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Development of an Efficient Process Towards the Benzimidazole BYK308944: A Key Intermediate in the Synthesis of a Potassium-Competitive Acid Blocker

Matthias Webel,*,† Andreas Marc Palmer,*,‡ Christian Scheufler,† Dieter Haag,§ and Bernd Müller§

NYCOMED GmbH, Department of Process Chemistry Research, Byk-Gulden-Strasse 2, D-78467 Konstanz, Germany, NYCOMED GmbH, Department of Medicinal Chemistry, Byk-Gulden-Strasse 2, D-78467 Konstanz, Germany, and NYCOMED GmbH, Department of Process Chemistry Development, Robert-Bosch-Strasse 8, D-78224 Singen, Germany

Abstract:

An entirely new synthesis of the important benzimidazole building block BYK308944 was elaborated using the Stobbe reaction as central element. BYK308944 constitutes an important intermediate for the preparation of 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles as potassium-competitive acid blockers. The new route relies on the hydroxymethylation of 1,2-dimethylimidazole as cheap starting material followed by oxidation of the corresponding alcohol and Stobbe condensation of the resulting aldehyde with diethyl succinate. All synthetic steps of this new approach were optimized particularly with the goal to establish a process amenable for large-scale preparation.

Introduction

Recently we reported on the "Large scale asymmetric synthesis of the 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole BYK405879 - a promising candidate for the treatment of acid-related diseases" (Figure 1).[1] In that article we also briefly described the preparation of the intermediate BYK308944 following a protocol from medicinal chemistry. Herein, we wish now to cover our activities concerning a completely new route to this material, particularly with respect to scale-up.

The original medicinal chemistry protocol uses 2-amino-3-nitrophenol (**1**) as an expensive starting material (Scheme 1). Taking into regard the rather lengthy linear synthesis, this exhibits a strong cost-contributing factor. Applying this material, the synthesis commences with the preparation of the respective benzyl-protected phenol followed by selective bromination. The C2 building block required for the formation of the benzimidazole system was introduced by acetylation of the amino function (**2**). In the next step, the nitro group was reduced, using a mixture of ferrous chloride and hydrazine (**3**). After dimethylation of the newly formed primary amino group (**4**), the cyclization to the benzimidazole scaffold was carried out (**5**), and the amide functionality was introduced by palladium-catalyzed amidocarbonylation in the presence of dimethylamine, leading to compound **6**. Finally, the last step comprises the debenzylation of **6**, affording the desired target compound BYK308944 (**7**).

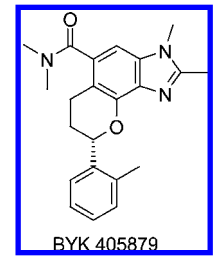

Figure 1. **Potassium-competitive acid blocker 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole - BYK405879.**

As already highlighted in our recent publication, the original medicinal chemistry route was strongly hampered by several steps that in general are not amenable for a large-scale manufacturing. Particularly, the use of hydrazine for the reduction of the nitro group as well as the application of cyanoborohydride for the reductive methylation of the primary amine moiety mark a significant drawback of the synthesis due to safety and toxicity concerns. Furthermore, the carbonylation reaction poses a strong hurdle, because only few companies possess the necessary equipment to safely perform this reaction due to the high toxicity of carbon monoxide. Additionally, the final debenzylation step is constrained by the use of high amounts of palladium on charcoal to drive this sluggish reaction to completion.

However, due to time pressure at the beginning of the development and the urgent need of material for early studies, we were forced to scale-up these procedures to multikilogram scale together with our external partner. Due to the problems faced in the course of this synthesis, it quickly turned out that a more practical and foremost safe alternative was needed. Thus, we started in parallel with our efforts to search for an alternative route.

Results and Discussion

Alternative Synthesis. Only few viable possibilities exist for the construction of benzimidazoles beside the traditional approach applied in the medicinal chemistry synthesis. Therefore, we decided right from the start to follow a strategy that is focused on the Stobbe reaction of aldehyde **10** with diethyl succinate (Scheme 2).[2,3] This reaction has been already exemplified in literature for a variety of heterocyclic aldehydes

* To whom correspondence should be addressed. Telephone: +49 7531 84 4563 (M.W.); +49 7531 84 4783 (A.M.P). Fax: +49 7531 849 4563 (M.W.); +49 7531 849 2087 (A.M.P.). E-mail: matthias.webel@nycomed.com; andreas.palmer@nycomed.com.

† Department of Process Chemistry Research, Konstanz.

‡ Department of Medicinal Chemistry, Konstanz.

§ Department of Process Chemistry Development, Singen.

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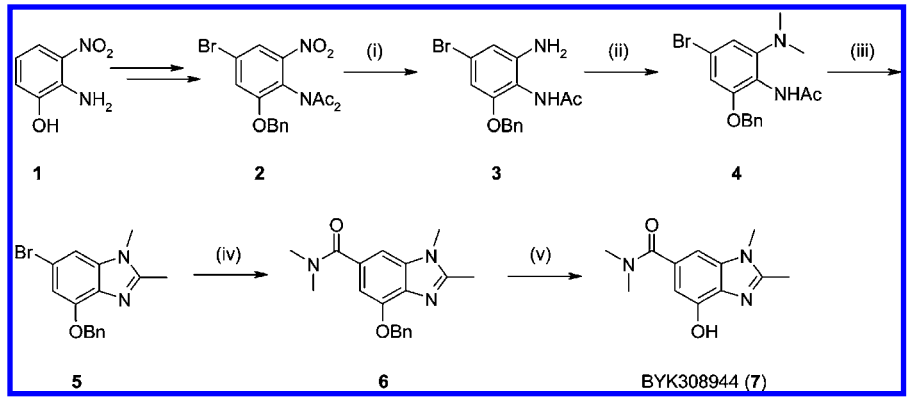
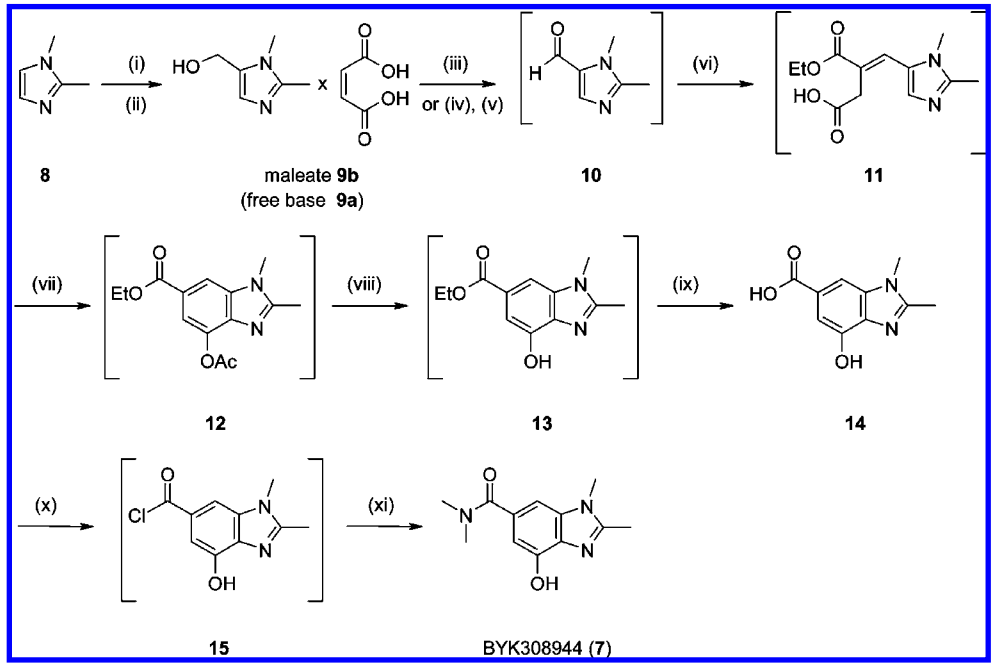
Scheme 1. **Original medicinal chemistry route towards BYK308944**[a]



[a] Reagents and conditions: (i) $FeCl_3$, charcoal, hydrazine hydrate, MeOH, 70−75 °C, 18 h, 82%; (ii) formaldehyde, $NaBH_3CN$, MeOH/AcOH, RT, 2 h, 84%; (iii) $POCl_3$, 75 °C, 2 h, 86%; (iv) $Pd(OAc)_2$, PPh_3, Me_2NH (2 M in THF), DMAP, 6 bar CO, DMF, 130 °C, 18 h, 95%; (v) Pd/C, H_2, MeOH, 50 °C, 3−9 h, >78%.

Scheme 2. **Alternative scale-up route towards BYK308944**[a]



[a] Reagents and conditions: (i) H_2CO (aq), NaOAc/AcOH, 90−96 °C, 43−50 h; (ii) maleic acid, 2-PrOH, 74−82 °C → 7−15 °C, 4−87 h, 40%; (iii) NaOCl/TEMPO, NaI, NaOH (aq), 8−20 °C, 2.25−24 h; (iv) K_3PO_4, t-BuOH, 75−85 °C, 1−2 h; (v) MnO_2, MsOH, t-BuOH, 75−85 °C, 14−18 h; (vi) diethyl succinate, NaOEt/EtOH, MeCN, 50−55 °C, 1−12 h, (vii) Ac_2O, MeCN, 75−85 °C, 1.75−3.5 h; (viii) HCl (aq), 50−70 °C, 0.5 h; (ix) HCl (aq), 102−112 °C, 3−5 h, 70%; (x) $SOCl_2$, cat. DMF, MeCN, 75−83 °C, 1−2 h; (xi) $HNMe_2 \times HCl$, NEt_3, 10−30 °C, 1.5−3 h, 70%.

containing, e.g., a furane,[4] pyrazole,[4c] thiophene,[4c,5] pyrrole,[6] or indole moiety.[7] Thus, we envisaged applying this procedure to our problem, i.e. the construction of the benzimidazole BYK308944 (**7**).

Hydroxymethylation. In order to utilize the Stobbe reaction for our purposes, it was necessary to gain access to aldehyde **10**. As this aldehyde is commercially available only in milligram to gram quantities, a synthesis had to be established. The hydroxymethylation of 1,2-dimethylimidazole (**8**) with formaldehyde constituted the first step in the synthesis of **10**.[8] Not surprisingly, this hydroxymethylation did not run regioselectively, and a mixture of both regioisomers (**9a** and **16**) along with dihydroxymethylated product **17** and remaining starting material **8** was obtained (Scheme 3). When the reaction was driven to an almost complete consumption of starting material, a rather long reaction time of 4−5 d was required that is not feasible from a practical point of view. Furthermore, after a reaction period of more than 2 d, only a minor increase of the desired product **9a** was noticed, whereas the amount of dihydroxymethylated product **17** rose to 20%. Thus, a total conversion of starting material had to be avoided. An optimum

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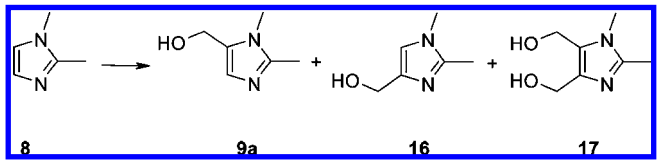
Scheme 3. **Hydroxymethylation of 1,2-dimethylimidazole (8)**



was found when the reaction was stopped after 50 h, at the latest. In this case, not more than 5−7% of the respective undesired isomers **16** and **17** were obtained in sum, leaving approximately 40% of unreacted starting material behind.

Despite these flaws, we decided to further elaborate this protocol, as both raw materials are inexpensive and commercially available in large quantities. During the preparation of our batches in the kilo-lab, at a reaction temperature of 90−95 °C, a noticeable amount of formaldehyde sublimed in the condenser leading to the risk of clogging and to a potential exposure problem through the open layout of the kilo-lab equipment (air exhaust). Hence, our effort with respect to pilot-plant batches was directed towards running the reaction preferably in a closed system. As our pilot-plant equipment is usually only capable of resisting a pressure of up to 4−6 bar, some batches were prepared in the autoclave to assess this problem. Luckily, almost no pressure increase could be observed, and therefore, the synthesis of further batches could be run safely in a closed vessel.

The workup consisted of an extraction that worked best when a pH value above 13 was maintained and *n*-butanol was used as extractant.

To our delight, a convenient separation procedure leading to the pure desired isomer **9a** was found using a simple precipitation step with maleic acid, as the maleate of the wrong isomer **16** remained in solution together with untransformed starting material **8**. This way, our product could be consistently isolated in yields around 40% as maleate **9b**, also on larger scale.

Oxidation with Manganese Dioxide. In the beginning of the project, the oxidation of the alcohol **9a** to the aldehyde **10** was elaborated using manganese dioxide (MnO_2) as oxidant[9] (Table 1). Initially, this reaction was sluggish or often completely stalled; thus, conversions were low and rarely exceeded 50% (entry 1). We quickly figured out that the quality of the applied manganese dioxide seemed to be of great importance (only technical grade MnO_2 with a purity of >90% and without specified mesh size was used). Particularly older batches of this reagent tended to compromise the reaction, and we assumed that this was attributed to a lowered activity of MnO_2 after longer storage times. Indeed, improvement was achieved either by using commercially available activated MnO_2 or MnO_2 that had been activated by prolonged heating in our laboratories. A screening for possible additives revealed a beneficial effect of acids, e.g., sulfuric acid (H_2SO_4) or methanesulfonic acid ($MeSO_3H$). However, applying H_2SO_4 as additive in an organic solvent led mainly to decomposition (entry 2). The reaction in pure sulfuric acid worked, albeit in low yields that could be slightly improved when activated MnO_2 was applied (entries 3 and 4). In contrast, when methanesulfonic acid was used as additive, the reactions performed remarkably better. Advantageously, methanesulfonic acid could be added in amounts as low as 10%, allowing longer reaction times without inducing the formation of side products as compared to sulfuric acid. But even here, despite the longer reaction times, further oxidant often had to be added several times in the course of reaction (entries 5 and 6).

The final breakthrough was achieved after identifying *tert*-butanol as superior solvent. Using a combination of *tert*-butanol, 10% of methanesulfonic acid and 4 equiv of MnO_2 (entry 7) led to a clean and complete conversion.

At a later stage, for our pilot-plant batches, Hyflo Super Cel was added, helping to prevent the precipitation of MnO_2 during the reaction and facilitating the filtration. Additionally, the amount of MnO_2 could be slightly reduced to 3 equiv.

Although this procedure worked well and reproducibly in our kilo-laboratories and initially in the pilot plant, the high amount of oxidant needed and the considerable waste stream made the reaction not very viable for larger scale, particularly from an environmental point of view. Furthermore, the oxidation was only feasible using the free imidazole base **9a** but not the maleate **9b** that was obtained during the separation process of the product mixture of the hydroxymethylation reaction.

Unfortunately, the release of the maleate **9b** proved to be problematic, since an aqueous-based release and extraction seemed to be impossible due to the good water solubility of the imidazole **9a**. Hence, we scrutinized the use of an alcoholate or a solid anorganic base such as potassium carbonate (K_2CO_3) in an appropriate alcoholic solvent. While with alcoholates some side products occurred, K_2CO_3 required elevated temperatures that in turn led to evolution of carbon dioxide. Finally, we found the optimal conditions by applying potassium phosphate in *tert*-butanol. This offered the additional advantage that the same solvent could be used for the release of **9a** and for the subsequent oxidation reaction of **9a** to **10**.

Alternative Oxidation Methods. Taking into account all the above-mentioned disadvantages, a better oxidation method was undoubtedly needed. We investigated a couple of different commonly used oxidation protocols (Table 2), including transition-metal catalyzed oxidations with sodium wolframate,[10] ruthenium trichloride,[11] and tetra-*N*-propylammonium perruthenate[12] (TPAP) using hydrogenperoxide (H_2O_2)/*N*-morpholine-*N*-oxide (NMO) as oxidants, respectively, and the trichloroisocyanuric acid (TCCA)/2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) system.[13] These protocols either did not work at all (entries 1−3) or delivered only modest yields of **10**, even in the presence of high amounts of expensive catalyst (entries 4, 5). Therefore, we decided to switch to a hypochlorite−TEMPO-based oxidation procedure.[14]

Hypochlorite−TEMPO-Based Oxidation. Starting the optimization experiments with the free base **9a**, the elaboration

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Table 1. **Oxidation of the alcohol 9a to the aldehyde 10 with mangenese dioxide**

entry	time, h	temp., °C	solvent	additives	MnO_2[a]	yield (**10**) %
1	16	reflux	DCM	–	**C**[c]	–[b]
2	1	reflux	MeCN	5% H_2SO_4 (10% aq)	**A**	dec
3	3	80	H_2SO_4 (10% aq)	–	**C**[c]	36
4	3	85	H_2SO_4 (10% aq)	–	**B**[c]	51
5	15	50	MeOH	10% $MeSO_3H$	**B**[c]	56
6	18	reflux	DCM	10% $MeSO_3H$	**B**[c]	94
7	15	80	t-BuOH	10% $MeSO_3H$	**B**	88

[a] **A** = MnO_2 activated at 150 °C overnight in vacuo. **B** = commercially activated MnO_2. **C** = unactivated MnO_2. [b] Incomplete conversion. [c] Fresh equivalents of MnO_2 added after filtration several times during reaction.

Table 2. **Alternative oxidation methods of the alcohol 9a to the aldehyde 10**

entry	oxidant	catalyst	conversion %	comments
1	H_2O_2	Na_2WO_4	–	no conv.
2	H_2O_2	$RuCl_3$	–	no conv.
3	H_2O_2/NMO	$RuCl_3$	–	minimal conv.
4	TCCA	TEMPO	~30	–
5	NMO	$[Pr_4N]RuO_4$	30	isolated yield, 8% catalyst

seemed initially a little laborious, and first trials were not successful, as under standard conditions ($NaHCO_3$ with KBr) mainly an ipso-substitution of the hydroxymethyl group with bromine (compound **18**) as well as a further aromatic substitution furnishing the dibrominated compound **19** was observed (Figure 2, Table 3, entry 1). Working without KBr as additive in DCM as solvent led exclusively to ipso-chlorination[15] (compound **20**, entry 2), while in ethyl acetate the reaction remained incomplete with only >40% conversion together with amounts of chlorinated byproduct (entry 3).

Finally, switching to another protocol, adding sodium iodide (NaI) instead of KBr promised to be a better alternative. At the beginning, 2.0 equiv of NaI were needed to prevent the occurrence of chlorinated byproduct along with a minimum of 2.0 equiv of NaOCl to observe a noteworthy conversion (Table 4, entries 1 and 2). Lowering the amount of NaI induced a distinct formation of the undesired chlorinated byproduct (e.g., **20**), also when the amount of hypochlorite was reduced at the same time (entry 3). The optimum temperature range was identified within 10−22 °C; below this temperature, accumulation was risked; at temperatures higher than 25 °C, TEMPO was deactivated[14] (entry 4). The reaction appeared relatively unsusceptible to the applied amount of TEMPO, as it worked almost equally well with only 0.01 equiv of this reagent; using 0.03 equiv afforded an only marginally higher yield (compare entries 5 and 6, Table 4). A considerable improvement could be achieved by increasing the pH value by adding more sodium hydrogen carbonate solution. Hereby, a nearly quantitative conversion was reached virtually immediately after the complete addition of the hypochlorite (entry 7). Moreover, it could be shown that an additional organic solvent was not required but the reaction could be carried out solely in water (entry 8).

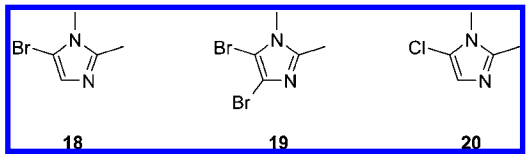

Figure 2. **Byproducts of the hypochlorite−TEMPO-based oxidation of the alcohol 9a.**

Subsequently, these optimized conditions were applied to the oxidation starting from the maleate **9b**. In order to adjust the proper pH value, NaOH solution was used. The reaction ran smoothly and completely with a slight excess (5%) of NaOCl (1.58 equiv) with respect to iodide and 0.01 equiv of TEMPO, using water as the only solvent (entry 9).

A starting pH of >6 was required to ensure a sufficient reaction rate, quickly ascending to 11−12 during the NaOCl dosing, resulting in a particularly fast reaction in this pH range (Figure 3). After completion of the NaOCl addition, the pH decreased to pH = 10 within 3 h and to pH = 8 after further 15 h.

These observations suggested to start the oxidation directly at pH 11−12 by adding the appropriate volume of NaOH from the beginning. This led indeed to an improvement, especially with regard to the amount of NaI that could be considerably reduced without any noticeable ipso-chlorination. Thus, the following optimized conditions were elaborated: pH = 11−12 (adjusted with NaOH), 0.01 equiv of TEMPO, 0.10 equiv of NaI, and 1.15 equiv of NaOCl at 8−20 °C (entry 10). Using these conditions, the reaction went to completion in usually less than an hour. The excess of oxidant was destroyed by sodium thiosulfate, and after workup the product **10** was telescoped to the next stage without isolation.

Stobbe Reaction. The following step, the Stobbe condensation, was initially elaborated as a fast-track solution using an excess of 10 equiv of diethyl succinate and 5 equiv of sodium ethylate. After completion of the reaction, the product **11** had to be extracted into water in order to remove the remaining diethyl succinate. Either a complete removal of the solvent or an extensive azeotropic distillation was mandatory to satisfyingly run the upcoming cyclization in the presence of the water-sensitive acetic anhydride. Although this could still be conducted in kilo-lab scale, it was obviously not very suitable for the pilot plant, also under economical aspects. Hence, we concentrated our efforts on the reduction of the applied amount of diethyl succinate. Although it appeared at the beginning that the amount of diethyl succinate could be reduced easily, we had to recognize

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Table 3. **Initial experiments on the hypochlorite−TEMPO-based oxidation of the alcohol 9a to the aldehyde 10**

entry	time, h	temp., °C	solvent	oxidant	additives	yield (**10**) %
1	6	0	DCM	NaOCl/TEMPO	$NaHCO_3$/KBr	—[a]
2	15	0−RT	DCM	NaOCl/TEMPO	$NaHCO_3$	—[b]
3	15	10−RT	EE	NaOCl/TEMPO	$NaHCO_3$	<40[c]

[a] Mixture of **18** and **19**. [b] Mainly ipso-chlorinated product **20**. [c] >50% starting material; chlorinated byproduct.

Table 4. **Optimization of the hypochlorite−TEMPO-based oxidation of the alcohol 9a to the aldehyde 10**

entry	temp., °C	NaI equiv	NaOCl[a] equiv	TEMPO equiv	base (aqueous solution)	product composition SM **9**/ product **10**/ chlorin. byproduct %
1	15	2.0	1.15	0.02	7.5 vol. $NaHCO_3$ (sat.)	65/21/0[b]
2	15	2.0	2.0	0.02	7.5 vol. $NaHCO_3$ (sat.)	4/79/0[b]
3	22	1.0	1.5	0.02	7.5 vol. $NaHCO_3$ (sat.)	21/57/9[b]
4	30	1.0	1.5	0.02	7.5 vol. $NaHCO_3$ (sat.)	32/45/9[b]
5	22	2.0	2.1	0.01	7.5 vol. $NaHCO_3$ (sat.)	5/78/0[b]
6	22	2.0	2.1	0.03	7.5 vol. $NaHCO_3$ (sat.)	2/83/0[b]
7	22	2.0	2.1	0.01	15 vol. $NaHCO_3$ (sat.)	0/90/1[c]
8	22	2.0	2.1	0.01	15 vol. $NaHCO_3$ (sat.)	0/90/1[c,e]
9	15	1.5	1.58	0.01	3.0 mL NaOH (10%)	3/97/0[d,e]
10	15	0.1	1.15	0.01	1.9 mL NaOH (40%)	0/97/0[d,e]

[a] Addition time 55 min. [b] Determined by HPLC 30 min after hypochlorite addition. [c] Determined by HPLC 10 min after hypochlorite addition. [d] Determined by HPLC overnight after hypochlorite addition using maleate **9b** as starting material. [e] No extra solvent used.

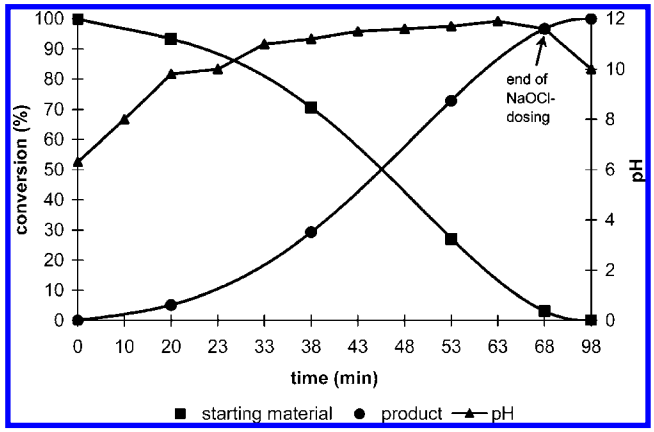

Figure 3. **Conversion and pH value in the course of the hypochlorite−TEMPO-based oxidation of the alcohol 9a to the aldehyde 10.**

that the decrease was limited to a minimum of 4.0 equiv (Table 5, entries 1 and 2).

The systematic screening of the reaction conditions included the stoichiometry of the applied reagents, their mode of addition, and possible solvents. These studies revealed that a good conversion was already reached with only 1.1 equiv of diethyl succinate and 1.1 equiv of sodium ethylate. The order and time of addition were absolutely decisive for this remarkable reduction of reagents. If sodium ethylate was dosed as last component, as done initially, the above-mentioned reduction of the stoichiometry of diethyl succinate led to a considerable decrease of conversion to 62% and an even greater loss in yield (entry 3). On the other hand, when the aldehyde **10** was added to a preformed mixture of diethyl succinate and sodium ethylate at 50 °C, the reaction proceeded in a quasi-instantaneous, dose-controlled manner. The yield increased proportionally with the addition time (entries 4−6). An optimum was reached with a conversion of >90% after 4 h (>80% after 1 h). In practice, the reaction was run using 2.5 equiv of diethyl succinate (entry 7) and 1.4 equiv of sodium ethylate with an addition time for the aldehyde **10** of 3−4 h for maximum yields.

A possible rationalization of these outcomes could derive from the mechanism of the Stobbe condensation[16] itself, as depicted in Scheme 4. The striking attribute of this mechanism is the generation of the γ-lactone **21**. This lactone can either decay to the desired product **11a** or react with a second molecule of aldehyde **10**, leading to the formation of a double-alkylated adduct **22**. Although this kind of adduct is known from literature,[17] we were not able to clearly prove its existence in our studies. We assume that any **22** formed in the course of the reaction would be prone to polymerization. Indeed, in the normal addition mode the side products were obtained as a tarry mass not suitable for analytical investigation.

Two possibilities exist to suppress the formation of the unwanted side product **22**, one consisting in the use of a reasonable excess of succinate to shift the equilibrium to γ-lactone **21**, reducing the amount of "free" aldehyde **10** that is able to undergo double-coupling, as it was realized in the initial procedure. The other possibility comprises the slow addition of the aldehyde **10** as final component with the same goal, to keep the aldehyde concentration as low as possible. Without doubt, the latter variant represented the better option.

The workup and isolation of the Stobbe condensation product **11a** proved to be tedious. Initial attempts to acidify the reaction mixture and to precipitate the product as a hydrochloride salt after azeotropic distillation were successful on small scale but did not work anymore in larger batches. This was due to prolonged distillation times, resulting in esterification with remaining ethanol or a transesterification with the present excess

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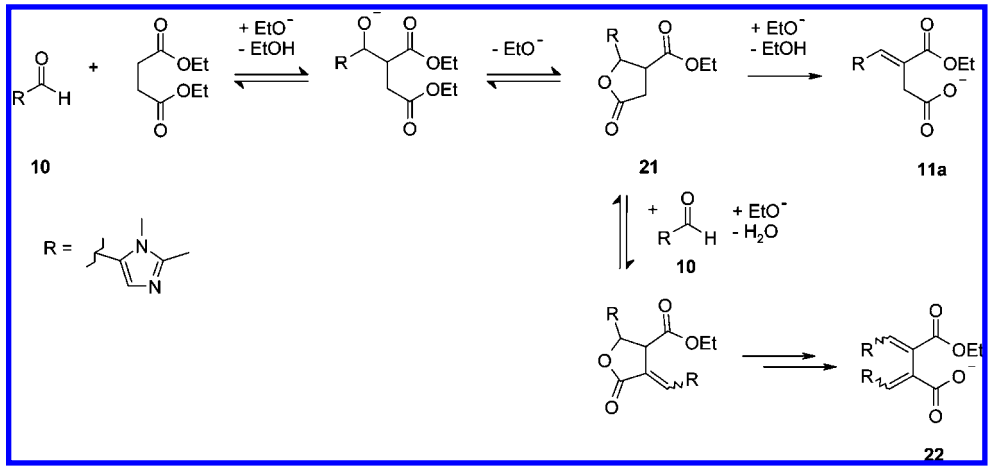
(17) Miguel del Corral, J. M.; Gordaliza, M.; Castro, A. M.; Salinero, M. A.; Dorado, J. M.; San Feliciano, A. *Synthesis* **2000**, 154–164.

Table 5. **Stobbe reaction of the aldehyde 10 with diethyl succinate**

entry	addition time h	diethyl succinate equiv	sodium ethylate equiv	temp. °C	conversion %
1	0.5[a]	7.5	3.0	50	88[c]
2	0.5[a]	4.0	2.0	50	75[c]
3	2[a]	1.1	1.1	50	62
4	1[b]	1.1	1.1	50	82
5	2[b]	1.1	1.1	50	85
6	4[b]	1.1	1.1	50	93
7	3−4[b]	2.5	1.4	50	95

[a] Addition of sodium ethylate. [b] Addition of aldehyde **10**. [c] Isolated yield.

Scheme 4. **Mechanism of the Stobbe condensation**



of diethylsuccinate, respectively, leading to the formation of the corresponding diester of **11a**. Therefore, we decided not to isolate the Stobbe adduct but to telescope it directly to the next step.

Intramolecular Cyclization. The starting point for the cyclization of the Stobbe adduct **11** to the benzimidazole **12** was a kilo-lab procedure using the crude isolated condensation residue (vide supra) in an excess of pure acetic anhydride (6.5 vol) and sodium acetate (Scheme 2).[18] Evidently, this was not viable for further scale-up, so we started the process improvement using the basic product mixture obtained under the optimized conditions.

In order to reasonably reduce the amount of acetic anhydride, the mixture had to be free of remaining alcohols (*tert*-butanol from the oxidation step, ethanol from the Stobbe reaction). This was easily achieved by careful azeotropic removal of these solvents with toluene. As a result, the stoichiometry of acetic anhydride could be reduced to 2.2 equiv, which was added over a period of 1−2 h to a warm toluene solution (75−85 °C), ensuring a relatively good cyclization. Surprisingly, upon further scale-up from 5 to 20 kg in the pilot plant a nonstirrable mass was formed during the azeotropic destillation that even damaged the slide ring sealing of the stirrer. The trouble shooting consisted of the addition of acetonitrile that in following batches effectively prevented agglutination. From that moment on toluene was completely substituted by acetonitrile, already at the stage of the azeotropic distillation. Although the process appeared rather robust at this point, an unsteadiness in yield was nevertheless noticed (yields 48−67%).

According to our observations, the reaction went considerably smoother when acetic anhydride was added immediately in larger portions compared to the originally longer addition times. A putative explanation could be derived from Scheme 5.[19] From a mechanistic point of view, for a complete cyclization, a minimum of 2 equiv of acetic anhydride is necessary; otherwise the reaction would stop at at the stage of one of the intermediates. These intermediates, particularly the conjugated ester **23**, are probably prone to side reactions or degradation (polymerizations etc.). Thus, either the large excess of acetic anhydride as applied for our initial kilo-lab batches, or presumably an inverse addition regime should be able to circumvent the problem.

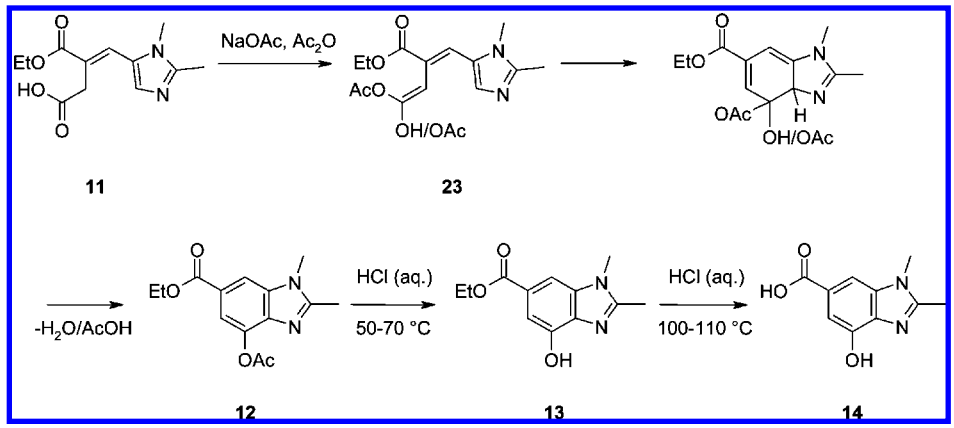
Indeed, if the addition order was inverted, and the product **11** of the Stobbe condensation was added to a preheated mixture of acetic anhydride and acetonitrile, the reaction seemed to be much more consistent and reproducibly delivered the expected benzimidazole **12** in higher yields.

In order to strengthen our hypotheses, an in-depth monitoring of both addition variants via reaction-IR was performed. Figure 4 displays a stacked IR spectrum acquired under the original conditions, i.e. adding acetic anhydride to a solution of starting material **11** at 85 °C over a period of 2 h. The formation of an intermediate at 1570 cm^{-1} is striking, ascending shortly after starting of the acetic anhydride dosing, then slowly decreasing during further stirring after the end of dosing. As this kind of accumulation is not noticed under the inverted dosing regime, this indeed seems to support our assumptions. That barely no

(18) Borsche, W.; Kettner, S.; Gillies, M.; Kuhn, H.; Manteuffel, R. *Liebigs Ann. Chem.* **1936**, *526*, 1–22.

(19) Baraldi, P. G.; Cacciari, B.; Spaluto, G.; Romagnoli, R.; Braccioli, G.; Zaid, A. N.; Pineda de las Infantas, M. J. *Synthesis* **1997**, 1140–1142.

Scheme 5. **Mechanism of the intramolecular cyclization of the imidazole 11 to the benzimidazole 12**



product peaks appear in this spectrum is due to the fact that most of the product **12** has precipitated together with byproduct in the reaction slurry and therefore cannot be monitored by IR. On the contrary, the inverted addition delivered a clear solution over the entire reaction course.

For the inverted addition (Figure 5) a typical IR output for a classical dose-controlled reaction is obtained. At 1710 cm^{-1} the peak caused by the phenyl ester moiety of the cyclized product **12** steeply rises right from the beginning of dosing, whereas a second product peak at 1770 cm^{-1} is partly overlapped by an absorption of acetic anhydride. The consumption of acetic anhydride in the course of the reaction is noticeable at 1820 cm^{-1}.

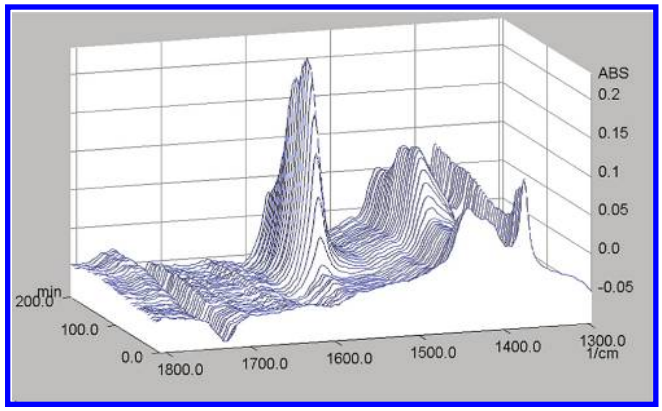


Figure 4. **Reaction-IR of the Stobbe cyclization of the imidazole 11 to the benzimidazole 12 - normal addition.**

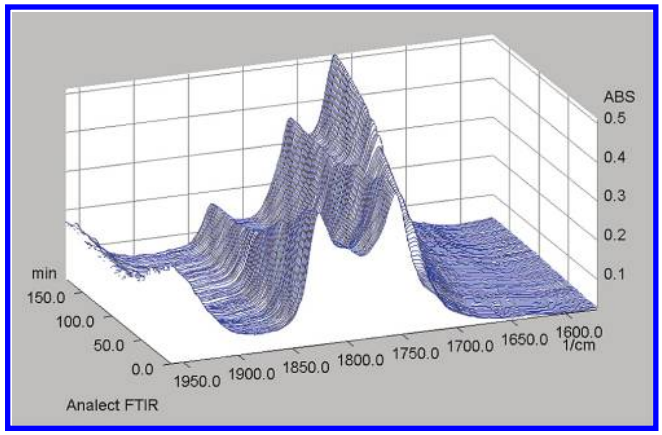


Figure 5. **Reaction-IR of the Stobbe cyclization of the imidazole 11 to the benzimidazole 12 - inverse addition.**

The upcoming deacetylation followed by saponification of the ester group was achieved with hydrochloric acid in two stages without any special problems (Schemes 2 and 5).

For the deacetylation, the acid was added at 50−70 °C until a pH value of 0.1−0.6 was reached. This was sufficient to immediately cleave the acetyl group (**13**). For the saponification to the carboxylic acid **14**, the solvent was stripped at elevated temperature under ambient pressure followed by subsequent heating at 100−110 °C.

Amide Formation. Although the final amide formation as a standard reaction was not expected to cause many problems, it turned out to be troublesome (Scheme 2).

Preliminary experiments to achieve the amidation via the acid chloride **15** seemed not very promising at the beginning. Thus, we decided to postpone a comprehensive elaboration to a later point in time. Furthermore, a direct conversion of the ethyl ester **13** to the amide **7** with a number of amine sources, irrespective of the nature of the applied amine and the reaction conditions (up to 140 °C in various solvents), afforded either no product at all or complex mixtures.

The reaction with carbonyldiimidazole (CDI) constituted a quick solution. But even this conversion was challenging. More than 2 equiv of CDI were mandatory due to the presence of the free phenol group, consuming one equivalent of CDI. This led to an increased evolution of carbon dioxide. Subsequently, an aqueous solution of dimethylamine was added, the solvent (DMF) was removed, and the product **7** was precipitated as hydrochloride in only 50% yield.

Concerning these drawbacks, a better alternative was urgently needed. A more thorough screening of the conditions for the formation of the acid chloride **15** showed that this could be conveniently obtained in acetonitrile at 70−80 °C with 1.4 equiv of thionyl chloride. Unfortunately, the acid chloride **15** is only sparingly soluble in acetonitrile, thus forming a suspension that is not suitable for a quench with aqueous dimethylamine solution. The application of either dimethylamine in THF or dimethylamine hydrochloride followed by triethylamine appeared to be feasible solutions. The latter variant was finally chosen, mainly for economical reasons, and worked out for our pilot-plant batches.

Conclusion

In summary, a feasible large-scale access to the benzimidazole BYK308944 (**7**) has been found. This new route allows the use of much cheaper starting materials and exhibits a shorter and also safer alternative compared to the original medicinal chemistry synthesis.

All difficulties arising in this new route could be successfully overcome: Although the hydroxymethylation of 1,2-dimethylimidazole (**8**) could not be accomplished in a selective manner, the mixture (**8**, **9a**, **16**, **17**) could be successfully separated by precipitation with maleic acid. The upcoming oxidation of alcohol **9a** to the aldehyde **10** was initially elaborated utilizing manganese dioxide as oxidant, switching later to a more economic hypochlorite−TEMPO-based oxidation protocol. For this optimization a variety of variables had to be taken into account.

Due to their mechanistically complex nature, a lot of effort had to be put into the challenging Stobbe reaction of aldehyde **10** with diethyl succinate and the subsequent cyclization of imidazole **11** to the benzimidazole **12**. Finally, the amide formation could be achieved by transformation of the carboxylic acid **14** to the acid chloride **15** and subsequent reaction of **15** with dimethylamine hydrochloride.

In order to facilitate the whole synthesis, most of the reactions were elaborated to be telescoped to the appropriate next stage. In fact, in this eight-step sequence only two intermediates and the final product had to be isolated. Finally, all stages were carried out in pilot-plant scale.

Experimental Section

General. All chemicals were purchased from the major chemical suppliers and used without any further purification. 1,2-Dimethylimidazole (**8**) and 2-amino-3-nitrophenol (**1**) were purchased from Merck (46 €/kg) and AK-Scientific (450 $/100 g), respectively. Manganese dioxide of the following qualities has been applied: Screening: **A** = Merck (105957, powder LAB, >90%), **B** = Aldrich (63548, technical, activated, >90%); Pilot-plant batches = Merck (8.05958, precipitated, active, >90%). Hypochlorite solution was purchased from Hedinger (S012121001001) and the assay measured before use. The progress of the reaction was monitored on Macherey-Nagel HPTLC plates Nano-SIL 20 UV_{254} (0.20 mm layer, nano silica gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. The reactions to **11**, **12**, and **14** were additionally monitored by HPLC on a Merck Hitachi HPLC-system using the following conditions: Zorbax SB C8, 150 cm × 4.6 mm × 3.5 μm, flow 1.0 mL/min; wavelength = 275 nm; temperature 30 °C; eluent A = MeCN, B = 10 mmol K_2HPO_4; injection volume: 10 μL of ∼0.3% solution in A/B, 1:1 v/v; gradient (0−5 min) A = 2%, B = 98%; (35 min) A = 60%, B = 40%; (38−45 min) A = 2%, B = 98%. For the detection of **9b** and **10**, the same HPLC method and conditions were used with the exception of wavelength = 229 nm. Column chromatography was performed with Merck silica gel 60 (70−230 mesh ASTM) with the solvent mixtures specified in the corresponding experiment. Spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). Melting points (mp) were taken in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker AV 300 FT-NMR spectrometer at a frequency of 300 MHz, or a Bruker AV 400 FT-NMR spectrometer at a frequency of 400 MHz. ^{13}C NMR spectra were acquired with a Bruker AV 400 FT-NMR spectrometer at a frequency of 100 MHz. DMSO-d_6 was used as solvent. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) or DMSO as an internal standard (^{1}H: δ_{TMS} = 0.00 ppm; ^{13}C δ_{DMSO} = 39.50 ppm). High-resolution mass spectra were obtained on an Agilent LC/MSD TOF instrument using electrospray ionization (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer. Karl Fischer titration was performed on a Metrohm KF Coulometer 756 KF (Metrohm 774 Sample Oven Processor). FT-IR spectra were recorded using an Analect ChemEye from Hamilton Sundstrand-Applied Instrument Technologies with a Fibreoptic MIR Diamond ATR-Probe from IFS Aachen on a FlexyLab-reactor system by Systag.

(1,2-Dimethyl-1H-imidazol-5-yl)methanol Maleate (9b). Hydroxymethylation. At a temperature of 10−25 °C, 1,2-dimethylimidazole (**8**) (10.0 kg, 104 mol) and sodium acetate (17.1 kg, 208 mol) were dissolved under stirring in formaldehyde (78.0 L, 37% aqueous solution) and acetic acid (14.0 L, 99%). The reaction mixture was heated to 90−96 °C and stirred for 43−50 h. Subsequently, the mixture was cooled to 10−50 °C and diluted with water (40.0 L). A pH of ≥13 was adjusted by slow addition (0.5−1.0 h) of sodium hydroxide solution (65.0 L, 40% aqueous solution). 1-Butanol (55.0 L) was added at 10−25 °C, and the layers were separated. The organic layer was collected, and the aqueous phase was washed with 1-butanol (2 × 27.0 L). The combined organic phases were washed (15 min) with saturated aqueous sodium thiosulfate solution (2 × ∼25.0 L) at 10−25 °C. The solvent (95−100 L) was stripped under vacuum (50−75 °C) and the product precipitated to some extent. The obtained crude mixture, consisting of the two regioisomers **9a** and **16**, dihydroxylated product **17**, remaining starting material **8**, and a residual amount of 1-butanol (∼10 L), was directly used in the following step (salt formation). **Precipitation as Maleic Acid Salt.** At a temperature of 40−60 °C, the crude mixture obtained in the formylation step was dissolved in 2-propanol (33.0 L), and maleic acid (8.9 kg, 76.7 mol) was added. The solution was heated to 74−82 °C, stirred for 10−60 min under these conditions, cooled to 35−45 °C, and inoculated with crystals of (1,2-dimethyl-1*H*-imidazol-5-yl)methanol maleate (**9b**). After seeding, the mixture was cooled to 15−25 °C within 1−3 h, and stirring was continued for 2−72 h. Finally, the suspension was cooled to 7−15 °C and stirred for 1−12 h. At this temperature, the suspension was centrifuged, and the product was washed with 2-propanol (8−12 L) and dried overnight *in vacuo* at 50 °C, affording 10.1 kg (40% yield) of the pure title compound **9b** (stoichiometric ratio with respect to maleic acid 1:1): mp 105−107 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.55 (s, 3 H, 2-CH_3), 3.67 (s, 3 H, N−CH_3), 4.53 (s, 2 H, $C\underline{H}_2OH$), 6.05 (s, 2 H, maleic acid), 7.40 (s, 1 H, 4-H). **Free base 9a**: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.24 (s, 3 H, 2-CH_3), 3.48 (s, 3 H, N−CH_3), 4.37 (s, 2 H, $C\underline{H}_2OH$), 5.02 (bs, 1 H, $CH_2O\underline{H}$), 6.60 (s, 1 H, 4-H). ^{13}C NMR (DMSO-d_6,

100 MHz): δ = 12.9, 29.9, 52.8, 125.0, 131.6, 144.7. Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 56.56; H, 7.87; N, 22.09. HRMS (ESI) *m/z* $C_6H_{11}N_2O$ $[M + H]^+$ Calcd: 127.0866. Found: 127.0872.

1,2-Dimethyl-1*H*-imidazole-5-carbaldehyde (10). Variant A. The reaction vessel was charged at room temperature with (1,2-dimethyl-1*H*-imidazol-5-yl)methanol maleate (**9b**) (10.0 kg, 41.2 mol), sodium iodide (0.62 kg, 4.13 mol), TEMPO (39.0 g, 0.25 mol), and water (7.0 L). At 15−25 °C, sodium hydroxide solution (8.5 kg, 40% aqueous solution) was slowly added (0.5−1.5 h) under stirring until a pH value of 11.5−12.5 was reached. At 8−20 °C, sodium hypochlorite solution (∼25 L, ∼47 mol, 1.15 equiv, ∼10% aqueous solution) was slowly added (2−4 h) under stirring. The mixture was stirred at 8−20 °C until complete conversion of the starting material was accomplished (15−45 min, 20 h max). Sodium thiosulfate (1.97 kg, 12.5 mol) was added at 10−25 °C and the reaction mixture stirred for further 30−60 min under these conditions, inducing a color change from green to yellow. The suspension was filtered and the solid washed with acetonitrile (34 L). The combined biphasic liquids were retransferred into the reaction vessel and stirred for 15 min. The layers were separated, and the aqueous phase was extracted with acetonitrile (2 × 34 L). The combined organic layers were heated to 60−75 °C, and the solvent was removed in vacuo (90−95 L). If the water content of the residue was higher than 1%, more acetonitrile (20 L) was added and stripped at 60−75 °C in vacuo. The residue was filtrated and the filter cake washed with acetonitrile (5 L). The crude product solution of **10** was directly submitted to the next step (Stobbe condensation). **Variant B.** At room temperature, the reaction vessel was charged with (1,2-dimethyl-1*H*-imidazol-5-yl)methanol (**9a**) (500 g, 3.96 mol), manganese dioxide (1.38 kg, 15.5 mol), methanesulfonic acid (25.7 mL, 0.4 mol), and *tert*-butanol (6.25 L). The reaction mixture was heated to 75−85 °C and stirred for 18−22 h. After completion of the reaction, the mixture was cooled to 35−45 °C and filtered, and the filter cake washed with a mixture of methanol/dichloromethane (∼1 L, 1:1). The filtrate was heated to 50−100 °C, the solvent was removed in vacuo, and the remaining solid was dried overnight in vacuo at 50 °C, affording 490 g (99% yield) of the pure title compound **10**: mp 73−75 °C. **Variant C.** An inertized reaction vessel was charged at room temperature with (1,2-dimethyl-1*H*-imidazol-5-yl)methanol maleate (**9b**) (10.0 kg, 41.2 mol), potassium phosphate (17.5 kg, 82.4 mol), and *tert*-butanol (50.0 L). This mixture was heated to 75−85 °C for 1−2 h under stirring. Subsequently, it was cooled to 60−70 °C, filtrated over a pressure filter, and rinsed with hot (60−70 °C) *tert*-butanol (30.0 L). The solution was transferred into a second inertized vessel, and Hyflo Super Cel (10.0 kg), manganese dioxide (10.0 kg, 124 mol), and methanesulfonic acid (0.2 L, 3.1 mol) were added. The mixture was heated to 75−85 °C for 14−18 h under stirring, cooled again to 60−70 °C followed by filtration over a pressure filter. The filter cake was washed with hot (60−70 °C) *tert*-butanol (40.0 L). All of the filtrate was transferred back to the vessel and concentrated *in vacuo* at 45−65 °C. This concentrated solution was used without further purification for the next step (Stobbe condensation). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.38 (s, 3 H, 2-CH_3), 3.80 (s, 3 H, N−CH_3), 7.77 (s, 1 H, 4-H), 9.63 (s, 1 H, CHO). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 12.6, 31.8, 131.6, 142.7, 152.7, 179.3. Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 56.59; H, 6.47; N, 22.04. HRMS (ESI) *m/z* $C_6H_9N_2O$ $[M + H]^+$ Calcd: 125.0709. Found: 125.0713.

4-(1,2-Dimethyl-1*H*-imidazol-5-yl)-3-(ethoxycarbonyl)but-3-enoic Acid (11). A stirred mixture of diethyl succinate (17.5 kg, 100 mol) and sodium ethylate solution (19.2 kg, 56.5 mol, 20% in ethanol) was heated to 50−55 °C. At this temperature, a solution of 1,2-dimethyl-1*H*-imidazole-5-carbaldehyde (**10**) (5.0 kg, 40.3 mol, dissolved in 15.0 L acetonitrile) was slowly added (3−4 h), and stirring was continued for 1−12 h under these conditions. If the amount of remaining starting material was higher than 2% (TLC), more sodium ethylate solution (∼1.4 kg) was added over 15−30 min and the reaction time extended for further 1−2 h. When complete transformation was accomplished, the solvent was removed *in vacuo* at 60−75 °C and acetonitrile (42 L) was added. Another portion of solvent (∼20 L) was removed *in vacuo* at 50−70 °C. The resulting solution of the title product **11** was directly transferred to the next reaction step (cyclization). A product sample was isolated by removing the solvent (rest amounts of acetic acid were detected). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.26 (t, J = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 2.35 (s, 3 H, 2-CH_3), 3.48 (s, 2 H, CH_2), 3.56 (s, 3 H, N−CH_3), 4.20 (q, J = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 7.15 (s, 1 H, C═H), 7.52 (s, 1 H, 4-H), 12.60 (bs, 1 H, COOH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.2, 14.1, 30.3, 34.3, 60.5, 122.4, 126.2, 127.3, 130.8, 166.8, 171.5. HRMS (ESI) *m/z* $C_{12}H_{17}N_2O_4$ $[M + H]^+$ Calcd: 253.1183. Found: 253.1173.

Ethyl 4-(Acetyloxy)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (12). The vessel was charged with acetic anhydride (9.9 kg, 97 mol) and acetonitrile (9 L), and the mixture was heated to 75−85 °C. At this temperature, the residual solution from the Stobbe condensation (4-(1,2-dimethyl-1*H*-imidazol-5-yl)-3-(ethoxycarbonyl)but-3-enoic acid) (**11**) was added under vigorous stirring over a period of 1−2 h. Stirring was continued for 45−90 min under these conditions. If the amount of remaining starting material was higher than 2% (TLC), more acetic anhydride (∼0.4 kg) was added over 15−30 min and the reaction time extended for further 1−2 h. The reaction solution of the title compound was used without isolation for the next reaction step (cleavage of the acetyl group). The analytical data were obtained by taking a sample and removing the solvent: mp: 166−169 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.33 (t, J = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 2.37 (s, 3 H, 2-CH_3), 2.56 (s, 3 H, $COCH_3$), 3.81 (s, 3 H, N−CH_3), 4.35 (q, J = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 7.52 (d, J = 1.3 Hz, 1 H, 7-H), 8.04 (d, J = 1.3 Hz, 1 H, 5-H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.5, 14.2, 20.6, 30.2, 60.7, 109.6, 114.9, 123.1, 137.3, 138.4, 140.0, 156.0, 165.6, 168.7. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.83; N, 10.06. HRMS (ESI) *m/z* $C_{14}H_{17}N_2O_4$ $[M + H]^+$ Calcd: 277.1183. Found: 277.1189.

Ethyl 4-Hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (13). At a temperature of 50−70 °C, water (18 L) was added to the reaction solution of ethyl 4-(acetyloxy)-1,2-

dimethyl-1*H*-benzimidazole-6-carboxylate (**12**) and the pH adjusted with hydrochloric acid (~18 L, 20% aqueous solution) to a value of 0.1−0.6. Under these conditions, the acetyl protecting group was cleaved. The title compound was not isolated.

4-Hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylic Acid (14). At ambient pressure, the solvent (~50 L) was removed at 80−105 °C and the reaction mixture stirred at 102−112 °C for 1.5−2.5 h. Another portion of solvent (2 × ~5 L) was stripped at this temperature (without application of vacuum) and the remaining mixture stirred for 1.5−2.5 h. If the amount of remaining ethyl 4-hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate (**13**) was higher than 2% (HPLC), more hydrochloric acid (~4 L) was added over a period of 5−15 min at 50−70 °C, the reaction time extended for further 1.5−2.5 h, and the solvent removed as described above. At 50−70 °C, water (23 L) was added over a period of 5−30 min. A pH value of 4.5−5.0 was adjusted by addition of sodium hydroxide solution (40% aqueous solution) over a period of 0.5−1 h, and a thick suspension was obtained. The suspension was cooled to 15−30 °C over 1−4 h, to 8−15 °C over 0.5−2 h, stirred for 0.5−2 h and centrifuged. The filter cake was washed with water (~8 L) and dried overnight *in vacuo* at 50 °C affording 5.8 kg (70% yield) of the pure title compound **14**: mp, dec at >300 °C. ^{1}H NMR (D_2O + NaOD, 400 MHz): δ = 2.41 (s, 3 H, 2-CH_3), 3.49 (s, 3 H, N−CH_3), 6.94 (d, J = 1.4 Hz, 1 H, 7-H), 7.07 (d, J = 1.4 Hz, 1 H, 5-H). ^{13}C NMR (D_2O + NaOD, 100 MHz): δ = 12.3, 29.4, 97.0, 111.0, 131.9, 136.0, 136.8, 152.2, 157.3, 176.9. HRMS (ESI) *m/z* $C_{10}H_{11}N_2O_3$ $[M + H]^+$ Calcd: 207.0764. Found: 207.0772.

4-Hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (7). The vessel was charged with 4-hydroxy-1,2-dimethyl-1*H*-benzimidazole-6-carboxylic acid (**14**) (5.0 kg, 24.3 mol), acetonitrile (40 L), dimethylformamide (93 mL, 1.21 mol), and the mixture heated to 75−83 °C. At this temperature, thionyl chloride (4.0 kg, 33.6 mol) was slowly added (2−3 h) under stirring. The mixture containing acid chloride **15** was stirred at 75−83 °C for 1−2 h, cooled to 10−30 °C, and dimethyl ammonium chloride (3.6 kg, 44.1 mol) was added in two portions. Over 1.5−3 h, triethylamine (12.3 kg, 121.6 mol) was added under cooling, maintaining a temperature of 10−30 °C. Finally, water (25 L) was added, the mixture heated to 60−80 °C and the solvent (~47 L) removed *in vacuo*. The reaction mixture was cooled to 10−20 °C over 3 h and stirred further for at least 1 h. The crystallized product **7** was centrifuged and the filter cake washed with water (~10 L). The filter cake was dried overnight *in vacuo* at 55 °C, affording 4.0 kg (70% yield) of the pure title compound **7**: mp, dec at 239−241 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.51 (s, 3 H, 2-CH_3), 2.96 (s, 6 H, N{CH_3}$_2$), 3.69 (s, 3 H, N−CH_3), 6.53 (d, J = 1.3 Hz, 1 H, 7-H), 6.98 (d, J = 1.3 Hz, 1 H, 5-H), 9.95 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.3, 29.8, 34.9, 100.0, 105.7, 130.5, 132.0, 136.9, 147.7, 151.4, 170.9. Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.85; H, 6.50; N, 18.01. HRMS (ESI) *m/z* $C_{12}H_{16}N_3O_2$ $[M + H]^+$ Calcd: 234.1237. Found: 234.1237.

Acknowledgment

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Supporting Information Available

Analytical data of byproducts **18**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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