ORGANIC LETTERS

2012
Vol. 14, No. 13
3458–3461

Enantioselective Synthesis of a Dual Orexin Receptor Antagonist

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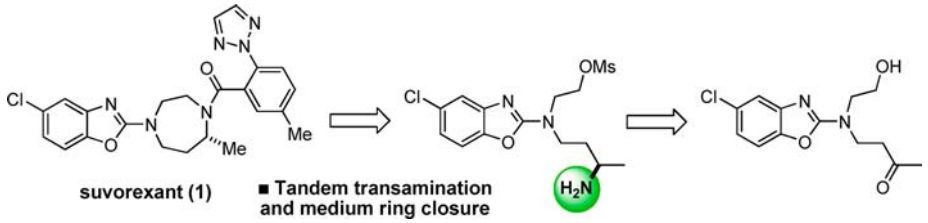
Received May 22, 2012

ABSTRACT



A concise, enantioselective synthesis of the potent dual orexin inhibitor suvorexant (1) is reported. Key features of the synthesis include a mild copper-catalyzed amination, a highly chemoselective conjugate addition, and a tandem enantioselective transamination/seven-membered ring annulation. The synthesis requires inexpensive starting materials and only four linear steps for completion.

Orexins A and B are excitatory neuropeptides that stimulate wakefulness and play a central role in regulation of the sleep cycle.[1] Small molecule anta of orexin receptors OX_1R and OX_2R[2] have been found to promote sleep in multiple species.[3] Consequently, several laboratories have pursued the design of selective orexin receptor antagonists for the treatment of primary insomnia.[4] Suvorexant (**1**) is a potent, brain-penetrant dual orexin receptor antagonist recently disclosed by Merck & Co. currently in phase III clinical trials.[5] A synthetic approach toward **1** has been recently described,[6] that served as inspiration to design a novel approach that might increase overall throughput with reduced cost and environmental impact to satisfy projected commercial supply.

A key feature of **1** is the core chiral diazepane ring (**2**), which had previously been assembled using a ruthenium-catalyzed asymmetric reductive amination.[7] This method achieved high levels of enantioselectivity (94% ee) but required the use of a transition metal catalyst and dichloromethane as solvent, both of which we hoped to eliminate to lessen the environmental impact of the process. Therefore an alternative bond disconnection was envisioned taking advantage of biocatalytic transamination technology (Figure 1).[8] Specifically, an asymmetric transamination of a

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(2) (a) De Lecea, L.; Kilduff, T. S.; Peyron, C.; Gao, X.-B.; Foye, P. E.; Danielson, P. E.; Fukuhara, C.; Battenberg, E. L. F.; Gautvik, V. T.; Bartlett, F. S., II; Frankel, W. N.; Van Den Pol, A. N.; Bloom, F. E.; Gautvik, K. M.; Sutcliffe, J. G. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 322. (b) Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.; Tanaka, H.; Williams, S. C.; Richardson, J. A.; Kozlowski, G. P.; Wilson, S.; Arch, J. R. S.; Buckingham, R. E.; Haynes, A. C.; Carr, S. A.; Annan, R. S.; McNulty, D. E.; Liu, W.; Terret, J. A.; Elshourbagy, N. A.; Bergsma, D. J.; Yanagisawa, M. *Cell* **1998**, *92*, 573.

(3) (a) Boss, C.; Brisbare-Roch, C.; Jenck, F.; Aissaoui, H.; Koberstein, R.; Sifferlen, T.; Weller, T. *Chemia* **2008**, *62*, 974. (b) Boss, C.; Brisbare-Roch, C.; Jenck, F. *J. Med. Chem.* **2009**, *52*, 891.

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(5) Cox, C. D.; Breslin, M. J.; Whitman, D. B.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Roecker, A. J.; Mercer, S. P.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Reiss, D. R.; Harrell, C. M.; Murphy, K. L.; Garson, S. L.; Doran, S. M.; Prueksaritanont, T.; Anderson, W. B.; Tang, C.; Roller, S.; Cabalu, T. D.; Cui, D.; Hartman, G. D.; Young, S. D.; Koblan, K. S.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. *J. Med. Chem.* **2010**, *53*, 5320.

(6) Baxter, C. A.; Cleator, E.; Brands, K. M. J.; Edwards, J. S.; Reamer, R. A.; Sheen, F. J.; Stewart, G. W.; Strotman, N. A.; Wallace, D. J. *Org. Process Res. Dev.* **2011**, *15*, 367.

(7) Strotman, N. A.; Baxter, C. A.; Brands, K. M. J.; Cleator, E.; Krska, S. W.; Reamer, R. A.; Wallace, D. J.; Wright, T. J. *J. Am. Chem. Soc.* **2011**, *133*, 8362.

(8) For reviews on biocatalytic transformations, see: (a) De Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260. (b) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, *40*, 1412. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 138.

10.1021/ol3014123
Published on Web 06/22/2012

ketone (**4**) that bears a suitable leaving group might allow for a tandem transamination/medium ring annulation, completing the diazepane system. With reports of very highly (>98% ee) enantioselective biocatalytic reactions and the renewable nature of enzymatic catalysts it was proposed that this approach might offer advantages in both reaction performance and environmental sustainability. Furthermore, if the leaving group for the annulation could be derived from activation of an alcohol, then compound **4** could be constructed from inexpensive starting materials including ethanolamine (**6**, $6/kg) and methyl vinyl ketone (**7**, $13/kg).

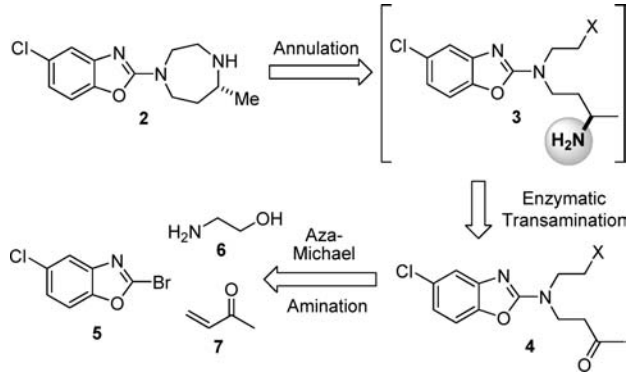
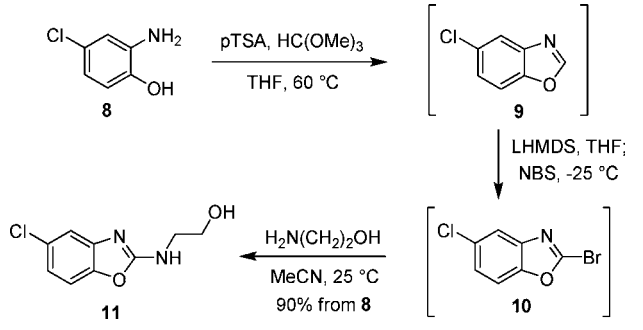


Figure 1. Tandem transamination/ring annulation strategy.

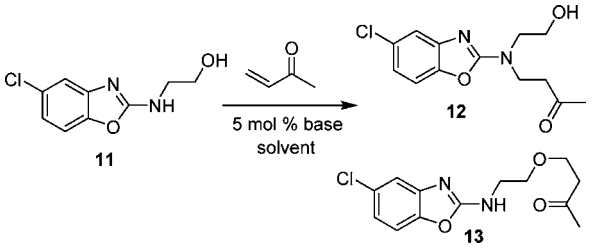
To investigate this synthetic strategy we first sought an efficient synthesis of ketone **4** amenable to evaluation of a number of possible leaving groups. First, an acid catalyzed condensation of commercially available phenol **8** with trimethyl orthoformate provided benzoxazole **9** (Scheme 1).[9] The reaction stream of **9** was then partially distilled to remove methanol and then used directly in a subsequent lithiation/bromination sequence to furnish bromide **10**. This bromide could then be reacted directly with ethanolamine *in situ* to provide alcohol **11** without any intermediate chromatography or isolation in 90% overall yield from **8**.[10]

Scheme 1. One-Pot Synthesis of Alcohol **11**



To access the proposed transamination substrate (**4**) it remained to append a ketone and activate the alcohol as a suitable leaving group. Investigations focused on an aza-Michael addition of alcohol **11** to methyl vinyl ketone (Table 1). The critical limitation of this reaction was found to be achieving chemoselectivity between the amine and alcohol functionalities, as each could react independently providing ketones **12** and **13**. Furthermore the reaction was found to be thermodynamically driven to a mixture of the two ketone products along with side products including double alkylation, retro-Michael, and decomposition of the hetreocycle.[11] A careful survey of reaction conditions was conducted, varying solvent and base composition to improve chemoselectivity and yield.

Table 1. Optimization Studies for Aza-Michael Addition of **11**



entry[a]	base	solvent	yield (%)[b]	**12**:**13**[c]
1	DBU[d]	CH_3CN	61	4:1
2	pyrrolidine	CH_3CN	2	1:1
3	PPh_3	CH_3CN	7	3:1
4	Cs_2CO_3	CH_3CN	65	11:1
5	Cs_2CO_3	THF	57	6:1
6	Cs_2CO_3	*i*PrOAc	39	13:1
7	Cs_2CO_3	DMF	73	16:1
8	Cs_2CO_3	DMAc	70	14:1
9	K_2CO_3	DMF	86	21:1
10	Na_2CO_3	DMF	89	32:1
11	Na_3PO_4	DMF	90	30:1
12	NaOH	DMF	93	37:1
13	NaOH[e]	DMF	95	42:1

[a] All reactions were conducted with 1.25 equiv of MVK and 5 mol % base at 1 M solvent concentration and 23 °C under nitrogen unless otherwise noted. [b] Isolated yield of **12**. [c] Ratio determined by HPLC. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [e] Run with 1 mol % 10 M NaOH.

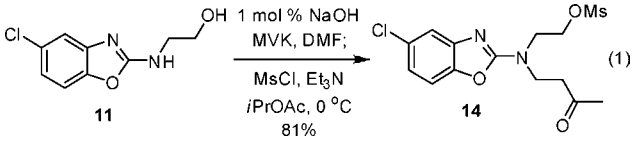
DBU was found to be sufficiently basic to promote the aza-Michael reaction, but yield and selectivity were moderate (Table 1, entry 1). A range of less basic tertiary

(9) For related heterocyclic condensations, see: (a) Vechorkin, O.; Hirt, N.; Hu, X. *Org. Lett.* **2010**, *12*, 3567. (b) Cioffi, C. L.; Lansing, J. J.; Yüksel, H. *J. Org. Chem.* **2010**, *75*, 7942.

(10) The synthesis of aminobenzoxazoles from benzoxazoles has also been reported via direct oxidative methods; see: (a) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (b) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (c) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem. Int. Ed.*. **2011**, *50*, 11511. (d) Li, Y.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *J. Org. Chem.* **2011**, *76*, 5444. (e) Lamani, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, *76*, 7938.

(11) This decomposition largely consisted of opening of the oxazole by addition of ethanolamine to the C2 position. For related reactions, see: (a) LaMattina, J. L.; Mularski, C. J. *Tetrahedron Lett.* **1984**, *25*, 2957. (b) Walker, F. J.; Kraus, K. G. *J. Heterocycl. Chem.* **1987**, *24*, 1585. (c) Kokel, B. 1996, *37*, 3849.

amines failed to promote reactivity, although slight reactivity was seen with pyrrolidine or triphenylphosphine (entries 2–3). Higher yields and selectivities were observed with inorganic bases (entries 4–13). A solvent survey with cesium carbonate revealed DMF to be a preferable solvent with 73% yield and 16:1 chemoselectivity (entry 7). To our delight, a range of alkali carbonates and phosphates mediated the reaction with excellent yields and selectivities (entries 9–11). However, occasional reproducibility problems were observed on increasing reaction scale because of the limited solubility of the inorganic salts. It was realized that the active catalyst was likely trace hydroxide from adventitious water. Therefore aqueous sodium hydroxide was evaluated as a catalyst and found to promote the conjugate addition in 95% yield and 42:1 selectivity as a 1 mol % additive (entry 13). These conditions were then applied to a one-step synthesis of mesylate **14** from alcohol **11**, following the aza-Michael with mesylation and crystallization of the product in 81% yield (eq 1).



With mesylate **14** in hand, the stage was set to evaluate the crucial transamination sequence. However, a highly selective transamination of the ketone (**4** to **3**, Figure 2) is only one of several possible issues anticipated in the proposed tandem reaction. The benzoxazole had proven earlier to be labile to nucleophilic attack, and the transamination event might initiate an intramolecular ring opening (**4** to **15**). Also, the desired amine (**2**) had been previously reported to be capable of isomerization (**2** to **17**),[6] which in our studies occurred in a pH range of 3 to 12.[12] The leaving group (X) could be susceptible to hydrolysis under basic reaction conditions; however basic conditions would be required for the annulation step to proceed. A high-yielding process would have to balance these competing factors successfully.

Several (*R*)-selective transaminases are commercially available,[13] but an initial survey found many to be insufficiently reactive to achieve significant conversion.[14] However, the (*R*)-selective transaminase evolved specifically for the sitagliptin manufacturing process[15] provided good conversion and exceptionally high enantioselectivty in the transamination of **14** (Table 2, entry 1, >99% ee).

(12) Below pH 3 amine **2** is predominantly doubly protonated, and above pH 12 it is free based. High or low pH regimes suppress intermediate **16**, which arises from a singly protonated species, and therefore isomerization is also suppressed.

(13) For synthetic applications of (*R*)-selective transaminases, see: (a) Truppo, M. D.; Turner, N. J.; Rozzell, D. *Chem. Commun.* **2009**, 2127. (b) Koszelewski, D.; Clay, D.; Rozzell, D.; Kroutil, W. *Eur. J. Org. Chem.* **2009**, 2289. (c) Koszelewski, D.; Tauber, K.; Faber, K.; Kroutil, W. *Trends Biotechnol.* **2010**, *28*, 324.

(14) An unoptimized lead of 8% yield was found using ATA-117 (Codexis) as the transaminase.

(15) This is an evolved variant of ATA-117; see round 11 transaminase in: Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, *329*, 305.

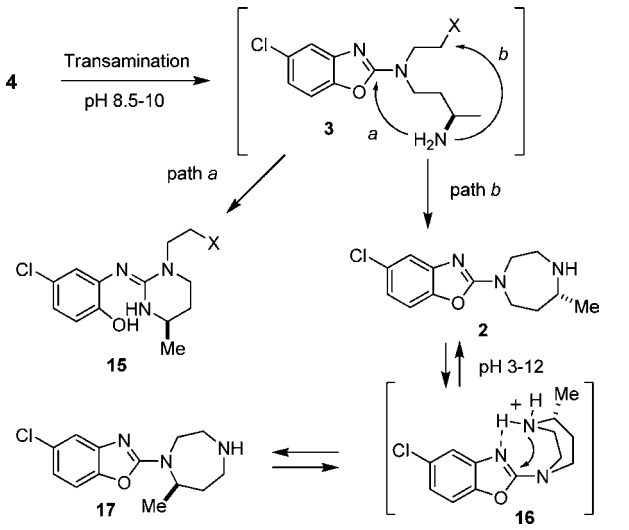
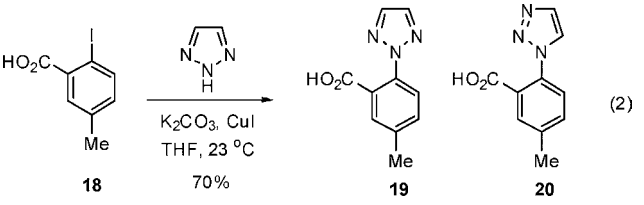


Figure 2. Side reactions competing with annulation step.

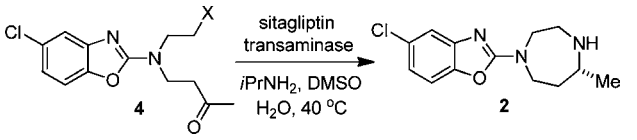
Furthermore, the desired tandem annulation to **2** was observed during the reaction. However, signficant amounts of side products **15** and **17** were observed, and yield was also impacted by hydrolysis of the sulfonate activating group. A range of sulfonates were examined under identical conditions (entries 2–5), but mesylate **14** was ultimately superior in overall profile. The tosylate provided better selectivity against formation of guanidine **15** (entry 2), but slower reaction kinetics and poorer sulfonate stability resulted in a diminished yield, likely because of its reduced solubility in the mixed aqueous reaction medium. Interestingly, an alkyl chloride provided clean reactivity in the transamination (entry 6) but only **15** was observed as a product because the chloride was apparently insufficiently reactive to compete with the benzoxazole ring-opening pathway. By rendering the pH of the reaction more basic (entries 7–10), formation of **15** and **17** could be reduced. However, at a pH of 10 or greater, yield was diminished because of sulfonate and enzyme instability (entries 9–10). Using a moderate pH and a slow addition protocol for **14** provided a useful balance between the reactivity and purity profile (entry 11, 71% yield).[16] Notably, in all cases shown here enantioselectivity was greater than 99%.

With a method in hand to produce **2**, it remained to complete the synthesis of **1** by amide formation with



triazole acid **19**. This acid was synthesized via an Ullman-type copper catalyzed amination of 1,2,3-triazole which had initially suffered from moderate regioselectivity.[6]

Table 2. Tandem Transamination/Annulation Optimization



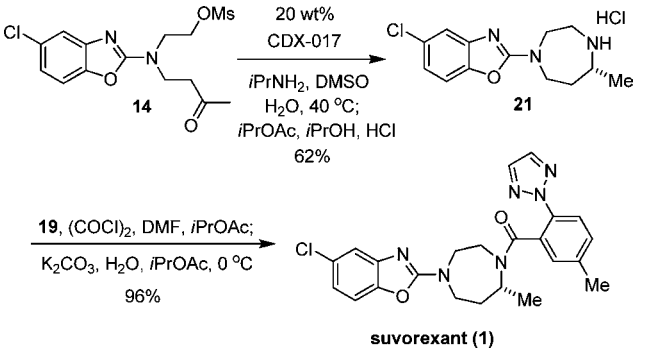
entry[a]	pH	X	yield (%)[b]	**15** (%)[b]	**17** (%)[b]
1	8.5	OMs	60	10	12
2	8.5	OTs	45	3	9
3	8.5	OSO_2(4-FPh)	38	4	6
4	8.5	OSO_2CH_2Cl	10	2	3
5	8.5	ONs[c]	17	3	4
6	8.5	Cl	0	92	0
7	9.0	OMs	63	9	9
8	9.5	OMs	65	8	4
9	10.0	OMs	58	4	3
10	11.0	OMs	8	1	1
11[d]	9.5	OMs	71	6	2

[a] All reactions were conducted at 40 °C with 20 wt % CDX-017, 0.5 wt % pyridoxal 5′-phosphate, and 6 equiv of iPrNH$_2$·HCl in a DMSO/water solution buffered to target pH by triethanolamine. [b] Assay yield determined by HPLC. [c] p-Nitrobenzenesulfonate. [d] **14** added via syringe pump over 6 h as DMSO solution.

Interestingly, improved regioselectivity was observed at rt in the absence of an exogenous ligand (eq 2, 88:12 **19:20**).[17] Regioisomerically pure **19** could then be obtained in 70% yield through crystallization.[19]

Following workup of the transamination, amine **2** was crystallized directly as its HCl salt (**21**) and coupled with acid **19** under Schotten–Baumann conditions[19] to produce suvorexant (**1**) in a volume efficient process in 96% yield after crystallization (Scheme 2).

Scheme 2



In conclusion, a concise, enantioselective synthesis of suvorexant, a potent and selective dual orexin receptor antagonist for the treatment of primary insomnia, has been developed. This approach features an unusual tandem transamination/medium ring annulation to produce the core diazepane that proceeds in greater than 99% ee. The entire synthesis requires only four linear steps for completion and proceeds in 43% overall yield without the need for chromatography. Use of halogenated solvents or heavy metal catalysts has been eliminated, rendering this synthesis attractive for a more sustainable large scale commercial supply.

Acknowledgment. The authors would like to thank Dr. Debra J. Wallace (Merck) for helpful discussions.

Supporting Information Available. Experimental proceudres, compound characterization, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) The mass balance consists of **12** from hydrolysis of the sulfonate and oligomers dervied from intermolecular alkylation of amine **3**.

(17) For examples of rt Ullman-type couplings, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(18) For Pd-catalyzed regioselective C–N couplings of triazoles, see: Ueda, S.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8944.

(19) Sonntag, N. O. V. *Chem. Rev.* **1952**, *52*, 237.