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Efficient synthesis of a 7-azabicyclo[2.2.1]heptane based GlyT1 uptake inhibitor

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ABSTRACT

An efficient synthetic route based on generation and subsequent electrophilic reaction of a Boc-protected azabicyclo[2.2.1]heptane anion to prepare a potent GlyT1 uptake inhibitor (**1**) is described.

Glycine transporter type 1 (GlyT1) primarily serves to regulate synaptic levels of glycine in the immediate vicinity of the NMDA receptor (NMDAr). Therefore, inhibitors of GlyT1 would be expected to raise brain glycine levels and increase NMDAr-mediated neurotransmission, which should lead to improvement in schizophrenia symptoms[1] without the toxic effects of direct NMDAr agonists. Inhibition of GlyT1 has been widely investigated, leading to the discovery of a few advanced clinical candidates from various pharmaceutical companies.[2] Recently Roche reported Phase II clinical study results of **R1678** in schizophrenia patients which met both its primary and secondary endpoints.[3] Our own efforts in this therapeutic area identified compound **1** to be a potent inhibitor of GlyT1 (IC_{50} ~3 nM). This Letter describes our effort to develop an efficient, scalable, and high-yielding synthesis of **1** (Fig. 1).

Our initial route (Scheme 1) to **1** started from known 7-azabicyclo[2.2.1]heptane-1-carboxylic acid **2**,[4] which was prepared in eight steps (~20% overall yield) from commercially available starting material.[4b] Carboxylic acid **2** was first esterified and then converted to Boc carbamate **3** in high yield. Subsequent conversion of **3** to an aldehyde intermediate was followed by condensation with (*R*)-*tert*-butyl sulfinamide to give chiral imine **4**. The addition of phenyl lithium to imine **4** at −78 °C afforded sulfinamide **5a** with a high level of stereoselectivity. The *t*-butyl sulfinamide protecting group of **5a** was then selectively removed[5] using HCl (3 equiv) in methanol/1,4-dioxane, and the resulting amine was treated with 2,6-dimethyl benzoyl chloride to give amide **6**. Cleavage of the Boc group was followed by methylation using either Eschweiler–Clarke[6] or direct alkylation conditions to provide final compound **1** in 10 steps and ~20% overall yield from amino acid **2**.

There were several limitations associated with this synthetic route. The lengthy synthetic sequence made structure activity relationship (SAR) exploration slow and inefficient. Large scale preparation of key intermediates and final compounds was labor intensive and of questionable feasibility. To address these issues,

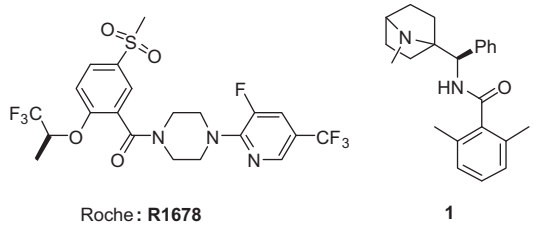
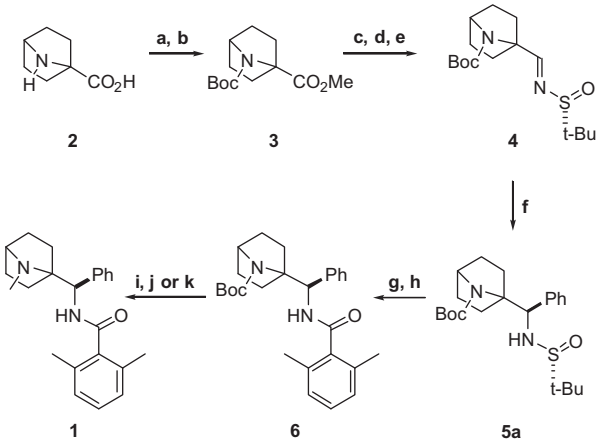


Figure 1. Chemical structure of GlyT1 inhibitors: **R1678** and **1**.



Scheme 1. Reagents and conditions: (a) AcCl, MeOH, 90%; (b) Boc_2O, Et_3N, CH_2Cl_2, 85%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 97%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 82%; (e) (*R*)-2-methylpropane-2-sulfinamide, $Ti(OEt)_4$, THF, 70%; (f) PhLi, THF, −78 °C, 90%; (g) HCl in MeOH/dioxane (3 equiv), quant.; (h) 2,6-dimethylbenzoyl chloride, Et_3N, CH_2Cl_2, 87%; (i) 4 N HCl/1,4-dioxane, 97%; (j) 37% formaldehyde, formic acid, reflux, 60%; (k) Me_2SO_4, NaOH, H_2O/dioxane, 50%.

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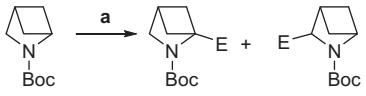


Scheme 2. Reagents and conditions: (a) *s*-BuLi, TMEDA, ether, 0 °C or −78 °C, electrophile.

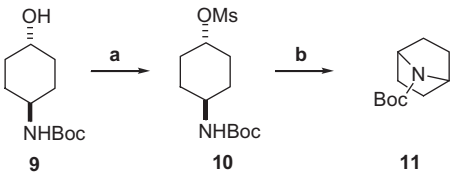
we embarked on the exploration of other potential synthetic routes to **1**.

Beak et al. have reported that α-methylenes adjacent to *N*-Boc carbamates can be functionalized via lithiation in the presence of TMEDA or sparteine.[7] In 2002, Krow et al. reported the temperature dependent regioselective lithiation and subsequent reactions of *N*-Boc protected azabicyclo[2.1.1]hexane (**7**)[8] (Scheme 2). Using this work as a template, we investigated the lithiation and substitution reactions of analogous azabicycle **11**, noting that the symmetry of *N*-Boc azabicyclo[2.2.1]heptane eliminates the regioselectivity issue encountered by Krow.[9]

We prepared several hundred grams of azabicycle **11** from Boc protected *trans*-4-aminocyclohexanol (**9**) using a two-step mesylation and base-assisted intramolecular cyclization strategy (Scheme 3).[10] Mesylate intermediate **10** was used directly in the cyclization step without further purification, and crude azabicycle **11** could be purified by flash column chromatography or vacuum distillation (bp 82–85 °C, 0.4 mbar). It is also noteworthy that **11** was used next despite the presence of elimination byproduct (10–15% Boc-3-amino cyclohexene).

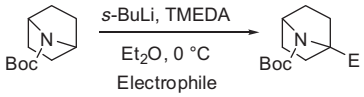
With compound **11** in hand, we were now poised to investigate deprotonation and subsequent electrophilic addition. Various reaction conditions were explored: temperature (−78 °C, −30 °C, 0 °C, rt), solvent: (THF, Et_2O or MTBE), base (*s*-BuLi, *t*-BuLi, KDA, LICKOR, LiTMP, etc.) and additive (TMEDA). As detailed in Table 1, the optimal conditions for this reaction involved addition of *s*-BuLi to a premixed solution of **11** and TMEDA in Et_2O at 0 °C, followed by the addition of suitable electrophiles. Thus, a deuterium quench with CD_3OD (entry 1) provided **12** in good yield with loss of a methine proton based on NMR analysis. Alcohol **13** was obtained upon quenching with DMF and employing a reductive workup (entry 2). Applying this methodology to the novel and efficient preparation of **2**, bubbling excess carbon dioxide through the lithiation reaction mixture produced amino acid **14** (entry 3), which was then converted to **2** by removal of the Boc group. Simple alkyl halides, such as methyl iodide (entry 4), aldehydes (entry 5), and Weinreb amides (entry 6) also reacted readily with the anion of **11**.

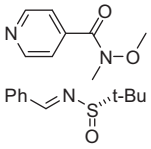
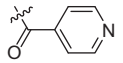
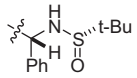
We were also gratified to determine that condensation of chiral imine **19** with the anion of **11** resulted in formation of key intermediate **5b** in 85% yield with high diastereoselectivity (>10:1 (*R*,*R*):(*S*,*R*)) in the newly formed stereogenic center. It should be noted that the stereochemistry of chiral sulfinamide **19** used in this transformation is opposite that used in initial synthetic route (imine **4**). The rationale for the stereoselectivity can be predicted from the proposed transition states which are shown in Figure 2.[11]



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, quant.; (b) *t*-BuOK, THF, 80%.

Table 1
Lithiation and electrophilic additions of azabicycle **11**[a]



Entry	Electrophile	E	Product (%yield)
1	CD_3OD	D	**12** (75)
2[b]	DMF	H_2COH	**13** (57)
3[c]	CO_2	COOH	**14** (53)
4	MeI	Me	**15** (90)
5	*c*-PrCHO	CH(*c*-Pr)OH	**16** (50)
6			**17** (80)
7	19		**5b** (85)

[a] Reaction condition: *s*-BuLi was added to the solution of **11** and TMEDA in Et_2O at 0 °C, followed by the addition of suitable electrophiles.
[b] Workup includes $NaBH_4$ reduction.
[c] CO_2 dried by passage through anhydrous $CaSO_4$ prior to use.

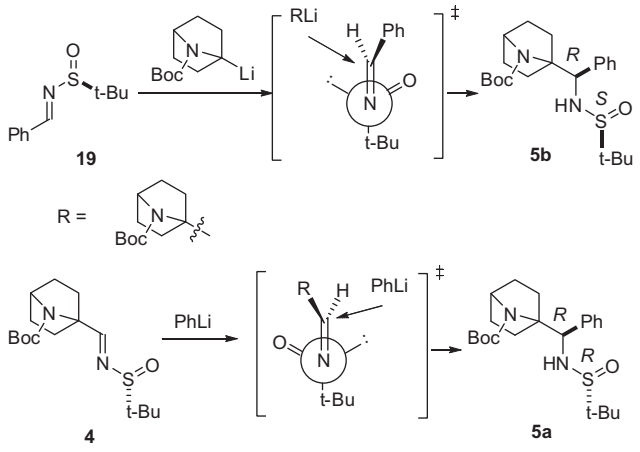
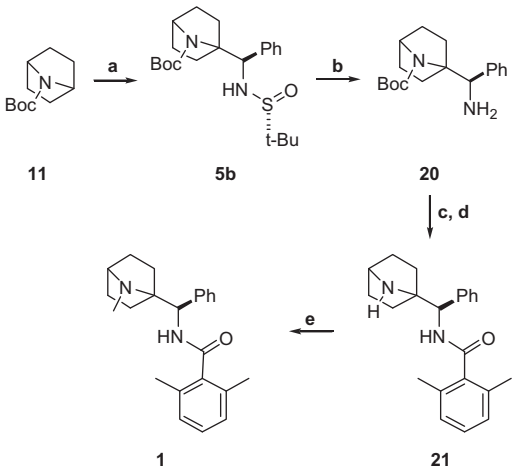


Figure 2. Proposed transition states of anion addition to chiral imines.

With this methodology validated, we sought to apply it to the large scale synthesis of compound **1**. We were initially concerned about an exotherm associated with deprotonation of **11** and subsequent addition to imine **19** because of the low flash point of ether (−45 °C). Therefore, 1.3 equiv of *s*-BuLi was added over 25 min to a pre-cooled mixture of *N*-Boc protected azabicycloheptane **11** and TMEDA in Et_2O at −25 °C. The internal temperature was kept under −25 °C during the addition process. After an additional 20 min at −25 °C, the anion solution was cooled to −50 °C, and the pre-cooled solution of imine **19** in Et_2O was added.[12] Neutralization with aqueous NH_4Cl afforded a crude mixture of diastereomers in a 12:1 (*R*,*R*):(*S*,*R*) ratio. The major isomer **5b** (*R*,*R*) was directly isolated in 50% yield upon recrystallization of the crude mixture from hot hexanes.

Upon scale up, we made several modifications in the following steps leading to compound **1**. A solution of major isomer **5b** in methanol was treated with 1.1 equiv of 4 N HCl in 1,4-dioxane to give the primary amine **20** in quantitative yield.[13] A CH_2Cl_2 solution of **20** and 2 equiv DIPEA was then treated with 2,6-dimethylbenzoyl chloride at 0 °C to afford the crude amide, which



Scheme 4. Reagents and conditions: (a) *s*-BuLi, TMEDA, Et_2O, −25 °C to −50 °C, (*S*)-**19**, 50%; (b) 1.1 equiv HCl in MeOH/1,4-dioxane, quant.; (c) 2,6-dimethylbenzoyl chloride, DIPEA, CH_2Cl_2, 90%; (d) 4 N HCl in 1,4-dioxane, 97%; (e) 37% formaldehyde, formic acid, reflux, 61%.

was sufficiently pure after acid/base workup to be used in the next step without further purification. The Boc group was easily removed[14] when exposed to HCl in 1,4-dioxane and CH_2Cl_2. The secondary amine **21** was then subjected to Eschweiler–Clarke reaction conditions to install the *N*-methyl group. The crude product was first filtered through a pad of basic alumina and then directly recrystallized from hexanes to give compound **1** (28 g, 61% yield) in >99% purity (Scheme 4).[15]

In conclusion, we have demonstrated that the anion of *N*-Boc protected azabicyclo[2.2.1]heptane can be generated via lithiation and subsequently reacted with a wide variety of electrophiles to prepare substituted azabicycloheptanes. Based on this methodology, an efficient and scalable synthesis of GlyT1 uptake inhibitor **1** from *N*-Boc azabicyclo[2,2,1]heptane was achieved in five steps and 26% overall yield. This route was also sufficiently flexible to allow the synthesis of a number of potential GlyT1 inhibitors to explore the SAR in this series.

Acknowledgments

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12. *Preparation of tert-butyl 1-((R)-((S)-1,1-dimethylethyl-sulfinamido)(phenyl) methyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**5b**)**:** A solution of *tert*-butyl 7-azabicyclo[2.2.1]heptane-7-carboxylate (**11**) (192 g, 975 mmol) and TMEDA (0.164 L, 1100 mmol) in 1.7 L of anhydrous diethyl ether was stirred with an overhead mechanical stirrer and kept under a nitrogen atmosphere. The stirring solution was cooled to an internal temperature between −30 °C and −25 °C, and 1.4 M *s*-BuLi in cyclohexane (0.754 L, 1050 mmol) was added over a 25 min period while maintaining the internal temperature in the same range. The turbid, pale amber reaction mixture was stirred at −25 °C for an additional 20 min. During this time, in a separate flask was prepared a solution containing (*S*,*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (170 g, 812 mmol) in 300 mL of diethyl ether cooled in a −78 °C dry ice/acetone bath. After the anion solution had stirred for the required amount of time, it was cooled to an internal temperature of −50 °C and the cooled imine solution was cannulated into the anion solution over 45 min (internal temp maintained between −55 °C and −45 °C during addition). The reaction mixture was then allowed to slowly warm up to 5 °C over the course of 4.5 h before being quenched by slow addition of satd aq NH_4Cl solution (300 mL over 10 min—gas evolution observed). The quenched mixture was stirred for 15 min, and the layers were separated. The aqueous layer was washed with diethyl ether, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. ^1H NMR of the crude product showed approx. 12:1 diastereoselectivity. The semi-solid residue was recrystallized from hot hexanes to give the desired product **5b** (170 g, 51% yield), and the mother liquor was collected to give 209 g of an amber semi-solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.49 (d, J = 7.17 Hz, 2H), 7.20–7.34 (m, 3H), 5.46 (s, 2H), 4.15 (t, J = 4.64 Hz, 1H), 1.94–2.09 (m, 1H), 1.60 (d, J = 10.12 Hz, 3H), 1.41 (s, 9H), 1.29–1.38 (m, 3H), 1.16–1.23 (m, 1H), 1.12 (s, 9H). MS (+ESI): m/z: 407.3 $(M+H)^+$.
13. *Preparation of (R)-tert-butyl 1-(amino(phenyl)methyl)-7-azabicyclo[2.2.1] heptane-7-carboxylate* (**20**): To a cooled (ice bath) solution of *tert*-butyl 1-((*R*)-((*S*)-1,1-dimethylethylsulfinamido)(phenyl) methyl)-7-azabicyclo-[2.2.1]heptane-7-carboxylate **5b** (185 g, 455 mmol) in MeOH (500 mL) was added 4 M HCl in dioxane (125 mL, 500 mmol) dropwise over 1 h. The reaction mixture was stirred at 0 °C for an additional 2.5 h, then the solvent was removed in vacuo. The residue was treated with concd $NaHCO_3$ and extracted with CH_2Cl_2 (2×). The organic extracts were combined, dried over Na_2SO_4, filtered, and the product (quantitative yield—of suitable purity) was kept as a solution in CH_2Cl_2 for subsequent use. MS (+ESI): m/z: 303.2 $(M+H)^+$.
14. *Preparation of (R)-N-(7-azabicyclo[2.2.1]heptan-1-yl(phenyl)methyl)-2,6-dimethylbenzamide* (**21**): To a cooled (ice bath) reaction flask containing a solution of (*R*)-*tert*-butyl 1-(amino(phenyl)methyl)-7-azabicyclo[2.2.1]-heptane-7-carboxylate (64 g, 212 mmol) and DIPEA (73.9 mL, 423 mmol) in CH_2Cl_2 (440 mL), stirring under a nitrogen atmosphere, was added a solution of 2,6-dimethylbenzoyl chloride (35.7 g, 212 mmol) in CH_2Cl_2 (150 mL) dropwise over 45 min. The reaction mixture was stirred at room temperature for 16 h and then partitioned between CH_2Cl_2 and water. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The organic extracts were combined and washed successively with 0.5 N aq HCl and 0.5 N aq NaOH before being dried over $MgSO_4$, filtered and reduced in volume in vacuo to give (*R*)-*tert*-butyl 1-((2,6-dimethylbenzamido)(phenyl)methyl)-7-azabicyclo [2.2.1]-heptane-7-carboxylate of suitable purity as a solution in CH_2Cl_2 (300 mL). To this was added 4 M HCl in 1,4-dioxane (130 mL, 520 mmol), and the reaction mixture was stirred for 16 h before being concentrated in vacuo. The residue was partitioned between Et_2O and 0.5 N aq HCl, and the layers were separated. The aqueous layer was made basic (to pH 8–9) by cautious addition of 5 N aq NaOH. The mixture was then extracted with CH_2Cl_2 (3×) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to give crude (*R*)-*N*-(7-azabicyclo[2.2.1]heptan-1-yl(phenyl) methyl)-2,6-dimethylbenzamide (**21**) of suitable purity to be used directly in the next step (57 g, 81% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 1.20–1.31 (m, 1H), 1.38–1.51 (m, 5H), 1.62–1.72 (m, 1H), 1.75–1.85 (m, 1H), 2.25 (s, 6H), 3.52–3.57 (m, 1H), 5.42 (d, J = 7.9 Hz, 1H), 6.84 (br s, 1H), 7.00 (d, J = 7.3 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.27–7.31 (m, 1H), 7.32–7.40 (m, 4H). MS (+ESI): m/z: 335.2 $(M+H)^+$.
15. *Preparation of (R)-2,6-dimethyl-N-((7-methyl-7-azabicyclo-[2.2.1]heptan-1-yl)(phenyl)methyl)benzamide* (**1**)**:** To a solution of (*R*)-*N*-(7-azabicyclo[2.2.1]-heptan-1-yl(phenyl)methyl)-2,6-dimethyl benzamide (**21**; 44 g, 132 mmol) in formic acid (100 mL, 2600 mmol) was added 37% aqueous formaldehyde (50 mL, 635 mmol) The solution was heated in a 100 °C oil bath for 18 h. An additional amount of both formic acid (50 mL) and 37% aqueous formaldehyde solution (25 mL) was added and heating was continued for 18 h. The reaction mixture was reduced in volume in vacuo and then cautiously treated with 5% aq $NaHCO_3$ (gas evolution). The resulting basic mixture was extracted with

CH_2Cl_2 (3×), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was filtered through basic alumina (CH_2Cl_2 and EtOAc wash) and the filtrate was concentrated in vacuo to give a slightly off-white foam. This was dissolved in hot hexane and needlelike crystals formed upon cooling. The cooled mixture was allowed to stand for 18 h, and the crystals were collected by vacuum filtration before being dried under high vacuum to afford (*R*)-2,6-dimethyl-*N*-((7-methyl-7-azabicyclo[2.2.1]-heptan-1-yl)(phenyl)methyl)benzamide (**1**; 28.07 g, 61% yield) with >99% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.22 (m, 3H), 1.32–1.40 (m, 1H), 1.62 (br s, 1H), 1.67–1.81 (m, 2H), 1.93–2.03 (m, 1H), 2.27 (s, 3H), 2.34 (s, 6H), 3.21 (t, J = 4.7 Hz, 1H), 5.10 (d, J = 4.0 Hz, 1H), 6.60 (br s, 1H), 7.01 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.26–7.28 (m, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.36–7.40 (m, 2H). MS (+ESI): m/z: 349.3 $(M+H)^+$.