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An Efficient Multigram Synthesis of the Potent Histamine H_3 Antagonist GT-2331 and the Reassessment of the Absolute Configuration

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Abstract: GT-2331 is a potent histamine H_3 antagonist which has entered clinical trials. Efficient multigram syntheses of this compound and its enantiomer are described. The literature reports that GT-2331 is the dextrorotatory (+), more potent, enantiomer of 4-[2-(5,5-dimethylhex-1-ynyl)cyclopropyl]-1*H*-imidazole with the absolute configuration of (1*R*,2*R*)-**1**. However, we found that the dextrorotatory, more potent, enantiomer of 4-[2-(5,5-dimethylhex-1-ynyl)cyclopropyl]-1*H*-imidazole has the (1*S*,2*S*) absolute configuration. We suggest a reconsideration of the absolute configuration of GT-2331.

The histamine H_3 receptor, discovered 20 years ago,[1] is a presynaptic autoreceptor[2] that regulates the release and synthesis of histamine. Recent data have shown that this receptor also modulates the release of other neurotransmitters, such as acetylcholine, dopamine, GABA, glutamate, noradrenaline, and serotonin.[3] Neuropharmacological studies of the histaminergic system have shown the potential for H_3 antagonists as therapeutic agents for disorders involving sleep, thermoregulation, cognition, food intake, and memory formation.[4]

Since the discovery of H_3 receptors, various laboratories have developed potent and selective H_3 antagonists.[5] The first such agent to enter clinic trials was GT-2331 (Cipralisant).[6] Because researchers may need to test GT-2331 as an experimental reference agent, we report an efficient synthesis and also an important finding suggesting that the absolute configuration assigned to the compound in the literature[7] be reconsidered (Figure 1). The reported preparation for GT-2331 is shown in Scheme 1. The synthesis used chiral column chromatography to resolve the enantiomers of intermediate **3**, of which the (1*R*,2*R*) enantiomer was then converted to GT-2331 in several steps. Recently, a kilogram-scale fractional crystallization chiral separation utilizing chiral α-methylbenzylamine has been described to prepare intermediate **4**.[8]

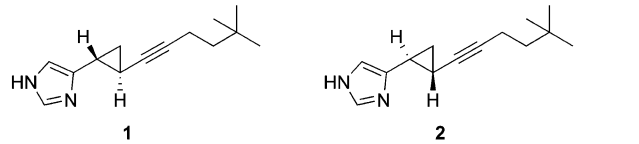

FIGURE 1. Structures reported for GT-2331 and its enantiomer.

We encountered several problems with key steps of the reported synthetic route describing the synthesis of GT-2331 (Scheme 1). Several commercially available chiral columns were tested, yet in our hands, none gave sufficient separation of the enantiomers of the *n*-butyl ester **3** to be practical for the preparation of multigram quantities targeted. Also, despite several trials, the alkylation of acetylene **5** with 3,3-dimethylbutyl iodide gave less than a 10% yield, due to the propensity of the acetylenyl anion to induce elimination of HI from the alkyl iodide and generate 3,3-dimethylbut-1-ene. For these reasons, an alternative synthesis of GT-2331 was sought.

We began this approach by attempting to resolve the acid **7**[9] (Scheme 2), using the Oppolzer sultam as a chiral auxiliary to form diastereomers (**6a** + **6b**), which could be separated by methods other than chiral chromatography. The camphorsultam diastereomers **6a** and **6b** have been reported to be separable with silica gel chromatography.[10] We were gratified to confirm that **6a** and **6b** could be separated by flash chromatography on

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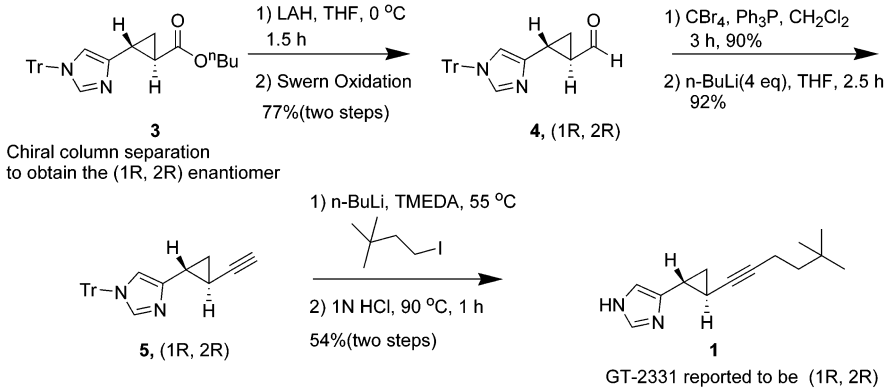
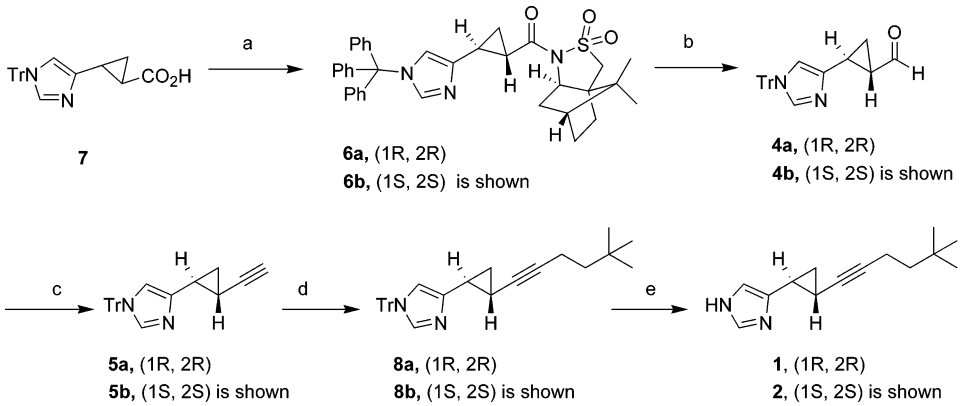
SCHEME 1. Literature Route to GT-2331



SCHEME 2. Revised Synthesis of Enantiomers of 4-[2-(5,5-Dimethylhex-1-ynyl)cyclopropyl]-1*H*-imidazole[a]



[a] Reagents and conditions: (a) (1*S*)-(−)-2,10-camphorsultam, DBU/CDI, 40 °C, 46% of single diastereomer after two columns; (b) DIBALH, CH_2Cl_2, −78 °C, 3−5 h, 87%; (c) TMSC(Li)N_2, THF, −78 to 0 °C, 5 h, 74%; (d) 1.1 equiv of *n*-BuLi, 1.1 equiv of TMEDA, 1.1 equiv of HMPA, −20 °C, then, 3,3-dimethylbutyl triflate, −20 to 0 °C, 75%; (e) 2 N HCl, EtOH, 70 °C, 85%.

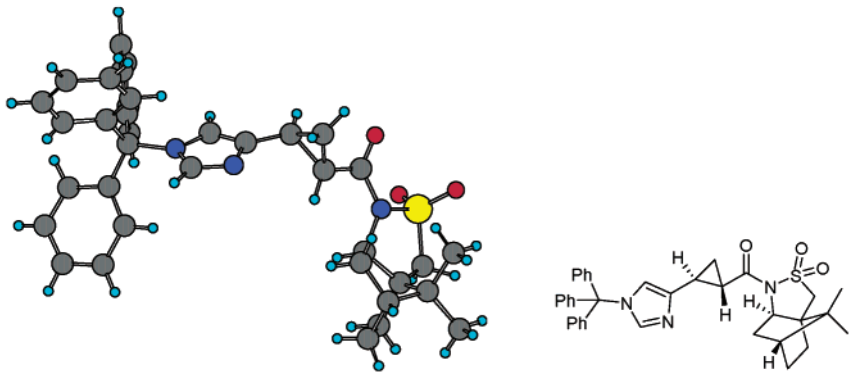


FIGURE 2. X-ray structure of compound **6b** (1*S*,2*S*).

silica gel on a multigram scale with clean separation of the diastereomers. The structure of **6b** was confirmed by X-ray crystallography to be (1*S*,2*S*) as shown in Figure 2. The separated diastereomers **6a** and **6b** of the camphorsultam were efficiently reduced with DIBALH in one step to give aldehydes **4a** and **4b**, respectively, in 88% yield. Utilizing the Colvin rearrangment,[11] aldehydes **4a** and **4b** were treated with TMSC(Li)N_2 to give acetylenes **5a** and **5b** in one step in 74% yield. We found that the yield of the coupling reaction of acetylenes **5a** and **5b** could be dramatically improved by the use of 3,3-dimethylbutyl triflate as the reactive alkylating agent, instead of 3,3-dimethylbutyl iodide, and by running the reaction in the presence of 1.1 equiv of TMEDA and 1.1 equiv of HMPA. These conditions were able to greatly reduce the amount of 3,3-dimethylbut-1-ene side product and provided yields of 75%. After removal of the trityl groups of **8a** and **8b** with HCl in ethanol, both enantio-

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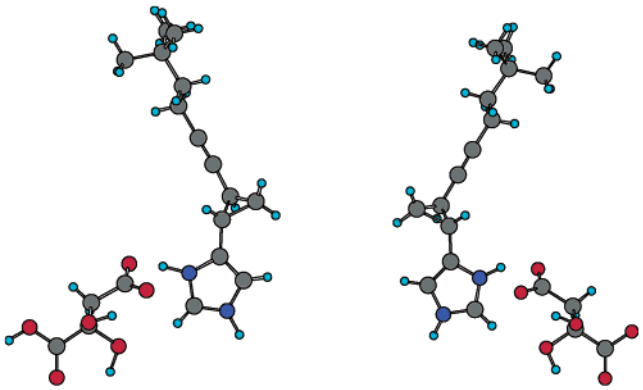


FIGURE 3. X-ray structure of the L-tartrate of compound **2** (1*S*,2*S*) and the D-tartrate of compound **1** (1*R*,2*R*).

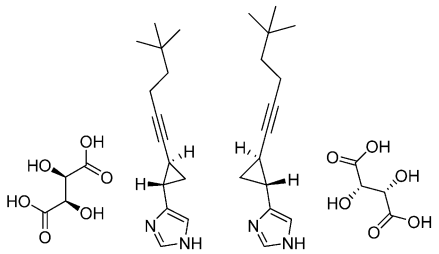
mers of the target product GT-2331 were obtained as **1** (1*R*,2*R*) and **2** (1*S*,2*S*), respectively.

The 1:1 D-tartaric acid salt of **1** (1*R*,2*R*) was prepared in methanol, as was the 1:1 L-tartaric acid salt of **2** (1*S*,2*S*). Both salts were recrystallized from ethyl acetate/methanol (1:1) to provide crystals suitable for X-ray crystallographic analysis. The ORTEP diagrams of **1** (1*R*,2*R*) and **2** (1*S*,2*S*) are shown in Figure 3.

The histamine H_3 receptor affinities were determined in rat cortical membranes.[12,13] The literature[7] reports that GT-2331 is the dextrorotatory, more potent, enantiomer of 4-[2-(5,5-dimethylhex-1-ynyl)cyclopropyl]-1*H*-imidazole and has the (1*R*,2*R*) absolute configuration of structure **1**. In contrast to that report, we found that (1*S*,2*S*) enantiomer **2** is the more potent enantiomer and its optical rotation sign is dextrorotatory. The opposite enantiomer **1** (1*R*,2*R*) was found to have levorotatory optical rotation and was 12-fold less potent than the (1*S*,2*S*) enantiomer **2** (Table 1). Interestingly, the rotation values we obtained are approximately twice as large as the reported values.

Previous studies with H_3 agonists possessing a cyclopropyl imidazole moiety lend additional support to our finding that GT-2331 possesses (*S*,*S*) stereochemistry. Two independent groups observed that the (*S*,*S*) enantiomer of 1-(1*H*-imidazole-4-yl)-2-aminopropane was more potent in binding to the H_3 receptor than the (*R*,*R*) enantiomer,[14] which is in contrast to the work of Khan et al.[10]

TABLE 1. Radioligand Binding and Optical Rotation for Enantiomers 1 and 2



2, (1S, 2S) **1**, (1R, 2R)

	compd and absolute configuration	$[\alpha]^{20}_D$ (*c*, MeOH)	rat H_3 binding affinity (nM)
lit.[7] data	**1** (1*R*,2*R*)	+140 (0.5)	0.12
	2 (1*S*,2*S*)	−131 (0.83)	5.3
data from this report	**1** (1*R*,2*R*)	−247 (0.52)	3.2[a]
	2 (1*S*,2*S*)	+277 (0.5)	0.26[a]

[a] Average of >12 experiments.

In summary, efficient syntheses of the enantiomers **1** and **2** have been demonstrated. By using the described synthetic route, we synthesized 14 g of **2** in 38% overall yield starting from **7**. A discrepancy was found between the physical properties and H_3 receptor binding data for compounds **1** and **2**, compared to the values reported in the literature. For these reasons, we suggest a reconsideration of the literature reported assignment of the absolute configuration of these compounds. In our work, we find that the more potent enantiomer of 4-[2-(5,5-dimethylhex-1-ynyl)cyclopropyl]-1*H*-imidazole is the (1*S*,2*S*) enantiomer **2**.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR spectra for all the compounds. X-ray crystallographic data for compounds **6b**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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