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Side-chain modified analogues of histaprodifen: Asymmetric synthesis and histamine H_1-receptor activity

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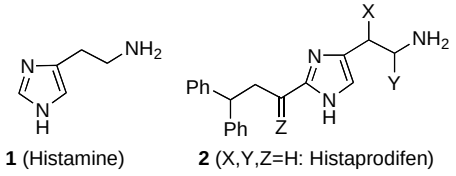
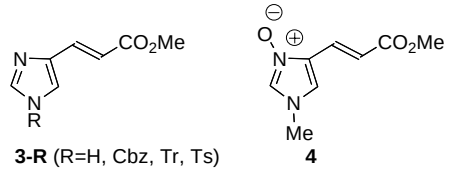
Abstract—New analogues of histaprodifen with polar side chains have been stereoselectively synthesized and evaluated as histamine H_1-receptor agonists. As a key transformation the asymmetric aminohydroxylation has been used, which was successfully realized for the first time on an imidazolyl derivative. While all chiral analogues proved to be weak H_1-receptor antagonists, an achiral keto derivative of histaprodifen turned out to be the first 2-acylated histamine congener displaying partial H_1-receptor agonism (relative potency 12%).

During the last 25 years, numerous histamine H_1-receptor mediated effects have been described[1] emphasizing the important physiological and pathophysiological role of histamine (**1**) (Fig. 1). Although the search for highly potent and subtype-selective H_1-receptor agonists has been an arduous task for several years,[2] many derivatives have arisen from the class of 2-substituted histamines,[3] which display improved potency and selectivity.[4,5] Recently histaprodifen (**2**, X, Y, and Z = H)[6] has been identified as a potent histamine derivative offering a starting point for systematic development of highly potent and selective histamine H_1-receptor agonists. The aim of our present study was to develop analogues of **2** (X, Y, and Z ≠ H) to get additional information about structure–activity relationships of histamine H_1-receptor agonists. In particular, we wanted to investigate the effect of additional polar groups attached to the ethylamine side chain, posing the additional challenge to introduce such groups in a regio-, diastereo-, and enantioselective manner.



1 (Histamine) **2** (X,Y,Z=H: Histaprodifen)

Figure 1.



3-R (R=H, Cbz, Tr, Ts) **4**

Figure 2.

As a suitable starting material toward side-chain modified derivatives of **1** and **2**, we envisioned readily available urocanic acid methyl ester (**3-H**, Fig. 2). The required amino group in β-position to the imidazole moiety could be introduced via an asymmetric aminohydroxylation (AA) reaction,[7] which has proved to be especially useful with cinnamates as substrates, but on the other hand is also known to be problematic in the presence of nitrogen containing heterocycles. Indeed, it has been reported that various imidazolyl derivatives **3-R** fail completely to give the AA.[8] Moreover, our attempts to utilize the *N*-oxides such as **4** for the AA, which in the case of pyridineacrylates proved to be the method of choice to achieve amino-[9] and dihydroxylations,[10] were also not successful.

Keywords: Histamine; Histaprodifen; Asymmetric aminohydroxylation; Urocanic acids; Imidazole.
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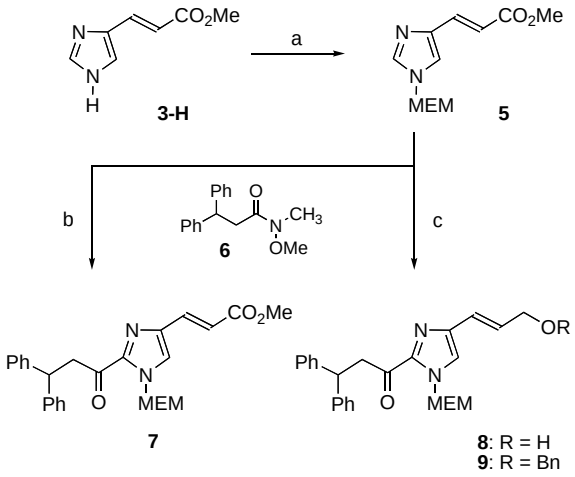
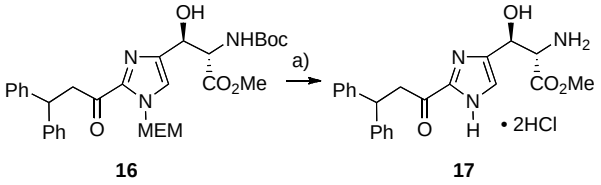
In an important contribution by Pyne and co-workers it was demonstrated that *N*-protected urocanic ethers having an acetyl group in 2-position are amenable toward osmium-catalyzed asymmetric dihydroxylations.[11] Keeping the side chain in 2-position of histaprodifen in mind, we therefore envisioned **7**–**9** as a starting point for asymmetric aminohydroxylation reactions (Scheme 1).

Thus, treatment of **3-H** with 2-methoxyethoxymethyl chloride (MEM-Cl) gave rise to a 9:1 mixture of *N*-alklated regioisomers, from which **5**, being the major one, could be separated by chromatography. Subsequently, metallation with LDA and trapping with the Weinreb amide **6** gave rise to **7** in moderate yield. Alternatively, **5** could be reduced to the corresponding allylic alcohol, into which after protection the side chain was introduced again via **6** to yield **8** and **9**, respectively.



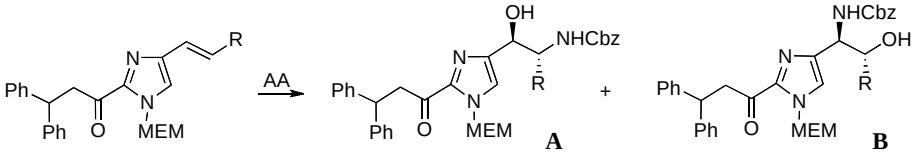
Scheme 1. Reagents and conditions: (a) NaH, MEM-Cl, DMSO, 0–80 °C, 6 h, 72%; (b) LDA (2 equiv), **6**, THF, 0 °C → rt, 2 h, 48%; (c) Synthesis of **8**: i—DIBAL-H, CH_2Cl_2, 0 °C → rt, 12 h, 86%; ii—TBDMS-Cl, imidazole, DMF, rt, 1 h, 96%; iii—*n*-BuLi, THF, −78 °C, 1 h, then **6**, −78 °C 1 h, then rt, 1 h, 69%; iv—TBAF, THF, rt, 1.5 h, 92%; Synthesis of **9**: i—DIBAL-H, CH_2Cl_2, 0 °C → rt, 12 h, 86%; ii—NaH, benzyl bromide, DMF, 0 °C → rt, 16 h, 82%; iii—*n*-BuLi, THF, −78 °C, 1 h, then **6**, −78 °C 1 h, then rt, 1 h, 67%.

Indeed, **7**–**9** could be utilized as substrates for the osmium-catalyzed aminohydroxylation (Table 1) with moderate results, nevertheless, succeeding for the first time with imidazolyl derivatives in this transformation. In agreement with the general trend observed in AA reactions with aromatic substrates, in the presence of $(DHQ)_2PHAL$ the amino group is preferentially introduced in the benzylic position (regioisomer **B**, entries 1, 4). To obtain a better ratio of regioisomers with respect to the desired histamine analogues **A**, the pseudoenantiomeric ligand $(DHQD)_2AQN$ was employed. Although the ratio of regioisomers could not be reversed as it is known in the case of cinnamates, at least the formation of **A** was somewhat improved (Table 1, entries 2, 3, and 7). Changing the solvent to acetonitrile/water considerably improved the rate and yield of the reaction with **7**, as well as the enantioselectivity of



Scheme 2. Reagents and conditions: (a) i—HCl (aq), MeOH, reflux 1 h; ii—H_2SO_4 (cat), MeOH, reflux, 30 h, 75% (over two steps).

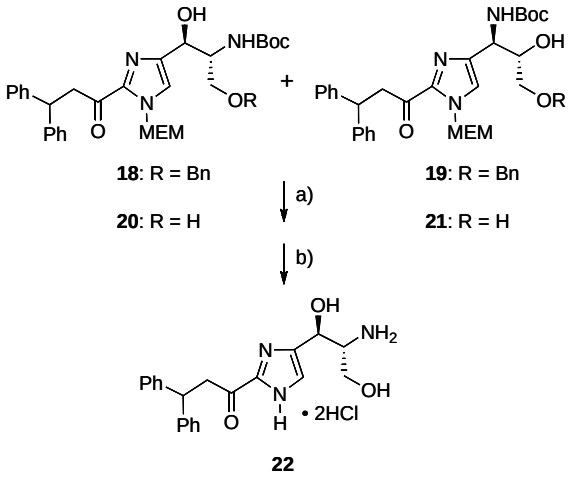
Table 1. Asymmetric aminohydroxylation of imidazolyl derivatives **7**–**9**[a]



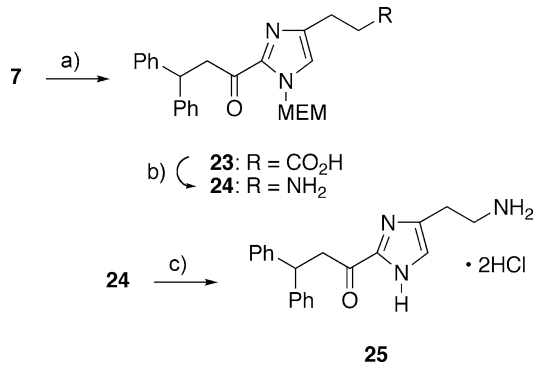
Entry	Substrate	Ligand	Solvent	Reaction time [h]	Product ratio of regioisomers[b]	Yield[c] [%]	% ee[d]	
							A	**B**
1	**7**	$(DHQ)_2PHAL$	*n*-PrOH/H_2O (1.5:1)	30	*ent*-(**10**/**11**) = 1:3	52	56	53
2	**7**	$(DHQD)_2AQN$	*n*-PrOH/H_2O (1.5:1)	30	**10**/**11** = 1:1	56	54	52
3	**7**	$(DHQD)_2AQN$	MeCN/H_2O (3:1)	4	**10**/**11** = 1:1	72	75	87
4	**8**	$(DHQD)_2AQN$	MeCN/H_2O (1.5:1)	1	**12**/**13** = 1:3	63	0	nd
5	**9**	$(DHQ)_2PHAL$	*n*-PrOH/H_2O (1.5:1)	1	*ent*-(**14**/**15**) = 1:3.3	56	nd	nd
6	**9**	$(DHQD)_2AQN$	*n*-PrOH/H_2O (1.5:1)	1	**14**/**15** = 1:3	65	nd	nd
7	**9**	$(DHQD)_2AQN$	MeCN/H_2O (3:1)	1	**14**/**15** = 1:1.5	67	48[e]	nd

[a] Reagents and conditions: $K_2OsO_2(OH)_4$ (4 mol %), ligand (5 mol %), BnOC(O)NNaCl (5 mol %) at 25 °C.
[b] Ratio determined by ^1H NMR, for substrate **8** and **9** ratio determined after N-Cbz to N-Boc conversion.
[c] Isolated yields as a mixture of regioisomers.
[d] Determined by HPLC on Chiracel™ OD/ODH (nd, not determined).
[e] Determined after conversion to **19** by HPLC on Chiracel™ OD/ODH.

the products (Table 1, entries 2, 3). Surprisingly, the allyl alcohol **8** and allyl ether **9** were considerably more reactive than the ester **7**, however, with the former substrates the undesired regioisomer **B** was always favored, even when the AQN ligand was employed. Moreover, only racemic products were obtained with the allyl alcohol **8** (entry 4). Preparatively most useful appeared to be the formation of **10** and **11** mediated by $(DHQD)_2AQN$ (entry 3), giving useful yields and selectivities that allowed us to arrive at regio- and enantiomerically pure products at the next stage in the reaction sequence.



Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2, THF, 40 bar, 40 °C, 48 h, 62%; (b) i—$NaIO_4$, 1,4-dioxane, H_2O, rt, 2.5 h, 87% based on **18**; ii—HCl (aq), MeOH, reflux 1 h, 95%.



Scheme 4. Reagents and conditions: (a) i—10% Pd/C, H_2, MeOH, rt, 16 h, 98%; ii—LiOH, THF/MeOH/H_2O [3:1:1], 0 °C → rt, 6 h, 95%; (b) i—$(COCl)_2$, CH_2Cl_2, 0 °C → rt 3 h; ii—TMS-N_3, CH_2Cl_2, 0 °C → rt, 5 h; iii—BnOH, toluene, reflux, 120 °C, 18 h , 86% over three steps; iv—10% Pd/C, H_2, MeOH, rt, 16 h, 86%; (c) concd HCl/MeOH/H_2O [1:1:1], reflux, 1.5 h, 97%.

Single-step exchange[12] of the nitrogen protecting group on the mixture of **10/11** from Cbz to Boc (10% Pd/C, H_2, MeOH, Boc_2O, rt, 3 h, 96% yield) allowed the facile separation of **16** by column chromatography, which was obtained enantiomerically pure in 40% yield after recrystallization (28% yield starting from **7**), along with the corresponding regioisomer being obtained in 48% yield. The structure of **16** could be confirmed by X-ray analysis.[13] Finally, deprotection of **16** was achieved by treatment with HCl, resulting also in partial cleavage of the methyl ester, which was subsequently remedied by reesterification with MeOH to give rise to **17**[14] (Scheme 2).

Similarly, the mixture of **14/15** was converted to the *N*-Boc derivatives **18/19** (94% yield). However, at this stage separation of the regioisomers was still not possible. Therefore, the mixture was debenzylated and subsequently treated with $NaIO_4$ to cleave the diol in the undesired regioisomer **21** (Scheme 3). This way, **20** could be obtained as a single diastereomer with moderate enantiomeric excess (48% ee), which was subsequently deprotected to **22**.[15]

As the missing link to allow a meaningful assessment of the influence of the modified ethylamine side chain in **17** and **22** with respect to **2**, the histaprodifen analogue **25** being acylated instead of alkylated in 2-position could be synthesized in a straightforward way (Scheme 4).[16]

All new compounds were screened in vitro for functional interaction with histamine H_1-receptors of guinea-pig ileum according to standard procedures (Table 2).[17] Neither (*rac*)-**17** nor the enantiopure **17** or the diastereomerically pure **22** elicited ileal contractions (Table 2). Only at higher concentrations (30–100 μM), these com-

Table 2. Interaction with histamine H_1-receptors (guinea-pig ileum)[a]

Compound	Agonism			Affinity[b]	N[c]
	E_{max} ± SEM	pEC_{50} ± SEM	Rel potency [%]	pD'_2 ± SEM	
(*rac*)-**17**	0	—	—	3.80 ± 0.09	7
17	0	—	—	4.61 ± 0.12	9
22	0	—	—	4.08 ± 0.14	6
24	0	—	—	5.05 ± 0.12	4
25	75 ± 3	5.78 ± 0.08	12	nd	9
Mepyramine[d]	0	—	—	9.07 ± 0.03[e]	34
2[d]	100	6.74 ± 0.02	111	6.04 ± 0.05[f]	34[g]
1	100	6.70 ± 0.02	100	—	>95

[a] Experimental protocol and definition of parameters see Ref. 6 and literature cited therein.
[b] Determined at 10–100 μM unless otherwise indicated.
[c] Number of experiments for agonism or affinity determination.
[d] Data from Ref. 6.
[e] pA_2 value, determined at 0.3–100 nM.
[f] pK_P value, determined at 3–30 μM.
[g] $N = 12$ for affinity measurement.

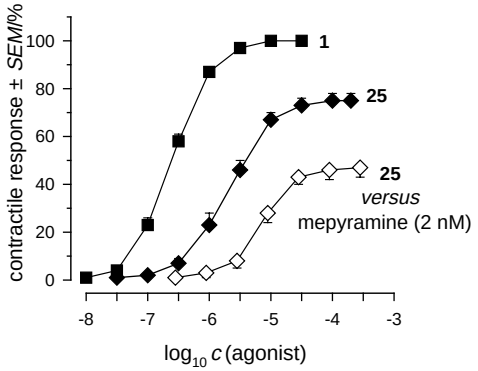


Figure 3. Contraction of guinea-pig ileum by **1** (■, $N = 9$) and **25** in the absence (♦, $E_{max} = 75 \pm 3\%$, $N = 9$) and presence (◇, $47 \pm 4\%$, $N = 5$) of mepyramine (2 nM). Rel potency of **25** was 12% (95% conf limits 9–17%), pA_2 of mepyramine was 9.08 ± 0.11. Data from three animals. For protocol, see Ref. 6.

pounds depressed the effect of **1** without producing a rightward shift of the agonist curve. Thus, in contrast to the potent reference antagonist mepyramine (nanomolar affinity, $pA_2 = 9.07$), they have to be classified as weak non-competitive H_1-receptor blockers ($pD'_2 < 5$).

Compared with the lead **2**, the new antagonists are endowed with several chemical modifications. It was of special interest to understand the influence of the carbonyl group attached to C2 of the imidazole, since 2-acylated histamine derivatives have never been studied so far. To our surprise compound **25**, a '*keto histaprodifen*,' turned out to be a moderate partial H_1-receptor agonist, displaying approximately 12% relative potency compared with its parent compound **2**. The contractile effect was mediated by H_1-receptors since mepyramine (2 nM), a reference H_1-receptor antagonist, successfully blocked the effect of **25** (Fig. 3) with the expected nanomolar affinity. The N1-protected precursor of **25**, **24**, failed to stimulate H_1-receptors which is in agreement with the current concept of H_1-receptor agonist SAR.[2]

It is concluded that the lack of H_1-receptor agonist activity observed for aminohydroxylation products structurally related to **2** ((*rac*)-**17**, **17**, **21**) is due to the additional oxygen-containing polar functionalities attached to the ethylamine side chain of **2**. The keto derivative **25** is the first 2-acyl derivative of **1** reported which is capable of stimulating histamine H_1-receptors. This finding may be of importance since 2-acyl congeners of **1** are available much more conveniently than their 2-alkyl counterparts.

Acknowledgments

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13. Details on the X-ray structure of **16** can be obtained from the Cambridge Crystallographic Data Center quoting CCDC 286008.
14. Analytical data for **17**: $R_f = 0.16$ (SiO_2, ethyl acetate/methanol 7:3); white solid; mp 147–154 °C; $[\alpha]_D^{22}$ −14.3 (*c* 0.6, CH_2Cl_2); ^1H NMR (300 MHz CD_3OD) δ: 3.73 (s, 3 H, CO_2CH_3), 3.79 (dd, $J = 1.89$, 7.82 Hz, 2H, CH_2CO), 3.87 (d, $J = 3.60$ Hz, 1H, $CHNH_2$), 4.75 (t, $J = 7.82$ Hz, 1H, $CHCH_2$), 5.11 (dd, $J = 0.72$, 3.60 Hz, 1H, CHOH), 7.09–7.31 (m, 11H, aromatic); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 44.5, 47.6, 52.8, 60.3, 70.3, 118.0 , 127.4, 128.9, 129.0, 128.5, 145.6, 145.6, 146.3, 174.5, 190.4; IR (neat) $\tilde{\nu}$: 3300–2500 (broad), 1754, 1715, 1599, 1495, 1219, 1039, 747, 698, 613 cm^{-1}; HRMS: calcd for $C_{22}H_{23}N_2O_4$: 393.1689. Found: 393.1688.
15. Analytical data for **22**: $R_f = 0.27$ (SiO_2, CH_2Cl_2/MeOH/NH_3 7:3:0.2); white glassy solid; mp 122–127 °C; $[\alpha]_D^{22}$ −4.8 (*c* 0.6, MeOH, 48% ee); ^1H NMR (600 MHz, DMSO) δ: 3.43 (dd, $J = 5.97$, 11.10 Hz, 1H, CHOH), 3.47 (m, 1H, $CHNH_3$), 3.55 (dd, $J = 3.93$, 11.10 Hz, 1H, CHOH), 3.87 (dd, $J = 7.77$, 17.15 Hz, 1H, CHCO), 3.93 (dd, $J = 7.77$, 17.15 Hz, 1H, CHCO), 4.68 (dd, $J = 7.77$, 7.77 Hz, 1H, $CHCH_2$), 4.85 (d, $J = 6.98$ Hz, 1H, CHOH), 4.98 (s, very broad, 2H, imidazole NH and CH_2OH), 7.12–7.35 (m, 10H, Ph-*H*), 7.51 (s, 1H, imidazole 5-*H*), 8.06 (s, broad 3H, $CHNH_3$); ^{13}C NMR (150.9 MHz, DMSO) δ: 43.2, 45.4, 56.5, 58.3, 63.2, 121.0, 126.1, 127.5, 128.3, 128.5, 139.9, 142.5, 144.0, 187.2; IR (neat) $\tilde{\nu}$: 3400–3020 (broad), 2890, 1703, 1676, 1599, 1493, 1396, 1223, 1044, 1022, 990, 731, 699, 613 cm^{-1}; HRMS: calcd for $C_{21}H_{23}N_3O_3$: 365.1739. Found: 365.1732.
16. Analytical data for **25**: $R_f = 0.13$ (SiO_2, CH_2Cl_2/MeOH/NH_3 10:1:0.2); white solid; mp 180–182 °C; ^1H NMR (300 MHz, DMSO) δ: 2.97 (t, $J = 7.25$ Hz, 2H, CH_2CH_2N), 3.13 (tq, $J = 7.25$, 6.03 Hz, 2H, CH_2NH_3), 3.93 (d, $J = 7.68$ Hz, CH_2CO), 4.68 (t, $J = 7.68$ Hz, 2H, $CHCH_2CO$), 5.1–6.5 (s, very broad, imidazole NH), 7.12–7.41 (m, 10H, Ph-*H*), 7.54 (s, 1H, imidazole 5-*H*), 8.24 (s, broad 3H, CH_2NH_3); ^{13}C NMR (75.5 MHz, DMSO) δ:

23.5, 37.6, 43.5, 45.3, 121.5, 126.3, 127.6, 128.4, 141.4, 144.1, 186.3; IR (KBr) $\tilde{\nu}$: 3448, 3029, 1699, 1495, 1213, 1034, 749, 702, 567 cm^{-1}; HRMS: calcd for $C_{20}H_{21}N_3O$: 319.1685. Found: 319.1685.

17. In brief, isolated whole segments of guinea-pig ileum were mounted under isotonic conditions (preload 0.5 g) in *Tyrode*'s solution. In the continuous presence of the anticholinergic blocker atropine (100 nM), concentration–effect curves for **1** or compounds under study were recorded in a cumulative manner in the absence and presence of either reference or potential H_1-receptor antagonist. For details, see Ref. 6.