# Design, Synthesis, and Structure−Activity Relationships of Acetylene-Based Histamine $H_3$ Receptor Antagonists

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New, potent, and selective histamine $H_3$ receptor antagonists have been synthesized by employing the use of (1) an appropriately positioned nonpolar acetylene spacer group, (2) either a two-carbon straight chain linker or a conformationally restricting *trans*-cyclopropane ring between the C-4 position of an imidazole headgroup and the acetylene spacer, and (3) a Topliss operational scheme for side-chain substitution for optimizing the hydrophobic domain. Compounds **9**−**18** are examples synthesized with the two-carbon straight chain linker, whereas **26**−**31** are analogues prepared by incorporation of the *trans*-(±)-cyclopropane at the C-4 position of an imidazole headgroup. Synthesis of both the (1*R*,2*R*)- and (1*S*,2*S*)-cyclopropyl enantiomers of the most potent racemic compound **31** ($K_i = 0.33 \pm 0.13$ nM) demonstrated a stereopreference in $H_3$ receptor binding affinity for the (1*R*,2*R*) enantiomer **32** ($K_i = 0.18 \pm 0.04$ nM) versus the (1*S*,2*S*) enantiomer **33** ($K_i = 5.3 \pm 0.5$ nM). (1*R*,2*R*)-4-(2-(5,5-Dimethylhex-1-ynyl)cyclopropyl)-imidazole (**32**) is one of the most potent histamine $H_3$ receptor antagonists reported to date.

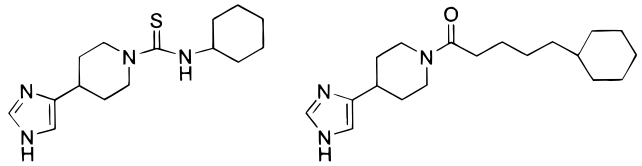
## Introduction

The discovery of the existence of a third type of histamine receptor,[1] the $H_3$ receptor, and the development of the subtype-selective agonist, (*R*)-α-methylhistamine, and antagonist, thioperamide, have stimulated a heightened interest in exploring the role of histamine as a neurotransmitter.[2] The histamine $H_3$ receptor was originally characterized as a presynaptic autoreceptor that controls the synthesis and release of histamine.[3] Thus, on histaminergic neurons at the presynaptic site, activation of $H_3$ receptors leads to an inhibition of histamine synthesis from L-histidine and an inhibition of histamine release. Contrarily, administration of the $H_3$ antagonist, thioperamide, has been shown to lead to an increase in histamine levels in the rat anterior hypothalamus, as determined by microdialysis.[4]

Evidence has since accumulated regarding the colocalization of modulating $H_3$ heteroreceptors on serotonergic,[5] cholinergic,[6] noradrenergic,[7] dopaminergic,[8] and peptidergic[9] neurons. The abundant distribution of $H_3$ receptors in the central nervous system (CNS) and the detection of histamine $H_3$ heteroreceptors on enterochromaffin-like cells of rat stomach,[10] as well as on lung[11] and cardiac tissues,[12] have brought consideration of the $H_3$ receptor as significantly important in the concerted regulation of various (patho)physiological processes.

Most pharmacological studies concerning antagonist ligand modulation of the $H_3$ receptor have focused on the potential use of these agents in the treatment of CNS disorders. Thioperamide (**1**) (Chart 1), the first selective histamine $H_3$ antagonist, has been shown to have wake-promoting, arousal, and antiepileptic properties.[13−15] Medicinal chemistry efforts initiated to develop new, selective, and potent $H_3$ receptor antagonists have focused much of their attention on improving blood−brain barrier penetration. GT-2016 (**2**) has been described as a prototype non-thiourea $H_3$ antagonist

**Chart 1**



**1** **2**

that exhibits good $H_3$ receptor affinity and selectivity, as well as excellent blood−brain barrier penetration and dose-dependent increases in histamine release in the cerebral cortex.[16] As an outcome of the many structure−activity relationship (SAR) efforts in this drug discovery area, it has been suggested that $H_3$ receptor antagonists exhibit three common and essential structural features: imidazole headgroup, spacer, and hydrophobic tail group.[17−19] These features are illustrated for GR-175737 (**3**),[20] clobenpropit (**4**),[21] and the less potent antagonist verongamine (**5**)[22] (Chart 2).

The approach that we took to develop new, selective, and potent $H_3$ antagonists with good blood−brain barrier penetration differs in several ways from previous studies and is the subject of this full account of our preliminary communication.[23] First, an investigation of the effect of using a nonpolar and linear acetylene moiety as a spacer group was undertaken. A variety of polar spacer groups such as amides, thioamides, guanidines, ureas, thioureas, esters, carbamates, and thiocarbamates have been shown to have utility for synthesizing potent $H_3$ antagonists. Second, we examined the outcome of replacing the two-carbon straight chain linking the imidazole headgroup and the spacer, an integral feature of many histamine-derived antagonists (illustrated for **3** and **5**), with a conformationally restricting *trans* chiral cyclopropane ring. The use of the *trans*-cyclopropane linker can provide compounds that can have either a (1*R*,2*R*) or (1*S*,2*S*) configuration.

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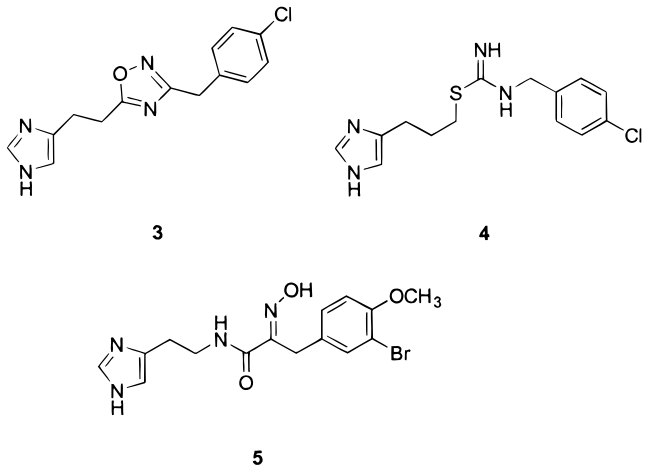
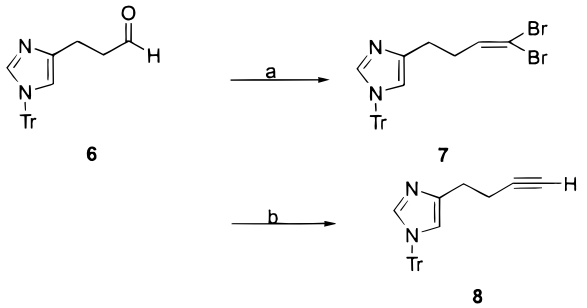
**Chart 2**



**3** **4** **5**

**Scheme 1**[a]



**6** **7** **8**

[a] (a) $PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C, 3 h, 90%; (b) *n*-BuLi (2 equiv), THF, −78 °C, 2.5 h, 91%.

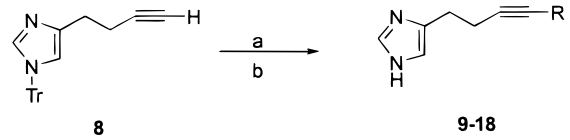
Therefore, the most potent of these derivatives was prepared in both enantiomeric pure forms in order to determine if these compounds exhibited different receptor binding affinities due to their opposite stereochemical configuration. Finally, $H_3$ receptor binding affinity of the new acetylene-containing ligands was optimized by preparing compounds with aliphatic hydrophobic tail groups following Topliss tree guidelines.[24] Thus, the SAR studies described herein were determined by independently modifying the linker and the hydrophobic tail, keeping the acetylene spacer as a constant.

## Chemistry

The acetylene **8** is prepared in straightforward manner from known aldehyde **6** by standard treatment with $CBr_4$ and triphenylphosphine to give vinyl dibromide **7** followed by treatment with 2 equiv of *n*-BuLi at −78 °C to provide **8** (Scheme 1).[23] The series of compounds **9**−**18** (Table 1) containing the two-carbon straight chain linker between the imidazole headgroup and the acetylene spacer was prepared by alkylation of the corresponding acetylene carbanion of **8** with the requisite aliphatic iodides followed by trityl deprotection (Scheme 2).

The most productive reaction conditions for the alkylation of **8** were determined to be generation of the carbanion of **8** with *n*-BuLi−TMEDA complex in THF at −20 °C followed by reaction with 1.5 equiv of aliphatic iodides at room temperature (1 h) and then at 55 °C for 24−36 h (Scheme 2). Typical yields for these reactions ranged from 60% to 90% and were very substrate-dependent. Alkylations using KHMDS, NaHMDS, or

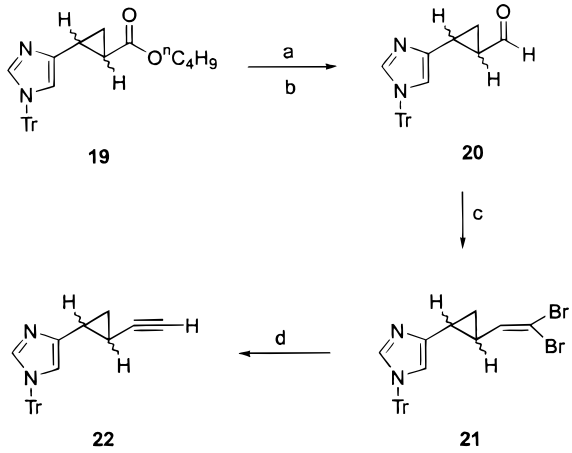
**Scheme 2**[a]



**8** **9-18**

[a] (a) *n*-BuLi−TMEDA, R-I, 55 °C, 24−36 h; (b) 1 N HCl, 90 °C, 1 h.

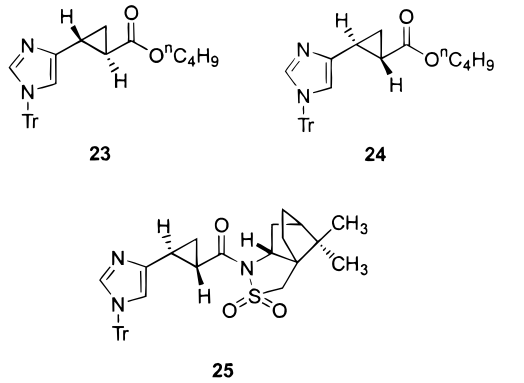
**Scheme 3**[a]



**19** **20** **21** **22**

[a] (a) $LiAlH_4$ (1.5 equiv), THF, 0 °C, 1.5 h; (b) Swern oxidation, 77% (two steps); (c) $CBr_4$, $Ph_3P$, $CH_2Cl_2$, 3 h, 90%; (d) *n*-BuLi (4 equiv), THF, 2.5 h, 92%.

**Chart 3**

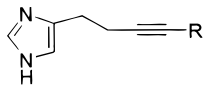


**23** **24** **25**

NaH to generate the carbanion of **8** gave no reaction. Reactions using *n*-BuLi in THF, but performed in the presence of HMPA (1 equiv), gave good yields and required no heating.

The racemic cyclopropane-containing terminal acetylene **22** was used as starting material for the preparation of the series of compounds **26**−**31** (Table 2), containing the cyclopropane bridge between the imidazole headgroup and the acetylene spacer. The synthesis of the key acetylene intermediate **22** (Scheme 3) is similar to the preparation of its straight chain analogue **8** but proceeds from the racemic mixture of *trans*-butyl 2-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclopropanecarboxylate (**19**).[25] The alkylation reactions with **22** and subsequent trityl deprotection of products were performed in a fashion similar to that of the straight chain series. Chiral (1*R*,2*R*)-**32** and (1*S*,2*S*)-**33** (Table 2) were prepared from the corresponding enantiomerically pure esters **23** and **24** (Chart 3), respectively. These esters were obtained in gram quantities by resolution of the racemic mixture **19** using a chiral column.[26] The abso-

**Table 1.** In Vitro Histamine $H_3$ Receptor Binding Affinities of Compounds **9**−**18**



| compd | R | $K_i$ (nM) |
|---|---|---|
| **9** | H | 66.3 ± 5.5 |
| **10** | $CH_2CH_3$ | 79 ± 22 |
| **11** | $(CH_2)_2CH_3$ | 27 ± 7.5 |
| **12** | $(CH_2)_2CH(CH_3)_2$ | 3.7 ± 1.1 |
| **13** | $(CH_2)_2$-cyclo-$C_5H_9$ | 0.9 ± 0.3 |
| **14** | $(CH_2)_2$-cyclo-$C_6H_{11}$ | 2.9 ± 0.2 |
| **15** | $(CH_2)_4C_6H_5$ | 3.5 ± 1.0 |
| **16** | $(CH_2)_2$-*tert*-butyl | 0.8 ± 0.04 |
| **17** | $(CH_2)_4CH_3$ | 5.6 ± 1.0 |
| **18** | $(CH_2)_6CH_3$ | 2.8 ± 0.7 |

lute configurations of the cyclopropane ring of derivatives **23** and **24** were established from the X-ray crystal structure obtained for sultam derivative **25**.[27]

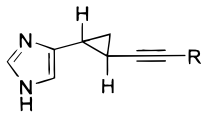
## Results and Discussion

Our previous SAR studies[28] and results obtained by others[17,18] have demonstrated the usefulness of incorporating aliphatic hydrocarbon side chains into the hydrophobic tail. However, for this new series of acetylene-containing $H_3$ antagonists, a more systematic approach was used to maximize our chances of synthesizing the most potent compounds in this series by employing a Topliss operational scheme for side-chain substitution.[24] In the straight chain series, compound **10** was chosen as the base compound for these studies. The rationale for this choice came from molecular modeling studies which were discussed in a preliminary account of this work.[23] The $H_3$ receptor binding data for all of the compounds containing a two-carbon straight chain between the imidazole headgroup and the acetylene spacer are reported in Table 1. The base compound **10** had $H_3$ receptor binding affinity of $K_i = 79 \pm 22$ nM, whereas its methyl-substituted analogue **11** had a $K_i = 27 \pm 7.5$ nM. On the premise that a $+\pi$ (hydrophobic) effect would be the most probable, compounds **12** and **17** were synthesized in which an isopropyl group or a *n*-propyl group, respectively, replaced the methyl group of **11**. Both compounds exhibited improvements in binding affinity with respect to **10** and **11**. Because an increase in activity was observed, the $+\pi$ branch of the Topliss tree was followed and the cyclopentyl derivative **13** prepared. This derivative also exhibited improved binding affinity with a $K_i = 0.95 \pm 0.3$ nM. As suggested by Topliss,[24] the cyclohexyl and phenethyl analogues **14** and **15** were synthesized. These compounds showed no improvement in activity and suggested that the optimum hydrophobicity ($\pi$ factor) had been obtained with the cyclopentyl substitution in **13**.

Since the optimum $\pi$ value had been obtained with **13**, it remained to be determined if activity could be increased with increasing $-\sigma^*$ values; therefore, analogue **16** was prepared. The bulky *tert*-butyl substitution was tolerated quite well, and **16** exhibited a $K_i = 0.8 \pm 0.1$ nM.

Several SAR studies involving the development of new $H_3$ receptor antagonists have focused on optimizing receptor affinity by studying the influence of chain length between a polar spacer group and either a lipophilic aromatic or a cycloalkyl substituent.[17−19,21,29] However, acetylenic compounds containing longer carbon chains and with only alkyl substitution such as **17** and **18** are as potent as **14** and **15** which contain shorter chains accompanied by cyclohexyl or phenyl substituents. Interestingly, the unsubstituted terminal acetylene **9**, which is derived from deprotection of our key synthetic intermediate **8**, shows approximately the same binding affinity as **10** (66.3 ± 5.5 vs 79 ± 22 nM).

**Table 2.** In Vitro Histamine $H_3$ Receptor Binding Affinities of Compounds **26**−**33**



| compd | cyclopropane config | R | $K_i$ (nM) |
|---|---|---|---|
| **26** | (±)-cyclopropyl | $(CH_2)_2CH_3$ | 5.1 ± 0.8 |
| **27** | (±)-cyclopropyl | $(CH_2)_2CH(CH_3)_2$ | 6.5 ± 1.5 |
| **28** | (±)-cyclopropyl | $(CH_2)_2$-cyclo-$C_5H_9$ | 1.43 ± 0.3 |
| **29** | (±)-cyclopropyl | $(CH_2)_2$-cyclo-$C_6H_{11}$ | 1.8 ± 1.0 |
| **30** | (±)-cyclopropyl | $(CH_2)_4C_6H_5$ | 15.9 ± 0.6 |
| **31** | (±)-cyclopropyl | $(CH_2)_2$-*tert*-butyl | 0.33 ± 0.13 |
| **32** | (1*R*,2*R*)-cyclopropyl | $(CH_2)_2$-*tert*-butyl | 0.12 ± 0.04 |
| **33** | (1*S*,2*S*)-cyclopropyl | $(CH_2)_2$-*tert*-butyl | 5.3 ± 0.5 |

Recently, a new series of $H_3$ receptor antagonists that contain a chiral cyclopropane bridge as an integral structural feature has been prepared.[28] Therefore, it was anticipated that cyclopropyl replacement of the two-carbon straight chain between the imidazole headgroup and the acetylene spacer in compounds from Table 1 would produce conformationally restricted analogues that would also exhibit a stereopreference in their binding affinities for the $H_3$ receptor. Table 2 shows the $H_3$ receptor binding data for all racemic and chiral cyclopropyl-containing compounds prepared in this study. The racemic mixture of compounds **26**−**31** demonstrates approximately equipotent $H_3$ receptor binding affinity in comparison to their straight chain congeners. The racemic mixture **30** is 4−5 times less potent than **15**. However, the racemic mixtures of cyclopentyl derivative **28** and the *tert*-butyl analogue **31** have the best activities within the cyclopropyl series and follow the trend shown in the straight chain series. Since the racemate **31** exhibited the highest potency, each of the chiral enantiomers was prepared. The (1*R*,2*R*)-cyclopropane **32** ($K_i = 0.18 \pm 0.04$ nM) was at least 1 order of magnitude more potent than its (1*S*,2*S*) analogue **33** ($K_i = 5.3 \pm 0.5$ nM). Compound **32** is one of the most potent $H_3$ receptor antagonists prepared to date. Apparently, the combination of the (1*R*,2*R*) configuration of the cyclopropyl ring with the nonpolar but linear acetylene spacer places the *tert*-butyl-containing hydrophobic tail in a preferred orientation with the imidazole headgroup.[30]

**Pharmacology.** The $H_3$ antagonist properties of compounds **13**, **14**, and **32** were evaluated in vitro for their ability to block the $H_3$ agonist-induced inhibition of norepinephrine (NE) release from cardiac synaptosomes. In this experimental design, an $H_3$ agonist produces complete blockade of $K^+$-induced NE release via action at presynaptic $H_3$ heteroreceptors. Coincubation of compound **13**, **14**, or **32** with an $H_3$ agonist resulted in complete attenuation of the agonist-induced modulation of NE release.[23,31] Furthermore, compound

**32** was also found to attenuate $H_3$ agonist-induced inhibition of the neurogenic contractions of the isolated guinea pig jejunum. These studies clearly demonstrate functional $H_3$ antagonist activity for compounds **13**, **14**, and **32**.[23,31]

## Conclusions

New potent and selective classes of histamine $H_3$ receptor antagonists have been identified from SAR studies that employed the use of (1) a nonpolar acetylene spacer group, (2) conformationally restricting cyclopropane ring attachment at the C-4 position of an imidazole headgroup, and (3) a Topliss operational scheme for side-chain substitution. The combination of acetylene spacer, *trans*-cyclopropane ring incorporation, and aliphatic hydrophobic side-chain substitution provided a new series of potent $H_3$ receptor antagonists.

## Experimental Section

All reagents were obtained from commercial suppliers and were used without further purification. Solvents used were either AR or HPLC grade. Thin-layer chromatography was performed on K6F silica gel 60A. Preparative column chromatography was performed on silica gel (230−400 $\mu$m) under pressure. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Varian VXR 300-MHz spectrometer. Chemical shifts are reported in ppm ($\delta$) relative to internal standard tetramethylsilane. All $J$ values are given in hertz (Hz). High-resolution (EI) mass spectra were recorded on a KRATOS MS 50 spectrometer at 70 eV. All compounds gave correct HRMS. HPLC analysis was performed on a Perkin-Elmer Quanternary 200 Ic pump using a reverse-phase column (Phenomenex Prodigy, 5-$\mu$m o.d.S(2), 150- × 4.6-mm i.d.) for compounds **9**−**18**. Compounds **26**−**33** were analyzed on a Perkin-Elmer Quanternary 200 Ic pump using a chiral column (Chiralcel, 10-$\mu$m o.d.) polysaccharide type (250- × 4.6-mm i.d.).

A representative method for the synthesis of all compounds is illustrated in General Procedure for the Alkylation of Acetylenes **8** and **22**. Most compounds are oils and turned to sticky solids at room temperature after a few days.

**3-(1-(Triphenylmethyl)imidazol-4-yl)propanal (6)**. To a solution of oxalyl chloride (2.0 M solution, 194 mL, 0.39 mol) in dichloromethane (300 mL) was added dimethyl sulfoxide (55 mL, 0.78 mol) dropwise at − 78 °C. The mixture was stirred at −78 °C for 10 min, and a solution of 3-(1-(triphenylmethyl)-imidazol-4-yl)propan-1-ol (102 g, 0.28 mol) in dichloromethane (800 mL) was added. Stirring was continued at −78 °C for 10 min. Triethylamine (155 mL, 1.1 mol) was added and the reaction brought to room temperature. The organic layer was separated, washed with water, and dried ($Na_2SO_4$). Purification by flash column chromatography (EtOAc/hexane, 1:1) gave **6** as a white solid: 100 g (99%); mp 94−95 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.86 (brt, $J$ = 1.5 Hz, 1H), 7.45 (m, 10H), 7.20 (m, 6H), 6.65 (s, 1H), 2.99 (m, 4H).

**4-(4,4-Dibromobut-3-enyl)-1-(triphenylmethyl)imidazole (7)**. Triphenylphosphine (2.59 g, 9.85 mmol) was added in portions to a 0 °C solution of carbon tetrabromide (2.17 g, 6.56 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 0 °C for 20 min. A solution of **6** (1.2 g, 3.28 mmol) in dichloromethane (5 mL) was added. Stirring was continued at 0 °C for 3 h and treated with aqueous saturated sodium bicarbonate solution. The organic layer was separated, washed with water, and dried ($Na_2SO_4$). The crude product was purified by flash column chromatography (EtOAc/hexane, 1:9) giving **7** as a solid: 1.52 g (90%); mp 115−116 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.41 (s, 1H), 7.33 (m, 9H), 7.12 (m, 6H), 6.54 (s, 1H), 6.34 (t, $J$ = 7.2 Hz, 1H), 2.67 (t, $J$ = 7.2 Hz, 1H), 2.42 (dd, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 142.0, 138.9, 137.9, 129.7, 128.1, 118.5, 89.2, 32.5, 25.9. Anal. ($C_{26}H_{22}N_2Br_2$) C, H, N.

**4-But-3-ynyl-1-(triphenylmethyl)imidazole (8)**. *n*-BuLi (2.5 M in hexane, 50 mL, 0.125 mol) was added to a solution of **7** (16.0 g, 0.03 mol) in dry tetrahydrofuran (400 mL) at −78 °C. Stirring was continued for 2.5 h, and the mixture was treated with aqueous saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate, and the organic layer was separated, washed with water, and dried ($Na_2SO_4$). Purification by flash column chromatography (EtOAc/hexanes, 3:8) gave **8** as a solid: 10.0 g (91%); mp 126−128 °C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.83 (s, 1H), 7.42 (s, 1H), 2.95 (t, $J$ = 6.9 Hz, 2H), 2.60 (dt, $J$ = 2.4 and 6.9 Hz, 2H), 2.36 (t, $J$ = 2.4 Hz, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 134.9, 128.9, 117.7, 82.8, 71.6, 24.8, 18.8. Anal. ($C_{26}H_{22}N_2$) C, H, N.

**General Procedure for the Alkylation of Acetylenes 8 and 22**. *n*-BuLi (2.5 M, 1.3 equiv) was added to TMEDA (1.3 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min and cooled to −20 °C. A 1.0 M solution of acetylene (**8** or **22**) (1.0 equiv) in tetrahydrofuran was added to the *n*-BuLi−TMEDA complex. After 45 min a solution of alkyl iodide (1.5 equiv) in tetrahydrofuran was added, and the reaction was stirred at 55 °C for 24−36 h. The reaction mixture was treated with water and extracted with ethyl acetate. The organic layer was separated, washed with water, and dried ($Na_2SO_4$). The crude product was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford pure products in 60−90% yield.

**Synthesis of (1*R*,2*R*)-4-(2-(5,5-Dimethylhex-1-ynyl)cyclopropyl)imidazole (32) and General Procedure for the Removal of the Triphenylmethyl Protecting Group**. A solution of (1*R*,2*R*)-4-(2-(5,5-dimethylhex-1-ynyl)cyclopropyl)-1-(triphenylmethyl)imidazole (2.5 g, 5.5 mmol) in ethanol (20 mL) and hydrochloric acid (2.0 N, 35 mL) was heated at 85−90 °C for 20−30 min. The mixture was cooled to room temperature and filtered. The filtrate was basified ($NaHCO_3$) and extracted (EtOAc). The organic layer was separated, washed with water, and dried ($Na_2SO_4$). The crude product was purified by flash column (EtOAc/MeOH, 99:1) and gave **32** as a waxy solid: 1.14 g (96%).

**4-But-3-ynylimidazole (9)**. Acetylene **8** (0.15 g) was trityl-deprotected and gave acetylene **9** as an oil: 0.04 g (86%); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.83 (s, 1H), 7.42 (s, 1H), 2.95 (t, $J$ = 6.9 Hz, 2H), 2.60 (dt, $J$ = 2.4 and 6.9 Hz, 2H), 2.36 (t, $J$ = 2.4 Hz, 1H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 134.9, 128.9, 117.7, 82.8, 71.6, 24.8, 18.8; HRMS (EI) calcd for $C_7H_8N_2$ 120.6875, found 120.069.

**4-Hex-3-ynylimidazole (10)**. Acetylene **8** (0.2 g, 0.55 mmol) was treated with iodoethane (0.13 g, 0.83 mmol) and gave the alkylated acetylene (0.18 g), which was subsequently trityl-deprotected giving acetylene **10** as an oil: 0.04 g (49%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (s, 1H), 6.83 (s, 1H), 2.80 (t, $J$ = 7.2 Hz, 2H), 2.45 (m, 2H), 2.15 (m, 2H), 1.08 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 134.4, 118.0, 82.5, 79.0, 69.0, 26.5, 19.2, 14.2, 12.4; HRMS (EI) calcd for $C_9H_{11}N_2$ (M − 1) 147.09222, found 147.09231.

**4-Hept-3-ynylimidazole (11)**. Acetylene **8** (0.14 g, 0.38 mmol) was treated with iodopropane (0.1 g, 0.57 mmol) and gave alkylated acetylene (0.13 g), which was trityl-deprotected and gave the alkylated acetylene **11** as an oil: 0.06 g (87%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.33 (brs, 1H), 7.55 (s, 1H), 6.83 (s, 1H), 2.79 (t, $J$ = 7.2 Hz, 2H), 2.47 (t, $J$ = 7.2 Hz, 2H), 2.10 (t, $J$ = 7.2 Hz, 2H), 1.46 (m, 2H), 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 135.7, 134.4, 117.8, 80.9, 79.6, 26.6, 22.4, 20.7, 19.2, 13.4; HRMS (EI) calcd for $C_{10}H_{13}N_2$(M − 1)161.10788, found 161.10771. Anal. ($C_{14}H_{18}N_2O_4$-(maleate salt)) C, H, N.

**4-(7-Methyloct-3-ynyl)imidazole (12)**. Acetylene **8** (0.21 g, 0.59 mmol) was treated with 1-iodo-3-methylbutane (0.18 g, 0.88 mmol) providing the alkylated acetylene (0.09 g), which was trityl-deprotected and gave acetylene **12** as an oil: 0.03 g (25%, overall yield); $R_f$ 0.3 (EtOAc/MeOH, 95:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.55 (s, 1H), 6.82 (s, 1H), 5.96 (brs, 1H), 2.78 (t, $J$ = 7.2 Hz, 2H), 2.45 (t, $J$ = 7.2 Hz, 2H), 2.12 (t, $J$ = 7.5

Hz, 2H), 1.37 (m, 1H), 0.85 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 135.7, 134.4, 117.9, 81.2, 79.4, 37.9, 27.1, 26.5, 22.4, 22.1, 19.2, 16.7; HRMS (EI) calcd for $C_{12}H_{17}N_2$ (M − 1) 189.13918, found 189.13966.

**4-(6-Cyclopentylhex-3-ynyl)imidazole (13)**. Acetylene **8** (0.21 g, 0.38 mmol) was treated with cyclopentylethyl iodide (0.2 g, 0.88 mmol) to give the alkylated acetylene (0.09 g), which was trityl-deprotected and gave acetylene **13** as an oil: 0.04 g (33%, overall yield); $R_f$ 0.4 (EtOAc/MeOH, 95:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.57 (s, 1H), 6.84 (s, 1H), 2.79 (t, $J$ = 7.2 Hz, 2H), 2.46 (t, $J$ = 7.2 Hz, 2H), 2.15 (t, $J$ = 7.2 Hz, 2H), 1.0−1.8 (m, 11H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 134.8, 117.6, 83.2, 78.5, 40.6, 36.6, 33.4, 26.2, 25.5, 19.2, 18.6; HRMS (EI) calcd for $C_{14}H_{19}N_2$ (M − 1) 215.15483, found 215.15497.

**4-(6-Cyclohexylhex-3-ynyl)imidazole (14)**. Acetylene **8** (0.5 g, 1.3 mmol) was treated with cyclohexylethyl iodide (0.72 g, 2.8 mmol) to give alkylated acetylene (0.38 g) which was trityl-deprotected and gave acetylene **14** as an oil: 0.18 g (73%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (s, 1H), 6.82 (s, 1H), 2.78 (t, $J$ = 7.1 Hz, 2H), 2.45 (m, 2H), 2.10 (m, 2H), 1.64 (m, 5H), 1.34 (t, $J$ = 7.1 Hz, 2H), 1.19 (m, 4H), 0.84 (m, 2H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 134.4, 118.2, 100.0, 84.4, 79.4, 36.6, 36.5, 32.8, 26.5, 26.4, 26.1, 19.1, 16.1; HRMS (EI) calcd for $C_{15}H_{21}N_2$ (M − 1) 229.17047, found 229.17127. Anal. ($C_{19}H_{26}N_2O_4$(maleate salt)) C, H, N.

**4-(8-Phenyloct-3-ynyl)imidazole (15)**. Acetylene **8** (0.2 g, 0.55 mmol) was treated with 4-phenyl-1-iodobutane (0.21 g, 0.82 mmol) and gave the alkylated acetylene (0.17 g), which was trityl-deprotected and gave acetylene **15** as an oil: 0.07 g (49%, overall yield); $R_f$ 0.5 (EtOAC/MeOH, 95:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (s, 1H), 7.42 (m, 2H), 7.23 (m, 3H), 6.94 (s, 1H), 2.94 (t, $J$ = 6.9 Hz, 2H), 2.71 (t, $J$ = 7.2 Hz, 2H), 2.54 (m, 2H), 2.36 (m, 2H), 2.1 (m, 2H), 1.8 (m, 2H); HRMS (EI) calcd for $C_{17}H_{19}N_2$ (M − 1) 251.15483, found 251.15428.

**4-(7,7-Dimethyloct-3-ynyl)imidazole (16)**. Acetylene **8** (0.2 g, 0.55 mmol) was treated with 3,3-dimethyl-1-iodobutane (0.26 g, 1.2 mmol) to give the alkylated acetylene (0.07 g), which was trityl-deprotected and gave acetylene **16** as an oil: 0.02 g (14%, overall yield); $R_f$ 0.5 (EtOAc/MeOH, 95:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (s, 1H), 6.86 (s, 1H), 2.85 (t, $J$ = 6.9 Hz, 2H), 2.76 (t, $J$ = 7.2 Hz, 2H), 2.07 (m, 2H), 1.46 (m, 2H), 1.02 (s, 9H); HRMS (EI) calcd for $C_{13}H_{21}N_2$ (M + 1) 205.17047, found 205.1700.

**4-Non-3-ynylimidazole (17)**. Acetylene **8** (0.21 g, 0.59 mmol) was treated with 1-iodopentane (0.18 g, 0.88 mmol) to give the alkylated acetylene (0.18 g), which was trityl-deprotected and gave acetylene **17** as an oil: 0.07 g (62%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.57 (s, 1H), 6.84 (s, 1H), 2.79 (t, $J$ = 7.2 Hz, 2H), 2.47 (t, $J$ = 7.2 Hz, 2H), 2.12 (t, $J$ = 7.2 Hz, 2H), 1.46 (m, 2H), 1.31 (m, 4H), 0.87 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 135.5, 134.2, 118.1, 81.4, 79.5, 31.1, 28.7, 26.4, 22.2, 19.1, 18.7, 14.0; HRMS (EI) calcd for $C_{12}H_{19}N_2$ (M + 1) 191.15483, found 191.15483.

**4-Undec-3-ynylimidazole (18)**. Acetylene **8** (0.20 g, 0.55 mmol) was treated with 1-iodoheptane (0.27 g, 1.2 mmol) to give the alkylated acetylene (0.18 g), which was trityl-deprotected and gave acetylene **18** as an oil: 0.08 g (81%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.56 (s, 1H), 6.83 (s, 1H), 2.78 (t, $J$ = 7.2 Hz, 2H), 2.46 (m, 2H), 2.14 (m, 2H), 1.46 (m, 2H), 1.26 (m, 8H), 0.86 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 135.4, 134.3, 117.6, 81.3, 79.2, 31.6, 28.9, 28.7, 26.2, 22.5, 19.0, 18.6, 14.0; HRMS (EI) calcd for $C_{14}H_{21}N_2$ (M − 1) 217.17047, found 217.17128.

**(±)-2-(1-(Triphenylmethyl)imidazol-4-yl)cyclopropanecarbaldehyde (20)**. **Step 1.** Lithium aluminum hydride (1.0 M solution in THF, 16.66 mL, 16.66 mmol) was added to a solution of butyl 2-(1-(triphenylmethyl)imidazol-4-yl)cyclopropanecarboxylate (5 g, 11.1 mmol) in dry tetrahydrofuran (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. The mixture was treated with water (0.4 mL), 10% sodium hydroxide (0.4 mL), and water (1.2 mL). The suspension was filtered through Celite and washed with ethyl acetate. The filtrate was dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude alcohol (4.8 g).

**Step 2.** Dimethyl sulfoxide (2.68 mL, 37.8 mmol) was added dropwise (30 min) to a solution of oxalyl chloride (2.0 M solution, 9.4 mL, 18.9 mmol) in dichloromethane (20 mL) at − 78 °C. A solution of alcohol from step 1 (4.8 g (crude), 12.6 mmol) in $CH_2Cl_2$ (80 mL) was added over 30 min at −78 °C. Stirring was continued for 30 min, and then triethylamine (7.1 mL, 50.4 mmol) was added dropwise. At that time the cooling bath was removed, and the reaction was warmed to room temperature and treated with an aqueous saturated ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude aldehyde was purified by flash column chromatography (EtOAc/hexanes, 1:3) and gave **20** as a white solid: 3.2 g (77% (two steps)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.24 (d, $J$ = 4.8 Hz, 1H), 7.30 (m, 10H), 7.11 (m, 6H), 6.64 (s, 1H), 2.49 (m, 1H), 2.26 (m, 1H), 1.62 (m, 2H).

**(±)-4-(2-(2,2-Dibromovinyl)cyclopropyl)-1-(triphenylmethyl)imidazole (21)**. To a solution of carbon tetrabromide (10.2 g, 30.6 mmol) in dichloromethane (100 mL) at 0 °C was added triphenylphosphine (16.1 g, 61.4 mmol) in portions over 20 min. Stirring was continued at 0 °C for 30 min. A solution of **20** (5.8 g, 15.34 mmol) in dichloromethane (30 mL) was added. After 40 min the reaction mixture was treated with an aqueous saturated ammonium chloride solution. The organic layer was separated, washed with water, and dried ($Na_2SO_4$). The crude product was filtered rapidly through a silica gel column (EtOAc/hexane, 1:3) to give **21** as a white solid: 7.3 g (90%); mp 188−190 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30 (m, 10H), 7.11 (m, 6H), 6.58 (s, 1H), 5.89 (d, $J$ = 9.3 Hz, 1H), 1.99 (m, 2H), 1.42 (m, 1H), 1.02 (m, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$. 142.0, 140.5, 139.7, 137.9, 129.7, 128.1, 117.7, 86.5, 25.4, 18.3, 15.0. Anal. ($C_{27}H_{22}N_2Br_2$) C, H, N.

**(±)-4-(2-Ethynylcyclopropyl)-1-(triphenylmethyl)imidazole (22)**. A solution of **21** (4.2 g, 7.86 mmol) in tetrahydrofuran (50 mL) was treated with *n*-BuLi (2.5 M in hexane, 12.6 mL, 31.4 mmol) at − 78 °C. The reaction mixture was stirred for 2.5 h or until HPLC analysis showed the reaction to be complete and then quenched by the addition of saturated $NH_4Cl$. The reaction mixture was extracted (EtOAc), and the organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:4) and gave **22** as a white solid: 2.9 g (98%); mp 157−158 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (m, 10H), 7.11 (m, 6H), 6.62 (s, 1H), 2.11 (m, 1H), 1.83 (d, $J$ = 2.1 Hz, 1H), 1.64 (m, 1H), 1.35 (m, 1H), 1.17 (m, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$. 142.2, 139.4, 138.1, 129.8, 128.1, 118.1, 86.4, 64.6, 19.5, 16.2, 9.1.

**(±)-4-(2-Pent-1-ynylcyclopropyl)imidazole (26)**. Acetylene **22** (0.1 g, 0.27 mmol) was treated with 1-iodopropane (0.07 g, 0.4 mmol) to give the alkylated acetylene (0.07 g), which was trityl-deprotected and gave acetylene **26** as an oil: 0.02 g (49%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.51 (s, 1H), 6.81 (s, 1H), 2.10 (m, 2H), 2.02 (m, 1H), 1.46 (t, $J$ = 7.2 Hz, 2H), 1.41 (m, 1H), 1.15 (m, 1H), 1.05 (m, 1H), 0.97 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 139.4, 135.9, 115.9, 82.2, 77.4, 23.5, 21.5, 19.6, 16.5, 13.7, 10.6; HRMS (EI) calcd for $C_{11}H_{15}N_2$ (M − 1) 175.12352, found 175.12380.

**(±)-4-(2-(5-Methylhex-1-ynyl)cyclopropyl)imidazole (27)**. Acetylene **22** (0.1 g, 0.27 mmol) was treated with 1-bromo-3-methylbutane (0.8 g, 0.54 mmol) to give the alkylated acetylene (0.07 g), which was trityl-deprotected and gave acetylene **27** as an oil: 0.02 g (37%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80 (s, 1H), 6.80 (s, 1H), 2.12 (m, 3H), 1.61 (m, 3H), 1.35 (q, $J$ = 7.2 Hz, 1H), 1.27 (brm, 1H), 1.16 (m, 1H), 0.85 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 137.9, 134.4, 114.9, 81.3, 38.0, 27.2, 22.2, 18.3, 16.7, 16.0, 9.7; HRMS (EI) calcd for $C_{13}H_{17}N_2$ (M − 1) 201.13918, found 201.13958.

**(±)-4-(2-(4-Cyclopentylbut-1-ynyl)cyclopropyl)imidazole (28)**. Acetylene **22** (0.2 g, 0.5 mmol) was treated with cyclopentylethyl iodide (0.07 g, 0.4 mmol) to give the alkylated acetylene (0.85 g), which was trityl-deprotected and gave acetylene **28** as an oil: 0.04 g (33%, overall yield); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.51 (s, 1H), 6.81 (s, 1H), 2.14 (m, 2H), 2.04 (m, 1H), 1.88 (m, 1H), 1.80 (m, 2H), 1.65−1.39 (m, 7H),

1.17−1.02 (m, 4H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 137.9, 134.5, 114.9, 81.14, 39.3, 35.4, 32.2, 25.0, 18.1, 15.9, 9.7; HRMS (EI) calcd for $C_{15}H_{19}N_2$ (M − 1) 227.15483, found 227.15589.

**(±)-4-(2-(4-Cyclohexylbut-1-ynyl)cyclopropyl)imidazole (29)**. Acetylene **22** (0.17 g, 0.45 mmol) was treated with 2-cyclohexyl-1-iodoethane (0.13 g, 0.54 mmol) to give the alkylated acetylene (0.06 g), which was trityl-deprotected and gave acetylene **29** as an oil: 0.02 g (21%, overall yield); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.51 (s, 1H), 6.81 (s, 1H), 2.14 (m, 2H), 2.04 (m, 1H), 1.72 (m, 5H), 1.42 (m, 1H), 1.35 (m, 3H), 1.29−1.02 (m, 5H), 0.9 (m, 2H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 137.9, 134.3, 114.8, 81.2, 36.8, 36.6, 32.9, 26.6, 26.2, 18.3, 16.3, 16.1, 9.8; HRMS (EI) calcd for $C_{16}H_{22}N_2$ (M − 1) 241.17047, found 241.17079.

**(±)-4-(2-(6-Phenylhex-1-ynyl)cyclopropyl)imidazole (30)**. Acetylene **22** (0.1 g, 0.27 mmol) was treated with 4-phenyl-1-iodobutane (0.1 g, 0.4 mmol) to give the alkylated acetylene (0.11 g), which was trityl-deprotected and gave acetylene **30** as an oil: 0.054 g (63%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (s, 1H), 7.28−7.15 (m, 5H), 6.79 (s, 1H), 2.60 (t, $J$ = 7.8 Hz, 2H), 2.15 (dt, $J$ = 1.5 and 6.9 Hz, 2H), 2.07 (m, 1H), 1.69 (m, 2H), 1.52 (m, 3H), 1.25 (m, 1H), 1.13 (m, 1H); $^{13}$C NMR (300 MHz, $CD_3OD$) $\delta$ 142.3, 136.6, 134.1, 128.3, 125.7, 114.8, 81.2, 35.4, 30.5, 28.5, 18.6, 17.6, 16.2, 10.0; HRMS (EI) calcd for $C_{18}H_{19}N_2$ (M − 1) 263.15482, found 263.15373.

**(±)-4-(2-(5,5-Dimethylhex-1-ynyl)cyclopropyl)imidazole (31).** Acetylene **22** (0.1 g, 0.27 mmol) was treated with 3,3-dimethyl-1-iodobutane (0.1 g, 0.4 mmol) to give the alkylated acetylene (0.04 g), which was trityl-deprotected and gave acetylene **31** as an oil: 0.02 g (35%, overall yield); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 6.81 (s, 1H), 2.08 (m, 3H), 1.52 (brm, 1H), 1.41 (m, 2H), 1.22 (m, 1H), 1.14 (m, 1H), 0.87 (s, 9H); $^{13}$C NMR (750 MHz, $CD_3OD$) $\delta$ 137.6, 134.3, 114.9, 80.9, 78.1, 43.3, 36.8, 30.3, 18.1, 16.0, 14.3, 9.8; HRMS (EI) calcd for $C_{14}H_{21}N_2$ (M + 1) 217.17047, found 217.17120. Anal. ($C_{18}H_{24}N_2O_4$(maleate salt)) C, H, N.

**(+)-(1*R*,2*R*)-4-(2-(5,5-Dimethylhex-1-ynyl)cyclopropyl)-imidazole (32)**. The (1*R*,2*R*) enantiomer of acetylene **22** (4.5 g, 12.1 mmol) was treated with 3,3-dimethyl-1-iodobutane (3.8 g, 18 mmol) to give the alkylated acetylene (3.0 g), which was trityl-deprotected and gave acetylene **32** as an oil: 1.4 g (54%, overall yield); mp 173−175 °C; $[\alpha]^{20}_D = +140$ ($c$ = 0.5, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.49 (s, 1H), 6.77 (s, 1H), 2.07 (m, 3H), 1.49 (m, 1H), 1.41 (m, 2H), 1.19 (m, 1H), 1.12 (m, 1H), 0.85 (s, 9H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 138.4, 134.6, 115.1, 81.2, 77.8, 43.3, 30.2, 28.9, 18.5, 15.8, 14.2, 9.5; HRMS (EI) calcd for $C_{14}H_{19}N_2$ (M − 1) 215.15483, found 215.15501. Anal. ($C_{18}H_{24}N_2O_4$(maleate salt)) C, H, N.

**(−)-(1*S*,2*S*)-4-(2-(5,5-Dimethylhex-1-ynyl)cyclopropyl)-imidazole (33)**. The (1*S*,2*S*) enantiomer of acetylene **22** (0.4 g, 1.07 mmol) was treated with 3,3-dimethyl-1-iodobutane (0.29 g, 1.6 mmol) to give the alkylated acetylene (0.25 g), which was trityl-deprotected and gave acetylene **33** as an oil: 0.09 g (41%, overall yield); $[\alpha]^{20}_D = -131$ ($c$ = 0.83, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 6.81 (s, 1H), 2.08 (m, 3H), 1.54 (m, 1H), 1.42 (m, 2H), 1.25 (m, 1H), 1.16 (m, 1H), 0.85 (s, 9H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 137.9, 134.5, 115.1, 81.0, 78.0, 43.2, 30.2, 28.9, 18.1, 15.0, 14.2, 9.6; HRMS (EI) calcd for $C_{14}H_{19}N_2$ (M − 1) 215.15483, found 215.15386.

**Histamine $H_3$ Receptor Binding Assay**. Histamine $H_3$ receptor affinity was determined in rat cortical membranes using the $H_3$ agonist ligand [$^3$H]-$N^\alpha$-methylhistamine (78.9 Ci/mmol; DuPont NEN Research Products, Boston, MA). The binding assay was carried out in propylene tubes in a total volume of 0.2 mL of 50 mM $Na^+$ phosphate buffer (pH 7.4), containing 75−100 $\mu$g of tissue protein and 0.8−1.2 nM [$^3$H]-$N^\alpha$-methylhistamine. Compounds (1−2 mg) were dissolved in water or a small aliquot (80 $\mu$L) of 10% HCl. Compounds were further diluted with water to the desired concentration. Nonspecific binding was accounted for by the inclusion of thioperamide (10 $\mu$M). The samples were incubated for 40 min at 25 °C. Samples were filtered through glass fiber filters, presoaked with 0.3% poly(ethylenimine), using an Inotech cell harvester. The filters were rapidly washed three times with 25 mM Tris buffer containing 145 mM NaCl (pH 7.4, 4 °C). Competition experiments were analyzed, and $K_i$'s were determined using the equation: $K_i = IC_{50}/(1 + ([\text{ligand}]/K_d)$.

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**Supporting Information Available:** $^1$H NMR spectra, high-resolution mass spectra, and HPLC purity data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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