the 200-L reactor. After the solution was clear, it was transferred into the 64-L reactor via a 5-μm PAL filter. As soon as the 64-L reactor contained 30−40 L, solvent was removed at 70−80 °C (head temperature 60−70 °C) and 300 mbar. At the end of the filtration, the filter cake was washed with warm (50 °C) *n*-butanol (57 kg), and the filtrate was added to the 64-L reactor. The distillation was resumed in the 64-L reactor until approximately 40 L of residual volume (a total of 140−160 L was removed). An aliquot was sampled at approximately 60 °C to determine the water content by Karl Fischer. Water was added to adjust to 2.5−3.5% water. The mixture was cooled to 0 °C within 3 h and filtered. The filter cake was washed with AcOEt (2 × 38 kg) and dried in a tray dryer at 70 °C, <100 mbar for 15 h to afford **4**·2HCl (monohydrate) as an off-white powder. Yield: 12.1 kg (59%). Mp 174 °C (DSC peak temperature); assay (HPLC method 2, free base): 72.4% (theoretical maximum 73% w/w for monohydrate dihydrogen chloride salt); purity (HPLC method 2): 100.0% a/a, t_R = 3.4 min; water: 5.2% (Karl Fischer); sulphated ash: 0.51%; ICP: Pd < 0.1 ppm, Na: 0.17%, Cl: 20.9%; color: R7; ^{1}H NMR (D_6-DMSO): δ 14.48−15.81 (br s, 2 H), 9.34 (br s, 2 H), 7.00 (s, 2 H), 4.48−5.64 (br 1, 2 H), 3.95 (s, 6 H), 3.23 (t, J = 7.4 Hz, 2 H), 2.86−2.97 (m, 2 H), 2.5 (s, under DMSO peak, 3 H), 2.23 (quint, J = 7.5 Hz, 2 H); ^{13}C NMR (D_6-DMSO): δ 152.9, 141.2, 122.9, 106.8, 56.7, 47.2, 32.5, 23.8, 23.6. Data of analytical sample: Anal. Calcd. For $C_{13}H_{19}N_3O_2$·2 HCl·H_2O: C: 45.89; H: 6.81; N: 12.35; O: 14.10; Cl: 20.84. Found: C: 45.11; H: 6.51; N: 12.22; O: 14.44; Cl: 21.05.

***tert*-Butyl 2-((1*R*,2*R*,4*R*)-2-Hydroxy-5-phenylbicyclo-[2.2.2]oct-5-en-2-yl)acetate (Mixture of Diastereoisomers, 6 and 7).** To a 2.5 M solution of hexyl lithium in hexane (12.6 L, 31.5 mol, 1.25 equiv) in toluene (60 L, 12 vol) at −15 °C was added dropwise diisopropylamine (4.6 L, 32.8 mol, 1.3 equiv) between −15 °C and +5 °C. The resulting solution was stirred at −15 to −10 °C for 10 min. The suspension was cooled to −25 °C and *tert*-butyl acetate (4.25 L, 31.5 mol, 1.25 equiv) was added dropwise between −25 and −15 °C. The mixture was aged at −25 °C for 10 min. It was cooled to −80 °C, and a solution of **3** (5.0 kg, 25.2 mol, 1 equiv) in toluene (10 L, 2 vol) was added dropwise between −85 and −75 °C in 30−45 min. The resulting turbid solution was stirred at −78 °C for 30 min, warmed to −25 °C, and quenched with 20% w/w citric acid (30 L, 6 vol) at <10 °C. The organic layer was separated and washed with water (20 L, 4 vol) at 20 °C to pH ≥ 5−7. The organic phase was concentrated to 7−8 vol at atmospheric pressure. EtOH (absolute, 90 L) was added, and the solution was again concentrated to 7−8 vol. The solution was used as such in the next stage as a mixture of diastereoisomers (dr: 4.8:1). Yield: 100%, used as is. Purity (HPLC method 1): 76.6% a/a (**6**), t_R 12.5 min; 16.0% a/a (**7**), t_R 13.0 min; $[M - t\text{Bu} - H_2O + 1]^+$ = 241. An analytical sample was purified by chromatography over silica gel. ^{1}H NMR ($CDCl_3$): δ 7.45−7.43 (m, 2H), 7.38−7.35 (m, 2H), 7.29−7.25 (m, 1H), 6.51 (br d, J = 6.9 Hz, 1H), 4.1 (br s, 1H), 3.16 (br s, 1H), 2.68−2.67 (m, 1H), 2.40−2.34 (m, 3H), 1.85−1.80 (m, 1H), 1.76−1.73 (m, 1H), 1.49 (br s, 10 H), 1.42−1.33 (m, 1H), 1.24−1.15 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 172.9, 144.8, 138.6, 128.5 (2 C), 127.2, 127.1, 124.8 (2 C), 81.6, 74.1, 47.5, 42.1, 41.7, 33.8, 28.1 (3 C), 24.3, 19.7.

2-((1*R*,2*R*,4*R*)-2-Hydroxy-5-phenylbicyclo[2.2.2]oct-5-en-2-yl)acetic Acid (2). KOH (3.3 kg, 50.4 mol, 2 equiv) in water (10 L) at 30−35 °C was added to the previously described solution of **6** and **7** (dr 4.8:1) in EtOH. The resulting turbid mixture was heated at reflux (∼80 °C) for 1 h. The reaction mixture was cooled to 35 °C and concentrated to ∼5 vol. 2-Methyl-THF (64 L) and water (12 L) were added, and the mixture was concentrated to ∼5 vol. 2-Methyl-THF (17 L), and 2 M HCl (5.6 L) were added to the mixture until pH ≈ 2.0 at 10−20 °C. Water (12 L) was added, and the mixture was heated and stirred at 35 °C to obtain a good separation. The following solvent exchange was repeated 3 times: the organic phase was concentrated at atmospheric pressure to 38 L, AcOEt (40 L) was added, and the solution was concentrated at reduced pressure to 38−40 L at ≤45 °C. At 1 atm, the solution was allowed to cool to 65 °C. At this temperature, crystallization started. The mixture was stirred at 55−65 °C for 1 h. The suspension was cooled to 5 °C. It was filtered over filter cloth, and the filter was washed with cold (∼5 °C) AcOEt (8 L). The filter cake was dried under a flow of nitrogen for 10 h. Yield: 3.83 kg (59%, two steps). Purity (HPLC method 1): 99.0% a/a, t_R 1.52 min, $[M - H_2O + 1]^+$ = 241; ^{1}H NMR (MeOD): δ 7.42−7.39 (m, 2H), 7.33−7.29 (m, 2H), 7.24−7.20 (m, 1H), 6.51(dd, J = 7.0, 1.8 Hz, 1H), 4.87 (br s, 2H), 3.15−3.12 (m, 1H), 2.75−2.72 (m, 1H), 2.42 (br s, 2H), 2.33−2.25 (m, 1H), 1.83−1.76 (m, 1H), 1.69−1.68 (m, 2H), 1.43−1.36 (m, 1H), 1.23−1.15 (m, 1H); ^{13}C NMR (MeOD): δ 174.2, 145.1, 138.5, 128.1 (2 C), 126.6, 126.5, 124.5 (2 C), 74.0, 46.8, 41.8, 41.1, 33.8, 23.9, 19.4.

***N*-(3-(4,7-Dimethoxy-1*H*-benzo[*d*]imidazol-2-yl)-propyl)-2-((1*R*,2*R*,4*R*)-2-hydroxy-5-phenylbicyclo[2.2.2]-oct-5-en-2-yl)-*N*-methylacetamide (8).** A reactor was charged with EDCI·HCl (5.2 kg, 27.1 mol, 1.27 equiv), HOBT hydrate (1.47 kg, 10.9 mol, 0.5 equiv), and **4**·2 HCl (7.73 kg, 24.0 mol, 1.1 equiv). THF (105 L) was added. In another reactor, Et_3N (11.05 kg, 109.2 mol, 5 equiv) was added at 15−25 °C to a solution of **2** (5.54 kg, 21.4 mol, 1.0 equiv) in THF (22 L). The solution of **2** was added dropwise at 10 to 25 °C to the first vessel. The reaction mixture was stirrred at 20−25 °C for 23−30 h until conversion (HPLC method 1) was >98%. THF was exchanged with DCM under reduced pressure at 45 °C. At 10−20 °C, the organic phase was washed twice (33 and 24 kg respectively) with 2 M HCl followed by 2 M NaOH to reach pH = 12 and water (27 L). DCM was exchanged to THF under reduced pressure at 45 °C, and the resulting solution of **8** was used as such. Yield: 10.2 kg (97%, used as is); weight of the solution: 59.72 kg, concentration by evaporation of an aliquot: 21.0% w/w, HPLC assay of the aliquot: 81.3% w/w. Purity (HPLC method 1): 97.4% a/a, t_R 3.11 min, $[M + 1]^+$ = 490; water content: 0.05% w/w; ^{1}H NMR (major rotamer, MeOD): δ 7.42−7.39 (m, 2H), 7.32−7.28 (m, 3H), 7.23−7.19 (m, 1H), 7.16−7.12 (m, 1H), 6.96 (br s, 2H), 6.50 (dd, J = 6.9, 1.7 Hz, 1H), 4.0 (br s, 6H), 3.55−3.51 (m, 2H), 3.14−3.10 (m, 3H), 3.05 (br s, 3H), 2.72−2.69 (m, 1H), 2.54−2.52 (m, 2H), 2.33−2.23 (m, 1H), 2.17−2.08 (m, 2H), 1.82−1.74 (m, 1H), 1.71−1.50 (m, 2H), 1.42−1.29 (m, 1H), 1.21−1.13 (m, 1H); ^{13}C NMR (MeOD): δ 173.6, 152.8, 145.2, 141.1, 138.4, 128.1 (2 C), 127.9, 126.7, 126.6, 124.4 (2 C), 123.0, 106.0 (2 C), 74.8, 55.5 (2 C), 48.6, 46.2, 44.0, 41.7, 41.6, 35.0, 33.8, 24.4, 23.9, 23.5, 19.4.

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(1*R*,2*R*,4*R*)-2-(2-((3-(4,7-Dimethoxy-1*H*-benzo[*d*]-imidazol-2-yl)propyl) (methyl)amino) ethyl)-5-phenylbicyclo[2.2.2]oct-5-en-2-ol (9). A reactor was charged with 10% w/w solution of lithium aluminium hydride in THF (15.9 L, 41.9 mol, 2.0 equiv). THF was added (41 L), and the resulting solution was cooled to 0−10 °C. The above solution of crude **8** in THF (17.4% w/w, 58.45 kg, 20.8 mol) was added dropwise to keep the temperature <15 °C. The reaction mixture was allowed to warm up to 20 °C for 1.5 h. A solution of KOH (1.61 kg, 1 wt relative to LAH) in water (3.2 L, 2 wt relative to LAH) was added cautiously at 0−15 °C followed by water (1.6 L, 2 wt relative to LAH). The suspension was stirred at 0−15 °C for 10 min. After filtration over Celite, the filtrate was washed with THF (2 × 20 L) and concentrated under reduced pressure to 7.5 vol at T ≤ 45 °C. THF (20 L) was added, and the solution was concentrated under reduced pressure to 7.5 vol at $T \leq 45$ °C. The solution of **9** in THF (H_2O: 0.87% w/w) was used as such in the next stage. Yield: 9.0 kg (91%, used as is); weight of the solution: 63.15 kg, concentration by evaporation of an aliquot: 14.3% w/w. Purity (HPLC method 1): 98.3% a/a, t_R 1.85 min, $[M + 1]^+$ = 476. An analytical sample was purified by chromatography over silica gel. ^{1}H NMR (MeOD): δ 7.38−7.36 (m, 2H), 7.30−7.27 (m, 2H), 7.21−7.18 (m, 2H), 6.60 (br s, 2H), 6.48 (br d, J = 6.9 Hz, 1H), 3.91 (s, 6H), 3.11−3.09 (m, 1H), 2.88 (t, J = 7.4 Hz, 2H), 2.63−2.59 (m, 3H), 2.46 (t, J = 7.4 Hz, 2H), 2.33−2.22 (m, 2H), 2.25 (s, 3H), 2.05−1.97 (m, 2H), 1.80−1.75 (m, 1H), 1.64−1.50 (m, 4H), 1.40−1.34 (m, 1H), 1.19−1.13 (m, 1H); ^{13}C NMR (MeOD): δ 153.4, 144.5, 138.6, 128.1 (2 C), 127.0, 126.5, 124.4 (3 C), 102.1 (2 C), 76.0, 67.4, 56.5, 54.9 (2 C), 52.5, 42.1, 41.4, 40.7, 38.6, 33.9, 26.1, 25.8, 25.3, 25.1, 24.3, 19.3.

(1*R*,2*R*,4*R*)-2-(2-((3-(4,7-Dimethoxy-1*H*-benzo[*d*]-imidazol-2yl)propyl)(methyl)amino)ethyl)-5-phenylbicyclo[2.2.2]oct-5-en-2-ol Oxalate (9·2 $C_2H_2O_4$). A THF solution of **9** (63.15 kg, 14.3% w/w) was charged into a reactor. THF was exchanged with *i*PrOH at 50 °C under reduced pressure, and the resulting solution was transferred into a drum. A solution of oxalic acid dihydrate (5 kg, 39.9 mol, 2.1 equiv) in water (9 L), *i*PrOH (18 L) and AcOEt (9 L) was stirred at 70−75 °C. The above-prepared solution of **8** was added dropwise. The mixture was heated to 70−75 °C for 15 min. AcOEt (100 L) was added, followed by aging at 70−75 °C for 2 h. The reaction mixture was allowed to cool to 5 °C over 4 h and filtered (filtration time: 38 h), rinsed with AcOEt and dried under a flow of nitrogen for 3 days. Yield: 10.80 kg (87%, 3 steps). KF: 3.0% w/w; purity (HPLC method 1): 96.5% a/a, t_R 1.85 min, $[M + 1]^+$ = 476; ^{1}H NMR (D_6-DMSO): δ 8.9 (br s, 4H), 7.39−7.37 (m, 2H), 7.32−7.27 (m, 2H), 724−7.19 (m, 1H), 6.59 (br s, 2H), 6.53 (dd, J = 6.9, 1.4 Hz, 1H), 3.85 (br s, 6H), 3.23−3.08 (m, 5H), 2.93−2.89 (m, 2H), 2.73 (br s, 3H), 2.54−2.50 (m, 1H), 2.20−2.10 (m, 3H), 1.77−1.65 (m, 3H), 1.54−1.40 (m, 2H), 1.30−1.24 (m, 1H), 1.09−1.02 (m, 1H); ^{13}C NMR (D_6-DMSO): δ 163.7 (4 C), 152.8, 144.2, 142.9, 138.5, 129.8, 128.9, 127.9 (2 C), 127.3, 125.0 (2 C), 103.1, 73.7, 67.5, 56.1 (2 C), 55.3, 51.6, 42.0, 41.6, 37.5, 33.4, 26.1, 25.6, 24.6, 21.9, 20.2.

(1*R*,2*R*,4*R*)-2-(2-((3-(4,7-Dimethoxy-1*H*-benzo[*d*]-imidazol-2-yl)propyl)(methyl)amino)ethyl)-5-phenylbicyclo[2.2.2]oct-5-en-2-yl Isobutyrate (1). 9·2 $C_2H_2O_4$ (10.75 kg, 16.4 mol) was suspended in 2-methyl-THF (85 L). A solution of 85% KOH (5.40 kg, 82.0 mol, 5 equiv) in water (41 L) was added dropwise until pH > 13 to afford a clear biphasic mixture. The layers were separated, and the organic layer was dried azeotropically. Et_3N (4.20 kg, 41.0 mol, 2.5 equiv) was added to the solution of **9** in 2-methyl-THF at 0−5 °C. Isobutyroyl chloride (2.65 kg, 24.7 mol, 1.5 equiv) was added at 0−10 °C over 15 min. (***Caution**: delay in exotherm!*) The turbid mixture was allowed to warm to rt and then stirred for 45 min. At this point, 92.7% conversion (HPLC method 3) was observed. Et_3N (1.50 kg, 14.8 mol, 0.9 equiv) was added at 0−10 °C over 5 min, followed by isobutyroyl chloride (1.55 kg, 14.8 mol, 0.9 equiv) at 0−10 °C over 5 min. After 45 min, full consumption of the starting material was observed (HPLC method 3). 30% w/w NaOMe in MeOH (10.55 kg, 49.4 mol, 3 equiv) was added dropwise at 0−10 °C. Stirring was continued for 45−60 min at 10−15 °C. Water (53 L) was added at 10−20 °C to the organic phase. The layers were separated. 10% w/w citric acid solution (50 L) was added at 10−20 °C until 5.5 ≤ pH ≤ 6.5. The phases were separated, and 10 wt % NaOH (∼1 equiv) was added until pH ≥ 13. After phase separation, the organic phase was washed with water (32 L) and concentrated at reduced pressure to 5−6 vol AcOEt (85 L) was added, and the solution was concentrated at ≤45 °C under reduced pressure to 5−6 vol. This exchange with AcOEt was repeated twice. The solution of **1** in AcOEt was used as such in the next step. Yield: 8.79 kg (98%, used as is); weight of the solution: 45.3 kg, concentration by evaporation of an aliquot: 19.4% w/w. Purity (HPLC method 3): 98.8% a/a, t_R 3.26 min, $[M + 1]^+$ = 546, ^{1}H NMR (MeOD): δ 7.39−7.37 (m, 2H), 7.31−7.27 (m, 2H), 7.23−7.20 (m, 1H), 6.59 (br s, 2H), 6.42 (dd, J = 7.1, 1.6 Hz, 1H), 3.90 (s, 6H), 3.25−3.22 (m, 1H), 3.15−3.14 (m, 1H), 2.86 (t, J = 7.4 Hz, 2H), 2.55−2.48 (m, 1H), 2.42−2.37 (m, 4H), 2.18 (s, 3H), 2.16−2.11 (m, 1H), 2.08−1.87 (m, 6H), 1.72−1.64 (m, 2H), 1.45−1.38 (m, 1H), 1.25−1.18 (m, 1H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (MeOD) δ 176.8, 153.0, 146.0, 142.8, 137.9, 129.3, 128.1 (2 C), 126.9, 124.9, 124.5 (3 C), 102.2, 85.4, 56.6, 54.8 (2 C), 51.2, 40.7, 40.0, 38.6, 36.1, 34.7, 34.3, 33.3, 26.4, 23.7, 23.6, 19.7, 19.0, 18.1, 18.0.

(1*R*,2*R*,4*R*)-2-(2-((3-(4,7-Dimethoxy-1*H*-benzo[*d*]-imidazol-2-yl)propyl)(methyl)-amino)ethyl)-5-phenylbicyclo[2.2.2]oct-5-en-2-yl Isobutyrate Maleate (1·2 $C_4H_4O_4$). A filtered solution of crude **1** in AcOEt (45.0 kg, 19.4% w/w) was heated at 35−40 °C for 10 min. EtOH (7 L) was added. A filtered solution of maleic acid (3.7 kg, 32.0 mol, 2.0 equiv) in MeOH (7 L) was slowly added at 35−40 °C over 10−15 min. After a rinse with EtOH (2.5 L), the solution was stirred at 35−40 °C for 30 min. Seed crystals (10 g) were added at 35 ± 1 °C. The mixture was stirred at 35−40 °C for 2 h. The suspension was cooled to 20 °C over 2 h. AcOEt (181 L) was added at 20−25 °C over 1 h. The mixture was cooled to 5 °C over 1 h. The suspension was filtered, and the filter cake was washed with AcOEt (3 × 17.5 L). The white solid was dried under a flow of nitrogen for 2 days. Yield (9.40 kg, 74%, two steps). Purity (HPLC method 3): 99.7% a/a, t_R 3.26 min, $[M + 1]^+$ = 546, ^{1}H NMR (MeOD): δ 7.33−7.20 (m, 5H), 6.73 (br s, 2H), 6.41 (dd, J = 7.0, 1.3 Hz, 1H), 6.25 (s, 4H), 3.91 (s, 6H), 3.30−3.11 (m, 9H), 2.86 (s, 3H), 2.63−2.56 (m, 1H), 2.53−2.38 (m, 2H), 2.31−2.24 (m, 2H), 2.05−1.93 (m, 2H), 1.76−1.69 (m, 2H), 1.47−1.39 (m, 1H), 1.29−1.22 (m, 1H), 1.20 (d, J = 2.4 Hz, 3H), 1.18 (d, J = 2.4 Hz, 3H); ^{13}C NMR (MeOD) δ 176.9, 168.8, 151.8, 146.3, 141.9, 137.7, 133.9 (4 C), 128.2 (2 C), 127.0, 126.1, 124.5 (3 C), 124.4, 104.3 (2 C), 84.6, 55.7, 55.1 (2 C), 51.3, 40.4, 38.8, 38.5, 34.6, 33.2, 33.0, 25.0, 23.6, 21.5, 19.6, 18.0, 17.9; HRMS (ESI) for [M +

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H^+] $C_{33}H_{44}N_3O_4$: Calcd. 546.3332; Found: 546.3334. Anal. Calcd. For $C_{41}H_{51}N_3O_{12}$: C: 63.31; N: 5.40; O: 24.68. Found: C: 63.23; N: 5.31; O: 24.85.

■ ASSOCIATED CONTENT

Supporting Information

Analytical methods and characterization data of **1**, **4**·2 HCl, **12a** and **12b**, DSC traces of **11** and **12**, X-ray analyses of *rac*-**6**, and experimental details for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Part of this work was preliminarily disclosed: Funel, J.-A. In *Practical Synthesis of L/T Calcium Channel Blocker ACT-280778*, 30th SCI Process Development Symposium, Cambridge, UK, December 5−7, 2012; Funel, J.-A.; In *Practical Synthesis of 5-Phenylbicyclo[2.2.2] oct-5-en-2-one toward L/T Calcium Channel Blocker ACT-280778. Application of the Diels−Alder Reaction on kg-Scale*, 1st Smart Synthesis and Advanced Purification Conference, April 21−23, 2013; Lyon, FR.

(2) (a) Hilpert, K.; Hubler, F.; Renneberg, D. WO/2008/132679A1, 2008. (b) Hubler, F.; Hilpert, K.; Renneberg, D. WO/2009/130679A1, 2009.

(3) Funel, J.-A.; Schmidt, G.; Abele, S. *Org. Process Res. Dev.* **2011**, *15*, 1420−1427.

(4) Abele, S.; Schwaninger, M.; Fierz, H.; Schmidt, G.; Funel, J.-A.; Stoessel, F. *Org. Process Res. Dev.* **2012**, *16*, 2015−2020.

(5) (a) Abele, S.; Inauen, R.; Funel, J.-A.; Weller, T. *Org. Process Res. Dev.* **2012**, *16*, 129−140. (b) Abele, S.; Funel, J.-A. WO/2012/052943A1, 2012. (c) Abele, S.; Funel, J.-A. WO/2012/052939A2, 2012.

(6) Abele, S.; Inauen, R.; Spielvogel, D.; Moessner, C. *J. Org. Chem.* **2012**, *77*, 4765−4773.

(7) Z-GABA (**14**): CHF 3000/kg.

(8) Differential scanning calorimetry (DSC) of a mixture **11a**:**11b** = 7.7:1 shows an exotherm with left limit 290 °C, peak 338 °C, and the decomposition energy of −3154 kJ/kg.

(9) Phillips, M. A. *J. Chem. Soc.* **1928**, 2393−2399.

(10) Glutamic acid: Cescon, L. A.; Day, A. R. *J. Org. Chem.* **1962**, *27*, 581−586. (b) *β*-Alanine: Revankar, G. R.; Siddappa, S.; Umarani, D. C. *Indian J. Chem.* **1964**, *2*, 489−490. (c) Sarcosine: Cardwell, T. J.; Edwards, A. J.; Harthorn, R. M.; Holmes, R. J.; McFasyen, W. D. *Aust. J. Chem.* **1997**, *50*, 1009−1015. (d) 4-Dimethylaminobutanoic acid: Menichincheri, M.; Ballinari, D.; Bargiotti, A.; Bonomini, L.; Ceccarelli, W.; D'Alessio, R.; Fretta, A.; Moll, J.; Polucci, P.; Soncini, C.; Tibolla, M.; Trosset, J. Y.; Vanotti, E. *J. Med. Chem.* **2004**, *47*, 6466−6475.

(11) (a) Hammershøj, P.; Reenberg, T. K.; Pittelkow, M.; Nielsen, C. B.; Hammerich, O.; Christensen, J. B. *Eur. J. Org. Chem.* **2006**, 2786−2794. (b) After completion of this work, a similar dinitration−hydrogenation sequence was reported: Besset, T.; Morin, C. *Synthesis* **2009**, 1753−1756.

(12) Maybe indicative of NO_x formed during reaction.

(13) Bulk amounts of 1,4-dimethoxybenzene (**5**) are typically delivered as white chips. Delumping with a mortar gave faster dissolution; however, on large scale, **5** was used as received.

(14) Two consecutive crystallizations from HOAc (8−9 vol) improved the regioisomeric ratio from 8.8:1 to 29:1 with a yield of 60%. One crystallization from toluene (4−6 vol) raised the ratio to 13:1 with 90% yield.

(15) On kilo-scale, the quench on a water/ice mixture was endothermic: the temperature was −20 °C after quench. A mixture of conc. HNO_3 and ice (2:1) is commonly known as freezing mixture to reach −50 °C.

(16) (a) Hydrogenation of **12a** on PtO_2: Weinberger, L.; Day, A. R. *J. Org. Chem.* **1959**, *24*, 1451−1455. (b) With sodium dithionite: Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *28*, 1329−1340. (c) With H_2 on Pd/C in AcOEt, see ref 11.

(17) (a) Kosak, J. R. *Chem. Ind. (Dekker)* **1988**, *33 (Catal. Org. React.)*, 135−147. (b) Tong, W. R.; Seagraves, R. L.; Wiederhorn, R. *Loss Prev.* **1977**, *11*, 71−75.

(18) When the filtration was performed carefully under inert conditions, the clear filtrate was yellow that turned pink and finally dark-violet after short contact with air.

(19) When running the hydrogenation with a pure sample of the regioisomer **11b**, the yield was <20%, although the Celite filter bed was copiously washed with EtOH and acetone (280 vol). The ^{1}H NMR of this product was differerent from that of **12a** and corresponded to **12b**.

(20) The black solution was stable for 1−2 weeks at rt in the dark. Longer storage led to precipitation of a sticky tar.

(21) (a) The lower yield with aqueous HCl was attributed to the water solubility of **12a**. (b) The stoichiometry of the salt was proven by elemental analysis and chloride titration.

(22) Considering the 88% content of **11a** in the starting material and the assay of the crude product prior to HCl salt formation, the maximum theoretical yield is approximately 80%. Hence, approximately 10% of the product was lost in the mother liquor. This was corroborated by HPLC assay of the mother liquor; when the temperatures for filtration were 10 and 5 °C, 10.4% and 8.9% w/w of **12** HCl were detected, respectively.

(23) HCl and water have a negative azeotrope with a bp of 110 °C and 20.2% w/w HCl. The HCl concentration varied between 18.5 and 21.5% for seven consecutive batches on 10-kg scale.

(24) Although dichloromethane gave a similar recovery during the extraction at pH 12, it was not appropriate for the salt formation and crystallization.

(25) The redox activity of demethylated benzoquinone-2,5-diamines is used in coordination chemistry, molecular switches, and catalysis, see: Schweinfurth, D.; Weisser, F.; Sarkar, B. *Nachr. Chem.* **2009**, *57*, 462−466.

(26) Demethylation of related dimethoxybenzimidazoles, see: (a) Alvarez, F.; Ghérardi, A.; Nebois, P.; Sarciron, M.-E.; Pétavy, A.-F.; Walchshofer, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 977−979. (b) Weinberger, L.; Day, A. R. *J. Org. Chem.* **1959**, *24*, 1451−1455.

(27) (a) A neat melt process followed by distillation as described for the condensation of caprolactame or pyrrolidinone with *o*-phenylenediamine led to decomposition: Botta, A. DE 2321054, 1973; Botta, A. *Liebigs Ann. Chem.* **1976**, 336−337. (b) A basic method that relied on the condensation with a nitrile in the presence of sodium methoxide only gave traces of product with decomposition: Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. R. *J. Med. Chem.* **1998**, *41*, 2709−2719. (c) 2-Imino-1-methylpyrrolidinone as electrophile for the nucleophilic attack by 2,5-dimethoxyaniline gave no product: Rasmussen, C. R.; Gardocki, J. F.; Plampin, J. N.; Twardzik, B. L.; Reynolds, B. E.; Molinari, A. J.; Schwartz, N.;

Bennetts, W. W.; Price, B. E.; Marakowski, J. *J. Med. Chem.* **1978**, *21*, 1044−1054. (d) No product was obtained via *N*-chloroamidines of 2,5-dimethoxyaniline: Ichikawa, M.; Nabeya, A.; Muraoka, K.; Hisano, T. *Org. Prep. Proced. Int.* **1978**, *10*, 205−209. (e) A recent protocol relying on the use of NaH as base for the reaction of *N*-methylbenzimidazoles with carbonitriles was not tried: Sluiter, J.; Christoffers, J. *Synlett* **2009**, 63−66.

(28) Charcoal treatments (Acticarbone 3S, CECA, 1 wt) of (a) the reaction mixture, 80 °C, 2 h, and of (b) the *n*-butanol phase after basification with 32% NaOH, 50 °C, 2 h.

(29) More benzimidazole **4**·2 HCl had to be added to reach full conversion, and the phase separations were difficult due to intensive coloration.

(30) A degassed solution of the diamine hydrochloride **12a**·HCl in water−acetonitrile in the dark got colored within 6−12 h, whereas the same solution containing 0.5% w/w sodium sulfite did not show coloration within several days. However, as long as the solvents and reagents were degassed with N_2, no effect on the color of the product **4**·2HCl was observed.

(31) Chapter 2.2.2, red colors R1−R7, higher numbers indicating less colorized solutions.

(32) There is no direct example with the bicyclo[2.2.2]octene framework. However, the following references allow the comparison with additions to related bicyclic systems: Devaux, J. F.; Hanna, I.; Lallemand, J. Y.; Prange, T. *J. Org. Chem.* **1993**, *58*, 2349−2350. (b) Almqvist, F.; Torstensson, L.; Gudmundsson, A.; Frejd, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 376−377. (c) Olsson, C.; Helgesson, S.; Frejd, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1484−1493.

(33) Freshly prepared LDA gave full conversion in contrast to the commercially available solution.

(34) No conversion was observed when a Reformatsky-type reaction (using Zn and *tert*-butyl bromoacetate) was attempted.

(35) *i*PrOH was also suitable as the solvent for diastereoselective crystallization, but gave 5−10% reduction in yield.

(36) For a recent review on industrial applications of the Diels−Alder reaction: Funel, J.-A.; Abele, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3822−3863; *Angew. Chem.* **2013**, *125*, 3912−3955.

(37) Details to be disclosed elsewhere.

(38) (a) Fleming, M. P.; Harrington, P. J. WO/98/49149A1, 1998; (b) Harrington, P. J.; Wong, J. WO/98/49148A1, 1998.

(39) On 3.5-kg scale, the solid reagents (1 equiv carboxylic acid **2**, 1 equiv benzimidazole **4** and 1.1 equiv CDMT) were suspended in DCM. DIPEA was added followed by the addition of *N*-methylmorpholine. After 1−2 h at 20 °C, the reaction was completed.

(40) Impurity **19** posed less of an issue since it was converted as well to amine **9** and diol **22** after hydride reduction. The latter was ultimately purged away in the final crystallization step.

(41) It was observed that the filtration of aluminum salts derived from the hydrolysis with KOH as base performed better than with NaOH.

(42) Even though this issue was anticipated in the laboratory, time constraints did not allow for removing this issue prior to scale up.

(43) Spontaneous deacylation of **10** to **1** was also detected in a crude batch of **10** exposed to daylight over a week.

(44) Abele, S.; Combes, S.; Funel, J.-A.; Hilpert, K.; Hubler, F.; Reichenbaecher, K.; Renneberg, D.; Von Raumer, M. WO/2010/046857A1, 2010.