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Stereoselective Synthesis of a New Muscarinic M_3 Receptor Antagonist, J-104129

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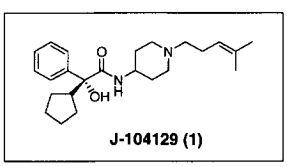
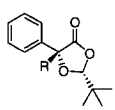
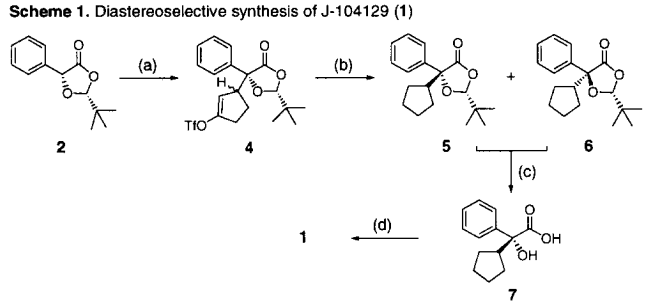
Abstract: A diastereoselective synthesis of J-104129 (**1**) was developed. A key step of this synthesis was Michael addition of enolate generated from *cis*-chiral dioxolane **2** to cyclopentenone, followed by hydrogenolysis of the resultant enol triflate **4**. A mixture of cyclopentyldioxolane (**5**, **6**) was hydrolyzed with sodium hydroxide to yield carboxylic acid **7** in 86% ee.

Anti-muscarinic agents have been used for obstructive airway diseases but their clinical use has been restricted by side effects that may be caused by non-selectiveness to receptor subtypes. One way to avoid these side effects is topical treatment with poorly absorbed non-selective agents by inhalation. Other possibilities include the development of M_3 selective antagonists with oral activity.[1] However, only a few compounds have been reported to display meaningful subtype selectivity for M_3 over M_2 receptors.[2]





Scheme 1. Diastereoselective synthesis of J-104129 (**1**)



Conditions: (a) LDA, 2-cyclopenten-1-one, THF, -78°C, then $PhN(Tf)_2$; (b) H_2, 10% Pd-C, AcONa, MeOH, 60% from **2**; (c) aq. NaOH, MeOH, 95%, 86% ee; (d) CDI, 4-amino-1-(4-methyl-3-pentenyl)piperidine 2HCl salt, i-Pr_2NEt, DMF, 72%.

In our program for developing new anti-muscarinic agents for bronchodilation that possess high selectivity for M_3 over M_2 receptors, we designed and synthesized a novel class of 4-acetamidopiperidine derivatives.[3,4] As a result, we identified J-104129 (**1**), which exhibited a *Ki* value of 4.2 nM for affinity with 120-fold selectivity for human cloned M_3 over M_2 receptors.

The optically pure acid **7**, a key intermediate of the synthesis of **1**, was reported to be obtained by repetitive

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recrystallization of the (-)-amphetamine salt of the racemic acid.[5] However, efficient synthesis of the acid **7** was desired to supply a large amount of **1**. In this paper, we describe a diastereoselective synthesis of **7** using chiral *cis*-dioxolane **2**, which led to the development of the synthetic method of **1**.

Alkylation of the enolate of **2** with reactive halides was reported to give dioxolane derivatives **3** while retaining the chirality of the starting material.[6] We applied this method to the synthesis of **7**. Although alkylation of **2** with cyclopentyl bromide was tried to introduce a cyclopentane moiety directly, the desired compound was not obtained, probably due to the bulkiness of the electrophile and the instability of the enolate at higher temperatures.[7] By contrast, Michael addition to cyclopentenone smoothly progressed. Treatment of the intermediate enolate with *N*-phenyltrifluoromethanesulfonimide gave the enol triflate **4**, which was hydrogenated with 10% Pd on carbon in the presence of sodium acetate to yield the inseparable mixture of diastereomers **5** and **6** in a ratio of 93:7 in 60% yield from **2**. The mixture was hydrolyzed with sodium hydroxide to afford the acid **7** with 86% ee. After recrystallization of its (-)-cinchonidine salt, optically pure **7** (99% ee) was obtained in 70% yield. Transformation of the acid **7** to **1** was achieved in the usual manner. X-ray crystallographic analysis of its (*R*)-mandelic acid salt as shown in Figure 1 indicates that the absolute configuration of the acid **7** is *R*.[8]

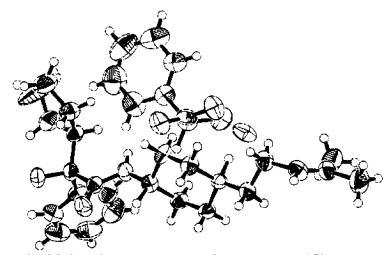

Figure 1. Molecular structure of J-104129 (*R*)-mandelic acid hydrate. The displacement ellipsoids are drawn at the 50% probability level.

In conclusion, we developed an efficient diastereoselective synthesis of **7**, which will enable us to supply a large amount of J-104129 (**1**).

References and notes

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