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Synthesis of enantiopure 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles via asymmetric ketone hydrogenation in the presence of $RuCl_2$[Xyl-P-Phos][DAIPEN]

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ABSTRACT

The asymmetric hydrogenation of complex heterocyclic ketones **1** in the presence of the novel catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] and a base afforded the corresponding alcohols **2** in good enantiomeric purity. The outcome of the reaction depended on the substitution pattern of the ketone and the stoichiometry of the base. After optimization of the reaction conditions, the pure alcohols **2a** and **2b** were isolated in good yield (>70%) and enantiomeric purity (>93% ee) and used as key intermediates for the synthesis of the pharmaceutically active 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles **3a** and **3b**.

1. Introduction

Acid related diseases, such as gastroesophageal reflux disease (GERD), have a high prevalence and influence strongly the quality of life of the affected patients.[1] The reversible inhibition of the gastric proton pump enzyme (H^+/K^+-ATPase) represents an important approach in the development of drugs against these medical conditions. Over the past two decades, one important approach for the identification of potent potassium-competitive acid blockers (P-CABs) relied on the structural class of substituted imidazo[1,2-*a*]pyridines. Recently, we described the discovery and the enantioselective synthesis of tricyclic imidazo[1,2-*a*]pyridines, such as, for example, BYK 311319 **6** (R′ = R″ = Me, Ar = Ph) which are highly potent reversible inhibitors of the H^+/K^+-ATPase, and possess promising pharmaceutical properties.[2] Nevertheless, our work in the field of imidazo[1,2-*a*]pyrazines and pyrrolo[3,2-*b*]pyridines demonstrated that the imidazo[1,2-*a*]pyridine scaffold does not constitute an indispensable structural element of potent P-CABs.[3] Herein, we report the synthesis of enantiopure 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles of the general formula **3**, which are isomers of the 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines of the general formula **6**. The biochemical and pharmacological properties of these derivatives will be reported in due course.

The synthesis of the compounds of class **3** in enantiomerically enriched or enantiopure form was designed around the two key steps of asymmetric hydrogenation of ketones **1** and subsequent Mitsunobu cyclization of the resulting diols **2** (Scheme 1). A similar approach had already proven its value in the preparation of the related class of imidazopyridines **6**, via the reduction of precursor **4** and cyclization of **5**.[2,4] The ketones of the general formula **1** were prepared in an analogous manner to imidazopyridine ketones of the general formula **4**.[2,5]

The introduction, in the mid 90s, of catalysts of the type $RuCl_2$[PP][NN] ([PP] = chiral diphosphine, [NN] = chiral 1,2-diamine) represented a breakthrough in the field of the asymmetric catalytic reduction of aryl ketones.[6] Very high enantioselectivities and activities were obtained on a wide range of ketones, particularly when catalyst $RuCl_2$[Xyl-BINAP][DAIPEN] **8** was used (Fig. 1). A number of applications to industrially relevant molecules have been reported, including the asymmetric reduction of complex heterocyclic ketones.[7] As part of the research on a scalable efficient route to products **6**, we developed the catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], **9** (Fig. 1),[4,8] and successfully applied it to the asymmetric hydrogenation of ketones **4**, achieving high enantioselectivity (>95% ee) and high activity (up to a molar substrate to catalyst ratio, S/C, of 5000:1). The complex nature of the substrates required the development of new reaction conditions. While the asymmetric hydrogenation of aryl ketones is generally carried out in the presence of substoichiometric amounts of base (i.e., *t*-BuOK in 2-PrOH), in the case of substrates **4**, concern about the presence of the mildly acidic phenol group was overcome by

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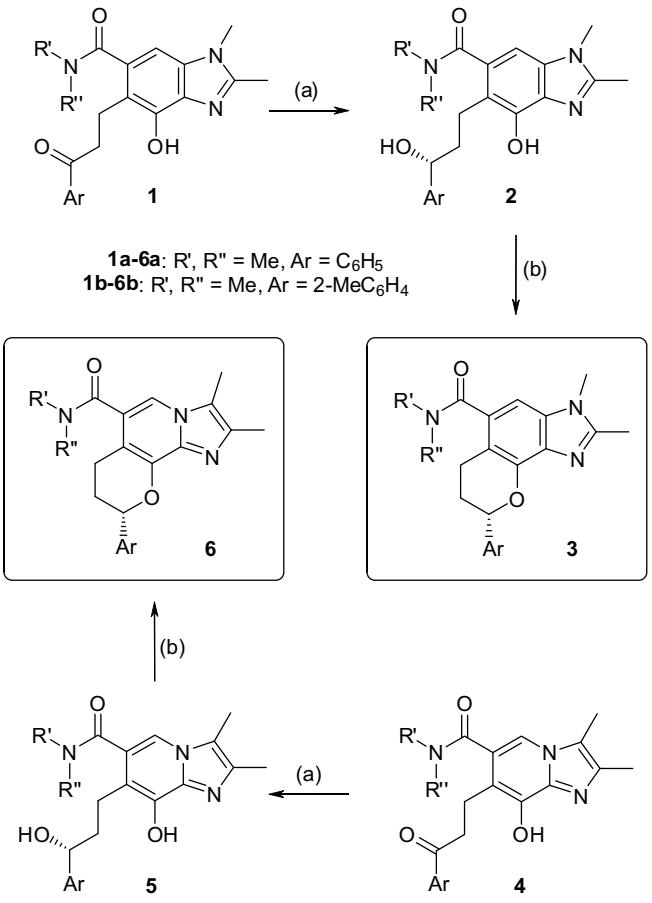


Scheme 1. Synthesis of enantiopure 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles **3** and 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **6**.

using 1 equiv of base to deprotonate the hydroxy function and a small excess of base to activate the catalyst. It was also found that the addition of a small amount of water (10–20%) had a beneficial effect on the conversion at lower catalyst loadings. Using a larger excess of base increased the reaction rates and no by-products were detected over the course of the reaction.

2. Results and discussion

2.1. Identification of a suitable method for the asymmetric reduction of ketone 1b

The asymmetric reduction of ketone **1b** (Ar = 2-methylphenyl and R′ = R″ = Me) was studied in a detailed manner using a HTS approach.[9] Over the course of such an experiment, 96 different hydrogenation reactions were assembled in glass vials under an inert atmosphere by a dispensing robot. The vials were placed on a metal plate in a reactor block. The block was set under hydrogen pressure and heated and shaken continuously to enable hydrogenation of the 96 reactions at identical pressure (80 bar) and temperature (80 °C). The substrate to catalyst ratio (S/C ratio) employed was 25. The reactions were stopped after 24 h of reaction time and subjected to supercritical fluid chromatography for analysis. In detail, 19 ligands of various ligand classes (Taniaphos, Josiphos, Walphos, Mandyphos, MeOBIPHEP, Naud oxazolines) were investigated.[10] Ligands belonging to the BINAP family were also included. Six different metal precursors were used for the in situ formation of the respective hydrogenation catalyst: $[Rh(nbd)Cl]_2$, $[Rh(nbd)_2]BF_4$, $[RuCl_2(p\text{-cymene})]_2$, $[Ru(cod)(OTFA)_2]$, $[RuCl_2(PPh_3)_3]$, $[Ir(cod)Cl]_2$ and $[Ir(cod)_2]BF_4$. Additionally, six different ruthenium precatalysts were employed. Six solvents (dichloromethane, methanol, 1,2-dichloroethane, toluene, 2-propanol, water) and five additives (triethylamine, tetrafluoroboric acid dimethyl ether complex, potassium *tert*-butylate, sodium hydroxide, potassium carbonate) were used over the course of the HTS screening. For the majority of the reactions, little to no conversion was observed. Only rhodium catalysts gave significant conversion and product formation. Neither the tested Noyori Ru-PP–NN systems nor the Naud catalysts gave conversions >50%. The observed ee values were rather low. In Table 1, the results of single experiments performed in a 50 ml autoclave are summarized. Catalyst **7** and ligand **10**, which had performed successfully on related substrates, and ligand **11** that constituted the most promising ligand identified in the course of the HTS screening, were used for these experiments.

The enzymatic reduction of ketone **1b** to the corresponding (*R*)-configured alcohol **2b** was also investigated applying various alcohol dehydrogenases (ADHs) and ADH variants derived from *Lactobacillus brevis*, *Thermoanerobacter*, *Rhodococcus*, *Candida parapsilosis*, *Lactobacillus kefir* and *Thermoanerobium brokii*.[11] However, none of the enzymes tested exhibited the potential to carry out the desired reduction.

2.2. Successful asymmetric reduction of ketones 1a and 1b using $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN]

Since no promising hydrogenation catalysts suitable for the efficient and enantioselective transformation of ketones **1** into alcohols **2** were identified in the course of the HTS screening, we focused on the complex $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **9**. As mentioned above, this catalyst has already proven its value in the transformation of the structurally related ketones **4**.[4] We first studied the hydrogenation of the 'parent' compound **1a** (Ar = Ph and R′ = R″ = Me) and used a procedure that was broadly based

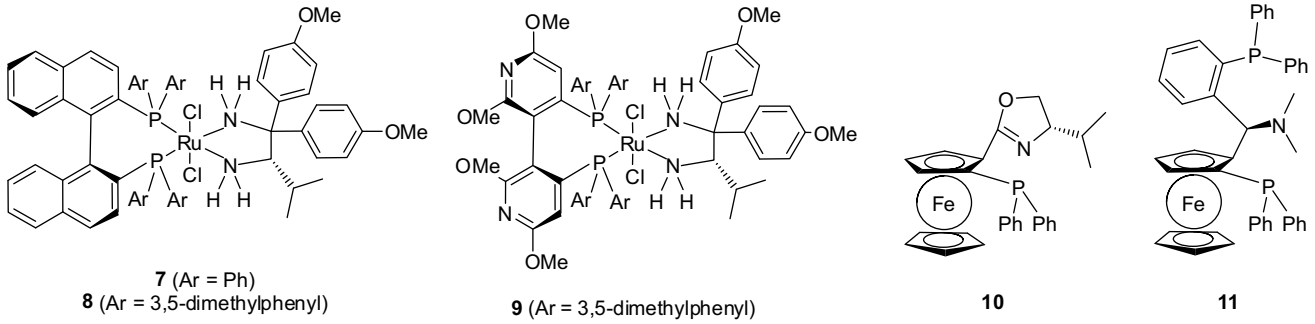


Figure 1. Structure of the catalysts $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN], **7**, $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN], **8**, $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], **9**, and the ligands Naud oxazoline N003-1, **10**, Taniaphos T001-1, **11**.

Table 1
Asymmetric catalytic hydrogenation of ketone **1b** (S/C = 100:1, t = 16–20 h, c = 0.1 M)

Entry	Metal	Ligand	Solvent	Additive	pH_2 (bar)	T (°C)	Conv.[a] (%)	% ee
1	$Rh(nbd)_2BF_4$	**11**	$MeOH/CH_2Cl_2$	—	80	80	100	13
2	$Rh(nbd)_2BF_4$	**11**	MeOH	—	80	80	100	15
3	$Rh(nbd)_2BF_4$	**11**	MeOH	—	80	50	60	16
4	$[RuCl_2(p\text{-cymene})]_2$	**11**	MeOH	Et_3N	60	80	<5	n.d.
5	$[RuCl_2(PPh_3)(\mathbf{10})]$		2-PrOH/TFE[b]	K_2CO_3	60	80	<5	n.d.
6	$RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN][c]		2-PrOH	*t*-BuOK	60	80	<10	n.d.

[a] Conversion determined by HPLC.
[b] TFE = trifluoroethanol.
[c] Catalyst **7** (depicted in Fig. 1).

Table 2
Asymmetric catalytic hydrogenation of ketone **1a**

Entry	Cat.	S/C	Base[a]	Solvent[b]	T (°C)	Conv.[c] (%)
1	**9**	500:1	1.2 equiv *t*-BuOK	2-PrOH	70	100
2	**9**	500:1	1.2 equiv *t*-BuOK	2-PrOH/10% H_2O	70	100
3	**9**	500:1	25% aq KOH	50% *t*-BuOH/25% 2-PrOH	70	100
4	**9**	1000:1	1.2 equiv *t*-BuOK	2-PrOH/10% H_2O	70	62–94
5	**9**	1000:1	1.5 equiv *t*-BuOK	2-PrOH/10% H_2O	70	86
6	**9**	1000:1	1.2 equiv *t*-BuOK	2-PrOH/10% H_2O	75	79
7	**9**	1000:1	1.2 equiv *t*-BuOK	2-PrOH/20% H_2O	75	51
8	**9**	1000:1	10% aq KOH	40% *t*-BuOH/50% 2-PrOH	70	89
9	**9**	1000:1	25% aq KOH	50% *t*-BuOH/25% 2-PrOH	70	92
10	**8**	250:1	1.2 equiv *t*-BuOK	2-PrOH	70	100
11	**8**	500:1	1.2 equiv *t*-BuOK	2-PrOH	70	65

[a] 1 M solution of *t*-BuOK in *t*-BuOH or 10 M aq KOH solution.
[b] Reactions were run in a Biotage Endeavour: 25 bar H_2, 16 h, substrate concentration of 0.25 M (entries 1–3, 10 and 11) or 0.33 M (entries 4–9).
[c] Conversion determined by HPLC and/or ^1H NMR.

on the protocol followed for the reduction of imidazo[1,2-*a*]pyridines **4** (Table 2, Scheme 1). In the presence of catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], **9**, and 1.2 equiv of base, the reduction proceeded smoothly overnight at S/C 500:1, with anhydrous solvents (Table 2, entry 1) as well as with wet solvents (entry 2). Since it can be expected that the addition of water to potassium *tert*-butylate causes the formation of potassium hydroxide, it was also proven that the use of excess aqueous potassium hydroxide was effective for producing the desired reaction (entry 3). Under the same reaction conditions at S/C 1000:1 the reaction proceeded in a less reliable manner (entry 4, 62–94% conversion). Whereas a slight increase of the base stoichiometry (entry 5) or reaction temperature (entry 6) appeared to be beneficial, a decrease in conversion was observed in the presence of higher amounts of water (entry 7). Again, in the presence of excess aqueous potassium hydroxide, the reaction approached full conversion (entries 8 and 9). At S/C 500:1, $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] **8** was found to be less active than $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], **9**, (entry 11 vs entry 1) and, in order to achieve full conversion, the catalyst loading was increased to S/C 250:1 (entry 10). Since at the time a suitable analytical method was not available, the preliminary experiments of Table 2 could not be analyzed for enantioselectivity. The enantioselectivity was later determined by capillary electrophoresis (CE) on isolated samples of **2a** and was found to be consistently very high (>97% ee) when the catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **9** had been used. On the other hand, an isolated sample of product **2a** obtained from $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] **8** (entry 10) showed surprisingly low enantiomeric purity (25% ee). The asymmetric reduction of ketone **1a** was then performed on a 2 g scale (S/C = 310:1, 1.45 equiv of *t*-BuOK, 80 bar H_2, 65 °C, 23 h) and diol **2a** was isolated in 70% yield and 98% ee.

In general it was found that benzimidazole ketone **1a** was less reactive than the corresponding imidazo[1,2-*a*]pyridine **4a** (Ar = Ph and R′ = R″ = Me). Furthermore, it was thought that the presence of water would further reduce the already limited solubility of substrates **1** and the use of neat organic solvents was preferred for further development.

Compound **3b** (Ar = 2-methylphenyl, R′ = R″ = Me) was considered the most interesting member of the class and the hydrogenation of **1b** was studied on a larger scale. High enantioselectivity was first demonstrated on small scale under the conditions already tested for **1a** (Table 3), although at reduced catalyst loadings due to the reduced reactivity of the substrate which, in turn, can be attributed to its increased steric bulk. At S/C 250:1 some erosion of enantioselectivity took place when a higher amount of base was used (Table 3, entry 3).

Table 3
Asymmetric catalytic hydrogenation of ketone **1b**

Entry	Cat.	S/C	Base[a,b]	Conv.[c] (%)	ee[d] (%)
1	**9**	100:1	2.7 equiv *t*-BuOK	100	92–95
2	**9**	250:1	1.7 equiv *t*-BuOK	100	95
3	**9**	250:1	2.7 equiv *t*-BuOK,	100	89–92

[a] Reactions were run in a Biotage Endeavour: 2-PrOH, 30 bar H_2, 65 °C, 16 h, substrate concentration of 0.18 M.
[b] 1 M solution of *t*-BuOK in *t*-BuOH.
[c] Conversion determined by HPLC and/or ^1H NMR.
[d] Ee determined by HPLC.

The hydrogenation of substrate **1b** was then reproduced in 100 ml to 2 l autoclaves (Scheme 1). On a 35 g scale using an S/C ratio of 100:1, the transformation proceeded smoothly in the presence of 1.1 equiv of *t*-BuOK (2-PrOH, 80 bar H_2, 70 °C, 20 h) and the diol **2b** was isolated in good yield (76%) and enantiomeric purity (93.8% ee). However, when the hydrogenation was conducted at an S/C ratio of 250:1 and the amount of base was increased to 1.7 equiv under otherwise identical reaction conditions, the desired product **2b** was formed in mixture with a by-product, which could be isolated by chromatography, it was fully character-

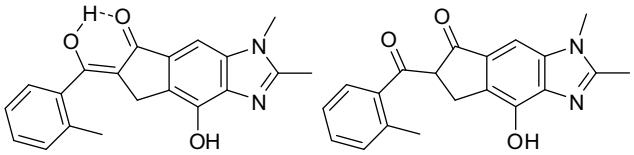


Figure 2. Structure of by-product **12b** formed during catalytic asymmetric hydrogenation of ketone **1b**.

ized and identified as compound **12b** (Fig. 2). Compound **12b** was presumably caused by formation of a reactive enolate that then attacked the amido group. An analogous by-product has never been detected in the imidazopyridine class. The absence of such a side reaction in the latter class of substrates may be attributed to the different electronic nature of the heterocyclic scaffold (thus producing a different activation of the carboxamide group towards nucleophilic attack) or to the higher reactivity of imidazopyridine ketones, **4** (thus disfavouring the competitive cyclization side reaction). Although the use of high base concentrations is generally expected to increase the reaction rate, the formation of side products of type **12** discouraged the use of a large excess of base for the hydrogenation of ketones **1**, above the 1 equiv required for neutralization of the phenol moiety.

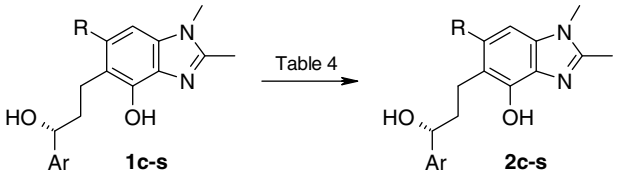
2.3. Application of the hydrogenation method on structurally related ketones 1c–1s

The interest in the class of compounds **3** prompted us to expand upon the scope of the substrates under examination (Table 4). Different substitution patterns at the aryl moiety and at the amido group were explored and it was found that the results of the asymmetric hydrogenation step varied to a surprisingly large degree. The effect of different aryl groups was explored first, while keeping the dimethylamido group fixed (Table 4, entries 1–10). The reduction of the isomeric fluorophenyl-substituted ketones **1c** and **1d** was conducted at high S/C ratios and in the presence of water. Although quantitative conversion occurred in the presence of 1.1–1.5 equiv of base, the corresponding alcohols **2c** and **2d** were isolated in rather low yield (entries 1 and 2). The presence of an *ortho*-substituent on the aromatic ring of the ketones **1** generally gave high selectivity but at, the same time, a diminished activity towards reduction. Consequently, when the hydrogenation was performed in the presence of 2.0–2.75 equiv of base, significant amounts of by-products **12** were formed, which were isolated by chromatography (17–32% yield) and their structure confirmed by NMR spectroscopy (entries 3–6). The corresponding alcohols **2e**–**2h** were obtained with an enantiomeric purity of 72–88% ee. On the other hand, when the hydrogenation was conducted in the presence of only 1.1 equiv of base, the alcohols were obtained with better enantiomeric purity and no by-product **12** was isolated (entries 7 and 8).

Furthermore, no by-products **12** were isolated over the course of the reduction of the thiophene ketones **1k**–**1l** (entries 9 and 10). Interestingly, the thiophen-2-yl-substituted alcohol **2k** was obtained in an enantiomeric purity of 80% ee (entry 9), whereas the structurally related 2-methyl-thiophen-3-yl-substituted alcohol **2l** was obtained in a much higher enantiomeric purity of 96% ee (entry 10).

Surprisingly, a high chemoselectivity was obtained when the pyrrolidinamido group was present instead of the dimethylamido group (entry 11). Substrates containing other amido substituents (entries 13, 14 and 16) gave different results, possibly reflecting the different levels of activation towards nucleophilic attack from the ketone enolate. The presence of the azetidine ring (entry 13) brought a significant amount of by-products. Only the use of a large excess of base gave conversion but afforded almost exclusively a mixture of by-products (including **12b**). The very low solubility of some substrates also played a role, for example, in the case of the *N*-monosubstituted amides **1p** and **1r** (entries 14 and 16). The comparison of the results obtained for the reduction of ketones **1n**/**1o** (entries 12 and 13) and **1q**/**1r** (entries 15 and 16) is of special interest: the asymmetric reduction of **1n** and **1q**, which possess a phenyl residue instead of a 2-methylphenyl substituent, was feasible even at high S/C ratios of 430–500:1 and afforded the alcohols **2n** and **2q** in 32% and 52% yield, respectively. On the other hand, the enantioselectivity was compromised under these conditions (77–85% ee as compared to 95% ee). Ketone **1s**, which possesses a methyloxymethylene residue rather than a carboxamide group, reacted smoothly in the presence of 1.4 equiv of base and the corresponding chiral alcohol **2s** was obtained in 71% yield and 98% ee (entry 17).

Table 4
Asymmetric catalytic hydrogenation of ketones **1c**–**1s**



c-l: R = C(O)NMe$_2$
c: Ar = 2-F-phenyl
d: Ar = 4-F-phenyl
e: Ar = 2-Cl-phenyl
f: Ar = 2-CF$_3$-phenyl
g: 2-Et-phenyl
h: 2-Me-4-F-phenyl
i: 2-(MeOCH$_2$)-phenyl
j: 2-(BnOCH$_2$)-phenyl
k: thiophen-2-yl
l: 2-Me-thiophen-3-yl

m, o, p, r, s: Ar = 2-Me-phenyl
m: R = C(O)pyrrolidine
o: R = C(O)azetidine
p: R = C(O)NH(c-Pr)
r: R = C(O)NHMe
s: R = CH$_2$OMe

n, q: Ar = phenyl
n: R = C(O)azetidine
q: R = C(O)NHMe

Entry	SM	S/C	Base[a] (equiv)	Conditions[b]	Yield/ee[c] (%)	Yield (%)
1	**1c**	300:1	1.5	A[d]	**2c**: 49/96[e]	
2	**1d**	500:1	1.1	A[d]	**2d**: 35/88	
3	**1e**	100:1	2.7	B	**2e**: 48/88	**12e**: 26
4	**1f**	100:1	2.0	C	**2f**: 16/72	**12f**: 31
5	**1g**	100:1	2.75	B	**2g**: 51/86	**12g**: 32
6	**1h**	100:1	2.75	B	**2h**: 61/83	**12h**: 17
7	**1i**	100:1	1.1	C	**2i**: 66/97	
8	**1j**	100:1	1.1	C	**2j**: 64/96	
9	**1k**	100:1	1.5	C	**2k**: 62/80	
10	**1l**	100:1	1.1	C	**2l**: 63/96	
11	**1m**	100:1	2.7	C	**2m**: 94/91	
12	**1n**	430:1	1.2	A[d]	**2n**: 32/85	
13	**1o**	100:1	~6	C	**2o**: 10/95	**12b**: 69
14	**1p**	100:1	2.75	C	**2p**: 45/98	
15	**1q**	500:1	1.2	A[d]	**2q**: 52/77	
16	**1r**	100:1	6.25	C	**2r**: 30/95	
17	**1s**	100:1	1.4	A	**2s**: 71/98	

[a] Base: 10 M aq solution of KOH (entries 13, 16), 1 M solution of *t*-BuOK in *t*-BuOH (all other entries).
[b] Conditions: A: 100 ml Premex Hastelloy autoclave, 80 bar H_2; B: 25 ml Parr microreactor, 25 bar H_2; C: 8 × 10 ml Biotage Endeavour, 25 bar H_2; A–C: 2-PrOH/*t*-BuOH, 65–80 °C, 16–20 h.
[c] Ee measured by HPLC or capillary electrophoresis.
[d] Hydrogenation in the presence of 4–10% of H_2O.
[e] Enantiomeric purity was determined after Mitsunobu cyclization.

2.4. Transformation of chiral diols into target compounds 3

The transformation of alcohols **2** to target compounds **3** was achieved under standard conditions that had previously been developed for the imidazopyridine class (Scheme 1):[2,5] when a

mixture of alcohol **2**, triphenylphosphine and DIAD in THF was stirred at room temperature, the corresponding 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole **3** typically was formed over the course of several minutes. The cyclization always took place with high stereoselectivity and, within the limit of experimental error, the enantiopurity of the final products **3** reflected the enantiopurity of the alcohols **2**, for example, target compounds **3a** and **3b** were obtained in 77% yield (95.8% ee)/84% yield (95.6% ee).

3. Conclusion

In conclusion, we have reported a three-step synthesis of enantiomerically enriched 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles **3** comprising the preparation of prochiral ketones **1**, the asymmetric hydrogenation of these substrates and the Mitsunobu cyclization of the obtained diols **2**. For the asymmetric hydrogenation step, a variety of catalysts were screened using a HTS method. However, the novel Noyori type complex $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **9** was the only catalyst suitable for the effective transformation of ketones **1** affording alcohols **2** in moderate to good yields and excellent enantiomeric purity. The outcome of the asymmetric reduction and the rate of the competing base-catalyzed reaction leading to by-products **12** depended on the substitution pattern of the respective ketone **1**. After optimization of the reaction conditions, target compounds **3a** and **3b** were obtained in good yield. Nevertheless, the therapeutic significance of 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles **3** makes the development of a cost-effective process an on-going effort.

4. Experimental

4.1. General

All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. 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 CH_2Cl_2/MeOH as 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 solvent. The chemical shifts are reported as parts per million (δ ppm) with tetramethylsilane (TMS) or DMSO as the internal standard (^{1}H: δ_{TMS} = 0.00 ppm; ^{13}C δ_{DMSO} = 39.50 ppm). High resolution mass spectra were obtained on a Bruker Daltonics MicroTOF Focus instrument using electrospray ionization (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer. The enantiomeric purity of the target compounds and of selected intermediates was determined by capillary electrophoresis (CE, see Section 4.3) and/or high pressure liquid chromatography (HPLC, see Section 4.4).

4.2. General procedure for the asymmetric hydrogenation of ketones 1c–1s

The hydrogenation reactions were conducted at 65–80 °C in a 8 × 10 ml Biotage Endeavour apparatus, a 25 ml Parr microreactor or a 100 ml Premex Hastelloy autoclave using either *t*-BuOK (1 M in *t*-BuOH) or KOH (10 M in H_2O) as base and mixtures of *t*-BuOH/2-PrOH as solvent. In some cases, water was added (see Table 4). In all cases, >95% conversion of substrate **1** was obtained. The crude products **2c–2s** were isolated by work up with aqueous NH_4Cl solution/CH_2Cl_2 and, except for product **2r** (44% mass recovery), 74–100% mass recovery was obtained. The crude products were purified by column chromatography (silica gel, eluant: CH_2Cl_2/MeOH) and—in some cases—by an additional crystallization step. The reactions were conducted in analogy to the detailed experimental procedures given for the synthesis of diols **2a** and **2b**.

4.3. Determination of the enantiomeric purity of alcohols by capillary electrophoresis 2b, 2d–2i, 2l–2r

The separation of enantiomers by CE was performed using the following experimental set-up (t_M = migration time): Capillary: 56/64.5 cm × 50 μm barefused silica bubble (Agilent). 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 (except for **2e**), 10 °C (**2e**). Detection: Diode array 219/226 nm.

4.4. Determination of the enantiomeric purity of alcohols by HPLC 2j–2k, 2s

The separation of enantiomers by HPLC was performed using the following experimental set-up (t_R = retention time): column: Daicel Chiralpak AD-H, 250 × 4.6 mm, 5 μm, flow rate: 1 ml/min, diode array detection at 218 nm, eluant: see corresponding experiment.

4.5. Analysis of the crude products (conversion, enantiomeric excess) by HPLC (2e–2i, 2l–2m, 2o–2p, 2r), 'HPLC analytical method'

The analysis of the crude products by HPLC was performed with a Merck LichroCART 250-4, Chiradex (5 μg) column applying the conditions specified in the corresponding experiment. For all other alcohols **2**, the conversion was judged from the ^{1}H NMR-spectrum of the crude product, and the enantiomeric excess was determined by the reported CE/HPLC-method.

4.6. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-phenylpropyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2a

In a flask filled with argon, ketone **1a** (2.0 g, 5.5 mmol) was suspended in 2-PrOH (2.8 ml) and H_2O (4.1 ml). *t*-BuOK (1 M in *t*-BuOH, 8.0 ml), *t*-BuOH (20 ml) and **9** (22 mg, 0.017 mmol, S/C 310:1) were added and the mixture was transferred into a 100 ml Premex Hastelloy autoclave and hydrogenated for 23 h at 65 °C and 80 bar H_2-pressure. After cooling to rt and releasing of the H_2-pressure, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography [SiO_2, eluant: CH_2Cl_2/MeOH = 14:1 (v/v)]. Two batches of the title compound were obtained, which were crystallized from acetone: Batch 1: 0.5 g of a beige solid (25% yield, mp 261–263 °C), batch 2: 0.9 g of a beige solid (45% yield, 97.4% ee, mp 263–265 °C). Determination of the enantiomeric purity by CE (capillary: Agilent bubble-cell 64.5 cm × 75 μm; buffer: 50 mM sodium phosphate, pH 2.5; chiral selector: 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; 30 kV; 10 °C): t_M [(3*S*)] = 16.1 min/1.3 area %; t_M [(3*R*)] = 16.4 min/98.7 area %; 97.4% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.73 (br s, 1H, 2′-H_a), 1.91 (br s, 1H, 2′-H_b), 2.20–2.85 (m, 2H, 1′-H_a, 1′-H_b), 2.49 (s, 3H, 2-CH_3), 2.68 (s, 3H, N(CH_3)$_2$), 2.89 (s,

3H, $N(CH_3)_2$), 3.64 (s, 3H, 3-CH_3), 4.48 (br t, 1H, 3′-H), 5.13 (br s, 1H, OH), 6.70 (s, 1H, 4-H), 7.21 (m_c, 1H, Ph), 7.30 (m_c, 4H, Ph), 9.87 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.1 (2-CH_3), 23.4 (C-1′), 29.7 (3-CH_3), 33.8, 38.3 (CON(CH_3)$_2$), 72.6 (C-3′), 97.6 (C-4), 125.9, 126.4, 127.8 (Ph), 116.1, 131.3, 132.0, 135.0, 145.7, 146.0, 150.8 (4 °C), 170.7 (CON(CH_3)$_2$), overlay of C-2′ signal with DMSO signals. HRMS (ESI) *m/z* $C_{21}H_{26}N_3O_3$ $[M+H]^+$ calcd: 368.1969, found: 368.1954.

4.7. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)-propyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2b

In a flask filled with argon, ketone **1b** (35.0 g, 92 mmol) was suspended in degassed 2-PrOH (340 ml) and *t*-BuOK solution (1 M in *t*-BuOH, 101 ml) was slowly added. The yellow suspension was stirred at rt until a solution was obtained (20 min). Catalyst **9** (1.14 g, 0.92 mmol, S/C 100:1) was added and stirring was continued for several min. The brown solution was transferred into a 2 l autoclave with glass inlay, purged with H_2 (3×) and hydrogenated at 70 °C and 80 bar pressure for 20 h. After cooling to rt and releasing of the H_2-pressure, the reaction mixture was poured into a stirred mixture of satd NH_4Cl solution (400 ml) and CH_2Cl_2 (700 ml). The phases were separated and the aq phase extracted with CH_2Cl_2 (2 × 80 ml). The combined organic phases were washed with water (400 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue (41 g of a green foam, 94.9% ee) was dissolved in hot acetone (100 ml). Upon cooling to rt, crystallization started. After a period of 3 h at rt and 2 h at 0 °C, the precipitate was isolated by filtration, washed with acetone (20 ml) and Et_2O (40 ml) and dried in vacuo. The title compound was isolated in the form of a colourless solid (26.5 g, 76% yield, 93.8% ee).—mp 215–217 °C. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 19.9 min/3.1 area %; t_M [(3*R*)] = 20.7 min/96.9 area %; 93.8% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.70 (br s, 1H, 2′-H_a), 1.89 (br s, 1H, 2′-H_b), 2.22 (s, 3H, C_6H_4–CH_3), 2.30–3.00 (m, 2H, 1′-H_a, 1′-H_b), 2.51 (s, 3H, 2-CH_3), 2.70 (s, 3H, $N(CH_3)_2$), 2.94 (br s, 3H, $N(CH_3)_2$), 3.65 (s, 3H, 3-CH_3), 4.71 (br s, 1H, 3′-H), 5.04 (br s, 1H, OH), 6.73 (s, 1H, 4-H), 7.09 (m_c, 2H, C_6H_4–CH_3), 7.16 (m_c, 1H, C_6H_4–CH_3), 7.42 (m_c, 1H, C_6H_4–CH_3), 10.18 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.0 (2-CH_3), 18.5 (C_6H_4–CH_3), 24.0 (C-1′), 29.7 (3-CH_3), 33.9 (CON(CH_3)$_2$), 38.3 (CON(CH_3)$_2$, C-2′), 69.1 (C-3′), 97.7 (C-4), 125.3, 125.5, 126.1, 129.7 (C_6H_4–CH_3), 116.3, 131.2, 132.1, 133.7, 135.0, 144.2, 145.8, 150.9 (4 °C), 170.9 (CON(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.

4.8. 5-[(3*R*)-3-(2-Fluorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2c

Preparation according to Section 4.2: mp 264–266 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.79 (m_c, 2H), 2.50 (s, br s), 2.68 (s, br s, 4H), 2.88 (s, 3H), 3.64 (s, 3H), 4.82 (br t, 1H), 5.26 (br s, 1H), 6.70 (s, 1H), 7.17 (m_c, 3H), 7.49 (dt, 1H), 9.80 (br s, 1H).

4.9. 5-[(3*R*)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2d

Preparation according to Section 4.2: mp 276–277 °C. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 21.4 min/6.2 area %; t_M [(3*R*)] = 21.8 min/93.3 area %; 87.6% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.80 (br s, 2H), 2.40, 2.49 (br s, s), 2.68 (s, br s, 4H), 2.89 (s, 3H), 3.64 (s, 3H), 4.50 (t, 1H), 5.19 (br s, 1H); 6.70 (s, 1H), 7.12 (t, 2H), 7.33 (dd, 2H), 9.90 (br s, 1H).

4.10. 5-[(3*R*)-3-(2-Chlorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2e

Preparation according to Section 4.2: foamy solid. HPLC analytical method (see Section 4.5): eluant: methanol/water = 25/75, 1 ml/min, t_R (enantiomer 1) = 19.2 min, t_R (enantiomer 2) = 24.8 min, t_R (**1e**) = 27.6 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 21.9 min/5.8 area %; t_M [(3*R*)] = 23.7 min/94.2 area %; 88.4% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.69 (br s, 1H), 1.81 (br s, 1H), 2.38, 2.50 (br s, s), 2.69, 2.70 (s, br s, 4H), 2.89 (s, 3H), 3.64 (s, 3H), 4.89 (br s, 1H), 5.34 (br s, 1H), 6.70 (s, 1H), 7.24 (m_c, 1H), 7.35 (m_c, 2H), 7.58 (d, 1H), 9.78 (br s, 1H).

4.11. 4-Hydroxy-5-{(3*R*)-3-hydroxy-3-[2-(trifluoromethyl)-phenyl]propyl}-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2f

Preparation according to Section 4.2: mp 219–221 °C. HPLC analytical method (see Section 4.5): eluant: methanol/water = 15/85, 0.8 ml/min, t_R (enantiomer 1) = 12.8 min, t_R (enantiomer 2) = 17.2 min, t_R (**1f**) = 21.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 21.0 min/13.7 area %; t_M [(3*R*)] = 21.4 min/86.3 area %; 72.6% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.67 (m_c, 1H), 1.89 (m_c, 1H), 2.50 (br s, s), 2.69 (s, 3H), 2.92 (br s, s, 4H), 3.64 (s, 3H), 4.85 (br s, 1H), 5.43 (br s, 1H), 6.70 (s, 1H), 7.43 (m_c, 1H), 7.66 (m_c, 2H), 7.77 (m_c, 1H), 9.93 (br s, 1H).

4.12. 5-[(3*R*)-3-(2-Ethylphenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2g

Preparation according to Section 4.2: mp 135–137 °C. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 13.5 min, t_R (enantiomer 2) = 19.4 min, t_R (**1g**) = 28.1 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 20.5 min/6.8 area %; t_M [(3*R*)] = 21.8 min/93.2 area %; 86.4% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.12 (t, 3H), 1.75 (br s, 2H), 2.40 (br s), 2.50 (s), 2.58 (q), 2.70, 2.83, 2.94 (s, br s, s, 7H), 3.65 (s, 3H), 4.74 (br s, 1H), 5.01 (br s, 1H), 6.71 (s, 1H), 7.13 (m_c, 3H), 7.41 (m_c, 1H), 9.75 (br s, 1H).

4.13. 5-[(3*R*)-3-(4-Fluoro-2-methylphenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2h

Preparation according to Section 4.2: foamy solid. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 17.5 min, t_R (enantiomer 2) = 23.7 min, t_R (**1h**) = 19 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 22.5 min/8.4 area %; t_M [(3*R*)] = 23.7 min/91.6 area %; 83.2% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.78 (br s, 2H), 2.23 (s, 3H), 2.36 (br s), 2.51 (s), 2.69 (s, 3H), 2.93 (s, br s, 4H), 3.65 (s, 3H), 4.67 (br s, 1H), 5.08 (br s, 1H), 6.71 (s, 1H), 6.96 (m_c, 2H), 7.42 (m_c, 1H), 9.82 (br s, 1H).

4.14. 4-Hydroxy-5-{(3*R*)-3-hydroxy-3-[2-(methoxymethyl)-phenyl]propyl}-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2i

Preparation according to Section 4.2: foamy solid. HPLC analytical method (see Section 4.5): eluant: methanol/water: 15/85, 1 ml/min, t_R (enantiomer 1) = 9.0 min, t_R (enantiomer 2) = 12.0 min, t_R (**1i**) = 15.0 min. Determination of the enantiomeric

purity by CE (see Section 4.3): t_M [(3*S*)] = 20.4 min/1.3 area %; t_M [(3*R*)] = 20.6 min/98.7 area %; 97.4% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.81 (m_c, 2H), 2.48 (s, br s), 2.70 (s, 3H), 2.94 (s, br s, 4H), 3.24 (s, 3H), 3.65 (s, 3H), 4.40 (s, 2H), 4.75 (br s, 1H), 5.04 (br s, 1H), 6.71 (s, 1H), 7.22 (m_c, 3H), 7.47 (m_c, 1H), 9.76 (br s, 1H).

4.15. 5-[(3*R*)-3-{2-[(Benzyloxy)methyl]phenyl}-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2j

Preparation according to Section 4.2: foamy solid. Determination of the enantiomeric purity by HPLC (see Section 4.4): eluant: *n*-heptane/ethanol = 70/30, t_R [(3*R*)] = 14.1 min/98.2 area %, t_R [(3*S*)] = 25.9 min/1.8 area %, 96.4% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.60–2.02 (br m, 2 H), 2.20–2.63 (br m), 2.50 (s), 2.69 (s, 3H), 2.94 (s, 3H), 3.63 (s, 3H), 4.44 (m_c, 4H), 4.76 (br s, 1H), 5.12 (br s, 1H), 6.72 (s, 1H), 7.26 (m_c, 8H), 7.48 (m_c, 1 H), 9.85 (br s, 1H).

4.16. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-thienyl)propyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2k

Preparation according to Section 4.2: mp 264–265 °C. Determination of the enantiomeric purity by HPLC (see Section 4.4): eluant: *n*-heptane/ethanol = 80/20, t_R [(3*R*)] = 21.0 min/88.8 area %, t_R [(3*S*)] = 23.1 min/9.9 area %, 79.9% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.92 (br s, 2H), 2.50 (s), 2.71 (s, br s, 4H), 2.95 (s, 3H), 3.65 (s, 3H), 4.73 (br t, 1H), 5.48 (br s, 1H), 6.72 (s, 1H), 6.95 (m_c, 2H), 7.37 (dd, 1H), 9.80 (br s, 1H).

4.17. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methyl-3-thienyl)propyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide 2l

Preparation according to Section 4.2: foamy solid. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (both enantiomers) = 7.0 min, t_R (**1l**) = 10.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 20.0 min/2.1 area %; t_M [(3*R*)] = 21.0 min/97.9 area %; 95.8% ee. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.10, 2.24 (br s, br s, 5H), 2.59, 2.63 (s, br s, 4H), 2.82 (s, 3H), 3.12, 3.14 (br s, s, 4H), 3.67 (s, 3H), 4.64 (m_c, 1H), 6.69 (s, 1H), 6.96 (d, 1H), 7.03 (d, 1H).

4.18. 5-[(3*R*)-3-Hydroxy-3-(2-methylphenyl)propyl]-1,2-dimethyl-6-(pyrrolidin-1-ylcarbonyl)-1*H*-benzimidazol-4-ol 2m

Preparation according to Section 4.2: HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 21.8 min, t_R (enantiomer 2) = 30.9 min, t_R (**1m**) = 32.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 21.0 min/4.6 area %; t_M [(3*R*)] = 21.7 min/95.4 area %; 90.8% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.71 (m_c, 3H), 1.82 (m_c, 3H), 2.22 (s, 3H), 2.50 (br s), 2.60 (s, 3H), 2.78 (br s, 1H), 3.00 (br s, 2H), 3.38 (m_c, 2H), 3.72 (s, 3H), 4.72 (t, 1H), 5.17 (br s, 1H), 6.97 (s, 1H), 7.13 (m_c, 3H), 7.40 (d, 1H), 9.92 (br s, 1H).

4.19. 6-(Azetidin-1-ylcarbonyl)-5-[(3*R*)-3-hydroxy-3-phenylpropyl]-1,2-dimethyl-1*H*-benzimidazol-4-ol 2n

Preparation according to Section 4.2: mp 265–266 °C. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 23.1 min/7.6 area %; t_M [(3*R*)] = 23.8 min/92.4 area %; 84.8% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.83 (m_c, 2H), 2.15 (m_c, 2H), 2.50, 2.55 (s, m_c), 2.77 (m_c, 1H), 3.66 (s, 3H), 3.80 (t, 2H), 3.93 (t, 2H), 4.48 (t, 1H), 5.21 (br s, 1H), 6.81 (s, 1H), 7.26 (m_c, 5H), 9.80 (br s, 1H).

4.20. 6-(Azetidin-1-ylcarbonyl)-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-1,2-dimethyl-1*H*-benzimidazol-4-ol 2o

Preparation according to Section 4.2: foamy solid. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 14.9 min, t_R (enantiomer 2) = 20.4 min, t_R (**1o**) =: 26.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 20.9 min/2.4 area %; t_M [(3*R*)] = 21.7 min/97.6 area %; 95.2% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.69 (m_c, 1H), 1.84 (m_c, 1H), 2.16 (m_c, 2H), 2.20 (s, 3H), 2.51 (s), 2.65 (m_c, 1H), 2.86 (m_c, 1H), 3.68 (s, 3H), 3.81 (m_c, 2H), 3.96 (m_c, 2H), 4.68 (br s, 1H), 5.16 (br s, 1H), 6.83 (s, 1H), 7.09 (m_c, 2H), 7.16 (m_c, 1H), 7.44 (m_c, 1H), 9.78 (br s, 1H).

4.21. *N*-Cyclopropyl-4-hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-1,2-dimethyl-1*H*-benzimidazole-6-carboxamide 2p

Preparation according to Section 4.2: mp 299–300 °C. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 11.0 min, t_R (enantiomer 2) = 15.0 min, t_R (**1p**) = 18.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 22.0 min/0.8 area %; t_M [(3*R*)] = 23.1 min/99.2 area %; 98.4% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 0.54 (m_c, 2H), 0.65 (m_c, 2H), 1.75 (m_c, 2H), 2.21 (s, 3H), 2.50 (s), 2.80 (m_c, 3H), 3.66 (s, 3H), 4.65 (t, 1H), 5.19 (d, 1H), 6.85 (s, 1H), 7.10 (m_c, 3H), 7.43 (m_c, 1H), 8.17 (d, 1H), 9.63 (br s, 1H).

4.22. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-phenylpropyl]-*N*,1,2-trimethyl-1*H*-benzimidazole-6-carboxamide 2q

Preparation according to Section 4.2: mp 247–249 °C. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 24.5 min/11.7 area %; t_M [(3*R*)] = 25.3 min/87.7 area %; 76.5% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.85 (m_c, 2H), 2.50, 2.53 (s, m_c), 2.71, 2.77 (d, m_c, 4H), 3.66 (s, 3H), 4.46 (br t, 1H), 5.25 (br s, 1H), 6.88 (s, 1H), 7.25 (m_c, 5H), 8.00 (q, 1H), 9.70 (br s, 1H).

4.23. 4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-*N*,1,2-trimethyl-1*H*-benzimidazole-6-carboxamide 2r

Preparation according to Section 4.2: mp 238–240 °C. HPLC analytical method (see Section 4.5): eluant: methanol/water = 20/80, 1 ml/min, t_R (enantiomer 1) = 18.0 min, t_R (enantiomer 2) = 25.0 min, t_R (**1r**) = 27.0 min. Determination of the enantiomeric purity by CE (see Section 4.3): t_M [(3*S*)] = 20.7 min/2.6 area %; t_M [(3*R*)] = 21.7 min/94.7 area %; 94.7% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.67 (m_c, 1H), 1.87 (m_c, 1H), 2.18 (s, 3H), 2.50 (s), 2.70, 2.72 (m_c, d, 4H), 2.91 (m_c, 1H), 3.66 (s, 3H), 4.66 (m_c, 1H), 5.23 (d, 1H), 6.89 (s, 1H), 7.07 (m_c, 2H), 7.14 (m_c, 1H), 7.43 (d, 1H), 8.05 (q, 1H), 9.69 (br s, 1H).

4.24. 5-[(3*R*)-3-Hydroxy-3-(2-methylphenyl)propyl]-6-(methoxymethyl)-1,2-dimethyl-1*H*-benzimidazol-4-ol 2s

Preparation according to Section 4.2: foamy solid. Determination of the enantiomeric purity by HPLC (see Section 4.4): eluant: *n*-hexane/isopropanol = 80/20, t_R [(3*R*)] = 16.9 min/99.1 area %, t_R [(3*S*)] = 19.2 min/0.9 area %, 98.2% ee. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.76 (m_c, 2H), 2.21 (s, 3H), 2.49 (s), 2.64 (m_c, 1H), 2.81 (m_c, 1H), 3.22 (s, 3H), 3.64 (s, 3H), 4.39 (s, 2H), 4.75 (br t,

1H), 5.04 (br d, 1H), 6.84 (s, 1H), 7.14 (m_c, 3H), 7.46 (d, 1H), 9.49 (br s, 1H).

4.25. (8*S*)-*N*,*N*,2,3-Tetramethyl-8-phenyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide 3a

To a suspension of diol **2a** (1.3 g, 3.5 mmol) and PPh_3 (2.7 g, 10.2 mmol) in THF (60 ml), DIAD (2.1 ml, 10.5 mmol) was added and the mixture stirred for 15 min at rt. The reaction was concentrated in vacuo, the residue was treated with satd NH_4Cl solution (100 ml) and extracted with ethyl acetate (2 × 100 ml). The combined organic phases were washed with saturated NH_4Cl solution (20 ml) and H_2O (20 ml), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography [SiO_2, eluant: EtOAc/MeOH = 9:1 (v/v)] to afford 1.03 g of the title compound. Crystallization from diisopropyl ether (20 ml) furnished the pure title compound **3a** (0.95 g of a white solid, 77% yield; 95.8% ee): mp 226–227 °C. Determination of the enantiomeric purity by CE (capillary: Agilent bubble-cell 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; 30 kV; 20 °C): t_M [(8*S*)] = 19.7 min/97.9 area %; t_M [(8*R*)] = 21.0 min/2.1 area %; 95.8% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.08 (m_c, 1H, 7-H_a), 2.23 (m_c, 1H, 7-H_b), 2.47 (s, 3H, 2-CH_3), 2.55 (m_c, 1H, 6-H_a), 2.77, 2.81 (s, m_c, 4H, CON(CH_3)$_2$, 6-H_b), 3.00 (s, 3H, CON(CH_3)$_2$), 3.67 (s, 3H, 3-CH_3), 5.21 (dd, $^3J_{7,8}$ = 9.8 Hz, $^3J_{7,8}$ = 2.0 Hz, 1H, 8-H), 6.92 (s, 1H, 4-H), 7.34 (m_c, 1H, Ph), 7.41 (m_c, 2H, Ph), 7.47 (m_c, 2H, Ph). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.3 (2-CH_3), 21.6 (C-6), 28.8 (C-7), 29.7 (3-CH_3), 33.9, 37.9 (CON(CH_3)$_2$), 76.6 (C-8), 99.4 (C-4), 126.0, 127.7, 128.3 (Ph), 109.6, 131.0, 131.5, 135.4, 141.4, 145.3, 151.2 (4 °C), 170.0 (CON(CH_3)$_2$). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.27; H, 6.69; N, 12.02. HRMS (ESI) *m/z* $C_{21}H_{24}N_3O_2$ $[M+H]^+$ calcd: 350.1863, found: 350.1853.

4.26. (8*S*)-*N*,*N*,2,3-Tetramethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide 3b

To a suspension of diol **2b** (26.0 g, 68.1 mmol) and PPh_3 (35.0 g, 133 mmol) in dry THF (600 ml), DIAD (27.7 ml, 27.0 g, 134 mmol) was added over a period of 10 min. A yellow solution was obtained, which was stirred for 5 min at rt and concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2, eluant: EtOAc/MeOH = 100:2 (v/v)]. Evapouration of the corresponding fractions afforded the title compound **3b** in 84% corrected yield (23.0 g of a colourless foam containing 10 wt-% of EtOAc, 95.6% ee). After intense drying in vacuo, an amorphous solid was obtained: mp 126–128 °C. Determination of the enantiomeric purity by HPLC (column: Daicel Chiralpak AD-H, 250 × 4.6 mm, 5 μm; eluant: *n*-heptane/EtOH: 80:20 (v/v); flow rate: 1 ml/min, detection at 218 nm): t_R [(8*R*)] = 10.2 min/2.2 area %, t_R [(8*S*)] = 13.7 min/97.8 area %, 95.6% ee. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.98 (m_c, 1H, 7-H_a), 2.22 (m_c, 1H, 7-H_b), 2.38 (s, 3H, C_6H_4–CH_3), 2.49 (s, 3H, 2-CH_3), 2.62 (br s, 1H, 6-H_a), 2.81 (s, 3H, CON(CH_3)$_2$), 2.90 (br s, 1H, 6-H_b), 3.02 (s, 3H, CON(CH_3)$_2$), 3.67 (s, 3H, 3-CH_3), 5.32 (dd, $^3J_{7,8}$ = 10.4 Hz, $^3J_{7,8}$ = 1.9 Hz, 1H, 8-H), 6.92 (s, 1H, 4-H), 7.24 (m_c, 3H, C_6H_4–CH_3), 7.47 (m_c, 1H, C_6H_4–CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 13.2 (2-CH_3), 18.6 (C_6H_4–CH_3), 22.2 (C-6), 27.8 (C-7), 29.7 (3-CH_3), 33.9, 37.9 (CON(CH_3)$_2$), 74.3 (C-8), 99.4 (C-4), 125.6, 125.9, 127.5, 130.2 (C_6H_4–CH_3), 109.7, 131.0, 131.5, 134.8, 135.3, 139.3, 145.7, 151.2 (4 °C), 170.0 (CON(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.

4.27. (6*Z*)-8-Hydroxy-6-[hydroxy(2-methylphenyl)methylene]-2,3-dimethyl-6,7-dihydroindeno[5,6-*d*]imidazol-5(3*H*)-one 12b

In a flask filled with argon, ketone **1b** (3.5 g, 9.2 mmol) was dissolved in 2-PrOH (34 ml) and *t*-BuOK solution (1 M in *t*-BuOH, 16 ml) was slowly added. The suspension was stirred for 30 min at rt and catalyst **9** (46 mg, 37 μmol, S/C 250:1) was added. The reaction mixture was transferred into a 100 ml Premex Hastelloy autoclave, and hydrogenated at 70 °C and 80 bar pressure for 22 h. After cooling to rt and releasing of the H_2-pressure, the suspension was poured into a mixture of satd NH_4Cl solution (80 ml) and CH_2Cl_2 (200 ml). The phases were separated and the aq phase was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic phases were washed with water (50 ml), dried over sodium sulfate and concentrated in vacuo. The residue (3.2 g of a green foam) was purified by column chromatography [SiO_2, eluant: CH_2Cl_2/MeOH = 10:1 (v/v)]. The title compound **12b** was eluted first and purified further by crystallization from acetone (520 mg of a yellow solid, mp 267–269 °C, 17% yield). The chiral alcohol **2b** was eluted next and crystallized from acetone to afford 1.6 g (45% yield) of a colourless solid (mp 205–206 °C). In DMSO-d_6 a mixture of the enol tautomer of **12b** and the diketo tautomer of **12b** was observed (87:13 ratio). If traces of MeOH were added, the 6-H signal of the diketo form was quenched, whereas the ratio of tautomers remained the same. ^{1}H NMR signals of the enol tautomer of **12b** (DMSO-d_6, 400 MHz): δ = 2.39 (s, 3H, C_6H_4–CH_3), 2.57 (s, 3H, 2-CH_3), 3.43 (s, 2H, 7-H), 3.77 (s, 3H, 3-CH_3), 7.28–7.48 (m_c, 4H, 4-H, C_6H_4–CH_3), 7.57 (m_c, 1H, C_6H_4–CH_3). ^{13}C NMR signals of the enol tautomer of **12b** (DMSO-d_6, 100 MHz): δ = 13.5 (2-CH_3), 19.3 (C_6H_4–CH_3), 26.8 (C-7), 30.0 (3-CH_3), 95.6 (C-4), 111.7 (C-6), 125.7, 128.3, 129.9, 131.1 (C_6H_4–CH_3), 125.9, 132.7, 134.1, 135.8, 136.3, 137.7, 144.0, 153.9 (4 °C), 171.8 (HO-*C*=C), 195.1 (C=O). ^{1}H NMR signals of the diketo tautomer of **12b** (DMSO-d_6, 400 MHz): δ = 2.37 (s, 3H, C_6H_4–CH_3), 2.57 (s, 3H, 2-CH_3), 3.25-3.40 (m, 2H, 7-H), 3.74 (s, 3H, 3-CH_3), 4.98 (m_c, 1 H, 6-H), 7.28–7.48 (m_c, 4H, 4-H, C_6H_4–CH_3), 7.96 (m_c, 1H, C_6H_4–CH_3). ^{13}C NMR signals of the diketo tautomer of **12b** (DMSO-d_6, 100 MHz): δ = 13.5 (2-CH_3), 20.6 (C_6H_4–CH_3), 26.5 (C-7), 30.0 (3-CH_3), 59.4 (C-6), 96.0 (C-4), 125.8, 129.8, 130.4, 130.6, 131.5, 137.2, 137.6, 137.9, 144.1, 154.6 (C_6H_4–CH_3, 4 °C), 200.0 (C=O), 200.6 (C=O). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.70; H, 5.44; N, 8.34. HRMS (ESI) *m/z* $C_{20}H_{19}N_2O_3$ $[M+H]^+$ calcd: 335.1390, found: 335.1398.

4.28. (6*Z*)-8-Hydroxy-6-[hydroxy(2-chlorophenyl)methylene]-2,3-dimethyl-6,7-dihydroindeno[5,6-*d*]imidazol-5(3*H*)-one 12e

Mp 277–279 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.57 (s, 3H), 3.46 (s, 2H), 3.78 (s, 3H), 7.49 (s, 1H), 7.55 (m_c, 2H), 7.67 (m_c, 2H), 10.11 (br s, 1H), mixture of enol form and diketo form (93:7), only ^{1}H NMR signals of enol form reported.

4.29. (6*Z*)-8-Hydroxy-6-[hydroxy(2-trifluorophenyl)-methylene]-2,3-dimethyl-6,7-dihydroindeno[5,6-*d*]imidazol-5(3*H*)-one 12f

^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.57 (s, 3H), 3.38 (s, 2H), 3.78 (s, 3H), 7.48 (s, 1H), 7.86 (m_c, 4H), 10.09 (br s, 1H), mixture of enol form and diketo form (88:12), only ^{1}H NMR signals of enol form reported.

4.30. (6*Z*)-8-Hydroxy-6-[hydroxy(2-ethylphenyl)methylene]-2,3-dimethyl-6,7-dihydroindeno[5,6-*d*]imidazol-5(3*H*)-one 12g

Mp 258–260 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.16 (t, 3H), 2.57 (s, 3H), 2.73 (q, 2H), 3.40 (s, 2H), 3.78 (s, 3H), 7.42, 7.47 (m_c, s,

5H), 10.10 (br s, 1H), mixture of enol form and diketo form (91:9), only ^{1}H NMR signals of enol form reported.

4.31. (6*Z*)-8-Hydroxy-6-[hydroxy(4-fluoro-2-methylphenyl)-methylene]-2,3-dimethyl-6,7-dihydroindeno[5,6-*d*]imidazol-5(3*H*)-one 12h

Mp 296–297 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.40 (s, 3H), 2.57 (s, 3H), 3.43 (s, 2H), 3.78 (s, 3H), 7.23 (m_c, 2H), 7.47 (s, 1H), 7.65 (m_c, 1H), 10.12 (br s, 1H), mixture of enol form and diketo form (84:16), only ^{1}H NMR signals of enol form reported.

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