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An improved synthesis of Lu AA20465

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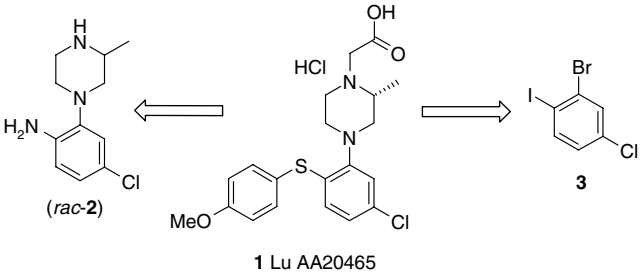
Abstract—A solution phase synthesis for the preparation of the glycine transporter 1 (GlyT1) inhibitor Lu AA20465 is presented, which relies on the straightforward assembly of the target molecule through a series of innovative reaction steps. The key steps include a regioselective amination reaction, a chemoselective reduction of an aryl nitro group, a diazotization and iodination sequence under nonaqueous conditions and a copper catalyzed thioarylation reaction.

Compelling evidence exists suggesting that an impairment in NMDA neurotransmission is involved in the pathophysiology of schizophrenia.[1] As glycine is an obligatory co-agonist at the NMDA receptor complex,[2] one strategy, to restore the NMDA function in Schizophrenic patients, is to inhibit GlyT1: a transporter known to be co-expressed in the brain with NMDA receptor and which is responsible for the selective reuptake of glycine into glial and neuronal cells.[3] As a result, considerable efforts[4] have been focused on the development of a wide variety of selective GlyT1 inhibitors from which Lu AA20465 **1** was recently claimed by Lundbeck to be in late stage preclinical development.[5]

The synthesis of a range of close derivatives was originally developed on solid phase and involved a number of relatively cumbersome steps, including the use of an iron-assisted S_NAr displacement reaction and a photolytic decomplexation as key steps.[6] Consequently the team, at Lundbeck, developed two additional routes to access molecules of this type (Scheme 1). The first involved a solution phase approach which relied on a low yielding copper-assisted diazotization (11%) and a S-arylation reaction from *rac*-**2** as a key step.[7] A second improved route involved the implementation of two regioselective Pd-catalyzed reactions: a S-arylation and a N-arylation reaction using the trihalo-benzene derivative **3** as a key building block.[5]

Herein we wish to report on our recent efforts to develop a more practical, straightforward and scaleable route to



Scheme 1. Lundbeck strategies for the synthesis of Lu AA20465.

1 (Scheme 2). Our strategy inherited the excellent regioselectivity already known for the reaction of 2-methylpiperazine with **4a** in the racemic synthesis of **5**. Unsurprisingly, when using (*R*)-2-methylpiperazine, the first step proceeded in excellent yield to afford **5** with complete regioselective control. It is also important to note that the use of the dinitro derivative **4b** as the electrophile (K_2CO_3, EtOH, H_2O, reflux, 1 h) led to lower yields (71%) of the desired product **5** with significant amounts of the undesired 4-substituted product being formed. We believed the low efficiency in the original sequence of diazotization and thioarylation was due to the presence of the piperazine NH. As a result, we decided to protect this group, whereupon we quickly discovered that a benzyloxycarbonyl (Cbz) group was the favoured choice and **5** was efficiently transformed into **6**, under standard conditions, in quantitative yield. Selective reduction of the nitro group in the presence of the Cl atom and the Cbz group was best performed using an iron, acetic acid mixture to give **7** in 77% yield. The only side product obtained was the acetyl protected

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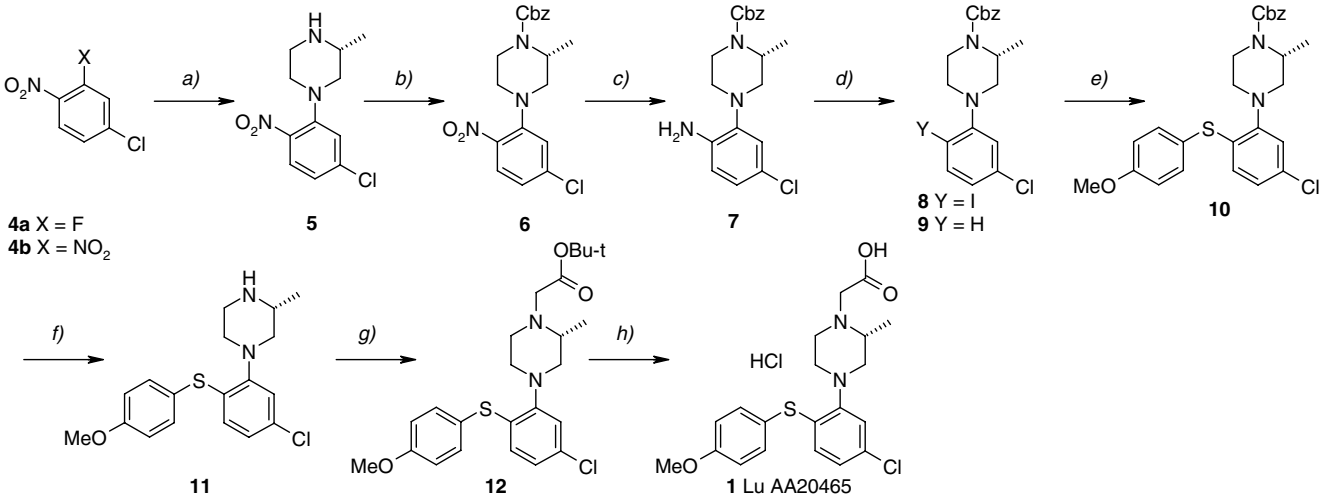

Scheme 2. Synthesis of Lu AA20465.[11] Reagents and conditions: (a) (*R*)-2-methylpiperazine, Et_3N, DMF, 80 °C, 3 h, 98%; (b) CbzCl, $CHCl_3$, $NaHCO_3$, 0 °C, 98–100%; (c) Fe, AcOH, 60 °C, overnight, 77%; (d) *i*$AmNO_2$, CsI, CuI, I_2, DME, 60 °C, 1.5 h, 69%; (e) 4-methoxythiophenol, CuI (5 mol %), *N*-methylglycine, KOH, dioxane, reflux, on, 63%; (f) HCl in dioxane (4 N), then concd HCl (dropwise), reflux, 3 × 1.5 h, 88%; (g) *t*-butyl bromoacetate, Hünig's base, DMF, rt, on, 91%; (h) HCl (5 N), dioxane, 60 °C, 1 h, 69%.

aniline in approximately 5% yield which could be easily removed by chromatography. In our hands, the diazotization and S-arylation sequence, delivered the desired compound **11** in yields of less than 10%, using (*R*)-**2** according to the originally published route. When the same reaction conditions were ran on the Cbz protected compound **7**, we routinely obtained yields of ~30% for the reduced product **9** with yields of less than 5% for the desired product **10**. As a result, we attempted to proceed stepwise and, in the absence of the 4-methoxythiophenol, it was possible to isolate yields of up to 36% for **8**. Since this was not suitable for further scale up, we investigated alternative diazotization methods.[8] The use of a neutral nonaqueous method provided the desired product **8** in a much improved 69% yield. After screening a range of conditions,[9] the subsequent S-arylation was best performed following the methods developed by Liu and co-workers,[10] (employing *N*-methyl glycine as an important additive) to afford **10** in 63% yield on a multigram scale with minimum formation of the reduced product **9**. Cbz-deprotection was best achieved under the acidic conditions detailed in Scheme 2 to provide **11** in 88% yield. It should be noted that standard hydrogenolytic methods failed. Appendage of the acetic acid unit using ethyl bromoacetate, although proceeding in acceptable yield (>50%) was deemed inefficient since basic hydrolysis with NaOH caused significant difficulties in the isolation of the final product. We found this sequence was best performed by telescoping the remaining steps where treatment of Hünig's base with *t*-butyl bromoacetate in DMF, provided **12** in 91% yield followed by hydrolysis in HCl (5 N) in dioxane to give the target compound **1** Lu AA20465 in 69% yield. The use of *t*-butyl bromoacetate was much preferred over the originally reported ethyl bromoacetate since it offered significant advantages in the late stage purification of the final product.

In conclusion, we have developed an efficient 8-step strategy for the enantioselective synthesis of **1** Lu AA20465 starting from (*R*)-methylpiperazine and 4-chloro-2-fluoronitrobenzene **4**. A main improvement from the original route was the straightforward implementation of a Cbz protecting group strategy which, although adds two more individual steps to the reaction sequence, allowed all key steps to be performed in good to excellent yields and facilitated the isolation of preparatively useful quantities of the target compound. The key steps include a regioselective amination reaction, a chemoselective reduction of an aryl nitro group, a diazotization and iodination sequence under nonaqueous conditions and a copper catalyzed thioarylation reaction.

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11. All compounds shown in Scheme 2, were individually isolated and fully characterized by ^{1}H NMR and MS with optical rotation measured and purity assessed by HPLC. Known compounds were compared to the previously reported data.[5] *Selected Experimental Details for Key reaction steps*. *Step (a)*: To a solution of 4-chloro-2-fluoro-nitrobenzene **4** (5.0 g, 28.5 mmol) in DMF (56 mL) and triethylamine (7.9 mL, 57.0 mmol) was added (*R*)-2-methylpiperazine (2.85 g, 28.5 mmol) and the resulting mixture was heated at 80 °C for 3 h. After cooling to rt, the mixture was poured into water and extracted with ethyl acetate. Drying the combined organic layers over sodium sulfate, followed by filtration, evaporation and purification on silica gel (eluting with DCM–MeOH) afforded **5** (7.13 g, 98%) as a light red solid. *Step (c)*: To a mixture of **6** (9.28 g, 24.0 mmol) in acetic acid (270 mL) was added iron powder (8.1 g, 145 mmol) and the resulting mixture was heated at 60 °C overnight. After cooling to rt, the mixture was evaporated and slurried in ethyl acetate. It was then filtered and the filtrate poured into water and extracted with ethyl acetate. Drying the combined organic layers over sodium sulfate, followed by filtration, evaporation and purification on silica gel (eluting with EtOAc–heptane) afforded **7** (6.56 g, 77%) as a light yellow gum. *Step (d)*: To a solution of **7** (5.4 g, 15 mmol) in 1,2-dimethoxyethane (63 mL) was successively added cesium iodide (3.93 g, 15.0 mmol), iodine (1.92 g, 8.0 mmol), cuprous iodide (893 mg, 5.0 mmol) and isoamylnitrite (9.53 mL, 91 mmol) and the resulting mixture was heated at 60 °C for 1.5 h. After cooling to rt, the mixture was partitioned between ammonium chloride (saturated solution) and ethyl acetate and then the whole mixture filtered through celite. The organic layer was then separated, washed with sodium sulfite (5% solution), dried over sodium sulfate, filtered, evaporated and purified on silica gel (eluting with EtOAc–heptane) to afford **8** (4.93 g, 69%) as a light yellow gum. *Step (e)*: A solution of **8** (4.87 g, 10 mmol) in dioxane (21 mL) was added to a mixture of copper iodide (99 mg, 1 mmol), 4-methoxythiophenol (1.77 g, 12 mmol), *N*-methylglycine (184 mg, 2 mmol) and potassium hydroxide pellets (1.69 g, 26 mmol). The resulting light brown suspension was then heated under reflux overnight. After cooling to rt, the mixture was extracted with ethyl acetate. Drying the combined organic layers over sodium sulfate, followed by filtration, evaporation and purification on silica gel (eluting with EtOAc–heptane) afforded **10** (3.13 g, 63%) as a colourless gum.