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Synthesis of Imifuramine and Its Stereoisomers Exhibiting Histamine H_3-Agonistic Activity

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Abstract: *The four possible stereoisomers of a novel imidazole C-nucleoside derivative were synthesized by the efficient use of a PhSe group. Among them, (+)-4(5)-[(2R,5R)-5-(aminomethyl)tetrahydrofuran-2-yl]imidazole (imifuramine) was indicated as a novel type of histamine H_3-agonist by a brain microdialysis method.*

The histamine H_3 receptors[1] exist on the histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.[2] This type of receptor can be also found in many peripheral tissues. (R)-α-Methylhistamine, imetit and immepip, which are potent and selective H_3-agonists, have been well used as pharmacological tools.[3] H_3-Agonists are regarded as a target for development of new therapeutics for bronchial asthma.[3,4] On the other hand, theoretical calculations of some H_3-agonists have predicted the importance of an intramolecular hydrogen-bonding between the cationic primary amine and the N atom of the imidazole.[5]

We recently reported the β-stereoselective synthesis of C-4 linked imidazole nucleosides.[6] On the basis of these studies, we envisioned that, while the *cis*-isomer (**1**) could adopt a folded conformation[7] through intramolecular hydrogen-bonding, the *trans*-isomer (**2**) would form the extended one (Fig. 1). In this paper, we report the synthesis of four isomers of novel imidazole C-nucleoside derivatives **1**,**2** using a synthetic method characterized by use of a PhSe group for the formation of the tetrahydrofuran ring. It is of particular interest to find from the preliminary results using an *in vivo* brain microdialysis[8] that, among them, only (+)-**2** (imifuramine) exhibited histamine H_3-agonistic activity .

Phenylselenation[9] of γ-butyrolactone (-)-**3**[10] provided α-and β-selenolactones **4**α and **4**β, both of which were used as substrates to prepare key intermediates **9** and **10** (Scheme 1) . Reduction of the major isomer **4**α with DIBAL-H followed by an addition of 5-lithioimidazole **6**[6] to the resulting lactol **5**α gave a diol **7***R* (73%)

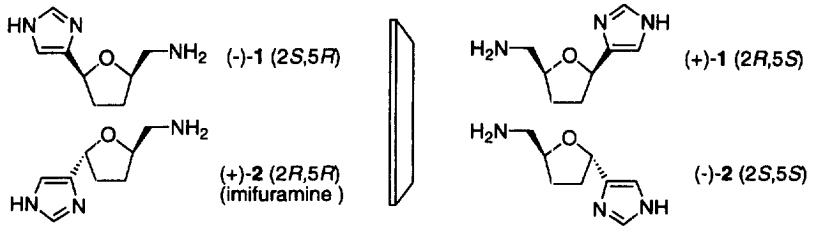
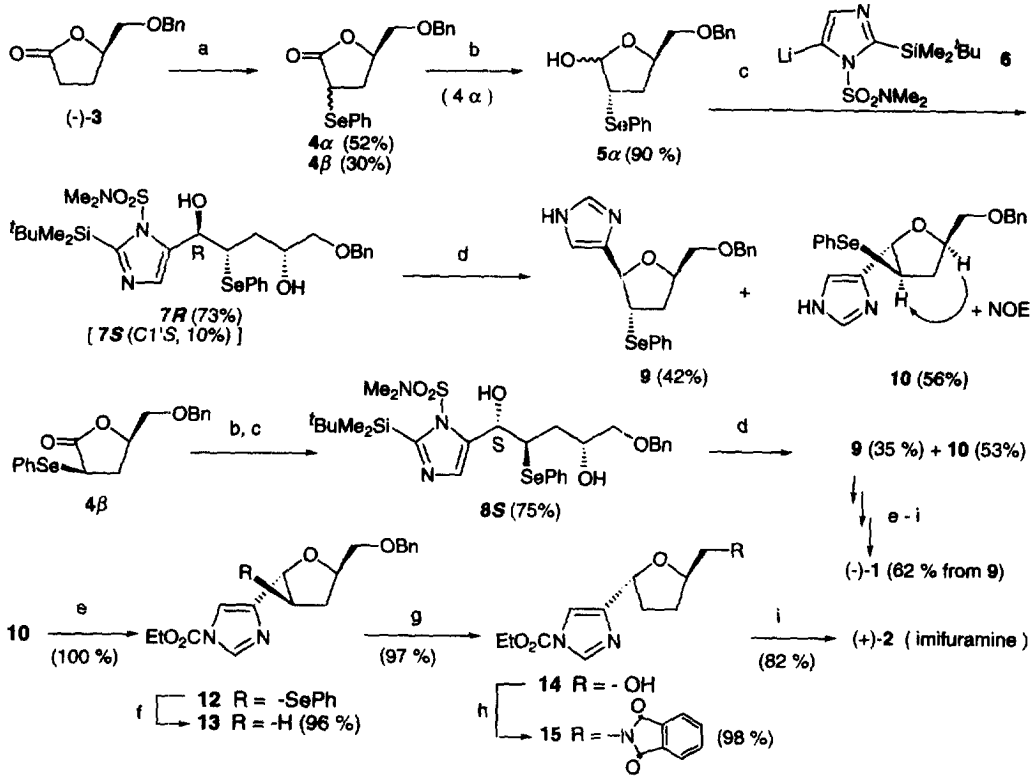


Fig. 1

PII: S0040-4039(99)00202-6



Reagents and conditions: a) (i) LHMDS, TMSCl; (ii) PhSeBr; b) DIBAL ; c) (i) **6** (3.3 eq.), THF, -70℃ to -50℃ then r.t.; d) (i) aq. 1.5N HCl-THF (1:1), reflux, 1h; (ii) benzene, reflux, 1h, Dean- Stark water separator; e) $ClCO_2Et$, Py; f) Et_3B, Bu_3SnH; g) $Pd(OH)_2$-C, cyclohexene; h) 4-$Me_2NC_6H_4PPh_2$, Phthalimide, DIAD; i) hydrazine hydrate

Scheme 1

with a C1'*R* configuration, together with C1' epimer **7*S*** (10%). In ^{1}H-NMR, their C1' configurations were assigned by a small $J_{1',2'}$ coupling constant (2.7 Hz) of minor isomer **7*S*** compared to that of **7*R*** (5.9 Hz) having a 1', 2'-antiparallel orientation.[6] The *anti*-selectivity for **7*R*** may be accounted for by a chelation-cyclic model as shown in Fig. 2. Deprotection of **7*R*** under reflux in HCl-THF afforded easily separable β- and α-nucleosides **9**[11] (22%) and **10**[11] (38%) together with *trans*-olefin **11**[11] (26%).[12] If water in the reaction mixture was removed as an azeotrope with benzene, the yields of **9** and **10** were improved to 42% and 56% from **7*R***, respectively.[13] In ^{1}H-NMR, the two C5' protons (δ 3.58, 3.80) of β-anomer **9** were individually observed and shifted downfield compared to those (δ 3.46) of α-anomer **10**. These results presumably reflect the rotational hindrance of the C4'-C5' bond and deshielding effects due to imidazole. The correctness of the assignment was indicated by the positive NOE between C2' and C4'-protons in **10**. The formation of **9** and **10** can be reasonably rationalized as shown in Fig. 3. The reaction of **7*R*** with HCl generates olefin **11** by a *trans*-stereospecific elimination of PhSeCl. Recombination[14] of **11** and PhSeCl gives β- and α-anomers **9**, **10** *via* a phenylselenium-induced cyclization at both sides of the double bond of **11**. Similar treatment of **8*S***[15] derived from minor lactone **4β**, provided **9** (35%) and **10** (53%). To date, this synthetic approach for the preparation of C-nucleosides using a combination of the elimination of PhSeCl and selenocyclization has not been reported.[16]

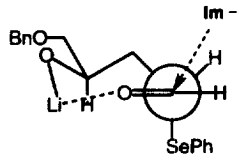
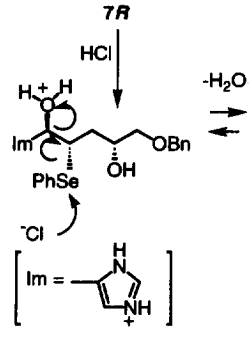


Fig. 2



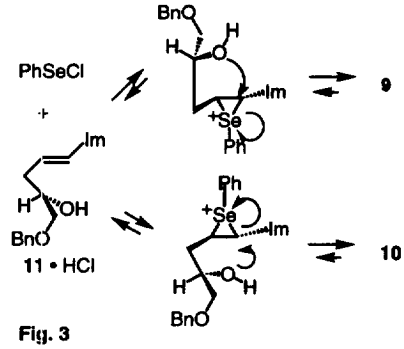


Fig. 3

Ethoxycarbonylation[7] of the α–anomer **10** gave **12** which was then converted into **13** by free radical deselenylation.[17] Debenzylation of **13** and subsequent phthaloylimination afforded 5'-substituted phthalimide **15**. Double deprotection of **15** with hydrazine hydrate yielded (+)-**2**, imifuramine.[18] Alternatively, synthesis of (-)-**1**[18] was attained in 62% overall yield from β-anomer **9** by the synthetic procedures previously described. The structures of **1** and **2** were determined by ^{1}H-NMR in which the upfield chemical shift of 4'-H (δ 4.04) for **1** was observed in comparison with that (δ 4.17) for **2**.[19] Their configuration counterparts (+)-**1** and (-)-**2** were also synthesized starting from (+)-**3** by the same methodology.

Using an *in vivo* microdialysis method[8], we examined whether the four synthesized stereoisomers had any effect on the release of histamine in the brain of rats. Among them, only imifuramine exhibited H_3-agonistic activity. The administration of 10 μM of imifuramine to the perfusion fluid decreased histamine release to about 30% of the basal release. Further, the co-infusion of the H_3-antagonist, clobenpropit[3] (10 μM), fully antagonized this effect and increased histamine release to about 160% of the basal levels (Fig. 4). The activity of imifuramine measured by the microdialysis was approximately equal to that of immepip.[20] These facts support the H_3 agonistic activity of imifuramine. The other three isomers had no effect on the histamine release at 10 μM concentration.

The synthesis and biological evaluation of related imidazol C-nucleoside derivatives are in progress in our laboratories.

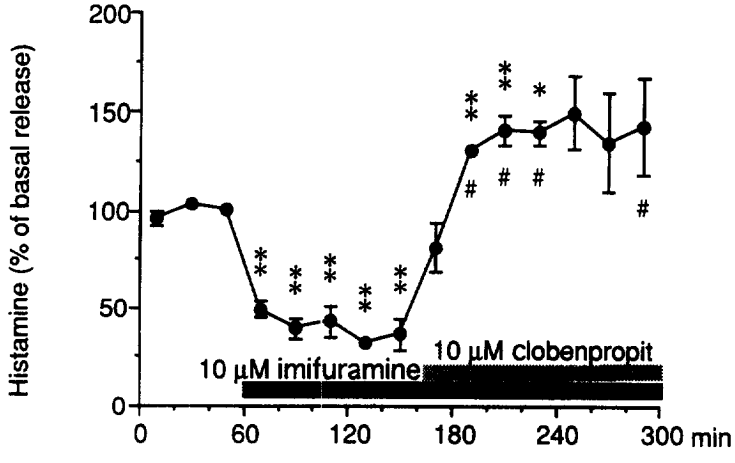


Fig. 4 Effects of imifuramine and clobenpropit on the release of histamine from the anterior hypothalamic area of rats. The average value in the first three samples was taken as the basal release. Results are expressed as percentages of the basal release and are means (±) S.E.M. for four rats. The duration of imifuramine (solid) and clobenpropit (shaded) infusion is indicated by horizontal bars.

* $p<0.05$, ** $p<0.01$ significantly different from the basal release, and # $p<0.05$ significantly different from the preceding fraction of the administration of clobenpropit.

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11. **9**: oil; ORD (c 1.03, EtOH)[α]^{23}(nm): +33.2° (589), +85.9° (400), +240.0° (308). ^{1}H-NMR ($CDCl_3$): δ 2.05 (ddd, 1H, J= 4.8 Hz, 6.9 Hz, $J_{3'a,3'b}$ = 13.6 Hz, 3'-Ha), 2.47 (dt, 1H, J = 7.7 Hz, $J_{3'a,3'b}$ = 13.6 Hz, 3'-Hb), 3.58 (dd, 1H, $J_{4',5'a}$ = 3.5 Hz, $J_{5'a,5'b}$ = 10.4 Hz, 5'-Ha), 3.80 (m, 2H, 2'-H and 5'-Hb), 4.40 (m, 1H, 4'-H), 4.52 (s, 2H, C$\underline{H}_2$Ph), 4.98 (d, 1H, $J_{1',2'}$ = 4.8 Hz, 1'-H), 6.70 (s, 1H, 5-H), 7.00 (s, 1H, 2-H), 7.13-7.45 (m, 10H, Ph×2). **10**: needles: mp 117.5-118.5℃; ORD (c 1.52, EtOH)[α]^{22}(nm): -21.1° (589), -58.1° (400), -170.3° (308). ^{1}H-NMR ($CDCl_3$): δ 1.90 (ddd, 1H, $J_{2',3'a}$ = 9.8 Hz, $J_{3'a,4'}$ = 8.5 Hz, $J_{3'a,3'b}$ = 12.7 Hz, 3'-Ha), 2.49 (quint, 1H, J = 6.8 Hz, $J_{3'a,3'b}$ = 12.7 Hz, 3'-Hb), 3.46 (d, 2H, $J_{4',5'}$ = 4.9 Hz, 5'-H), 3.91 (dt, 1H, J = 8.1 Hz, $J_{2',3'}$ = 9.8 Hz, 2'-H), 4.33 (m, 1H, 4'-H), 4.49 (s, 2H, C$\underline{H}_2$Ph), 4.84 (d, 1H, $J_{1',2'}$ = 8.1Hz, 1'-H), 6.70 (s, 1H, 5-H), 7.06-7.40 (m, 11H, Ph ×2 and 2-H). **11**: oil; ^{1}H-NMR ($CDCl_3$): δ 2.33 (t, 2H, J = 6.8 Hz, 3'-H), 3.37 (dd, 1H, $J_{4',5'a}$ = 7.5 Hz, $J_{5'a,5'b}$ = 9.6 Hz, 5'-Ha), 3.50 (dd, 1H, $J_{4',5'b}$ = 3.4 Hz, $J_{5'a,5'b}$ = 9.6 Hz, 5'-Hb), 3.88 (m, 1H, 4'-H), 4.50 (s, 2H, C$\underline{H}_2$Ph), 6.10 (dt, 1H, $J_{2',3'}$ = 7.4 Hz, $J_{1',2'}$ = 16.1 Hz, 2'-H), 6.32 (d, 1H, $J_{1',2'}$ = 16.2 Hz, 1'-H), 6.86 (s, 1H, 5-H), 7.28 (s, 5H, Ph), 7.49 (s, 1H, 2-H).
12. Cyclization of **7*S*** did not proceed under refluxing HCl-THF, but only diol having an unsaturated imidazole was obtained.
13. A solution of **7*R*** (1.32 g, 2.03 mmol) in THF (24 ml) was refluxed with 1.5*N* HCl (9 ml) for 1h, and then diluted with benzene (50ml). The resulting mixture was further refluxed to remove water for 1h as an azeotrope using a Dean-Stark water separator. The workup and purification gave **9** (0.35 g, 42%) and **10** (0.46 g, 55%).
14. It was supported by the fact that a reaction of the **11** with PhSeCl smoothly proceeded to give **9** and **10** in refluxing THF.
15. Only the **8*S*** was obtained from lactol **5**β without the formation of C-1'epimer.
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18. (+)-**2**: ORD (c 1.41, EtOH)[α]^{23}(nm): +5.7° (589), +25.5° (400), +102.1° (300). ^{1}H-NMR (CD_3OD) δ : 1.61-1.82 (m, 1H, 3'-Ha), 2.02-2.38 (m, 3H, 2'-H and 3'-Hb), 2.73 (d, 2H, J = 6.0 Hz, 5'-H), 4.17 (m, 1H, 4'-H), 5.02 (t, 1H, J= 6.5 Hz, 1'-H), 7.02 (s, 1H, 4-H), 7.64 (s, 1H, 2-H). (-)-**1**: ORD (c 0.53, EtOH)[α]^{23}(nm): -22.9° (589), -57.2° (400), -131.4° (300). ^{1}H-NMR (CD_3OD) δ : 1.68-2.35 (m, 4H, 2'-H and 3'-H), 2.75 (m, 2H, 5'-H), 4.04 (m, 1H, 4'-H), 4.93 (overlapped with H_2O signal in CD_3OD, 1'-H), 7.03 (s, 1H, 4-H), 7.65 (s, 1H, 2-H).
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