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Unusual Pyrimidine Participation: Efficient Stereoselective Synthesis of Potent Dual Orexin Receptor Antagonist MK-6096

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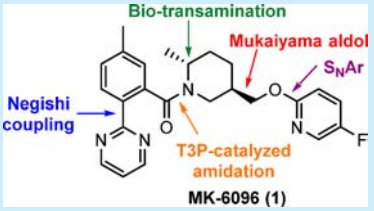
Supporting Information

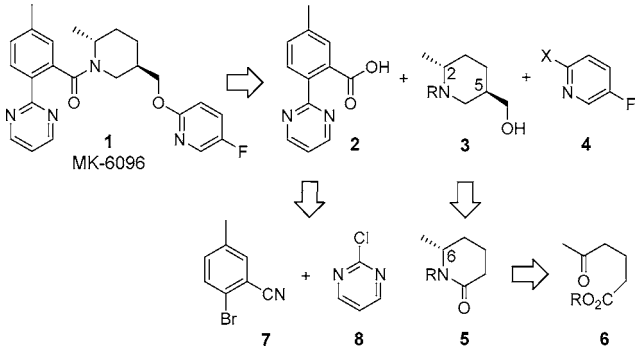
ABSTRACT: An asymmetric synthesis of dual orexin receptor antagonist MK-6096 (**1**) is described. Key steps for the *trans*-2,5-disubstituted piperidinyl ether fragment include a biocatalytic transamination, a *trans*-selective Mukaiyama aldol, and a regioselective pyridyl S_NAr process. The pyrimidyl benzoic acid was synthesized via a Negishi coupling and a nitrile hydrolysis. Coupling of the two fragments via a catalytic T3P-mediated amidation completed the synthesis. Unusual behaviors in the hydrolysis of pyrimidyl benzonitrile and the amide coupling of the pyrimidyl benzoic acid are also described.



Insomnia, with an estimated incidence of 10−15% in the general population and 30−60% in elderly, is one of the most common neuropsychiatric disorders and is closely linked with a host of other diseases including depression, obesity, cardiovascular disease, cancer and chronic pain.[1] Current pharmacological therapies rely primarily on sedative-hypnotics that modulate GABA receptor function and may produce undesirable effects. Recent discovery of neuropeptides Orexin-A and -B that regulate arousal and sleep/wake control by hypothalamic signaling through the Orexin 1 and 2 receptors has opened up new avenues for the treatment of sleep disorders.[2] Small molecule dual Orexin receptor antagonists (DORA) suvorexant and almorexant have been shown to effectively promote sleep in animals as well as demonstrate clinical efficacy.[3] Recently, our discovery efforts identified MK-6096 (**1**)[4] as a potent, reversible, orally bioavailable and structurally distinct piperidine-derived DORA that is currently being evaluated in clinical studies for insomnia.

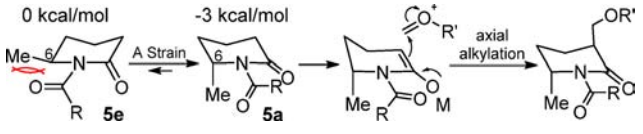
To support further studies, we required an efficient synthesis of **1** suitable for large scale preparation. Although the previous synthesis was amendable to kilogram scale preparation,[5] we felt that improvement of synthetic efficiency was necessary as we progressed toward a manufacturing route. Our retrosynthetic dissections of **1** at the amide and ether bonds afforded three deceptively simple fragments: biaryl acid **2**, piperidine **3**, and fluoropyridine **4** (Scheme 1). The main challenges include the following: (1) efficient establishment of the *trans* C2 and C5 stereogenic centers in piperidine **3**; (2) atom economical and regioselective ether bond formation between **3** and **4** without using activating and protecting groups; (3) cost-effective, concise synthesis of biaryl acid **2** that minimizes the number of expensive Pd-catalyzed cross-couplings; and (4) economical final amide bond formation without using excess T3P. Herein we report the development of an efficient asymmetric synthesis of **1** and the unusual chemistry of pyrimidine participation observed in the synthesis of **2** and the final amide bond formation.

Scheme 1. Retrosynthetic Analysis of MK-6096 (1)



To address the diastereoselectivity problem in the synthesis of piperidine **3**, we sought a stereoselective alkylation of lactam **5** with formaldehyde or its equivalent. We rationalized that the preferred conformation of **5** would be **5a**, which places the C6 methyl group in the axial position due to $A^{1,3}$ strain between the carbonyl group on the lactam nitrogen and the methyl group (Scheme 2).[6] This was supported by DFT calculations which

Scheme 2. Stereoselectivity of Aldol Reaction



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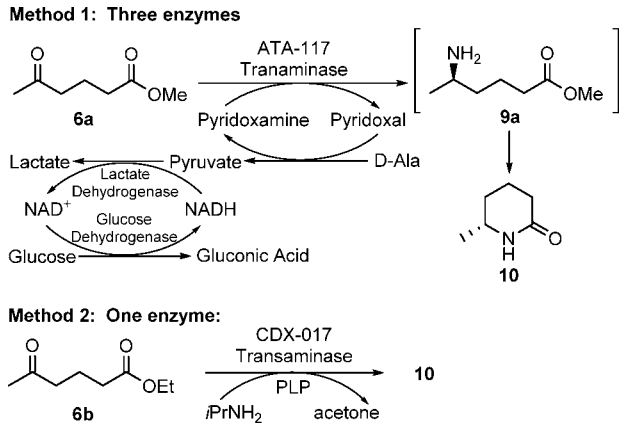
showed **5a** is favored over **5e** by ~3 kcal/mol (R = *t*BuO).[7] The aldol reaction of enolate of **5a** is expected to proceed in a *trans*-diaxial fashion to afford the *trans* product.[8] Indeed, exclusive *trans* product was observed under both anionic (with *N*-Boc) and cationic (with *N*-benzoyl) Mukaiyama aldol reaction[9] conditions.

The synthesis of **1** began with the preparation of lactam **10** via a transaminase catalyzed reaction of keto-esters **6a/b** (Scheme 3).[10] Under a three-enzyme system using D-Ala as the ammonia

Scheme 3. Biocatalytic Transamination Routes to 10

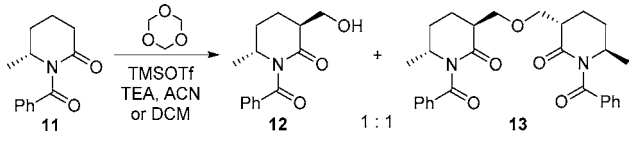


source, crystalline lactam **10** was isolated in 91% yield and >99.7% ee from **6a** after an alkaline workup which promoted lactamization of the intermediate amino ester **9a** and denaturation of the enzymes for a smooth filtration. A potential more cost-effective one-enzyme system employing isopropylamine as the ammonia source afforded **10** in similar high ee in 75−80% yield. The higher pH required (pH 9.5 vs 7.4 for the three-enzyme system) by the one-enzyme system led to the spontaneous lactamization of the amino ester intermediate. This also led to the ethyl ester **6b** as the preferred substrate for improved stability.

Next, we evaluated lactam nitrogen protecting groups (Boc, Cbz, benzyl, and benzoyl) for lactam **10** under both anionic and cationic aldol reaction conditions. The Mukaiyama aldol reaction with the *N*-benzoyl group emerged as the preferred method because of the higher overall yield and better substrate stability, whereas the *N*-Boc lactam lithium enolate was unstable at > −50 °C. Treatment of **10** with benzoyl chloride afforded compound **11** in 96% yield after crystallization.[11]

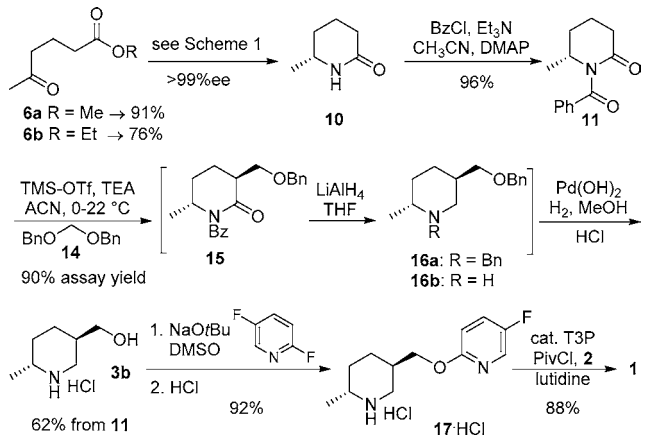
Initial studies of the Mukaiyama aldol reaction of **11** with 1,3,5-trioxane using TMSOTf/TEA afforded a 1:1 mixture of the desired *trans* hydroxymethylated product **12** and ether dimer **13** (Scheme 4).[12] This problem was solved by replacing trioxane with dibenzyloxymethane (**14**), which proceeded smoothly in the Mukaiyama aldol reaction. The *trans* diastereoselectivity in both cases were >99 to 1. Under optimized conditions, addition of 2.1 equiv of TMSOTf to a solution of lactam **11**, 1.05 equiv of **14**, and 2.2 equiv of triethylamine in acetonitrile at 0−20 °C

Scheme 4. Mukaiyama Aldol with 1,3,5-Trioxane



afforded piperidine **15** in 90% assay yield (Scheme 5). Alternatively, the Mukaiyama aldol could be conducted with

Scheme 5. Synthesis of 1 via Mukaiyama Aldol



$TiCl_4$/Hunig's base to afford **15** in 91% yield, however, with a slightly lower dr (96:4 *trans*/*cis*). After workup, crude **15** containing some benzyl alcohol, **14**, and triethylammonium triflate salt was used directly in the next step.

Reduction of crude lactam **15** using $BH_3{\cdot}SMe_2$ afforded a 1:2 mixture of *trans* monobenzylated and bis-benzylated piperidines **16a/b** in good yield; however, breaking the intermediary boron complexes required aging in aqueous HCl for 20 h. Alternatively, $LiAlH_4$ reduction of **15** proceeded in similar efficiency and was conveniently worked up with an aqueous Rochelle salt solution, thus avoiding the long workup cycle time required with borane reduction.

The crude benzyloxy piperidines **16a/b**, containing minor amounts of benzyl alcohol and **14**, were directly debenzylated under hydrogenolysis conditions. Initially, using catalytic $Pd(OH)_2$ in MeOH, the reaction stalled with accumulation of **16b**. Subsequently, hydrogenolysis in the presence of Boc_2O or HCl led to complete cleavage of both benzyl groups within 4 h at 40 psi and 40 °C. The HCl method directly afforded hydroxypiperidine HCl salt **3b** as a crystalline solid in high purity after a solvent switch to THF/IPA. The overall yield of hydroxymethylpiperidine **3b** from **6a** was 48% which is a 2.4-fold improvement over the previous synthesis.

For the synthesis of amino ether **17**, we explored a direct coupling of amino alcohol **3b** and 2,5-difluoropyridine. On treatment with NaO*t*Bu in DMSO, the alkoxide of **3b** underwent a regioselective S_NAr coupling at the C2 position to afford amino ether **17**·HCl in 92% yield. The regioselectivity was >99.5% at C2 over C5. No double displacement product was detected.

To prepare biaryl acid **2**, we envisioned a one-step synthesis from 2-bromo-5-methylbenzoic acid via a Negishi coupling reaction. Formation of the corresponding lithium dianion occurred at −85 °C in the presence of 2.05 equiv of *n*-butyllithium. Metal exchange with $ZnCl_2$, followed by Negishi coupling with 2-chloropyrimidine in the presence of 2% $PdCl_2$ and 2% *n*-Bu_3P at 60 °C, afforded biaryl acid **2** in 50% isolated yield on a multigram scale. However, when the chemistry was scaled up to multikilograms, biaryl acid **2** was obtained in only 12% yield. It appeared that the lithium dianion precipitated at −85 °C, which required significantly longer reaction times resulting in decreased yields. Attempts to warm up the

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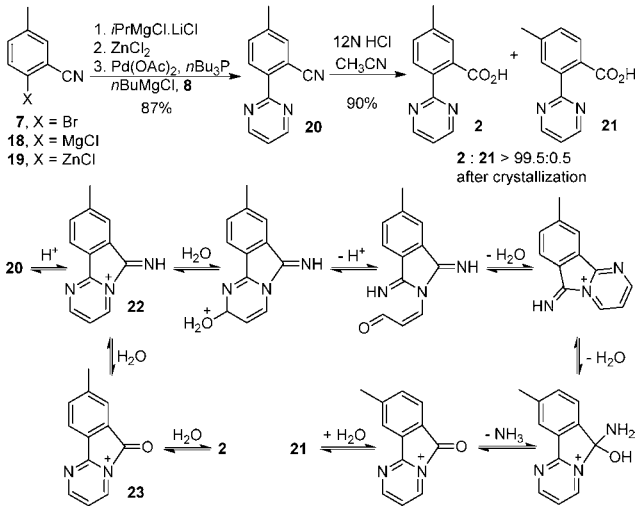
temperature of the reaction mixture to increase the solubility of the lithium dianion resulted in decomposition.

To address the stability/solubility issues with the lithium dianion, we explored the Negishi coupling utilizing 2-bromo-5-methylbenzonitrile (**7**) (Scheme 6). Grignard **18** was generated

Scheme 6. Synthesis of 2 and Proposed Mechanism to 21



in >99% conversion from **7** using Knochel's method at −15 °C and was found to be unstable on warming from −13 °C to +13 °C over 15 h, where the HPLC purity dropped from 95% to 23%, thus precluding a Kumada coupling. After quenching **18** with $ZnCl_2$, the Negishi coupling of **19** with 2-chloropyrimidine (**8**) proceeded in the presence of 1 mol % of palladium and 4 mol % of *n*-Bu_3P to give biaryl nitrile **20** in 90% isolated yield. The catalyst was generated from $Pd(OAc)_2$ and *n*Bu_3P with *n*-BuMgCl activation.

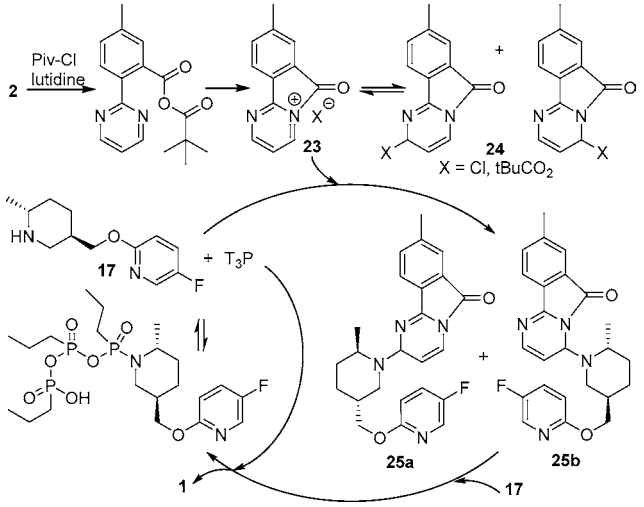
Our initial studies for the hydrolysis of isomerically pure nitrile **20** under various aqueous acid conditions afforded desired **2** and surprisingly apparent methyl migrated product **21** in as high as 15% yield (e.g., 5 N HCl at 40 °C afforded **2** and **21** in an 89:11 ratio).[13] Further optimization of the reaction found that using 12 N HCl (12 equiv) and 1−3 volumes of CH_3CN while running the reaction at lower temperature (from 0 to 20 °C) led to an increased selectivity up to 98.9:1.1. LCMS showed the conversion of nitrile **20** to pyrimidinium **22** was very fast, whereas the conversion of **22** to acid **2** was slow, which required 24−48 h for full conversion. **2** was isolated in 90% yield after crystallization.

A possible mechanism for the conversion of the biaryl nitrile **20** to the biaryl acid **2** and regioisomer **21** is shown in Scheme 6. The key feature of the mechanism was the participation of the pyrimidine nitrogen forming the pyrimidinium, which was responsible for the hydrolysis rate acceleration and the rearranged byproduct. It appeared that the pathway leading to **21** via openning of the pyrimidine ring could be suppressed under certain conditions as discussed above.

The final amide coupling of **2** and **17**·HCl was surprisingly challenging as discussed previously.[5] Typical amide coupling reagents gave poor yields of **1**, and ultimately 1-propylphosphonic anhydride (T3P)[14] was found to be the only effective reagent providing the desired reactivity and afforded **1** in 64% isolated yield. The first generation synthesis used excess T3P (3.4 equiv) for the coupling which is not economical for large scale manufacturing. After extensive screening, we found that either 1.5 equiv of 2-Cl-1-methylpyridinium iodide or pivaloyl chloride with only a catalytic amount of T3P produced comparable results. Because of costs associated with 2-Cl-1-methylpyridinium iodide, pivaloyl chloride was selected for further development. After optimization, the amidation was achieved using 0.05 equiv of T3P with pivaloyl chloride as the stoichiometric dehydrating agent and 2,6-lutidine as the base. The amidation reaction was successfully demonstrated on a multikilogram scale to afford **1** in 88% isolated (>95% assay yield) and excellent purity.

NMR studies of the amidation reaction led us to propose the following mechanism (Scheme 7). Upon activation of the

Scheme 7. Possible Mechanism of T3P-Mediated Amidation of 2 and 17



carboxylic acid, pyrimidine nitrogen participated in forming acyliminium ion **23** which reacted reversibly with Cl^- and pivolate leading to intermediates **24**. Amino ether **17** then added to the pyrimidine ring of **23** or **24** forming intermediates species **25a/b**. **25a/b** precipitated from the reaction mixture, and their structures were confirmed by NMR analyses.[15] These intermediates were inert until re-exposure to T3P which enhanced the leaving group ability of the amino ether and resulted in the desired amide bond formation through rearomatization of the pyrimidine. It appeared that T3P is uniquely suited for promoting this later transformation relative to other amide coupling reagents.

In summary, a highly stereoselective, efficient synthesis of **1** was demonstrated. The *trans*-2,5-disubstituted piperidine **3b** was efficiently constructed via a biotransamination and a *trans*-selective Mukaiyama aldol reaction. A highly chemo- and regioselective S_NAr reaction furnished pyridyl ether **17**. Biaryl acid **2** was prepared in two steps via Negishi coupling and nitrile hydrolysis. Finally, a catalytic T3P-mediated amide coupling furnished **1**. When compared with the previous synthesis to **1**, the current route is one step shorter and produces more than 3-fold higher overall yield (37% vs 11%). The unusual behaviors in nitrile hydrolysis and amidation were due to pyrimidine participation.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) See Supporting Information for hydrolysis screening results. **21** was observed spectroscopically (NMR, LCMS, and HPLC) but not isolated.

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(15) The crude **25a/b** mixture ratio ranged from 1:1 to 2:1.