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Synthesis of 4-aza analog of ramelteon: a novel tricyclic 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine derivative as melatonin receptor ligand

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ABSTRACT

The 4-aza analog of ramelteon (−)-**1**, a novel tricyclic 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine derivative, was synthesized via the intramolecular inverse electron demand Diels–Alder reaction followed by fluoride-induced desilylation–cyclization.

Indeno[5,4-*b*]furan, the central core of ramelteon[1] (Fig. 1), is a novel angular tricyclic ring system that mimics the 5-methoxy indole core of melatonin.[2] Melatonin, a neurohormone secreted from the pineal gland, exerts a sleep-promoting effect through the activation of melatonin receptors (MT_1 and MT_2). Ramelteon shows more potent agonistic activity against these receptors than does the natural ligand melatonin and has been marketed for the treatment of insomnia.[3] This type of angular tricyclic ring system appears not only in the melatonin receptor ligands but also in many biologically active compounds such as serotonin (5-HT) ligands, including subtype selective ligands for $5\text{-}HT_{2c}$ receptor.[4] Therefore, this class of structure inspires the design and synthesis of its structural analogs, which could be of value for SAR studies, additional interaction for receptors, subtype selectivity, and the identification of novel biological activity. In this regard, we displaced the carbon atom at the 4-position of indeno[5,4-*b*]furan with nitrogen, and novel tricyclic cyclopenta[*d*]furo[2,3-*b*]pyridine derivative, 4-aza analog of ramelteon **1**, was synthesized as a melatonin receptor ligand (Fig. 1). A literature survey revealed that there are no reports on such unique tricyclic cyclopenta[*d*]furo[2,3-*b*]pyridines and their synthesis methods. Herein, we report an efficient procedure for the synthesis of 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine, which is converted to the 4-aza analog of ramelteon **1**.

Initially, we focused on the retrosynthetic analysis of tricyclic ketone **2**, which could be readily converted to **1** via the synthesis route reported for ramelteon[1,5] (Scheme 1). The cyclopentane ring

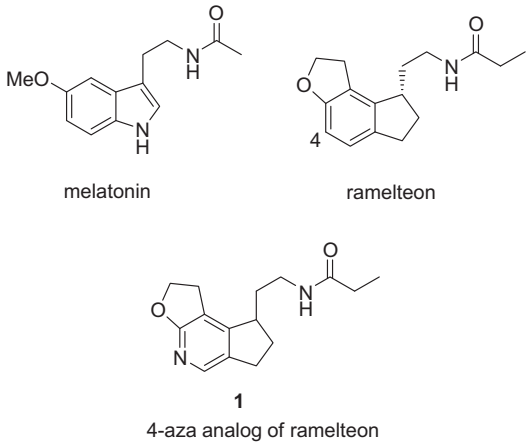

Figure 1. Chemical structures of melatonin, ramelteon, and 4-aza analog of ramelteon **1**.

of ramelteon could be constructed by Friedel–Crafts cyclization; however, the electron-deficient nature of the central pyridine ring in **2** made the use of the aforementioned reaction difficult. Hence, we attempted to synthesize the cyclopentane ring by fluoride-induced desilylation–cyclization[6] of propanal derivative **3**. 4,5-Difunctionalized 2,3-dihydrofuro[2,3-*b*]pyridine **4**, which could be obtained from pyrimidine **5** by the intramolecular inverse electron demand Diels–Alder reaction,[7] was selected as the key intermediate.

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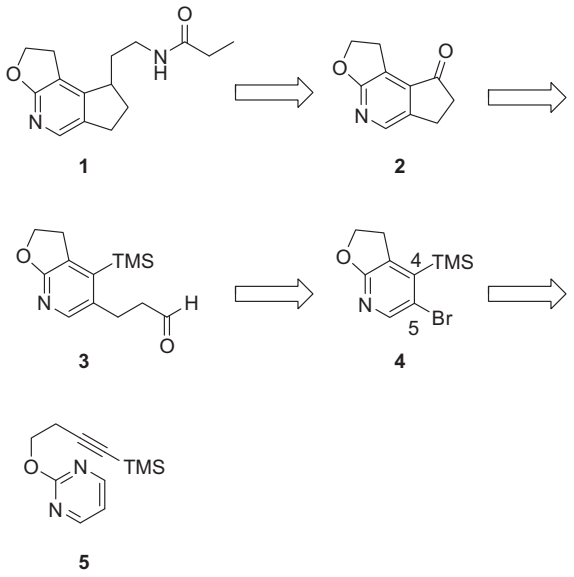
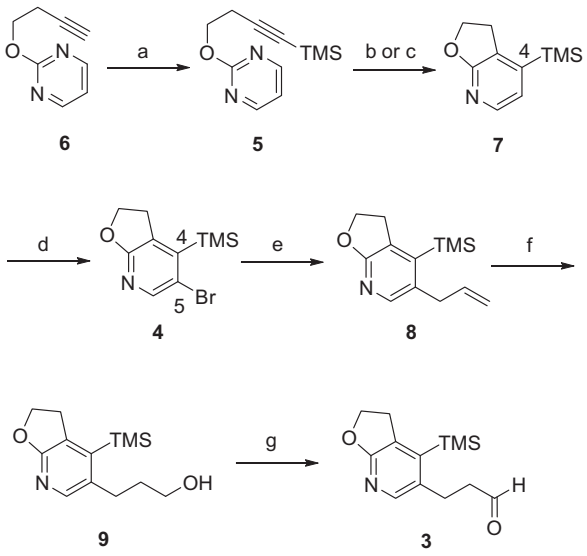


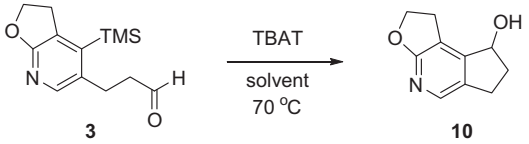
Scheme 1. Retrosynthesis of the 4-aza analog of ramelteon **1**.



Scheme 2. Synthesis of 2,3-dihydrofuro[2,3-*b*]pyridine. Reagents and conditions: (a) LDA, TMSCl, THF, −78 °C, 91%; (b) nitrobenzene, microwave heating, 220 °C, 67%; (c) nitrobenzene, 200 °C, 14%; (d) Br_2, $NaHCO_3$, CH_2Cl_2, rt, 80%; (e) allyltributyltin, $PdCl_2(PPh_3)_2$, DMF, 100 °C, 96%; (f) $BF_3{\cdot}Et_2O$, 9-BBN, 0 °C; then, *N,N,N,N*-tetramethylethlenediamine, 30% H_2O_2 aq, 2.5 M NaOH aq., rt, 66%; (g) IBX, DMSO, rt, 87%.

The synthesis of 2,3-dihydrofuro[2,3-*b*]pyridine is described in Scheme 2. For the direct access to the introduction of a substituent at the 4-position of the ring, the intramolecular inverse electron demand Diels–Alder reaction[7] of 2-(3-butynyloxy)pyrimidine was carried out. A trimethylsilyl (TMS) group was introduced at the terminal position of the known alkyne **6**[7], and the resulting tethered alkyne **5** was subjected to the heating condition following the experimental procedure described by Frissen et al.[7] When **5** was heated in nitrobenzene at 200 °C for 24 h, the desired 4-trimethylsilyl 2,3-dihydrofuro[2,3-*b*]pyridine **7** was obtained in very low yield (14%), and most of the starting material was recovered. The extremely slow reaction rate might due to steric repulsion of the TMS group on the alkyne side chain. To activate the reaction, we attempted the microwave irradiation, and microwave heating of **5** at 220 °C for 10 h afforded the target compound **7** in 67% yield (at higher temperatures, degradation of **7** was observed). Subsequent regioselective bromination at the 5-position of **7** gave the desired 4,5-difunctionalized 2,3-dihydrofuro[2,3-*b*]pyridine **4** in 80% yield. Propanal derivative **3** was synthesized by Stille coupling[8] of bromide **4** with allyltributyltin, followed by hydroboration with 9-BBN/$BF_3{\cdot}Et_2O$[6] and subsequent oxidation with 2-iodoxybenzoic acid (IBX).

Table 1
Fluoride-induced desilylation–cyclization reaction of **3**. Method A: Heating of a suspension of **3** and TBAT at 70 °C; method B: Dropwise addition of a solution of **3** to a pre-heated (70 °C) suspension of TBAT



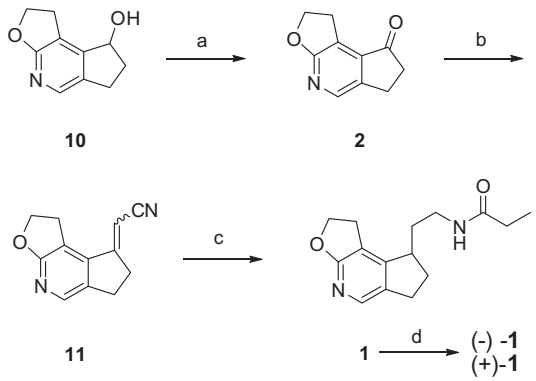
Entry	Solvent	Method	Yield (%)
1	MeCN	A	39
2	Toluene	A	Decomp.
3	DME	A	56
4	DME	B	71

Construction of the cyclopentane ring by fluoride-induced desilylation–cyclization (Table 1) was investigated. This cyclization method was reported by Beierle et al.[6] for the synthesis of louisianin C, which has a cyclopentapyridine ring as the core skeleton. As per their procedure, **3** was heated up to 70 °C with tetrabutylammonium difluorotriphenylsilicate (TBAT)[6] in acetonitrile. However, the reaction gave the desired product only in moderate yield (39%, entry 1) accompanied by a large amounts of byproducts. For the improvement of the chemical yield, we optimized the reaction solvent first. The use of toluene resulted in the decomposition of **3** (entry 2), while the use of 1,2-dimethoxyethane (DME), a polar solvent, resulted in enhanced chemical yield (56%, entry 3). Then, we fixed DME as the solvent and modified the reaction procedure to suppress the intermolecular reaction, since the byproducts were thought to be formed from the polymerization of **3**. Dropwise addition of a solution of propanal **3** in DME to a pre-heated (70 °C) suspension of TBAT in DME (method B) resulted in increased reaction yield (71%, entry 4).

After successful preparation of the novel 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine scaffold, compound **10** was then converted to the 4-aza analog of ramelteon **1** (Scheme 3). Oxidation of cyclopentanol derivative **10** by tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[9] afforded the key intermediate **2** in 68% yield. Introduction of the amide side chain in ketone **2** was achieved by following the synthesis procedure reported for ramelteon.[1,5] Horner–Wadsworth–Emmons reaction of **2** with diethylcyanophosphonate gave nitrile **11** as a mixture of *E*/*Z* isomers. Hydrogenation of **11** over Raney cobalt (ODHT-60), followed by acylation and hydrogenation over Pd/C, afforded target compound **1** as a racemic mixture. The optically active isomers (−)-**1** and (+)-**1** were obtained by chiral resolution using preparative HPLC.[10]

The (−)-**1** isomer exhibited potent binding affinities[11] for melatonin receptors (MT_1: K_i = 3.4 nM, MT_2: K_i = 1.3 nM), while (+)-**1** exhibited negligible affinities (MT_1: K_i = >10,000 nM, MT_2: K_i = >10,000 nM). This result demonstrated that the 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine scaffold is a potent mimic of the 5-methoxyindole core of melatonin.

In conclusion, a method for synthesizing a novel 1,6,7,8-tetrahydro-2*H*-cyclopenta[*d*]furo[2,3-*b*]pyridine was successfully developed; this synthesis involved intramolecular inverse electron



Scheme 3. Synthesis of 4-aza analog of ramelteon **1**. Reagents and conditions: (a) TPAP, NMO, molecular sieves 4 Å, MeCN, rt, 68%; (b) NaH, $(EtO)_2POCH_2CN$, THF, 0 °C, 91%; (c) (1) H_2, Raney cobalt (ODHT-60), NH_3, EtOH, rt; (2) EtCOCl, Et_3N, CH_2Cl_2, 0 °C; (3) 10% Pd/C, H_2, EtOH, rt, 56%. (d) HPLC resolution (CHIRALPAK AS).

demand Diels–Alder reaction followed by fluoride-induced desilylation–cyclization. 4-Aza analog of ramelteon (−)-**1** was synthesized and demonstrated that this scaffold is a potent mimic of the 5-methoxy indole core of melatonin. The method described herein can be extended to the synthesis of many valuable analogs that can be used for the identification of a wide variety of biologically active compounds as well as melatonin receptor ligands.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and supporting data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.147.

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10. The racemic **1** (515 mg) was subjected to the chiral resolution using HPLC (CHIRALPAK AS™, hexane/ethanol = 84:16, containing 0.1% diethylamine) to afford (−)-**1** (short retention time, 237 mg, >99% ee) and (+)-**1** (long retention time, 241 mg, >99% ee). (−)-**1**: $[\alpha]_D^{20} = -72.8$ ($c = 0.59$, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, $J = 7.4$ Hz), 1.56–1.71 (1H, m), 1.74–1.90 (1H, m), 1.99–2.13 (1H, m), 2.20 (2H, q, $J = 7.4$ Hz), 2.25–2.40 (1H, m), 2.69–2.94 (2H, m), 3.07–3.41 (5H, m), 4.46–4.72 (2H, m), 5.50 (1H, br s), 7.80 (1H, s). (+)-**1**: $[\alpha]_D^{20} = +75.6$ ($c = 0.59$, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, $J = 7.7$ Hz), 1.57–1.70 (1H, m), 1.75–1.90 (1H, m), 2.00–2.13 (1H, m), 2.20 (2H, q, $J = 7.7$ Hz), 2.25–2.38 (1H, m), 2.69–2.94 (2H, m), 3.08–3.39 (5H, m), 4.50–4.67 (2H, m), 5.49 (1H, br s), 7.80 (1H, s).
11. The binding affinities of (−)-**1** and (+)-**1** were evaluated based on the method of Kato et al.[3] using 2-[^{125}I]-iodomelatonin as radioligand in CHO cells expressing human melatonin receptor (MT_1 or MT_2). The dissociation constant of the compound for the receptor (K_i) was calculated using the following equation: $K_i = IC_{50}/(1 + L/K_d)$, where L and K_d represent the concentration and the affinity constant of 2-[^{125}I]melatonin in the binding assay, respectively.