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DIASTEREOSELECTIVE SYNTHESIS OF *trans*-2-(1-TRIPHENYLMETHYL-1*H*-IMIDAZOL-4-YL)CYCLOPROPANECARBOXYLIC ACIDS: KEY INTERMEDIATES FOR THE PREPARATION OF POTENT AND CHIRAL HISTAMINE H_3 RECEPTOR AGENTS

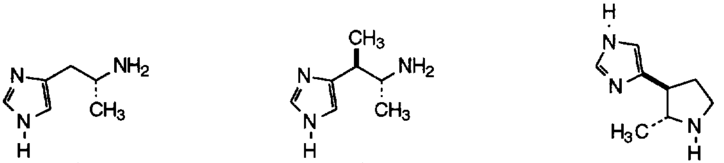
M. Amin Khan,* Stephen L. Yates, Clark E. Tedford, Kristin Kirschbaum,[a]
and James G. Phillips*

Gliatech Inc., 23420 Commerce Park Rd., Cleveland, Ohio 44122 and
[a]Department of Chemistry, University of Toledo, Toledo Ohio 43606.

Abstract: Procedures for the preparation of both enantiomers of *trans*-2-(1-triphenylmethyl-1*H*-imidazol-4-yl)-cyclopropanecarboxylic acid are described. The key step in the synthesis is a 3:1 diastereoselective cyclopropanation of (5*R*)-*trans*-4-aza-10,10-dimethyl-3-thia-4-(3-(1-triphenylmethyl-1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione using trimethylsulfoxonium ylide. These cyclopropanes are useful for the preparation of H_3 receptor agents. © 1997 Elsevier Science Ltd.

It has been demonstrated that potent and selective histamine H_3 receptor agonists possess distinct stereochemical features.[1-3] Three of the most potent agonists reported thus far are (2*R*)-(1*H*-imidazol-4-yl)prop-2-ylamine **1**, (2*R*,3*S*)-3-(1*H*-imidazol-4-yl)but-2-ylamine **2**, and Sch 49648, (2*R*,3*S*)-4-(2-methylpyrrolidin-3-yl)-1*H*-imidazole **3** (Figure 1).

Figure 1



1 **2** **3**

Preparation of a racemic mixture of *trans*-2-(1*H*-imidazol-4-yl)cyclopropylamine (**4** and **5**) has been reported by Burger et al.[4] This mixture has been disclosed as an agonist (Figure 2).[5] To date, the receptor affinity of the individual enantiomers (**4** and **5**) have not been published.

Figure 2

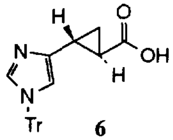
4 **5**

Selective and potent histamine H_3 receptor antagonists such as thioperamide (K_i = 4.3 nM),[2] clobenpropit (K_i = 0.18 nM),[6] iodoproxyfan (K_i = 0.3 nM),[7] GR 176737 (K_i = 7 nM),[8] and GT-2016 (K_i = 40 nM)[9] have also been recently developed. None of these reported antagonists exhibit any stereochemical presentations.

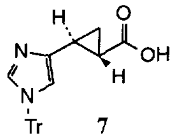
Enantiomerically pure cyclopropane ring systems are contained in numerous biologically active naturally occurring substances. In this regard, various research groups have described methods for the asymmetric synthesis of disubstituted, as well as tri- and tetrasubstituted cyclopropane derivatives.[10] These procedures are now being applied with diligence to the preparation of cyclopropane analogs of some important pharmacologically active agents.[5,10-11] However, many of these methods have limitations in scaleup, or in the production of heterocyclic containing cyclopropane compounds.

We envisioned that replacement of histamine with the cyclopropyl analogs **4** or **5** in the synthesis of new H_3 antagonists would produce conformationally restricted derivatives. It was contemplated that these analogs would also exhibit a stereo preference in their binding affinities for the H_3 receptor. Therefore, as part of our medicinal chemistry studies directed towards the preparation of new H_3 receptor ligands, we initiated synthetic investigations focused towards the stereoselective preparation of both *trans* cyclopropanes **6** and **7** (Figure 3).[12] The development of conformationally restricted H_3 antagonists were contemplated as being accessible from these intermediates. These studies would also allow us to determine the histamine H_3 receptor affinity of each enantiomer of the racemic mixture of *trans*-2-(1*H*-imidazol-4-yl)cyclopropylamine (**4** and **5**).

Figure 3



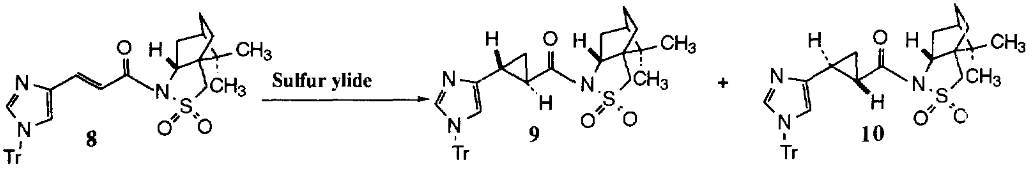
6



7

Our investigations were designed to evaluate the stereochemical outcome of adding a sulfur ylide to the chiral Michael acceptor **8** (Scheme 1). The addition of dimethyloxosulfonium methylide to (-)-menthyl cinnamates had been previously reported to proceed to give the (1*R*, 2*R*)-*trans*-2-arylcyclopropanecarboxylic acids in 3-4% excess, upon hydrolysis of the esters.[13] We anticipated that Oppolozer's camphor sultam chiral auxillary could enhance the diastereoselectivity of our analogous stepwise cyclopropanation reaction. There are now many reports of Michael addition reactions to chiral N-enoyl camphor sultam derivatives proceeding in high yield, and with good to excellent face discrimination.[14] Furthermore, there is ample precedent that suggests that these cyclopropyl-sultam derivatives could be converted to the desired carboxylic acid intermediates **6** and **7**.

Scheme 1



The chiral Michael açceptor **8** was prepared as shown in scheme 2. Urocanic acid was treated in dry DMF with one equiv of 1,1'-carbonyldiimidazole at rt followed by the addition of 1.5 equiv of *(1R)-(+)-2,10*-camphorsultam and 1 equiv of DBU. The N-acylation of the (1*R*)-(+)-2,10-camphorsultam proceeds in high yields (96%) to provide the acryloyl derivative **11**. The ease and efficiency of this conversion is noteworthy in regard to the recent methodology reported by Ho and Mathre[15], as well as Thom and Kocienski[16] for the preparation of N-acryloyloxazolidinones and sultams. (5*R*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-(3-(1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione **11** is trityl protected effectively in chloroform in the presence of triethylamine to give **8** in 97% yield.

The cyclopropanation of sultam **8** with trimethylsulfoxonium iodide proceeded in DMSO:THF (1:1) to give on the average of three runs a 3:1 mixture of (1*S*,2*S*)-cyclopropane-sultam **10** and (1*R*,2*R*)-cyclopropane-sultam **9**, respectively (see scheme 1).[17] The conversion of N-acryloyl derivative **8** to the diastereomeric mixture of cyclopropanes **9** and **10** proceeded in 80% isolated chemical yield. The mixture of cyclopropanes was separated by flash chromatography using ethyl acetate:hexanes (1:1). The major diastereoisomer **10** was recrystallized from warm ethanol to provide a suitable sample for X-ray crystallographic analysis. An ORTEP diagram of **10** is shown in figure 4. Cyclopropanation reactions using the the (1*S*)-(+)-2,10-camphorsultam chiral auxillary proceeded in similar fashion.

Scheme 2

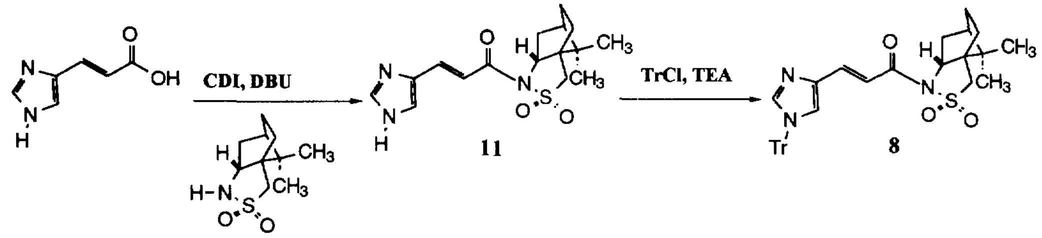
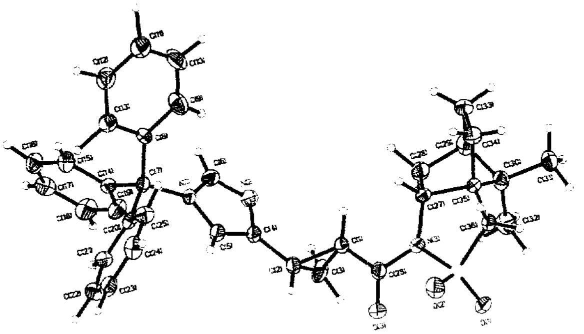


Figure 4



Ortep diagram of 10

Treatment of the major cyclopropane diastereoisomer **10** with LiOH in THF:H_2O at rt for 24 h gave (1*S*,2*S*)-*trans*-2-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropanecarboxylic acid **7** in greater than 90% yield. Similarly, **9** provided (1*R*,2*R*)-*trans*-2-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropanecarboxylic acid **6**.[18]

Each cyclopropanecarboxylic acid was converted individually to the desired amine by modifications[19] of the procedures previously outlined by Burger et al.[4] Thus, cyclopropanecarboxylic acid **7** was converted to (1*S*, 2*S*)-*trans*-2-(*1H*-imidazol-4-yl)cyclopropylamine **5**, and **6** gave (1*R*, 2*R*)-*trans*-2-(1*H*-imidazol-4-yl)cyclopropylamine **4** (see figure 2). The histamine H_3 receptor affinity (K_i) for cyclopropylamine **4** and cyclopropylamine **5** were determined according to the methods of Tedford et al.[9] and were 3.5 ± 0.5 nM and 23 ± 1 nM, respectively.[20]

Summary: Our preliminary studies demonstrate that Oppolozer's sultam chiral auxillary is effective for inducing useful diastereoselectivity in stepwise sulfur ylide cyclopropanation reactions with an acyclic substrate. Efforts are continuing to optimize the diastereoselectivity of these cyclopropanation reactions. This methodology provides chiral 2-(4-imidazolyl)cyclopropyl derivatives that are useful for preparing conformationally restricted novel histamine H_3 receptor agents.[12] X-ray crystallographic analysis of the cyclopropyl-sultam intermediate **10** identifies the absolute configuration of the cyclopropane ring. Finally, the (*R*,*R*)-cyclopropylamine derivative **4** has been shown to have an order of magnitude stronger binding affinity for the H_3 receptor in comparison to its (*S*,*S*) analog **5**.

Acknowledgements: We would like to thank Professor David R. Williams for suggesting that we try Oppolozer's chiral sultam auxillary for these sulfur ylide cyclopropanations. We are deeply grateful to Professors Stephen Hanessian and Henry Rapoport for an educational class in cyclopropane ring representation.

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17. The ratio of diastereoisomers **9** and **10** was determined by HPLC analysis. Using a chiralcel OD column, Regis Technologies serial # 0112201, and an eluent of 95:5:0.1 hexanes:isopropyl alcohol:DEA, flow rate 1 mL/ min, **9** had a retention time of 29.46 min, whereas **10** had a retention time of 33.57 min.
18. The optical purities of the carboxylic acids **6** and **7**, prepared by LiOH hydrolysis of cyclopropyl-sultams **9** and **10**, respectively, were 96% and 97%, respectively, and were determined by conversion of the acids to their *n*-butyl esters. The enantiomers (1*R*,2*R*)-*trans*-butyl 2-[1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropanecarboxylate **12** and (1*S*,2*S*)-*trans*-butyl 2-[1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropanecarboxylate **13** could be separated on a multigram scale using chiral column technology. Using a chiralcel OD column, Regis Technologies serial # 0112201, and an eluent of 90:10 hexanes:isopropyl alcohol, flow rate 1 mL/ min, **12** had a retention time of 5.787 min, whereas **13** had a retention time of 7.815 min. These esters **12** and **13** were independently converted to carboxylic acids **6** and **7**, respectively.
19. The amines **4** and **5** were obtained from the trityl protected acids **6** and **7**, respectively, using the following modifications: Curtius rearrangement in the presence of benzyl alcohol (instead of ethanol) to give the corresponding benzyl carbamates; deprotection via catalytic hydrogenation using 10% Pd(C), (H_2, 1 atm, rt, in methanol); and trityl deprotection using 2N HCl (90 °C, 30 min).
20. The ^{1}H NMR (300 MHz) and mass spectral data for **4** and **5** were consistent with data reported in 4.

Selected experimental and analytical data:

(5*R*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-(3-(1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione 11. To a suspension of urocanic acid (1.38 g, 10.0 mmol) in anhydrous dimethylformamide (20 mL) at rt under nitrogen was added 1,1'-carbonyldimidazole (1.62 g, 10.0 mmol). The reaction mixture was stirred for 1 h at 40 °C, and then *(1R)-(+)*-2,10-camphorsultam (3.22 g, 15.0 mmol) and DBU (1.49 mL, 10.0 mmol) were added. The reaction mixture was stirred at 40 °C for 6 h, cooled to rt, and then partitioned between ethyl acetate (150 mL) and 5% hydrochloric acid (50 mL). The organic layer was separated, washed with water (50 mL), followed by saturated sodium bicarbonate solution (75 mL), and then dried over anhydrous magnesium sulfate. The organic solvents were removed by rotary evaporation, and the crude product purified by flash column chromatography. Elution with ethyl acetate:hexanes (20:80) gave 3.28 g of a white solid (97%): mp 206 - 208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.68 (d, J = 15.3 Hz, 1H), 7.38 (s, 1H), 7.05 (d, J = 15.3 Hz, 1H), 4.40 (br s, 1H), 3.96 (m, 1H), 3.48 (AB q, J = 13.8 Hz, 2H), 2.13 (m, 2H), 1.89 (m, 3H), 1.40 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); DCIMS obsd.: 336 $(M+1)^+$; Anal. calc for $C_{16}H_{21}N_3O_3S$: C, 57.29; H, 6.30; N, 12.52. Found: C, 56.93; H, 6.37; N, 12.36.

(5*R*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-(3-(1-triphenylmethyl-1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione 8. To a chloroform (80 mL) solution of (5*R*)-*trans*-4-aza-10,10-dimethyl-3-thia-4-(3-(1H-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione **11** (3.35 g, 10.0 mmol) and triethylamine (1.53 mL, 11.0 mmol) at rt was added portionwise triphenylmethyl chloride (3.34 g, 12.0 mmol). The solution was stirred at rt for 12 h, and then washed with 2 x 200 mL of water. The chloroform layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The product was precipitated with ethyl acetate:hexanes (20:80) providing 5.43 g (96%) of a white solid, mp 272 - 275 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 14.9 Hz, 1H), 7.44 (s, 1H), 7.33 (m, 9H), 7.18 (d, J = 14.9 Hz, 1H), 7.10 (m, 6H), 7.06 (s, 1H), 3.95 (m, 1H), 3.44 (AB q, J = 13.7 Hz, 2H), 2.12 (m, 2H), 1.85 (m, 3H), 1.36 (m, 2H), 1.16 (s, 3H), 0.94 (s, 3H); DCIMS obsd.: 578 $(M-1)^+$; Anal. calc for $C_{35}H_{35}N_3O_3S \cdot 1.5\ H_2O$: C, 69.51; H, 6.33; N, 6.94. Found: C, 69.36; H, 5.84; N, 6.72; $[\alpha]_D^{RT}$ -57° (c 0.43, $CHCl_3$)

(1*S*,2*S*,5*R*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-((2-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropyl)carbonyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione 10. To mixture of trimethylsulfoxonium iodide (2.20 g, 10.0 mmol) and sodium hydride (0.244 g, 10.2 mmol, 60% dispersion in mineral oil) under nitrogen atomsphere at rt was added dropwise with stirring 25 mL of anhydrous dimethylsulfoxide. After addition of the dimethylsulfoxide was complete, the mixture was stirred for 45 min, and then a solution of **8** (5.31 g, 9.2 mmol) in THF:DMSO (1:1, 80 mL) was added dropwise over 30 min. The solution was stirred at rt for 1 h, and then at 60 °C for 6 h. The reaction was monitored by thin-layer chromatography. After completion, the reaction was cooled to rt and poured onto 100 mL of cold 2 N hydrochloric acid. This mixture was extracted with 150 mL of ethyl acetate and the organic layer was sequentially washed with 100 mL of saturated sodium bicarbonate solution, 100 mL of water, and then dried over anhydrous magnesium sulfate. The filtrate was concentrated in vacuo. The ratio of cyclopropane sultam diastereoisomers produced in the reaction was determined by HPLC analysis of the crude product mixture. HPLC analysis of three separate runs revealed that the major:minor diastereoisomer ratio was 75:25. The mixture of diastereoisomers was separated and purified by flash column chromatography using ethyl acetate:hexanes (1:1) as eluent to give 4.25 g of the major isomer and 1.06 g of the minor isomer (80%). The major isomer was recrystallized from warm ethanol to obtain a sample for X-ray analysis. Major isomer **10**: mp 233 - 235 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 10H), 7.10 (m, 6H), 6.62 (s, 1H), 3.87 (m, 1H), 3.44 (AB q, J = 13.8 Hz, 2H), 2.62 (m, 1H), 2.55 (m, 1H), 2.09 (m, 2H), 1.85 (m, 3H), 1.54(m, 1H), 1.49 (m, 1H), 1.34 (m, 2H), 1.16 (s, 3H), 0.94 (s, 3H); DCIMS obsd.: 592 $(M+1)^+$; Anal. calc. for $C_{36}H_{37}N_3O_3S \cdot 1\ EtOH$: C, 71.66; H, 6.64; N, 6.59. Found: C, 71.42; H, 6.37; N, 6.71; $[\alpha]_D^{RT}$ -58° (c 0.52, $CHCl_3$). Minor isomer, **(1*R*,2*R*,5*R*)-*trans*-9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 9H), 7.17 (s, 1H), 7.09 (m, 6H), 6.74 (s, 1H), 3.84 (m, 1H), 3.70 (AB q, J = 13.8 Hz, 2H), 2.54 (m, 1H), 2.40 (m, 1H), 2.03 (m, 2H), 1.85 (m, 3H), 1.71(m, 1H), 1.40 - 1.26 (m, 3H), 1.17 (s, 3H), 0.95 (s, 3H).

X-ray crystal data for 10: $C_{36}H_{37}N_3O_3S$, monoclinic, space group $P2_1$, a = 8.8827 (9), b = 10.5599 (10), c = 16.1375 (15) A, β = 92.942 (2)°, V = 1511.7 (3) A^3, Z = 2, D_c = 1.300, λ = 0.71073 A, F(000) = 628. 8200 reflections (5637 unique) were collected at 293 (1) K on a plate-shaped crystal with approximate dimensions of 0.50 x 0.10 x 0.02 mm using a Siemens Smart Platform diffractometer. Data collection was performed using three different ϕ settings and 0.3° increment ω scans, $2\Theta < 52.00°$. Corrections for absorption and decay were applied using SADABS (Sheldrick, G. M., University of Gottingen, 1996). Solution by direct methods

(SHELXL-86; Sheldrick, G. M., Acta Cryst. **1990**, A46, 467) and refinement by full matrix least squares on F^2 using all 5637 unique data (SHELXL-93; Sheldrick, G. M., University of Gottingen, 1993). The final refinements included anisotropic thermal parameters for all non-hydrogen atoms, isotropic thermal parameters for all hydrogen atoms and converged to $wR_2 = 0.1293$ (F^2, all data) and $R_1 = 0.0586$ (F, 2852 reflections with $I > 2\ \sigma(I)$). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

(1*S*,2*S*)-*trans*-2-(1-Triphenylmethyl-1*H*-imidazol-4-yl)cyclopropanecarboxylic acid 7. To 75 mL of a THF:H_2O (2:1) solution of sultam **10** (5.32 g, 9.0 mmol) at rt. was added 1.51 g (36.0 mmol) of $LiOH \cdot H_2O$. When the reaction was complete (TLC analysis), water (20 mL) was added, and the reaction mixture was extracted with ethyl acetate (50 mL). The aqueous phase was acidified to pH 6 with 0.5 N hydrochloric acid. The precipitate obtained was filtered off and air dried to give 3.5 g of white solid (90 %), mp 218 - 223 °C dec. ^1H NMR (300 MHz, CD_3OD) δ 7.38 (m, 10H), 7.15 (m, 6H), 6.79 (s, 1H), 2.35 (m, 1H), 1.83 (m, 1H) 1.40 (m, 1H), 1.30 (m, 1H); DCIMS obsd 395 $(M+1)^+$; $[\alpha]_D^{RT}$ -16° (c 0.63, $CHCl_3$).

***(1R,2R)-trans*-2-(1-Triphenylmethyl-1H-imidazol-4-yl)cyclopropanecarboxylic acid 6**. $[\alpha]_D^{RT}$ +19° (c 0.76, $CHCl_3$).

(5*S*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-(3-(1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione: mp 212 - 214 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.68 (d, *J* = 15.3 Hz, 1H), 7.34 (s, 1H) 7.02 (d, *J* = 15.3 Hz, 1H), 3.96 (m, 1H), 3.47 (AB q, *J* = 13.8 Hz, 2H), 3.33 (br s, 1H), 2.13 (m, 2H), 1.89 (m 3H), 1.40 (m, 2H), 1.16 (s, 3H), 0.96 (s, 3H); DCIMS obsd.: 336 $(M+1)^+$; Anal. calc for $C_{16}H_{21}N_3O_3S$: C, 57.29 H, 6.30; N, 12.52. Found: C, 56.96; H, 6.53; N, 12.86.

(5*S*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-(3-(1-triphenylmethyl-1*H*-imidazol-4-yl)prop-2-enoyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione: white solid, mp 268 - 270 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15.0 Hz, 1H), 7.51 (s, 1H), 7.33 (m, 10H), 7.18 (s, 1H) 7.10 (m, 6H), 3.96 (m, 1H), 3.45 (AB q, *J* = 13.8 Hz, 2H), 2.14 (m, 2H), 1.86 (m, 3H), 1.38 (m, 2H), 1.16 (s, 3H), 0.94 (s, 3H); DCIMS obsd.: 578 $(M+1)^+$; Anal. calc. for $C_{35}H_{35}N_3O_3S \cdot 0.5\ H_2O$: C71.65; H, 6.17; N, 7.16. Found: C, 71.43; H, 5.98; N, 7.02; $[\alpha]_D^{RT}$ +60° (c 2.1, $CHCl_3$).

(1*R*,2*R*,5*S*)-*trans*-4-Aza-10,10-dimethyl-3-thia-4-((2-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropyl)carbonyl)tricyclo[5.2.1.0<1,5>]decane-3,3-dione: Major isomer from reaction with (1*S*)-(+)-2,10-camphorsultam chiral auxillary, mp 233 - 235°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 7.10 (m, 6H), 6.62 (s, 1H), 3.87 (m, 1H), 3.43 (AB q, *J* = 13.8 Hz, 2H), 2.60 (m, 2H), 2.11 (m, 2H), 1.86 (m, 3H), 1.51 (m, 1H), 1.48 (m, 1H), 1.34 (m, 2H), 1.17 (s, 3H), 0.94 (s, 3H); DCIMS obsd.: 592 $(M+1)^+$; $[\alpha]_D^{RT}$ +61° (c 0.2, $CHCl_3$). Minor isomer: **(1*S*,2*S*,5*S*)-*trans***. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 10H), 7.10 (m, 6H), 6.75 (s, 1H), 3.84 (m, 1H), 3.43 (AB q, *J* = 13.8 Hz, 2H), 2.56 (m, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 1.84 (m, 2H), 1.74 (m, 2H), 1.51 (m, 1H), 1.48 (m, 1H), 1.33 (m, 2H), 1.17 (s, 3H), 0.95 (s, 3H).

Histamine H_3 Receptor Binding Assay: Histamine H_3 receptor affinity was determined in rat cortical membranes using the H_3 selective agonist ligand, $[^3H]$-N-α-methylhistamine (78.9 Ci/mmole, DuPont NEN Research Products, Boston, MA) according to 9. The binding assay was carried out in polypropylene tubes in a total volume of 0.4 mL of 50 mM Na^+ Phosphate buffer (pH 7.4), containing 150-200 mg of tissue protein and 0.8-1.2 nM $[^3H]$-Na-methylhistamine. Nonspecific binding (NSB) was accounted for by the inclusion of thioperamide (10 μmol). The samples were incubated for 40 min at 25 °C. Samples were filtered through glass fiber strips, pre-washed with 0.3% polyethyleneimine, using a Brandell cell harvester. The filters were rapidly washed three times with 4 ml of 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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