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A practical synthesis of (1S,4S)-2,5-diazabicyclo[2.2.1]heptane

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ABSTRACT

The rigid piperazine homologue 2,5-diazabicyclo[2.2.1]heptane (DBH) finds extensive application in medicinal chemistry and pharmaceutical research, but access to this scaffold is non-trivial. This letter details a concise synthetic sequence that gives ready access to DBH on gram scale. The route features a Staudinger reduction of an azide to facilitate a transannular cyclisation

The importance of nitrogen-containing heterocycles in the field of drug discovery is highlighted by the fact that 'heterocycle synthesis' is the second most frequently performed reaction in pharmaceutical laboratories, and the synthesis of N-heterocycles accounts for more than 89% of those reactions.[1] One such N-heterocycle that has found extensive use in medicinal chemistry is the rigid piperazine homologue (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane (DBH, **1**, Fig. 1). Some prominent examples of DBH-containing molecules are shown in Figure 1 and include the fluoroquinolone antibiotic danofloxacin (**2**). (**2**) is a bacterial DNA-gyrase inhibitor that is widely administered in veterinary medicine as its mesylate salt.[2,3] Researchers at Abbott Laboratories have used the DBH stereoisomers to develop a series of potent α7 neuronal nicotinic acetylcholine receptor (nAChR) ligands, such as pyridazine **3**, which exhibit selectivity over the α4β2 subtype.[4] Interestingly, **3** was shown to bind at the α7 nAChR with 23 times greater affinity than the corresponding (1*R*,4*R*) enantiomer, highlighting the specificity of this rigid piperazine homologue. Selective activation of α7 nAChRs represents a potential therapeutic strategy for the treatment of cognitive deficits associated with Alzheimer's disease (AD) and schizophrenia, and several α7 nAChR agonists have entered clinical trials.[5–7] Similarly, chemists at Wyeth have used DBH to confer potency and selectivity to a series of pyrazolopyrimidine type I B-Raf kinase inhibitors including **4**, which displays effective antiproliferative activity against multiple tumor cell lines.[8] Researchers at Merck have investigated 6-aminonicotinamides that incorporate a DBH unit, exemplified by **5**, as potent and selective histone deacetylase 1 (HDAC) inhibitors with antitumor activities.[9]

Beyond medicinal chemistry, *N*,*N*′-dimethyl-DBH (**6**) has found application as a potential ligand for asymmetric catalysis.[10] Melgar-Fernández and co-workers reported the synthesis and evaluation of various DBH-containing molecules as potential ligands for the enantioselective addition of diethylzinc to aldehydes as well as chiral Lewis acid activators for asymmetric Diels–Alder reactions.

The utility of this compound has inspired several groups to devise synthetic strategies to **1**, but none of these are entirely satisfactory, due to problems with reproducibility and scalability. For instance, the first synthesis of **1**, reported by Portoghese and Mikhail in 1966 (Scheme 1), started from *trans*-4-hydroxy-L-proline

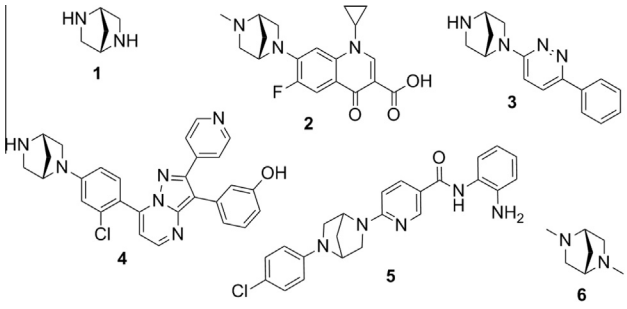

Figure 1. (1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptane (DBH, **1**), and several bioactive DBH-containing molecules.

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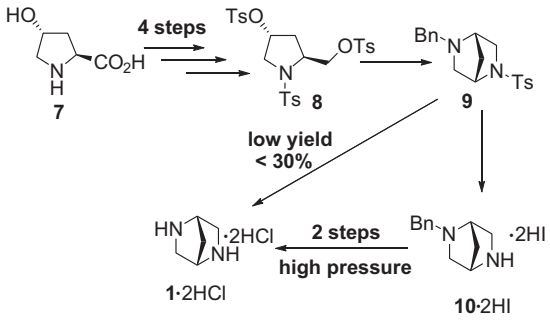
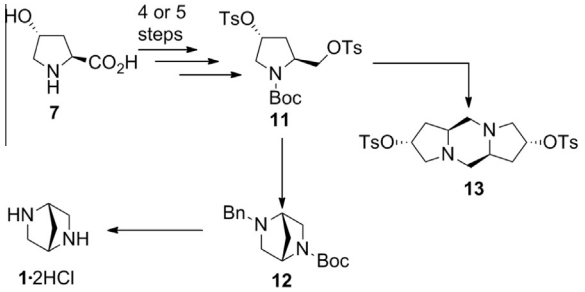


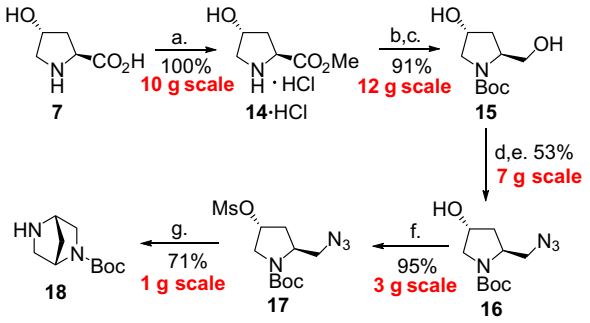
Scheme 1. Portoghese's synthesis of DBH (**1**).

(**7**). After several functional group manipulations, compound **8** was generated and subjected to a double displacement reaction with benzylamine to give **9**.[11] Although that key cyclisation step was accomplished smoothly, unveiling **1** proved highly problematic. Concomitant removal of the toluenesulfonamide and benzyl protecting groups of **9** using sodium in liquid ammonia delivered the desired product **1** in low yield (<30%), a stepwise deprotection regime was therefore investigated. Subjecting **8** to the action of concentrated hydroiodic acid and red phosphorus in refluxing acetic acid gave the expected benzylated product as its dihydroiodide salt (**10**·2HI) in 76% yield. However, **10** proved resistant to subsequent hydrogenolysis, necessitating conversion into the corresponding dihydrochloride, which underwent hydrogenolysis to give **1** as its dihydrochloride salt (**1**·2HCl). Attempts to remove the benzyl protecting group of **9** prior to sulfonamide cleavage gave poor yields of the corresponding product.

Other synthetic efforts towards **1** have built upon Portoghese's general strategy with attempted improvements of individual steps, and/or alternative protecting group strategies.[12,13] Jordis and co-workers reported the synthesis of **1** from **7** using an N-Boc protecting group strategy (Scheme 2). Boc-protected distosylate **11** was synthesized in moderate yield over 4 steps from **7**.[14] The key double displacement cyclisation of **11** with benzylamine to give **12** was reported to proceed under autoclave conditions of high temperature and pressure, and in refluxing toluene. However, subsequent attempts by Yakovlev and co-workers to replicate the double displacement cyclisation of **11** gave DBH **1** in low yield. The major reaction product was identified as **13** (Scheme 2),[15] a finding confirmed in our laboratory. Yakovlev and co-workers proposed that under the forcing reaction conditions, thermolysis of the Boc protecting group gave an intermediate that underwent dimerization to **13**.[15] By lowering the reaction temperature to 40–45 °C (in benzene), compound **12** was obtained in good yield (78%), albeit after 45 days. Additionally, the 20 °C difference in melting point range reported for compound **12** by the two research groups pointed to a discrepancy in the synthetic outcome of the reactions. In our hands, attempts to transform **11** into **12** under a



Scheme 2. Refined syntheses of DBH (**1**).



Scheme 3. Gram-scale synthesis of protected DBH **18**. Reagents and conditions: (a) MeOH, HCl; (b) $(Boc)_2O$, Et_3N; (c) $LiBH_4$; (d) TsCl, py; (e) $TMSN_3$, TBAF; (f) MsCl, Et_3N; (g) PPh_3, H_2O.

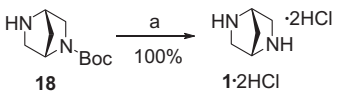
range of conditions never gave yields exceeding 29% (see Supplementary data). Furthermore, formation of the ditosylate **11** was itself problematic, and substantial quantities of the product arising from monotosylation of the primary hydroxyl group were always obtained.

Our ongoing interest in the medicinal chemistry of DBH derivatives for use as α7 nAChR agonists[16] prompted the development of a new synthetic route to **1**, starting from inexpensive **7** (Scheme 3).

Methyl esterification of **7** quantitatively afforded **14** as its hydrochloride salt. Protection of the amino group of **14** as its *tert*-butyl carbamate followed by chemoselective reduction of the ester, gave diol **15** in excellent yield over two steps, without the need for chromatography. Selective tosylation of the primary hydroxyl group of **15** followed by azide displacement gave **16**. The secondary hydroxyl group of **16** was then activated by treatment with mesyl chloride to give **17**. Staudinger reduction of azide **17** resulted in spontaneous transannular cyclisation as the liberated primary amino group displaced the mesyl group, furnishing the mono-protected DBH building block **18** in excellent yield. (An increased yield of 97% was achieved when conducting the cyclisation on a 200 mg scale). Although this route employs trimethylsilyl azide, it avoids high reaction temperatures and pressures, and has the advantage of short reaction times. Trimethylsilyl azide is generally considered a safer alternative to sodium azide and has been used in the one pot multigram synthesis of the antiviral agent (−)-oseltamivir (Tamiflu®).[17] The great advantage of this sequence is that each operation can be performed on multigram scale, providing synthetically useful quantities of **18** in short order. Compound **18** is amenable to storage at 0 °C for at least 3 months prior to use.

Finally, unlike previously reported DBH building blocks, removal of the carbamate protecting group is facile (Scheme 4). Treatment of **18** with hydrochloric acid gave **1** as its dihydrochloride salt in quantitative yield.

In summary, our need for gram quantities of rigid piperazine homologue **1**, has led us to develop a highly practical, gram-scale synthesis of the mono-protected DBH compound **18**. This molecule is available as a single stereoisomer, is amenable to synthetic manipulation, and can be stored for extended periods. This new



Scheme 4. Carbamate deprotection of **18**. Reagents: (a) MeOH, HCl.

synthetic strategy should enable expanded application of this rigid piperazine homologue.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.092.

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