Organic Process Research & Development **2008,** *12,* 1170–1182

Large-Scale Asymmetric Synthesis of the 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazole BYK 405879: A Promising Candidate for the Treatment of Acid-Related Diseases

Andreas M. Palmer,*[,†] Matthias Webel,*[,‡] Christian Scheufler,[‡] Dieter Haag,[§] and Bernd Müller[§]

NYCOMED GmbH, Department of Medicinal Chemistry and NYCOMED GmbH, Department of Process Chemistry Research, 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:

A process for the synthesis of the potassium-competitive acid blocker BYK 405879 (8) was established based on the approach used in medicinal chemistry (asymmetric hydrogenation of prochiral ketone 15 and Mitsunobu cyclization of the resulting alcohol 34). Several critical reaction steps were optimized. The synthesis of prochiral ketones was accomplished using ethyl 3-(2-methylphenyl)-3-oxopropanoate instead of 1-[1-(2-methylphenyl)vinyl]pyrrolidine, a reagent that was difficult to prepare and possesses limited shelf life. The catalyst loading of the asymmetric hydrogenation step was reduced significantly from a S/C ratio of 100:1 to a S/C ratio of 2500:1 by benzyl protection of ketone 15. After the Mitsunobu cyclization, the removal of byproduct was easily accomplished through acid−base extraction, and pure BYK 405879 (8) was then obtained by means of crystallization in the presence of succinic acid.

1. Introduction

Acid-related diseases, such as gastroesophageal reflux disease (GERD), have a high prevalence and a strong impact on the quality of life of the affected patients.[1,2] Moreover, they represent a significant economical burden. Whereas the most common symptom of GERD is frequent heartburn, more serious diseases including esophagitis and/or esophageal cancer may result if the disease remains untreated. Although the pathogenesis of GERD is complicated, the reflux of gastric acid into the esophagus was identified as one major factor.[3] The inhibition of the gastric proton pump enzyme (H^+/K^+-ATPase) located in the parietal cell provides a valuable approach for the treatment of GERD.[4] Irreversible inhibitors of the H^+/K^+-ATPase (PPIs), e.g. lansoprazole, omeprazole, or pantoprazole have already been available for some time and are a popular choice for the therapy of GERD. Due to its systemic character, the PPI treatment marked a major breakthrough compared to the classical therapy with antacids. Nevertheless, PPIs exhibit substantial interpatient variability and often fail to provide a complete cure. Hence, several pharmaceutical companies are engaged in the development of potassium-competitive acid blockers (P-CABs). Due to their different mode of action (reversible inhibition of the gastric proton pump enzyme), P-CABs might be able to overcome some limitations observed during the PPI treatment of GERD.[5−8]

In the course of our P-CAB lead optimization program, we identified several compounds belonging to the classes of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **3** (e.g., BYK 311319, **4**) and 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles **7** (e.g., BYK 405879, **8**) that are potent reversible inhibitors of the gastric proton pump enzyme and possess promising pharmacological properties.[9,10] Consequently, we designed an asymmetric synthesis that permitted the ready preparation of multigram quantities of target compounds **3** and **7** (Scheme 1).[10,11]

In both classes, the same retrosynthetic strategy was applied comprising the asymmetric catalytic hydrogenation of ketones **1** and **5** and subsequent Mitsunobu cyclization of the resulting

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

† NYCOMED GmbH, Department of Medicinal Chemistry, Konstanz, Germany.

‡ NYCOMED GmbH, Department of Process Chemistry Research, Konstanz, Germany.

§ NYCOMED GmbH, Department of Process Chemistry Development, Singen, Germany.

(1) Modlin, I. M.; Sachs, G. *Acid Related Diseases: Biology and Treatment*; Schnetztor-Verlag: Konstanz, Germany, 1998.

(2) Heartburn, hiatal hernia, and gastroesophageal reflux disease (GERD); NIH: Washington, DC, 2003; Publication No. 03-0882; http://digestive.niddk.nih.gov/ddiseases/pubs/gerd/index.htm.

(3) Vesper, B. J.; Altman, K. W.; Elseth, K. M.; Haines, G. K., III; Pavlova, S. I.; Tao, L.; Tarjan, G.; Radosevich, J. A. *Chem. Med. Chem.* **2008**, *3*, 552–559.

(4) Shin, J. M.; Vagin, O.; Munson, K.; Kidd, M.; Modlin, I. M.; Sachs, G. *Cell. Mol. Life Sci.* **2008**, *65*, 264–281.

(5) Parsons, M. E.; Keeling, D. J. *Expert Opin. Invest. Drugs* **2005**, *14*, 411–421.

(6) Fass, R.; Shapiro, M.; Dekel, R.; Sewell, J. *Aliment. Pharmacol. Ther.* **2005**, *22*, 79–94.

(7) Vakil, N. *Aliment. Pharmacol. Ther.* **2004**, *19*, 1041–1049.

(8) Andersson, K.; Carlsson, E. *Pharmacol. Ther.* **2005**, *108*, 294–307.

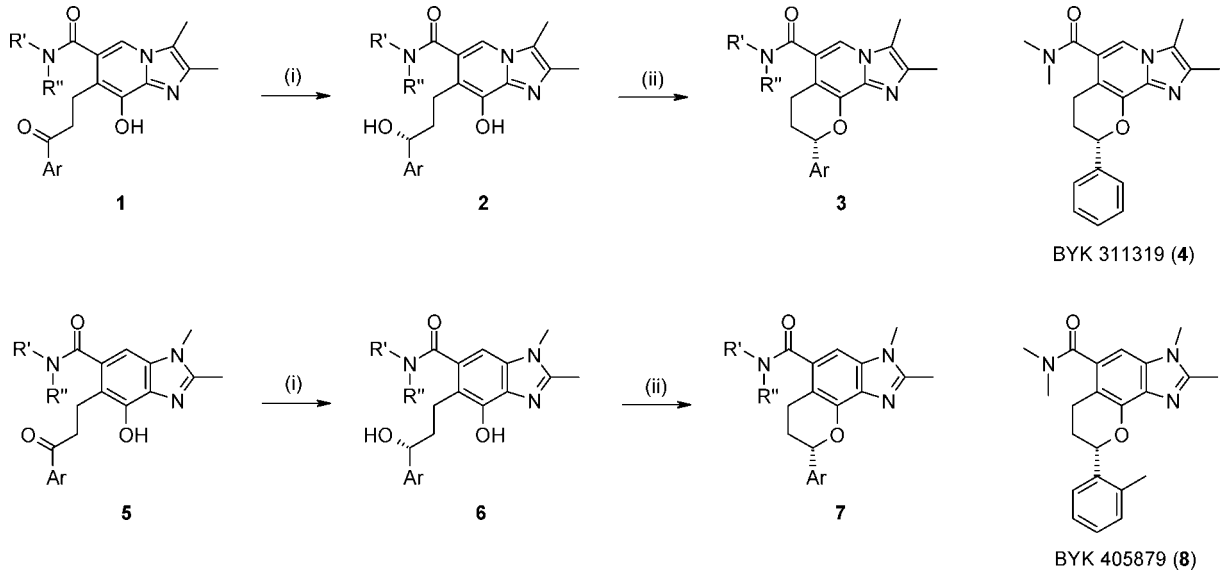
(9) (a) Palmer, A. M.; Grobbel, B.; Jecke, C.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W.-A.; Kromer, W. *J. Med. Chem.* **2007**, *50*, 6240–6264. (b) Buhr, W.; Chiesa, M. V.; Zimmermann, P. J.; Brehm, C.; Simon, W.-A.; Kromer, W.; Postius, S.; Palmer, A. Patent application WO 2005/058325, 2005.

(10) (a) Palmer, A. M.; Chiesa, V.; Holst, H. C.; Le Paih, J.; Zanotti-Gerosa, A.; Nettekoven, U. *Tetrahedron: Asymmetry* **2008**, *19*, 2102−2110. (b) Buhr, W.; Chiesa, M. V.; Zimmermann, P. J.; Brehm, C.; Palmer, A.; Postius, S.; Kromer, W.; Simon, W.-A.; Senn-Bilfinger, J. Patent Application WO 2004/087701, 2004. (c) Chiesa, M. V.; Palmer, A.; Buhr, W.; Zimmermann, P. J.; Brehm, C.; Simon, W.-A.; Postius, S.; Kromer, W.; Zanotti-Gerosa, A. Patent application WO 2006/136552, 2006.

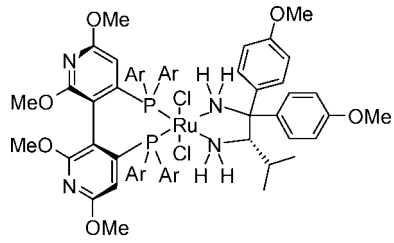
(11) (a) Palmer, A. M.; Nedden, H.; Zanotti-Gerosa, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1310–1327. (b) Palmer, A.; Buhr, W.; Zimmermann, P. J.; Brehm, C.; Chiesa, M. V.; Zanotti-Gerosa, A. Patent application WO 2007/141253, 2007.

10.1021/op800177x CCC: $40.75
Published on Web 09/25/2008

Scheme 1[a]



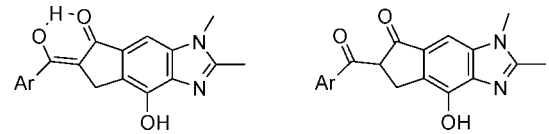
[a] Step (i): asymmetric hydrogenation; step (ii): Mitsunobu cyclization.



9 (Ar=3,5-dimethylphenyl)

Figure 1. **Structure of the hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 9.**

diols **2** and **6** affording P-CABs **3** and **7**. In collaboration with Johnson Matthey, Catalysis and Chiral Technologies, we developed for the hydrogenation reaction the previously unknown catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **9** (Figure 1), which belongs to the class of Noyori catalysts of the general formula $RuCl_2$[PP][NN].[10−14] The $RuCl_2$[PP][NN]-catalyzed hydrogenation of ketones is typically performed in the presence of catalytic amounts of a base using 2-propanol as a solvent.[15] However, due to the presence of the acidic phenol group, an excess of the base was required for the reduction of ketones **1** and **5** (one equivalent of base to deprotonate the phenol moiety and a small excess to activate the hydrogenation catalyst).[10,11] Despite the similarity of ketones **1** and **5**, the efficiency of the hydrogenation reaction varied considerably between the two structural classes. In the imidazo[1,2-*a*]pyridine class, the hydrogenation of ketones **1** was feasible at high S/C ratios



10 (enol form) **10** (diketo form)

Figure 2. **Structure of byproduct 10 formed during catalytic asymmetric hydrogenation of ketone 5.**

giving the corresponding chiral alcohols **2** in excellent yields and optical purities (e.g., R′ = R″ = Me, Ar = Ph: 1.2 equiv of *t*-BuOK, catalyst **9**, S/C = 1000:1, 2-PrOH, *t*-BuOH, H_2O, 80 bar H_2, 65 °C, 22 h, 93% yield, 98% ee or 1.1 equiv of *t*-BuOK, catalyst **9**, S/C = 5000:1, 2-PrOH, *t*-BuOH, H_2O, 25 bar H_2, 75 °C, 15 h, 75% yield, 97% ee).[11] In contrast, in the benzimidazole class, higher amounts of hydrogenation catalyst were required to ensure a smooth transformation of ketones **5** to diols **6** (e.g., R′ = R″ = Me, Ar = Ph: 1.5 equiv of *t*-BuOK, catalyst **9**, S/C = 310:1, 2-PrOH, *t*-BuOH, H_2O, 80 bar H_2, 65 °C, 23 h, 70%, 98% ee).[10] Moreover, under certain reaction conditions (high S/C ratio, presence of a large excess of a base), a competing reaction was observed.[10] The formation of side products **10** (Figure 2) is explained by the fact that the presence of an excess of a base not only increased the rate of the asymmetric hydrogenation reaction, but also resulted in the formation of a reactive enolate species that attacked the carboxamide moiety of the respective ketone **5**. A comparable side reaction has never been observed in the class of imidazo[1,2-*a*]pyridines. The Mitsunobu cyclization of the diols **2** and **6** was performed under standard conditions using triphenylphosphine and DIAD and the optical purity of the target compounds **3** and **7** always reflected the enantiopurity of the respective alcohols **2** and **6**.[10,11]

During the in-depth profiling of P-CABs belonging to the structural classes **3** and **7**, the tetrahydrochromeno[7,8-*d*]imidazole BYK 405879 (**8**) emerged as a promising candidate for clinical studies and several kilograms of material were required for the short-term. It was therefore decided to use the synthetic strategy applied in medicinal chemistry as an initial basis for

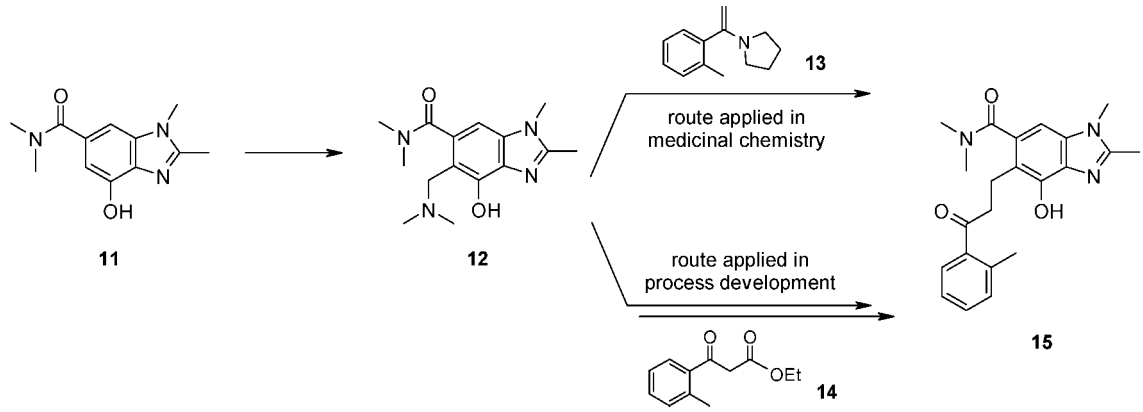
(12) Xyl-P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridinyl; DAIPEN: 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

(13) (a) Wu, J.; Chen, H.; Kwok, W. H.; Lam, K. H.; Zhou, Z. Y.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539–1543. (b) Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 7908–7910. (c) Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *Chem. Eur. J.* **2003**, *9*, 2963–2968.

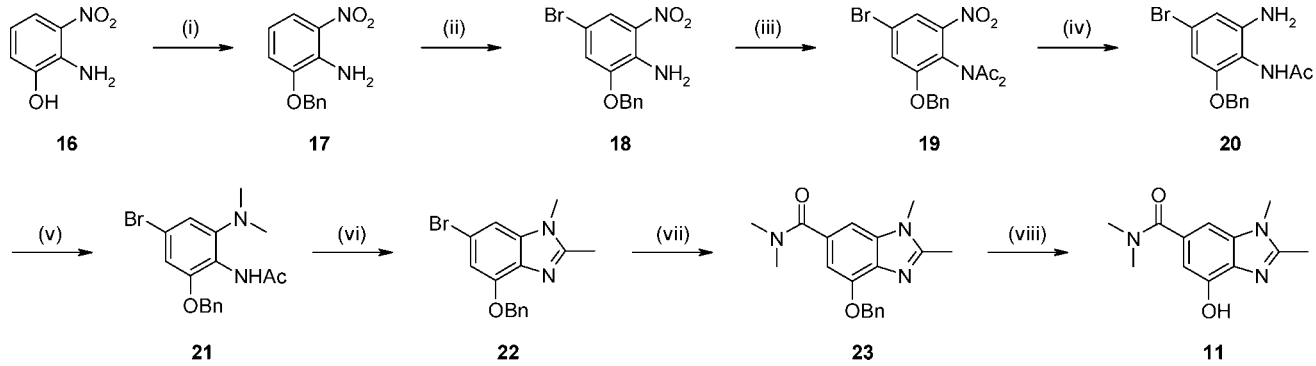
(14) Johnson Matthey, Catalysis and Chiral Technologies, 28 Cambridge Science Park, Milton Road, Cambridge, CB4 0FP, United Kingdom.

(15) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

Scheme 2



Scheme 3[a]



[a] Reagents and conditions: (i) benzyl chloride, K_2CO_3, NaI, EtOH, 55−78 °C, 5 h; (ii) NBS, ethyl acetate, 75−85 °C, 3 h, Σ68%; (iii) Ac_2O, MsOH, 120 °C, 1−1.5 h, 82%; (iv) $FeCl_3$, charcoal, hydrazine hydrate, MeOH, 70−75 °C, 18 h, 82%; (v) formaldehyde, $NaBH_3CN$, MeOH/AcOH, rt, 2 h, 84%; (vi) $POCl_3$, 75 °C, 2 h, 86%; (vii) $Pd(OAc)_2$, PPh_3, Me_2NH (2 M in THF), DMAP, 6 bar CO, DMF, 130 °C, 18 h, 95%; (viii) Pd/C, H_2, MeOH, 50 °C, 3−9 h, >78%.

process development and to optimize the respective reaction steps. At the beginning of the upscale work, the following topics were identified as major issues:

(1) The prochiral ketone **15** used as starting material for the asymmetric hydrogenation reaction was prepared by transformation of the Mannich base **12** with 1-[1-(2-methylphenyl)vinyl]pyrrolidine (**13**), which has a limited shelf life (Scheme 2). Furthermore, the preparation of enamine **13** could not be performed under standard conditions (acid, azeotropic removal of water) and required the use of corrosive titanium tetrachloride. Consequently, the possibility to accomplish the alkylation of the Mannich base **12** using ethyl 3-(2-methylphenyl)-3-oxopropanoate (**14**) instead of the enamine **13** was investigated.

(2) The asymmetric reduction of ketone **15** was done with a low S/C ratio of 100:1. Due to the high price of the catalyst **9**, a cost-effective process could not be achieved under these reaction conditions.

(3) Though there are some examples where the Mitsunobu reaction has been applied successfully in process chemistry, the removal of byproduct and the purification of the desired product often turned out to be tedious.[16]

Here, we would like to report our results with respect to the optimization of these reaction steps and the large-scale synthesis of BYK 405879 (**8**).[17] With exception of the Mitsunobu cyclization, all reactions were performed in multikilogram scale. An optimized procedure for the preparation of the building block **11** will be reported in due course.

2. Results and Discussion

2.1. Access to Building Block 11. Although the approach to benzimidazole **11** pursued in medicinal chemistry consisted of a rather long linear sequence comprising of 8 steps and contained at least three critical steps, it was decided to use this reaction pathway to attain a prompt access to sufficient quantities of intermediate **11** urgently needed for the production of API (**8**) to support the early development phase (Scheme 3).[18] Accordingly, the synthesis was carefully scaled up taking into account all necessary security measures.

Benzyl protection of commercially available 2-amino-3-nitrophenol (**16**) and subsequent bromination of the resulting intermediate **17** afforded 2-(benzyloxy)-4-bromo-6-nitroaniline (**18**), which in turn was transformed with acetic anhydride into the diacetyl derivate **19**. The reduction of the nitro group and concomitant cleavage of one acetyl group from substrate **19** was accomplished with a mixture of iron(III) chloride and

(16) (a) Nishino, Y.; Komurasaki, T.; Yuasa, T.; Kakinuma, M.; Izumi, K.; Kobayashi, M.; Fujiie, S.; Gotoh, T.; Masui, Y.; Hajima, M.; Takahira, M.; Okuyama, A.; Kataoka, T. *Org. Process Res. Dev.* **2003**, *7*, 649–654. (b) Wallace, M. D.; McGuire, M. A.; Yu, M. S.; Goldfinger, L.; Liu, L.; Dai, W.; Shilcrat, S. *Org. Process. Res. Dev.* **2004**, *8*, 738–743. (c) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253–258.

(17) Palmer, A.; Webel, M.; Scheufler, C.; Müller, B.; Haag, D.; Brehm, C.; Chiesa, M. V.; Zimmermann, P. J.; Buhr, W. Patent Application WO 2008/074858, 2008.

(18) Chiesa, V.; Palmer, A.; Brehm, C.; Grundler, G.; Senn-Bilfinger, J.; Simon, W.-A.; Postius, S.; Kromer, W.; Buhr, W.; Zimmermann, P. J. Patent Application WO 2004/054984, 2004.

hydrazine hydrate and therefore was considered critical. However, the reaction was feasible on a multi kilogram scale and the aniline derivative **20** was isolated in 60−80% yield. The bis-methylation of **20** was performed by reductive amination using formaldehyde and sodium cyanoborohydride. Although the transformation resulted in a 70−90% yield, the concerns related to the toxicity of sodium cyanoborohydride still need to be addressed. Benzimidazole **22** was obtained by treatment of diamine **21** with phosphorous oxychloride. Finally, the synthesis of key intermediate **11** was completed by palladium-catalyzed amidocarbonylation of bromide **22** under conditions described in literature and hydrogenolytic cleavage of the benzyl protecting group.[19] In particular, the carbonylation step was considered a major drawback due to the toxicity of carbon monoxide and the fact that only few contract manufacturers offer the special equipment necessary for handling carbon monoxide on a reasonable scale. Furthermore, hydrogenolytic debenzylation was sluggish and required an unacceptably high amount of catalyst (up to 15%).

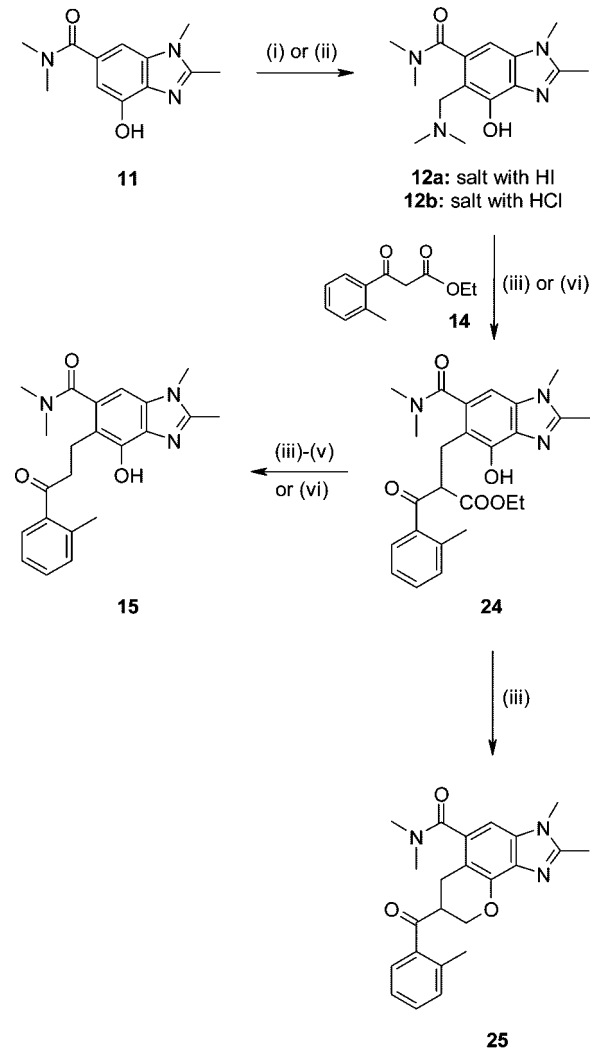
2.2. Large-Scale Synthesis of Ketone 15. For the preparation of ketone **15** *via* the two routes proposed in Scheme 2, the Mannich base **12** was required as starting material. Building block **12** was prepared by the reaction of benzimidazole **11** with Eschenmoser's salt and successful transformation of **11** was accomplished with both dimethylmethylideneammonium iodide and dimethylmethylideneammonium chloride, leading to **12a** or **12b** respectively.

The original protocol was not suitable for larger scale because it used dichloromethane as a solvent and included a laborious extractive workup procedure. Consequently, an optimized procedure was developed which employed a mixture of water and 2-propanol as a solvent (Scheme 4). The addition of triethylamine proved to be beneficial, as the reaction had sometimes stalled and had not gone to completion. This protocol allowed for the isolation of the precipitated product **12** directly from the reaction mixture *via* filtration or centrifugation and its direct use for the next reaction step without any purification.

Despite these improvements, it quickly turned out that the major drawback of this procedure was the insufficient supply and the high price of Eschenmoser's salt. Although several suppliers claimed to be able to deliver kilogram quantities, we often ran short of this raw material due to delivery problems. Therefore, we examined the *in situ* generation of Eschenmoser's salt from formaldehyde and dimethylammonium chloride. This procedure worked smoothly in pilot plant scale, using 2-propanol as the solvent and triethylamine as the base and, after the subsequent addition of **11,** the expected product **12** was obtained in comparable yields as when Eschenmoser's salt was employed.

For initial and fast supplies of API at the outset of the development, enamine **13** was used for the preparation of ketone **15** (Scheme 2), but the handling disadvantages (oily liquid with limited shelf life, difficult preparation) rendered this route not particularly amenable for large scale; consequently, an alternative was sought. Brief examination of the use of β-ketoester **14**, which was prepared by condensation of 2-methylbenzoic acid with ethyl acetate or purchased from an external supplier, showed that the alkylation of Mannich base **12** worked in principle, but was hampered by disappointing yields of about 30% (Scheme 4). However, since the whole concept looked promising, it was decided to put more effort into optimizing the reaction. It was quickly recognized that one key factor, particularly in regard to the following reduction step, was the complete decarboxylation of intermediate **24** to ketone **15**. As specified further in section 2.3, erosion of the enantiomeric excess was observed when starting material **15** containing residual amounts of the nondecarboxylated intermediate **24** was submitted to the asymmetric reduction step. Therefore, we had to ensure reaction conditions leading to fully decarboxylated product **15** which in turn seemed to compromise the yield. A further problem arising in the course of the optimization was the formation of the undesired byproduct **25**. Ether **25** seemed to arise from intermediate **24**, involving an unexplained reduction of the carboxylic acid moiety. In later development phases,

Scheme 4[a]



[a] Reagents and conditions: i) Eschenmoser's salt (1.3 equiv), Et_3N (0.25 equiv), 2-PrOH, rt, 16 h, 100% **12a**; (ii) $[NMe_2H_2]^+Cl^-$ (1.3 equiv), Et_3N (0.3 equiv), 2-PrOH, addition of aq formaldehyde (1.3 equiv), 35−45 °C, 1−3 h, 100% **12b**; (iii) **14** (1.4 equiv), NaOH (2.0 equiv), toluene, H_2O, rfl., 8 h; (iv) citric acid, *n*-BuOH, H_2O, Σ53%; (v) aq NH_3 (25 wt %), CH_2Cl_2, H_2O, 82%; (vi) Na-*tert*-pentylate (25% in toluene, 2.3 equiv), toluene/DMF, 55−85 °C, 2.5−4 h, addition of water, reflux, 2−3 h, 90%.

(19) (a) Head, R. A.; Ibbotson, A. *Tetrahedron Lett.* **1984**, *25*, 5939–5942. (b) Horino, H.; Sakaba, H.; Arai, M. *Synthesis* **1989**, 715–718.

employing Mannich base **12b** derived from *in situ* generated Eschenmoser's salt, byproduct **25** was no longer observed.

As a consequence, much optimization work was performed, which included the choice of an appropriate base and solvent and modifications of the reaction temperature and concentration as well as the equivalents of the employed ketoester **14**. Finally, a preliminary procedure was found, which produced the desired ketone **15** on kilogram scale. In this optimized procedure the transformation of Mannich base **12** was performed in a biphasic reaction mixture consisting of toluene/aqueous sodium hydroxide solution, and the ketone **15** typically was obtained in 40−50% yields after precipitation as the citric acid salt, subsequent release by treatment with a base, and crystallization from acetone.

Although this process allowed the fast production of several kilograms of **15** in our kilolabs, it was far from optimal. The yields were not satisfying, the purification procedure was laborious, and dichloromethane was used for extraction. Therefore, a further stage of development was required and finally achieved by the use of potassium *tert*-pentylate as a base in a homogeneous mixture of toluene and DMF. In our pilot plants, this procedure was easily carried out on a multikilogram scale and gave a tremendous improvement in yield to over 90%. Moreover, ketone **15** was obtained in excellent purity, and the additional purification step with citric acid was no longer required.

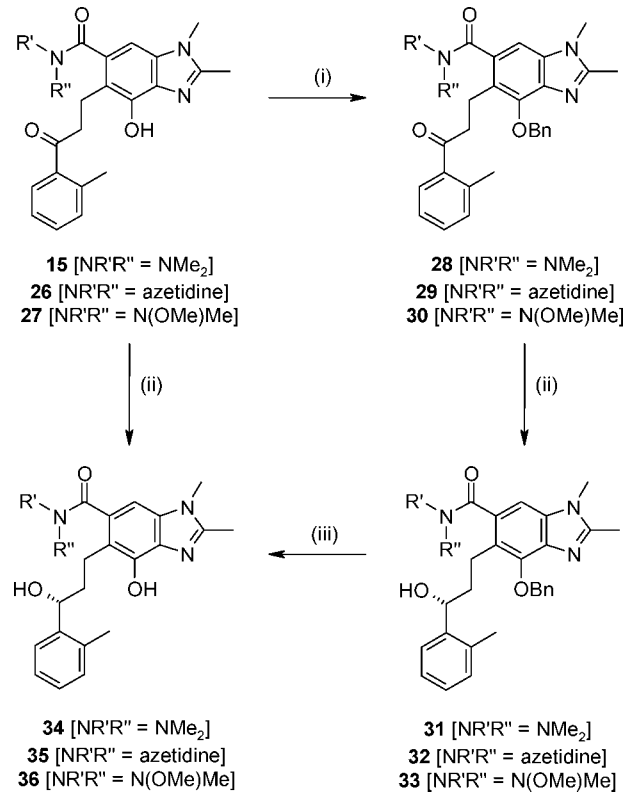
2.3. Optimization of the Asymmetric Hydrogenation Reaction. The results obtained in the course of our previous investigations indicated that the outcome of the asymmetric hydrogenation depended on the substitution pattern of the respective ketone **5** and on the amount of base employed.[10] It was also demonstrated that, in the absence of catalyst **9**, the base-catalyzed side reaction leading to products **10** was slow at room temperature but fast at 70 °C.

A total of 52 experiments was conducted to judge the influence of pressure, reaction time, solvent, S/C ratio, substrate concentration, amount of base, and the quality of the starting material on the outcome of the reduction of the ketone **15** to the alcohol **34** (Scheme 5). A representative summary of these experiments is shown in Table 1.

An important finding was that the outcome of the reaction depended on the quality of the starting material (Table 1, entries 1−3). The optical purity of the chiral alcohol **34** differed significantly when two batches of ketone **15** possessing HPLC purities of 98.9% and 95.3% were reduced under identical reaction conditions. An ee value of 89.0% was determined for the first batch of product **34** (entry 1), whereas the second batch possessed an optical purity of only 61.7% ee (entry 2). Since the HPLC chromatogram suggested the presence of intermediate **24** in the less pure batch, we investigated whether this derivate was responsible for the unexpected drop in the enantioselectivity. Indeed, when a mixture of ketone **15** (95%) and the intermediate **24** (5%) was reduced in the presence of the catalyst **9** (S/C = 100:1), the alcohol **34** was obtained with an optical purity of only 59.9% ee (entry 3).

The following conclusions can be drawn from the results listed in Table 1:

Scheme 5[a]



[a] Reagents and conditions: (i) benzyl bromide (1.0−1.1 equiv), K_2CO_3 (1.0−1.1 equiv), DMF, rt or 65 °C, 4−17 h, **28**: 83%, **29**: 81%, **30**: 90%; (ii) $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], *t*-BuOK; 2-PrOH, *t*-BuOH, H_2, see Tables 1, 3 and 4; (iii) Method A: Pd/C, H_2, EtOH or MeOH, rt, 3−18 h, **34**: 89−95%, **35**: 69%, **36**: 82%; Method B: Pd/C, 1,4-cyclohexadiene, rt−55 °C, 4 h, **34**: 92%.

(1) At a S/C ratio of 100:1, the reduction of ketone **15** proceeded in a reliable manner (entries 4−7) affording alcohol **34** in optical purities of 84.2−93.3% ee. Whereas the increase of substrate concentration exerted a beneficial influence on the enantioselectivity of the reduction (entry 6), the optical purity of alcohol **34** was compromised in the presence of higher amounts of potassium *tert*-butylate (entry 7). At a S/C-ratio of 250:1, only 66% conversion was achieved under standard conditions (entry 13). Quantitative transformation of ketone **15** to alcohol **34** was achieved either by increasing the amount of potassium *tert*-butylate (entry 14), the reaction time (entries 15, 16), the substrate concentration (entries 16, 17), and/or the hydrogen pressure (entry 17). The optical purity of diol **34** depended on the substrate concentration of ketone **15**. If 0.21 and 0.5 M solutions of ketone **15** were used for the hydrogenation reaction, the diol **34** was isolated in an optical purity of ∼80% ee (entries 14 and 15) and ∼90% ee (entries 16 and 17), respectively. At a S/C ratio of 200:1, the reduction of ketone **15** proceeded in a reliable manner (225 g scale, entry 12) affording alcohol **34** in 80% yield, 96.0% chemical purity, and 94.2% optical purity. According to the hydrogen uptake curve, complete transformation of ketone **15** occurred within a period of 8 h.

(2) As expected, the base-catalyzed background reaction was favoured in the presence of higher amounts of base and at high S/C ratios. At a S/C ratio of 100:1, pure batches of alcohol **34** were isolated (see Table 2). On the other hand, if the

Table 1. **Asymmetric hydrogenation of ketone 15 ($RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], 2-PrOH, *t*-BuOH, 65−70 °C)**

entry	scale (g)/additive	purity of **15** (%)[a]	S/C ratio	*t*-BuOK[b] (equiv)	concn (mol/L)	*p* H_2 (bar)	time (h)	conv[c] (%)	ee[d] of **34** (%)
1	5	98.9	100:1	1.1	0.21	80	20	100	89.0
2	4	95.3	100:1	1.1	0.21	80	20	100	61.7
3	4/+5% **24**	98.8	100:1	1.1	0.21	80	20	100	59.9
4	70	98.7	100:1	1.1	0.21	80	20	100	90.6
5	31	98.7	100:1	1.1	0.21	80	48	100	90.3
6	10	97.7	100:1	1.1	0.5	80	20	100	93.3
7	4.7	98.8	100:1	1.7	0.25	80	20	100	84.2
8	4/+10% H_2O	98.4	100:1	1.1	0.21	80	20	47	88.2
9	10	96.0	100:1	1.1	0.5	30	20	100	95.1
10	10	96.0	100:1	1.1	0.5	10	20	100	97.0
11	10	96.0	100:1	1.1	0.5	5−8	20	96	94.8
12	225	96.0	200:1	1.1	0.5	80	20	100	94.2
13	4	98.8	250:1	1.1	0.21	80	20	66	83.9
14	4	98.6	250:1	1.4	0.21	80	20	100	78.1
15	4	98.6	250:1	1.1	0.21	80	72	98	80.5
16	10	98.4	250:1	1.1	0.5	80	48	100	90.5
17	10	96.0	250:1	1.1	0.5	120	20	100	91.2
18	17/without 2-PrOH	96.0	250:1	1.1	0.9	80	20	100	86.0
19	17/without 2-PrOH	96.0	300:1	1.1	0.9	120	20	100	84.3

[a] Purity determined by HPLC on the isolated product. [b] A 1 M solution of potassium *tert*-butylate in *tert*-butanol was used. [c] 87−98% crude product after workup (distribution between CH_2Cl_2/saturated NH_4Cl solution), conversion determined by HPLC. [d] Optical purity determined by capillary electrophoresis.

Table 2. **Purification of crude alcohol 34 by crystallization**

entry	entry from Table 1	ee (crude; %)	method of purification[a]	yield (%)	chemical purity (%)	ee (%)
1	1	89.0	A	78	98.9	89.4
2	5	90.3	B	83	98.3	90.3
3	6	93.3	B	71	98.9	93.2
4	9	95.1	B	79	98.3	96.8
5	12	94.2	B	80	96.5[b]	94.0
6	4	90.6	C	70	99.4	95.4
7	14	78.1	C	46	94.0[b]	93.0
8	15	80.5	C	59	95.5[b]	95.5
9	16	90.5	C	51	95.5[b]	94.9
10	7	84.2	D	39	97.3	93.9

[a] Method A: crystallization from 2-propanol in the presence of oxalic acid (1.5 equiv) and treatment of the corresponding salt with CH_2Cl_2/$NaHCO_3$ solution. Method B: crystallization from acetone. Method C: crystallization from acetone in the presence of L-(+)-mandelic acid (1.2 equiv) and treatment of the corresponding salt with CH_2Cl_2/$NaHCO_3$ solution. Method D: crystallization from ethyl methyl ketone and further purification of the mother liquor according to method A. [b] Samples contained 2.0−4.9% of byproduct **10**.

Table 3. **Asymmetric hydrogenation of O-protected ketones 28−30 ($RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], 2-PrOH, *t*-BuOH)**

entry	ketone	S/C ratio	*t*-BuOK (equiv)	*p* (bar)	*T* (°C)	time (h)	concn (mol/L)	yield (%)	ee (%)[a]
1	**28**	100:1	1.1	100	70	17	0.5	68[b]	−/99.5
2	**28**	100:1	0.1	100	70	17	0.5	72[b]	−/98.8
3	**28**	250:1	0.1	100	70	17	0.5	59[b]	−/98.8
4	**28**	350:1	0.1	80	65	20	0.5	75[c]	98.5/100
5	**28**	500:1	0.1	80	65	20	0.5	72[c]	98.7/99.2
6	**28**	700:1	0.1	80	70	18	0.5	75[c]	97.7/99.7
7	**28**	1000:1	0.1	80	70	18	0.5	95[d]	98.6/−
8	**28**	1500:1	0.1	80	70	18	0.5	70[c]	98.2/98.9
9	**28**	2500:1	0.1	80	70	18	0.5	100[d]	98.2/−
10	**28**	3500:1	0.1	80	70	18	0.5	66[c]	96.3/98.7
11	**28**	5000:1	0.1	80	70	18	0.5	70[c]	96.6/99.2
12	**28**	2000:1	0.1	10	70	18	0.5	73[c]	96.7/98.2
13	**28**	3500:1	0.1	10	70	18	0.5	74[c]	96.3/99.2
14	**29**	100:1	0.1	80	70	17	0.29	82[c]	−/99.5
15	**29**	2000:1	0.1	80	70	17	0.29	83[c]	−/99.7
16	**30**	50:1	0.4	80	70	17	0.11	49[b]	−/98.2

[a] Optical purity reported for crude alcohol/purified sample. [b] Purification by column chromatography. [c] Purification by crystallization from acetone. [d] Crude product.

hydrogenation was conducted with S/C ratios of 200:1 or 250:1, the isolated samples of alcohol **34** contained 2−5% of byproduct **10** which could be removed after Mitsunobu cyclization.

(3) Interestingly, lower enantioselectivities were obtained if *tert*-butanol was used as the reaction solvent instead of a mixture of 2-propanol and *tert*-butanol (compare entries 16 and 18). In contrast to our findings from the imidazo[1,2-*a*]pyridine series, the presence of water had a negative influence on the reaction rate (entry 8).[11]

(4) The asymmetric reduction was also feasible applying low hydrogen pressures of 5−8, 10, and 30 bar instead of 80 bar (entries 9−11). On the other hand, the increase of hydrogen pressure was beneficial for the outcome of the reaction at higher S/C ratios (entries 17 and 19).

(5) High concentrations of starting material **15** were found to be beneficial for a fast, clean, and enantioselective conversion of ketone **15** to alcohol **34** (compare entries 4 and 6/entries 15 and 16). Using a high substrate concentration of 0.9 M, the reaction was also feasible at a S/C ratio of 300:1 (entry 19).

Typically, the asymmetric reduction of ketone **15** afforded alcohol **34** in an optical purity of 85−90% ee. As can be seen from Table 2, several crystallization procedures for the purification of crude **34** were developed.

The chemical purity was increased by crystallization of the crude product from acetone (Table 2, entries 2−5). Alternatively, alcohol **34** was converted into its oxalate salt and isolated in pure form by subsequent treatment of the corresponding salt with a base (Table 2, entry 1).

Two methods were available for the enhancement of both the optical and chemical purity of alcohol **34**. Treatment of the crude product with L-(+)-mandelic acid afforded the corresponding salt from which the pure alcohol **34** was released by treatment with a base (Table 2, entries 6−9). Alternatively, an increase of the optical purity was secured by crystallization of crude **34** from ethyl methyl ketone. Interestingly, in this solvent, the racemic mixture turned out to be less soluble than the (3*R*)-enantiomer, and the alcohol **34** was obtained in 39% yield and

Table 4. **Asymmetric hydrogenation of ketone 28 in a 10 L Premex Hastelloy autoclave ($RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 9, 2-PrOH, *t*-BuOH, c = 0.50 M, 80−100 bar H_2, 70 °C, 20 h)**

entry	ketone	*t*-BuOK (1 M solution)	catalyst	yield
1	1000 g/2.13mol	213 mL/0.21 mol	2.65 g (S/C = 1000:1)	946 g/94%
2	1000 g/2.13mol	213 mL/0.21 mol	1.06 g (S/C = 2500:1)	1711 g/85%
3	1000 g/2.13mol	213 mL/0.21 mol	1.06 g (S/C = 2500:1)	
4	1000 g/2.13mol	213 mL/0.21 mol	1.06 g (S/C = 2500:1)	
5	1000 g/2.13mol	213 mL/0.21 mol	1.06 g (S/C = 2500:1)	2543 g/90%
6	818 g/1.74mol	174 mL/0.17 mol	0.90 g (S/C = 2500:1)	

93.9% ee by subsequent crystallization from the mother liquor (Table 2, entry 10).

At this stage of the optimization of the asymmetric hydrogenation reaction, the reduction of 1 kg of ketone **15** still required 33 g of catalyst **9** (equivalent to a S/C ratio of 200:1). By applying these conditions on a 225 g scale, the corresponding alcohol **34** was isolated in 80% yield and 94% ee. Due to the high price of the hydrogenation catalyst (220 Euros/g), this option was economically not viable, and alternatives were evaluated.

The low catalytic activity could either be attributed to the chelating properties of the nitrogen atom of the benzimidazole ring and the hydroxy group or to the steric bulk of the ortho-methylphenyl substituent. In the first case, the introduction of a base-resistant protecting group, preferably also stable towards hydrolytic cleavage, was expected to diminish the chelating properties of the substrate and promote a successful outcome of the reaction in the presence of less hydrogenation catalyst. Furthermore, protection of the acidic phenol moiety should allow the use of substoichiometric amounts of base since deprotonation of the phenol group prior to activation of the catalyst no longer occurs.

Consequently, we decided to investigate the asymmetric reduction of the benzyl-protected ketone **28** in the presence of $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **9**. The starting material **28** and the structurally related substrates **29** and **30** were obtained by conversion of the respective phenolic ketone **15**, **26** and **27** with benzyl bromide under basic conditions (potassium carbonate) and reslurrying of the obtained crude products (Scheme 5).

In order to determine the maximum S/C ratio for the asymmetric reduction of the benzyl-protected ketone **28** in the presence of catalyst **9**, a series of hydrogenation experiments was conducted in a 100 mL Premex Hastelloy autoclave using 10 g of starting material (Table 3). At a S/C ratio of 100:1, almost identical results were obtained in the presence of stoichiometric (entry 1) or catalytic amounts of potassium *tert*-butylate (entry 2). The experiments listed in entry 2−11 were performed in the presence of 0.1 equivalents of potassium *tert*-butylate using varying amounts of catalyst **9**. The enantioselectivity of the reduction was determined at the stage of the crude alcohol **31** and after purification, which was accomplished either by column chromatography or by crystallization from acetone. To our delight, up to a S/C ratio of 5000:1, neither the yield nor the optical purity of alcohol **31** was compromised. At a S/C ratio of 7500:1, the reaction rate decreased, and in the course of 18 h, only 44% conversion to alcohol **31** took place (80 bar hydrogen pressure, 70 °C). Also, the enantioselectivity of the reduction was slightly reduced (94.4% ee).

It was also shown that the high pressure of 80 bar that typically had been used to increase the reaction rate was not required (entries 12 and 13). At a hydrogen pressure of 10 bar and a S/C ratio of 2000:1 and 3500:1, respectively, complete conversion of ketone **28** was accomplished, and the alcohol **31** was isolated in 73−74% yield and 98.2−99.2% ee. However, at a S/C ratio of 5000:1 the reduction did not go to completion using the standard reaction time of 17 h and a lower hydrogen pressure of 10 bar (35% conversion, 98.5% ee). These findings are particularly important because they allow the use of standard pilot-plant vessels for hydrogenation instead of the often size-limited and specialized autoclave equipment, leading to a higher throughput and a better cost-effectiveness.

Since the ketone **28** showed significantly higher reactivity than its O-unprotected analogue **15**, we decided to reinvestigate the asymmetric hydrogenation of substrates that had previously turned out to be challenging. In the case of ketones **26** and **27**, the reaction rate of the hydrogenation was low, and consequently, large quantities of byproduct **10** (Ar = 2-methylphenyl) were formed.[10] In contrast to these findings, the asymmetric reduction of the benzyl-protected analogues **29** and **30** proceeded smoothly and afforded the corresponding enantiopure alcohols **32** and **33** in good yields (Table 3, entries 14−16). In the case of ketone **29** containing an azetidine carboxamide moiety, it was demonstrated that identical results were obtained using S/C ratios of 100:1 and 2000:1, respectively (entries 14 and 15). The reduction of ketone **30** possessing a Weinreb amide substituent was only demonstrated at a S/C ratio of 50:1 (entry 16).

Next, we repeated the asymmetric hydrogenation reaction of ketone **28** in a 2 L Premex Hastelloy autoclave using a substrate concentration of 0.18 M (32 g of starting material **28**) and a S/C ratio of 500:1 under otherwise identical reaction conditions (0.1 equiv of potassium *tert*-butylate, 2-propanol/*tert*-butanol, 80 bar hydrogen pressure, 70 °C, 20 h). The optical purity of the crude product (97.4% ee) was enhanced by crystallization from acetone, and the pure alcohol **31** was isolated in 79% yield and 99.5% ee.

We then turned our attention to the asymmetric reduction of ketone **28** on a kilogram scale using a 10 L Premex Hastelloy autoclave, the largest autoclave available at our research site. Since this autoclave was employed for different catalytic reactions using a variety of transition metal complexes, we were concerned about the presence of impurities that might reduce the activity of the hydrogenation catalyst **9** or compromise the enantioselectivity of the reduction. For this reason, we first conditioned the reaction vessel by heating a solution of catalyst **9** in 2-propanol and then confirmed the successful removal of potential impurities by asymmetric reduction of acetophenone

in the presence of catalyst **9** and catalytic amounts of potassium *tert*-butylate. Since the corresponding hydrogenation product, (1*R*)-1-phenylethanol, was obtained in excellent optical purity, we examined the asymmetric reduction of ketone **28**. As can be seen from Table 4, clean conversion took place at S/C ratios of 1000:1 and 2500:1, and the alcohol **31** was obtained in 85−94% yield. In the course of these experiments the workup procedure was optimized: On a small scale, the reaction mixture was quenched with saturated ammonium chloride solution, and alcohol **31** was extracted with dichloromethane. At larger scale, the reaction mixture was neutralized with acetic acid and diluted with water at a temperature of 50−55 °C. The product **31** crystallized out and was isolated in a convenient manner. The combined batches listed in Table 4 were crystallized from 2-propanol, and the alcohol **31** was isolated in 81% yield and an optical purity of 98.5% ee.

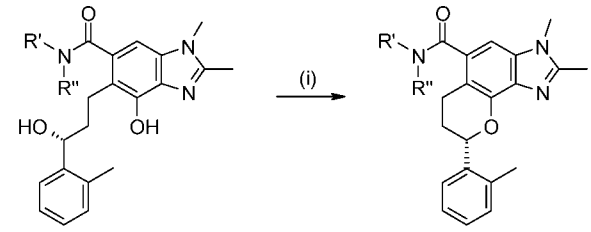
Cleavage of the protecting group was then accomplished either by catalytic hydrogenation (palladium on charcoal, hydrogen) or by catalytic transfer hydrogenation (palladium on charcoal, 1,4-cyclohexadiene). The hydrogenolysis proceeded equally well with crude batches or pure batches of benzyl ether **31** (obtained by crystallization from acetone) and afforded the diol **34** in 89−95% yield. The ruthenium and palladium content of the 5 kg batch of diol **34** was analyzed, and values of 11 ppm (Ru) and 27 ppm (Pd) were determined. The heavy metal content was reduced further in the course of the Mitsunobu cyclization to BYK 405879 (**8**) and the subsequent purification of the API, and always met the specification threshold for total heavy metals of <20 ppm. In the same manner, hydrogenolytic cleavage of the benzyl protecting group present in substrates **32** and **33** furnished the respective diols **35** and **36** in 69−82% yields.

In summary, the catalyst loading could be reduced significantly by the presence of the benzyl protecting group, and only 1 g of hydrogenation catalyst was required for the asymmetric reduction of 1 kg of ketone **28**. Both the introduction and the cleavage of the protecting group were accomplished in good yield applying standard reaction conditions.

2.4. Optimization of the Mitsunobu Cyclization. For the ring-closure reaction of diol **34** to our development candidate **8**, the originally used Mitsunobu conditions (DIAD/triphenylphosphine) initially seemed to be the best choice. However, as mentioned before, the removal of the typical Mitsunobu byproduct (diisopropyl hydrazine-1,2-dicarboxylate/triphenylphosphine oxide) was troublesome and often required chromatography; thus, a more convenient protocol had to be established. A first look at the reaction itself, yielding normally about 50−60% (cf. Scheme 6, target compounds **37** and **38** prepared in medicinal chemistry), revealed some potential for improvement. It quickly turned out that yields could be improved considerably by using toluene instead of THF as a solvent together with careful control of the temperature of the exothermic reaction.

With respect to the workup, an aqueous extraction with dilute hydrochloric acid seemed to be most suitable to partly remove the byproduct of the Mitsunobu reaction. The aqueous phase was subsequently extracted with methylisobutyl ketone in order to separate further impurities, the pH readjusted to 10−12 by

Scheme 6[a]



34 [NR'R" = NMe_2]
35 [NR'R" = azetidine]
36 [NR'R" = N(OMe)Me]

8 [NR'R" = NMe_2]
37 [NR'R" = azetidine]
38 [NR'R" = N(OMe)Me]

[a] Reagents and conditions: (i) Method A (process development): PPh_3 (1.3 equiv), DIAD (1.3 equiv), toluene, <25 °C, then salt formation with succinic acid, **8**: 80%; Method B (medicinal chemistry): PPh_3 (1.3 equiv), DIAD (1.3 equiv), THF, rt, 0.5−1 h, **37**: 59%, 99.2% ee; **38**: 47%, 97.0% ee.

addition of aqueous ammonia solution, and the product **8** extracted with methylisobutyl ketone. Further purification was accomplished by precipitation of the product as the succinic acid salt from methylisobutyl ketone. This salt of target compound **8** was isolated typically in over 80% yield and with practically no deterioration in the enantiomeric excess overall (as compared to the starting diol **34**). Although minor erosion of the optical purity seemed to take place during the cyclization reaction, this finding is of no practical relevance since the enantiomeric excess of the material could easily be upgraded by subsequent salt formation and crystallization. The free base was returned from the acid salt by treatment with aqueous ammonia solution, extraction, and final crystallization from isopropyl acetate, furnishing BYK 405879 (**8**) in excellent purity.

Since the required amount of BYK 405879 (**8**) was supplied on time, some minor issues associated with the Mitsunobu cyclization that might be disadvantageous for further upscale have not yet been eliminated, nor has the process been transferred from our kilolabs to the pilot plant. For the same reason, diol **34** with high enantiomeric excess derived from the asymmetric reduction/deprotection of O-benzyl protected ketone **28** was not employed on a larger scale for the Mitsunobu reaction (see Experimental Section). Furthermore, the preliminary results indicating that the asymmetric reduction of ketone **28** can be conducted under low pressure, and thus circumvent the use of autoclave equipment, remain to be confirmed on a larger scale.

Figure 3 illustrates the results of the X-ray analysis obtained for the 2:1 salt of BYK 405879 (**8**) with succinic acid. Interestingly, there were two possible structure solutions: a centrosymmetric solution which would indicate a racemic compound and a solution with two independent molecules of **8** and one molecule of succinic acid in the crystallographic asymmetric unit. Although the structure showed a so-called pseudosymmetric behaviour, in reality, the structure is indeed chiral. In solid state, the system shows no ionic properties, and the hydrogens of the dicarboxylic acid are clearly localized at the oxygens of the acid functions. The hydroxy functions are donors of a strong intermolecular hydrogen bond interaction to the nitrogens of the imidazole moieties. The succinic acid constitutes a bridge-like link between two molecules of BYK 405879 (**8**), forming nearly linear hydrogen bonds. The

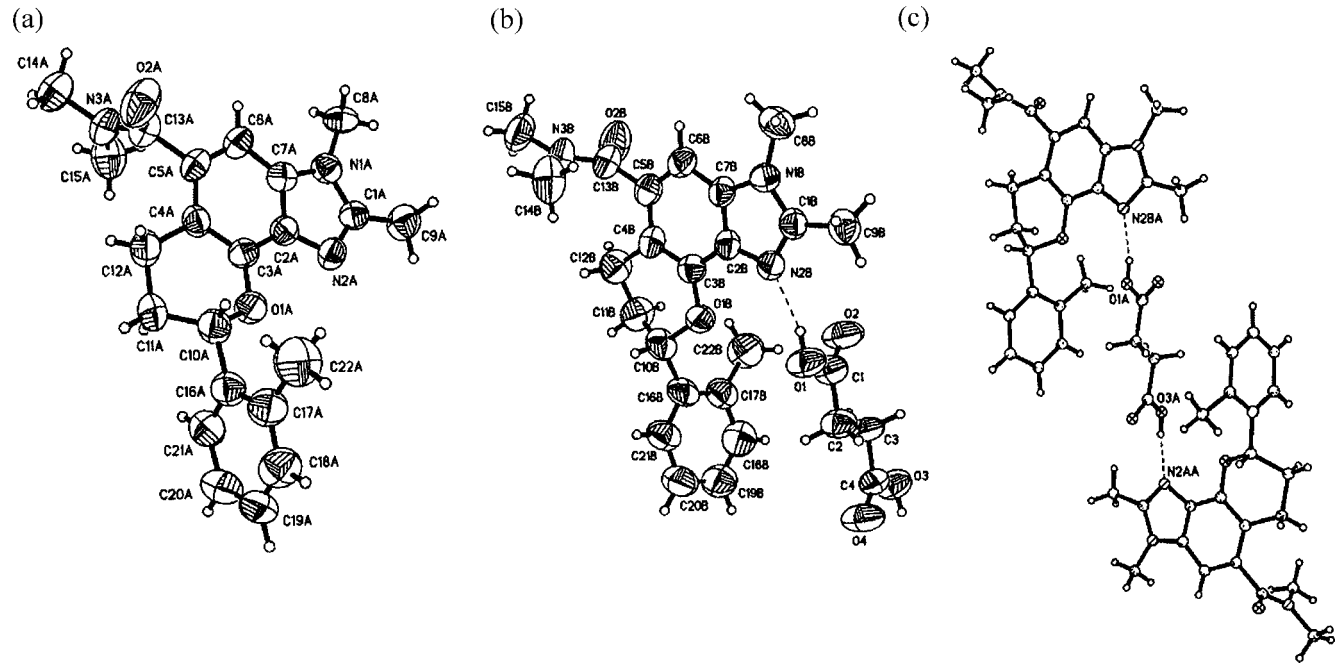


Figure 3. **X-ray analysis of the salt of BYK 405879 (8) with succinic acid: (a) molecule A with X-ray numbering system; (b) molecule B and succinic acid with X-ray numbering system; (c) hydrogen bond situation.**

hypothesis that a perpendicular orientation of the aryl moiety to the heterocyclic scaffold is required to effect potent inhibition of the H^+/K^+-ATPase was supported by the results of the X-ray analysis: The flat benzimidazole moiety of both molecules of **8** have a nearly perpendicular orientation to the methylphenyl moiety with angles between these planes of 83.2° (molecule A) and 76.5° (molecule B), respectively.

3. Conclusion

In summary, we have developed an efficient asymmetric synthesis that permitted the preparation of kilogram quantities of the potassium-competitive acid blocker BYK 405879 (**8**). Suitable strategies were identified to overcome the challenges associated with the medicinal chemistry route. The Mannich base **12** was prepared using cheap reagents (dimethylammonium chloride/formaldehyde) instead of expensive Eschenmoser's salt. Ketone **15** was obtained in good yield and reproducible quality by alkylation of Mannich base **12** with β-ketoester **14**. In contrast to enamine **13** used previously for the preparation of ketone **15**, β-ketoester **14** is readily available and can be stored for an indefinite period. By introducing a benzyl protecting group, the asymmetric ketone reduction could be performed at high S/C ratios, affording alcohol **31** in high yields and excellent optical purities. After cleavage of the protecting group, BYK 405879 (**8**) was obtained by Mitsunobu reaction and could be purified in an effective manner by acid−base extraction and crystallization in the presence of suitable acids. Finally, most steps, except for the asymmetric reduction and the Mitsunobu cyclization, were conducted successfully at a pilot-plant scale. Despite the three additional steps required for the introduction and removal of the benzyl protecting group and the final crystallization of the API **8** in the presence of succinic acid, the overall yield was improved considerably in comparison to that of the medicinal chemistry route (43% versus 25% overall yield based on benzimidazole **11**).

4. Experimental Section

General. All chemicals were purchased from the major chemical suppliers and used without any further purification. The syntheses of the hydrogenation catalyst **9** and the ketones **26** and **27** were performed using the methods described previously.[9−11] 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 a solvent system. 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 DRX 200 FT-NMR spectrometer at a frequency of 200 MHz, 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 a solvent. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) or DMSO as an internal standard (^{1}H: $\delta_{TMS} = 0.00$ ppm; ^{13}C $\delta_{DMSO} = 39.50$ ppm). High-resolution mass spectra were obtained on an Agilent LC/MSD TOF instrument using electrospray ionisation (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer. The optical purity of the target compounds and of selected intermediates was determined by capillary electrophoresis (CE) and/or high pressure liquid chromatography (HPLC). The experimental conditions for the separation of the enantiomers are given for each example in the Experimental Section. The heavy metal content of diol **34** was determined by inductively coupled plasma optical emissions spectroscopy (ICP-OES) using a Perkin-Elmer Optima 3000

DV instrument with Perkin-Elmer ICP WinLab software. Sample preparation was done by digestion of the sample with nitric acid (65% m/v, 170 °C, 3 h). The content was calculated by an external linear calibration line according to the monograph 2.2.22 "atomic emission spectrometry", method 1 of the Ph. Eur. fifth edition. Ruthenium and palladium standard solutions (1000 mg/L) were used as a reference. The heavy metal content of the final API **8** was determined according to the guidelines (Ph. Eur. 2.4.8 method C). Karl Fischer titration was performed on a Metrohm KF Coulometer 756 KF (Metrohm 774 Sample Oven Processor).

(8*S*)-*N*,*N*,2,3-Tetramethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (8). To a suspension of diol **34** (obtained by direct asymmetric hydrogenation of ketone **15** in the presence of catalyst **9**, 565 g, 1.48 mol, 91.6% ee) and triphenylphosphine (505 g, 1.93 mol) in toluene (14 L), was added dropwise DIAD (380 mL, 1.93 mmol). The temperature was maintained below 25 °C in the course of the addition, and an auburn solution was obtained. After reaction completion, the mixture was extracted with hydrochloric acid (1 N, 2 × 2.5 L). The aqueous phase was washed with methylisobutyl ketone (3 × 1 L). The combined organic phases were discarded. The pH value of the aqueous phase was adjusted to 10−12 by addition of 25% aqueous ammonia solution, and the product was extracted with methylisobutyl ketone (2 × 2 L). The combined organic phases were concentrated under reduced pressure, yielding the crude title compound (750 g).

Salt Formation with Succinic Acid. The crude product (750 g) was dissolved in methylisobutyl ketone (2.2 L). Succinic acid (96 g, 0.815 mol) was added and the mixture heated to 80 °C for several min. The suspension was allowed to cool to room temperature, and stirring was continued for 17 h. The precipitate was isolated by filtration and dried *in vacuo* at 50 °C. This afforded the title compound as a succinate salt (525 g of a colorless solid, 83% yield, 90.2% ee, HPLC purity >97%, stoichiometric ratio with respect to succinic acid, 1:0.53); mp 192−194 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.99 (m_c, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.42 (s, 4 H), 2.47 (s, 3 H), 2.65 (m_c, 1 H), 2.81, 2.91 (s, m_c, 4 H), 3.02 (s, 3 H), 3.68 (s, 3 H), 5.32 (dd, 1 H), 6.92 (s, 1 H), 7.24 (m_c, 3 H), 7.47 (m_c, 1 H).

Preparation of the Title Compound from Its Salt with Succinic Acid. The salt of the title compound with succinic acid (876 g, 2.05 mol) was suspended in dichloromethane (2.0 L), and water was added (0.5 L). To this suspension, 25% aqueous ammonia solution (0.4 L) was added under stirring. The mixture was stirred for further 0.5 h, the organic phase separated, and the aqueous phase extracted with dichloromethane (3 × 0.5 L). The combined organic phases were washed with water (0.2 L), coevaporated with methylisobutyl ketone (2 × 1.0 L), and the residue was dissolved in isopropyl acetate (1.0 L) at 80 °C. The solution was allowed to cool to room temperature over 3 h while the product precipitated. The precipitate was isolated by filtration and dried *in vacuo* at 50 °C. This afforded the title compound (682 g of a colorless solid, 92% yield, 90.2% ee, HPLC purity >99%); mp 179−181 °C. Determination of the optical purity by HPLC (column: Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm; eluant: *n*-heptane/ethanol, 85:15; flow rate: 1 mL/min; detection wavelength: 218 nm): t_R [(8*R*)-enantiomer] = 5.3 min/4.91 area %, t_R [(8*S*)-enantiomer] = 6.7 min/95.09 area %, 90.2% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.98 (m_c, 1 H, 7-H_a), 2.22 (m_c, 1 H, 7-H_b), 2.38 (s, 3 H, $C_6H_4-C\underline{H}_3$), 2.49 (s, 3 H, 2-CH_3), 2.62 (bs, 1 H, 6-H_a), 2.81 (s, 3 H, $CON(CH_3)_2$), 2.90 (bs, 1 H, 6-H_b), 3.02 (s, 3 H, $CON(CH_3)_2$), 3.67 (s, 3 H, 3-CH_3), 5.32 (dd, $^3J_{7,8}$ = 10.4 Hz, $^3J_{7,8}$ = 1.9 Hz, 1 H, 8-H), 6.92 (s, 1 H, 4-H), 7.24 (m_c, 3 H, $C_6\underline{H}_4-CH_3$), 7.47 (m_c, 1 H, $C_6\underline{H}_4-CH_3$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.2 (2-CH_3), 18.6 ($C_6H_4-\underline{C}H_3$), 22.2 (C-6), 27.8 (C-7), 29.7 (3-CH_3), 33.9, 37.9 ($CON(\underline{C}H_3)_2$), 74.3 (C-8), 99.4 (C-4), 125.6, 125.9, 127.5, 130.2 ($\underline{C}_6H_4-CH_3$), 109.7, 131.0, 131.5, 134.8, 135.3, 139.3, 145.7, 151.2 (4° carbon atoms), 170.0 ($\underline{C}ON(CH_3)_2$). Anal. Calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.71; H, 6.90; N, 11.55. HRMS (ESI) *m*/*z* $C_{22}H_{26}N_3O_2$ $[M + H]^+$ Calcd: 364.2020. Found: 364.2010. For the determination of heavy metals and water content, an exemplary batch used for toxicity studies was analyzed: heavy metals, total: <20 ppm; water content (Karl Fischer titration): 0.02%.

5-[(Dimethylamino)methyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1H-benzimidazole-6-carboxamide hydroiodide (12a). Benzimidazole **11** (1.5 kg, 6.43 mmol) was suspended in a mixture of triethylamine (220 mL, 1.58 mol) and 2-propanol (12.0 L). Eschenmoser's salt (dimethylmethylidene ammonium iodide; 1.55 kg, 8.36 mol) was added and the suspension stirred for 16 h at room temperature. The precipitate was isolated by filtration and dried *in vacuo* (50 °C), yielding a mixture of the title compound with 2-propanol (10 mol %) and triethylamine (1 mol %): 2.8 kg, quantitative yield. This transformation was also feasible using dimethylmethylidene ammonium chloride as a reagent. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.04 (d, 2-PrOH), 1.21 (t, NEt_3), 2.59 (s, 3 H), 2.77 (s, 6 H), 2.96 (s, 3 H), 3.10 (s, 3 H), 3.77 (s, 3 H), 4.25 (s, 2 H), 7.17 (s, 1 H), exchangeable protons not visible. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 8.6 (NEt_3), 13.3, 25.4 (2-PrOH), 30.2, 34.4, 35.0, 42.3, 45.8 (NEt_3), 53.9, 61.9 (2-PrOH), 100.6, 106.3, 131.4, 137.0, 148.2, 152.7, 170.6. HRMS (ESI) *m*/*z* $C_{15}H_{23}N_4O_2$ $[M + H]^+$ Calcd: 291.1816. Found: 291.1815.

5-[(Dimethylamino)methyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1H-benzimidazole-6-carboxamide hydrochloride (12b). A mixture of benzimidazole **11** (5.0 kg, 21.43 mol) and dimethylammonium chloride (2.3 kg, 28.20 mol) in triethylamine (0.65 kg, 6.42 mol) and 2-propanol (35.0 L) was heated to 35−45 °C, and formaldehyde (37% in water, 2.3 kg, 28.34 mol) was added over a period of 1−3 h at this temperature. While adding the formaldehyde, the reaction mixture was inoculated with several grams of product. After complete addition of the formaldehyde, the mixture was stirred further 1−3 h at 35−45 °C. Methylisobutyl ketone (35.0 L) was added, and 15 L of distillate was removed at 35−60 °C *in vacuo*. The reaction mixture was cooled to 10−20 °C and stirred for a minimum of 1 h at this temperature. The precipitate was isolated by filtration and dried *in vacuo* (50 °C), yielding a mixture of the title compound with isopropanol (1 mol %) and triethylamine (10 mol %): 7.0 kg, quantitative yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.04 (d, 2-PrOH), 1.22 (t, NEt_3),

2.58 (s, 3 H), 2.73 (s, 6 H), 2.93 (s, 3 H), 3.04 (q, NEt_3), 3.08 (s, 3 H), 3.75 (s, 3 H, m_c, 2-PrOH), 4.25 (s, 2 H), 7.13 (s, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 8.3 (NEt_3), 13.2, 25.4 (2-PrOH), 30.0, 33.8, 34.9, 42.1, 45.1 (NEt_3), 53.4, 100.5, 106.2, 131.5, 131.6, 137.0, 148.3, 152.6, 170.4. HRMS (ESI) *m/z* $C_{15}H_{23}N_4O_2$ $[M + H]^+$ Calcd: 291.1816. Found: 291.1824.

4-Hydroxy-*N*,*N*,1,2-tetramethyl-5-[3-(2-methylphenyl)-3-oxopropyl]-1H-benzimidazole-6-carboxamide (15). *Method A.* Mannich base **12b** (800 g, 2.34 mol) was dissolved in 2 N sodium hydroxide solution (2.3 L) and water (2.0 L) and added over a period of 1 h to a refluxing solution of ethyl 3-(2-methylphenyl)-3-oxopropanoate (669 g, 3.24 mol) in water (4.0 L) and toluene (4.0 L). The reaction mixture was stirred for 8 h at reflux. At room temperature, the precipitate was isolated by filtration and dried *in vacuo* (50 °C), yielding 902 g of the crude title compound.

Salt Formation with Citric Acid. Over a period of 1 h, an aqueous solution of citric acid (1.3 M, 4.4 L) was added to a suspension of the crude product (902 g, 2.38 mol) in *n*-butanol (5.0 L). The suspension was stirred for 60 h at room temperature. The salt of the title compound with citric acid was isolated by filtration and dried *in vacuo* (50 °C): 778 g (1.26 mol) of a colorless solid, 53% yield (stoichiometric ratio with respect to citric acid: 1:1.75). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.42 (s, 3 H), 2.52 (s, 3 H), 2.80 (s, 3 H), 3.00, 3.07 (s, bm_c, 7 H), 3.67 (s, 3 H), 6.78 (s, 1 H), 7.30 (m_c, 2 H), 7.42 (m_c, 1 H), 7.70 (m_c, 1 H), 10.00 (bs, 1 H).

Preparation of the Title Compound from Its Salt with Citric Acid. A suspension of the salt of the title compound with citric acid (1020 g) in dichloromethane (6.0 L) and water (4.0 L) was neutralized with 25% aqueous ammonia solution (~400 mL, pH 8−9). The phases were separated, and the aqueous phase was extracted with dichloromethane (4.0 L). The combined organic phases were washed with water (1.0 L, and the solvent was evaporated. The residue was suspended in hot acetone (1.2 L), the suspension was cooled down, and the product was isolated by filtration and dried *in vacuo* (50 °C). The pure title compound was obtained in 82% yield (553 g, HPLC purity >96%).

Method B. The inertized reaction vessel was charged with Mannich base **12b** (5.0 kg, 15.3 mol), β-ketoester **14** (3.8 kg, 18.4 mol), and 35 L of toluene. The suspension was heated to 55−62 °C, and a solution of potassium *tert*-pentylate (25% in toluene, 17.4 kg, 34.5 mol) in DMF (10 L) was added over a period of 2−3 h. The mixture was heated to 75−85 °C, stirred at this temperature for 0.5−1 h, and diluted with water (40 L). After a period of 2−3 h at reflux, 54 L of the solvents was stripped off, the reaction mixture was cooled to 15−25 °C, and stirring was continued for 2−5 h at this temperature. The suspension was cooled further to 7 to −15 °C, stirred for another 1−2 h, and centrifuged. After drying *in vacuo* at 50 °C, 5.2 kg (90% yield) of the title compound was obtained; mp 209−211 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.42 (s, 3 H), 2.48 (s), 2.77, 2.80, 3.00, 3.05 (s, bm_c, s, bm_c, 10 H), 3.67 (s, 3 H), 6.78 (s, 1 H), 7.30 (m_c, 2 H), 7.42 (m_c, 1 H), 7.70 (m_c, 1 H), 10.00 (bs, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.0, 20.6, 22.4, 29.8, 34.0, 38.4, 42.0, 98.0, 115.2, 125.8, 128.4, 131.1 (2×), 131.6, 132.0, 135.2, 136.8, 137.7, 145.9, 151.2, 170.7, 203.9. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.76; H, 6.62; N, 10.83. HRMS (ESI) *m/z* $C_{22}H_{26}N_3O_3$ $[M + H]^+$ Calcd: 380.1969. Found: 380.1964.

4-Benzyloxy-*N*,*N*,1,2-tetramethyl-5-[3-(2-methylphenyl)-3-oxopropyl]-1H-benzimidazole-6-carboxamide (28). The inertized reaction vessel was charged with ketone **15** (5.0 kg, 13.2 mol), potassium carbonate (2.0 kg, 14.5 mol), and DMF (10 L). The suspension was heated to 50−58 °C, and benzyl chloride (1.83 kg, 14.5 mol) was added over a period of 1.5−2 h. The mixture was stirred for 1.5−3 h at this temperature, and aqueous ammonia solution (25%, 0.45 kg) was added over a period of 10−30 min. Subsequently, cyclohexane (20 L) was added within 15−30 min followed by addition of water (40 L) over a period of 1−1.5 h. The suspension was stirred further for 0.5−1 h, cooled to 8−15 °C over 3−24 h, and filtrated over an agitated pressure filter dryer. The filtrate was discarded. To the crude product on the filter dryer were added cyclohexane (20 L) and water (40 L), and the suspension was stirred for 0.5−1 h at 30−40 °C and for another 30 min at 8−15 °C. The title compound was isolated by filtration and dried *in vacuo* (50 °C): 5.3 kg (85% yield); mp 146−148 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.36 (s, 3 H), 2.56 (s, m_c, 4 H), 2.74 (s, 3 H), 2.95, 2.99 (bs, s, 6 H), 3.71 (s, 3 H), 5.80 (s, 2 H), 7.03 (s, 1 H), 7.27 (m_c, 5 H), 7.40 (m_c, 3 H), 7.52 (m_c, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.4, 20.5, 22.6, 29.8, 34.0, 38.4, 42.3, 73.2, 101.2, 119.4, 125.7, 127.7, 127.8, 128.2 (2×), 131.0, 131.5 (2×), 133.2, 136.4, 136.6, 137.6, 137.9, 146.3, 151.6, 170.2, 203.6. Anal. Calcd for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65; N, 8.95. Found: C, 73.53; H, 6.74; N, 8.82. HRMS (ESI) *m/z* $C_{29}H_{32}N_3O_3$ $[M + H]^+$ Calcd: 470.2438. Found: 470.2445.

4-Benzyloxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-*N*,*N*,1,2-tetramethyl-1H-benzimidazole-6-carboxamide (31). In a 10 L autoclave equipped with a glass inlay and filled with nitrogen, ketone **28** was suspended in dry 2-propanol (entries 1−5: 4000 mL; entry 6: 3500 mL). Potassium *tert*-butylate solution (1 M in *tert*-butanol) and the hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] were added (for quantities, see Table 4). The autoclave was purged with hydrogen (3×), and the reaction mixture was hydrogenated at 70 °C and 80−100 bar pressure for 20 h.

Workup of Sample 1. The reaction mixture was cooled to 35 °C, transferred into a glass vessel, neutralized with acetic acid (12.2 mL, addition at a temperature of 65 °C), and diluted with water (8 L, addition over a period of 0.25 h). The solution was cooled to 15−20 °C, and precipitate was formed. The title compound was isolated by filtration under pressure and dried *in vacuo* at a temperature of 50 °C (682 g of a colorless solid, 68% yield). The filtrate was concentrated (removal of 2.5 L of 2-propanol/water). The warm solution was transferred into a glass vessel and gradually cooled to 10 °C. Further 264 g of the title compound (26% yield) was isolated by filtration under pressure.

Workup of Samples 2 and 3. In the autoclave, the reaction mixtures were neutralized by addition of acetic acid (12.2 mL each) and transferred into a 60 L vessel. At a temperature of 50−55 °C, 24 L of water was added over

a period of 1 h. Stirring was continued for 1 h, and the mixture was gradually cooled to 15−20 °C. The title compound was isolated by filtration under pressure and dried *in vacuo* at a temperature of 50 °C (1711 g of a colorless solid, 85% yield).

Workup of Samples 4−6. Samples 4−6 were purified as described above for samples 2 and 3.

The three batches listed in Table 4 were combined and suspended in acetone (20 L). The suspension was stirred for 4.5 h at 50 °C, for 17 h at room temperature, and for 1.5 h at 10 °C. The title compound was isolated by filtration and dried *in vacuo* (50 °C): 4236 g of a colorless solid, 73% yield. The mother liquor was concentrated to 25% of its original volume and stirred for 17 h at room temperature. Another batch of the title compound was obtained by filtration: 455 g of a colorless solid, 8% yield; mp 160−163 °C. Determination of the optical purity by HPLC (column: Daicel Chiralcel OD-H, 250 mm × 4.6 mm, 5 μm; eluant: *n*-heptane/ethanol,: 90:10; flow rate: 1 mL/min; 40 °C; detection wavelength: 218 nm): t_R [(3*R*)-enantiomer] = 18.2 min/98.14 area %, t_R [(3*S*)-enantiomer] = 20.9 min/0.78 area %, 98.4% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.60 (m_c, 1 H), 1.80 (m_c, 1 H), 2.16 (s, 3 H), 2.54 (s, m_c, 4 H), 2.67 (s, 3 H), 2.94 (s, m_c, 4 H), 3.68 (s, 3 H), 4.67 (bs, 1 H), 5.00 (bs, 1 H), 5.71 (s, 2 H), 6.96 (s, 1 H), 7.11 (m_c, 3 H), 7.34 (m_c, 4 H), 7.44 (m_c, 2 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.4, 18.4, 24.3, 29.7, 33.9, 38.3, 38.7, 69.1, 73.2, 101.1, 120.9, 125.4, 125.5, 126.1, 127.5, 127.6, 128.1, 129.7, 131.6, 133.4, 133.6, 136.1, 138.1, 144.0, 146.3, 151.4, 170.3. HRMS (ESI) *m/z* $C_{29}H_{34}N_3O_3$ $[M + H]^+$ Calcd: 472.2595. Found: 472.2592.

4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-*N*,*N*,1,2-tetramethyl-1H-benzimidazole-6-carboxamide (34). *Synthesis by Deprotection of Diol 31.* The inertized reaction vessel was charged with benzylated diol **31** (5.0 kg, 10.6 mol), palladium on charcoal (10%, type E101 Degussa, 50% H_2O, 250 g), and 40 L of methanol. Under vigorous stirring, the reactor was purged with hydrogen and the reaction mixture hydrogenated at 15−30 °C and 3−4 bar pressure for 3−5 h. Methanol (25 L) was added and the mixture heated to 45−55 °C. Subsequently, the mixture was filtrated through a layer of Hyflo Super Cel (1.5 kg) in a heated pressure filter (45−55 °C). The filter cake was washed with warm methanol (2 × 3 L), the complete filtrate was transferred back to the reaction vessel, and 53−57 L of the solvent was distilled off *in vacuo* at 50−60 °C. Crystallization was induced by inoculation of the solution with 5−10 g of seed crystals of product **34**. The mixture was further stirred for 1−1.5 h at 50−60 °C followed by addition of water (20 L). Another 5−7 L of the solvents was stripped off *in vacuo* at 50−60 °C. The suspension was cooled to 8−15 °C within 1−3 h, stirred for a minimum of 8 h, and finally centrifuged. The filter cake was washed with water (5−8 L), furnishing 3.6 kg (90% yield) of the title compound after drying *in vacuo* at 50 °C.

Synthesis by Direct Catalytic Hydrogenation of Ketone 15. To a flame-dried flask filled with argon and potassium *tert*-butylate (1 M solution in *tert*-butanol, 652 mL, 0.65 mol) was added a suspension of ketone **15** (225 g, 0.59 mol) in 2-propanol (520 mL). The mixture was stirred for 90 min at room temperature and the hydrogenation catalyst **9** (3.70 g, 3.0 mmol) added. After an additional 30 min, the dark-brown solution was transferred into a 2 L Premex Hastelloy autoclave with glass inlay. The reactor was purged with hydrogen (3×) and subjected to a hydrogen pressure of 80 bar. After a reaction time of 20 h at 70 °C, the autoclave was cooled and the reaction mixture poured on a stirred mixture of saturated ammonium chloride solution (2.2 L) and dichloromethane (3.3 L). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 300 mL). The combined organic phases were washed with water (2 × 1 L) and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The crude title compound (250 g of a green foamy solid, HPLC purity: 94.0%, optical purity: 94.2% ee) was crystallized from acetone (500 mL). The suspension was concentrated to a volume of 400 mL, stirred for 17 h at room temperature, and diluted with methyl *tert*-butyl ether (400 mL). After additional 2 h at 0 °C, the title compound was isolated by filtration, washed with methyl *tert*-butyl ether (200 mL) and dried *in vacuo*: 184 g of an off-white solid (80% yield, HPLC purity: 96.5% containing 2.0% of byproduct **10**, optical purity: 94.0% ee); mp 205−207 °C. Determination of the optical purity by CE (capillary: Agilent barefused silica bubble, 56.0/64.5 cm × 50 μm; buffer: 50 mM sodium phosphate (pH 2.5); chiral selector: 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; voltage: 30 kV; temperature: 20 °C; detection: diode array 219 nm): t_M [(3*S*)-enantiomer] = 19.8 min; t_M [(3*R*)-enantiomer] = 20.7 min; 94.0% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.70 (bs, 1 H, 2′-H_a), 1.89 (bs, 1 H, 2′-H_b), 2.22 (s, 3 H, $C_6H_4-C\underline{H}_3$), 2.30−3.00 (m, 2 H, 1′-H_a, 1′-H_b), 2.51 (s, 3 H, 2-CH_3), 2.70 (s, 3 H, $N(CH_3)_2$), 2.94 (bs, 3 H, $N(CH_3)_2$), 3.65 (s, 3 H, 3-CH_3), 4.71 (bs, 1 H, 3′-H), 5.04 (bs, 1 H, OH), 6.73 (s, 1 H, 4-H), 7.09 (m_c, 2 H, $C_6\underline{H}_4-CH_3$), 7.16 (m_c, 1 H, $C_6\underline{H}_4-CH_3$), 7.42 (m_c, 1 H, $C_6\underline{H}_4$-CH_3), 10.18 (bs, 1 H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.0 (2-CH_3), 18.5 ($C_6H_4-\underline{C}H_3$), 24.0 (C-1′), 29.7 (3-CH_3), 33.9 ($CON(\underline{C}H_3)_2$), 38.3 ($CON(\underline{C}H_3)_2$, C-2′), 69.1 (C-3′), 97.7 (C-4), 125.3, 125.5, 126.1, 129.7 ($\underline{C}_6H_4-CH_3$), 116.3, 131.2, 132.1, 133.7, 135.0, 144.2, 145.8, 150.9 (4° carbon atoms), 170.9 ($\underline{C}ON(CH_3)_2$). Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 68.98; H, 7.05; N, 10.52. HRMS (ESI) *m/z* $C_{22}H_{28}N_3O_3$ $[M + H]^+$ Calcd: 382.2125. Found: 382.2123.

Acknowledgment

We are grateful to SynphaBase (Muttenz, Switzerland) for providing us with kilogram quantities of benzimidazole **11**, Ms. Tanja Ramisch (Nycomed, Konstanz) for the determination of the optical purity of target compounds and intermediates by capillary electrophoresis and HPLC, Mr. Wolfgang Frey (University of Stuttgart) for the X-ray analysis of the salt of BYK 405879 (**8**) with succinic acid, Mr. Burkhard Grobbel, Mr. Bernd Marenski, Ms. Melanie Horn and Mr. Oliver Meyer (Nycomed, Konstanz) for

technical assistance, and to the Institute Fresenius (Berlin) for analysing the ruthenium and palladium content of selected samples.

Supporting Information Available

Experimental procedures for the synthesis of compounds **11**, **17**−**23**, **29**, **30**, **31** (screen of reaction conditions and asymmetric hydrogenation in 32 g scale), **32**, **33**, **34** (methods of purification), **35**−**38**. Analytical data of byproduct **25**. ^{1}H NMR spectra of compounds **8**, **12**, **15**, **28**−**38**. ^{13}C NMR spectra of compounds **8**, **12**, **15**, **28**, **29**, **31**, **32**, **34**, **35**, **37**, **38**. Details of the X-ray analysis of the salt of BYK 405879 (**8**) with succinic acid. This information is available free of charge *via* the Internet at http://pubs.acs.org.

Received for review July 29, 2008.

OP800177X