Synthesis and Evaluation of 7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines as Potassium-Competitive Acid Blockers†

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7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines with excellent physicochemical and pharmacological properties were identified that represent interesting candidates for further development as potassium-competitive acid blockers (P-CABs). The title compounds were prepared following synthetic pathways that relied either on a Claisen rearrangement/cross-metathesis reaction or on the (asymmetric) reduction of prochiral ketones. The influence of the character of the substituents R^3, R^6, and Ar on the biological activity and the physicochemical properties of the target compounds was examined. In contrast to the parent system (R^6 = H), compounds in which R^6 represents a carboxamide residue generally show improved in vivo activity and favorable pK_a/log *D* values. Whereas variation of R^3 is useful to obtain target compounds with modified basicity and lipophilicity, strong inhibition of the H^+/K^+-ATPase and potent in vivo activity is observed for R^3 = methyl only. Small modifications of the aryl group, e.g., replacement of hydrogen versus a fluoro atom or a methyl group, are allowed. The (9*S*)-enantiomers are responsible for the gastric acid secretion inhibiting action, whereas the (9*R*)-enantiomers are virtually inactive.

1. Introduction

Gastroesophageal reflux disease (GERD[a]), the backward flow of the stomach's contents into the esophagus, is a digestive condition that affects 20% of the American population and often becomes manifest in heartburn, which is characterized by burning pain that radiates through the chest, neck, and throat.[1,2] Peptic ulcer disease, estimated to affect 14.5 million people in the United States, is a chronic inflammation of the stomach and duodenum and is responsible for a large economic burden. The formation of a peptic ulcer is favored by two factors, the hypersecretion of acid and a weakened resistance of the protective mucous coating of the stomach and duodenum.[3,4] The inhibition of acid secretion and the neutralization of formed acid constitute effective approaches for the treatment of both diseases.[1,3] A whole series of compounds that inhibit gastric acid secretion by blockade of the gastric proton pump enzyme (H^+/K^+-ATPase) are known. The compounds designated as proton pump inhibitors (PPIs), for example, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and tenatoprazole, bind irreversibly to H^+/K^+-ATPase and have been available as therapeutics for a long time already. A new class of compounds designated as acid pump antagonists (APAs) or as potassium-competitive acid blockers (P-CABs) bind reversibly to H^+/K^+-ATPase. Although PPIs are considered as the gold standard for the treatment of acid-related diseases, P-CABs might offer some therapeutic advantages, such as better symptom control and faster healing.[5−8]

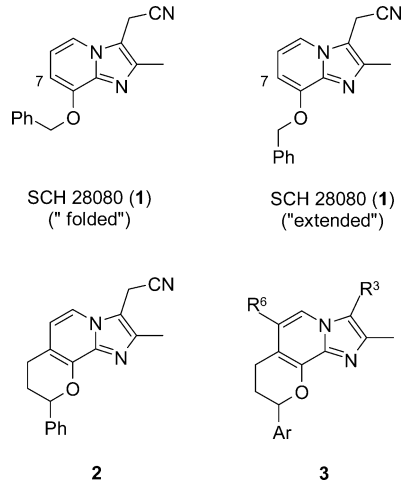

Figure 1. Imidazo[1,2-*a*]pyridines as potassium-competitive acid blockers for the treatment of GERD.

In the past 2 decades, one important approach for the identification of potent P-CABs relied on the structural class of substituted imidazo[1,2-*a*]pyridines. The inhibitor SCH 28080 (**1**) represents the clinical prototype of this series (Figure 1). SCH 28080 (**1**) inhibits the gastric proton pump enzyme (H^+/K^+-ATPase) by a kinetically competitive and reversible inhibition mechanism with respect to the potassium ion and shows excellent antisecretory and cytoprotective properties.[9−11] However, the clinical development of SCH 28080 (**1**) was stopped due to extensive metabolism and associated liver toxicity.[10]

One approach to synthesize advanced chemical analogues of SCH 28080 was based on results from molecular modeling, which suggested that in the gas phase, SCH 28080 could adopt various "folded" conformations (i.e., the phenyl ring is directed toward and over the imidazo[1,2-*a*]pyridine ring system) close to the global minimum of energy.[11] On the other hand, single-crystal X-ray analysis revealed that solid SCH 28080 existed

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† Design of novel P-CABs, V. Part 1: Zimmerman, P. J.; Buhr, W.; Brehm, C.; Palmer, A. M.; Feth, M. P.; Senn-Bilfinger, J.; Simon, W. A. Novel indanyl-substituted imidazo[1,2-*a*]pyridines as potent reversible inhibitors of the gastric H^+/K^+-ATPase. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5374−5378. Part 2: Palmer, A. M.; Grobbel, B.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Holst, H. C.; Simon, W. A. Preparation of tetrahydroimidazo[2,1-*a*]isoquinolines and their use as inhibitors of gastric acid secretion. *Bioorg. Med. Chem.* **2007**, *15*, 7647−7660. Part 3: Zimmermann, P. J.; Brehm, C.; Buhr, W.; Palmer, A. M.; Volz, J.; Simon, W. A. Novel imidazo[1,2-*a*]pyrazine derivatives as potent reversible inhibitors of the gastric H^+/K^+-ATPase. *Bioorg. Med. Chem.* **2007**, doi.1016/j.bmc.2007.09.009. Part 4: Palmer, A. M.; Münch, G.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W. A. 5-Substituted 1*H*-pyrrolo[3,2-*b*]pyridines as inhibitors of gastric acid secretion. *Bioorg. Med. Chem.* **2007**, doi 10.1016/j.bmc.2007.10.017.

[a] Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; APA, acid pump antagonist; P-CAB, potassium competitive acid blocker; Piv, pivaloyl; TxDMS, thexyldimethylsilyl; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; CDI, carbonyldiimidazole; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; DPEN, 1,2-diphenylethylenediamine; DAIPEN, 1,1-di-4-anisyl-2-isopropyl-1,2-ethylenediamine; MTPACl, α-methoxy-α-trifluoromethylphenylacetyl chloride; CE, capillary electrophoresis; t_M, migration time; t_R, retention time.

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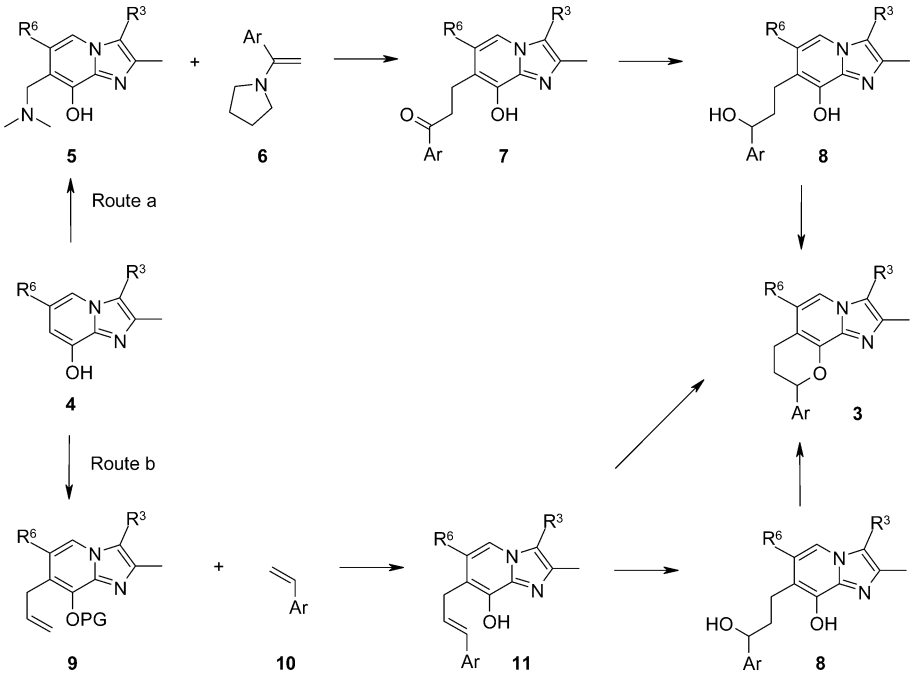
Scheme 1



in an "extended" conformation (i.e., the phenyl ring is oriented out and away from the heterocyclic nucleus).[9] By synthesis of simple analogues that imitated these conformations, it was shown that an "extended" relationship between the phenyl group and the heterocyclic nucleus was required for effective binding to H^+/K^+-ATPase.[11] Subsequently, the tricyclic imidazo[1,2-*a*]pyridine **2** was synthesized in which the pyrano ring was considered to enforce this requisite extended relationship and to mimic a 7-methyl substituent, which would be effective in overcoming the toxic properties of **1** while its desirable antisecretory effects were retained (Figure 1).[11,12]

In the course of our efforts to identify a new generation of P-CABs, which would be distinguished from former P-CABs by a high degree of efficacy and safety, we considered the 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **2** as an interesting lead compound for the synthesis of tricyclic imidazo[1,2-*a*]pyridines of the general formula **3** (Figure 1).[13−15] Since the 3-cyanomethyl moiety was identified as the metabolic "hot spot" of SCH 28080 (**1**), our first goal was to identify potent inhibitors that are devoid of the 3-cyanomethyl moiety and, as a result, would not be prone to undergo metabolic degradation by oxidative decyanation.

One possible problem associated with the replacement of the cyanomethyl moiety versus another residue at R^3 is the alteration of the pK_a value of the heterocyclic system. The imidazo[1,2-*a*]pyridine **2** possesses a favorable pK_a value of 6.0, which represents an optimum balance between (a) the request for a basic compound, since the protonated species is the active form at the site of action in the parietal cell, and (b) the concept of developing weakly basic P-CABs that would accumulate in acidic compartments.[8,16] Selective accumulation of the inhibitor in acidic departments would diminish the interaction with other enzymes and might translate in to an improved safety profile.

Apart from the option to modify the pK_a value by the character of the substituent R^3, we considered the possibility of adjusting the pK_a value by the character of the substituent R^6, e.g., to reduce the pK_a value by the presence of an electron-withdrawing carboxamide substituent.

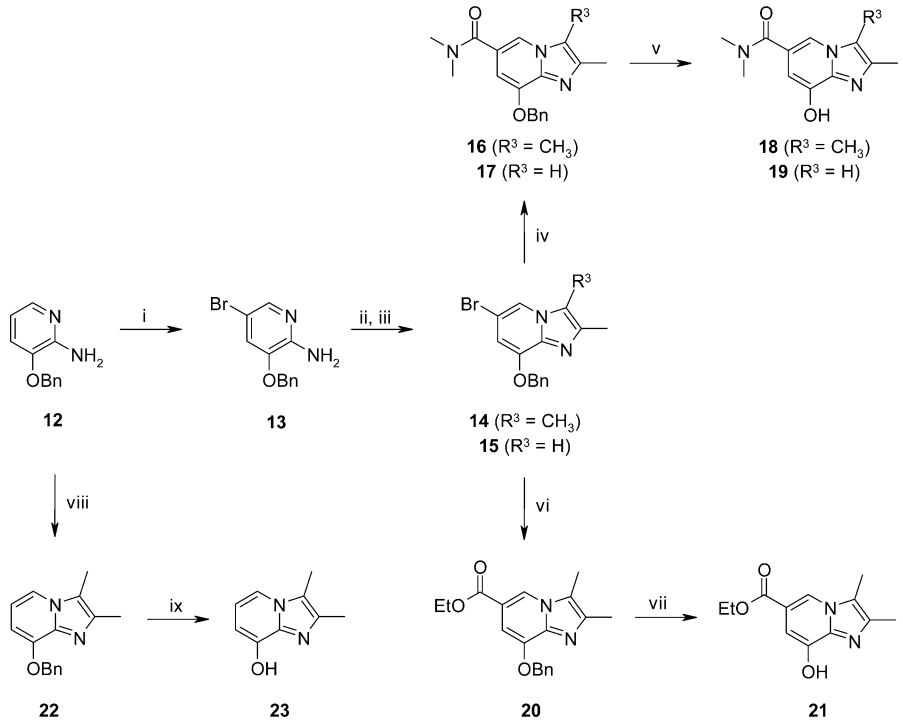
Consequently, we searched for synthetic routes toward tricyclic imidazopyridines of the general formula **3** that would fulfill the following criteria: (a) the rapid introduction/interconversion of substituents R^3, R^6, and Ar to evaluate the pharmacological and physicochemical properties of a variety of compounds **3** and to establish a structure−activity relationship and (b) the possibility to prepare interesting target compounds in an enantioselective manner.

2. Chemistry

2.1. Retrosynthesis of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines. In the search for synthetic routes that allow a flexible and/or enantioselective preparation of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **3**, we examined the two pathways depicted in Scheme 1. Both approaches use building blocks of the general formula **4** as starting material. Pathway a relies on the synthesis of prochiral ketones **7** by conversion of Mannich bases **5** with pyrrolidine enamines **6**, which can be converted into target compounds **3** by reduction and subsequent dehydration of the resulting diols **8**.[12−15,17] In pathway b, olefins of the general formula **11** are prepared by the cross-metathesis reaction of imidazopyridine building blocks **9** with styrene derivatives **10**.[14,15,18] Tricyclic imidazopyridines **3** are obtained from alkenes **11** either in a direct manner by acid-catalyzed cyclization or by a two-step sequence comprising hydroboration and dehydration of the resulting diols **8**.[14,15] Enantioselective synthesis of tricyclic imidazopyridines should be feasible by applying either pathway, since the key step of each pathway (ketone reduction/hydroboration) can be performed in an asymmetric manner.[19−25]

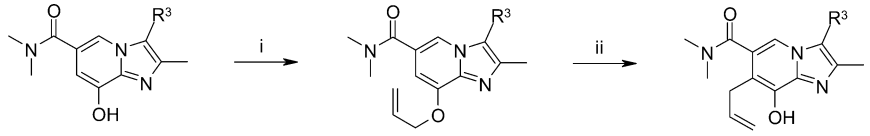
2.2. Preparation of Building Blocks for Pathways a and b. In order to prepare the building blocks required for both synthetic approaches, 2-amino-3-benzyloxypyridine (**12**) was brominated under acidic conditions (Scheme 2). The resulting 2-amino-3-benzyloxy-5-bromopyridine (**13**) was transformed either with 2-bromo-3-butanone or with chloroacetone, furnishing the corresponding imidazo[1,2-*a*]pyridines **14** and **15**. Using THF as a solvent, the hydrohalide salts of **14** and **15** crystallized from the reaction mixture and, although long reaction times had to be taken into account, both derivatives were isolated in good yield. The carboxamide substituent was introduced by a palladium-catalyzed amidocarbonylation reaction by applying

Scheme 2[a]



[a] Reagents and conditions: (i) Br_2, HOAc, H_2SO_4, 0 °C, 2.5 h, 83%. (ii) Bromobutanone, THF, reflux, 6 d, 76%. (iii) Chloroacetone, THF, 60 °C, 11.5 d, 59%. (iv) $Pd(OAc)_2$, PPh_3, Et_3N, Me_2NH (2 N in THF), CO, 120 °C, 18.5 h (**16**, 76%; **17**, 77%). (v) Hydrogenation: Pd/C, H_2, MeOH, rt, 2.5−18 h (**18**, 96%; **19**, 98%). Transfer hydrogenation: Pd/C, 1,4-cyclohexadiene, EtOH, reflux, 7 h (**18**, 77%). (vi) $Pd(OAc)_2$, PPh_3, Et_3N, EtOH, CO, 120 °C, 17 h, 87%. (vii) Pd/C, 1,4-cyclohexadiene, EtOH, reflux, 18 h, 80%. (viii) Bromobutanone, THF, reflux, 44 h, 67%. (ix) Pd/C, 1,4-cyclohexadiene, EtOH, reflux, 4 h, 83%.

Scheme 3[a]



[a] Reagents and conditions: (i) allyl bromide, K_2CO_3, DMF, rt, 18.5 h (**24**, 67%; **25**, 70%). (ii) Melting, 160 °C, 0.75 h (**26**, 76%; **27**, 66%).

conditions that had been described in the literature.[26] The carboxamides **16** and **17** were isolated in 76 and 77% yield. Under similar reaction conditions (when dimethylamine was substituted versus ethanol), 6-bromoimidazo[1,2-*a*]pyridine **14** could be transformed into the corresponding ethyl ester **20**.[26] Finally, the benzyl protective group of intermediates **16**, **17**, and **20** was cleaved by catalytic hydrogenation or catalytic transfer hydrogenation, affording the building blocks **18**, **19**, and **21**. In the case of the imidazopyridine **18**, all reactions were performed in a multikilogram scale. In the same manner, the 6-unsubstituted imidazopyridine **23** was prepared in two steps from 2-amino-3-benzyloxypyridine (**12**): First, the imidazopyridine scaffold was formed by condensation of **12** with 2-bromo-3-butanone. Second, the benzyloxy protective group was cleaved by catalytic hydrogenation of **22**, affording building block **23**.

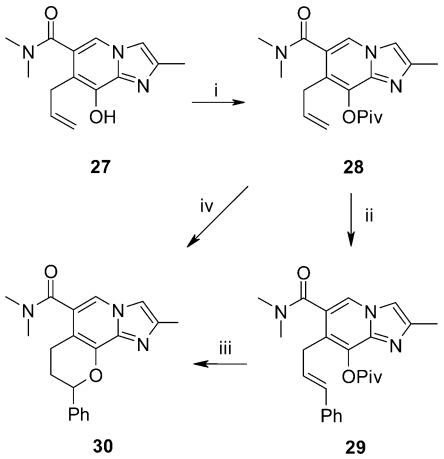
Subsequently, building blocks **18** and **19** were transformed into olefins **26** and **27** suitable for cross-metathesis by applying a two-step sequence comprising an O-allylation reaction and a Claisen rearrangement (Scheme 3). The latter reaction proceeded smoothly under solvent-free conditions, when the *O*-allyl ethers **24** and **25** were heated to a temperature of 160 °C.

2.3. Synthesis of tricyclic imidazopyridines by cross metathesis. We then investigated the cross-metathesis reaction of 7-allyl-substituted imidazo[1,2-*a*]pyridines with different styrene derivatives.[18] No conversion was observed, when a solution of the phenolic imidazopyridine **26** and styrene in dichloromethane was heated to 40 °C in the presence of second-generation Grubbs catalyst. Since this was probably due to the chelating interaction of the ruthenium catalyst with the 8-hydroxyimidazo[1,2-*a*]pyridine moiety, we examined the use of different protective groups.

First, a pivaloyl protective group was introduced into the imidazo[1,2-*a*]pyridine **27** by applying standard conditions. To our delight, the cross-metathesis reaction of the pivaloic ester **28** with *trans*-stilbene was now feasible, and the corresponding olefin **29** was isolated in 53% yield. When the intermediate **29** was subjected to acidic conditions, both cleavage of the protective group and cyclization occurred, and the pyranoimidazopyridine **30** was isolated in 91% yield. The cross-metathesis/cyclization reaction could also be conducted in one pot, which afforded the target compound **30** in 64% yield (Scheme 4).

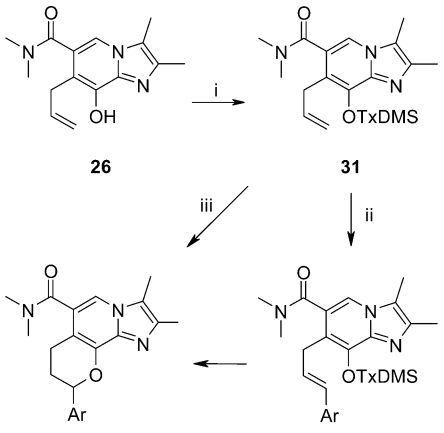
Second, we examined the use of the thexyldimethylsilyl

Scheme 4[a]



[a] Reagents and conditions: (i) pivaloyl chloride, K_2CO_3, acetone, rt, 3 h, 72%. (ii) *trans*-Stilbene, second-generation Grubbs catalyst, CH_2Cl_2, 40 °C, 18 h, 53%. (iii) 85% H_3PO_4, 80 °C, 0.75 h, 91%. (iv) *trans*-stilbene, second-generation Grubbs catalyst, CH_2Cl_2, 40 °C, 18 h, then 85% H_3PO_4, 80 °C, 1 h, 64%.

Scheme 5[a]

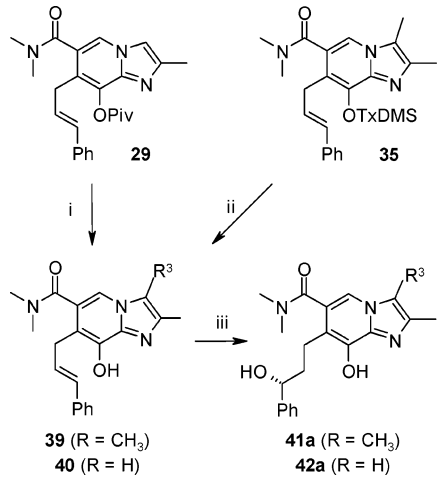


[a] Reagents and conditions: (i) chloro(dimethyl)thexylsilane, imidazole, DMF, rt, 1 h, 93%. (ii) *trans*-Stilbene, second-generation Grubbs catalyst, CH_2Cl_2, 40 °C, 19 h, 58%. (iii) 2-Methylstyrene, 2-fluorostyrene, or 4-fluorostyrene, second-generation Grubbs catalyst, 40 °C, 4 h−5 d, then 85% H_3PO_4, 80−100 °C, 1.5−2 h (**36**, 29%; **37**, 56%; **38**, 21%).

protective group for the cross metathesis reaction of the 2,3-dimethylimidazo[1,2-*a*]pyridine **26** with different styrenes (Scheme 5). The silyl ether **31** was prepared by imidazole-catalyzed condensation of the phenolic imidazopyridine **26** with chlorodimethylthexylsilane. Transformation of **31** with 2-methylstyrene, 2-fluorostyrene, and 4-fluorostyrene afforded the corresponding tricyclic imidazopyridines **36**−**38** in moderate yields without isolation of the intermediate products **32**, **33**, and **34** of the cross-metathesis reaction. In the case of *trans*-stilbene, the product **35** of the cross-metathesis reaction was isolated in 58% yield.

2.4. Asymmetric Hydroboration of Olefins Obtained by Cross-Metathesis. The asymmetric hydroboration of olefins **39** and **40**, which were prepared from their O-protected precursors **29** and **35** by base/TBAF-mediated cleavage of the protective group with isopinocampheylborane, was studied next (Scheme 6).[25] The hydroborating agent was obtained by treatment of commercially available (*R*)-Alpine-boramine with borontrifluoride etherate and was added to a solution of the corresponding olefin **39** or **40** in THF.[25] After a reaction time of 2.5−5 h, the corresponding alcohol **41a** or **42a** was obtained by oxidative workup. The hydroboration reaction proceeded with good regioselectivity; however, the enantiomeric purity of the alcohols **41a** and **42a** was low (30% ee). The 3-methyl-substituted imidazo[1,2-*a*]pyridine **41a** was isolated in 50% yield, whereas its 3-unsubstituted analogue **42a** was obtained in 18% yield only.

Scheme 6[a]



[a] Reagents and conditions: (i) NaOH, MeOH, H_2O, rt, 1 h, 50 °C, 1 h, 55%. (ii) TBAF, THF, rt, 0.5 h, 81%. (iii) (1) (*R*)-Alpine-boramine, BF_3−OEt_2, THF, rt, 2−2.5 h; (2) addition of **39** or **40**, THF, rt, 2−5 h; (3) H_2O_2, KOH, EtOH, H_2O, 0.25−0.5 h (**41a**, 50%, 27.8% ee; **42a**, 18%, 32.2% ee).

2.5. Conversion of the Key Intermediate 30 into 3-Substituted Tetrahydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines. A variety of 3-substituted imidazopyridines was prepared by electrophilic substitution of the 3-H derivative **30** (Scheme 7):

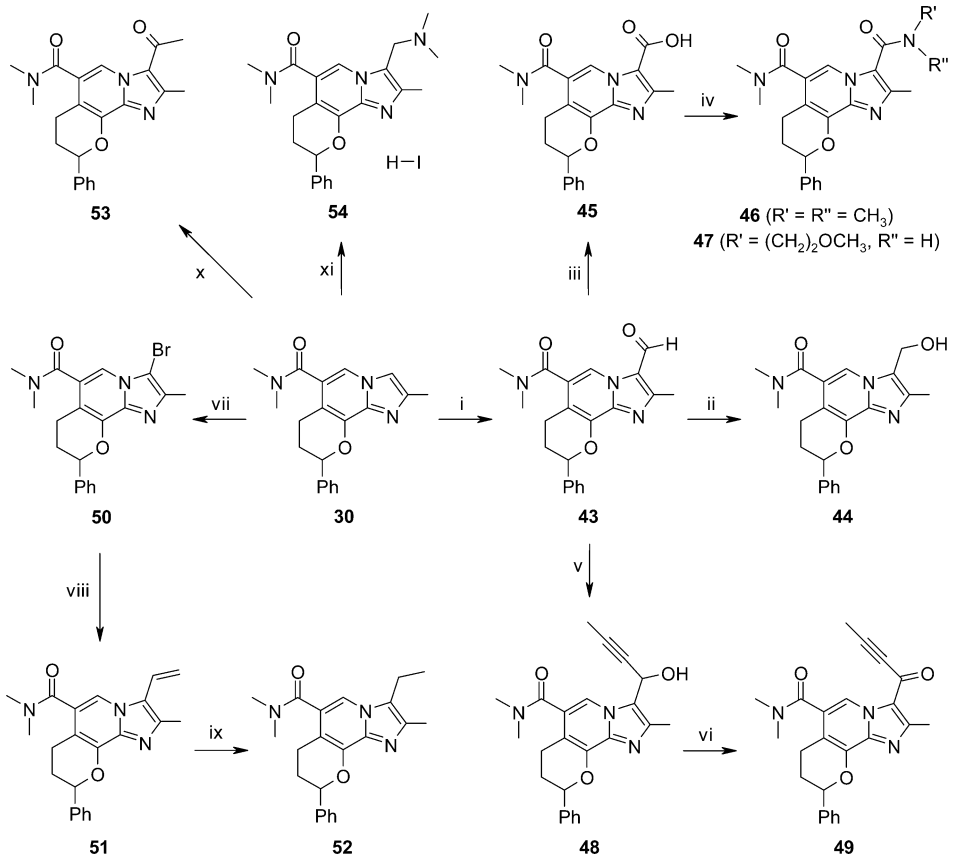
Vilsmeier formylation of **30** afforded the aldehyde **43**, which was transformed further by following one of the three following pathways: (a) Reduction with sodium borohydride furnished the alcohol **44**. (b) The carboxamides **46** and **47** were secured by oxidation of the aldehyde **43** to the carboxylic acid **45** and TBTU-mediated coupling with dimethylamine/2-methoxyethylamine, respectively.[27] (c) Grignard addition of propinylmagnesium bromide and subsequent oxidation of the propargyl alcohol **48** afforded the unsaturated ketone **49**.

The 3-bromoimidazopyridine **50** was prepared by transformation of **30** with *N*-bromosuccinimide. The 3-vinyl substituent was introduced by Stille coupling of **50** with tributylvinylstannane. Catalytic hydrogenation of the resulting olefin **51** afforded the 3-ethyl-substituted imidazopyridine **52**. The use of Lindlar catalyst was crucial for the outcome of the hydrogenation reaction, since more active hydrogenation catalysts (e.g., palladium on charcoal) not only reduced the carbon−carbon double bond but also cleaved the pyrano ring.[28]

Substitution of **30** was also accomplished with other electrophiles, e.g., acetic anhydride or Eschenmoser's salt, affording the 3-acetyl derivative **53** and the Mannich base **54**.

2.6. Synthesis of Prochiral Ketones and Their Use for the Preparation of Racemic 7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines. Treatment of the building blocks **18**, **21**, and **23**, which served as starting materials for the synthesis of prochiral ketones, with Eschenmoser's salt furnished the corresponding Mannich bases **55**, **56**, and **57**. When these intermediates were heated in the presence of 1-(1-arylvinyl)-pyrrolidines, the ketones **61**−**67** were formed. These reactions are believed to proceed via the α,β-unsaturated ketones **58**−**60**, which subsequently react with the corresponding 1-(1-

Scheme 7[a]



[a] Reagents and conditions: (i) (1) $POCl_3$, DMF, rt, 1 h; (2) **30**, DMF, 60 °C, 3 h, 92%. (ii) $NaBH_4$, rt, 0.75 h, 58%. (iii) Sulfamic acid, sodium chlorite, THF, H_2O, 0 °C, 1.25 h, 65%. (iv) (1) TBTU, CH_2Cl_2, rt, 1 h; (2) amine, rt, 1−1.5 h [**46**, $HNMe_2$ (2 M in THF), 97%; **47**, methoxyethylamine, 70%]. (v) Propinylmagnesium bromide, THF, −78 °C, 1 h, 0 °C, 2 h, 96%. (vi) MnO_2, CH_2Cl_2, rt, 1 h, 86%. (vii) NBS, $CHCl_3$, CH_2Cl_2, −78 °C, 0.75 h, 90%. (viii) Tributyl(vinyl)stannane, $(PPh_3)_2PdCl_2$, 1,4-dioxane, 100 °C, 3 h, 72%. (ix) Lindlar catalyst ($Pd/CaCO_3/Pb$), H_2, MeOH, rt, 4 h, 89%. (x) Ac_2O, MsOH, 140 °C, 1.5 d, 46%. (xi) Eschenmoser's salt, CH_2Cl_2, rt, 0.5 h, 97%.

Table 1. Conversion of Ketones into Tricyclic Imidazopyridines

ketone	R^6	Ar	diol	% yield	target compd	method[a]	% yield
61	$CONMe_2$	phenyl	**41**	76	**74**	A	24
						B	92
62	$CONMe_2$	2-methylphenyl	**68**	crude	**36**	B	∑46
63	$CONMe_2$	2-fluorophenyl	**69**	crude	**37**	B	∑94
64	$CONMe_2$	4-fluorophenyl	**70**	crude	**38**	B	∑85
65	$CONMe_2$	2-thienyl	**71**	crude	**75**	C	∑35
66	CO_2Et	phenyl	**72**	75	**76**	A	69
67	H	phenyl	**73**	24	**77**	A	87

[a] See Scheme 9 for a description of methods A−C

arylvinyl)pyrrolidine, either by hetero-Diels−Alder reaction or by Michael addition (Scheme 8).[17]

The ketones **61**−**67** were transformed into the corresponding alcohols **41** and **68**−**73** by reduction with sodium borohydride. Finally, 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **36**−**38**, **74**, **76**, and **77** were secured by Brönsted (phosphoric acid) or Lewis acid (borontrifluoride etherate) catalyzed cyclization of the intermediate diols **41**, **68**−**70**, **72**, and **73**. The diol **71**, bearing a sensitive thiophene residue, was converted into the corresponding target compound **75** by intramolecular Mitsunobu reaction (Scheme 9 and Table 1).[29]

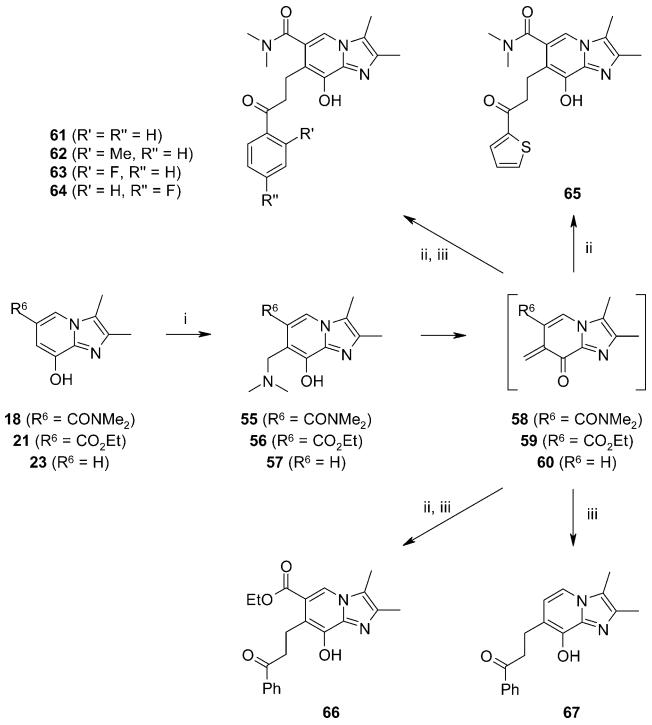
The ester **66** constitutes a useful starting material for the synthesis of other prochiral ketones (Scheme 10). The carbonyl function was protected by conversion of ketone **66** into the cyclic acetal **78**. Saponification of the ester function afforded carboxylic acid **79**, which in turn was subjected to TBTU-mediated amide coupling.[27] Finally, the 6-carboxamide substituted ketones **82** and **83** were obtained by acid-catalyzed cleavage of their acetal precursors **80** and **81**.

A variety of other 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines (**85**−**98**) was prepared by TBTU- or CDI-mediated coupling of different amines with the carboxylic acid **84**, which in turn was obtained by aqueous hydrolysis of its ester precursor **76** (Scheme 11 and Table 2).[27]

The 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **101**, which bears a 4,5-dihydro-1,3-oxazole residue as bioisosteric replacement of the carboxamide group, was also prepared using the carboxylic acid **84** as starting material (Scheme 12).[30] In a first step, the *N*-(2-hydroxyethyl) residue was introduced by treatment of **84** with thionyl chloride and 2-aminoethanol. In a second step, the hydroxyl group present in carboxamide **99** was converted into a leaving group and cyclization to the title compound **101** was accomplished, albeit in low yield, by heating of the resulting intermediate **100** in DMF.

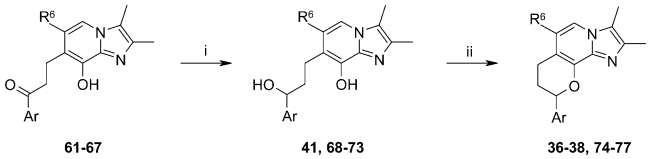
2.7. Synthesis of Enantiopure Tricyclic Imidazopyridines by Asymmetric Reduction of Prochiral Ketones. A variety of methods are available to reduce ketones in an asymmetric manner, e.g., enzymatic reduction,[19] asymmetric hydrosilylation,[20] or hydroboration using either a chiral boron reagent[21] or an achiral boron reagent in combination with a chiral catalyst.[22] The ruthenium-catalyzed hydrogenation[23] or transfer hydrogenation[24] constitutes one of the most prominent methods for the synthesis of chiral alcohols. We focused our attention on the hydrogenation of ketones **61**, **82**, and **83** using Noyori catalysts of the type $RuCl_2$[diphosphine][diamine].[23] In the case of the ketone **61**, only modest enantioselectivity was achieved using

Scheme 8[a]



[a] Reagents and conditions: (i) Eschenmoser's salt, CH_2Cl_2, rt, 10 min−2.5 h. (ii) 1-(1-Arylvinyl)pyrrolidine, K_2CO_3, DMF, 50 °C, 0.5−4 h [**61**, 1-(1-phenylvinyl)pyrrolidine, 49%; **62**, 1-[1-(2-methylphenyl)vinyl]pyrrolidine, 54%; **63**, 1-[1-(2-fluorophenyl)vinyl]pyrrolidine, 51%; **64**, 1-[1-(4-fluorophenyl)vinyl]pyrrolidine, 46%; **65**, 1-(1-thiophen-2-ylvinyl)pyrrolidine, 45%; **66**, 1-(1-phenylvinyl)pyrrolidine, 55%]. (iii) 1-(1-Phenylvinyl)pyrrolidine, toluene, 90−100 °C, 0.25−1 h (**61**, 79%; **66**, 84%; **67**, 48%).

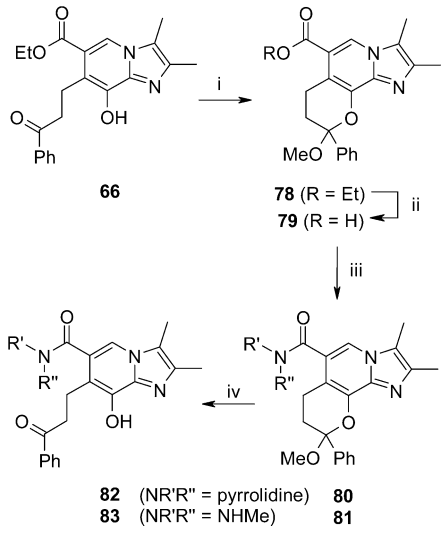
Scheme 9[a]



[a] Reagents and conditions (see Table 1): (i) $NaBH_4$, MeOH or EtOH, rt, 0.5−2.75 h. (ii) Method A, BF_3-OEt_2, rt, CH_2Cl_2, 3−5 h; method B, 85% H_3PO_4, 80 °C, 0.25−1 h; method C, PPh_3, DIAD, THF, rt, 0.25 h.

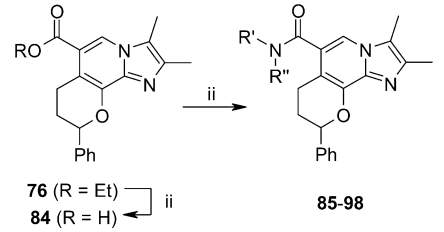
$RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN] as hydrogenation catalyst (37% ee). The optical purity of the alcohol **41a** increased significantly, when (*S*)-DAIPEN was used as diamine ligand. The synthesis of the optical antipode **41b** was also feasible, when $RuCl_2$[(*R*)-BINAP][(*R*)-DAIPEN] was employed as hydrogenation catalyst. To our delight, this methodology could be extended to other substrates, and the asymmetric hydrogenation of the ketones **82** and **83** afforded the alcohols **102a** and **103a** in high yields and good optical purity (Scheme 13). Having the alcohols **41a**, **41b**, **102a**, and **103a** in hand, we examined their transformation into enantiopure 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]-pyridines by Mitsunobu cyclization. Since the Mitsunobu reaction proceeds under complete conversion of configuration at the stereogenic center, complete transfer of the stereochemical information, which had been introduced by asymmetric hydrogenation, into the target compound should occur.[31] Indeed, when the alcohols **41a**, **41b**, **102a**, and **103a** were treated with triphenylphosphine and diisopropyl azodicarboxylate, the tricyclic imidazo[1,2-*a*]pyridines **74a**, **74b**, **90a**, and **86a** were isolated without loss of optical purity (Scheme 13).

Scheme 10[a]



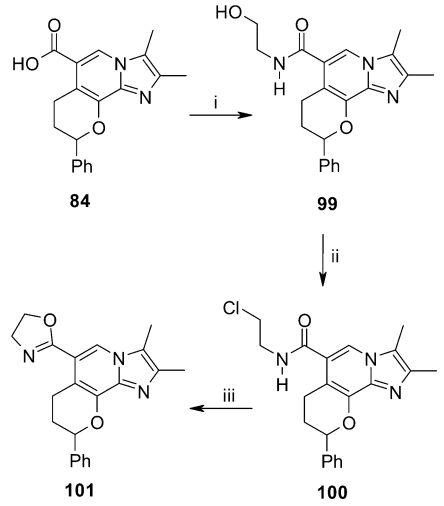
[a] Reagents and conditions: (i) 2,2-dimethoxypropane, CH_2Cl_2, MsOH, reflux, 6 h, 88%. (ii) KOH, MeOH, H_2O, 55 °C, 2 h, 97%. (iii) (1) TBTU, CH_2Cl_2, reflux, 2 h; (2) amine, rt, 1 h [**80**, pyrrolidine; **81**, H_2NMe (8 M solution in EtOH)]. (iv) 1 N HCl, THF, 50 °C, 5−7 h (**82**, Σ46%; **83**, Σ73%).

Scheme 11[a]



[a] Reagents and conditions (see Table 2): (i) KOH, MeOH, H_2O, 50 °C, 2 h, 71%. (ii) Method A, (1), TBTU, CH_2Cl_2, rt or reflux, 0.75−2 h; (2) amine, rt or 50 °C, CH_2Cl_2 or DMF, 0.5−2.5 h; method B, (1) CDI, THF, 40 °C, 2 h; (2) DBU, amine, rt, 1 h−2.5 d.

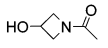
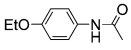
Scheme 12[a]



[a] Reagents and conditions: (i) (1) $SOCl_2$, CH_2Cl_2, DBU, rt, 24 h; (2) 2-aminoethanol, CH_2Cl_2, rt, 2.5 h, 44%. (ii) $SOCl_2$, rt, 1 h, 70%. (iii) DMF, 150−170 °C, 0.75 h, 14%.

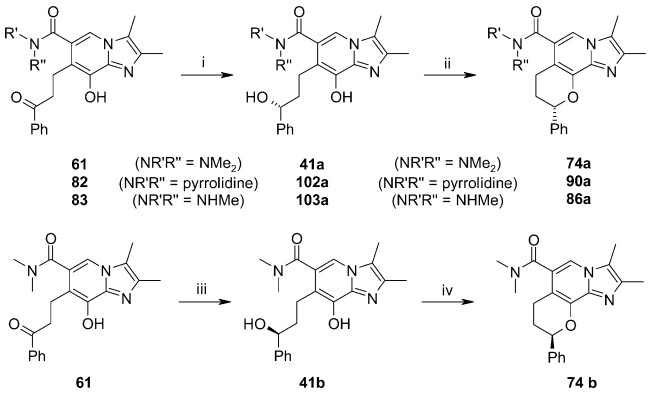
In order to assess the configuration of the stereogenic center, we used the method described by Mosher et al.[32] To this end, the mixture of the alcohols **41a** and **41b** obtained by catalytic hydrogenation of **61** in the presence of $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN] was converted into the corresponding silyl ether **104**.

Table 2. Preparation of Target Compounds by Amide Coupling

Compound	(CO)NR'R''	Yield (Method)[a]
85		64 % (A)
86		58 % (A)
87		78 % (A)
88		15 % (A)
89		88 % (A)
90		45 % (A)
91		36 % (A)
92		45 % (A)
93		47 % (A)
94		39 % (A)
95		49 % (A)
96		71 % (B)
97		13 % (B)
98		33 % (A)

[a] See Scheme 11 for a description of methods A and B.

Scheme 13[a]

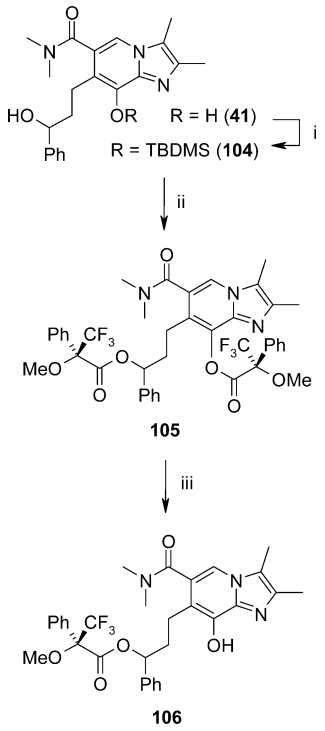


[a] Reagents and conditions: (i) method A, $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN], KOtBu, 2-PrOH, H_2, 80 °C, 18 h (**41a**, 82%, 37% ee); method B, $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN], KOtBu, 2-PrOH, H_2, rt, 1 d (**41a**, 92%, 86% ee; **102a**, 78%, 87% ee; **103a**, 80%, 92% ee). (ii) PPh_3, DIAD, THF, rt, 1−1.5 h (**74a**, 58%, 85% ee; **90a**, 50%, 87% ee; **86a**, 14%; 94% ee). (iii) $RuCl_2$[(*R*)-BINAP][(*R*)-DAIPEN], KOtBu, 2-PrOH, H_2, rt, 1 d, 87%, 96% ee. (iv) PPh_3, DIAD, CH_2Cl_2, rt, 3 min, 42%, 96% ee.

Upon treatment with (*S*)-(+)-MTPACl, the protective group was cleaved and diester **105** was obtained rather than the desired monoester **106**. Fortunately, when a solution of the diester **105** was allowed to stand for 10 days in deuterated chloroform, selective hydrolysis of the phenolic ester occurred and monoester **106** was obtained in 72% yield (Scheme 14).

Mosher and co-workers have shown that the conformation depicted in Figure 2 is highly preferred for this class of compounds.[32] In the (3*R*)-diastereomer **106a**, the methoxy function is located over the aromatic radical. The shielding effect

Scheme 14[a]



[a] Reagents and conditions: (i) Et_3N, TBDMSCl, CH_2Cl_2, reflux, 5.25 h, 73%. (ii) (*S*)-(+)-MTPACl, pyridine, CCl_4, CH_2Cl_2, rt, 6 h, 30%; (iii) $CDCl_3$, rt, 10 d, 72%.

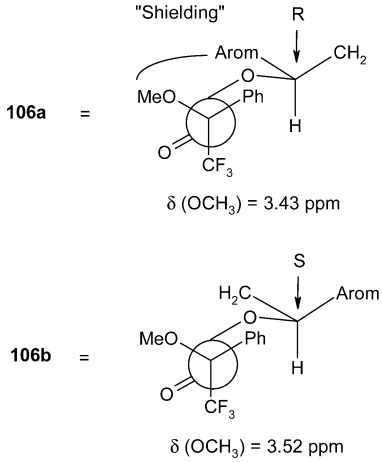


Figure 2. Assignment of the configuration of the stereogenic center of the diols **106a** and **106b** using the method of Mosher et al.

of the aromatic electron cloud results in an upfield shift of the ^{1}H NMR signal of the methoxy group as compared to the (3*S*)-diastereomer **106b**. In the ^{1}H NMR spectrum of the diastereomeric mixture (**106**), the signals of the methoxy groups were observed at 3.43 ppm (major)/3.52 ppm (minor), respectively. Thus, catalytic hydrogenation under the conditions reported above mainly furnishes the (3*R*)-diol **41a**. Since the Mitsunobu etherification proceeds under inversion of configuration of the stereogenic center, the (9*S*)-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **74a** is isolated as the major product.[31] This should also apply for the asymmetric reduction of prochiral ketones of the general formula **7**, which are structurally related to ketone **61**.

2.8. Enantiopure Tricyclic Imidazopyridines by HPLC Separation of the Corresponding Racemates. In order to secure fast access to a wide variety of enantiopure 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines, the separation of

Table 3. HPLC Separation of Racemic 7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines into Their Enantiomers

				(9*S*)-enantiomers			(9*R*)-enantiomers			HPLC conditions	
compd	R^3	R^6	Ar	% yield	mp, °C	$[\alpha]_D^{20a}$ deg	% yield	mp, °C	$[\alpha]_D^{20a}$ deg	CHIRALPAK column	eluant
36	Me	(CO)NMe_2	*o*-Me-phenyl	48	foam	−49 (0.45)	48	foam	39 (0.42)	AD-H	*n*-heptane/EtOH 85:15
37	Me	(CO)NMe_2	*o*-F-phenyl	47	210	−84 (0.47)	47	210	75 (0.47)	AD-H	*n*-heptane/EtOH 85:15
38	Me	(CO)NMe_2	*p*-F-phenyl	50	255	−72 (0.47)	50	255	60 (0.39)	AD-H	*n*-heptane/EtOH 85:15
44	CH_2OH	(CO)NMe_2	phenyl	46	178	−65 (0.56)	46	178	62 (0.53)	AD	*n*-heptane/EtOH 9:1
50	Br	(CO)NMe_2	phenyl	48	161	−54 (0.51)	48	162	64 (0.45)	AD	EtOH/MeOH 1:1
52	Et	(CO)NMe_2	phenyl	48	211	−82 (0.54)	48	212	58 (0.52)	50801	EtOH
53	(CO)Me	(CO)NMe_2	phenyl	48	261	−30 (0.46)	48	260	25 (0.46)	AD-H	*n*-heptane/EtOH 85:15
74	Me	(CO)NMe_2	phenyl	46	254	−53 (0.63)	47	254	53 (0.61)	AD	EtOH/MeOH/Et_2NH 5:5:0.1
85	Me	(CO)NH_2	phenyl	45	349	nd	45	349	nd	AD	*n*-heptane/EtOH 7:3
86	Me	(CO)NH(Me)	phenyl	43	253	−56 (0.53)	43	250	56 (0.53)	ASV	CH_3CN/Et_2NH 100:0.1
89	Me	(CO)azetidine	phenyl	48	248	−50 (0.50)	48	247	26 (0.50)	50801	EtOH
90	Me	(CO)pyrrolidine	phenyl	45	269	−60 (0.55)	45	246	45 (0.55)	50801	EtOH
92	Me	(CO)NH(c-Pr)	phenyl	48	273	−50 (0.56)	48	270	35 (0.44)	AD-H	*n*-heptane/EtOH 85:15
98	Me	(CO)NMe(OMe)	phenyl	48	215	−64 (0.53)	47	215	64 (0.53)	AD-H	*n*-heptane/EtOH 80:20

[a] The $[\alpha]_D^{20}$ values of all target compounds were determined in chloroform using the concentration (g/100 cm^3) specified in parentheses. In the case of the target compounds **74a** and **74b**, dichloromethane was used as solvent.

their racemic precursors using chiral HPLC columns was investigated as an alternative approach. The conditions for the separation and the analytical data of the target compounds are summarized in Table 3: Enantiomeric separation of a number of tricyclic imidazopyridines bearing different substituents R^3 and R^6 was accomplished using different CHIRALPAK columns. With exception of target compound **86b** (96.5−97.0% ee), all enantiomers were obtained with an optical purity of >98% ee.

3. Biological and Physicochemical Evaluation of the Target Compounds

The efficacy of all 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines was assessed using several in vitro and in vivo models. First, the IC_{50} value of the inhibition of the gastric proton pump enzyme (H^+/K^+-ATPase) isolated from hog gastric mucosa was determined in a competitive binding assay. Second, the inhibition of [^{14}C]dimethylaminopyridine accumulation in intact gastric glands was assessed, which serves as an indirect parameter for the inhibition of acid secretion in this in vitro model of the mammalian stomach. Finally, the influence of the target compounds on the pentagastrin-stimulated acid secretion of the perfused rat stomach (Ghosh Schild rat) after intraduodenal administration was investigated. Furthermore, the basicity (pK_a value) and lipophilicity (log *D* value) of all racemic 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines was determined.

The data are summarized in Tables 4−6. In all series, the pronounced effect of the configuration of the stereogenic center on the in vitro and in vivo activity is obvious. The (9*S*)-enantiomer seems to be responsible for the gastric acid secretion inhibiting action of the compounds, whereas the (9*R*)-antipodes are virtually inactive. The (9*R*)-imidazopyridine **36b** represents a noteworthy exception of this trend (Table 6): Its in vitro activity is comparable to that of the corresponding (9*S*)-imidazopyridine **36a** and its in vivo activity is reduced by a factor of only 3.

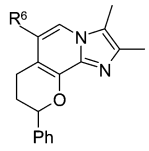
3.1. Influence of the Residue R^6 on Physicochemical Properties and Biological Activity. In the case of the unsubstituted derivative **77**, the good in vitro activity does not translate into significant reduction of acid output in the Ghosh Schild rat (Table 4). Compounds with good in vivo activity and reduced pK_a values are obtained by introduction of an amide residue in the 6-position. Whereas the pK_a value lies in the range of 6.5−7.1 for all amide residues, lipophilicity and pharmacological activity strongly depend on the nature of the substituents attached to the carboxamide residue (Table 4):

3.1.1. Hydrogen/Alkyl Aubstitution. Strong inhibition of H^+/K^+-ATPase and significant reduction of the [^{14}C]dimethylaminopyridine accumulation in gastric glands is observed, if the amide residue R^6 is unsubstituted or substituted by one or two methyl groups (**85**, **86**, **74**). In all cases, also significant activity in the Ghosh Schild rat model was observed. Substitution of the amide residue by two larger alkyl groups results in decreased pharmacological activity (**87**). All derivatives show favorable log *D* values in the range of 2.5−3.2.

3.1.2. Substitution by Cyclic Amines. If the carboxamide residue contains a cyclic amine, the pharmacological activity depends on the ring size and decreases in the order azetidine (**89**), pyrrolidine (**90**), and aziridine (**88**). On the other hand, the three derivatives show comparable effects in the gastric glands model. From the decrease of activity observed for compound **91** (R^6 = (3-hydroxyazetidino)carboxamide), it can be concluded that the presence of a polar hydroxyl group seems to be unfavorable.

3.1.3. Cycloalkyl Substitution. Again, if the carboxamide residue is substituted by a cycloalkyl residue, the pharmacological activity depends on the ring size (cyclopropyl **92** preferred

Table 4. Biological and Pharmacological Evaluation of Target Compounds with Different Residues R^6



Cpd.	R^6	Config.	H^+/K^+-ATPase[a]	Gastric Glands[b]	Ghosh Schild rat[c]	pK_a	log D
77	H	rac.	6.9	6.5	1 / 26 %	7.73	3.50
74a		(9*S*)	6.8	6.7	0.22		
74		rac.	5.8	6.3	0.5	7.15	2.83
74b		(9*R*)	5.4	5.6	3 / 36 %		
85a		(9*S*)		5.8	1.0		
85		rac.	5.9	5.6	0.8	6.52	2.53
85b		(9*R*)		4.6	3 / 30 %		
86a		(9*S*)	6.3	5.7	0.3 / 62 %		
86		rac.	5.6	6.0	0.6	6.74	2.80
86b		(9*R*)	4.4	5.3	3 / 38 %		
87		rac.	5.2	6.1	1 / 23 %	6.75	3.20
88		rac.	5.3	6.4	1 / 35 %	6.63	2.90
89a		(9*S*)	6.4	7.3	0.2		
89		rac.	6.2	6.4	1 / 75 %	6.64	2.60
89b		(9*R*)	5.1	5.8	3 / 37 %		
90a		(9*S*)	6.4	6.7	1.0		
90		rac.	5.8	6.5	1 / 47 %	6.73	2.83
90b		(9*R*)	4.5	5.6	3 / 27 %		
91		rac.	5.9	4.2	3 / 54 %	6.63	2.19
92a		(9*S*)	5.7	7.0	0.25		
92		rac.	6.0	6.0	1 / 82 %	6.69	3.22
92b		(9*R*)	5.1	5.7	3 / 40 %		
93		rac.	5.2	6.4	1 / 26 %	6.68	3.76
94		rac.	5.5	6.6	0.3	6.59	5.00
95		rac.	>6.0	6.7	1 / 33 %	6.57	4.30
96		rac.	4.2	n. i.[d]	3 / 38 %	2.50, 7.18	1.90
97		rac.	5.3	n. i.[d]	1 / 36 %	6.44, 7.58	1.53
98a		(9*S*)	5.6		0.4		
98		rac.	5.8	6.4	0.4	6.49	2.60
98b		(9*R*)	4.5		3 / 20 %		
101		rac.	6.0	6.1	2.0		
76		rac.	6.0	5.6	1 / 34 %	6.35	4.56
84		rac.	5.2	4.6	3 / 15 %	7.33, 2.65	0.7

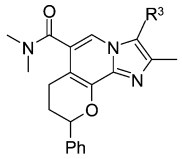
[a] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa. [b] pIC_{50} value of the inhibition of [^{14}C]dimethylaminopyridine accumulation in intact gastric glands. [c] Pentagastrin-stimulated acid secretion of the perfused rat stomach: ED_{50} (μmol/kg) or reduction (%) at dose (μmol/kg). [d] No inhibition (n.i.)

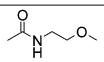
over cyclobutyl **93**), whereas comparable inhibition in the gastric glands model is observed. The log *D* value of the cyclopropyl carboxamide **92** is acceptable. On the other hand, the cyclobutyl carboxamide **93** is a rather lipophilic compound.

3.1.4. Aryl Substitution. The increase of lipophilicity is even more pronounced, if R^6 represents an aromatic carboxamide residue. Both aniline derivatives **94** and **95** reduce the [^{14}C]-dimethylaminopyridine accumulation in gastric glands in a significant manner. Despite its high lipophilicity, the aniline carboxamide **94** shows considerable pharmaceutical activity in the Ghosh Schild rat.

3.1.5. Other Substituents. Hydrophilic compounds with low in vitro and in vivo inhibitory activity are obtained if R^6 represents a carboxamide residue that contains a basic center (methansulfonamide **96**, piperazine carboxamide **97**). In contrast, the Weinreb amide **98** combines good in vitro and in vivo activity with favorable physicochemical properties. In compound **101**, the carboxamide residue has been replaced by the bioisosteric 4,5-dihydro-1,3-oxazole motif. This modification did not affect the in vitro activity (**101** vs **85**). However, the bioisoster **101** inhibited the acid output in the Ghosh Schild rat in a less potent manner than carboxamide **85**.

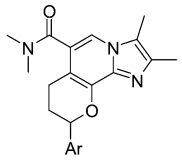
Table 5. Biological and Pharmacological Evaluation of Target Compounds with Different Residues R^3



Cpd.	R^3	Config.	H^+/K^+-ATPase[a]	Gastric Glands[b]	Ghosh Schild rat[c]	pK_a	log D
74a		(9*S*)	6.8	6.7	0.22		
74		rac.	5.8	6.3	0.5	7.15	2.83
74b		(9*R*)	5.4	5.6	3 / 36 %		
44a		(9*S*)	5.8	5.1	5.0		
44		rac.	5.6	4.5	1 / 55 %	5.86	1.52
44b		(9*R*)	4.2	n. i.[d]	>6.0		
46		rac.	n. i.[d]		1 / 26 %	4.51	1.69
47		rac.	n. i.[d]		1 / 54 %	4.38	1.95
48		rac.	<4.0		1 / 22 %	5.58	2.50
49		rac.	6.2	n. i.[d]	1 / 43 %	3.20	3.20
50a		(9*S*)	5.0	5.2	1.5		
50		rac.	4.9	4.9	1.0	4.68	3.20
50b		(9*R*)	<4.0	4.5	3 / 38 %		
52a		(9*S*)	5.5	5.9	1.2		
52		rac.	5.0	5.7	1 / 30 %	6.7	3.0
52b		(9*R*)	4.4	5.0	3 / 20 %		
53a		(9*S*)	<4.0	n. i.[d]	1.0		
53		rac.	<4.0	n. i.[d]	1 / 55 %	3.73	2.55
53b		(9*R*)	<4.0	n. i.[d]	3 / 31 %		
54		rac.	5.0		1 / 20 %	7.77, 4.09	1.8

[a] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa. [b] pIC_{50} value of the inhibition of [^{14}C]dimethylaminopyridine accumulation in intact gastric glands. [c] Pentagastrin-stimulated acid secretion of the perfused rat stomach: ED_{50} (μmol/kg) or reduction (%) at dose (μmol/kg). [d] No inhibition (n.i.).

Table 6. Biological and Pharmacological Evaluation of Target Compounds with Different Residues Ar



Cpd.	Ar	Config.	H^+/K^+-ATPase[a]	Gastric Glands[b]	Ghosh Schild rat[c]	pK_a	log D
74a		(9*S*)	6.8	6.7	0.22		
74		rac.	5.8	6.3	0.5	7.15	2.83
74b		(9*R*)	5.4	5.6	3 / 36 %		
36a		(9*S*)	6.3	6.6	0.4		
36		rac.	6.2	6.7	0.4	6.74	2.76
36b		(9*R*)	6.1	6.6	1.3		
37a		(9*S*)	6.3	7.1	0.2		
37		rac.	5.9	6.2	1 / 73 %	6.78	2.80
37b		(9*R*)	5.3	6.4	3 / 42 %		
38a		(9*S*)	6.5	6.8	0.25		
38		rac.	6.2	6.4	0.35	6.74	2.78
38b		(9*R*)	5.7	6.0	1.5		
75		rac.	5.3	6.2	1 / 46 %	6.64	2.05

[a] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa. [b] pIC_{50} value of the inhibition of [^{14}C]dimethylaminopyridine accumulation in intact gastric glands. [c] Pentagastrin-stimulated acid secretion of the perfused rat stomach: ED_{50} (μmol/kg) or reduction (%) at dose (μmol/kg). [d] No inhibition (n.i.).

The data presented for the ethyl ester **76** illustrates that, in the case of R^6, carboxamide substituents are preferred over carboxylic esters. The good in vitro activity of the lipophilic ester **76** does not translate into significant pharmacological

effects in the Ghosh Schild rat. This might be due to rapid metabolic cleavage of **76**, furnishing the inactive carboxylic acid **84**.

3.2. Influence of the Residue R^3 on Physicochemical Properties and Biological Activity. The data presented in Table 5 clearly demonstrate that the nature of the residue R^3 exerts a strong influence on the pK_a value and the lipophilicity of the corresponding tricyclic imidazopyridine. Replacement of the methyl group (**74**) versus a hydroxymethyl residue (**44**) results in a decrease in basicity of 1.3 log units. A similar effect was also observed for the alcohol **48**. The pK_a value can be decreased even further by introduction of a bromo atom (**50**; $\Delta pK_a = 2.5$), an amide residue (**46**, **47**; $\Delta pK_a = 2.6-2.8$), or a carbonyl group (**49**, **53**; $\Delta pK_a = 3.4-3.95$). Generally, the target compounds presented in Table 5 show favorable log *D* values, with the exception of the rather hydrophilic derivatives **44** and **46**.

The character of the residue R^3 also possesses a pronounced influence on the antisecretory activity of the corresponding target compound. Structural modifications of **74** (R^3 = methyl), e.g., homologation of the methyl group (**52**; R^3 = Et) or replacement of a hydrogen atom versus a hydroxyl group (**44**; $R^3 = CH_2$-OH) or a dimethylamino group (**54**; $R^3 = CH_2NMe_2$), resulted in compounds with significantly reduced in vitro and in vivo activity. Also, none of the imidazopyridines **46**, **47**, **49**, **50**, and **53**, bearing either a 3-bromo, a 3-carboxamide, or a 3-carbonyl substituent, showed noteworthy activity.

3.3. Influence of the Residue Ar on Physicochemical Properties and Biological Activity. From the data presented in Table 6, it can be concluded that small modifications of the phenyl residue are allowed, like replacement of hydrogen versus a fluoro atom or introduction of a methyl group in the ortho position. The derivatives **36**, **37**, **38**, and **74** show comparable in vitro and in vivo activity. Interestingly, the replacement of hydrogen versus a fluoro atom or a methyl group does not alter the lipophilicity of the target compounds (**36**, **37**, **38**, **74**) but results in a pronounced decrease of basicity ($\Delta pK_a = 0.4$). Bioisosteric replacement of the phenyl group versus a thiophene residue furnishes target compound **75**, which possesses highly favorable physicochemical properties. On the other hand, thiophene derivative **75** shows reduced inhibition of the gastric proton pump enzyme and less potent reduction of acid output in the Ghosh Schild rat as compared to its phenyl analogue **74**.

4. Conclusion

A variety of tricyclic imidazopyridines were prepared following synthetic pathways that relied either on a Claisen rearrangement/cross-metathesis reaction or on the preparation/reduction of prochiral ketones.

The influence of the character of the substituents R^3, R^6, and Ar on the biological activity and the physicochemical properties of the target compounds was examined. In contrast to the parent system (R^6 = H), compounds where R^6 represents a carboxamide residue generally showed improved in vivo activity and favorable pK_a/log *D* values. SAR data indicate that the carboxamide substituent $NR^{31}R^{32}$ preferrably should be chosen to be hydrogen, low alkyl, alkoxy, or cyclopropyl. Alternatively, $NR^{31}R^{32}$ could represent a cyclic amine. Whereas variation of R^3 is useful to obtain target compounds with modified basicity and lipophilicity, the character of the substituent R^3 is vital for potent inhibition of the gastric proton pump enzyme. Strong inhibition of the H^+/K^+-ATPase and potent in vivo activity was observed for R^3 = methyl only. Small modifications of the aryl group, e.g., replacement of hydrogen versus a fluoro atom or a methyl group are allowed. The corresponding compounds are less basic than the parent system and show comparable in vitro and in vivo activity.

Several target compounds were obtained in an enantiopure manner, either by chemical synthesis (Noyori reduction of prochiral ketones) or by HPLC separation. It was found that the (9*S*)-enantiomers were responsible for the gastric acid secretion inhibiting action, whereas the (9*R*)-enantiomers were virtually inactive.

In summary, we identified several 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines with excellent physicochemical and pharmacological properties that represent interesting candidates for further development as potassium-competitive acid blockers.

5. Experimental Section

5.1. Chemistry. General. All chemicals were purchased from the major chemical suppliers as the highest purity grade and used without any further purification. 1-(1-Arylvinyl)pyrrolidines were prepared by titanium tetrachloride mediated condensation of the corresponding acetophenone derivative with pyrrolidine (see White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213−214). The hydrogenation catalysts $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN] and $RuCl_2$-[(*S*)-BINAP][(*S*)-DAIPEN] are commercially available from Strem Chemicals or can be prepared according to the procedure given by Noyori and Ohkuma (*Angew. Chem.* **2001**, *113*, 40−75). The progress of the reaction was monitored on Macherey-Nagel HPTLC plates (Nano-SIL 20 UV_{254}, 0.20 mm layer, nano-silica gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. 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 vapor 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 200.1 MHz or a Bruker AV 400 FT-NMR spectrometer at a frequency of 400.1 MHz. $CDCl_3$ or DMSO-d_6 was used as solvent. The chemical shifts are reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. 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 results of the elemental analyses (see Supporting Information) suggest that the title compounds contain variable amounts of crystal water (anhydrous compounds, hemihydrates, hydrates). This might account for the fact that in some cases melting point deviations between different batches of a title compound or between racemic title compounds and their corresponding enantiomers were observed. 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 by HPLC are given for each example in the Experimental Section. The separation by CE was performed using one of the following experimental setups: instrument, Agilent CE-3D; capillary, Agilent bubble-cell 64.5 cm × 50 μm (method A), Agilent bubble-cell 64.5 cm × 75 μm (method B), Agilent barefused silica bubble 48.5 cm × 50 μm (method C); buffer, Agilent 50 mM sodium phosphate, pH 2.5 (all methods); chiral selector, Cyclolab 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (all methods); voltage, 30 kV (all methods); temperature, 10 °C (methods A and B), 20 °C (method C). The number of the methods employed for the corresponding analysis is given in parentheses in the Experimental Section. The purity of the prochiral ketones that served as substrates for the asymmetric catalytic hydrogenation reaction was assessed by HPLC. The following experimental procedure was employed: column, 150 × 4.6 mm XTerra RP 18 5 μm; mobile phase, 0.01 M KH_2PO_4 (pH 2.0)/acetonitrile/water 90:10:0 (v/v/v) (0 min) to 15:80:5 (v/v/v) (30 min); flow rate, 1.0

mL/min; 30 °C. The retention time of the title compounds (detection at 237−245 nm) is given for each example in the Experimental Section.

3-Benzyloxy-5-bromopyridin-2-ylamine (13). A four-neck 1000 mL flask was charged with 10% sulfuric acid (500 mL). At ambient temperature, pyridine **12** (25.0 g, 125 mmol) was added under stirring. At 0 °C, to the mechanically stirred brown solution was added a mixture of bromine (24.0 g, 150 mmol) and acetic acid (82.4 g, 1.37 mol) dropwise over a period of 90 min. The resulting yellow suspension was stirred for 2.5 h at 0 °C and then poured onto ice water (500 mL). A pH value of 8 was adjusted by addition of ammonia solution (25 wt %, 220 mL). The aqueous phase was extracted with dichloromethane (4 × 1 L). The combined organic phases were washed with water (300 mL), dried over sodium sulfate, and concentrated under reduced pressure. The remaining black solid (34.7 g) was purified by column chromatography [600 g of silica gel; eluant, petroleum ether/ethyl acetate = 7:3 (v/v)]. The title compound (28.8 g, 83% yield) was isolated as a slightly yellow solid: mp 99 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 4.84 (bs, 2 H), 5.04 (s, 2 H), 7.08 (d, 1 H), 7.40 (m_c, 5 H), 7.71 (d, 1 H); HRMS calcd for $C_{12}H_{12}BrN_2O$ *m*/*z* (MH^+) 279.0128, found 279.0099.

8-Benzyloxy-6-bromo-2,3-dimethylimidazo[1,2-*a*]pyridine (14). 3-Bromo-2-butanone (66.1 g, 46.0 mL, 0.44 mol) was added to a solution of pyridin-2-ylamine **13** (82.0 g, 0.29 mol) in THF (800 mL). The reaction mixture was refluxed for 48 h and the precipitate formed was removed by filtration and washed with THF. Water (800 mL) and dichloromethane (300 mL) were added to the solid, and the title compound was freed-up from its hydrobromide salt by addition of 6 N sodium hydroxide solution. The organic phase was diluted with dichloromethane (500 mL), the phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 300 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The title compound (50.5 g, 52% yield) was obtained as a colorless solid. The mother liquor was treated with another portion of 3-bromo-2-butanone (66.1 g, 46.0 mL, 0.44 mol) and was heated to reflux for 4 d further. The precipitate formed within this period was removed by filtration and treated as described above. A further 22.6 g of the title compound was obtained (24% yield, 76% overall yield): mp 172−173 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.34, 2.41 (2 s, 6 H), 5.29 (s, 2 H), 6.53 (d, 1 H), 7.40 (m_c, 5 H, Ph), 7.57 (d, 1 H); HRMS calcd for $C_{16}H_{16}BrN_2O$ *m*/*z* (MH^+) 331.0441, found 331.0427.

8-Benzyloxy-6-bromo-2-methylimidazo[1,2-*a*]pyridine (15). Compound **15** was obtained in 59% yield from pyridin-2-ylamine **13** by applying a procedure similar to that described for the preparation of **14**, using chloroacetone instead of 3-bromo-2-butanone (for further details, see Supporting Information): sticky yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.43 (s, 3 H), 5.28 (s, 2 H), 6.52 (d, 1 H), 7.37 (m_c, 6 H), 7.79 (d, 1 H).

8-Benzyloxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (16). A solution of 6-bromoimidazo[1,2-*a*]pyridine **14** (27.0 g, 82 mmol) in THF (400 mL) was treated with palladium acetate (2.7 g, 12 mmol), triphenylphosphine (12.6 g, 48 mmol), triethylamine (26 mL), and dimethylamine (400 mL, 2 M solution in THF, 800 mmol). In an autoclave, the reaction mixture was subjected to a carbon monoxide pressure of 10 bar and a temperature of 120 °C. The reaction mixture was kept at this temperature for 18.5 h, cooled to room temperature, and concentrated in vacuo. The oily residue was dissolved in dichloromethane (400 mL) and water (400 mL). The aqueous phase was extracted with dichloromethane (2 × 400 mL). The combined organic phases were filtered, washed with water (2 × 400 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude product (49 g of a brown oil) was purified by column chromatography [1 kg of silica gel; eluant, dichloromethane and, after removal of triphenylphosphine, dichloromethane/methanol = 15:1 (v/v)]. Two batches of the title compound (18.3 g + 13.0 g of a yellow-brown sticky solid) were obtained, which contained 26/21 mol % of triphenylphosphine oxide (as determined by ^{1}H NMR spectroscopy). These samples were further purified by treatment with boiling diethyl ether (200 mL). The title compound was isolated by filtration, washed with diethyl ether (2 × 40 mL), and dried in vacuo (24.5 g of a colorless solid which contained 16 mol % of triphenylphosphine oxide, 76% yield): mp (purified sample) 152 °C; ^{1}H NMR (purified sample, DMSO-d_6, 200 MHz) δ = 2.29, 2.38 (2 s, 6 H), 2.97 (s, 6 H), 5.31 (s, 2 H), 6.69 (d, 1 H), 7.44 (m_c, 5 H), 7.94 (d, 1 H); HRMS calcd for $C_{19}H_{22}N_3O_2$ *m*/*z* (MH^+) 324.1707, found 324.1718.

8-Benzyloxy-2-methylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (17). Compound **17** was obtained in 77% yield from 6-bromoimidazo[1,2-*a*]pyridine **15** by applying a procedure similar to that described for the preparation of **16** (for further details, see Supporting Information): beige solid; mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.47 (s, 3 H), 2.95 (bs, 6 H), 5.35 (s, 2 H), 6.43 (d, 1 H), 7.40 (m_c, 6 H), 7.88 (d, 1 H); HRMS calcd for $C_{18}H_{20}N_3O_2$ *m*/*z* (MH^+) 310.1550, found 310.1541.

8-Hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (18): (a) Transfer Hydrogenation. 1,4-Cyclohexadiene (6.03 g, 7.12 mL, 75.3 mmol) and palladium catalyst (10% on charcoal, 0.49 g) were added to a suspension of 8-benzyloxyimidazo[1,2-*a*]pyridine **16** (4.87 g, containing 16 mol % of triphenylphosphine oxide, 13.0 mmol) in ethanol (40 mL). The mixture was refluxed for 7 h, cooled, and filtered. The residue was washed with dichloromethane (40 mL). The combined organic phases were concentrated under reduced pressure. The remaining solid (3.37 g) was washed with acetone/diethyl ether (20 mL/20 mL) and dried in vacuo. This afforded 2.33 g of the title compound (colorless solid, 77% yield): mp 278 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.31, 2.37 (2 s, 6 H), 2.99 (s, 6 H), 6.42 (d, 1 H), 7.80 (d, 1 H); HRMS calcd for $C_{12}H_{16}N_3O_2$ *m*/*z* (MH^+) 234.1237, found 234.1229.

(b) Hydrogenation. A solution of 8-benzyloxyimidazo[1,2-*a*]-pyridine **16** (37.3 g, 115 mmol) in dry methanol (420 mL) was treated with hydrogenation catalyst (10 wt % palladium on charcoal, 3.7 g). A hydrogen pressure of 1 bar was applied and the reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was filtered and the filter cake was suspended in dichloromethane (200 mL). The suspension was stirred for several minutes and filtered, and the combined filtrates were evaporated to dryness. This afforded 25.9 g of the title compound (colorless solid, 96% yield): mp 276−277 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.36, 2.40 (2 s, 6 H), 3.10 (s, 6 H), 6.73 (d, 1 H), 7.62 (d, 1 H); HRMS calcd for $C_{12}H_{16}N_3O_2$ *m*/*z* (MH^+) 234.1237, found 234.1226.

8-Hydroxy-2-methylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (19). Compound **19** was obtained in 98% yield from 8-benzyloxyimidazo[1,2-*a*]pyridine **17** by applying a procedure similar to that described for the preparation of **18** (catalytic hydrogenation) (for further details, see Supporting Information): beige solid; mp 230−232 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.44 (s, 3 H), 3.10 (bs, 6 H), 6.74 (d, 1 H), 7.31 (s, 1 H), 7.89 (d, 1 H), 8.96 (bs, 1 H); HRMS calcd for $C_{11}H_{14}N_3O_2$ *m*/*z* (MH^+) 220.1081, found 220.1088.

8-Benzyloxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (20). Compound **20** was obtained in 87% yield from 6-bromoimidazo[1,2-*a*]pyridine **14** by applying a procedure similar to that described for the preparation of **16**, using ethanol instead of dimethylamine (for further details, see Supporting Information): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.40 (t, 3 H), 2.43, 2.44 (2 s, 6 H), 4.39 (q, 2 H), 5.35 (s, 2 H), 7.03 (d, 1 H), 7.34, 7.52 (2 m_c, 5 H), 8.25 (d, 1 H); HRMS calcd for $C_{19}H_{21}N_2O_3$ *m*/*z* (MH^+) 325.1547, found 325.1562.

8-Hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (21). Compound **21** was obtained in 80% yield from 8-benzyloxyimidazo[1,2-*a*]pyridine **20** by applying a procedure similar to that described for the preparation of **18** (catalytic transfer hydrogenation) (for further details, see Supporting Information): mp 241 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.33 (t, 3 H), 2.32, 2.42 (2 s, 6 H), 4.33 (q, 2 H), 6.86 (d, 1 H), 8.26 (d, 1 H); HRMS calcd for $C_{12}H_{15}N_2O_3$ *m*/*z* (MH^+) 235.1077, found 235.1084.

8-Benzyloxy-2,3-dimethylimidazo[1,2-*a*]pyridine (22). Compound **22** was obtained in 67% yield from pyridin-2-ylamine **12** by applying a procedure similar to that described for the preparation of **14** (for further details, see Supporting Information): colorless solid; mp 120−122 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.29 (s, 3 H), 2.35 (s, 3 H), 5.27 (s, 2 H), 6.72 (m_c, 2 H), 7.42 (m_c, 5 H), 7.77 (d, 1 H); HRMS calcd for $C_{16}H_{17}N_2O$ *m*/*z* (MH^+) 253.1335, found 253.132.

2,3-Dimethylimidazo[1,2-*a*]pyridin-8-ol (23). Compound **23** was obtained in 83% yield from 8-benzyloxyimidazo[1,2-*a*]pyridine **22** by applying a procedure similar to that described for the preparation of **18** (catalytic transfer hydrogenation) (for further details, see Supporting Information): mp 210−212 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.31 (s, 3 H), 2.35 (s, 3 H), 6.45 (d, 1 H), 6.70 (t, 1 H), 7.65 (d, 1 H), 8.56 (bs, 1 H); HRMS calcd for $C_9H_{11}N_2O$ *m*/*z* (MH^+) 163.0866, found 163.0862.

8-Allyloxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (24). 8-Hydroxyimidazo[1,2-*a*]pyridine **18** (50.0 g, 0.22 mol) was dissolved in dry DMF (1 L). Potassium carbonate (29.7 g, 0.22 mol) and allyl bromide (31.2 g, 0.26 mol) were added, and the reaction mixture was stirred at room temperature for 18.5 h. The solvent was removed under reduced pressure and the residue was dissolved in saturated ammonium chloride solution (250 mL) and chloroform (500 mL). The phases were separated, and the aqueous phase was extracted with chloroform (2×). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography [800 g of silica gel; eluant, ethyl acetate/methanol = 9:1 (v/v)]. The title compound (40.0 g, 67% yield) was isolated in the form of a yellow solid. Traces of impurities (approximately 14 mol %) were visible in the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.39, 2.46 (2 s, 6 H), 3.10 (s, 6 H), 4.80 (dt, 2 H), 5.33 (dd, 1 H), 5.47 (dd, 1 H), 6.14 (ddt, 1 H), 6.53 (d, 1 H), 7.69 (d, 1 H); HRMS calcd for $C_{15}H_{20}N_3O_2$ *m*/*z* (MH^+) 274.1550, found 274.1543.

8-Allyloxy-2-methylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (25). Compound **25** was obtained in 70% yield from 8-hydroxyimidazo[1,2-*a*]pyridine **19** by applying a procedure similar to that described for the preparation of **24** (for further details, see Supporting Information): yellowish oil; traces of impurities (approximately 5 mol %) were visible in the ^{1}H NMR spectrum; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.46 (s, 3 H), 3.09 (s, 6 H), 4.79 (dt, 2 H), 5.33 (dd, 1 H), 5.45 (dd, 1 H), 6.15 (ddt, 1 H), 6.48 (d, 1 H), 7.33 (s, 1 H), 7.87 (d, 1 H); HRMS calcd for $C_{14}H_{18}N_3O_2$ *m*/*z* (MH^+) 260.1394, found 260.1382.

7-Allyl-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (26). A flask containing neat 8-allyloxyimidazo[1,2-*a*]pyridine **24** (40.0 g, 0.15 mol) was put into an oil-bath that had been preheated to 160 °C. After a period of 50 min at 160 °C, the reaction mixture solidified, forming a dark brown solid. The crude product was cooled to room temperature and was treated with a mixture of acetone and diethyl ether [1:1 (v/v), 200 mL], at which point a beige solid precipitated. After a period of 20 min, the precipitate was removed by filtration, washed with diethyl ether, and dried in vacuo. Thus, 28.0 g of the pure title compound was isolated. The mother liquor was concentrated under reduced pressure and the residue (10 g of a brown solid) was purified by column chromatography [300 g of silica gel; eluant, ethyl acetate/methanol = 9:1 (v/v)] yielding another 2.2 g of the title compound (30.2 g, 76% overall yield): mp 245−247 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.35, 2.44 (2 s, 6 H), 2.87, 3.13 (2 s, 3 H), 3.55 (d, 2 H), 5.02, 5.07 (2 dd, 2 H), 5.97 (m_c, 1 H), 7.36 (s, 1 H), 10.76 (bs, 1 H); HRMS calcd for $C_{15}H_{20}N_3O_2$ *m*/*z* (MH^+) 274.1550, found 274.1543.

7-Allyl-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (27). Compound **27** was obtained in 66% yield from 8-allyloxyimidazo[1,2-*a*]pyridine **25** by applying a procedure similar to that described for the preparation of **26** (for further details, see Supporting Information): colorless solid; mp >190 °C (dec); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.43 (s, 3 H), 2.88 (s, 3 H), 3.11 (s, 3 H), 3.55 (bd, 2 H), 5.00, 5.07 (2 dd, 2 H), 5.98 (m_c, 1 H), 7.22 (s, 1 H), 7.53 (s, 1 H), 9.57 (bs, 1 H); HRMS calcd for $C_{14}H_{18}N_3O_2$ *m*/*z* (MH^+) 260.1394, found 260.1385.

2,2-Dimethylpropionic Acid 7-Allyl-6-dimethylcarbamoyl-2-methylimidazo[1,2-*a*]pyridin-8-yl Ester (28). To a suspension of 8-hydroxyimidazo[1,2-*a*]pyridine **27** (1.00 g, 3.9 mmol) in acetone (30 mL) were added potassium carbonate (0.53 g, 3.9 mmol) and pivaloyl chloride (0.93 g, 7.7 mmol). The yellow suspension was stirred for 3 h at room temperature. After addition of saturated ammonium chloride solution (20 mL) and water (10 mL), the reaction mixture was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product (1.46 g of a colorless solid) was purified by column chromatography (30 g of silica gel; eluant, ethyl acetate). The title compound was obtained in 72% yield (0.96 g of colorless solid): mp 178−180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.48 (s, 9 H), 2.41 (s, 3 H), 2.89 (s, 3 H), 3.08 (s, 3 H), 3.35 (d, 2 H), 5.04 (m_c, 2 H), 5.78 (m_c, 1 H), 7.28 (s, 1 H), 7.82 (s, 1 H).

2,2-Dimethylpropionic Acid 6-Dimethylcarbamoyl-2-methyl-7-((*E*)-3-phenylallyl)imidazo[1,2-*a*]pyridin-8-yl Ester (29). 7-Allylimidazo[1,2-*a*]pyridine **28** (9.30 g, 27.1 mmol) was dissolved in dichloromethane (140 mL) that had been degassed with argon. After addition of *trans*-stilbene (19.53 g, 108.4 mmol) and second-generation Grubbs catalyst (CAS 246047-72-3, 920 mg, 1.08 mmol, 4 mol %), a red solution was obtained. The reaction mixture was heated to 40 °C and was stirred for 18 h at this temperature. The crude product obtained on concentration of the green solution was purified by column chromatography [1.2 kg of silica gel; eluant, petroleum ether (to remove excess *trans*-stilbene) and then ethyl acetate]. A slightly green solid (6.6 g) was isolated, which consisted of the title compound (90 mol %, 53% yield) and untransformed starting material **28** (10 mol %, ratio determined by ^{1}H NMR analysis): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.49 (s, 9 H), 2.42 (s, 3 H), 2.79 (s, 3 H), 3.01 (s, 3 H), 3.53 (d, 2 H), 6.12 (dt, 1 H), 6.43 (d, 1 H), 7.24 (m_c, 6 H), 7.81 (s, 1 H).

2-Methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (30): Preparation from 29. A mixture of 7-((*E*)-3-phenylallyl)imidazo[1,2-*a*]pyridine **29** (6.05 g, 14.4 mmol) and 7-allylimidazo[1,2-*a*]pyridine **28** (0.55 g, 1.6 mmol) was treated with 200 mL of orthophosphoric acid (85%). The resulting green solution was heated for 50 min to 80 °C. The reaction mixture was cooled to room temperature, diluted with dichloromethane (200 mL), and neutralized with a 6 N solution of sodium hydroxide at 0 °C. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 200 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography [210 g of silica gel; eluant, ethyl acetate/methanol = 9:1 (v/v)]. Evaporation of the corresponding fractions afforded the title compound (4.4 g of a colorless solid, 91% yield): mp 189 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.26 (m_c, 2 H), 2.41 (s, 3 H), 2.58, 2.77 (2 m_c, 2 H), 2.94 (s, 3 H), 3.12 (s, 3 H), 5.31 (dd, 1 H), 7.40 (m_c, 6 H), 7.67 (s, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_2$ *m*/*z* (MH^+) 336.1707, found 336.1691.

Preparation from 28 (One-Pot Synthesis). In a flame-dried flask filled with argon, 7-allylimidazo[1,2-*a*]pyridine **28** (4.80 g, 14.0 mmol) was dissolved in dichloromethane (100 mL) which had been degassed with argon. After addition of *trans*-stilbene (10.10 g, 56.0 mmol) and second-generation Grubbs catalyst (CAS 246047-72-3, 475 mg, 0.56 mmol, 4 mol %), the solution was heated to 40 °C. The reaction mixture was stirred for 18 h at this temperature and was then concentrated under reduced pressure. A green solid was obtained which was treated with 100 mL of orthophosphoric acid (85%). The suspension was heated to 80 °C. After a period of 1 h, a clear solution was obtained which was cooled to room temperature and poured onto a mixture of ice water (50 mL) and dichloromethane (50 mL). A pH value of 8 was adjusted by addition of 6 N sodium hydroxide solution. The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue, 16 g of a

green solid, was purified by column chromatography [320 g of silica gel; eluant, petroleum ether (to remove excess *trans*-stilbene) and then ethyl acetate/methanol = 100:2 (v/v)]. The title compound (3.0 g, 64% yield) was isolated as a green foamy solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.26 (m_c, 2 H), 2.41 (s, 3 H), 2.58, 2.77 (2 m_c, 2 H), 2.94 (s, 3 H), 3.12 (s, 3 H), 5.31 (dd, 1 H), 7.40 (m_c, 6 H), 7.67 (s, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_2$ *m*/*z* (MH^+) 336.1707, found 336.1701.

7-Allyl-8-[dimethyl(1,1,2-trimethylpropyl)silanyloxy]-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (31). In a flame-dried flask filled with argon, a suspension of 8-hydroxyimidazo[1,2-*a*]pyridine **26** (3.60 g, 13.2 mmol) in dry DMF (50 mL) was treated with imidazole (1.52 g, 22.3 mmol) and chlorodimethylthexylsilane (slow addition of 4.40 mL, 4.00 g, 22.4 mmol). A brown solution was obtained, which was stirred for 1 h at room temperature. The reaction mixture was poured onto a mixture of ice (20 g), saturated ammonium chloride solution (30 mL), and dichloromethane (50 mL). The biphasic mixture was stirred for several minutes, the phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue, 7.5 g of a yellow-brown oil, was purified by column chromatography [150 g of silica gel; eluant, petroleum ether/ethyl acetate = 8:2 (v/v)]. This afforded the title compound in 93% yield (5.10 g of a colorless solid): mp 93−95 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.41 (s, 6 H), 0.96 (d, 6 H), 1.02 (s, 6 H), 1.83 (septet, 1 H), 2.31, 2.36 (2 s, 6 H), 2.84, 3.08 (2 s, 6 H), 3.50 (m_c, 2 H), 4.96 (m_c, 2 H), 5.84 (m_c, 1 H), 7.36 (s, 1 H).

8-[Dimethyl(1,1,2-trimethylpropyl)silanyloxy]-2,3-dimethyl-7-((*E*)-3-phenylallyl)imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (35). In a flame-dried flask filled with argon, 7-allyl-imidazo[1,2-*a*]pyridine **31** (5.00 g, 12.0 mmol) was dissolved in dry dichloromethane (200 mL) that had been degassed with argon. *trans*-Stilbene (8.70 g, 48.3 mmol) and second-generation Grubbs catalyst (CAS 246047-72-3, 0.40 g, 0.5 mmol, 3.9 mol %) were added, and the obtained red solution was heated to reflux for 19 h. The dark-brown reaction mixture was concentrated to a volume of 80 mL and loaded onto a column filled with 200 g of silica gel. The title compound was eluted using a mixture of petroleum ether and ethyl acetate [7:3 (v/v)]. The solvent was removed and the oily residue was dried in vacuo. A pale-red foam (3.70 g) was obtained [mixture of the title compound (93 wt %, 58% yield) and dimethyl(1,1,2-trimethylpropyl)silanol (7 wt %)]. Compound **35**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.44 (s, 6 H), 0.97 (d, 6 H), 1.03 (s, 6 H), 1.88 (septet, 1 H), 2.31, 2.37 (2 s, 6 H), 2.75, 3.03 (2 s, 6 H), 3.69 (bs, 2 H), 6.20 (dt, 1 H), 6.37 (d, *J* = 15.8 Hz, 1 H), 7.22 (m_c, 5 H), 7.34 (s, 1 H). Dimethyl(1,1,2-trimethylpropyl)silanol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.13 (s, 6 H), 0.87 (s, 6 H), 0.90 (d, 6 H), 1.64 (m_c).

2,3-Dimethyl-9-(2-methylphenyl)-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (36): Preparation from 31. Compound **36** was obtained in 29% yield from 7-allylimidazo[1,2-*a*]pyridine **31** by applying a procedure similar to that described for the preparation of **37**, using 2-methylstyrene instead of 2-fluorostyrene (for further details, see Supporting Information): foamy solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.18 (m_c, 2 H), 2.36, 2.37, 2.40 (3 s, 9 H), 2.78, 2.99 (m_c, s, 5 H), 3.15 (s, 3 H), 5.42 (dd, 1 H), 7.20 (m_c, 3 H), 7.43 (s, 1 H), 7.56 (m_c, 1 H); HRMS calcd for $C_{22}H_{26}N_3O_2$ *m*/*z* (MH^+) 364.2020, found 364.2016. Anal. ($C_{22}H_{25}N_3O_2$) H. C: calcd, 72.70; found, 71.82. N: calcd, 11.56; found, 10.76.

Preparation from 68. Compound **36** was obtained in 46% overall yield from diol **68** by applying a procedure similar to that described for the preparation of **37** (for further details, see Supporting Information): mp 198 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.18 (m_c, 2 H), 2.36, 2.37, 2.40 (3 s, 9 H), 2.78, 2.99 (m_c, s, 5 H), 3.15 (s, 3 H), 5.42 (dd, 1 H), 7.20 (m_c, 3 H), 7.43 (s, 1 H), 7.56 (m_c, 1 H); HRMS calcd for $C_{22}H_{26}N_3O_2$ *m*/*z* (MH^+) 364.2020, found 364.2008. Anal. ($C_{22}H_{25}N_3O_2$) H. C: calcd, 72.70; found, 71.80. N: calcd, 11.56; found, 11.06.

9-(2-Fluorophenyl)-2,3-dimethyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (37): Preparation from 31. In a flame-dried flask filled with argon, 7-allylimidazo[1,2-*a*]pyridine **31** (2.00 g, 4.8 mmol) was dissolved in dichloromethane (50 mL) that had been degassed with argon. After addition of 2-fluorostyrene (2.94 g, 24.1 mmol) and second-generation Grubbs catalyst (CAS 246047-72-3, 162 mg, 0.19 mmol, 4 mol %), the solution was heated to 40 °C. The reaction mixture was stirred for 17 h at this temperature and then concentrated under reduced pressure. A suspension of the residue in 25 mL of orthophosphoric acid (85%) was stirred at 100 °C (preheated oil bath). After a period of 2 h, a clear solution was obtained that was poured onto ice water (70 mL) and dichloromethane (100 mL). A pH value of 8 was adjusted by addition of 6 N sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The black, solid residue (5.6 g) was purified by column chromatography [225 g of silica gel; eluant, ethyl acetate/triethylamine = 100:1 (v/v)]. After removal of the solvent, the pure title compound (1.0 g of a colorless solid, 56% yield) was obtained: mp 202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.27 (m_c, 2 H), 2.36, 2.41 (2 s, 6 H), 2.61 (m_c, 1 H), 2.82 (m_c, 1 H), 2.95, 3.14 (2 s, 6 H), 5.60 (dd, 1 H), 7.09 (m_c, 2 H), 7.27 (m_c), 7.44 (s, 1 H), 7.60 (dt, 1 H); HRMS calcd for $C_{21}H_{23}FN_3O_2$ *m*/*z* (MH^+) 368.1769, found 368.1758.

Preparation from 69. The crude diol **69** (2.1 g) was dissolved in orthophosphoric acid (85 wt %, 20 mL). The suspension was heated at 80 °C (preheated oil bath). After a period of 30 min, a clear solution was obtained. After a reaction time of 1 h, the hot solution was poured onto ice water (100 mL) and dichloromethane (100 mL). The pH value of the biphasic mixture was adjusted to 8 by addition of 6 N sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 40 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A slightly yellow foamy solid remained which was dried in vacuo. The title compound was obtained in 94% yield (1.94 g): mp 203 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.23, 2.36, 2.41 (m_c, 2 s, 8 H), 2.61 (m_c, 1 H), 2.83, 2.95 (m_c, s, 4 H), 3.14 (s, 3 H), 5.60 (dd, 1 H), 7.09 (m_c, 2 H), 7.27 (m_c), 7.44 (s, 1 H), 7.60 (dt, 1 H); HRMS calcd for $C_{21}H_{23}FN_3O_2$ *m*/*z* (MH^+) 368.1769, found 368.1766. Anal. ($C_{21}H_{22}FN_3O_2$) C, H, N, F.

9-(4-Fluorophenyl)-2,3-dimethyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (38): Preparation from 31. Compound **38** was obtained in 21% yield from 7-allylimidazo[1,2-*a*]pyridine **31** by applying a procedure similar to that described for the preparation of **37**, using 4-fluorostyrene instead of 2-fluorostyrene (for further details, see Supporting Information): slightly green solid, mp 267−268 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.24 (m_c, 2 H), 2.36, 2.41 (2 s, 6 H), 2.68 (m_c, 2 H), 2.93, 3.13 (2 s, 6 H), 5.27 (dd, 1 H), 7.04 (t, 2 H), 7.43 (m_c, 3 H); HRMS calcd for $C_{21}H_{23}FN_3O_2$ *m*/*z* (MH^+) 368.1769, found 368.1751. Anal. ($C_{21}H_{22}FN_3O_2$) C, H, N, F.

Preparation from 70. Compound **38** was obtained in 85% overall yield from diol **70** by applying a procedure similar to that described for the preparation of **37** (for further details, see Supporting Information): colorless solid; mp 260 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.24 (m_c, 2 H), 2.36, 2.41 (2 s, 6 H), 2.68 (m_c, 2 H), 2.93, 3.13 (2 s, 6 H), 5.27 (dd, 1 H), 7.04 (t, 2 H), 7.43 (m_c, 3 H). Anal. ($C_{21}H_{22}FN_3O_2$) C, H, N, F.

8-Hydroxy-2,3-dimethyl-7-((*E*)-3-phenylallyl)imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (39). In a flask filled with argon, silyl ether **35** (1.10 g, 2.2 mmol) was dissolved in dry THF (20 mL). After slow addition of a 1 M solution of tetrabutylammonium fluoride in THF (3.30 mL, 3.3 mmol) a dark-green solution was obtained, which was stirred for 30 min at room temperature. The reaction mixture was poured onto a mixture of ice (10 g), saturated ammonium chloride solution (15 mL), and dichloromethane (30 mL). The biphasic mixture was stirred for several minutes, the phases were separated, and the aqueous phase

was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The oily residue (1.5 g) was purified by column chromatography [15 g of silica gel; eluant, dichloromethane and then dichloromethane/methanol = 20:1 (v/v)]. A green solid (900 mg) was obtained, which was suspended in diethyl ether (10 mL), isolated by filtration, washed with diethyl ether (10 mL), and dried in vacuo. The pure title compound (630 mg of a slightly gray solid) was isolated in 81% yield: mp 183−185 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.32, 2.35 (2 s, 6 H), 2.76, 2.96 (2 s, 6 H), 3.48 (d, 2 H), 5.26 (bs), 6.23, 6.34 (m_c, d, 2 H), 7.27 (m_c, 5 H), 7.69 (s, 1 H); HRMS calcd for $C_{21}H_{24}N_3O_2$ *m*/*z* (MH^+) 350.1863, found 350.1853. Anal. ($C_{21}H_{23}N_3O_2$) H, N. C: calcd, 72.18; found, 71.54.

8-Hydroxy-2-methyl-7-((*E*)-3-phenylallyl)imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (40). Pivaloic acid ester **29** was dissolved in methanol (200 mL). After dropwise addition of a 6 N sodium hydroxide solution (12 mL), the reaction mixture was stirred for 1 h at room temperature and for 1 h at 50 °C. The dark solution was concentrated to a volume of 30 mL. Water (30 mL) and dichloromethane (50 mL) were added, and the biphasic mixture was neutralized by addition of 6 N hydrochloric acid. The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and evaporated to dryness. A dark solid (5 g) was obtained, which was dissolved in a hot mixture of dichloromethane (20 mL) and acetone (60 mL). The stirred solution was allowed to cool to room temperature, at which point crystallization took place. Stirring was continued for 1 h at room temperature. The precipitate was isolated by filtration, washed with diethyl ether (10 mL), and dried in vacuo. The title compound was isolated in the form of a colorless solid (2.6 g, 55% yield): mp 188−190 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.35 (s, 3 H), 2.75 (s, 3 H), 2.94 (s, 3 H), 3.48 (d, 2 H), 6.28 (m_c, 2 H), 7.26 (m_c, 5 H), 7.59 (s, 1 H), 7.97 (s, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_2$ *m*/*z* (MH^+) 336.1707, found 336.1682.

8-Hydroxy-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo-[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (41). Over a period of 20 min, sodium borohydride (0.40 g, 10.6 mmol) was added to a solution of the ketone **61** (3.10 g, 8.5 mmol) in methanol (30 mL). The reaction mixture was stirred for 40 min at ambient temperature. Another portion of sodium borohydride (0.10 g, 2.6 mmol) was added and stirring was continued for another 30 min. The reaction mixture was then poured on a mixture of saturated ammonium chloride solution (50 mL), ice (20 g), and dichloromethane (100 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with saturated ammonium chloride solution (2 × 20 mL) and water (2 × 20 mL), dried over sodium sulfate, and evaporated to dryness. The residue was treated with acetone (12 mL). A colorless precipitate was formed that was washed with acetone and diethyl ether and dried. The title compound (2.10 g, 67% yield) was isolated as a colorless solid. The mother liquor (0.8 g) was purified by column chromatography [silica gel; eluant, dichloromethane/2-propanol = 20:1 (v/v)], yielding another 0.29 g (9% yield) of the title compound: mp 219−221 °C (after crystallization from acetone); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 5.69 (bs), 7.25 (m_c, 5 H), 7.59 (s, 1 H); HRMS calcd for $C_{21}H_{25}N_3O_3$ *m*/*z* (MH^+) 368.1969, found 368.1968.

8-Hydroxy-7-((*R*)-3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (41a): Synthesis via Asymmetric Hydroboration. A flame-dried flask filled with argon was charged with (*R*)-Alpine-boramine (CAS 67826-92-0, 1.50 g, 3.6 mmol). After addition of dry THF (8 mL), a colorless solution was obtained, which was treated with boron trifluoride diethyl etherate (0.92 mL, 1.03 g, 7.3 mmol). The solution was stirred for 2 h at room temperature. A colorless precipitate was obtained, which was removed by filtration and washed with cold THF (6 mL, argon atmosphere). The filtrates [containing (−)-monoisopinocampheylborane] were combined. A suspension of alkene **39** (0.42 g, 1.2 mmol) in dry THF (15 mL) was added slowly at room temperature, at which point a yellow solution was obtained. After a reaction time of 5 h, the solution was poured onto a cold mixture of aqueous potassium hydroxide solution (230 mg in 1.6 mL of water), ethanol (4 mL), and hydrogen peroxide (30 wt % in water, 1.6 mL). After a period of 30 min, the reaction mixture was poured onto saturated ammonium chloride solution (20 mL) and dichloromethane (40 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (1 × 10 mL). The combined organic phases were washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The crude product (1.9 g of a yellow oil) was purified by column chromatography [40 g of silica gel; eluant, dichloromethane (to remove isopinocampheol) and then dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions furnished a solid (320 mg), which was washed with acetone (1 mL), isolated by filtration, and dried in vacuo. The title compound was isolated in 50% yield (0.22 g of a colorless solid, optical purity 27.8% ee): mp 216−218 °C (after crystallization from acetone); determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 18.3 min/36.1 area %, t_M [(3*R*)-enantiomer] = 18.6 min/63.9 area %, 27.8% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 5.69 (bs), 7.25 (m_c, 5 H), 7.59 (s, 1 H); HRMS calcd for $C_{21}H_{26}N_3O_3$ *m*/*z* (MH^+) 368.1969, found 368.1952.

Synthesis via Asymmetric Keto Reduction with $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN]. The ketone **61** (2.00 g, 5.5 mmol), potassium *tert*-butylate (0.74 g, 6.6 mmol), and $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN] (CAS 329736-05-2, 110 mg, 0.11 mmol, S/C = 60:1) were dissolved in dry 2-propanol (150 mL) that had been degassed with argon. The homogeneous brown solution was transferred into a 300 mL autoclave, pressurized with hydrogen (45 bar), and heated to 80 °C. The reaction mixture was kept at 80 °C for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in water (50 mL) and the pH value of the solution was adjusted to 7.5 by addition of 2 N hydrochloric acid (2.4 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL). The pH value was readjusted and the extraction was repeated two more times. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue, a green-brown solid, was purified by column chromatography [100 g of silica gel; eluant, dichloromethane/methanol = 15:1 (v/v)]. The title compound was obtained as a gray solid (1.64 g, 36.8% ee, 82% yield) (the optical purity was determined at the stage of the silyl ether **104**): ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 7.25 (m_c, 5 H), 7.59 (s, 1 H).

Synthesis via Asymmetric Keto Reduction with $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN]. In a flame-dried flask filled with argon, the ketone **61** (10.00 g, 27.4 mmol) was suspended in dry 2-propanol (400 mL) that had been degassed with argon. After addition of potassium *tert*-butylate (3.70 g, 30.2 mmol), stirring was continued until a yellow solution was obtained (approximately 30 min). The hydrogenation catalyst $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] (CAS 212143-24-3, 240 mg, 0.21 mmol, S/C = 130:1) was added. The resulting red-yellow solution was stirred for 15 min at room temperature and was transferred under inert conditions into a 1 L autoclave equipped with a glass inlay. The reaction mixture was pressurized with hydrogen (40 bar) and was stirred for 24 h at room temperature. The brown solution was concentrated to a volume of 50 mL and poured onto a cold mixture of saturated ammonium chloride solution (120 mL) and dichloromethane (250 mL). A neutral pH value was adjusted by addition of 6 N hydrochloric acid. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 40 mL). The combined organic phases were washed with water (30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue, a green oil (15 g), was purified by column chromatography [150 g of silica gel; eluant, dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions afforded

the title compound (9.30 g of a pale-green solid, 92% yield, optical purity 85.8% ee): determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 20.2 min/7.1 area %, t_M [(3*R*)-enantiomer] = 20.5 min/92.9 area %, 85.8% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 5.69 (bs), 7.25 (m_c, 5 H), 7.59 (s, 1 H); HRMS calcd for $C_{21}H_{26}N_3O_3$ *m*/*z* (MH^+) 368.1969, found 368.1959.

8-Hydroxy-7-((*S*)-3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (41b). Compound **41b** was obtained in 87% yield from ketone **61** by applying a procedure similar to that described for the preparation of **41a**, using $RuCl_2$[(*R*)-BINAP][(*R*)-DAIPEN] (CAS 329735-86-6) instead of $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] (for further details, see Supporting Information): colorless solid; mp 215−217 °C (after crystallization from acetone); determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 18.5 min/97.7 area %, t_M [(3*R*)-enantiomer] = 19.0 min/2.3 area %, 95.5% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.33 (2 s, 6 H), 2.50 (bm_c), 2.78, 2.91 (2 s, 6 H), 4.49 (t, 1 H), 5.43 (bs), 7.25 (m_c, 5 H), 7.59 (s, 1 H); HRMS calcd for $C_{21}H_{26}N_3O_3$ *m*/*z* (MH^+) 368.1969, found 368.1963.

8-Hydroxy-7-((*R*)-3-hydroxy-3-phenylpropyl)-2-methylimidazo-[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (42a). Compound **42a** was obtained in 18% yield from alkene **40** by applying a procedure similar to that described for the preparation of **41a** (asymmetric hydroboration) (for further details, see Supporting Information): colorless solid; mp 223−224 °C; determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 17.6 min/33.2 area %, t_M [(3*R*)-enantiomer] = 17.8 min/64.8 area %, 32.2% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.33 (s, m_c, 4 H), 2.65 (m_c), 2.77, 2.89 (2 s, 6 H), 4.50 (t, 1 H), 7.25 (m_c, 5 H), 7.55 (s, 1 H), 7.88 (s, 1 H); HRMS calcd for $C_{20}H_{24}N_3O_3$ *m*/*z* (MH^+) 354.1812, found 354.1810.

3-Formyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (43). A flask containing dry DMF (10 mL) was cooled to 0 °C, and phosphorus oxychloride (1.14 g, 7.4 mmol) was added. The cooling bath was removed and the solution was stirred for 1 h at room temperature. The red reaction mixture was treated with a solution of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **30** (1.00 g, 3.0 mmol) in dry DMF (10 mL) and was heated to 60 °C. After a period of 3 h, the reaction mixture was poured on ice water (50 mL), neutralized by addition of 2 N sodium hydroxide solution, and extracted with dichloromethane (3 × 40 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The title compound (1.0 g, 92% yield) was obtained as a brown solid: mp 222−224 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.31 (m_c, 2 H), 2.72 (s, m_c, 4 H), 2.89, 2.95 (m_c, s, 4 H), 3.15 (s, 3 H), 5.34 (dd, 1 H), 7.39 (m_c, 5 H), 9.09 (s, 1 H), 9.99 (s, 1 H); HRMS calcd for $C_{21}H_{22}N_3O_3$ *m*/*z* (MH^+) 364.1656, found 364.1651.

3-Hydroxymethyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano-[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (44). A suspension of the aldehyde **43** (1.00 g, 2.8 mmol) in dry ethanol (30 mL) was treated with sodium borohydride (52 mg, 1.37 mmol). The reaction mixture was stirred for 40 min at room temperature. A clear solution was obtained which was poured on water (20 mL) and dichloromethane (50 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A yellowish, foamy solid remained which was crystallized from acetone (5 mL). The colorless precipitate was isolated by filtration and dried in vacuo, yielding 420 mg of the pure title compound (42% yield). The mother liquor was concentrated and the residue was purified by column chromatography [silica gel; eluant, ethyl acetate/methanol = 10:1 (v/v)]. This furnished a further 160 mg of the title compound (yellow solid, 16% yield): mp 186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.30, 2.37 (m_c, s, 5 H), 2.68 (m_c, 2 H), 2.90, 3.10 (2 s, 6 H), 4.85 (s, 2 H), 5.30 (dd, 1 H), 7.38 (m_c, 5 H), 7.81 (s, 1 H); HRMS calcd for $C_{21}H_{24}N_3O_3$ *m*/*z* (MH^+) 366.1812, found 366.1800. Anal. ($C_{21}H_{23}N_3O_3 \cdot 0.5H_2O$) C, H, N.

6-Dimethylcarbamoyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-3-carboxylic Acid (45). A solution of the aldehyde **43** (1.10 g, 3.0 mmol) in THF (30 mL) and water (20 mL) was treated with sulfamic acid (0.50 g, 5.1 mmol) and cooled to 0 °C. An aqueous solution (5 mL) of sodium chlorite (80% purity, 0.47 g, 4.2 mmol) was added dropwise. The reaction mixture was stirred for 1.25 h at 0 °C. After addition of an aqueous solution (5 mL) of sodium sulfite (0.65 g, 5.2 mmol), stirring was continued for 5 min. The reaction mixture was extracted with dichloromethane (2 × 50 mL). The organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue (750 mg) was dissolved in dichloromethane (10 mL) and water (10 mL). A pH value of 8 was adjusted by addition of 2 N sodium hydroxide solution (0.6 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic phases were discarded, and the aqueous phase was acidified to pH 5 by addition of 2 N hydrochloric acid (1 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL), diluted with saturated sodium chloride solution (5 mL), and extracted again with another portion of dichloromethane. The combined dichloromethane phases were dried over sodium sulfate and concentrated under reduced pressure to yield the title compound (450 mg of a colorless solid, 39% yield). The aqueous phase was concentrated to a volume of 5 mL. After addition of dichloromethane (10 mL), the pH value was readjusted to 5 by addition of 2 N hydrochloric acid (0.5 mL). Following the procedure described above, another 300 mg of the title compound was obtained (26% yield): mp 138 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.31 (m_c, 2 H), 2.69, 2.74 (m_c, s, 4 H), 2.91, 2.96 (m_c, s, 4 H), 3.16 (s, 3 H), 5.33 (dd, 1 H), 7.29 (m_c), 7.43 (m_c, 2 H), 8.93 (s, 1 H).

2-Methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-3,6-dicarboxylic Acid Bis(dimethylamide) (46). A solution of carboxylic acid **45** (0.120 g, 0.32 mmol) in dichloromethane (20 mL) was treated with TBTU (0.107 g, 0.33 mmol). The suspension was stirred for 1 h at room temperature. A 2 M solution of dimethylamine in THF (0.32 mL, 0.64 mmol) was added and stirring was continued for 1.5 h at room temperature. The reaction mixture was quenched by addition of water (20 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. This afforded the title compound in 97% yield (124 mg of a yellowish solid): mp 190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.26 (m_c, 2 H), 2.47 (s, 3 H), 2.61 (m_c, 1 H), 2.80 (m_c), 2.95 (s, 3 H), 3.10, 3.12 (2 s, 9 H), 5.33 (dd, 1 H), 7.39 (m_c, 5 H), 8.06 (s, 1 H); HRMS calcd for $C_{23}H_{27}N_4O_3$ *m*/*z* (MH^+) 407.2078, found 407.2066.

2-Methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-3,6-dicarboxylic Acid 3-[(2-Methoxyethyl)amide] 6-Dimethylamide (47). Compound **47** was obtained in 70% yield from carboxylic acid **45** by applying a procedure similar to that described for the preparation of **46** (for further details, see Supporting Information): colorless solid; mp 208 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.27 (m_c, 2 H), 2.61, 2.71 (m_c, s, 4 H), 2.84, 2.96 (m_c, s, 4 H), 3.11 (s, 3 H), 3.42 (s, 3 H), 3.64 (m_c, 4 H), 5.32 (dd, 1 H), 6.23 (bt, 1 H), 7.39 (m_c, 5 H), 9.01 (s, 1 H). Anal. ($C_{24}H_{28}N_4O_4$) H. C: calcd, 66.04; found, 65.23. N: calcd, 12.84; found, 12.34.

3-(1-Hydroxy-2-butynyl)-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (48). In a flame-dried flask filled with argon, aldehyde **43** was suspended in dry THF (50 mL). The suspension was cooled to −78 °C and propinylmagnesium bromide (11.0 mL of a 0.5 M solution in THF, 5.5 mmol) was added using a syringe. The reaction mixture was stirred for 1 h at −78 °C and for 2 h at 0 °C and then quenched by addition of water (30 mL) and dichloromethane (70 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were washed with water (20 mL) and saturated sodium

chloride solution (20 mL), dried over sodium sulfate, and concentrated in vacuo. A yellow foamy solid (1.07 g of a diasteromeric mixture of the title compound, 96% yield) was isolated: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.84, 1.85 (2 s), 2.25 (m_c, 2 H), 2.39 (s, 3 H), 2.60, 2.81 (2 m_c, 2 H), 2.93, 2.96 (2 s, $\sum$ 3 H), 3.12 (s, 3 H), 3.74 (m_c), 5.30 (m_c, 1 H), 5.85 (m_c, 1 H), 7.38 (m_c, 5 H), 8.14, 8.15 (2 s, $\sum$ 1 H); HRMS calcd for $C_{24}H_{26}N_3O_3$ *m*/*z* (MH^+) 404.1969, found 404.1970.

2-Methyl-3-(1-oxo-2-butynyl)-9-phenyl-7*H*-8,9-dihydropyrano-[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (49). A solution of alcohol **48** (500 mg, 1.24 mmol) in dichloromethane (20 mL) was treated with manganese dioxide (4.0 g, 46 mmol). The suspension was stirred for 1 h at room temperature and then filtered over Celite. Concentration of the filtrate yielded a yellow foamy solid, which was purified by column chromatography (silica gel; eluant, ethyl acetate). After evaporation of the corresponding fractions, the title compound was isolated in 86% yield (430 mg of a yellow solid): mp 216−217 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.16 (s, 3 H), 2.30 (m_c, 2 H), 2.70 (m_c, 1 H), 2.90, 2.91, 2.94 (s, m_c, s, 7 H), 3.14 (s, 3 H), 3.48 (s), 5.34 (dd, 1 H), 7.39 (m_c, 5 H), 9.28 (s, 1 H); HRMS calcd for $C_{24}H_{24}N_3O_3$ *m*/*z* (MH^+) 402.1812, found 402.1810. Anal. ($C_{24}H_{23}N_3O_3 \cdot H_2O$) C, H, N.

3-Bromo-2-methyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (50). 7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **30** (2.00 g, 6.0 mmol) was dissolved in a mixture of chloroform (10 mL) and dichloromethane (10 mL). The solution was cooled to −78 °C and *N*-bromosuccinimide (1.06 g, 6.0 mmol) was added. The reaction mixture was stirred for 45 min at −78 °C. The cooling bath was removed and saturated sodium bicarbonate solution (15 mL) was added. The phases were separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A light green foamy solid (2.7 g) was isolated, which was purified by column chromatography [80 g of silica gel; eluant, ethyl acetate/petroleum ether = 6:4 (v/v)]. The title compound was isolated as a beige solid (1.75 g, 71% yield). Futhermore, 0.5 g of a mixture of the title compound (96 wt %) and succinimide (4 wt %) was isolated (19% yield): mp 167−168 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.28 (m_c, 2 H), 2.45 (s, 3 H), 2.69 (m_c, 2 H), 2.93, 3.14 (2 s, 6 H), 5.32 (dd, 1 H), 7.38 (m_c, 5 H), 7.65 (s, 1 H). Anal. ($C_{20}H_{20}BrN_3O_2$) C, H, N, Br.

2-Methyl-9-phenyl-3-vinyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (51). In a flame-dried flask filled with argon, 3-bromo-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **50** (1.60 g, 3.9 mmol) was dissolved in dry 1,4-dioxane (50 mL). The solution was treated with tributylvinylstannane (1.48 g, 4.7 mmol) and bis(triphenylphosphino)palladium chloride (270 mg, 0.38 mmol) and stirred at a temperature of 100 °C (preheated oil bath). After 2 h, another portion of tributylvinylstannane (0.70 g, 2.2 mmol) and bis-(triphenylphosphino)palladium chloride (140 mg, 0.20 mmol) was added. The reaction was continued for 1 h at 100 °C. The reaction mixture was cooled to room temperature and concentrated in the presence of silica gel (3 g). The crude product was purified by column chromatography [120 g of silica gel; eluant, petroleum ether, then petroleum ether/ethyl acetate = 1:1 (v/v), and then petroleum ether/ethyl acetate = 2:8 (v/v)]. In order to achieve further purification, the title compound obtained after chromatography (1.3 g) was dissolved in ethyl acetate (20 mL) and water (15 mL). The pH was adjusted to 1.5 by addition of 2 N hydrochloric acid. The phases were separated, and the aqueous phase was extracted with ethyl acetate (10 mL). The organic phase was discarded and dichloromethane (20 mL) was added to the aqueous phase. The pH value was adjusted to 8 by addition of 2 N sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. This afforded the pure title compound in 72% yield (1.0 g of a yellow solid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.30 (m_c, 2 H), 2.54, 2.63 (s, m_c, 4 H), 2.79 (m_c, 1 H), 2.92, 3.13 (2 s, 6 H), 5.34 (dd, 1 H), 5.42 (d, 1 H), 5.56 (d, 1 H), 6.78 (dd, 1 H), 7.38 (m_c, 5 H), 7.75 (s, 1 H).

3-Ethyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (52). 3-Vinyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **51** (0.280 g, 0.77 mmol) was dissolved in dry methanol (20 mL). After addition of Lindlar catalyst (Pd/$CaCO_3$/Pb, 56 mg, 20 wt %), a hydrogen pressure of 1 bar was applied. The reaction mixture was stirred for 2 h at room temperature and another 28 mg (10 wt %) of catalyst was added. The hydrogenation was continued for 2 h. The catalyst was removed by filtration, the filtrate was concentrated, and the remaining yellow solid was dried in vacuo. The title compound was isolated in 89% yield (250 mg): mp 230 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.20 (t, 3 H), 2.26 (m_c, 2 H), 2.41 (s, 3 H), 2.57 (m_c, 1 H), 2.73, 2.84, 2.92 (m_c, q, s, 6 H), 3.13 (s, 3 H), 5.32 (dd, 1 H), 7.38 (m_c, 6 H). Anal. ($C_{22}H_{25}N_3O_2$) H. C: calcd, 72.70; found, 72.03. N: calcd, 11.56; found, 11.05.

3-Acetyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (53). 7*H*-8,9-Dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **30** (1.10 g, 3.3 mmol) was dissolved in acetic anhydride (50 mL). After addition of methanesulfonic acid (0.38 g, 3.9 mmol), the solution was heated for 1.5 d at 140 °C. The reaction mixture was concentrated and saturated sodium bicarbonate solution (90 mL) was added in order to adjust the pH value to 7−8. The aqueous phase was extracted with dichloromethane (2 × 70 mL, 1 × 30 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The brown residue was purified by column chromatography (silica gel; eluant, ethyl acetate), yielding 0.57 g of the title compound (colorless solid, 46% yield): mp 249−251 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.29 (m_c, 2 H), 2.61−3.00, 2.61, 2.80, 2.94 (m, 3 s, 11 H), 3.14 (s, 3 H), 5.34 (dd, 1 H), 7.38 (m_c, 5 H), 9.32 (s, 1 H); HRMS calcd for $C_{22}H_{24}N_3O_3$ *m*/*z* (MH^+) 378.1812, found 378.1793.

3-Dimethylaminomethyl-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide, Iodide Salt (54). 7*H*-8,9-Dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine **30** (0.250 g, 0.75 mmol) was dissolved in dry dichloromethane (10 mL), and Eschenmoser's salt (0.138 g, 0.75 mmol) was added. The reaction mixture was stirred for 30 min at room temperature and then evaporated to dryness. This afforded the title compound in 97% yield (377 mg of a colorless solid): mp 183−184 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.14, 2.27 (2 m_c, 2 H), 2.40 (s, 3 H), 2.55 (bs), 2.77, 2.90 (bs, s, 10 H), 3.04 (s, 3 H), 4.64 (bs, 2 H), 5.31 (dd, 1 H), 7.43 (m_c, 5 H), 8.29 (s, 1 H), 9.59 (bs, 1 H); HRMS calcd for $C_{23}H_{29}N_4O_2$ *m*/*z* (MH^+) 393.2285, found 393.2282.

7-Dimethylaminomethyl-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (55). Over a period of 30 min, Eschenmoser's salt (5.6 g, 30 mmol) was added to a solution of 8-hydroxyimidazo[1,2-*a*]pyridine **18** (5.5 g, 24 mmol) in dichloromethane (100 mL). The reaction mixture was stirred for 70 min at ambient temperature (formation of a yellow precipitate) and then poured on cooled, saturated sodium hydrogencarbonate solution (50 mL). The aqueous phase was extracted with dichloromethane (6 × 20 mL). The combined organic phases were washed with water (30 mL), dried over sodium sulfate, and evaporated to dryness. The title compound (6.5 g, 95% yield) was isolated as a colorless solid: mp 210 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.25 (s, 6 H), 2.29 (s, 3 H), 2.34 (s, 3 H), 2.85 (s, 3 H), 2.99 (s, 3 H), 3.53 (s, 2 H), 7.62 (s, 1 H); HRMS calcd for $C_{15}H_{23}N_4O_2$ *m*/*z* (MH^+) 291.1816, found 291.1804.

7-Dimethylaminomethyl-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (56). Compound **56** was obtained in 93% yield from 8-hydroxyimidazo[1,2-*a*]pyridine **21** by applying a procedure similar to that described for the preparation of **55** (for further details, see Supporting Information): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.41 (t, 3 H), 2.40 (s, 12 H), 4.19 (s, 2 H), 4.37 (q, 2 H), 8.04 (s, 1 H).

7-Dimethylaminomethyl-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine (57). Compound **57** was obtained in 62% yield from 8-hydroxyimidazo[1,2-*a*]pyridine **23** by applying a procedure similar to that described for the preparation of **55** (for further details, see Supporting Information). The crude title compound was subjected directly to the next reaction step (synthesis of the ketone **67**).

8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenylpropyl)imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (61): Method A. (a) In a flame-dried flask filled with argon, a suspension of 8-hydroxyimidazo[1,2-*a*]pyridine **18** (50.0 g, 214 mmol) in dry dichloromethane (1.2 L) was treated with Eschenmoser's salt (40.3 g, 218 mmol). The reaction mixture was stirred for 1 h at room temperature. In the beginning, a clear solution was obtained; within 10 min, the formation of a precipitate was observed. The solvent was then removed under reduced pressure. (b) The rotary evaporator was filled with argon. The residue (hydroiodide salt of compound **55**) was dissolved in dry DMF (1.1 L), which had been preheated to 50 °C. An almost clear solution was obtained, which was treated with potassium carbonate (30.4 g, 220 mmol) and 1-(1-phenylvinyl)-pyrrolidine (CAS 3433-56-5, 82.5 g, purity 90 wt %, 428 mmol). In a preheated oil bath, the brown solution was stirred for 30 min at 50 °C and then poured onto a stirred mixture of ammonium chloride (130 g), water (200 mL), ice (300 g), and dichloromethane (600 mL). Stirring was continued for several minutes and the pH value was adjusted to pH = 8 by addition of 6 N hydrochloric acid. The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with water (2 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure (DMF was removed at a temperature of 60 °C). A dark-brown, oily residue (80 g) was obtained which was dried in vacuo. (c) The residue (crude title compound) was purified by filtration over silica gel [500 g; eluant, ethyl acetate and then ethyl acetate/methanol = 8:2 (v/v)]. A red-brown solid was isolated (60 g of crude title compound, HPLC purity 88.08%) which was dried in vacuo, dissolved in methanol (200 mL), and treated with fumaric acid (25.5 g, 220 mmol). The brown suspension was stirred for 20 min at 40 °C, at which point a clear solution was obtained. The solution was concentrated under reduced pressure until a dense suspension was formed. Acetone (120 mL) was added and the mixture was concentrated again until a dense suspension was formed. The slurry was diluted with acetone (150 mL) and stirred at 40 °C (30 min), room temperature (19 h), and 0 °C (2 h). The salt of the title compound with fumaric acid (molar ratio 1:1) was isolated by filtration, washed with acetone (20 mL) and diethyl ether (50 mL), and dried in vacuo (51 g of a colorless solid, 49% yield, mp 196−198 °C). (d) The salt of the title compound with fumaric acid (50 g, 104 mmol) was added portionwise to a mixture of sodium bicarbonate (42 g, 500 mmol), water (400 mL), and dichloromethane (400 mL). The biphasic mixture was stirred for 5 min. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The organic phases were washed with water (2 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure. This afforded the title compound in the form of a colorless, foamy solid (37.7 g, 99% yield, 49% overall yield). The sample was pure by means of ^{1}H NMR spectroscopy and showed an HPLC purity of 99.07% (t_R = 9.4 min): mp 115−117 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.32, 2.37 (2 s, 6 H), 2.95 (s), 3.05 (bs), 3.14 (s, Σ 8 H), 3.42 (m_c, 2 H), 7.29 (s, 1 H), 7.47 (m_c, 3 H), 8.00 (m_c, 2 H); HRMS calcd for $C_{21}H_{24}N_3O_3$ *m*/*z* (MH^+) 366.1812, found 366.1821.

Method B. In a flame-dried flask under argon, intermediate **55** (free base, 3.2 g, 11 mmol) and 1-(1-phenylvinyl)pyrrolidine (3.1 g, 18 mmol) were dissolved in absolute toluene (50 mL). The solution was heated to 105 °C. After 15 min the reaction mixture was cooled to 0 °C and poured on a mixture of ice−water (50 mL) and dichloromethane (50 mL). The brown organic phase was removed and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and evaporated to dryness. The crude product (5 g of a brown solid) was purified by column chromatography (silica gel; eluant, dichloromethane). The title compound (3.2 g, 79% yield) was obtained as a brownish foam; traces of impurities were visible in the ^{1}H NMR spectrum of this compound: ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32 (s, 3 H), 2.36 (s, 3 H), 2.82 (m_c, 2 H), 2.89 (s, 3 H), 3.01 (s, 3 H), 3.21 (m_c, 2 H), 7.59 (m_c, 3 H), 7.95 (d, 2 H), 7.99 (s, 1 H); HRMS calcd for $C_{21}H_{24}N_3O_3$ *m*/*z* (MH^+) 366.1812, found 366.1815.

8-Hydroxy-2,3-dimethyl-7-[3-(2-methylphenyl)-3-oxopropyl]-imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (62). Compound **62** was obtained in 54% yield from 8-hydroxyimidazo-[1,2-*a*]pyridine **18** by applying a procedure similar to that described for the preparation of **61** (method A), using 1-[1-(2-methylphenyl)-vinyl]pyrrolidine (CAS 156004-72-7) instead of 1-(1-phenylvinyl)-pyrrolidine (for further details, see Supporting Information): colorless solid; mp 179−180 °C/182−183 °C; HPLC purity batch 1, 97.3%, batch 2, 99.6% (t_R = 10.7 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32, 2.35, 2.41 (3 s, 9 H), 2.79, 2.88 (m_c, s, 5 H), 3.01, 3.08 (s, m_c, 5 H), 5.45 (bs), 7.37 (m_c, 3 H), 7.71 (m_c, 2 H); HRMS calcd for $C_{22}H_{26}N_3O_3$ *m*/*z* (MH^+) 380.1969, found 380.1957. Anal. ($C_{22}H_{25}N_3O_3 \cdot H_2O$) C, H, N.

7-[3-(2-Fluorophenyl)-3-oxopropyl]-8-hydroxy-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (63). Compound **63** was obtained in 51% yield from 8-hydroxyimidazo-[1,2-*a*]pyridine **18** by applying a procedure similar to that described for the preparation of **61** (method A), using 1-[1-(2-fluorophenyl)-vinyl]pyrrolidine (CAS 237436-15-6) instead of 1-(1-phenylvinyl)-pyrrolidine (for further details, see Supporting Information): beige solid; mp 196 °C; HPLC purity 98.12% (t_R = 9.4 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32, 2.35 (2 s, 6 H), 2.89 (bm_c, s, 5 H), 2.99 (s, 3 H), 3.18 (bm_c, 2 H), 5.48 (bs), 7.33 (m_c, 2 H), 7.65, 7.69(m_c, s, 2 H), 7.81 (dt, 1 H); HRMS calcd for $C_{21}H_{23}FN_3O_3$ *m*/*z* (MH^+) 384.1718, found 384.1705.

7-[3-(4-Fluorophenyl)-3-oxopropyl]-8-hydroxy-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (64). Compound **64** was obtained in 46% yield from 8-hydroxyimidazo-[1,2-*a*]pyridine **18** by applying a procedure similar to that described for the preparation of **61** (method A), using 1-[1-(4-fluorophenyl)-vinyl]pyrrolidine (CAS 237436-54-3) instead of 1-(1-phenylvinyl)-pyrrolidine (for further details, see Supporting Information): beige solid: mp 221 °C; HPLC purity 97.83% (t_R = 9.9 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32, 2.35 (2 s, 6 H), 2.85, 2.88 (m_c, s, 5 H), 3.00 (s, 3 H), 3.19 (t, 2 H), 6.42 (bs, 1 H), 7.34 (t, 2 H), 7.70 (s, 1 H), 8.05 (q, 2 H); HRMS calcd for $C_{21}H_{23}FN_3O_3$ *m*/*z* (MH^+) 384.1718, found 384.1722.

8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-thiophen-2-ylpropyl)imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (65). Compound **65** was obtained in 45% yield from the crude intermediate **55** by applying a procedure similar to that described for the preparation of **61** (method A), using 1-(1-thiophen-2-ylvinyl)-pyrrolidine instead of 1-(1-phenylvinyl)pyrrolidine (for further details, see Supporting Information): beige solid; mp 234 °C; HPLC purity 99.04% (t_R = 8.3 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32, 2.36 (2 s, 6 H), 2.81, 2.89 (m_c, s, 5 H), 3.01 (s, 3 H), 3.14 (t, 2 H), 5.85 (bs), 7.24 (dd, 1 H), 7.71 (s, 1 H), 7.93 (dd, 1 H), 8.00 (dd, 1 H); HRMS calcd for $C_{19}H_{22}N_3O_3S$ *m*/*z* (MH^+) 372.1376, found 372.1364.

8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenylpropyl)imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (66): Method A. Compound **66** was obtained in 55% yield from 8-hydroxy-imidazo-[1,2-*a*]pyridine **21** by applying a procedure similar to that described for the preparation of **61** (method A) (for further details, see Supporting Information): colorless solid; mp 172−174 °C; HPLC purity 98.33% (t_R = 14.1 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.29 (t, 3 H), 2.34, 2.41 (2 s, 6 H), 3.23 (s, 4 H), 4.29 (q, 2 H), 6.30 (bs, 1 H), 7.51 (t, 2 H), 7.64 (t, 1 H), 7.98 (d, 2 H), 8.19 (s, 1 H); HRMS calcd for $C_{21}H_{23}N_2O_4$ *m*/*z* (MH^+) 367.1652, found 367.1657.

Method B. Compound **66** was obtained in 84% yield from intermediate **56** by applying a procedure similar to that described for the preparation of **61** (method B) (for further details, see

Supporting Information): brownish foam (90% purity according to ^{1}H NMR analysis); ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.39 (t, 3 H), 2.39 (s, 6 H), 3.46 (m_c, 4 H), 4.39 (q, 2 H), 7.46 (m_c, 3 H), 8.03 (d, 2 H), 8.10 (s, 1 H); HRMS calcd for $C_{21}H_{23}N_2O_4$ *m/z* (MH^+) 367.1652, found 367.1653.

3-(8-Hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridin-7-yl)-1-phenylpropan-1-one (67). Compound **67** was obtained in 48% yield from intermediate **57** by applying a procedure similar to that described for the preparation of **61** (method B) (for further details, see Supporting Information). The crude title compound was obtained as a brownish foam and was immediately subjected to the next reaction step (reduction to the diol **73**). HRMS calcd for $C_{18}H_{19}N_2O_2$ *m/z* (MH^+) 295.1441, found 295.1433.

8-Hydroxy-7-[3-hydroxy-3-(2-methylphenyl)propyl]-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (68). Compound **68** was obtained from ketone **62** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information). The crude title compound was isolated in the form of a yellow foam, which was directly used as starting material for the synthesis of **36**. ^{1}H NMR ($CDCl_3$ + traces of MeOD, 200 MHz) δ = 2.00 (bm_c, 2 H), 2.16 (s, 3 H), 2.35 (s, 3 H), 2.55 (s, 3 H), 2.91, 3.05, 3.12 (s, bm_c, s, 8 H), 4.81 (dd, 1 H), 7.07 (m_c, 4 H), 7.51 (d, 1 H); HRMS calcd for $C_{22}H_{28}N_3O_3$ *m/z* (MH^+) 382.2125, found 382.2112.

7-[3-(2-Fluorophenyl)-3-hydroxypropyl]-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (69). Compound **69** was obtained from ketone **63** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information). The crude title compound (colorless solid) was directly used as starting material for the synthesis of **37**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.90 (m_c, 2 H), 2.35, 2.56 (2 s, 6 H), 2.80, 2.95 (bs, s, 4 H), 3.14 (s, 3 H), 3.35 (m_c, 1 H), 4.90 (dd, 1 H), 6.88 (m_c, 1 H), 7.09, 7.14 (m_c, s, 3 H), 7.59 (m_c, 1 H); HRMS calcd for $C_{21}H_{25}FN_3O_3$ *m/z* (MH^+) 386.1874, found 386.1855.

7-[3-(4-Fluorophenyl)-3-hydroxypropyl]-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (70). Compound **70** was obtained from ketone **64** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information). The crude title compound (colorless solid) was directly used as starting material for the synthesis of **38**. ^{1}H NMR ($CDCl_3$ + traces of MeOD, 200 MHz) δ = 1.97 (bm_c, 2 H), 2.35 (s, 3 H), 2.56 (s, 3 H), 2.92, 3.14, 3.20 (2 s, bm_c, 8 H), 4.55 (dd, 1 H), 6.92 (t, 2 H), 7.17 (s, 1 H), 7.29 (m_c, 2 H).

8-Hydroxy-7-(3-hydroxy-3-thiophen-2-ylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (71). Compound **71** was obtained from ketone **65** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information). The title compound (colorless solid) was directly used as starting material for the synthesis of **75**: mp 157 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.09 (m_c, 2 H), 2.31 (s, 3 H), 2.48 (bs, 4 H), 2.91 (s, 3 H), 3.14, 3.33 (s, bs, 4 H), 4.80 (t, 1 H), 6.87 (m_c, 2 H), 7.11 (m_c, 2 H); HRMS calcd for $C_{19}H_{24}N_3O_3S$ *m/z* (MH^+) 374.1533, found 374.1536.

8-Hydroxy-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (72). Compound **72** was obtained in 75% yield from ketone **66** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information): almost colorless foam; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.40 (t, 3 H), 2.13 (m_c, 2 H), 2.40 (s, 3 H), 2.52 (s, 3 H), 3.26 (m_c, 1 H), 3.50 (m_c, 1 H), 4.39 (q, 2 H), 4.61 (dd, 1 H), 7.24 (m_c, 5 H), 7.95 (s, 1 H); HRMS calcd for $C_{21}H_{25}N_2O_4$ *m/z* (MH^+) 369.1809, found 369.1791.

7-(3-Hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridin-8-ol (73). Compound **73** was obtained in 24% yield from ketone **67** by applying a procedure similar to that described for the preparation of **41** (for further details, see Supporting Information): colorless solid; mp 183−185 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.85 (m_c, 2 H), 2.24 (s, 3 H), 2.33 (s, 3 H), 2.63 (m_c), 4.54 (t, 1 H), 6.64 (d, 1 H), 7.27 (m_c, 5 H), 7.58 (d, 1 H); HRMS calcd for $C_{18}H_{21}N_2O_2$ *m/z* (MH^+) 297.1598, found 297.1580.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (74). Lewis Acid Catalyzed Cyclization. Compound **74** was obtained in 24% yield from diol **41** by applying a procedure similar to that described for the preparation of **76** (for further details, see Supporting Information): colorless solid; mp 245−247 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.12 (m_c, 1H), 2.25 (s, bs, 4 H), 2.34 (s, 3 H), 2.49 (bs), 2.75 (m_c, 1 H), 2.86, 3.00 (2 s, 6 H), 5.26 (d, 1 H), 7.40 (m_c, 5 H), 7.80 (s, 1 H). Anal. ($C_{21}H_{23}N_3O_2$·0.5H_2O) H, N. C: calcd, 70.37; found, 70.84.

Broensted Acid Catalyzed Cyclization. Over a period of 15 min, portions of diol **41** (12.5 g, 34.0 mmol) were dissolved in orthophosphoric acid (85 wt %, 100 mL). The reaction mixture was heated at 80 °C (preheated oil bath). After a reaction time of 0.25 h, the reaction was quenched with ice and a pH value of 6.5 was adjusted by addition of 6 N sodium hydroxide solution. The aqueous solution was extracted with dichloromethane (3×). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel; eluant, ethyl acetate/methanol = 9:1 (v/v)]. The corresponding fractions were concentrated to a volume of 50 mL, and diisopropyl ether (200 mL) was added. After a period of 0.5 h, the title compound was isolated by filtration (10.9 g of a colorless solid, 92% yield): mp 253−254 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.12 (m_c, 1H), 2.25 (s, bs, 4 H), 2.34 (s, 3 H), 2.49 (bs), 2.75 (m_c, 1 H), 2.86, 3.00 (2 s, 6 H), 5.26 (d, 1 H), 7.40 (m_c, 5 H), 7.80 (s, 1 H).

(9*S*)-2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (74a). In a flame-dried flask filled with argon, (*R*)-diol **41a** (9.10 g, 24.8 mmol, 85.9% ee) was suspended in dry THF (330 mL). After addition of triphenylphosphine (19.50 g, 74.3 mmol) and dropwise addition of DIAD (15.20 g, 75.1 mmol), a dark-green solution was obtained, which was stirred for 80 min at room temperature. The reaction mixture was concentrated under reduced pressure and the residue (50 g of a green oil) was purified by column chromatography [250 g of silica gel; eluant, ethyl acetate, then ethyl acetate/methanol = 20:1 (v/v)]. A colorless solid (6.5 g) was obtained which was suspended in diethyl ether (30 mL). The precipitate was isolated by filtration, washed with diethyl ether (20 mL), and dried in vacuo, yielding 5.0 g of the title compound (58% yield, optical purity 85.2−85.4% ee): mp 258−260 °C; determination of the optical purity by HPLC (column, 250 × 4.6 mm CHIRALPAK AD-H 5 μm; mobile phase, ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate, 1 mL/min; 35 °C; detection at 243 nm), t_R [(9*R*)-enantiomer] = 4.0 min/7.3 area %, t_R [(9*S*)-enantiomer] = 4.4 min/92.7 area %, 85.4% ee; determination of the optical purity by CE, t_M [(9*S*)-enantiomer] = 19.5 min/92.6 area %, t_M [(9*R*)-enantiomer] = 20.3 min/7.4 area %, 85.2% ee (A); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.12 (m_c, 1H), 2.25 (s, bs, 4 H), 2.34 (s, 3 H), 2.49 (bs), 2.75 (m_c, 1 H), 2.86, 3.00 (2 s, 6 H), 5.26 (d, 1 H), 7.40 (m_c, 5 H), 7.80 (s, 1 H). Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

(9*R*)-2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (74b). Compound **74b** was obtained in 42% yield from (*S*)-diol **41b** (95.4% ee) by applying a procedure similar to that described for the preparation of **74a**, using dichloromethane instead of THF as solvent (for further details, see Supporting Information): mp 257−259 °C; determination of the optical purity by HPLC (column, 250 × 4.6 mm CHIRALPAK AD-H 5 μm; mobile phase, ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate, 1 mL/min; 35 °C; detection at 243 nm), t_R [(9*R*)-enantiomer] = 3.9 min/97.8 area %, t_R [(9*S*)-enantiomer] = 4.4 min/2.2 area %, 95.6% ee; determination of the optical purity by CE, t_M [(9*S*)-enantiomer] = 18.3 min/2.1 area %, t_M [(9*R*)-enantiomer] = 18.6 min/97.9 area %, 95.8% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.14 (m_c, 1H), 2.26 (s, m_c, 4 H), 2.35 (s, 3 H), 2.47 (m_c), 2.78, 2.87 (m_c, s, 4 H), 3.01 (s, 3 H), 5.26 (dd, 1 H), 7.42 (m_c, 5 H), 7.79 (s, 1 H);

HRMS calcd for $C_{21}H_{24}N_3O_2$ *m/z* (MH^+) 350.1863, found 350.1859. Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

2,3-Dimethyl-9-thiophen-2-yl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (75). Compound **75** was obtained in 35% yield from diol **71** by applying a procedure similar to that described for the preparation of **74a** (for further details, see Supporting Information): colorless solid; mp 241 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.25, 2.26, 2.34 (s, m_c, s, 8 H), 2.53 (m_c), 2.73, 2.87 (m_c, s, 4 H), 3.01 (s, 3 H), 5.56 (dd, 1 H), 7.08 (dd, 1 H), 7.23 (bd, 1 H), 7.57 (dd, 1 H), 7.79 (s, 1 H); HRMS calcd for $C_{19}H_{22}N_3O_2S$ *m/z* (MH^+) 356.1427, found 356.1418.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (76). In a flame-dried flask set under argon, a solution of diol **72** (250 mg, 0.68 mmol) in dichloromethane (15 mL) was treated with an excess of boron trifluoride etherate (1.71 mL, 13.6 mmol). The solution was stirred for 4 h at ambient temperature. The reaction mixture was quenched at 0 °C by addition of saturated ammonium chloride solution (20 mL). The pH was adjusted to 7 using 6 N sodium hydroxide solution (3 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with 20 mL of water and dried over sodium sulfate. After evaporation of the solvent, the residue (245 mg of a colorless solid) was purified by column chromatography [silica gel; eluant, petroleum ether/ethyl acetate = 1:1 (v/v)]. The title compound (164 mg, 69% yield) was obtained as a colorless solid: mp 146−147 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.41 (t, 3 H), 2.26, 2.42 (m_c, s, 8 H), 3.16 (m_c, 2 H), 4.38 (q, 2 H), 5.28 (dd, 1 H), 7.37 (m_c, 5 H), 8.22 (s, 1 H); HRMS calcd for $C_{21}H_{23}N_2O_3$ *m/z* (MH^+) 351.1703, found 351.1719.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine (77). Compound **77** was obtained in 87% yield from diol **73** by applying a procedure similar to that described for the preparation of **76** (for further details, see Supporting Information). beige solid: mp 163−165 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.14, 2.25 (m_c, s, 5 H), 2.34 (s, 3 H), 2.66 (m_c, 1 H), 2.94 (m_c, 1 H), 5.23 (dd, 1 H), 6.63 (d, 1 H), 7.43 (m_c, 5 H), 7.71 (d, 1 H); HRMS calcd for $C_{18}H_{19}N_2O$ *m/z* (MH^+) 279.1492, found 279.1479.

9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (78). 2,2-Dimethoxypropane (8.6 g, 10.1 mL, 83 mmol) was added to a solution of ketone **66** (2.00 g, 5.5 mmol) in dry dichloromethane (25 mL). After slow addition of methanesulfonic acid (0.68 g, 0.46 mL, 7.1 mmol), a dark brown solution was obtained, which was refluxed for 6 h. The reaction mixture was cooled and poured onto a stirred mixture of saturated sodium bicarbonate solution (25 mL) and dichloromethane (20 mL). The biphasic mixture was stirred for several minutes, and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The brown residue (3 g) was treated with diethyl ether (15 mL) and the resulting slurry was stirred for 15 min. The precipitate was isolated by filtration, washed with diethyl ether (5 mL), and dried in vacuo. The title compound (1.85 g of a colorless solid) was isolated in 88% yield: mp 184−186 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.35 (t, 3 H), 1.90 (m_c, 1 H), 2.34, 2.37, 2.43 (s, m_c, s, 7 H), 2.99, 3.12 (s, m_c, 5 H), 4.33 (q, 2 H), 7.49 (m_c, 3 H), 7.63 (m_c, 2 H), 8.36 (s, 1 H); HRMS calcd for $C_{22}H_{25}N_2O_4$ *m/z* (MH^+) 381.1809, found 381.1803.

9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid (79). To a suspension of ester **78** (1.80 g, 4.7 mmol) in methanol (40 mL) was added an aqueous solution of potassium hydroxide (0.56 g, 10.0 mmol, in 5 mL of water). The resulting red suspension was heated to 55 °C. After 30 min, a clear solution was obtained which was kept at 55 °C for 90 min. The reaction mixture was cooled and concentrated under reduced pressure. The wet residue was dissolved in water (40 mL) and 2 N hydrochloric acid was added to the stirred solution until a pH value of 2 was obtained. Stirring was continued for 1 h at room temperature and the precipitate that formed was isolated by filtration. The filter cake was washed with water (until the filtrate showed a neutral pH value) and acetone (5 mL) and was dried in vacuo. The title compound was isolated in 97% yield (1.6 g of colorless solid): mp 240−242 °C; ^{1}H NMR (DMSO-d_6 + traces of MeOD, 200 MHz) δ = 1.99 (m_c, 1 H), 2.51 (m_c), 3.06 (s, 3 H), 3.23 (m_c, 2 H), 7.52 (m_c, 3 H), 7.74 (m_c, 2 H), 8.68 (s, 1 H); HRMS calcd for $C_{20}H_{21}N_2O_4$ *m/z* (MH^+) 353.1496, found 353.1490.

(9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano-[2,3-*c*]imidazo[1,2-*a*]pyridin-6-yl)pyrrolidin-1-ylmethanone (80). In a flask filled with argon, a suspension of carboxylic acid **79** (2.00 g, 5.7 mmol) in dry dichloromethane (35 mL) was treated with TBTU (2.10 g, 6.5 mmol). The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. After addition of pyrrolidine (0.43 g, 0.50 mL, 6.0 mmol), a yellow solution was obtained, which was stirred for 1 h at room temperature. The reaction mixture was poured onto ice water (30 mL) and the stirred biphasic mixture was neutralized by addition of saturated sodium bicarbonate solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue (4 g of a yellow oil) was purified by column chromatography [90 g of silica gel; eluant, dichloromethane/methanol = 100:2 (v/v)]. A colorless foamy solid (1.9 g) was isolated, which was a mixture of the title compound (67 mol %), benzotriazol-1-ol (22 mol %), and tetramethylurea (11 wt %) (as judged by the ^{1}H NMR spectrum): ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.87, 2.07 (2 m_c, 5 H), 2.36, 2.42 (2 s, 6 H), 2.55 (m_c), 2.69 (tetramethylurea), 2.86, 3.02 (m_c, s, 4 H), 3.26 (m_c), 3.50 (t, 2 H), 7.48 [m_c, 3 H (title compound), 2 H (benzotriazol-1-ol)], 7.64, 7.72 [2 m_c, 2 H (title compound), 1 H (benzotriazol-1-ol)], 7.98 [d, 1 H (benzotriazol-1-ol)], 8.11 (s, 1 H); HRMS calcd for $C_{24}H_{28}N_3O_3$ *m/z* (MH^+) 406.2125, found 406.2123.

9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Methylamide (81). Compound **81** was obtained as mixture with benzotriazol-1-ol (39 mol %) and tetramethylurea (8 mol %) from carboxylic acid **79** by applying a procedure similar to that described for the preparation of **80**, using methylamine instead of pyrrolidine (for further details, see Supporting Information): ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.92 (m_c, 1 H), 2.39, 2.45 (2 s, m_c, 7 H), 2.69 (tetramethylurea), 2.80 (d, m_c, 4 H), 3.03, 3.05 (s, m_c, 4 H), 7.48 [m_c, 3 H (title compound), 2 H (benzotriazol-1-ol)], 7.67, 7.72 [2 m_c, 2 H (title compound), 1 H (benzotriazol-1-ol)], 7.99 [d, 1 H (benzotriazol-1-ol)], 8.21 (s, 1 H), 8.47 (bq, 1 H); HRMS calcd for $C_{21}H_{24}N_3O_3$ *m/z* (MH^+) 366.1812, found 366.1804.

[8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenylpropyl)imidazo-[1,2-*a*]pyridin-6-yl]pyrrolidin-1-ylmethanone (82). A solution of the crude acetal **80** (1.80 g) in THF (25 mL) was treated with 1 N hydrochloric acid (10 mL) and was heated to 50 °C for 5 h. The reaction mixture was allowed to cool to room temperature, poured onto a mixture of ice water (25 mL) and dichloromethane (30 mL), and neutralized by addition of 2 N sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated in vacuo. The title compound (1.2 g, HPLC purity 98.42%) was further purified by column chromatography [50 g of silica gel; eluant, ethyl acetate/methanol = 10:1 (v/v)]. This afforded the pure title compound in 46% overall yield [1.03 g of a colorless solid, HPLC purity 99.55% (t_R = 10.9 min)]: mp 257−258 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.84 (m_c, 4 H), 2.32, 2.36 (2 s, 6 H), 2.87 (m_c, 2 H), 3.24 (m_c, 4 H), 3.46 (m_c, 2 H), 6.85 (bs, 1 H), 7.52 (t, 2 H), 7.64 (t, 1 H), 7.77 (s, 1 H), 7.96 (d, 2 H); HRMS calcd for $C_{23}H_{26}N_3O_3$ *m/z* (MH^+) 392.1969, found 392.1955.

8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenylpropyl)imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Methylamide (83). Compound **83** was obtained in an overall yield of 73% from crude acetal **81** by applying a procedure similar to that described for the preparation of **82** (for further details, see Supporting Information): yellow solid;

mp 284−286 °C; HPLC purity 99.57% (t_R = 8.8 min); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.32, 2.38 (2 s, 6 H), 2.76 (d, 3 H), 2.98 (m_c, 2 H), 3.25 (m_c, 2 H), 5.95 (bs, 1 H), 7.52 (t, 2 H), 7.64 (t, 1 H), 7.82 (s, 1 H), 7.98 (d, 2 H), 8.34 (bq, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_3$ *m/z* (MH^+) 352.1656, found 352.1641.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid (84). A suspension of ester **76** (16.7 g, 48 mmol) in methanol (170 mL) and water (35 mL) was treated with potassium hydroxide (4.5 g, 80 mmol) and heated to 50 °C. After a reaction time of 2 h, the methanol was removed in vacuo. Water (400 mL) and dichloromethane (300 mL) was added, the pH was adjusted to 4.8 (isoelectric point of the title compound) by addition of 6 N hydrochloric acid, and stirring was continued for 30 min. A precipitate was formed which slowly dissolved after addition of dichloromethane (100 mL) and methanol (100 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried over sodium sulfate and concentrated to a volume of 50 mL. Upon addition of diethyl ether (100 mL), a colorless precipitate was formed. Stirring was continued for 30 min at 0 °C. The precipitate was isolated by filtration and dried in vacuo, yielding 9.1 g of the pure title compound (58% yield). The aqueous phase was saturated with sodium chloride and extracted with chloroform (1 × 400 mL, 2 × 100 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. This afforded another batch of the title compound (2.0 g, 13% yield): mp 318−320 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.09 (m_c, 1 H), 2.28 (s, m_c, 4 H), 2.40 (s, 3 H), 3.10 (m_c, 2 H), 5.25 (dd, 1 H), 7.43 (m_c, 5 H), 8.32 (s, 1 H); HRMS calcd for $C_{19}H_{19}N_2O_3$ *m/z* (MH^+) 323.1390, found 323.1383. Anal. ($C_{19}H_{18}N_2O_3$·0.5H_2O) C, H, N.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Amide (85). A suspension of carboxylic acid **84** (500 mg, 1.54 mmol) in dichloromethane (20 mL) was treated with TBTU (504 mg, 1.57 mmol). The reaction mixture was heated for 1 h at 40 °C and then allowed to cool to room temperature. Ammonia gas was bubbled through the suspension over a period of 30 min. The reaction mixture was poured onto water (20 mL), dichloromethane (30 mL) was added, and a pH value of 6 was adjusted by addition of 2 N hydrochloric acid. In order to facilitate the separation of the phases, a 10 mL portion of methanol was added. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The title compound (310 mg, 64% yield) was isolated in the form of a colorless solid: mp 346−348 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.09 (m_c, 1 H), 2.26 (m_c, s, 4 H), 2.38 (s, 3 H), 2.97 (m_c, 2 H), 5.24 (dd, 1 H), 7.41 (bs, m_c, 6 H), 7.85 (bs, 1 H), 7.98 (s, 1 H); HRMS calcd for $C_{19}H_{20}N_3O_2$ *m/z* (MH^+) 322.1550, found 322.1541.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Methylamide (86). Carboxylic acid **84** (1.50 g, 4.6 mmol) and TBTU (1.40 g, 4.4 mmol) were suspended in dichloromethane (50 mL). After a reaction time of 1 h at room temperature, methylamine (8.0 M solution in ethanol, 2 mL, 16 mmol) was added. Within 30 min, a clear solution was obtained, which was stirred for 2 h at room temperature. The reaction mixture was poured onto water (20 mL), the phases were separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic phases were washed with water (10 mL), dried over sodium sulfate, and concentrated in vacuo. The residue (1.1 g) was purified by column chromatography [silica gel; eluant, dichloromethane/methanol = 15:1 (v/v)]. Evaporation of the corresponding fractions afforded the title compound (0.90 g of a colorless solid, 58% yield): mp 255−257 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.09 (m_c, s), 2.26 (m_c, s, 4 H), 2.37 (s, 3 H), 2.78 (m_c, d, 4 H), 3.00 (m_c, 1 H), 5.24 (dd, 1 H), 7.41 (m_c, 5 H), 7.92 (s, 1 H), 8.32 (q, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_2$ *m/z* (MH^+) 336.1707, found 336.1704.

(9*S*)-2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Methylamide (86a). Compound **86a** was obtained in 14% yield from (*R*)-diol **103a** (92.0% ee) by applying a procedure similar to that described for the preparation of **74a** (for further details, see Supporting Information): mp 261−263 °C; determination of the optical purity by HPLC (column, 250 × 4.6 mm CHIRALPAK AD-H 5 μm; mobile phase, ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate, 0.8 mL/min; 35 °C; detection at 245 nm), t_R [(9*R*)-enantiomer] = 4.1 min/2.9 area %, t_R [(9*S*)-enantiomer] = 4.4 min/97.1 area %, 94.2% ee; determination of the optical purity by CE, t_M [(9*S*)-enantiomer] = 18.6 min/97.1 area %, t_M [(9*R*)-enantiomer] = 19.9 min/2.9 area %, 94.2% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.07 (m_c, 1H), 2.26 (s, m_c, 4 H), 2.37 (s, 3 H), 2.74, 2.77 (m_c, d, 4 H), 3.00 (m_c, 1 H), 5.24 (dd, 1 H), 7.42 (m_c, 5 H), 7.91 (s, 1 H), 8.32 (bq, 1 H); HRMS calcd for $C_{20}H_{22}N_3O_2$ *m/z* (MH^+) 336.1707, found 336.1696.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridine-6-carboxylic Acid Diethylamide (87). Compound **87** was obtained in 78% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using diethylamine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 178−180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 1.02 (t, 3 H), 1.17 (t, 3 H), 2.11 (m_c, 1 H), 2.26, 2.29 (s, m_c, 4 H), 2.35 (s, 3 H), 2.45 (m_c), 2.75 (m_c, 1 H), 3.19 (bq, 2 H), 3.45 (bs, 2 H), 5.27 (dd, 1 H), 7.42 (m_c, 5 H), 7.78 (s, 1 H); HRMS calcd for $C_{23}H_{28}N_3O_2$ *m/z* (MH^+) 378.2176, found 378.2154. Anal. ($C_{23}H_{27}N_3O_2$·0.5H_2O) C, H, N.

(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridin-6-yl)aziridin-1-ylmethanone (88). Compound **88** was obtained in 15% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using aziridine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 180−181 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.23 (m_c, 12 H), 3.08 (m_c, 2 H), 5.29 (dd, 1 H), 7.39 (m_c, 5 H), 8.31 (s, 1 H); HRMS calcd for $C_{21}H_{22}N_3O_2$ *m/z* (MH^+) 348.1707, found 348.1699.

(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo-[1,2-*a*]pyridin-6-yl)azetidin-1-ylmethanone (89). Compound **89** was obtained in 88% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using azetidine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 254 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.29, 2.37, 2.41 (m_c, 2 s, 10 H), 2.76 (m_c, 1 H), 2.99 (m_c, 1 H), 4.18 (bs, 4 H), 5.30 (dd, 1 H), 7.38 (m_c, 6 H); HRMS calcd for $C_{22}H_{24}N_3O_2$ *m/z* (MH^+) 362.1863, found 362.1852. Anal. ($C_{22}H_{23}N_3O_2$·0.5H_2O) C, H, N.

(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo-[1,2-*a*]pyridin-6-yl)pyrrolidin-1-ylmethanone (90). Compound **90** was obtained in 45% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using pyrrolidine instead of methylamine (for further details, see Supporting Information): mp 274 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.97 (m_c, 4 H), 2.26, 2.36, 2.41 (m_c, 2 s, 8 H), 2.62 (m_c, 1 H), 2.84 (m_c, 1 H), 3.24 (m_c, 2 H), 3.65 (t, 2 H), 5.31 (dd, 1 H), 7.38 (m_c, 6 H); HRMS calcd for $C_{23}H_{26}N_3O_2$ *m/z* (MH^+) 376.2020, found 376.2011. Anal. ($C_{23}H_{25}N_3O_2$) C, H, N.

(9*S*)-(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridin-6-yl)pyrrolidin-1-ylmethanone (90a). Compound **90a** was obtained in 50% yield from (*R*)-diol **102a** (87.4% ee) by applying a procedure similar to that described for the preparation of **74a** (for further details, see Supporting Information): mp 268−270 °C; determination of the optical purity by HPLC (column, 250 × 4.6 mm CHIRALPAK OD-H 5 μm; mobile phase, *n*-hexane/2-propanol = 9:1 (v/v); flow rate, 1 mL/min; 35 °C; detection at 220 nm), t_R [(9*R*)-enantiomer] = 35.5 min/6.3 area %, t_R [(9*S*)-enantiomer] = 43.1 min/93.7 area %, 87.4% ee; determination of the optical purity by CE, t_M [(9*S*)-enantiomer] = 19.7 min/93.6 area %, t_M [(9*R*)-enantiomer] = 20.4 min/6.4 area %, 87.2% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.85 (m_c, 4 H), 2.13 (m_c, 1H), 2.25 (s, m_c, 4 H), 2.35 (s, 3 H), 2.50 (m_c), 2.81 (m_c, 1 H), 3.26 (m_c, 2 H), 3.48 (t, 2 H), 5.25 (dd, 1 H), 7.42 (m_c, 5 H), 7.84 (s, 1 H); HRMS calcd for $C_{23}H_{26}N_3O_2$ *m/z* (MH^+) 376.2020, found 376.2010.

(3-Hydroxyazetidin-1-yl)(2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridin-6-yl)methanone (91). Compound **91** was obtained in 36% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using 3-hydroxyazetidine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 306−308 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.10 (m_c, 1 H), 2.26 (s, m_c, 4 H), 2.37 (s, 3 H), 2.66 (m_c, 1 H), 2.92 (m_c, 1 H), 3.85 (m_c, 2 H), 4.23 (m_c, 2 H), 4.50 (m_c, 1 H), 5.26 (dd, 1 H), 5.75 (m_c, 1 H), 7.42 (m_c, 5 H), 7.85 (s, 1 H); HRMS calcd for $C_{22}H_{24}N_3O_3$ *m*/*z* (MH^+) 378.1812, found 378.1798.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Cyclopropylamide (92). Compound **92** was obtained in 45% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using cyclopropylamine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 260 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 0.57 (m_c, 2 H), 0.70 (m_c, 2 H), 2.06 (m_c, 1 H), 2.26 (s, m_c, 4 H), 2.37 (s, 3 H), 2.66−3.08 (m, 3 H), 3.17 (d, MeOH), 4.07 (q, MeOH), 5.23 (dd, 1 H), 7.42 (m_c, 5 H), 7.86 (s, 1 H), 8.42 (d, 1 H); HRMS calcd for $C_{22}H_{24}N_3O_2$ *m*/*z* (MH^+) 362.1863, found 362.1853. Anal. ($C_{22}H_{23}N_3O_2$·0.5H_2O) C, H, N.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Cyclobutylamide (93). Compound **93** was obtained in 47% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using cyclobutylamine instead of methylamine (for further details, see Supporting Information): mp 257−258 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.79 (m_c), 1.90−2.50, 2.33, 2.40 (m, 2 s, 12 H), 2.84 (m_c, 1 H), 3.01 (m_c, 1 H), 4.55 (m_c, 1 H), 5.22 (dd, 1 H), 6.50 (d, 1 H), 7.39 (m_c, 6 H); HRMS calcd for $C_{23}H_{26}N_3O_2$ *m*/*z* (MH^+) 376.2020, found 376.2025.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Phenylamide (94). Compound **94** was obtained in 39% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using aniline instead of methylamine (for further details, see Supporting Information): colorless solid; mp 285−287 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.09 (m_c, 1 H), 2.29 (m_c, s, 4 H), 2.41 (s, 3 H), 2.77 (m_c, 1 H), 3.06 (m_c, 1 H), 5.28 (dd, 1 H), 7.11 (t, 1 H), 7.42 (m_c, 7 H), 7.73 (d, 2 H), 8.14 (s, 1 H), 10.37 (s, 1 H); HRMS calcd for $C_{25}H_{24}N_3O_2$ *m*/*z* (MH^+) 398.1863, found 398.1851.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid (4-Ethoxyphenyl)amide (95). Compound **95** was obtained in 49% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using 4-ethoxyaniline instead of methylamine (for further details, see Supporting Information): mp 223 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.42 (t, 3 H), 2.11 (m_c, 1 H), 2.27, 2.33, 2.39 (s, m_c, s, 7 H), 2.89 (m_c, 1 H), 3.10 (m_c, 1 H), 4.04 (q, 2 H), 5.14 (dd, 1 H), 6.87 (d, 2 H), 7.25 (m_c), 7.38 (m_c, 2 H), 7.44 (s, 1 H), 7.64 (d, 2 H), 8.71 (bs, 1 H). Anal. ($C_{27}H_{27}N_3O_3$) H, N. C: calcd, 73.45; found, 73.00.

***N*-(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carbonyl)methanesulfonamide (96).** A suspension of carboxylic acid **84** (0.80 g, 2.5 mmol) in dry THF (30 mL) was treated with *N*,*N*′-carbonyldiimidazole (0.80 g, 4.9 mmol). After a reaction time of 2 h at 40 °C a brown solution was obtained. DBU (0.75 g, 4.9 mmol) and methanesulfonamide (0.47 g, 4.9 mmol) was added and stirring was continued for 1 h at room temperature. The reaction mixture was poured onto water (30 mL) and dichloromethane (50 mL), the phases were separated, and the aqueous phase was extracted with dichloromethane (30 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue (1.5 g of a brown foamy solid) was purified by column chromatography [45 g of silica gel; eluant, dichloromethane/methanol = 100:3 (v/v)]. The corresponding fractions were evaporated and the title compound was isolated (0.70 g, 71% yield): mp 210 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.09 (m_c, 1 H), 2.30 (s, m_c, 4 H), 2.41 (s, 3 H), 3.00, 3.10 (s, m_c, 5 H), 5.28 (dd, 1 H), 7.44 (m_c, 5 H), 8.14 (s, 1 H); HRMS calcd for $C_{20}H_{21}N_3O_4S$ *m*/*z* (MH^+) 400.1326, found 400.1318.

(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridin-6-yl)piperazin-1-ylmethanone (97). Compound **97** was obtained in 13% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **96**, using piperazine instead of methanesulfonamide (for further details, see Supporting Information): ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.16, 2.25, 2.35 (m_c, 2 s, 8 H), 2.73 (bs, overlay with DMSO signal), 3.20 (bs, overlay with water signal), 3.58 (bs, 2 H), 5.27 (dd, 1 H), 7.43 (m_c, 6 H), 7.76 (s, 1 H); HRMS calcd for $C_{23}H_{27}N_4O_2$ *m*/*z* (MH^+) 391.2129, found 391.2121. Anal. ($C_{23}H_{26}N_4O_2$·0.5H_2O) C, H, N.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid Methoxymethylamide (98). Compound **98** was obtained in 33% yield from carboxylic acid **84** by applying a procedure similar to that described for the preparation of **86**, using *N*,*O*-dimethylhydroxylamine instead of methylamine (for further details, see Supporting Information): colorless solid; mp 192−193 °C (enantiomers **98a** and **98b**, mp 215−216 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 2.12 (m_c, 1 H), 2.26 (m_c, s, 4 H), 2.36 (s, 3 H), 2.54 (m_c), 2.81 (m_c, 1 H), 3.26 (s, 3 H), 3.57 (s, 3 H), 5.26 (dd, 1 H), 7.42 (m_c, 5 H), 7.92 (s, 1 H); HRMS calcd for $C_{21}H_{24}N_3O_3$ *m*/*z* (MH^+) 366.1812, found 366.1820.

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid (2-Hydroxyethyl)amide (99). A mixture of carboxylic acid **84** (0.50 g, 1.6 mmol) and thionyl chloride (0.34 mL, 0.55 g, 4.6 mmol) was diluted with dry dichloromethane (7 mL). The suspension was treated with DBU (0.24 mL, 0.24 g, 1.6 mmol) and stirred for 24 h at room temperature. The light-brown reaction mixture was evaporated to dryness and the residue was dissolved in dry dichloromethane (15 mL). The resulting suspension was cooled to 0 °C and a solution of 2-aminoethanol (0.17 mL, 0.17 g, 2.8 mmol) in dichloromethane (5 mL) was added. The reaction mixture was stirred for 2.5 h at room temperature. The precipitate was removed by filtration. The filtrate was concentrated in vacuo and the brown residue (0.9 g) was purified by column chromatography [36 g of silica gel; eluant, ethyl acetate/methanol = 10:1 (v/v)]. Evaporation of the corresponding fractions yielded the pure title compound (0.25 g of a colorless solid, 44% yield): mp 209−210 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.92 (m_c), 2.27 (m_c, s, 4 H), 2.41 (s, 3 H), 2.68 (m_c, 2 H), 3.46 (m_c, 2 H), 3.71 (m_c, 2 H), 4.97 (dd, 1 H), 7.14 (bt, 1 H), 7.27 (s), 7.42 (m_c, 5 H).

2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine-6-carboxylic Acid (2-Chloroethyl)amide (100). A solution of (2-hydroxyethyl)carboxamide **99** (0.30 g, 0.8 mmol) in thionyl chloride (0.40 mL, 0.65 g, 5.5 mmol) was stirred for 1 h at room temperature. It was then diluted with dichloromethane (30 mL) and water (5 mL) and a neutral pH value was adjusted by addition of saturated sodium bicarbonate solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic phases were dried over sodium sulfate, concentrated under reduced pressure, and dried in vacuo. The title compound was obtained in 70% yield (0.22 g of a colorless solid): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.14 (m_c), 2.32, 2.38 (2 s, m_c, 7 H), 2.85 (m_c, 1 H), 3.08 (m_c, 1 H), 3.75 (s, 4 H), 5.21 (dd, 1 H), 6.90 (bs, 1 H), 7.36 (m_c, 5 H), 7.60 (s, 1 H).

6-(4,5-Dihydrooxazol-2-yl)-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine (101). Three samples of (2-chloroethyl)carboxamide **100** (3 × 70 mg, 0.55 mmol) were transferred into microwave tubes and dissolved in dry DMF (3 × 3 mL). The yellow solution was heated to 150 °C for 20 min and to 170 °C for another 20 min. The reaction mixtures were combined and evaporated to dryness. The residue was purified by column chromatography [22 g of silica gel; eluant, ethyl acetate/methanol = 100:3 (v/v)]. Evaporation of the corresponding fractions furnished a red solid (106 mg, mixture of title compound with untransformed starting material as indicated by TLC analysis), which was further purified by preparative HPLC. The title compound was isolated in 14% yield (27 mg of a colorless solid): ^{1}H NMR ($CDCl_3$, 200

MHz) δ = 2.30, 2.40, 2.41 (m_c, 2 s, 8 H), 3.15 (m_c, 2 H), 4.09 (m_c, 2 H), 4.38 (m_c, 2 H), 5.30 (dd, 1 H), 7.39 (m_c, 5 H), 8.09 (s, 1 H); HRMS calcd for $C_{21}H_{22}N_3O_2$ *m/z* (MH^+) 348.1707, found 348.1723.

[8-Hydroxy-7-((*R*)-3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridin-6-yl]pyrrolidin-1-ylmethanone (102a). Compound **102a** was obtained in 78% yield from ketone **82** by applying a procedure similar to that described for the preparation of **41a** (asymmetric hydrogenation with $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN]) (for further details, see Supporting Information): pale-green solid; mp 252−254 °C; determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 20.2 min/6.3 area %, t_M [(3*R*)-enantiomer] = 20.4 min/93.7 area %, 87.4% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.77 (m_c, 6 H), 2.30, 2.33 (2 s, 6 H), 2.55 (m_c), 3.13, 3.34 (2 t, 4 H), 4.49 (t, 1 H), 5.93 (bs), 7.25 (m_c, 5 H), 7.65 (s, 1 H); HRMS calcd for $C_{23}H_{28}N_3O_3$ *m/z* (MH^+) 394.2125, found 394.2107.

8-Hydroxy-7-((*R*)-3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Methylamide (103a). Compound **103a** was obtained in 80% yield from ketone **83** by applying a procedure similar to that described for the preparation of **41a** (asymmetric hydrogenation with $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN]) (for further details, see Supporting Information): colorless solid; mp 250−252 °C; determination of the optical purity by CE, t_M [(3*S*)-enantiomer] = 19.2 min/4.0 area %, t_M [(3*R*)-enantiomer] = 19.6 min/96.0 area %, 92.0% ee (A); ^{1}H NMR (DMSO-d_6, 200 MHz) δ = 1.81 (m_c, 2 H), 2.30, 2.35 (2 s, 6 H), 2.72, 2.73 (m_c, d, 5 H), 4.47 (t, 1 H), 5.66 (bs), 7.33 (m_c, 5 H), 7.71 (s, 1 H), 8.26 (bq, 1 H); HRMS calcd for $C_{20}H_{24}N_3O_3$ *m/z* (MH^+) 354.1812, found 354.1801.

8-(*tert*-Butyldimethylsilanyloxy)-7-(3-hydroxy-3-phenylpropyl)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxylic Acid Dimethylamide (104). The diol **41** (200 mg, 0.54 mmol, product of the asymmetric hydrogenation of ketone **61** with $RuCl_2$[(*S*)-BINAP]-[(*S*,*S*)-DPEN]) was dissolved in dichloromethane (10 mL). Triethylamine (110 mg, 151 μL, 1.09 mmol) and a solution of *tert*-butyldimethylchlorosilane (179 mg, 1.19 mmol) in dichloromethane (5 mL) were added. The reaction mixture was heated to reflux for 5.25 h and then quenched by addition of saturated ammonium chloride solution (10 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. A green oil (296 mg) remained, which was purified by column chromatography (20 g of silica gel; eluant, ethyl acetate). The title compound was isolated in 73% yield (190 mg): determination of the optical purity by HPLC (column, 250 × 4.6 mm CHIRALPAK AD-H 5 μm (two columns), mobile phase, *n*-hexane/2-propanol = 83:17 (v/v); flow rate, 1 mL/min; 35 °C; detection at 220 nm), t_R [(3*R*)-enantiomer] = 10.0 min/68.4 area %, t_R [(3*S*)-enantiomer] = 10.6 min/31.6 area %, 36.8% ee; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 0.33, 0.44 (2 s, 6 H), 1.02 (s, 9 H), 2.00 (m_c, 2 H), 2.33, 2.37 (2 s, 6 H), 2.65 (m_c, 2 H), 2.88, 3.11 (2 s, 6 H), 4.58 (dd, 1 H), 7.26 (m_c, 5 H), 7.38 (s, 1 H).

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic Acid 6-Dimethylcarbamoyl-2,3-dimethyl-7-[3-phenyl-3-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxy)propyl]imidazo[1,2-*a*]pyridin-8-yl Ester (105). (*S*)-(+)-MTPACl (95 mg, 0.38 mmol) was dissolved in pyridine (810 μL) and carbon tetrachloride (810 μL). A solution of the protected diol **104** (100 mg, 0.21 mmol, containing the two enantiomers in a 7:3 ratio) in dichloromethane (500 μL) was added. The reaction mixture was stirred for 6 h at room temperature and then diluted with water (5 mL) and chloroform (10 mL). The phases were separated, and the aqueous phase was extracted with chloroform (2 × 10 mL). The organic phases were washed with saturated sodium chloride solution (5 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude product was dried thoroughly and then purified by column chromatography [10 g of silica gel; eluant, ethyl acetate/petroleum ether = 7:3 v/v)]. A yellowish oil (50 mg, 30% yield) was isolated that was characterized as diastereomeric mixture of the diester **105**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 2.00−2.60 (bs), 2.34, 2.37 (2 s, Σ 10 H), 2.73 (s, 3 H), 2.87, 2.97 (2 s, Σ 3 H), 3.44, 3.48 (2 s, $\sum$ 3 H), 3.79, 3.85 (2 s, $\sum$ 3 H), 5.61 (bt, 1 H), 7.30 (m_c, 10 H), 7.54 (m_c, 3 H), 7.63 (s, 1 H), 8.06 (m_c, 2 H).

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic Acid 3-(6-Dimethylcarbamoyl-8-hydroxy-2,3-dimethylimidazo[1,2-*a*]pyridin-7-yl)-1-phenylpropyl Ester (106). A solution of the diastereomeric mixture of the diester **105** (42 mg, 0.05 mmol) in deuterated chloroform was allowed to stand for 10 d at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography [2 × 6 g of silica gel; eluant, dichloromethane/methanol = 15:1 (v/v)]. A mixture of the diastereomeric esters of **106** was isolated in 72% yield: ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 2.05 (bs, 1 H), 2.17 (bs, 1 H), 2.29, 2.32 (2 s, 6 H), 2.48 (bs), 2.71, 2.75 (2 s, $\sum$ 3 H), 2.82, 2.84 (2 s, $\sum$ 3 H), 3.43, 3.52 (2 s, $\sum$ 3 H), 5.98 (m_c, 1 H), 7.41 (m_c, 10 H), 7.61, 7.62 (2 s, $\sum$ 1 H).

5.2. Biochemistry. Determination of Inhibitory Activity in a Competitive Binding Assay against H^+/K^+-ATPase from Hog Gastric Mucosa. Given data are the mean IC_{50} values from two or three independent determinations. The malachite green assay modified from Yoda and Hokin (*Biochem. Biophys. Res. Commun.* **1970**, *40*, 880−886) was used for the determination of H^+/K^+-ATPase IC_{50} (Lanzetta, P. A.; Alvarez, L. J.; Reinach, P. S.; Candia, O. A. *Anal. Biochem*. **1979**, *100*, 95−97). Pipes [piperazine-1,4-bis(2-ethanesulfonic acid)], sucrose, nigericin, Na-ATP, and malachite green were purchased from Sigma-Aldrich, and Tris [tris-(hydroxymethyl)aminomethane], KCl, and ammonium heptamolybdate tetrahydrate were from Merck, and $MgCl_2$ was from Fluka. Final assay concentrations: 4 mM Pipes/8 mM Tris buffer pH 7.4, 0.25 M sucrose, 1 mM KCl, 1 mM $MgCl_2$, 0.5−1 μg/100 μL nigericin (1:1 ratio with enzyme), 0.5−1 μg/100 μL enzyme (dependent on K^+-stimulated, specific activity), and 1 mM Na-ATP (high grade); reaction volume, 101 μL. Malachite green reagent was prepared by mixing 2 parts of malachite green stock solution (1.2 M in H_2O, protected from light and used within 12 weeks) with 1 part of ammonium heptamolybdate tetrahydrate stock solution (42 g/L in 4 N HCl) and was kept for 30 min at room-temperature prior to use. A Pipes/Tris buffer based solution with sucrose and $MgCl_2$ was prepared. Nigericin and enzyme were added to reach the final concentrations mentioned above; 80 μL/well of this mixture was placed into 96-well flat bottom plates (clear, polystyrol, Greiner bio-one), and 10 μL/well of KCl (1 mM final) was used for stimulation of the H^+/K^+-ATPase activity. Test substances were dissolved as 10 mM solutions in 100% DMSO, and 1 μL of substance solution was added in dilutions ranging from 1×10^{-4} to 1×10^{-9} M (final). The enzymatic reaction was started by addition of 10 μL ATP (1 mM final). The assay was incubated for 30 min at room temperature. The reaction was stopped by addition of 150 μL of malachite green reagent and incubated for another 15 min prior to photometric reading of the plate at 680 nm in a PowerWave HT Microplate spectral photometer (BioTek). The results were analyzed with GraphPad Prism software (Version 4.02) to calculate IC_{50} values by sigmoidal curve fitting. "Enzyme" refers to H^+/K^+-ATPase-containing vesicles prepared from hog gastric mucosa as described previously (Rabon, E. C.; Im, W. B.; Sachs, G. *Methods Enzymol*. **1988**, *157*, 649−654).

[^{14}C]Dimethylaminopyridine Accumulation in Intact Gastric Glands. Gastric acid secretion is stimulated by gastrin, histamine, and acetylcholine via the receptors on the parietal or the enterochromaffin-like cell. These physiologic stimuli influence the intracellular cyclic AMP and Ca^{2+} levels, thus leading to relocation and activation of H^+/K^+-ATPase. Instead of the physiologic agonists, the membrane-permeant dibutyryl-cyclic AMP was used to stimulate receptor-independent acid secretion in isolated gastric glands. Accumulation of the weak base [^{14}C]dimethylaminopyridine (^{14}C-AP) in the acidic compartment of the canaliculi serves as an indirect measure of acid secretion and forms the basis of measurement of acid secretion in this in vitro model of the mammalian stomach. Intact gastric glands were prepared from anesthesized New Zealand rabbits (weight 2−3 kg) by high-pressure perfusion of the

stomach, separation of the fundic mucosa, and subsequent collagenase digestion of fragments of the mucosa [Berglindh, T; Helander, H. F.; Obrink, K. J. *Acta Physiol. Scand.* **1976**, *97* (4), 401−414. Berglindh, T.; Obrink, K. J. *Acta Physiol. Scand.* **1976**, *96* (2), 150−159]. After the gastric glands were washed several times, they were suspended in Krebs−Henseleit solution containing 2 mg/mL rabbit serum albumin and 2 mg/mL glucose. Glands were incubated for 30 min at 37 °C in a shaker bath (200 osc/min) in the presence of 0.125 μM ^{14}C-AP (113 μCi/μmol) at pH 7.4. Glands were stimulated with 1 mM dibutyryl cAMP in the absence or presence of the corresponding inhibitor (concentration range 3 nM−100 μM). The reaction was stopped by centrifugation (10 s at 20 000*g*). After centrifugation, the accumulation of ^{14}C-AP in the glands was calculated as follows: radioactivity was measured in an aliquot of the supernatant (200 μL) and in the precipitate after dissolution in 1 mL of 1 N NaOH. In order to calculate the amount of protein, the Eppendorf tubes were weighed empty, with protein (wet weight), and with freeze-dried protein (dry weight). This ratio of supernatant and pellet protein radioactivity was used to calculate the accumulation of ^{14}C-AP in the glands. The inhibitor concentration required to achieve 50% inhibition (IC_{50}) of ^{14}C-AP accumulation was determined by fitting the equation for the expected inhibition pattern to the data points.

5.3. Pharmacology. Inhibition of Pentagastrin-Stimulated Acid Secretion of the Perfused Rat Stomach (Ghosh Schild Rat). The abdomen of anesthetized rats (CD rat, female, 200−250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening. After thorough rinsing (about 50−100 mL), warm (37 °C) physiological NaCl solution was continuously passed through the stomach (0.5 mL/min, pH 6.8−6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) was adjusted by titration with a freshly prepared 0.01 N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl was determined in the effluent in each case collected at an interval of 15 min. The gastric secretion was stimulated by continuous infusion of 1 μg/kg (1.65 mL/h) of iv pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e., after determination of 2 preliminary fractions). The substances to be tested were administered intraduodenally in a 2.5 mL/kg liquid volume 60 min after the start of the continuous pentagastrin infusion. The body temperature of the animals was kept at a constant 37.8−38 °C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

5.4. Physical Chemistry. General. The determination of dissociation constants (pK_a) and lipophilicity [log *P*, log *D* (pH 7.4)] were performed on a Sirius GL pK_a analyzer specifically designed for pH-metric pK_a and 1-octanol/water partition coefficient measurements (Sirius Analytical Instruments Ltd., Forest Row, UK).

Determination of Dissociation Constants. The pK_a values of the investigated compounds were determined by potentiometric cosolvent titrations in 0.15 mol/L KCl solutions in the pH range of 2.0−11.0 at 25 °C using methanol as cosolvent in varying portions and 0.5 mol/L KOH and HCl as titrants, respectively. Linear extrapolation to 0% cosolvent-content was performed by the Yasuda−Shedlovsky plot method implemented in the software RefinementPro 2 from SIRIUS (Avdeef, A.; Box, K. J.; Comer, J. E. A., Gilges, M.; Hadley, M.; Hibbert, C.; Patterson, W.; Tam, K. Y. *J. Pharm. Biomed. Anal.* **1999**, *20*, 631−641).

Determination of Distribution Coefficients. The distribution coefficients between 1-octanol and aqueous KCl solution were determined at 25 °C by potentiometric titrations in the pH range of 2.0−11.0. The titrations were performed in mixtures of 0.15 mol/L KCl solution and water-saturated 1-octanol with varying 1-octanol portions using 0.5 mol/L KOH and HCl as titrants, respectively. The dependence of log *D* values on pH was obtained by least-squares fitting of the experimental data to a theoretical function of the distribution coefficient *D* (RefinementPro2): Comer, J.; Tam, K. *Lipophilicity profiles: Theory and Measurement, in Pharmakokinetic Optimization in Drug Research: Biological, Physicochemical and Computational Strategies*; Testa, B., van de Waterbeemd, H., Folkers, G., Guy, R., Eds.; VHCA: Zurich, 2001; pp 275−304.

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Supporting Information Available: Detailed protocols for the preparation of all target compounds and intermediates whose synthesis is described in a general manner only in the Experimental Section and assessment of purity of all target compounds by HPLC and/or elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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