Tetrahedron Letters 49 (2008) 6079–6080

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A short and efficient synthesis of the NMDA glycine site antagonist: (3*R*,4*R*)-3-amino-1-hydroxy-4-methyl pyrrolidin-2-one (L-687,414)

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ARTICLE INFO

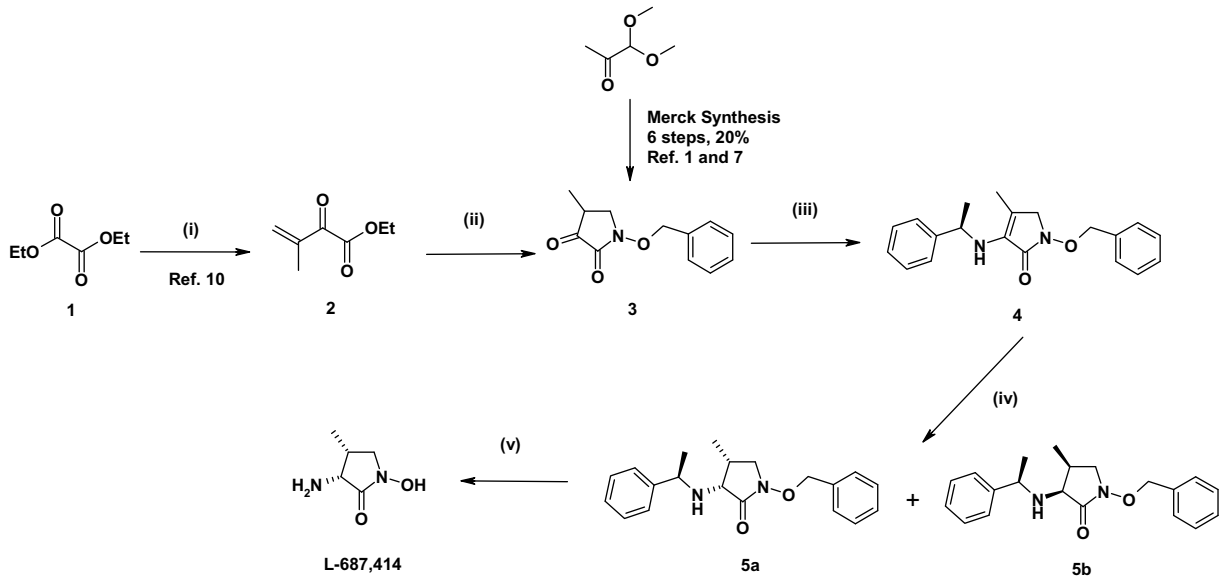
Article history:
Received 4 July 2008
Accepted 30 July 2008
Available online 6 August 2008

ABSTRACT

A short and efficient synthesis of the NMDA glycine site antagonist: (3*R*,4*R*)-3-amino-1-hydroxy-4-methyl pyrrolidin-2-one (L-687,414) is described.

L-687,414, (3*R*,4*R*)-3-amino-1-hydroxy-4-methyl-pyrrolidin-2-one (Scheme 1) is an antagonist at the glycine modulatory site of the *N*-methyl-D-aspartate (NMDA) receptor discovered at Merck Sharp and Dohme.[1] In contrast to many reported glycine site NMDA receptor antagonists, L-687,414 displays CNS-mediated actions after systemic administration. Indeed, robust anticonvulsant[2] and neuroprotective[3] properties of L-687414 injected intraperitoneally have been reported, suggesting good brain penetration.[4]

As a result, L-687,414 has proved to be a key tool for studying the behavioral relevance of the glycine site on the NMDA receptor.[5] However, further in vivo characterization has been hampered by the lack of efficient synthetic route permitting facile gram quantity production of this important CNS agent. To our knowledge, three syntheses of L-687,414 have been reported till now: from Merck,[1,6,7] Pfizer,[8] and from the Baldwin group.[9] The Merck and Baldwin routes are lengthy (10 and 13 steps, respectively) whereas



Scheme 1. Reagents and conditions: (i) Isopropenylmagnesium bromide, diethylether-THF, −70 °C, 20 min, quantitative yield; (ii) *O*-benzylhydroxylamine hydrochloride, diisopropylethylamine, DMF-ethylacetate, 0 °C, then 45 °C, 16 h, 40% yield; (iii) (*R*)-(+)-1-Phenylethylamine, methanol, reflux, 23 h, 95%; (iv) (a) PtO_2, H_2 (1 atm), acetic acid, ethylacetate, 0 °C, 15 h; (b) Chiral preparative HPLC (Chiralpak AD®), 40% yield of **5a** from **4**; (v) $Pd(OH)_2$, H_2 (1 atm), methanol, acetic acid, rt, 5 h, 86% yield.

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doi:10.1016/j.tetlet.2008.07.172

the Pfizer synthesis which is reported to be shorter (6 steps) starts from an optically active synthon which is no longer commercially available. In addition, the Pfizer route lacks efficient stereochemical control.

We describe here a short and efficient synthesis of L-687,414. In our approach, we set out to improve the original Merck route. In the Merck synthesis, key intermediate pyrrolidine-dione **3** was prepared in 6 steps with only 20% overall yield (4 chromatographies on silica gel were required).[6] In addition, one of the steps employed the hazardous oxidizing agent 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, making it difficult, for safety reason, to perform the reaction on a large scale. We found that **3** could actually be prepared in 2 steps only starting from diethyloxalate **1** with 40% overall yield, and no chromatographic separation. Indeed, **1** was first reacted with 1.2 equiv of isopropropenylmagnesium bromide in diethylether/THF at −70 °C as described by Villieras et al.[10] to provide ethyl-3-methyl-2-oxo-but-3-enoate intermediate **2** in quantitative yield. Remarkably, under these conditions, the Grignard reagent added to only one carbonyl function and no subsequent addition on the formed keto group (via 1,2-addition) or on the double bond (via 1,4-addition) of the product was observed. Pleasingly, the obtained intermediate **2** reacted smoothly with *O*-benzylhydroxylamine to provide, after a Michael addition followed by an in situ cyclization, the desired pyrrolidine-dione **3** in 40% yield.[11] This sequence could be performed easily on a large scale (>100 g). Product **3** was isolated upon crystallization of the crude material, and purification via chromatography was therefore not necessary. From intermediate **3** to the final compound L-687414, we improved the sequence described by Merck: First, the formation of enamine **4** with (*R*)-(+)-1-phenylethylamine proceeded with excellent yield (95%).[12] Next, the hydrogenation of **4** with platinum oxide was performed at 0 °C instead of at room temperature as described by Merck. Under these milder conditions, the cleavage of the benzyl ether protective group was not observed. Such cleavage was reported by Merck to take place at room temperature, necessitating a subsequent reprotection of the hydroxylamine function. In addition, and pleasingly, a significant improvement in the diastereoselectivity of the hydrogenation step in favor of the desired stereoisomer **5a** versus **5b** was observed when the reaction was performed at 0 °C (4:1 mixture obtained) instead of at room temperature (2:1 mixture obtained).[13] Furthermore, in our hands, the separation of this mixture on Waters PrepLC as described by Merck proved to be extremely inefficient due to poor separation. We found that much better discrimination between the two diastereoisomers was achieved by preparative chiral HPLC (Chiralpak AD®). Finally, deprotection of the required diastereoisomer **5a** with Pearlman's catalyst under an atmospheric pressure of hydrogen provided L-687,414 as its acetic acid salt in excellent yield (86%).[14]

In summary, a short (5 steps) and efficient synthesis of the NMDA glycine site antagonist L-687,414 has been established by improving the original Merck route. Key in our approach was the development of an extremely facile access to the intermediate pyrrolidine-dione **3** via a Michael-in situ cyclization protocol. With this synthetic route, multigram quantity of L-687,414 could be prepared making possible further in vivo characterization of this important CNS agent.

Acknowledgments

We would like to thank our colleagues from the Molecular Structure Research Department for NMR, MS and optical rotation measurement.

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11. *1-Benzyloxy-4-methyl-pyrrolidine-2,3-dione* **3**: To a solution of o-benzylhydroxylamine hydrochloride (119 g, 0.73 mol) in DMF (195 ml) and ethylacetate (780 ml) was added dropwise *N*-ethyldiisopropylamine (182 ml, 1.0 mol). After stirring for 1 h at rt, the reaction mixture was cooled to 0 °C, and **2** (136 g, 0.73 mol) was added dropwise. After stirring for 1 h at 0 °C and 4 h at RT, the reaction mixture was heated at 45 °C, stirred for 16 h, then quenched with 10% citric acid (1.3 l). The aqueous phase was extracted three times with *tert*-butylmethylether, the combined organic phases were washed successively with 1 M H_2SO_4, sat. NaCl, and satd $NaHCO_3$, then dried over Na_2SO_4 and concentrated. The residue was crystallized from *tert*-butylmethylether (1 l), dichloromethane (300 ml) and heptane (400 ml) to provide **3** as a white solid (64 g, 40% yield), mp: 130–132 °C (Ref.: mp: 129–132 °C),[7] existing predominantly at RT as its enol form in $CDCl_3$. ^1H NMR ($CDCl_3$) of enol: 1.81 (s, 3H), 3.61 (s, 2H), 5.02 (s, 2H), 6.48 (br s, 1H), 7.3–7.5 (m, 5H). MS: *m*/*z* (%): 219 (5%, M^+), 91 (100%, Bn).
12. *(R)-1-Benzyloxy-4-methyl-3-(1-phenyl-ethylamino)-1,5-dihydro-pyrrol-2-one* **4**: A solution of **3** (40 g, 0.18 mol) and (*R*)-(+)-1-phenylethylamine (46.9 g, 0.36 mol) in MeOH (500 ml) was refluxed under N_2 for 23 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (Eluent: heptane, ethylacetate 9:1) to provide **4** as a light yellow oil (56 g, 95% yield), $[\alpha]_D^{20}$ +56.5 (*c* 0.88, $CHCl_3$) (Ref.: $[\alpha]_D^{20}$ +59.7 (*c* 1.8, $CHCl_3$)).[7] ^1H NMR ($CDCl_3$): 1.45 (d, *J* = 6.7 Hz, 3H), 1.60 (s, 3H), 3.42 (d, *J* = 16.2 Hz, 1H), 3.50 (d, *J* = 16.2 Hz, 1H), 4.14 (br s, 1H), 4.64 (q, *J* = 6.4, 1H), 5.0 (s, 2H), 7.2–7.5 (m, 10H). MS: *m*/*z* (%): 323 (100%, $M+H^+$).
13. *(3R,4R)-1-Benzyloxy-4-methyl-3-(1-phenyl-ethylamino)-pyrrolidin-2-one* **5a**: To a solution of **4** (26.5 g, 82 mmol) in ethyl acetate (772 ml) were added acetic acid (80 ml) and Platinum (IV) oxid hydrate (1.3 g). The mixture was stirred with a mechanical stirrer and hydrogenated at 0 °C under atmospheric pressure for 15 h. The catalyst was filtered and the solvent evaporated in vacuo. The residue was azeotroped twice with toluene and then dissolved in ethyl acetate (200 ml). The solution was washed once with sat. $NaHCO_3$ (100 ml), dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (Eluent: heptane, ethylacetate 8:2) to provide 14.8 g of a yellow oil containing a 4/1 mixture of the diastereoisomers **5a** and **5b**. This mixture was separated by preparative chiral HPLC (column: Chiralpak AD®, eluent:heptane, isopropanol 85:15) to provide **5a** (less polar) as a light yellow oil (10 g, 40% yield) $[\alpha]_D^{20}$ +104.5 (*c* 1.16, $CHCl_3$). (Ref.: $[\alpha]_D^{20}$ +103 (*c* 1.6, $CHCl_3$)).[7] ^1H NMR ($CDCl_3$): 0.83 (d, *J* = 6.9 Hz, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.67 (br s, 1H), 1.90–1.98 (m, 1H), 2.75 (dd, *J* = 1.8 and 8.7 Hz, 1H), 3.16 (d, *J* = 7.5, 1H), 3.22 (dd, *J* = 6.0 and 8.7 Hz, 1H), 4.18 (q, *J* = 6.6, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 7.22–7.41 (m, 10H). MS: *m*/*z* (%): 325 (100%, $M+H^+$).
14. *(3R,4R)-3-Amino-1-hydroxy-4-methyl-pyrrolidin-2-one acetic acid salt-L-687,414*: To a solution of **5a** (9.8 g, 30 mmol) in methanol (150 ml) and acetic acid (3.2 ml) was added palladium hydroxide on charcoal 20% (2.4 g). The reaction mixture was hydrogenated under atmospheric pressure at rt for 5 h. The catalyst was filtered and the solvent was evaporated in vacuo. The residue was azeotroped three times with toluene. The colorless oil was crystallized from methanol (30 ml) and ether (30 ml). The white solid was stirred in ether (30 ml) for 2 h, filtered, and dried under high vacuum to provide L-687,414 as its acetic acid salt (4.92 g, 86%). mp: 110–113 °C. $[\alpha]_D^{20}$ +17 (*c* 0.932, MeOH). ^1H NMR (D_2O): 1.08 (d, *J* = 7.3 Hz, 3H), 1.85 (s, 3H), 2.80–2.84 (m, 1H), 3.25 (dd, *J* = 3.2 Hz and 9.7 Hz, 1H), 3.80 (dd, *J* = 6.8 Hz and 9.7 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 4.71 (s, 4H). MS: *m*/*z* (%): 130 (5%, M^+), 113 (100%, M-NH_3). Microanalysis: calcd (1/1 acetic acid salt): C: 44.20, H: 7.42, N: 14.73, found: C: 44.17, H: 7.31, N: 14.87. The free base was obtained as a white foam (97.4% yield) after chromatography on Si–tosic acid silica gel (Silicycle R60430B, eluent: methanol, then NH_3 in methanol, 2N): $[\alpha]_D^{20}$ +17.8 (*c* 0.81, MeOH)). (Ref.: $[\alpha]_D^{20}$ +16.5 (*c* 0.48, MeOH)).[7] ^1H NMR (D_2O): 1.00 (d, *J* = 7.2 Hz, 3H), 2.64 (m, 1H), 3.13 (dd, *J* = 3.0 Hz and 9.9 Hz, 1H), 3.68 (dd, *J* = 7.2 Hz and 10.2 Hz, 1H), 3.80 (d, *J* = 8.1 Hz, 1H), 4.71 (s, 3H). For practical reason, L-687,414 was used as its acetic salt for its evaluation in biological testing.