Tetrahedron Letters 55 (2014) 3143–3145

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective total synthesis of almorexant

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ARTICLE INFO

Article history:
Received 2 November 2013
Revised 28 March 2014
Accepted 28 March 2014
Available online 5 April 2014

Keywords:
Asymmetric synthesis
(*R*)-*tert*-Butanesulfinamide
N-Sulfinyl imine
Grignard reaction
S_N2 substitution

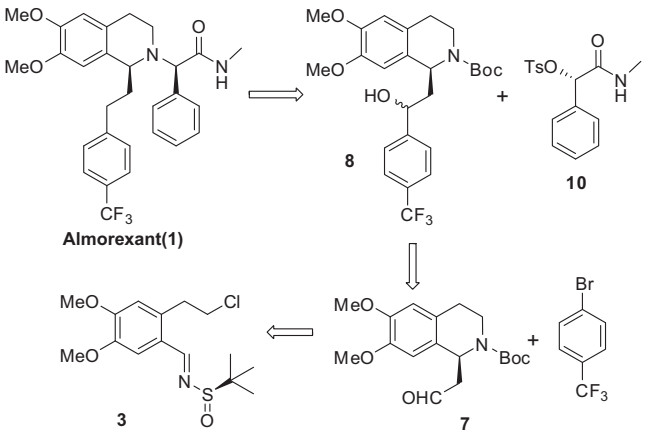
ABSTRACT

A highly stereoselective synthesis of almorexant has been achieved using (*R*)-*tert*-butanesulfinamide as a chiral source. The chiral tetrahydroisoquinoline core was constructed through allylation of chiral *N*-sulfinyl imine followed by ring closure of the secondary amide with a tethered halide. The chiral α-phenyl amide was introduced by means of S_N2 substitution of (*S*)-methyl 2-phenyl-2-(tosyloxy)acetate with chiral tetrahydroisoquinoline.

The neuropeptides, orexin A and orexin B are produced by neurons in the hypothalamus.[1,2] They play a key role in the regulation of various biological functions such as sleep/wake cycle.[3,4] Consequently, a variety of orexin antagonists have been developed to regulate the physiological functions of orexin receptors.[5] Among them, almorexant is a non-peptide antagonist of human orexin receptors,[6] which plays a major role in controlling the sleep/wake cycle and related hypothalamic functions.[2]

Almorexant comprises of a chiral tetrahydroisoquinoline core and a chiral α-phenyl amide. Indeed, the synthesis of almorexant involves multi-step processes such as Bischler–Napieralski cyclization and Noyori's ruthenium-catalyzed asymmetric transfer hydrogenation[7] of the corresponding 3,4-dihydroisoquinoline. Subsequently, the second step has been improved by asymmetric hydrogenation using chiral Ir/Tania-Phos catalyst.[8] Other methods for the construction of chiral tetrahydroisoquinoline core are based on iridium-catalyzed asymmetric intramolecular allylic amidation[9] and Ugi reaction.[10]

The *N*-*tert*-butanesulfinamide is a versatile chiral auxiliary for the asymmetric induction in the preparation of chiral amines.[11] Addition of an organometallic reagent to C=N bond of an enantiopure sulfinimine is one of the most elegant methods for the synthesis of chiral amines. The electron-withdrawing sulfinyl group is highly stereodirecting and activates the C=N bond effectively in nucleophilic addition reactions, and can easily be removed to provide the enantiopure amine derivatives.[12] However, the use of this useful chiral auxiliary in the total synthesis of complex natural products is still unexplored to a great extent. Inspired by its versatility in asymmetric synthesis, we attempted the total synthesis of almorexant using *N*-*tert*-butanesulfinamide as a source of chirality.



Scheme 1. Retrosynthetic approach of almorexant (**1**).

Following our interest on (*R*)-*tert*-butanesulfinamide chemistry,[13] we herein report a highly efficient total synthesis of almorexant (**1**) via the allylation of an enantiopure sulfinimine. Our retrosynthetic approach to the synthesis of almorexant (**1**) is depicted in Scheme 1. As per our synthetic strategy, almorexant could be accessed from tetrahydroisoquinoline **8** which can be prepared by Grignard reaction of the aldehyde **7** with *p*-trifluoromethyl phenylmagnesium bromide. The key intermediate **7** was

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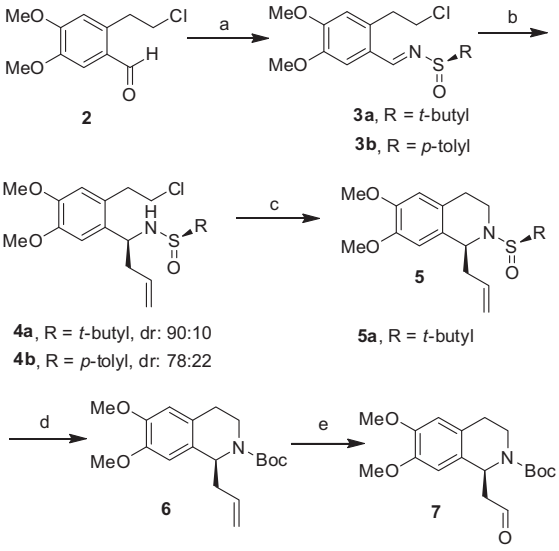
http://dx.doi.org/10.1016/j.tetlet.2014.03.130
0040-4039/

proposed to be obtained from enantiopure *N*-sulfinylimine **3** through the allylation and subsequent oxidation. Aldimine **3** could be prepared by the condensation of (*R*)-*tert*-butanesulfinamide with aryl aldehyde **2**.

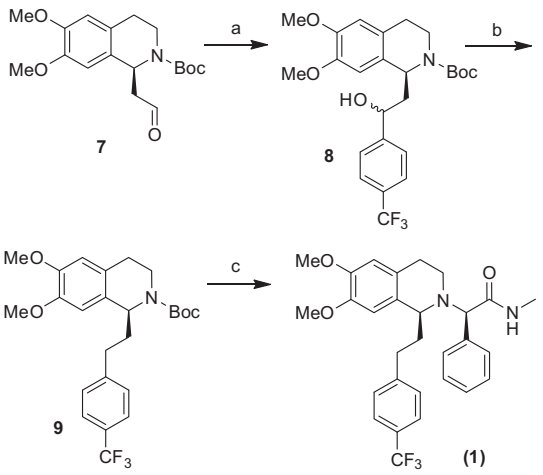
The synthesis of a key intermediate **7** is outlined in Scheme 2. Accordingly, we started the synthesis of tetrahydroisoquinoline core **7** from the chloro substituted aryl aldehyde **2**.[14] Treatment of chloro aldehyde **2** with (*R*)-*tert*-butanesulfinamide in the presence of $CuSO_4$ afforded the corresponding *N*-sulfinylimine **3a** in 80% yield.[15] Grignard reaction of *N*-sulfinylimine **3a** with allylmagnesium bromide at −78 °C in dichloromethane gave the homoallylic sulfinamide **4a** in 78% yield with 9:1 ratio of diastereomers[16] which can easily be separated by column chromatography. To improve the diastereoselectivity, we performed the allylation with *N*-sulfinylimine **3b** derived from (*R*)-*p*-tolylsulfinamide and chloro aldehyde **2**. However, the corresponding allyl derivative **4b** was obtained in 73% yield with 78:22 ratio of diastereomers. Therefore, we proceeded to the next step with **4a**. Base catalyzed intramolecular cyclization of the chloro amide **4a** in the presence of NaH in DMF at room temperature gave the cyclized product **5a** in 75% yield.[17] Deprotection of the sulfinyl group using ethanolic HCl afforded the tetrahydroisoquinoline in 80% yield.[18] Protection of the free amine with $(Boc)_2O$ in the presence of triethyl amine furnished the *N*-Boc derivative **6**.[15] Oxidative cleavage of the terminal olefin **6** using OsO_4, 2,6-lutidine, and $NaIO_4$ gave the aldehyde **7** in 80% yield in a single step (Scheme 2).[19]

Further treatment of aldehyde **7** with trifluoromethylphenyl magnesium bromide in THF at room temperature gave the hydroxy derivative **8** in 82% yield.[20] Mesylation of **8** with mesyl chloride in the presence of triethyl amine followed by reduction with LAH afforded the deoxygenated compound **9** in 62% yield over two steps.[21] Deprotection of Boc **9** using TMSOTf followed by S_N2 substitution of tosyl derivative **10** with secondary amino functionality in the presence of diisopropylethyl amine afforded the target almorexant (**1**) in 68% yield over two steps ($[\alpha]_D^{25}$ −25.0, *c* = 0.2, $CHCl_3$) (Scheme 3). The optical rotation and spectral data of (−)-almorexant (**1**)[22] are in agreement with the data reported in the literature.[9]

In summary, we have developed a highly efficient total synthesis of almorexant, a potent antagonist of human orexin receptors using (*R*)-*tert*-butanesulfinamide as a chiral source. Our synthetic route involves 11 steps in 9.7% overall yield, which is similar to other reported methods. The use of easily accessible chiral *tert*-butanesulfinamide makes this synthesis more simple, quite efficient, and attractive.



Scheme 2. Synthesis of aldehyde **7**. Reagents and conditions: (a) (*R*)-*tert*-butanesulfinamide, $CuSO_4$, CH_2Cl_2, 25 °C, 24 h, 80%; (b) AllylMgBr, CH_2Cl_2, −78 °C, 1 h, 78%; (c) NaH, DMF, 0 °C to rt, 6 h, 75%; (d) (i) EtOH/HCl, 1,4-dioxane, 5 h, 0 °C, (ii) Boc_2O, Et_3N, CH_2Cl_2, rt, 1 h, 75% (over two steps); (e) OsO_4, 2,6-lutidine, $NaIO_4$, 1,4-dioxane, 2 h, 80%.



Scheme 3. Synthesis of target molecule (**1**). Reagents and conditions: (a) *p*-trifluoromethylphenylmagnesium bromide, THF, rt 2 h, 82%; (b) (i) mesyl chloride, Et_3N, CH_2Cl_2, 0 °C, (ii) LAH, THF, 0 °C, 62% over two steps; (c) (i) TMSOTf, CH_2Cl_2, rt, 1 h, (ii) compound **10**, DIPEA, CH_3CN, reflux, 68% over two steps.

Acknowledgements

B.V.S. thanks CSIR, New Delhi for the financial support as a part of XII five year plan program under title ORIGIN (CSC-0108).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.130.

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22. Supporting Information.