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Multikilogram synthesis of a potent Bcl-2 selective antagonist. Part II. Manufacture of the 1,3-diamine moiety and improvement of the final coupling reaction.

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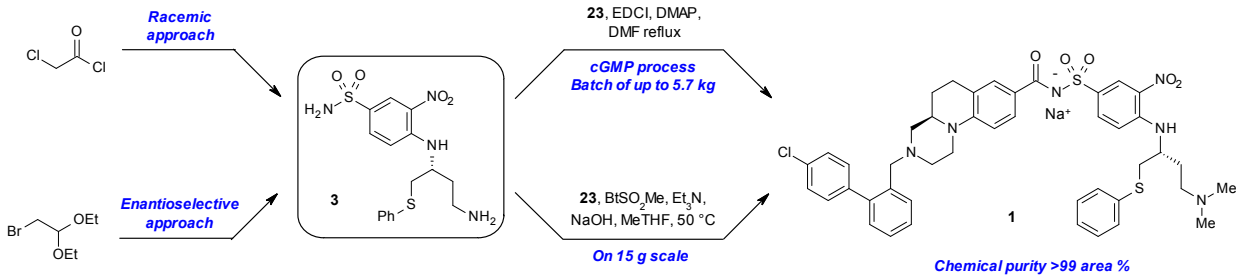
Table of Contents Graphic



ABSTRACT: This paper describes the synthesis of kilogram quantities of the sulfonamide moiety **3** involved in a coupling reaction with acid moiety **2** to provide batches of drug candidate **1** for preclinical studies and first-in-human clinical trials. A first approach relying on a chiral separation furnished the desired enantiomer of 1,3-diamine **20,** precursor of sulfonamide **3**. An enantiomeric synthesis of **20** using the Ellman's chiral auxiliary coupled with an aza-Reformatsky reaction to control the stereochemistry is also discussed. Coupling conditions of the final step involving EDCI to provide **1** under a cGMP process are detailed. An alternative approach using *N*-(1-methanesulfonyl)benzotriazole is also presented.

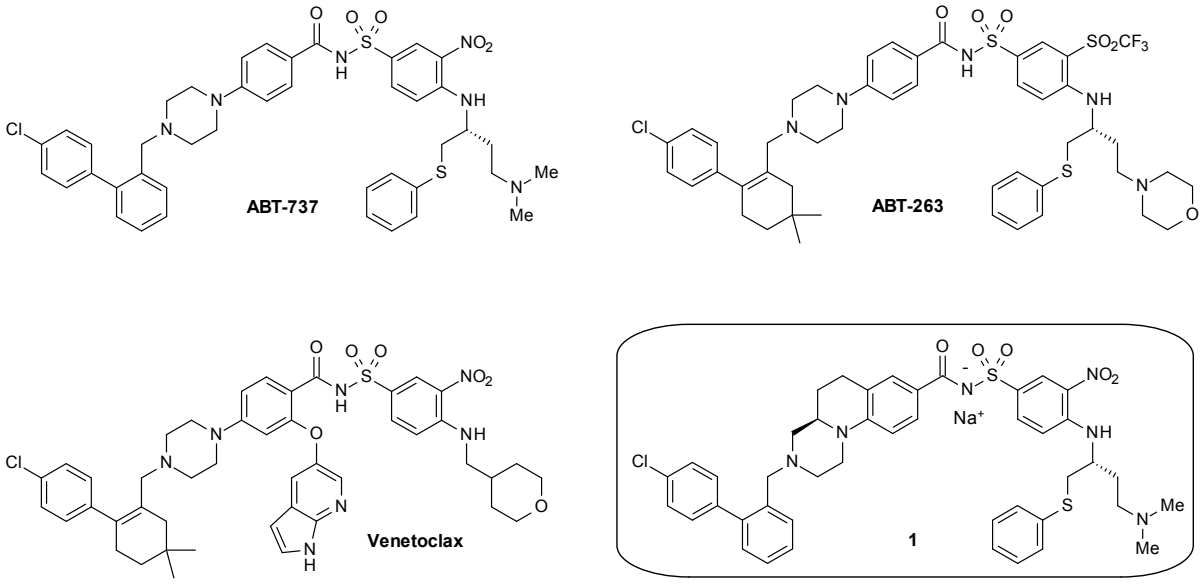
KEYWORDS: Bcl proteins, acylsulfonamide inhibitors, enantiopure 1,3-diamine, telescoped process.

Introduction

Finding innovative treatments to cure cancer has been a major challenge for the scientific community over the past decades. The discovery that B-cell lymphoma 2 (Bcl-2), a protein overexpressed in many types of cancer cells, promotes cells survival but not cells proliferation demonstrated that impaired apoptosis is a critical step in tumor development.[1] Finding inhibitors to antagonize the activities of Bcl-2 family proteins has been explored by medicinal chemists and resulted in the synthesis of small molecules like ABT-737, ABT-263 and Venetoclax, the latter being approved by the FDA in 2016 (Figure 1).[2] Despite encouraging results in terms of activity, ABT-737 suffered a moderate bioavailability and ABT-263 some dose-limiting toxicity. To overcome those issues, chemists at Servier identified compound **1** as promising drug candidate for the treatment of Bcl-2 dependent malignancies such as leukemias and lymphomas.[3] In a previous article (Multikilogram synthesis of a potent Bcl-2 selective antagonist. Part I.), we described the synthesis of the acid moiety that would ultimately be coupled with sulfonamide **3**.

This contribution describes the synthesis of sulfonamide moiety **3** following two different paths to prepare enantiopure 1,3-diamine **20**. Coupling conditions of the final step were evaluated and improved to manufacture kilogram quantities of API **1** under a cGMP process.

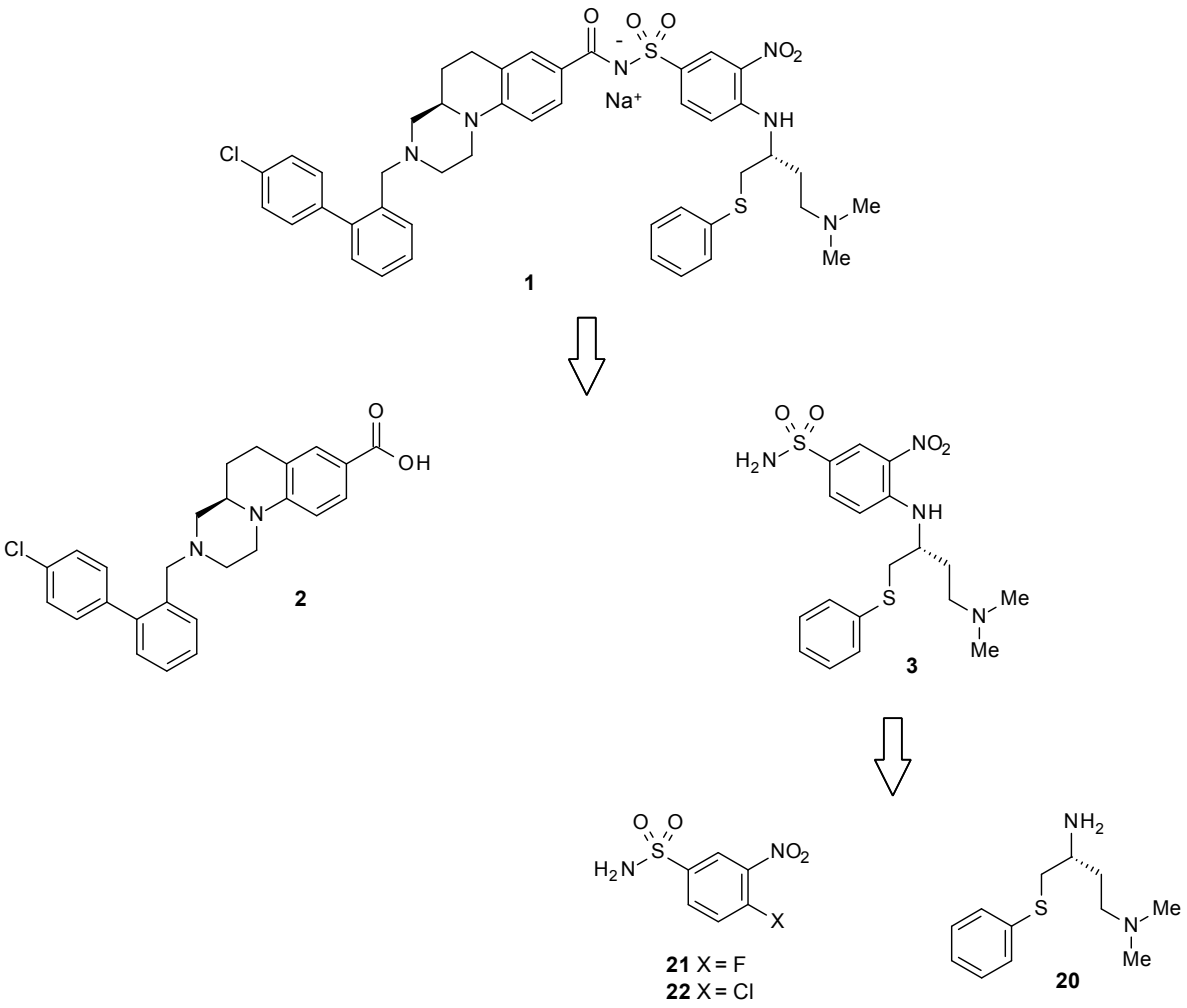
Figure 1. Structures of Bcl inhibitors



Results and Discussion

The strategy for the construction of compound **1** is outlined in the retrosynthesis shown in Scheme 1. The acylsulfonamide motif could be prepared by coupling acid **2** and sulfonamide **3**. The C-N bond could be installed by reacting commercially available halogenosulfonamides **21** or **22** with enantiopure 1,3-diamine **20**, the latter focusing most of our synthetic efforts. We wish to report herein the strategies developed to synthesize sulfonamide **3** and to couple this key intermediate with carboxylic acid **2**.

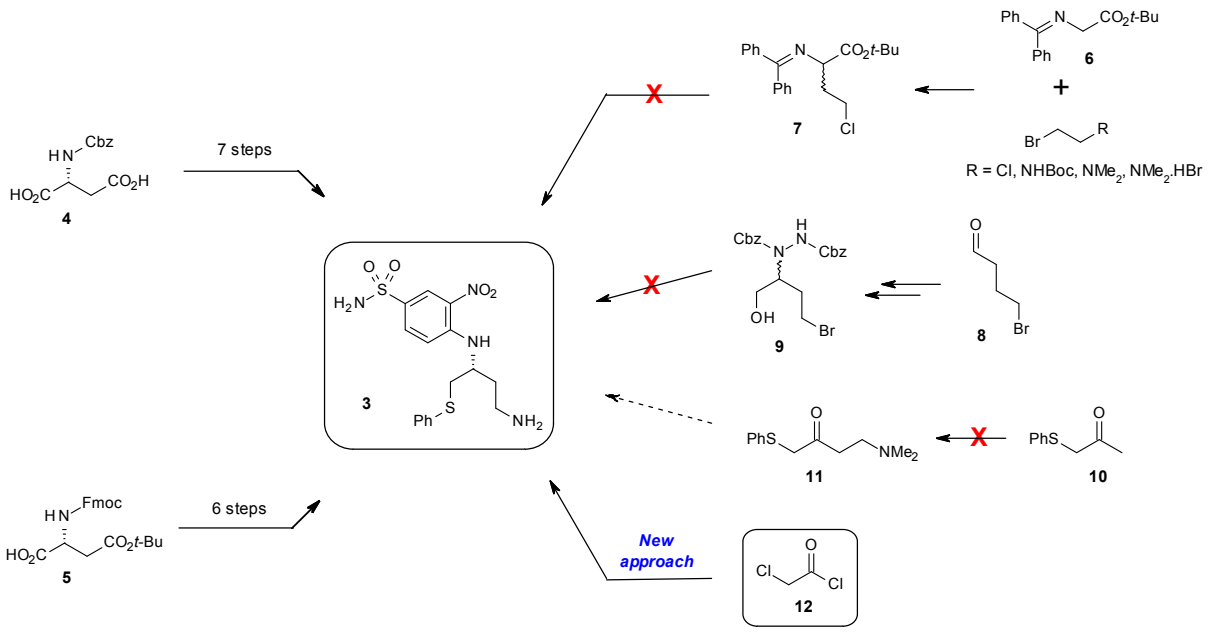
Scheme 1. Retrosynthetic analysis to access **1**



At the beginning of this project, precedents in the literature described the access to sulfonamide **3**. For example a seven-step synthesis was developed using N-protected D-aspartic acid **4** as chiral pool (Scheme 2).[4] Another six-step approach was also reported starting with Fmoc-Asp(O*t*-Bu)-OH **5**.[5] However we faced some difficulty when attempting to reproduce the conditions described in those two papers, especially during the scale up. Besides, the price of the starting materials (unnatural amino acids) could be a burden when one thinks about developing a commercial route. This prompted us to investigate alternative approaches allowing us to manufacture intermediate **3** on large scale.

1,3-Diamines are important chiral building blocks in the synthesis of bioactive compounds and ligands.[6] However, in contrary to vicinal diamines, limited methods for the direct synthesis of this motif have been documented.[7] We considered several alternative methods for the synthesis of **20** (Scheme 2). A first strategy was explored relying on the enantioselective alkylation of glycine derivative **6** by phase transfer catalysis.[8] Reacting **6** with KOH, *n*-Bu_4NBr and an excess of bromide derivative provided the desired intermediate **7** when R = Cl (degradation observed with other corresponding *N*-derivatives). However when **7** was exposed to $HNMe_2$, degradation occurred. A second approach was investigated taking advantage of a proline-catalyzed asymmetric α-hydrazination.[9] 4-Bromo-1-butanal **8** was prepared starting from the corresponding acid in a two-step sequence (BH_3.THF reduction in THF followed by oxidation of the resulting alcohol with TEMPO and bleach) and was treated with di-benzyl azodicarboxylate (DBAD) and L-proline to provide intermediate **9** after subsequent reduction of the aldehyde with $NaBH_4$. Although this approach seemed appealing, the overall yield to synthesize **9** was low (15%), starting from the commercially available acid precursor of **8**. Functionalization of intermediate **9** or of the resulting amine prepared by hydrogenolysis of the N-N bond proved to be challenging and forced us to envision a third approach. Mannich-type conditions were evaluated on ketone **10** using a mixture of paraformaldehyde, dimethylamine hydrochloride in acidic medium and provided complex reaction mixtures that were not valuable. Finally acid chloride **12** was selected as starting material; and we embarked on developing an alternative synthesis of key intermediate **3**.

Scheme 2. Existing and alternative approaches

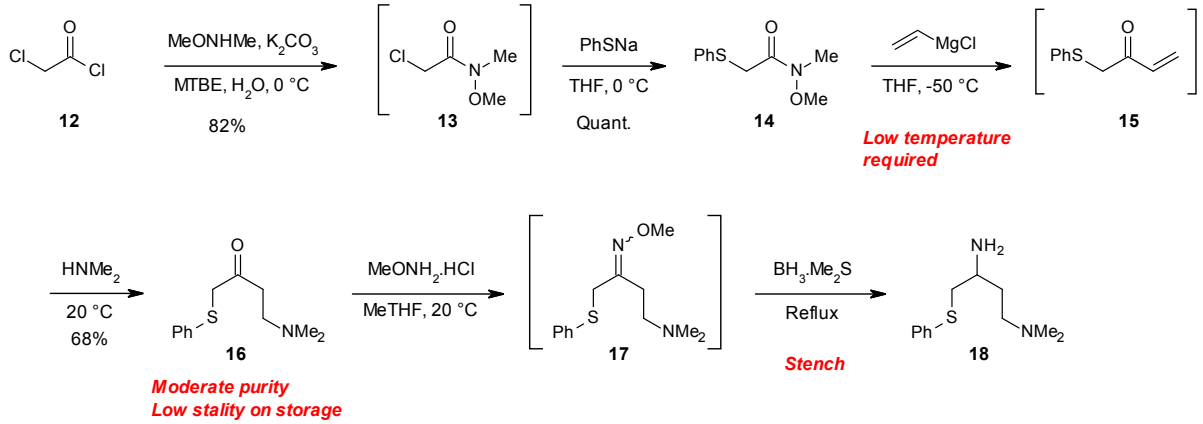


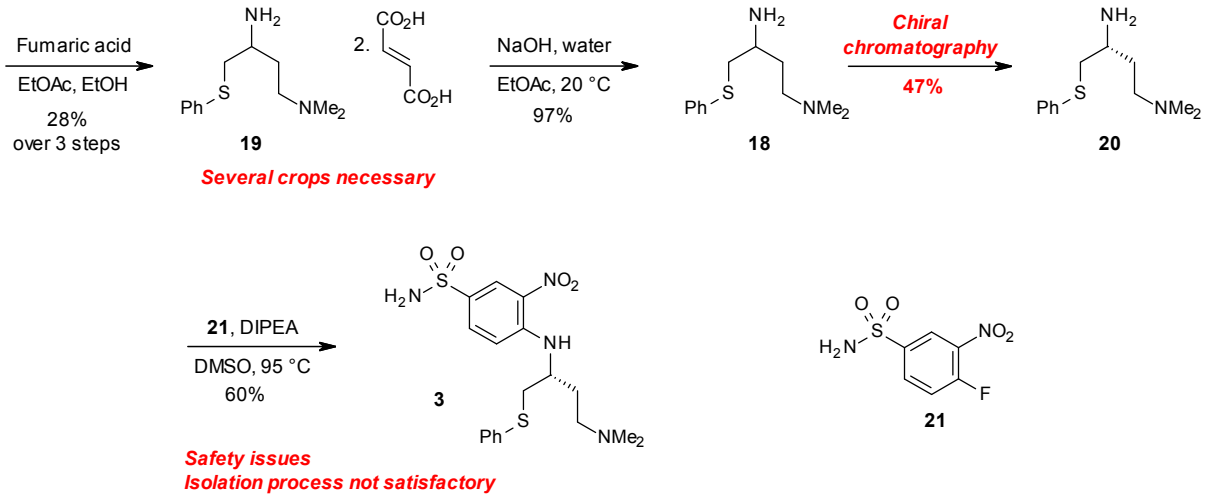
The synthesis of compound **3** starting from **12** is depicted in Scheme 3. Treatment of acid chloride **12** with MeONHMe under Schotten-Baumann conditions provided Weinreb amide **13** with a better purity than commercially available batches.[10] Nucleophilic substitution was carried out with sodium thiophenolate in THF and yielded to **14** as an oil after evaporation to dryness. A two-step sequence was then required to convert **14** into ketone **16**: Grignard addition and subsequent 1,4-addition of dimethylamine on **15**. Despite many efforts, both yield and purity stayed moderate and low temperature was required to limit chemical degradation. Besides, we found that ketone **16** was not stable on storage (due to a putative retro-Michael reaction) and had to be engaged in the next step quickly (loss of 8 area % by HPLC after 4 weeks at 5 °C). Reductive amination was initially evaluated to install the amine function. However condensation of α-methylbenzylamine or NH_3 in the presence of $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or H_2 failed to give the desired product. When condensation with $MeONH_2.HCl$ was performed in MeTHF, oxime **17** was obtained after basic aqueous wash as an *E/Z*: 6/4 mixture of isomers. Because of the moderate stability of **17**, this step was then telescoped with a $BH_3.Me_2S$-mediated reduction

and yielded to racemic amine **18** after concentration to dryness.[11] To efficiently purify this intermediate, treatment with fumaric acid in a mixture of EtOAc and EtOH provided the difumarate salt with >99 area % purity by HPLC and with a 28% yield over three steps.[12] Basic treatment was required before chiral chromatography which furnished desired amine **20** with a satisfactory enantiomeric excess of 98.2%. Aromatic nucleophilic substitution on compound **21** was then achieved in DMSO with the presence of DIEA and provided desired **3**.

Although this sequence allowed us to manufacture several kg of **3**, we identified few issues that could hamper a future commercial route. Handling $BH_3.Me_2S$ on large scale in the pilot plant was challenging in terms of health and safety since it disturbed some workers (foul smell). Also several crops were needed to isolate the whole amount of difumarate **19**. DSC studies on compound **21** showed that a suspected autocatalytic decomposition occurred at 160 °C with a heat flow of 2004 J/g corresponding to a ΔT_{ad} of 1000 °C (see Supporting Information). Finally, the isolation process was unsuitable for larger scale synthesis and furnished **3** with a moderate yield. Improvement was highly desirable and we started to search for alternative conditions.

Scheme 3. First generation synthesis of **3**





A quick survey was carried out on an *E/Z* mixture of **17** and conversion to **18** was evaluated with reducing agents such as BH_3.THF, a mixture $NaBH_4/ZrCl_4$ and Dibal-H.[13] BH_3.THF complex was not selected because of safety concerns on large scale and the couple $NaBH_4/ZrCl_4$ as well (in that case, we noticed a major exotherm when mixing $ZrCl_4$ and $NaBH_4$ together and also when quenching the reaction). When 3.2 equiv of Dibal-H were added (incomplete conversion if less), encouraging results were obtained and this process was evaluated in a reaction calorimeter (RC1) for safety reasons. As shown on Figure 2, a massive heat flow occurred at the beginning of Dibal-H addition with a maximum of 216 W/kg of reaction mass that corresponded to a ΔT_{ad} of 100 °C. Extended addition time was therefore recommended (2.5 hours instead of 1.5 proposed initially) so that the energy released could be overpowered by the feeding of the reactant in order to match with our cooling capacities. Concomitant gas evolution was also observed (46 L/kg of **17**) especially during the first 45 minutes of Dibal-H addition. DSC of the reaction mixture showed a first degradation between 61 and 218 °C and a second one between 297 and 391 °C, both of them with low energy (Figure 3). Hydrolysis was also evaluated in a RC1 prior to the pilot-plant batch (Figure 4). Here again the heat flow was high (maximum of 96 W/kg of reaction

mass that corresponded to a ΔT_{ad} of 49 °C) associated with a low accumulation (4% observed after addition of 17 wt % of Dibal-H). It was assumed that the heterogeneous nature of the reaction mixture was responsible for the shape of the heat flow curve. Extended time was therefore recommended (2 hours instead of 1) when the reaction mixture was added to aqueous NaOH. Gas evolution was linear and could be controlled by dosing.

Figure 2. Heat flow profile of Dibal-H addition

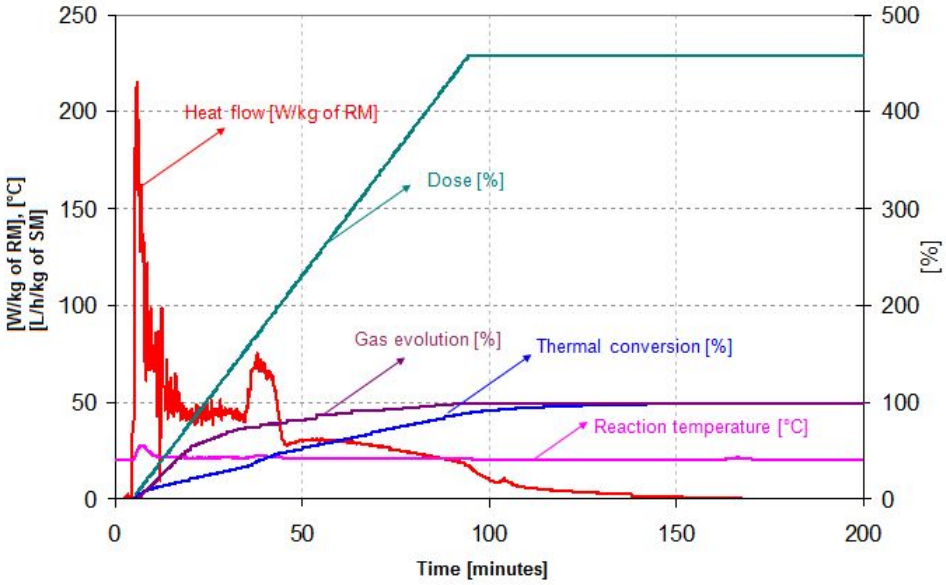


Figure 3. DSC profile of the reaction mixture after completion of Dibal-H addition

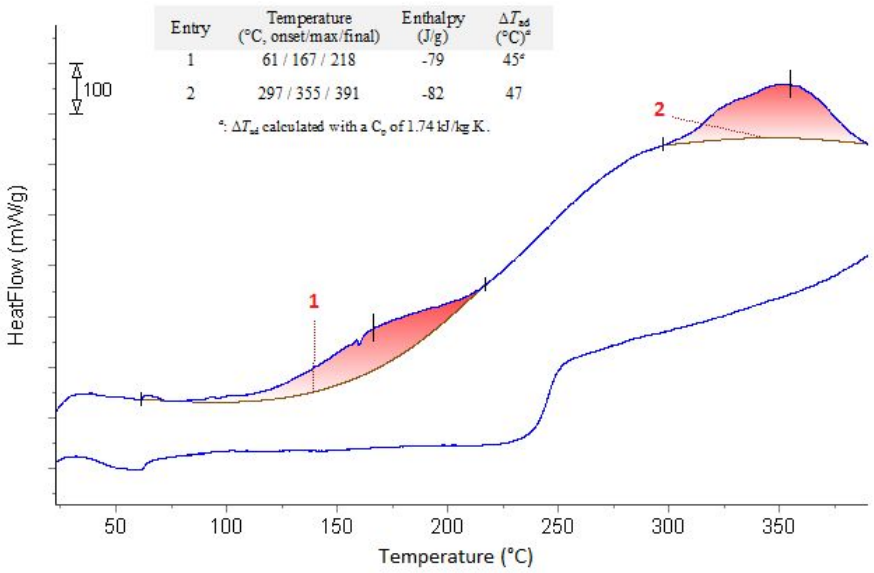
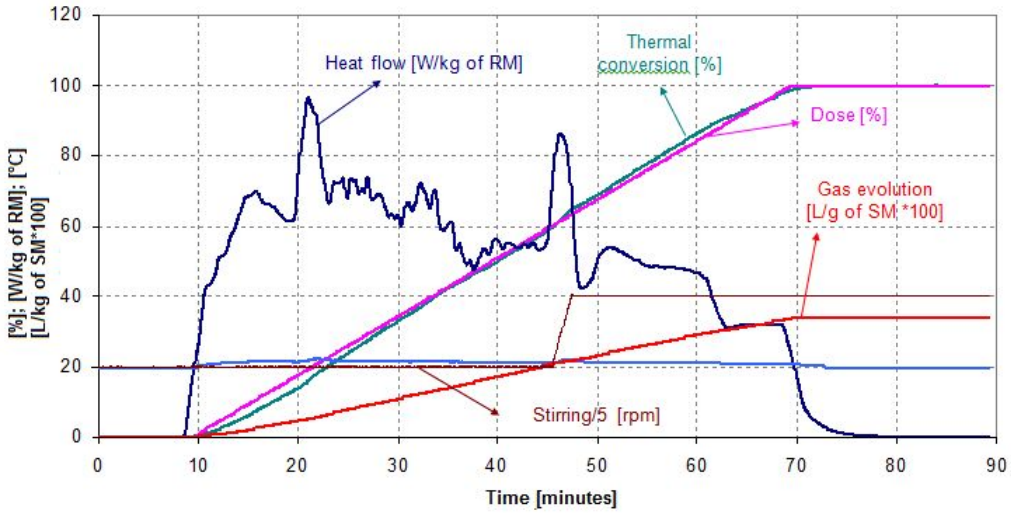


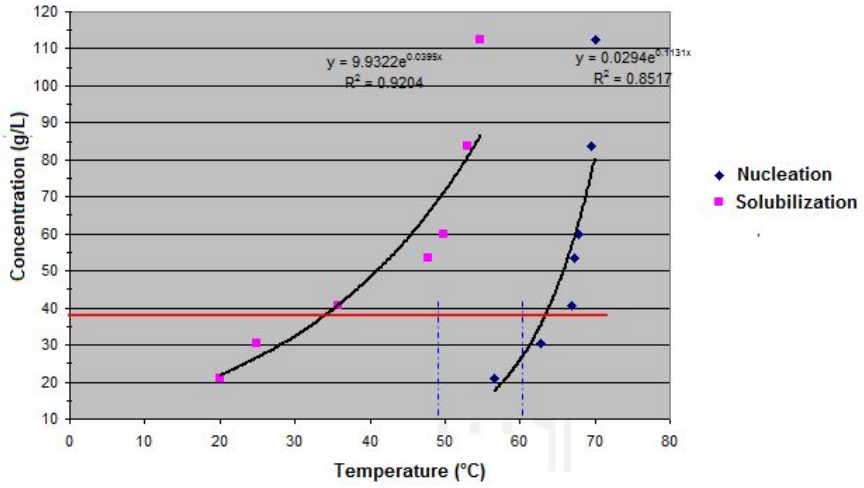
Figure 4. Heat flow profile of hydrolysis



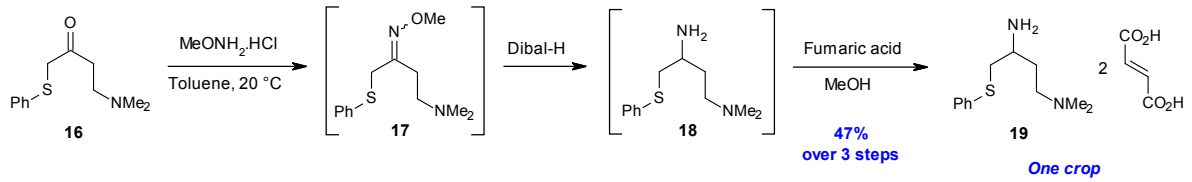
Since treatment with Dibal-H in toluene resulted in a complete conversion, we envisioned to telescope oxime formation, hydride reduction and salt formation in that solvent (see scheme 4). Gratifyingly condensation of ketone **16** with $MeONH_2.HCl$ in toluene (5 mL/g of **16**) gave a better purity than what was obtained in MeTHF (89 area % by HPLC instead of 85). At this stage, aqueous washes were necessary to insure a satisfactory conversion later on with Dibal-H.

Salt formation was also carried out in toluene with addition of an alcohol. In preliminary testing, MeOH provided a better yield than EtOH and was selected for further improvement. Using a Crystal 16 apparatus, a 65/35 (v/v) mixture of toluene/MeOH at 40 g/L (or 25 mL/g of **19**) was identified and a range between 50 and 60 °C was determined for seeding. To avoid any degradation, 50 °C was preferred. When we applied this sequence on 8 kg scale of **16** having a moderate purity (62 area % by HPLC), we were pleased to isolate **19** with 47% overall yield without any material left in the mother liquors. This process was also very efficient to remove impurities and provided **19** with a high purity (99.5 area %). The free base was obtained after aqueous NaOH treatment and enantiomers were separated by chiral chromatography to furnish enantiopure **20**.

Figure 5. Determination of the metastable zone of **19** with Crystal 16.

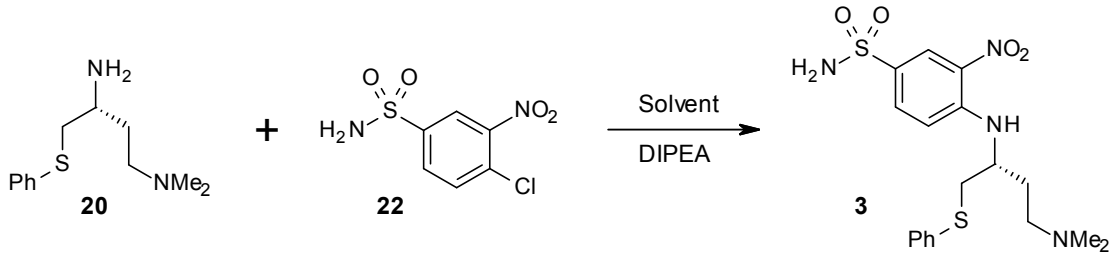


Scheme 4. New telescoped process to manufacture **19**



Since we had concerns with potential safety issues associated with fluoro-nitrophenyl compound **21**, conditions of aromatic nucleophilic substitution were revisited using chloride derivative **22**. In terms of safety, DSC studies showed that compound **22** was a better partner than **21** because decomposition started at 225 °C with a maximum reached at 306 °C (see Supporting Information). Aromatic nucleophilic substitution with amine **20** was consequently evaluated in 50 mL glass reactor with a reaction temperature limited at 90 °C to ensure process safety. This was performed using diisopropylethylamine (DIPEA) in various solvents and the results are summarized in Table 1. Formation of the desired product was observed in all solvents and DMSO proved to be by far the best option (entry 6 and 7). The reaction became sluggish when conducted at a lower temperature (entry 7). Thus 90 °C was found to be an acceptable compromise between kinetics and safety (entry 6). A sequential acid-base workup applied on crude **3** allowed removal of both excess of DIPEA and reactant **20**. Compound **3** was initially isolated by filtration after a solvent switch from EtOAc to MCH (methylcyclohexane). This process produced large hard balls that were difficult to drain and could cause damage to our vessels upon scale-up. Replacing MCH with *i*-PrOH was beneficial in terms of processability. A reslurry with MTBE was incorporated to remove traces of remaining **20** and to facilitate drying of the cake. Upon scale-up (3.6 kg of **20**), **3** was isolated with 74% yield and with a satisfactory purity of >99%.

Table 1. Screening of solvents on gram scale to synthesize **3**[a]



Entry	Solvent	**20** (%)[b]	**22** (%)[b]	**3** (%)[b]
1	AcOEt	11	25.8	57.2
2	*i*-PrOH	14	35	48.2
3	Toluene	11.6	23.1	51.4
4	DMF	44	5	32
5	NMP	3.5	19.2	57.6
6[c]	DMSO	0	3.6	81.7
7[d]	DMSO	4	8	73

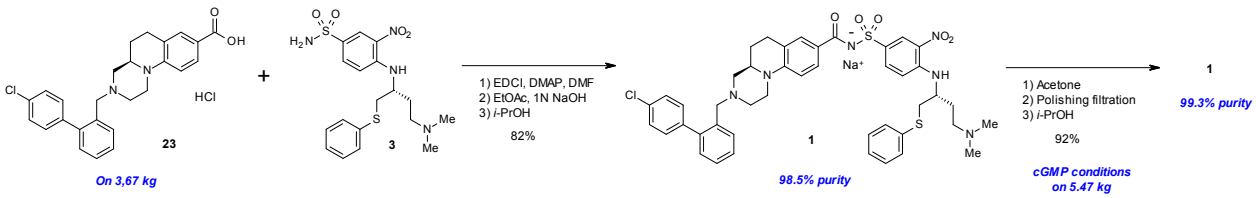
[a]Conditions: **20** (1.1 equiv), **22** (1.0 equiv), DIEA (4.5 equiv), 24 hours, 90°C. [b]Mesured by HPLC analysis of a sample of reaction mixture. [c]Isolated yield of 56%. [d]40 h, 60 °C.

End-game chemistry

Acylsulfonamides are an important class of compounds in medicinal chemistry as they serve as carboxylic acid bioisosters. They can be prepared by condensing carboxylic acids with sulfonamides ($RSONH_2$) using dehydrating agents such as EDC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide) for example. Addition of an excess of dimethylaminopyridine (DMAP) is usually required due to the low nucleophilicity of the sulfonamide. At the end of the reaction, the acylsulfonamide is obtained after an acidic workup to protonate the acylsulfonamide-DMAP salt.[14] Originally, coupling of partners **23** and **3** proceeded smoothly at 20 °C in DMF[15] with 2.5 equiv of EDC and 3 equiv of DMAP (see scheme of Table 2). Isolation proved to be a major issue since acylsulfonamide **24** was sparingly soluble in only few solvents (DMF, MeOH, EtOH,

CH_2Cl_2, THF) and attempts to crystallize it furnished either gels or gums. Isolation as hydrochloride salt was evaluated with aqueous HCl and provided the final product free of any residual solvent (at this stage, lyophillization was required). An alternative encouraging procedure was then developed and consisted in treating the reaction mixture with EtOAc and 1 N NaOH (Scheme 5). It allowed both elimination of residual DMF in the aqueous layer and formation of **1** (sodium salt of **24)** that was soluble in the organic phase. Solvent switch to *i*-PrOH furnished the desired API with 82% yield and 98.5% purity. In order to comply with cGMP requirements, a polishing filtration had to be incorporated in the process. Gratifyingly solubilization of **1** in 10 mL/g of refluxing acetone proceeded well and filtration at 40 °C was beneficial to remove traces of **2**. Solvent switch to *i*-PrOH and addition of MCH before filtration furnished the desired API with 92% yield and 99.3 area % purity on 5 kg scale.

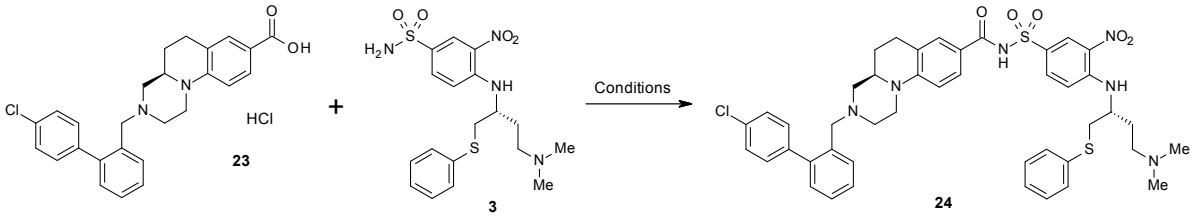
Scheme 5. Multikilogram-scale synthesis of **1**



Although this step was successful to manufacture the first batches of **1**, the following issues needed to be addressed to increase the practicality for scale-up: use of EDC (sticky oil, expensive, concerns about its chemical stability on storage), DMF as solvent in a late stage of the synthesis, tedious isolation process. Development of a second-generation process was undertaken and focused on identifying alternative coupling conditions. *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC-HCl), thionyl chloride, CDI, and propanephosphonic acid

anhydride (T3P) were selected and reacted with **23** (HCl salt). After 18 hours at 50 °C; the conversion was almost complete with EDC-HCl (entry 1, Table 2) and the product was isolated as follows: quench with aqueous NaOH, organic phase extracted with EtOAc, solvent switch to *i*-PrOH, reslurry with *i*-PrOH. However, the moderate purity coupled with the knowledge that EDC-HCl was both expensive and a suspected sensitizer encouraged us to switch to other coupling systems.[16] Scouting experiments showed that no product was formed with $SOCl_2$ (entry 2) and CDI (entry 3 and 4). With an excess of both Et_3N and T3P, 14% of desired product was observed at room temperature (entry 5) but reflux was deleterious since compound **3** degraded (entry 6). We then decided to proceed stepwise by neutralizing the hydrochloride before adding the coupling agent. Treatment with 2.1 equiv of Et_3N in EtOAc provided the carboxylate derivative in solution after filtration of the hydrochloride salts. This solution was then subjected to several activating agents (see Table 3).

Table 2. Survey of coupling conditions applied on **23**

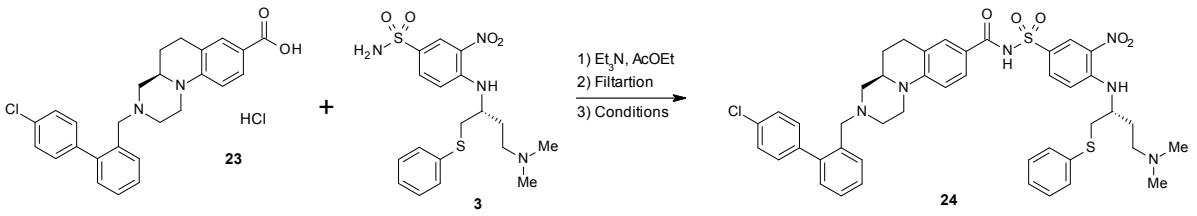


Entry	Conditions	**23** (%)[a]	**3** (%)[a]	**24** (%)[a]
1[b]	**3** (0.9 equiv), EDC-HCl (1.3 equiv), DMAP (2.9 equiv), DMF, 18 h at 50 °C	5.1	0.6	81.3
2	$SOCl_2$ (1.2 equiv), EtOAc, **3** (1.1 equiv), 6 h at reflux	16.6	74.0	-
3	CDI (1.2 equiv), EtOAc, **3** (1 equiv), DBU (1 equiv), 6 h at 50 °C	13.5	25.1	-

4	CDI (1.2 equiv), NMP, DBU (1 equiv), **3** (1 equiv), 3 h at 50 °C	12.8	29.4	-
5[c]	**3** (1.1 equiv), EtOAc, Et_3N (5 equiv), T3P (5 equiv), 12 h at 20 °C	23.4	0.5	13.9
6	**3** (1.1 equiv), EtOAc, Et_3N (5 equiv), T3P (5 equiv), 3 h at reflux	53.9	1.3	-

[a]Mesured by HPLC analysis of a sample of reaction mixture. [b]Quench with aqueous NaOH, organic phase extracted with EtOAc, solvent switch to *i*-PrOH, reslurred in *i*-PrOH. 65% yield, 96.2 area %purity. [c]No isolation.

Table 3. Step-wise sequence to couple **23** with 1.1 equiv of **3**



Entry	Conditions	**23** (%)[a]	**3** (%)[a]	**24** (%)[a]	Yield (%)[c]
1	$SOCl_2$ (2.5 equiv), EtOAc, 6 h at reflux	-	-	-	-
2[b]	CDI (1.5 equiv), THF, DBU (1 equiv), 3 h at reflux then **3** (1 equiv) and 20 h at reflux	12.2	25.4	10.8	-
3	EtOAc, Et_3N (2 equiv), T3P (5 equiv), 23 h at reflux	3.2	0.9	86.6	-
4[b]	EtOAc, Et_3N (2 equiv), T3P (5 equiv), 23 h at reflux	5.7	0.5	84.4	55
5	EtOAc, Et_3N (2 equiv), T3P (2 equiv), 20 h at reflux	34.4	12.2	12.0	-
6	EtOAc, T3P (5 equiv), 24 h at reflux	2.0	0.6	92.8	60
7	EtOAc, T3P (5 equiv), 30 h at reflux	1.6	0.4	94.0	63

[a]Mesured by HPLC analysis of a sample of reaction mixture. [b]With 1.0 equiv of **3**. [c]Isolated.

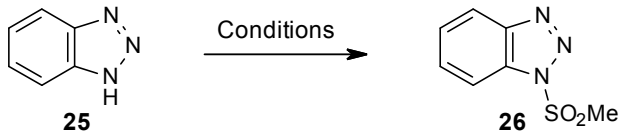
Except with $SOCl_2$ and CDI (entry 1 and 2), the two-step procedure provided encouraging results with T3P. The reaction proceeded well with an excess of both base and T3P at reflux (entry 3). Decreasing the amount of **3** resulted in a lower conversion (entry 4). The amount of T3P was also critical (entry 5). Assuming that the dimethylamine moiety of **3** could act as a base, we showed that Et_3N removal was not detrimental (entry 6 and 7). Since the reaction was sluggish, an extended time was beneficial in terms of conversion (entry 7). In that case, washing the reaction mixture twice with 6 N NaOH provided **1** with a disappointing quality of 96.9 area % after solvent switch to *i*-PrOH and subsequent crystallization. Since extra reslurries didn't improve the quality, the use of T3P was discontinued and we switched to *N*-(1-methanesulfonyl)benzotriazole **26** as coupling agent.

Synthesis of coupling agent 26

The preparation of *N*-acylbenzotriazoles has been previously reported by the Katritsky group.[17] Direct treatment of benzotriazole **25** with methanesulfonyl chloride in the presence of pyridine afforded desired *N*-(1-methanesulfonyl)benzotriazole **26** with 89% yield after concentration to dryness and recrystallization from benzene. Since large quantities of this coupling agent was anticipated, we thought there was room for improving this procedure and a quick survey of alternative conditions was undertaken (Table 4). Original conditions were reproduced and afforded the desired product with 48% yield after addition of water, concentration of the organic phase and recrystallization in toluene (entry 1). Replacing pyridine with Et_3N improved the yield (entry 2) but formation of benzotriazole was observed when the reaction mixture was heated to reflux for several hours. In MeTHF, Et_3N gave the best results in terms of kinetics (1 h compared to 6 h with 2,6-collidine and 22 h with pyridine) and conversion (entry 3, 4 and 5). However keeping **26** in MeTHF in order to telescope the reaction with **23** was precluded since some

degradation was observed on storage (loss of 10% purity after 72 hours at 4 °C).[18] Issues were overcome when **26** was prepared in THF using Et_3N as a base: addition of a solution of methanesulfonyl chloride in THF to the reaction mixture was required to control an exotherm. The reaction was complete after 1 hour and crystallization occurred after addition of water (entry 7). On 500 g scale, we were pleased to isolate **26** after filtration with 90% yield and >99 area % purity as a white powder stable on storage. This isolation process was by far more efficient than filtering Et_3N hydrochloride salts from the reaction mixture before adding water and separation of the phases (entry 6).

Table 4. Alternative conditions to prepare **26**

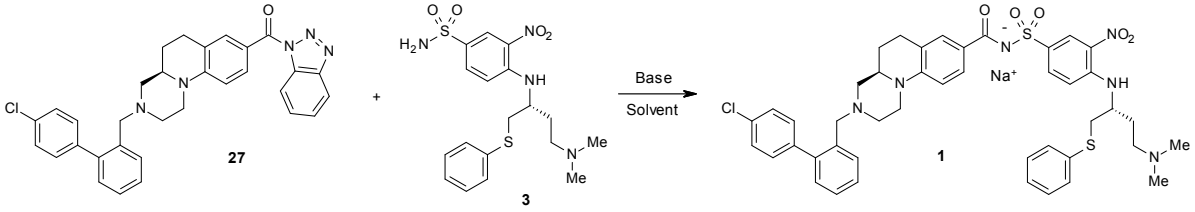


Entry[a]	Solvent, base (equiv), MesCl (equiv)	**25** (%)[g]	**26** (%)[g]	Yield (%)[h]	Purity (%)
1[b]	Toluene, pyridine (1.6), (1.2)	5.8	74.0	48	99.1
2[b]	Toluene, Et_3N (1.6), (1.2)	1.4	89.9	70	99.1
3[c]	MeTHF, pyridine (1.5), (1.3)	2.7	98.2	-	86.5
4[d]	MeTHF, 2,6-collidine (1.6), (1.4)	0.6	86.0	-	90.9
5[c]	MeTHF, Et_3N (1.5), (1.3)	0.1	99.4	-	98.8
6[e]	THF, Et_3N (1.3), (1.2)	0.5	99.2	57	96.6
7[f]	THF, Et_3N (1.5), (1.3)	0.6	99.2	87	99.7

[a]All reactions were run in round bottom flasks at 20 °C. [b]Addition of water, concentration of the organic phase and recrystallization in toluene. [c]Filtration of the reaction mixture, **26** obtained in solution. [d]Addition of water then phase separation. **26** obtained in solution. [e]Filtration of the reaction mixture, concentration to dryness, recrystallization in toluene. [f]Addition of water, filtration of the slurry. [g]Mesured by HPLC analysis of a sample of reaction mixture. [h]Isolated.

N-acetyl-benzotriazol **27** was then synthesized by the reaction of acid **23** with $BtSO_2Me$ in the presence of an excess of Et_3N (3.5 equiv). THF and MeTHF were selected as solvents and provided the active species in solution after filtration of the hydrochloride salts of Et_3N with a similar chemical purity (>90 area %; remaining **2** was <0.5 area %). Those solutions were then reacted with the anion of sulfonamide **3** prepared by reacting **3** with various bases as described in Table 5.[19]

Table 5. Survey of coupling conditions between **27** and **3** in the presence of a base



27 3 1

Entry	Conditions[a]	**1** (%)[b]	**3** (%)[b]	Yield (%)[c]	Purity (%)[d]
1	NaH (2.5 equiv), THF, 1 h	69.4	8.5	70	98.5
2	*t*-BuONa (2.1 equiv), THF, 3 h	58.2	5.9	59	98.9
3[e]	NaOH (1.9 equiv), THF, 22 h	63.0	5.2	65	98.1
4[e]	NaOH (1.9 equiv), MeTHF, 2 h	73.2	1.8	78	98.6
5[f]	NaOH (1.5 equiv), MeTHF, 2 h	75.7	1.0	81	98.8

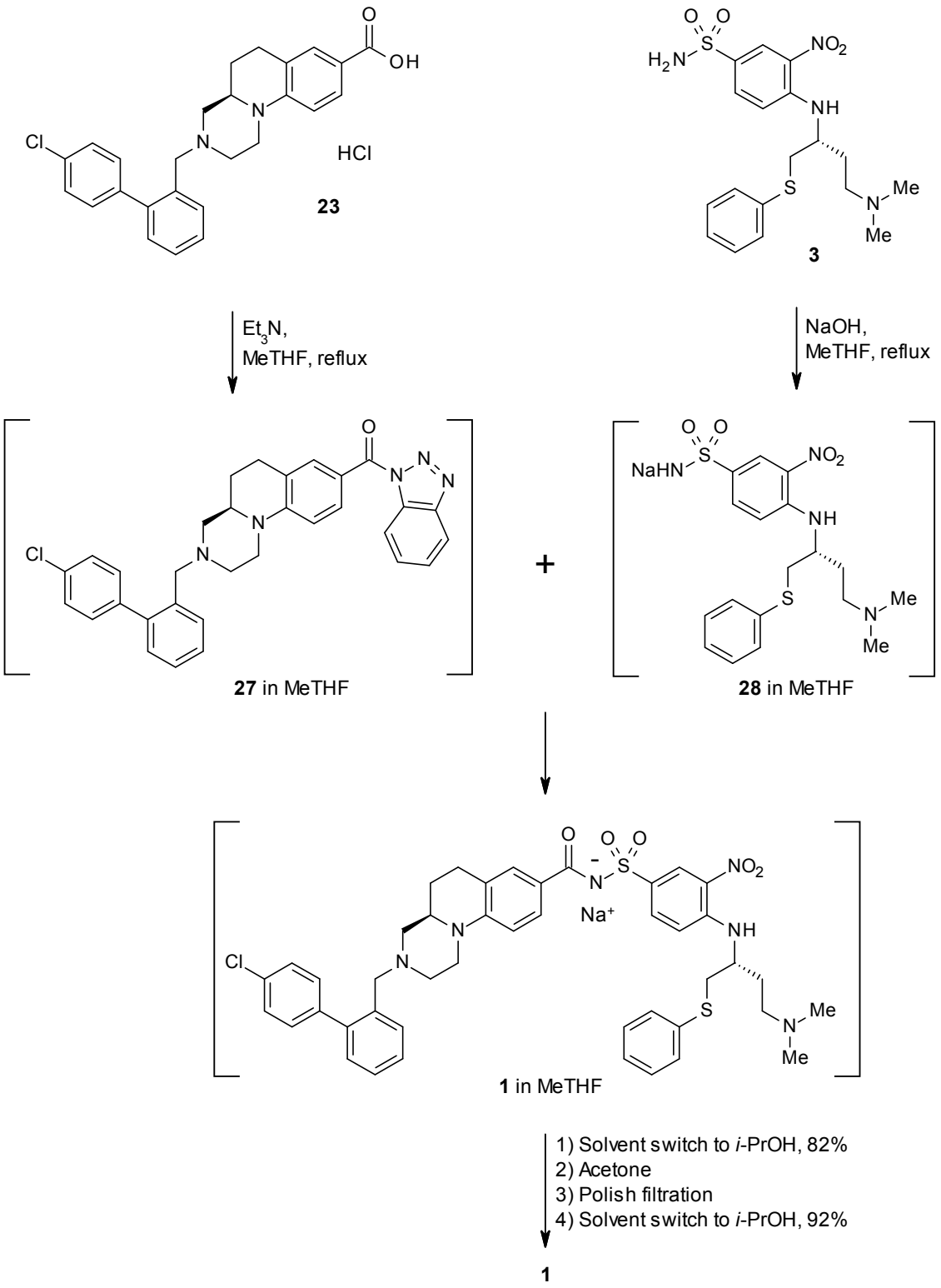
[a]All reactions run at reflux in round bottom flasks. [b]Mesured by HPLC analysis of a sample of reaction mixture. [c]Isolated. [d]After three reslurries in *i*-PrOH:MCH 87.5:12.5. [e]NaOH prills. [f]NaOH flakes.

Primary screening showed that the nature of the cation of the base was crucial to provide the desired product. For example, coupling reaction mediated with *n*-BuLi furnished the lithium salt of **1** and switching to the sodium analogue proved to be impraticable. This prompted us to choose bases constituted with sodium such as NaH, *t*-BuONa or NaOH. When 2.5 equiv of NaH 60% in

oil was used, deprotonation of sulfonamide **3** proceeded almost instantly at 20 °C (dark red color).[20] After 30 minutes, the mixture was heated to 40 °C and a solution of **27** was added slowly before heating at reflux for 1 hour. Quenching the reaction with water provided an organic phase containing 69.4 area % of **1**. The purity was improved to 94.4 % when the crude was reslurred in a mixture of *i*-PrOH:MCH 87.5:12.5 and even 98.9% after two more re-slurries (see entry 1). Despite the use of MCH to eliminate oil residues, we decided to evaluate other bases because we had concerns about our ability to detect and quantify those contaminants in the API. The same procedure was applied with *t*-BuONa and furnished the desired product with 59% yield and a satisfactory purity (entry 2).[21] However we observed a batch-to-batch variability when we repeated this reaction resulting in the formation of 10 to 22% of carboxylic acid **2**. This lack of reproducibility prompted us to switch to NaOH.

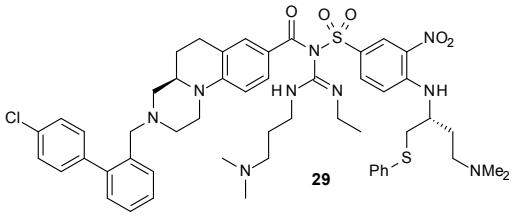
We noticed that the nature of both NaOH and solvent had a great impact on the outcome of the reaction. The rate of conversion was greatly improved using prills of NaOH when THF was replaced with MeTHF (entry 3 and 4).[22] Switching to NaOH flakes was also beneficial (entry 5) in terms of both equivalents (1.5 instead of 1.9) and conversion assuming it offered a better surface area than prills. In that case, 5% of carboxylic acid **2** was observed in the reaction mixture. Quenching with an aqueous solution of NaOH eliminated most of benzotriazole released during the reaction. Solvent switch to *i*-PrOH under vacuum at 50 °C was preferred rather than atmospheric pressure at 80 °C since less degradation was observed. Filtration of the slurry was facilitated by addition of a small amount of MCH and provided **1** with 98.5 area %. At this stage, compound **2** (initially 0.3 to 0.5%) was purged after solubilization of **1** in 10 mL/g of refluxing acetone followed by filtration at 40 °C.[23] Solvent switch to *i*-PrOH and addition of MCH to the reaction mixture furnished the desired API with 92% yield and 98.9 area % purity (Scheme 6).

Scheme 6. Coupling with $BtSO_2Me$ and isolation process

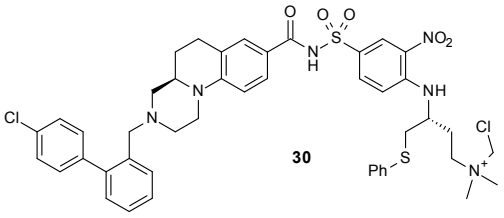


A closer look on the purity profile of the final product provided some information about the nature of major impurities (Figure 6). One advantage implementing the benzotriazole chemistry relied on the fact that impurity **29,** arising from condensation of EDCI on **1** and difficult to purge, no longer existed. Besides, we observed in early isolation studies the formation of **30** when CH_2Cl_2 was used as solvent in the presence of NaOH. This prompted us to switch to *i*-PrOH to avoid this side reaction. Compounds **31**, **32** and **33** were considered as daughter impurities arising from two side reactions of the Suzuki coupling that occurred during the synthesis of the biaryl motif: de-chlorination mediated with Pd to give **31** (see Multikilogram synthesis of a potent Bcl-2 selective antagonist. Part I.) and multiple Suzuki couplings to give **32** and **33**. Finally we suspected that Me_2NH contained traces of $MeNH_2$ and provided the mono *N*-methylated analogues of **3** to explain the formation of **33** and **34**. Fortunately our isolation process managed to purge those impurities to levels <0.10 %.

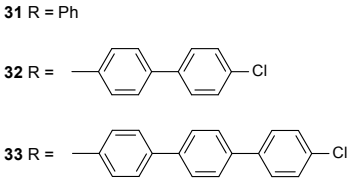
Figure 6. Identified process-related impurities.



29



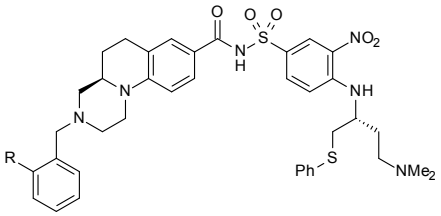
30

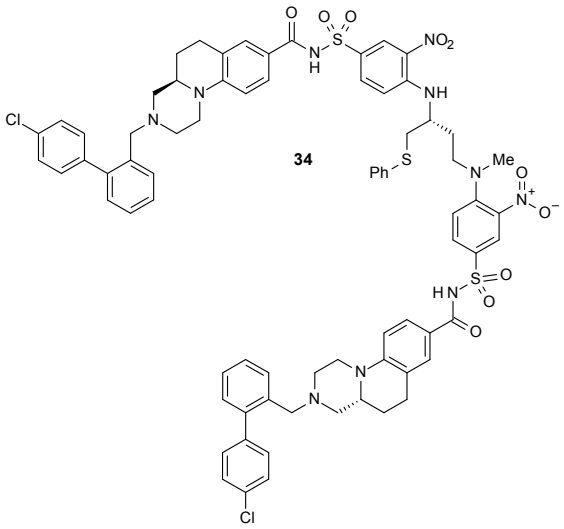


31 R = Ph

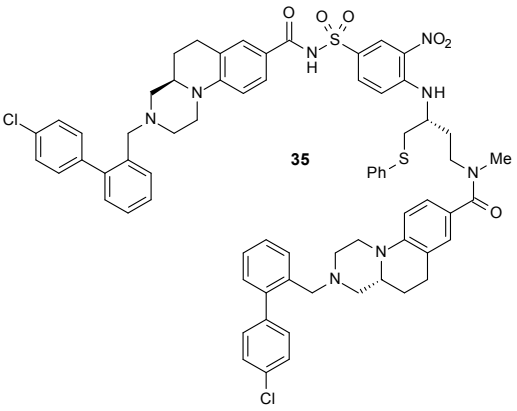
32 R =

33 R =





34



35

Epilogue

Access to chiral diamine **20** has been the one of the major challenge of this project. As reported above, efforts have been undertaken to develop an original synthesis to manufacture the first batches of **1**. They finally culminated with an asymmetric approach involving a diastereoselective aza-Reformatsky reaction coupled with a chemoselective amination under Mitsunobu conditions (Scheme 7).[24] Our strategy relied on the preparation of chiral sulfinimine using Ellman's *N-tert*-butanesulfinamide **38** that was reported to be a powerful auxiliary for the synthesis of chiral amines.[25] Bromide **36** was selected as starting material and was easily converted to sulfinimine

39 telescoping nucleophilic displacement with sodium thiophenolate, acetal deprotection into the corresponding aldehyde and condensation with *N*-*tert*-butanesulfinamide **38**. The aza-Reformatsky reaction was then the main hurdle we encountered. Formation of the Reformatsky reagent from activated zinc metal and α-bromoester is known to be a challenging reaction because it is highly exothermic after an unpredictable time of induction. To overcome this issue, a zinc-activation procedure using diisobutylaluminium hydride (Dibal-H) has been reported avoiding the need of reflux to activate zinc and limiting the induction period.[26] For safety reasons, the entire process was evaluated in RC1 on our substrates and the calorimetric profiles are shown below. Scouting experiments demonstrated that an excess of zinc (3 equiv) and 1.7 equiv of methyl bromoacetate were needed to obtain a satisfactory conversion. The Reformatsky reagent was prepared by suspending zinc in THF at 30 °C with vigorous stirring followed by subsequent addition of 0.1 equiv of bromide and 0.1 equiv of Dibal-H. A moderate heat output of 27 kJ/kg of reaction mass was monitored corresponding to an adiabatic rise of 15 °C (see Figure 7). When 1.6 equiv of methyl bromoacetate were added in 60 minutes at 45 °C, some heat accumulation was observed (15% estimated) followed by a sharp heat evolution. With a heat output of 270 kJ/kg and a ΔT_{ad} of 130 °C, we decided to extend the addition rate to 2 hours and to proceed step wise: add 15% of the total charge of methyl bromoacetate in 15 minutes (addition stopped if the reaction didn't start) and then remaining 85% in 105 minutes, controlling the addition rate if necessary. DSC showed two events with onsets at respectively 74 and 100 °C with low energy (Figure 8). A third event with an onset at 196 °C was also observed but was spread on a wide window of temperature. Addition of the sulfinimine proceeded at 20 °C (50% of the total charge added in 30 minutes followed by 50% in 15 minutes) with 4% of heat accumulation (Figure 9). This step was easily manageable in terms of safety (heat output of 30

kJ/kg associated with a ΔT_{ad} of 17 °C). DSC showed two events with onsets at 75 and 200 °C associated with moderate to low energy. A quench procedure using a 10% aqueous solution of citric acid was also evaluated and was finally replaced with a three-step procedure: addition of brine followed by aqueous citric acid and by brine.[27] To limit the heat release of the first addition of brine, it was recommended to extend the addition rate (10% of the total charge added in 10 minutes followed by 90% in 10 minutes, see Figure 10). Addition of citric acid over 20 minutes proceeded well with almost no accumulation and gave an acceptable heat evolution rate (Figure 11). It is worth mentioning that extra stirring was needed because the reaction mixture became thicker at 30% of total charge of citric acid. At 60%, the reaction mixture became more fluid and stirring more efficient. The second addition of brine required no specific attention. This procedure allowed us to isolate **40** after column chromatography on silica gel with a diastereoisomeric ratio of 94:6. Telescoping the reduction of the ester mediated with Red-Al and the Mitsunobu reaction was possible using toluene to provide **42** with >99 area % purity after purification on silica gel. Chiral diamine was obtained as difumarate **43** with >99% enantiomeric purity after telescoping removal of the chiral auxiliary and salt formation.

Scheme 7. Second-generation synthesis of enantiopure **20** isolated as difumarate salt **43**

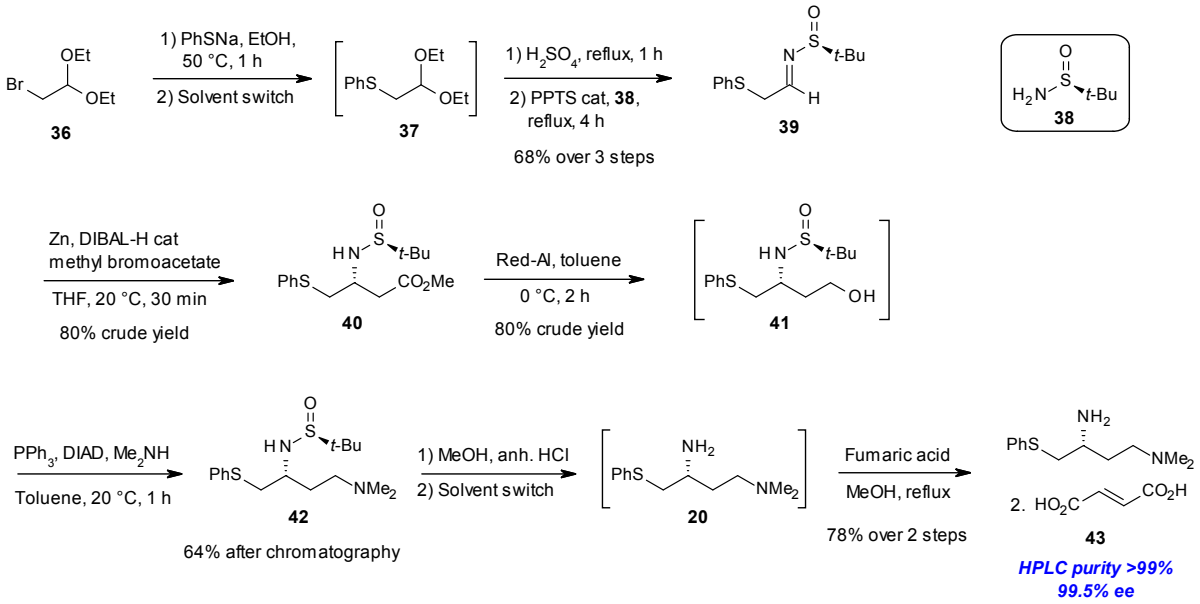


Figure 7. Heat flow profile for addition of methyl bromoacetate

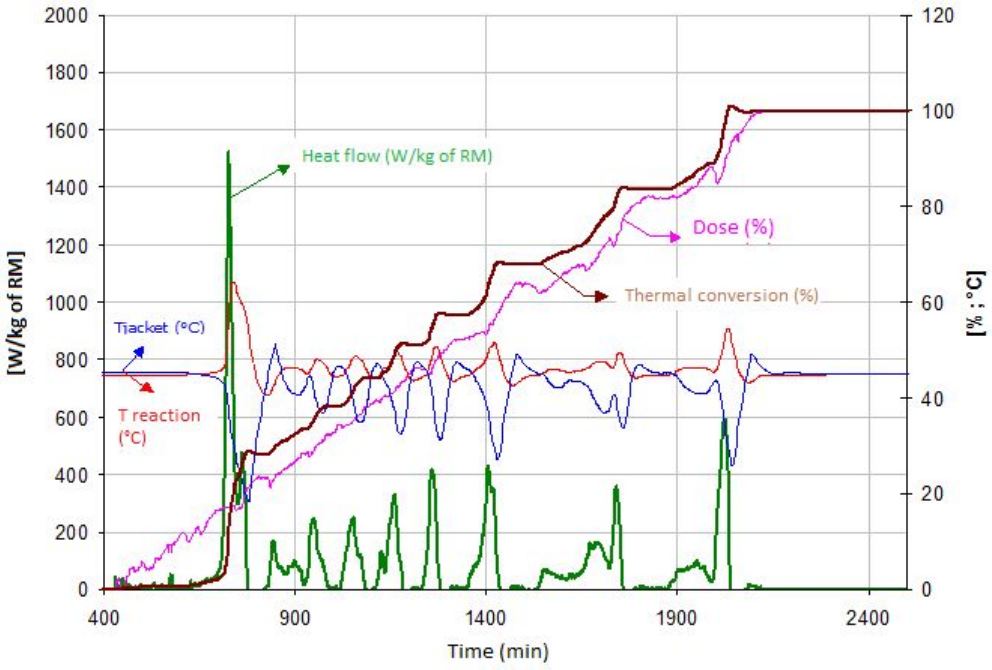


Figure 8. DSC thermogram of the organozinc mixture

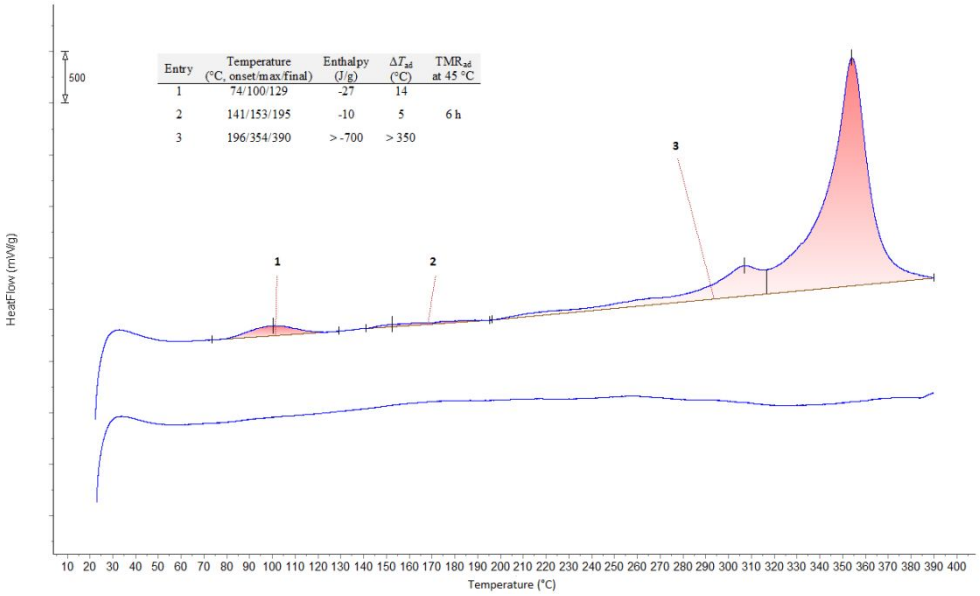


Figure 9. Heat flow for imine addition

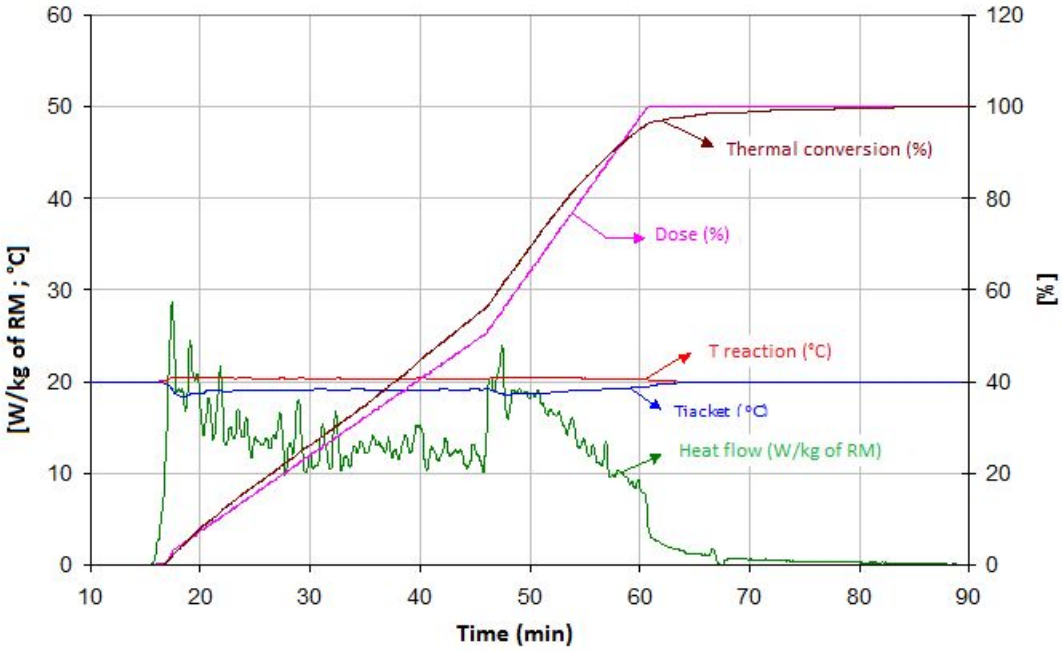


Figure 10. Heat flow profile for addition of brine

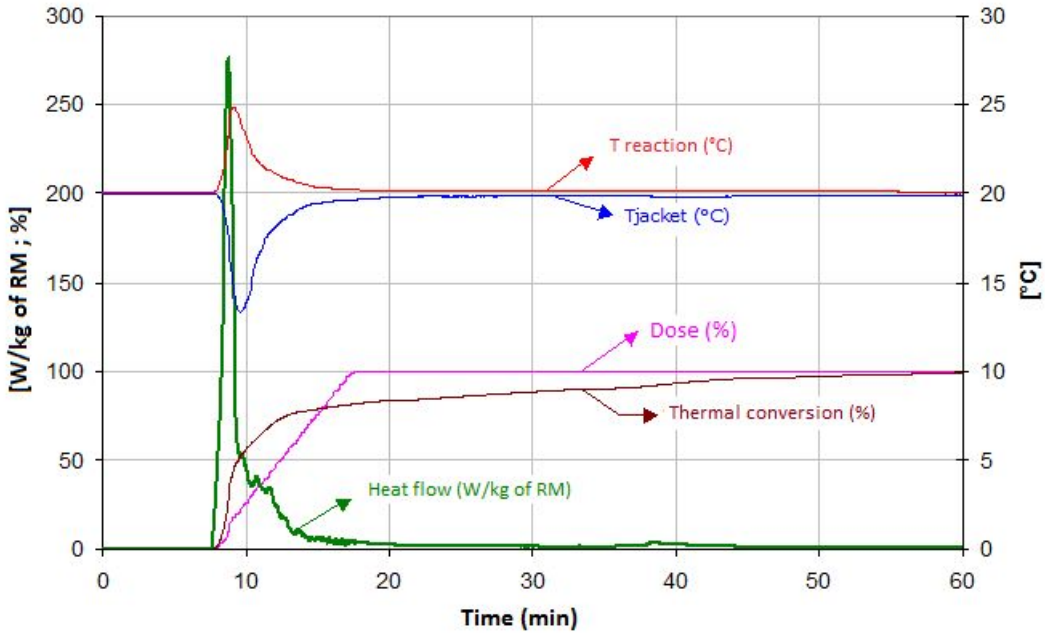
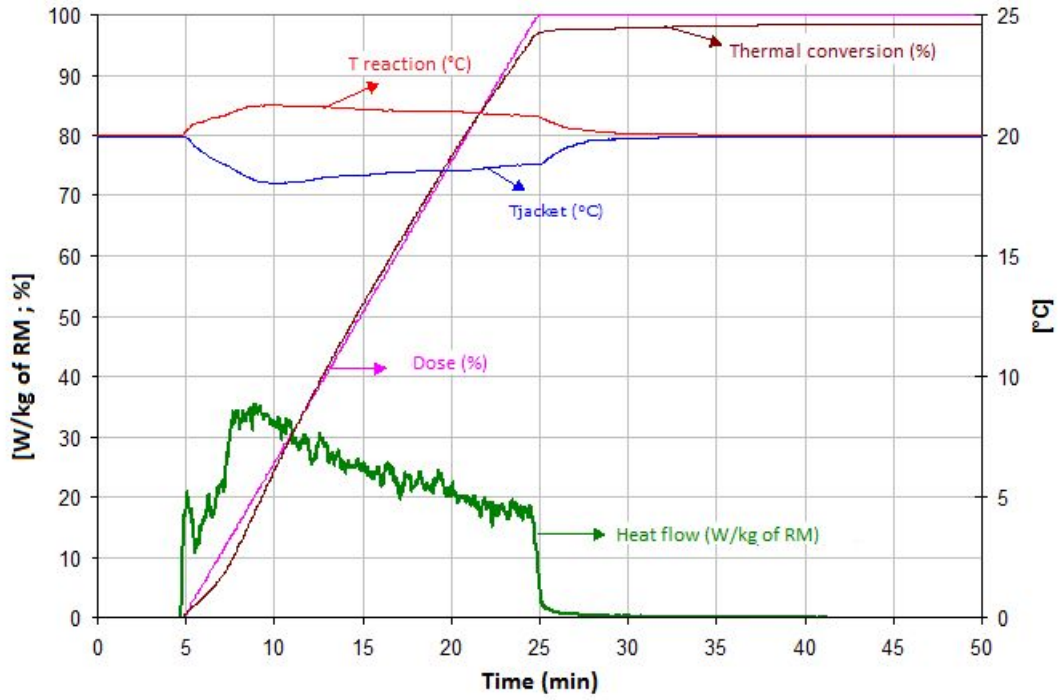


Figure 11. Heat flow profile for addition of citric acid



Conclusion

A new approach has been designed to manufacture enantiopure 1,3-diamine **20** starting with chloroacteyl chloride. Issues associated with the original synthesis have been addressed and batches of up to 3.6 kg were produced. Manufacture of sulfonamide **3** was improved in terms of safety and isolation of API **1** as well by implementing a polishing filtration that allowed the manufacture of a first clinical batch of 5.0 kg with a satisfactory purity. An asymmetric approach was also developed to synthesize enantiopure 1,3-diamine **20** involving an aza-Reformatsky reaction to install the stereocentre coupled with a chemoselective amination. Finally a practical and efficient procedure to manufacture benzotriazole **26** was developed to serve as activating agent in alternative coupling conditions between acid **23** and sulfonamide **3** to install the acylsulfonamide motif.

EXPERIMENTAL SECTION

General. All reagents and solvents were purchased from commercial suppliers and used without further purification. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker 400 MHz spectrometer in the indicated solvents. Chemical shifts are expressed in parts per million (ppm) and coupling constants are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

2-Chloro-*N*-methoxy-*N*-methyl-acetamide (13)

To 5000 L glass lined reactor flushed with nitrogen were charged N,O-dimethylhydroxylamine hydrochloride (14.9 kg, 152.6 mol, 0.8 equiv), a solution made of K_2CO_3 (46.36 kg, 335.5 mol, 1.8 equiv) and water (186 L) and the mixture was stirred at 15 ± 5 °C until a homogeneous

solution was obtained. MTBE (138 kg) was added and the mixture was cooled at 0 ± 5 °C. Chloroacetyl chloride **12** (20.68 kg, 183.1 mol, 1 equiv) was added drop-wise over 70 minutes. The feed line was rinsed with MTBE (22 kg) and the reaction mixture was vigorously stirred at 10 °C for 2 hours. The layers were separated and the aqueous phase was extracted twice with MTBE (55 kg). The organic extracts were combined, filtered through a 1 μm filter and concentrated under reduced pressure to give an oil that was dissolved with THF (126 kg). The solution of **13** (99.7 A % by HPLC) in THF was directly telescoped to the subsequent transformation. The yield was determined by evaporation of an aliquot (19.72 kg, 77% yield). Spectroscopic data were consistent with that previously reported in the literature.[28]

_N_-Methoxy-_N_-methyl-propanamide (14)

To a 250 L Hastelloy reactor flushed with nitrogen were charged K_2C0_3 (33.72 kg, 244.0 mol, 1.70 equiv), water (40 L) and the solution of **13** in THF (19.72 kg, 143.4 mol, 1 equiv). The feed line was rinsed with THF (18 kg) and thiophenol (15.80 kg, 142.6 mol, 1.0 equiv) was added over 10 minutes at 20 °C. The feed line was rinsed with THF (21 kg) and the reaction mixture was stirred for 2 hours. The reaction was judged complete by HPLC (<2 A % of **13**). Water (115 L) and CH_2Cl_2 (128 kg) were added and the reaction mixture was stirred for 20 minutes. The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2 (77 kg). The organic extracts were combined, washed with water (97 L) and concentrated under vacuum to afford **14** as an oil (12.68 kg, 97% yield). Purity: 96.2% by HPLC.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.04−3.21 (m, 3 H), 3.70 (s, 3 H), 3.97 (s, 2 H), 7.14−7.25 (m, 1 H), 7.26−7.35 (m, 2 H), 7.35−7.44 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 32.6, 34.6, 61.7, 126.4, 128.8, 129.4, 136.4, 169.4.

Column: X bridge C18 3.5 μm, 100 mm x 4.6 mm; flow rate 1.2 mL/min; temperature 40 °C; UV detection 210 nm; solvent system: water + 0.1% (v/v) CH_3SO_3H (A) and acetonitrile (B). Gradient: t=0 90A/10B; t=5 90A/10B; t=30 10A/90B; t=40 10A/90B. Concentration of **14** in a 1/1 mixture (v/v) of water/acetonitrile: 0.40 mg/mL. Amount injected: 2 μL. Retention time: 14.96 min.

4-(Dimethylamino)-1-phenylsulfanyl-butan-2-one (16)

Reactor 1. To a 250 L Hastelloy reactor flushed with nitrogen were charged **14** (15.8 kg, 74.8 mol, 1 equiv) and THF (76 kg). The mixture was cooled to -60 ± 5 °C and a 16.5% solution of vinylmagnesium chloride in THF (50.8 kg, 97.2 mol, 1.3 equiv) was added over 3 hours and the reaction mixture was stirred for 1 hour at -60 ± 5 °C.

Reactor 2. To a 350 L Hastelloy reactor flushed with nitrogen were charged water (11.7 L), 10 N HCl (16.5 kg), THF (23 kg) and the mixture was cooled at -40 ± 5 °C. The contents of *reactor 1* were added over 100 minutes to *reactor 2* to maintain the internal temperature <-40 °C. The vessel and transfer line were rinsed with THF (6.5 kg) and the resulting reaction mixture was slowly heated to 20 °C over 1.5 hour. Additional water (86 L) was added to the mixture followed by MTBE (38 kg) and the layers were split. The aqueous phase was extracted twice with MTBE (26 kg) and the organic phases containing ketone **15** were combined and engaged directly in the next step.

To a 350 L Hastelloy reactor flushed with nitrogen were charged the solution of ketone **15** and a 40% aqueous solution of dimethylamine (10.9 kg, 97.2 mol, 1.3 equiv). The reaction mixture was aged for 6 hours between 11 and 15 °C and was quenched by adding over 1.5 hour 1 N HCl (18.5 kg of 10 N HCl and 158 L of water). The layers were split and the organic phase was discarded.

The aqueous phase was washed with MTBE (76 kg) and then charged with 30% w/w aqueous NaOH (16.2 kg) followed by water (17 L). The mixture was stirred for 1 hour at 20 °C and MTBE (51 kg) was added. The layers were split and the aqueous phase was extracted with MTBE (38 kg). The organic phases were combined and concentrated under reduced pressure to provide an oil. The vessel was charged with EtOH (32 kg) and the resulting solution was concentrated under reduced pressure to provide **16** as an oil (8.0 kg, 48% yield). Purity: 62.4% by HPLC.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.61−2.73 (m, 6 H), 3.10−3.28 (m, 4 H), 4.09 (s, 2 H), 7.15−7.25 (m, 1 H), 7.27−7.39 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 35.2, 42.0, 42.5, 51.0, 126.1, 128.2, 129.0, 135.0, 202.0.

N^1,N^1-Dimethyl-4-phenylsulfanyl-butane-1,3-diamine difumarate (19)

To a 100 L reactor in stainless steel flushed with nitrogen were charged methoxyamine hydrochloride (3.55 kg, 42.5 mol, 1.19 equiv) and toluene (18.4 kg). The mixture was stirred at 20 °C and a solution of **16** (8.0 kg, 35.8 mol, 1 equiv) in toluene (14 kg) was added over 40 minutes. The addition funnel was rinsed with toluene (2.5 kg) and the resulting reaction mixture was stirred for 2.5 hours at 20 °C. It was judged complete by HPLC (< 0.5 area % of **16**) and was charged with an aqueous solution of NaOH (11.9 kg of a 30% solution of NaOH and 34.5 L of water). The reaction mixture was stirred for 30 minutes and the layers were split. The aqueous phase was discarded, the organic phase containing **17** was washed with a solution of NaCl (14 kg) in water (40 L) and was engaged in the next step without further purification.

To the former solution was added a 1.7 M solution of Dibal-H in toluene (67.7 kg, 118.2 mol, 3.3 equiv) over 3 hours to maintain the internal temperature < 25 °C. The feed line was rinsed with toluene (5 kg) and the reaction mixture was aged for 2 hours at 20 °C. It was judged complete by HPLC (sum of *E* and *Z* isomers < 2 A %) and was carefully added over 2.5 hours on an aqueous solution of NaOH (23.6 kg of a 30% solution of NaOH and 106 L of water). The mixture was aged for 2 hours and the layers were split. The aqueous phase was discarded and the organic phase was used without further purification in the salt formation.

To a 250 L enamel reactor flushed with nitrogen were charged fumaric acid (7.46 kg, 62.3 mol, 1.8 equiv) and MeOH (42.6 kg). The mixture was heated to reflux until complete dissolution and was then cooled to 60 °C. The toluene solution was added over 3.5 hours and the feed line was rinsed with MeOH (5.5 kg). The reaction mixture was stirred at 60 °C for 15 minutes and was then cooled to 50 °C in 30 minutes. Crystal seeds of **19** (80 g) were added and the mixture was aged at 50 °C for 2 hours and then cooled at 5 °C in 5 hours. After aging for 2 hours, the slurry was filtered and rinsed successively with EtOH (14 kg) and with MTBE (25 kg). The filter cake was dried under vacuum to provide **19** as an off-white solid (7.60 kg, 47% yield). Purity: 99.5% by HPLC.

Spectroscopic data were consistent with that previously reported in the literature.[24]

Column: Zorbax SB AQ 5 μm, 250 mm x 4.6 mm; flow rate 1 mL/min; temperature 40 °C; UV detection 210 nm; solvent system: water + 0.1% (v/v) CH_3SO_3H (A) and acetonitrile (B). Gradient: t=0 98A/2B; t=5 98A/2B; t=30 10A/90B; t=40 10A/90B ; t=43 98A/2B ; t=60 98A/2B. Concentration of **19** in A: 0.80 mg/mL. Amount injected: 5 μL. Retention time: 7.28 min.

N^1,N^1-Dimethyl-4-phenylsulfanyl-butane-1,3-diamine (18)

To a 650 L Hastelloy reactor flushed with nitrogen were charged **19** (19.58 kg, 42.9 mol, 1 equiv) and water (315 L). The mixture was stirred at 20 °C for 30 minutes to get a homogeneous suspension and a 30% aqueous solution of NaOH (34.2 kg, 257.3 mol, 6 equiv) was added over 10 minutes. After aging for 20 minutes, EtOAc (264 kg) was added and the mixture was stirred for 30 minutes at 20 °C. The layers were split and the aqueous phase was extracted twice with EtOAc (71 kg). The organic phases were combined and washed with water (78 kg). After phase separation the aqueous layer was discarded and the organic phase was concentrated to dryness under reduced pressure. The resulting oil was charged with *i*-PrOH (78 kg) and volatiles were removed under reduced pressure to provide **18** as fluid brown oil (8.36 kg, 87% yield). Purity: 99.3% by HPLC.

Spectroscopic data were consistent with that previously reported in the literature.[24]

(*R*)-*N*^{1},*N*^{1}-dimethyl-4-(phenylthio)butane-1,3-diamine (20)

Separation of enantiomers. Stationary phase: CHIRALPACK AD (particle size: 20 μm; porosity: 100 Å). Eluent: MeCN / *i*-PrOH / Et_2NH: 8/2/0.1. Batches of 1.5 kg of **18** were separated to provide after concentration under reduced pressure **20** as an oil (3.63 kg, 44% yield). Purity: 99.3% by HPLC. Enantiomeric purity: 98.5% by HPLC.

Spectroscopic data were consistent with that previously reported in the literature.[24]

Determination of enantiomeric excess. Column: Chiralpack AD 10 μm, 250 mm x 4.6 mm; flow rate 1.0 mL/min; temperature 20 °C; UV detection 254 nm; solvent system: acetonitrile/isopropanol/Et_2NH 90v/10v/0.1v. Concentration of **18** in methanol: 1.0 mg/mL. Amount injected: 5.0 μL. Retention time: 6.86 min (8.19 min for *S* isomer).

4-[[(1*R*)-3-(dimethylamino)-1-(phenylsulfanylmethyl)propyl]amino]-3-nitro-benzenesulfonamide (3)

To a 100 L enamel reactor flushed with nitrogen were charged **22** (3.49 kg, 14.8 mol, 0.9 equiv), DMSO (10.25 kg) and DIPEA (8.38 kg, 64.8 mol, 4 equiv). The mixture was stirred at 20 °C and a solution of **20** (3.63 kg, 16.2 mol, 1 equiv) in DMSO (10.3 kg) was added. The feed line was rinsed with DMSO (2 kg) and the reaction mixture was heated at 90 ± 5 °C for 24 hours. The mixture was cooled to 20 °C and was sample for IPC (**20** <1 A % by HPLC). The phases were split and the lower phase containing the desired product was charged with EtOAc (33 kg) and with 3 N HCl (6.95 kg of 10 N HCl diluted in 13.8 L of water). The mixture was stirred for 30 minutes, the phases were split and the aqueous phase was extracted with EtOAc (12.5 kg). The aqueous phase was then treated with a 30% aqueous solution of NaOH (22 kg) and EtOAc (14 kg) was added. The mixture was stirred for 30 minutes at 20 °C and the phases were split. The aqueous phase was extracted with EtOAc (19 kg), the organic phases were combined and washed with water (22 L). The resulting organic phase was subjected to a solvent swap with *i*-PrOH and the volume of solution was adjusted to a volume of 11 L. The mixture was cooled to 20 °C in 2 hours and was aged for 30 minutes. The resulting slurry was filtered and the cake was rinsed with MTBE (5 kg) and dried to afford **3** as a yellow solid (5.2 kg, 74% yield). Purity: 99.8% by HPLC. Enantiomeric purity: 99.5% by HPLC.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.75−1.89 (m, 1 H), 1.89−1.97 (m, 1 H), 2.11 (s, 6 H), 2.21 (dt, J = 12.0 Hz, J = 5.8 Hz, 1 H), 2.34−2.46 (m, 1 H), 3.23−3.44 (m, 2 H), 4.13 (d, J = 5.8 Hz, 1 H), 7.08 (d, J = 9.3 Hz, 1 H), 7.13−7.42 (m, 7 H), 7.72 (dd, J = 9.3 Hz, J = 2.5 Hz, 1 H), 8.40 (d, J = 2.5 Hz, 1 H), 8.63 (d, J = 8.8 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 30.6, 37.0, 45.0, 50.9, 54.9, 115.3, 124.7, 126.1, 128.9, 129.0, 129.4, 130.1, 132.4, 135.4, 146.2.

HRMS ESI (*m/z*) calcd for $C_{18}H_{24}N_4O_4S_2$ $[M+H]^+$ 425.1317, found 425.1329.

Column: X terra MS C18 3.5 μm, 150 mm x 4.6 mm; flow rate 1 mL/min; temperature 40 °C; UV detection 210 nm; solvent system: water + 0.1% (v/v) CH_3SO_3H (A) and acetonitrile (B). Gradient: t=0 90A/10B; t=20 10A/90B; t=20.01 90A/10B; t=30 90A/10B. Concentration of **3** in a 1/1 mixture (v/v) of A/B: 0.40 mg/mL. Amount injected: 3 μL. Retention time: 6.99 min.

Determination of enantiomeric excess. Column: Chiralcel IA 5 μm, 250 mm x 4.6 mm; flow rate 1.0 mL/min; temperature 40 °C; UV detection 254 nm; solvent system: heptane/ethanol/Et_2NH 80v/20v/0.1v. Concentration of **3** in ethanol: 0.3 mg/mL. Amount injected: 3.0 μL. Retention time: 9.0 min (11.1 min for *S* isomer).

Sodium (4a*R*)-3-[[2-(4-chlorophenyl)phenyl]methyl]-*N*-[4-[[(1*R*)-3-(dimethylamino)-1-(phenylsulfanylmethyl)propyl]amino]-3-nitro-phenyl]sulfonyl-1,2,4,4a,5,6-hexahydropyrazino[1,2-a]quinoline-8-carboxamide (1)

To a 100 L enamel reactor flushed with nitrogen were charged **23** (3.67 kg, 7.8 mol, 1 equiv), **3** (3.03 kg, 7.1 mol, 0.9 equiv), DMAP (1.82 kg, 14.9 mol, 1.9 equiv) DMF (29 kg). EDCI (1.58 kg, 10.2 mol, 1.3 equiv) was added, the reaction mixture was heated at 50 ± 5 °C in 30 minutes and stirred at this temperature for 6 hours. The reaction was judged complete by HPLC (1.4% of **3**) and was cooled to 20 °C. EtOAc (27 kg) and 1 N NaOH (30 L) were sequentially added and the mixture was stirred for 20 minutes. The layers were split and the aqueous phase was extracted twice with EtOAc (27 kg and 13.5 kg). The combined organic phases were washed sequentially with 1 N NaOH (30 L) and twice with brine (2 × 39 kg). The organic phase was filtered on a Pall

filter and the feed line was rinsed with EtOAc (7 kg). A solvent switch at constant volume with *i*-PrOH was then performed to displace EtOAc. The mixture was then refluxed for 3 hours and was cooled to 20 °C over 2 hours. Solids were collected by filtration, rinsed twice with *i*-PrOH (2 × 19 kg) and dried at 50 °C to provide **1** as a yellow powder (5.47 kg, 82% yield). Purity: 98.5% by HPLC.

To a 100 L enamel reactor flushed with nitrogen were charged **1** (5.47 kg, 6.35 mol, 1 equiv), acetone (52 kg) and the mixture was stirred at reflux for 20 minutes. The orange solution was cooled to 50 ± 5 °C and was filtered on a Pall filter. The filter was washed twice with acetone (2 × 5 kg) and the solution was concentrated to reach a final volume of 6 L/kg. A solvent switch at constant volume with *i*-PrOH was then performed to displace acetone. The orange suspension was then cooled to 20 °C and aged for 30 minutes. Solids were collected by filtration, rinsed with *i*-PrOH (13 kg) and dried at 50 °C to provide **1** as a yellow powder (5.04 kg, 92% yield). Purity: 99.3% by HPLC. Sum of *S,S*-, *S,R*- and *R,S*-diasteroisomers <0.5 A % by HPLC.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.54 (dd, J = 10.4, J = 4.9 Hz, 1 H), 1.61−1.85 (m, 3 H), 1.87−1.97 (m, 1 H), 1.97−2.07 (m, 1 H), 2.11 (s, 6 H), 2.22 (dt, J = 12.1 Hz, J = 5.8 Hz, 1 H), 2.32−2.45 (m, 1 H), 2.53−2.81 (m, 5 H), 2.83−2.98 (m, 1 H), 3.20−3.43 (m, 4 H), 3.76 (d, J = 12.1 Hz, 1 H), 4.03 (d, J = 5.3 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 1 H), 6.83 (d, J = 9.5 Hz, 1 H), 7.11−7.20 (m, 1 H), 7.20−7.29 (m, 3 H), 7.29−7.42 (m, 4 H), 7.44−7.57 (m, 7 H), 7.75 (dd, J = 9.0 Hz, J = 2.0 Hz, 1 H), 8.39−8.50 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 26.3, 26.5, 30.7, 37.1, 45.0, 46.0, 50.6, 52.5, 54.5, 55.1, 58.7, 59.2, 110.8, 113.3, 121.9, 125.6, 126.2, 127.2, 127.5, 127.9, 128.1, 129.0, 129.1, 129.4, 129.6, 129.9, 130.1, 131.1, 131.9, 133.6, 134.8, 135.2, 135.4, 139.7, 140.8, 145.2, 147.6, 170.2.

HRMS ESI (*m/z*) calcd for $C_{44}H_{47}N_6O_5S_2Cl$ $[M+H]^+$ 839.2816, found 839.2656.

Column: X bridge Shield RP18 3.5 μm, 100 mm x 4.6 mm; flow rate 1 mL/min; temperature 40 °C; UV detection 210 nm; solvent system: water + 0.1% (v/v) H_3PO_4 (A) and acetonitrile (B). Gradient: t=0 90A/10B; t=15 60A/40B; t=30 2A/98B; t=35 2A/98B ; t=35.01 90A/10B ; t=45 90A/10B. Concentration of **1** in a 1/1 mixture (v/v) of A/B: 0.25 mg/mL. Amount injected: 5 μL. Retention time: 15.68 min.

Determination of enantiomeric excess. Column: (*R,R*) Whelk-01 5 μm, 250 mm x 4.6 mm; flow rate 1.0 mL/min; temperature 30 °C; UV detection 315 nm; solvent system: heptane/1,2-dichloroethane/ethanol/TFA 50v/50v/6v/0.1v. Concentration of **1** in dichloromethane: 2 mg/mL. Amount injected: 10.0 μL. Retention time: 48.4 min (37.6 min for *S,S*; 43.1 min for *S,R*; 44.5 min for *R,S*).

_N_-(1-Methanesulfonyl)benzotriazole (26)

To a 25 L Hastelloy reactor flushed with nitrogen were charged benzotriazol **25** (0.5 kg, 4.20 mol, 1 equiv), THF (1.8 kg) and Et_3N (0.66 kg, 6.47 mol, 1.54 equiv). The feed line was rinsed with THF (0.5 kg) and the reaction mixture was stirred for 30 minutes at 20 °C. A solution of methanesulfonyl chloride (625 g, 5.46 equiv, 1.30 equiv) in THF (0.44 kg) was prepared and added with a dropping funnel over 20 minutes maintaining the internal temperature < 30 °C. The funnel was rinsed with THF (0.44 kg) and the reaction mixture was stirred for 1 hour. The resulting slurry was charged with water (10 L) and was stirred for 1 hour. The slurry was cooled at 5 °C and maintained at this temperature for 1 hour. The crystals were filtered off, washed twice with water (2 × 1.5 L) and dried in a vacuum oven to provide **26** as a white solid (751 g, 91% yield).

Spectroscopic data were consistent with that previously reported in the literature.[17]

Column: X Terra MS 3.5 μm, 100 mm x 4.6 mm; flow rate 1 mL/min; temperature 40 °C; UV detection 210 nm; solvent system: water + 0.1% (v/v) CH_3SO_3H (A) and acetonitrile (B). Gradient: t=0 90A/10B; t=30 10A/90B; t=35 90A/10B ; t=40 90A/10B. Concentration of **26** in B: 0.30 mg/mL. Amount injected: 5 μL. Retention time: 9.55 min.

Coupling of **23** with **3** mediated with **26** to provide **1**

Formation of the activated species. To a 250 mL cylindrical glass reactor flushed with nitrogen were charged **23** (15 g, 32 mmol, 1 equiv), **26** (8.86 g, 44.7 mmol, 1.4 equiv) and MeTHF (75 mL). Et_3N (15.6 mL, 112 mmol, 3.5 equiv) was added and the reaction mixture was stirred at reflux for 2 hours. Upon reaction completion (< 2% **23** by HPLC), the mixture was cooled to 20 °C and filtered. The filter was rinsed with MeTHF (15 mL) and the solution of **27** was used without further purification in the next step.

Formation of the anion and coupling reaction. To a 500 mL jacketed cylindrical reactor flushed with nitrogen were charged **3** (12.9 g, 30.4 mmol, 0.95 equiv), flakes of NaOH (1.92 g, 48 mmol, 1.5 equiv) and MeTHF (60 mL). After heating the mixture at 50 °C for 2 hours, the solution of **27** was added with a funnel that was rinsed with MeTHF (15 mL). After heating at reflux for 2 hours, the reaction was judged complete by HPLC (<0.2% **27**) and a solution of NaOH (prepared with 11 mL of 10 N NaOH and 90 mL of water) was added at 40 °C. The mixture was cooled to 20 °C and stirred for 30 minutes. Layers were split and the organic phase was washed with water (90 mL). The solution was concentrated under vacuum to reach a volume of approximately 100 mL and a solvent switch with *i*-PrOH was then performed to displace MeTHF. Solids were collected by filtration, rinsed sequentially with *i*-PrOH (15 mL) and MCH (15 mL), dried at 50 °C to provide **1** as a yellow powder (26 g, 90% yield). Purity: 98.7% by HPLC.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and ^{13}C spectra of compounds **16**, **3**, and **1**.

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Notes

The authors declare no competing financial interest.

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(20) When 1.5 equiv was used, only 27% of **1** in the reaction mixture.

(21) When 1.4 equiv was used, only 26% of **1** in the reaction mixture.

(22) Water released during formation of **28** is less soluble in MeTHF limiting its hydrolysis or hydrolysis of **27**.

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