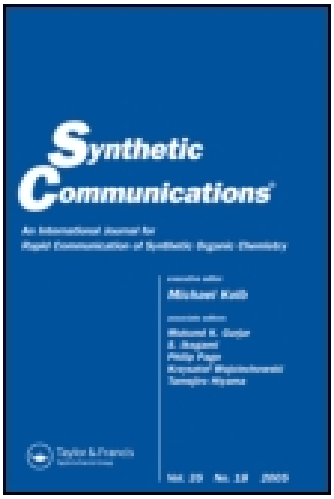

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ALTERNATIVE SYNTHESIS OF BILASTINE

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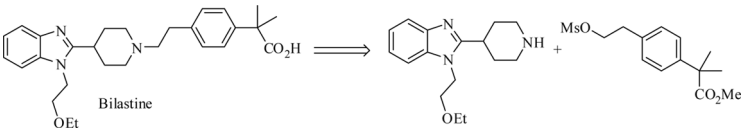
GRAPHICAL ABSTRACT



Abstract *A new and efficient synthesis of the non-sedating histamine H1 receptor antagonist Bilastine is reported. The new route employs a convergent strategy, with a longest linear sequence of five steps, giving slightly improved yields over the previous routes. The use of anhydrous metal-halogen exchange, hazardous ethylene oxide, and a tedious protection of the carboxylic acid function are all avoided.*

Keywords Bilastine; convergent synthesis; hydroboration-oxidation; Stille coupling; Suzuki coupling; vinyl boronic anhydride; vinyl stannane

INTRODUCTION

Bilastine, **1**, is an orally active, nonsedating, highly selective histamine H_1 receptor antagonist,[1–3] with indications for the treatment of allergic rhinitis. The drug was discovered by FAES Farma and has successfully completed two large-scale phase III clinical trials. Details of its pharmacological and toxicological profile have been discussed.[4–6] A second polymorph of the drug was patented in 2003.[7] As part of a custom synthesis program, we were required to prepare small amounts of bilastine as a reference marker. The literature route, shown in Scheme 1, starting with ester **2**, was evaluated initially.[8,9] This involved the preparation of an aryl ethylanol **5**, coupling the corresponding tosylate **6** with the commercially available piperidinylbenzimidazole **7**, and then elaborating the product, **8**, further by alkylation of the benzimidazole unit to give **9**. The use of a highly reactive organometallic intermediate requires the use of a dimethyloxazoline protecting group for the sensitive carboxylic acid unit. The protection was removed at the end of the sequence to provide bilastine **1**. The overall synthesis of bilastine from methyl 2-(4-bromophenyl)-2,2-dimethylacetate **3** took nine linear steps, with an overall yield of 23%. No

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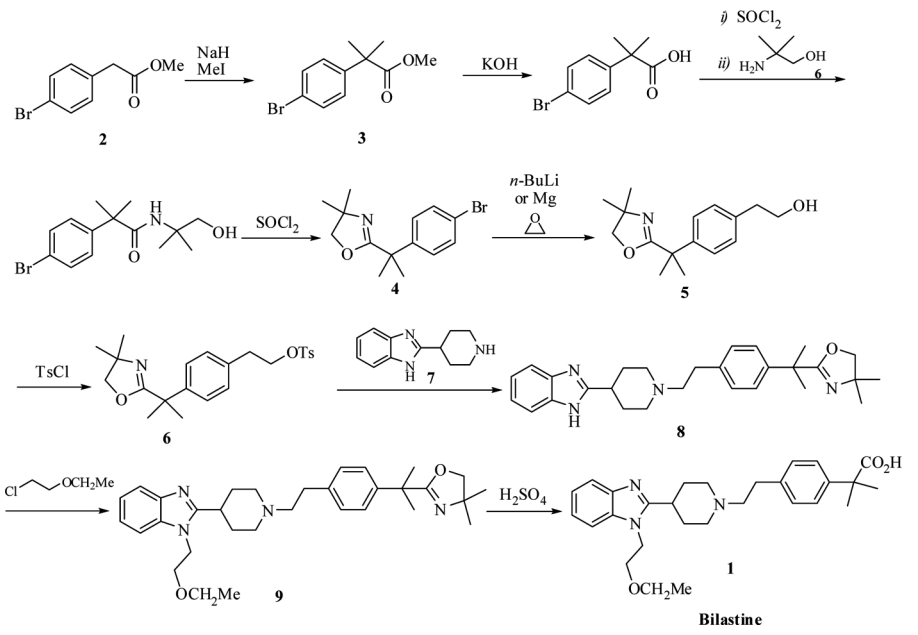
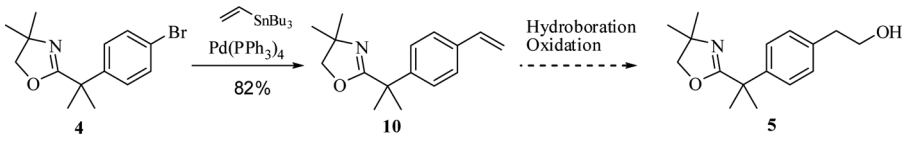


Scheme 1. Original synthesis of bilastine.

procedure or yield was given for the tosylation step, but it was assumed the reaction would proceed in 80–90% yield, and for the purposes of the calculation, a yield of 85% was assumed.

RESULTS AND DISCUSSION

Our initial work focused on reproducing the reported route, and the early stages of the synthesis worked as expected.[10] The preparation of ester **4** was evaluated using both the reported one-pot NaH/MeI and an alternative, sequential alkylation using lithium diisopropylamide (LDA)/MeI for the first methylation, and NaHMDS/MeI for the second. However, the installation of the hydroxyethyl unit onto the bromoarene **4** through metallation, followed by reaction with ethylene oxide, proved to be unreliable in our hands. Even after evaluation of a range of metallation conditions and additives, only poor yields of product **5** were obtained. Substitution of ethylene oxide with ethylene glycol cyclic sulfate or ethylene glycol ditosylate also failed to provide the desired product. As a result, an alternative approach to the key aryl ethanol was pursued. Replacement of the metallation/ethylene oxide sequence with a vinylation/hydroboration/oxidation strategy should, in principle, provide the same net transformation with good efficiency (Scheme 2). Preparation of the required styrene **10** via Stille coupling of bromide **4** with vinyl tributylstannane was achieved in good yield, after screening a number of conditions on a 100-mg scale (Table 1).[11] Scaling to 1-g scale provided the required styrene **10** in 82% yield. However, the subsequent hydroboration–oxidation sequence failed to give the required alcohol **5** under a range of conditions (Table 2).[12–14]



Scheme 2. Vinylation/hydroboration/oxidation approach to alcohol **5**.

Given these disappointing results, the overall approach to bilastine was reconsidered, particularly the requirement for protection of the carboxylic acid. A new, convergent approach was devised (Scheme 3). The key features of this approach include installation of the aryl hydroxyethyl unit following the vinylation/hydroboration/oxidation sequence discussed previously; carrying the carboxylic acid through the synthesis as a simple methyl ester; and alkylation of the benzimidazole fragment prior to coupling with the aryl ethanol. It was thought that these changes would provide a shorter, more efficient synthesis, with milder deprotection conditions at the end of the sequence.

The synthesis was executed as shown in Scheme 4. Thus, vinylation of aryl bromide **3** was achieved under the previously optimized Stille coupling conditions using vinyl tributylstannane[11] and provided the desired styrene **11** in up to 86% yield on a multigram scale. Alternatively, Suzuki coupling of **3** with vinylboronic anhydride also provided styrene **11** in 70% yield.[15] Hydroboration/oxidation of **11** was achieved, albeit in poor yield, using borane–dimethylsulfide (DMS) complex,

Table 1. Conditions screened for Stille coupling

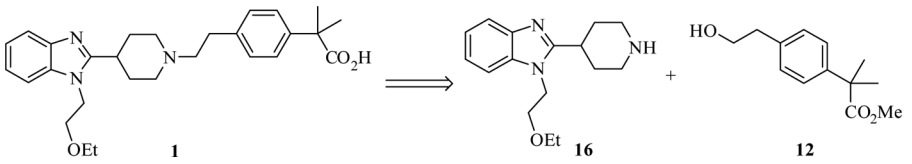
Entry	Conditions	Conversion to 10[a] (%)
1	$Bu_3SnCH{=}CH_2$ (1.05 equiv), $Pd(PPh_3)_4$ (5 mol%), CH_2Cl_2, reflux, 16 h	Trace
2	$Bu_3SnCH{=}CH_2$ (1.2 equiv), $Pd(PPh_3)_4$ (10 mol%), THF, reflux, 20 h	10
3	$Bu_3SnCH{=}CH_2$ (1.2 equiv), $Pd(PPh_3)_4$ (10 mol%), LiCl (1.2 equiv), DMF, 50 °C, 20 h[b]	70
4	$Bu_3SnCH{=}CH_2$ (2 equiv), $Pd(PPh_3)_4$ (10 mol%), LiCl (1.5 equiv), DMF, 70 °C, 20 h[b]	85
5	$Bu_3SnCH{=}CH_2$ (3 equiv), $Pd(PPh_3)_4$ (15 mol%), LiCl (2 equiv), DMF, 70 °C, 48 h[b]	82 (isolated yield)

[a]According to ^{1}H NMR analysis.
[b]Conditions directly switched to LiCl/DMF; DMF alone was not tested.

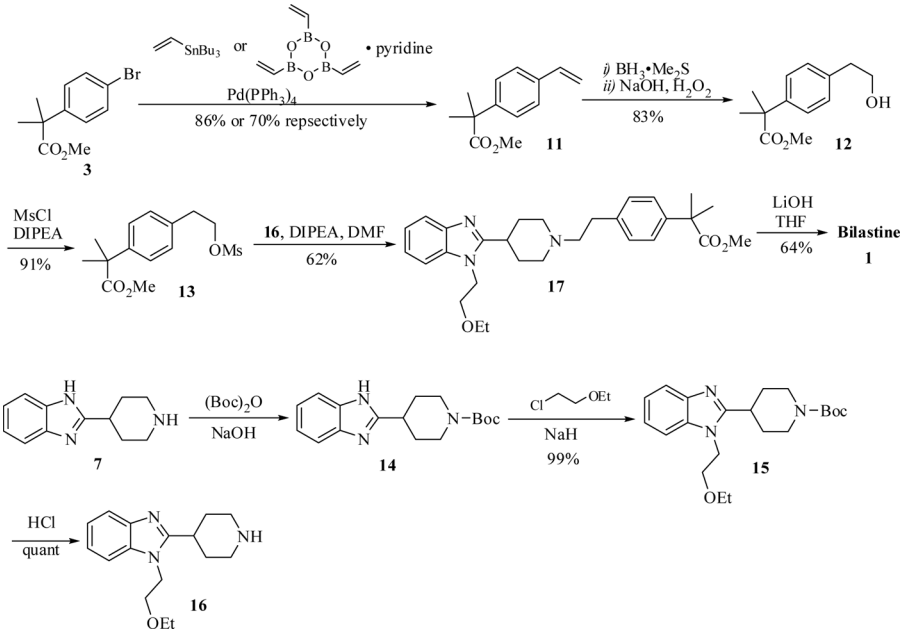
Table 2. Conditions screened for hydroboration/oxidation of **10**

Entry	Conditions	Comments
1	$BH_3 \cdot THF$, THF, reflux, 12 h	No reaction[a]
2	i) Catecholborane, PhH, ii) 1 M NaOH, 30% aq. H_2O_2, reflux, 16 h	Unknown by-product found; **10** not observed[a]
3	$NaBH_4$, $BF_3 \cdot Et_2O$, THF, rt, 24 h	No reaction[a]
4	9-BBN, THF, reflux, 16 h	No reaction[a]

[a]According to GC and TLC analysis.



Scheme 3. New disconnection.



Scheme 4. Alternative synthesis of bilastine.

although other approaches failed (Table 3).[12–14,16] Optimization (including increasing dilution) and scaling of the borane–DMS approach then provided the key aryl ethanol **12** in 83% yield on 1-g scale and 75% on a multigram scale. With the desired aryl ethanol unit in hand, both the corresponding tosylate and mesylate esters were prepared, with the latter, **13**, being obtained in greater yields.

Table 3. Hydroboration/oxidation conditions screened

Entry	Reaction conditions	Comments
1	$NaBH_4$, $AlCl_3$, diglyme, rt, 24 h	No reaction
2	Catechol borane, benzene, reflux, 16 h	Unknown by-product was isolated; no desired product was observed
3	9-BBN, THF, reflux, 48 h	No reaction
4	$BH_3 \cdot Me_2S$, THF, 1 M, rt, 2 h; NaOH, H_2O_2, rt, 2 h	19% yield
5	As entry 4 but 0.1 M concentration, 1-g scale	83% yield

To prepare the benzimidazole fragment, the commercially available piperidin-4-ylbenzimidazole **7** was Boc protected at the piperidine nitrogen in near quantitative yield, and the required ethoxyethyl group was efficiently installed using NaH and ethoxyethyl chloride. Quantitative deprotection furnished the second required fragment, **16**. With the two key fragments in hand, the conditions for the final coupling of **13** and **16** and the subsequent hydrolysis were screened. Coupling using diisoproplethyl amine (DIPEA) in dimethylformamide (DMF) gave **17** in 62% yield on a gram scale, and ester hydrolysis LiOH in tetrahydrofuran (THF)/MeOH/water (2:2:1) furnished bilastine in 64% yield.

CONCLUSIONS

In summary, an alternative synthesis of bilastine was developed. The new strategy avoids metal–halogen exchange and use of ethylene oxide and does not require protection of the carboxylic acid function as an oxazoline. The synthetic sequence provides the product in a slightly improved yield (26%) as compared to the existing approach, in a convergent synthesis with the longest linear sequence of five steps from the key 2-(4-bromophenyl)-2,2-dimethylacetate ester derivative.

EXPERIMENTAL

Proton and carbon NMR spectra were obtained on a Bruker AC 300 spectrometer at 300 MHz and 75 MHz, respectively. Proton spectra were referenced to TMS as an internal standard in a variety of deuterated solvents such as $CDCl_3$, DMSO-d_6, CD_3OD, and actone-d_6 (purchased from Aldrich or Cambridge Isotope Laboratories, unless otherwise specified). Melting points were obtained on a Mel-Temp II apparatus and are uncorrected. Electrospray ionization (ESI) mass spectra were obtained on a Shimadzu LCMS-2010 EV mass spectrometer. High-resolution mass spectra (HRMS) were performed on Finnigan MAT 95/XL-T spectrometer under electron impact (EI). High-performance liquid chromatographic (HPLC) analyses were obtained using a Varian Prostar 335 system with an Alltech Alltima C18 rocket column. Gas chromatograms were recorded on an Agilent Technologies G153014 system with a Restek Rtx-5 column.

4,4-Dimethyl-2-(2-(4-vinylphenyl)propan-2-yl)-4,5-dihydrooxazole (10)

A solution of $Pd(PPh_3)_4$ (118 mg, 0.10 mmol) and LiCl (57 mg, 1.35 mmol) in DMF (10 mL) was purged with argon for 15 min. Compound **4** (200 mg, 0.67 mmol) and vinyl tributylstannane (0.6 mL, 2.0 mmol) were added, and the reaction mixture was heated at reflux for 16 h. After cooling to room temperature, saturated KF aqueous solution (10 mL) was added, and the mixture was filtered through a celite pad. The filtrate was extracted with Et_2O (50 mL), and the ether layer was washed with H_2O (20 mL). The organic solvent was evaporated, and the residue was purified by column chromatography (silica gel, 10:90 EtOAc/hexanes) to provide **10** (134 mg, 82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, $J = 6.3$ Hz, 2H), 7.29 (d, $J = 6.3$ Hz, 2H), 6.64 (dd, $J = 17.7$ and 11.1 Hz, 1 H), 5.68 (d, $J = 17.7$ Hz, 1H), 5.19 (d, $J = 10.8$ Hz, 1H), 3.85 (s, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.30 (s, 6H).

Methyl 2-Methyl-2-(4-vinylphenyl)propanoate (11) via Stille Coupling

A solution of $Pd(PPh_3)_4$ (2.7 g, 2.34 mmol) and LiCl (2.0 g, 46.6 mmol) in DMF (150 mL) was purged with argon for 15 min. Compound **3** (6.0 g, 23.3 mmol) and vinyl tributylstannane (11 mL, 37.3 mL) were added, and the reaction mixture was heated at reflux for 16 h. After cooling to room temperature, saturated KF aqueous solution (60 mL) was added, and the mixture was filtered through a celite pad. The filtrate was extracted with Et_2O (500 mL), and the ether layer was washed with H_2O (100 mL). The organic solvent was evaporated, and the residue was purified by column chromatography (silica gel, 5:95 EtOAc/hexanes) to provide **11** (4.0 g, 86% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 6.64 (dd, $J = 10.8$ and 11.1 Hz, 1 H), 5.69 (d, $J = 11.1$ Hz, 1H), 5.20 (d, $J = 11.1$ Hz, 1H), 3.64 (s, 3H), 1.57 (s, 6H). HRMS (EI): m/z calcd. for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1150.

Methyl 2-Methyl-2-(4-vinylphenyl)propanoate (11) via Suzuki Coupling

A solution of **3** (100 mg, 0.39 mmol), vinylboronic anhydride–pyridine complex (140 mg, 0.58 mmol), $Pd(PPh_3)_4$ (45 mg, 0.039 mmol), and K_2CO_3 (54 mg, 0.39 mmol) in 4 mL DME/H_2O (40:1) was heated at 130 °C for 1 h using microwave irradiation (sealed system using a Biotage initiator). The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4. The solvent was evaporated, and purification by column chromatography (silica gel, 5:95 EtOAc/hexanes) gave **11** (55 mg, 70% yield) as a colorless oil.

Methyl 2-(4-(2-Hydroxyethyl)phenyl)-2-methylpropanoate (12)

A solution of **11** (1.00 g, 4.89 mmol) in THF (40 mL) was treated with $BH_3 \bullet Me_2S$ (1 equiv) at 0 °C, and the reaction was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with water (2.0 mL) and 3 M NaOH (1.1 mL), and then H_2O_2 (2.0 mL) was added 0 °C. The reaction was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with brine (100 mL). The organic extracts were dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (Redisep silica gel, 4:1 hexanes/EtOAc) to afford **12** (0.91 g, 83% yield) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, $J = 8.4$ Hz, 2H), 7.20 (dd, $J = 8.4$ Hz, 2H), 3.88 (q, $J = 6.3$ Hz, 2H), 3.65 (s, 3H), 2.87 (t, $J = 6.3$ Hz, 2H), 1.50 (s, 6H). HRMS (EI): m/z calcd. for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1255.

Methyl 2-Methyl-2-(4-(2-(methylsulfonyloxy)ethyl)-phenyl)propanoate (13)

A solution of **12** (150 mg, 0.67 mmol) in 5 mL toluene was treated with Et_3N (136 mg, 1.35 mmol) and MsCl (92 mg, 0.80 mmol) at 0 °C. The reaction was

gradually warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with brine and extracted with CH_2Cl_2 (20 mL). The organic extracts were dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (Redisep silica gel, 98:2 EtOAc/CH_2Cl_2) to afford **13** (184 mg, 91% yield) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, $J = 8.4$ Hz, 2H), 7.20 (dd, $J = 8.4$ Hz, 2H), 4.43 (t, $J = 6.9$ Hz, 2H), 3.65 (s, 3H), 3.06 (t, $J = 6.9$ Hz, 2H), 2.85 (s, 3H), 1.56 (s, 6H). HRMS (EI): m/z calcd. for $C_{14}H_{20}O_5S$: 300.1031. Found: 300.1040.

tert-Butyl 4-(1H-benzo[*d*]imidazol-2-yl)piperidine-1-carboxylate (14)

A solution of **7** (5.55 g, 27 mmol) in 150 mL dioxane/H_2O (2:1) was treated with 1 M NaOH (88 mL, 88 mmol) and $(Boc)_2O$ (6.02 g, 27 mmol) at 0 °C. The reaction was gradually warmed to room temperature and stirred for 16 h. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give **14** (7.33 g, 88% yield) as a brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 7.72 (bs, 1H), 7.61 (s, 1H), 7.24–7.20 (m, 2H), 4.25 (d, $J = 11.1$ Hz, 2H), 3.70–3.67 (m, 1H), 2.95 (t, $J = 12.0$ Hz, 2H), 2.13–1.95 (m, 4H), 1.41 (s, 9H).

tert-Butyl 4-(1-(2-ethoxyethyl)-1H-benzo[*d*]imidazol-2-yl)piperidine-1-carboxylate (15)

A solution of **14** (2.83 g, 9.39 mmol) in DMF (30 mL) was treated with NaH (0.38 g, 9.39 mmol), and the reaction was stirred at room temperature for 2 h. Ethoxyethyl chloride (1.02 g, 9.39 mmol) was added, and the reaction was heated at 60 °C for 16 h. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Redisep silica gel, 98:2 CH_2Cl_2/MeOH) to afford **15** (3.50 g, 99% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.70 (m, 1H), 7.31–7.28 (m, 1H), 7.24–7.20 (m, 2H), 4.35–4.26 (m, 4H), 3.72 (t, $J = 5.4$ Hz, 2H), 3.39 (q, $J = 6.9$ Hz, 2H), 3.22–3.10 (m, 1H), 2.92–2.80 (m, 2 H), 2.15–1.85 (m, 4H), 1.48 (s, 9H), 1.10 (t, $J = 6.9$ Hz, 3H).

1-(2-Ethoxyethyl)-2-(piperidin-4-yl)-1H-benzo[*d*]imidazole (16)

A solution of **15** (71 mg, 0.20 mmol) in 3 mL THF was treated with 1 M HCl (2 mL). The reaction was heated at reflux for 1 h and neutralized with 1 M NaOH. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give **16** (50 mg, 99% yield) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.73 (m, 1H), 7.33–7.31 (m, 1H), 7.25–7.20 (m, 2H), 4.74–4.72 (m, 1H), 4.31 (t, $J = 5.4$ Hz, 2H), 3.93–3.88 (m, 1H), 3.80–3.72 (m, 1H) 3.67 (t, $J = 5.4$ Hz, 2H), 3.18–2.89 (m, 3H), 2.80–2.70 (m, 1H), 2.38–2.48 (m, 1H), 2.25–1.85 (m, 6H). HRMS (EI): m/z calcd. for $C_{16}H_{23}N_3O$: 273.1841. Found: 273.1836.

Methyl 2-(4-(2-(4-(1-(2-Ethoxyethyl)-1H-benzo[*d*]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoate (17)

A solution of **16** (0.92 g, 3.38 mmol) in DMF (5 mL) was treated with **13** (1.22 g, 4.06 mmol) and DIPEA (1.31 g, 10.1 mmol). The reaction was heated at 80 °C for 16 h. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Redisep silica gel, 19:1 CH_2Cl_2/MeOH) to afford **17** (1.01 g, 62% yield) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.72 (m, 1H), 7.34–7.30 (m, 1H), 7.29–7.17 (m, 6H), 4.36 (t, $J = 5.4$ Hz, 2H), 3.73 (t, $J = 5.4$ Hz, 2H), 3.65 (s, 3H), 3.43 (q, $J = 6.9$ Hz, 2H), 3.16 (d, $J = 5.1$ Hz, 2H), 3.0–2.97 (m, 1H), 2.84–2.79 (m, 2H), 2.66–2.61 (m, 2H), 2.25–2.10 (m, 4H), 2.04 (bs, 2H), 1.57 (s, 6H), 1.13 (t, $J = 6.9$ Hz, 3H). HRMS (EI): m/z calcd. for $C_{29}H_{39}N_3O_3$: 447.2991. Found: 447.2978.

2-(4-(2-(4-(1-(2-Ethoxyethyl)-1H-benzo[*d*]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoic acid (1): Bilastine

A solution of **17** (170 mg, 0.36 mmol) in 10 mL MeOH/THF/H_2O (1:2:2) was treated with LiOH (15 mg, 0.63 mmol) and heated at 70 °C for 16 h. The reaction mixture was acidified with 1 M HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Redisep silica gel, 9:1 CH_2Cl_2/MeOH) to afford **1** (106 mg, 64% yield) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.63–7.49 (m, 2H), 7.39 (d, $J = 8.1$ Hz, 2H) 7.30–7.21 (m, 2H), 7.18 (d, $J = 8.1$ Hz, 2H), 4.50 (t, $J = 4.8$ Hz, 2H), 3.77 (t, $J = 4.8$ Hz, 2H), 3.58 (d, $J = 12.3$ Hz, 2H), 3.43 (q, $J = 6.9$ Hz, 3H), 3.12–3.07 (m, 2H), 2.97–2.82 (m, 4H), 2.28–2.17 (m, 4H), 1.51 (s, 6H), 1.08 (t, $J = 6.9$ Hz, 3H).

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