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First synthesis of 2,6-diazabicyclo[3.2.0]heptane derivatives

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ABSTRACT

The first synthesis of 6-phenyl-2,6-diazabicyclo[3.2.0]heptane **1** and its orthogonally protected precursor **2** is herein reported. Our strategy enables to chemically address the two nitrogen atoms of 2,6-diazabicyclo[3.2.0]heptane core individually and selectively, thus allowing rapid access to several subsets of widely substituted fused azetidines.

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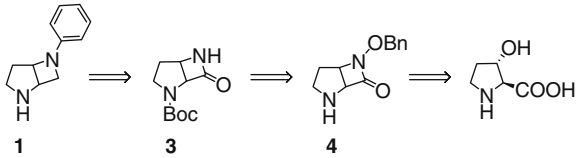
While fused 2-azetidinones, commonly known as β-lactams, are among the most useful aza heterocyclic compounds from both synthetic and medicinal chemistry points of view, the potential application of fused azetidines has been marginally explored. In 1991 Jacquet and collaborators reported the synthesis of racemic 3,6-diazabicyclo[3.2.0]heptanes,[1] but only very recently it has been demonstrated the ability of this core in reducing the conformational complexity of nicotinic receptor ligands and in enhancing the ligand subtype affinity.[2] As part of our efforts towards the identification and synthesis of constrained bis-amine building blocks able to modulate the activity of different active compounds, we became intrigued by the possibility to explore a synthetic approach to 6-phenyl-2,6-diazabicyclo[3.2.0]heptane. Since the synthesis of β-lactams is well documented, in a first attempt **1** was envisaged to derive from azetidinone **3**, which can be readily prepared starting from commercially available *trans*-3-hydroxy-L-proline via hydroxamate-mediated cyclization[3] (Scheme 1). The *trans*-3-hydroxy-L-proline was protected as *N*-*tert*-butylcarbamate and then coupled with *O*-benzylhydroxylamine using the water-soluble EDC to afford an intermediate hydroxamate, which was cyclized to **4** in excellent yield under Mitsunobu conditions (Scheme 2).[4,5]

Direct cleavage of the N–O bond of **4** could not be easily accomplished using most common N–O bond reduction protocols. The samarium diiodide-mediated reduction reported by Romo[6] was unsuccessful. Instead catalytic hydrogenolysis on Ni/Ra afforded quantitatively lactam **3** (Scheme 2). Unfortunately, this compound proved unsuitable for further elaborations. Reduction with $LiAlH_4$ in THF or Et_2O failed, yielding only starting material, whereas treatment with borane–THF complex quantitatively led to the monocyclic opened product **5**. This occurrence was attributed to the unprotected lactam N–H. To overcome this drawback, we decided to revert our strategy by first introducing the aromatic ring on **3** and then attempting reduction to amine. The use of Buchwald–Hartwig's reaction conditions[7] in the presence of $Pd_2(dba)_3$ as the catalyst was found to be successful for the N-arylation reaction, although **6** was isolated in poor yield. To our regret all attempts to reduce **6** proved ineffective thereby precluding access to **1**.

In order to devise an alternative route to access **1** via 2-azetidinone, a longer but efficient strategy was planned, assembling the azetidine ring with a *cis*-pyrrolidine approach, involving facile displacement of primary mesylate by a Cbz-protected amine. Scheme 3 outlines the achieved synthesis of monoprotected 2,6-diazabicyclo[3.2.0]heptane. Mesylate **8** was readily prepared in three steps starting from *trans*-3-hydroxy-L-proline. Treatment of **8** with NaN_3 afforded a mixture of azide **9** and the unsaturated ester **10**[8] in a 2:1 ratio.[9] After reduction under Staudinger's condition, the amino ester **11a**[10] was protected as the N-derivative **11b**, which was reduced to yield the alcohol **12a**. Whereas classical reduction using $LiAlH_4$ in THF failed, treatment with DIBAL-H in the presence of $BF_3{\cdot}Et_2O$ gave **12a** in satisfactory yield. The alcohol was converted into mesylate **12b**,[11] which was suitable to undergo an intramolecular cyclization to **2**.[12] Deprotection of the azetidinyl N-atom afforded 2-monoprotected 2,6-diazabicyclo[3.2.0]heptane



1 3 4

Scheme 1. Retrosynthetic analysis.

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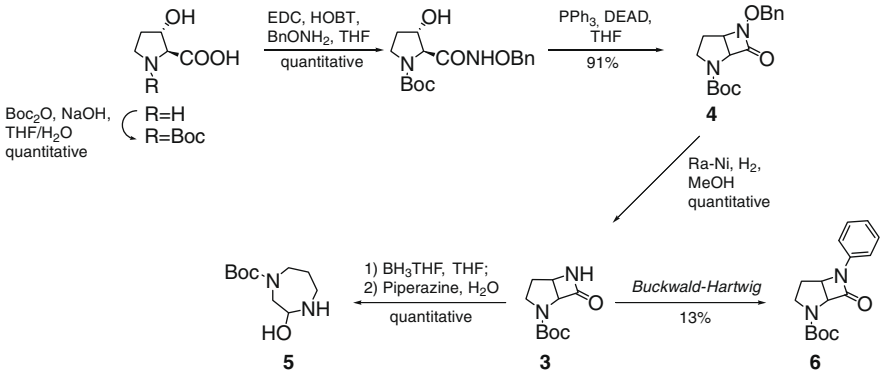
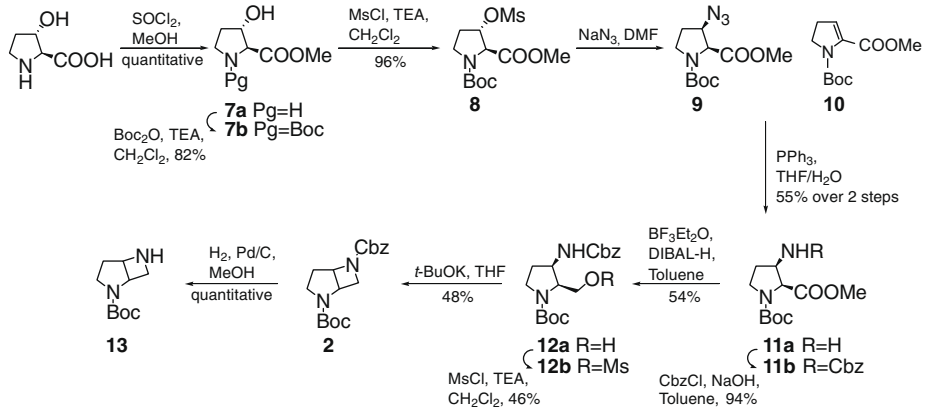
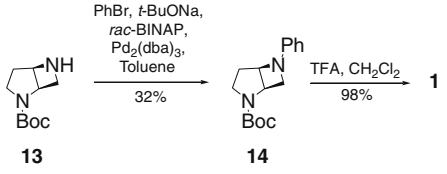


Scheme 2. First attempt to **1.**



Scheme 3. Total synthesis of 2,6-diazabicyclo[3.2.0]heptane core.



Scheme 4. Derivatization to **1**.

13,which could be condensed with bromobenzene to give **14**[13] with moderate yield. After removal of the Boc-protecting group under acidic conditions the desired 6-phenyl-2,6-diazabicyclo[3.2.0]heptane (**1**) was isolated in almost quantitative yield (Scheme 4).[14]

In conclusion, the first synthesis of 2,6-diazabicyclo[3.2.0]heptane, a fused azetidine with high potential to be used as a building block in medicinal chemistry, has been developed. The successful pathway includes the full derivatization of *trans*-3-hydroxy-L-proline, yielding monoprotected 2,6-diazabicyclo[3.2.0]heptane **13** after azidation/reduction, ring closure and removal of the Cbz-protecting group. Buchwald-Hartwig condensation with bromobenzene followed by N-deprotection gives access to the desired 6-phenyl-2,6-diazabicyclo[3.2.0]heptane. The achieved synthetic route has the advantage of affording orthogonally protected fused azetidine **2**, in which the two nitrogen atoms are chemically addressable individually and selectively. This will allow the rapid access to focused subsets of compounds containing the 2,6-diazabicyclo[3.2.0]heptane core with different substituents on the two nitrogen atoms.

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8. *4,5-Dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ster 2-methyl ester* (**10**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.77 (t, J = 3.0 Hz, 1H), 3.95 (d, J = 8.6 Hz, 1H), 3.90 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 2.65 (dd, J = 3.0, J = 8.6 Hz, 1H), 2.60 (dd, J = 2.8, J = 8.8 Hz, 1H), 1.47, 1.44 (2s, 9H).
9. The 2:1 ratio was established by analysis of ^{1}H NMR spectrum. Azide **9** was not isolated and reacted in the next reduction step without any purification.
10. *1-tert-Butyl 2-methyl 3-aminopyrrolidine-1,2-dicarboxylate* (**11a**): Step 1: NaN_3 (0.24 g, 3.71 mmol) was added to a solution of **8** (1.0 g, 3.10 mmol) in dry DMF (12 mL). The mixture was warmed to 100 °C and stirred at that temperature for 7 h. After cooling to room temperature, EtOAc was added. The organic layer was washed twice with saturated aqueous NH_4Cl solution, then dried (Na_2SO_4), filtered and concentrated under vacuum to afford a crude mixture of **9** and **10**

(0.73 g). Step 2: To a stirred 10:1 THF/H_2O emulsion (13.2 mL) containing that mixture (0.73 g) PPh_3 (0.91 g, 3.48 mmol) was added. The reaction mixture was heated to reflux and stirred at that temperature for 4 h. Volatiles were evaporated under vacuum. Chromatography of the crude residue over silica gel ($CHCl_3$/MeOH = 8:2) afforded **11a** as pale yellow oil (417 mg, 55% over 2 steps). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.28 (dd, J = 7.8, J = 13.8 Hz, 1H), 3.51–3.86 (m, 5H), 3.23–3.45 (m, 1H), 2.00–2.20 (m, 1H), 1.68–1.98 (m, 1H), 1.39, 1.43 (2s, 9H).

11. All pyrrolidine derivatives appear in NMR spectra as distinct pair of rotamers.
12. *2,6-Diaza-bicyclo[3.2.0]heptane-2,6-dicarboxylic acid 6-benzyl ester 2-tert-butyl ester* (**2**): Compound **12b** (0.10 g, 0.23 mmol) was dissolved in dry THF (2 mL) and *t*-BuOK (0.039 g, 0.345 mmol) was added. The mixture was stirred for 48 h at room temperature. EtOAc was added; the organic phase was washed twice with H_2O, then dried (Na_2SO_4), filtered and concentrated under vacuum. Chromatography of the crude residue over silica gel (PE/EtOAc = 7:3) afforded **2** as pale yellow oil (37 mg, 48%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.42 (m, 5H), 5.09 (s, 2H), 4.89 (t, J = 5.4 Hz, 1H), 4.24–4.58 (m, 1H), 4.02–4.21 (m, 1H), 3.73–3.97 (m, 1H), 3.40–3.59 (m, 2H), 2.08–2.39 (m, 1H), 1.67–1.82 (m, 1H), 1.44 (s, 9H).
13. *2,6-Diaza-bicyclo[3.2.0]heptane-2-carboxylic acid tert-butyl ester* (**14**): A mixture of amine **13** (0.064 g, 0.325 mmol), bromobenzene (0.051 mL, 0.487 mmol) and *t*-BuONa (0.047 g, 0.487 mmol) in dry toluene (3 mL) was degassed and purged with argon three times before the addition of *rac*-BINAP (0.012 g, 0.019 mmol) and $Pd_2(dba)_3$ (0.006 g, 0.0065 mmol). The resulting mixture was heated to 100 °C and stirred at that temperature for 10 h. After cooling to room temperature, EtOAc was added. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated under vacuum. Chromatography of the crude residue over silica gel (CH_2Cl_2) afforded **14** as pale yellow oil (0.028 g, 32%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (dd, J = 1.2, J = 8.4 Hz, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.46 (dd, J = 1.4, J = 8.8 Hz, 2H), 4.65 (t, J = 5.4 Hz, 1H), 4.33–4.59 (m, 1H), 3.77–4.02 (m, 2H), 3.55–3.76 (m, 2H), 2.15 (dd, J = 6.4, J = 13.0 Hz, 1H), 1.73–1.97 (m, 1H), 1.48 (s, 9H).
14. *6-Phenyl-2,6-diaza-bicyclo[3.2.0]heptane* (**1**): TFA (2.5 mL) was added to a solution of **14** (0.07 g, 0.26 mmol) in CH_2Cl_2 (20 mL). After 2 h volatiles were evaporated under vacuum to afford **1** as its trifluoroacetic salt (0.075 g, 98%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.44 (br s, 1H), 9.09 (br s, 1H), 7.17 (t, J = 7.4 Hz, 2H), 6.69 (t, J = 7.4 Hz, 1H), 6.48 (dd, J = 1.0, J = 7.6 Hz, 2H), 4.70 (t, J = 4.6 Hz, 1H), 4.11–4.60 (m, 1H), 3.33–4.05 (m, 4H), 2.20 (dd, J = 5.6, J = 14.0 Hz, 1H), 1.68–1.91 (m, 1H).