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An unexpected aminocyclopropane reductive rearrangement

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Abstract

A reductive rearrangement of aminocyclopropanes is described for the synthesis of *cis*- or *trans*-fused bicyclic 1,2-diaminocyclobutanes. Ionization of a cyclic aminal using $BF_3{\cdot}OEt_2$ induces rearrangement to a cyclobutyl iminium ion, which is subsequently reduced by Et_3SiH. Substitution with allyltrimethylsilane allows carbon incorporation, giving a quaternary center. Silyloxy-substituted cyclopropanes rearrange rapidly to cyclobutanones which react with $NaBH_4$ to provide 1,2-aminohydroxycyclobutanes. These aminals were generated by the reduction of a Boc-imide with DIBAL-H or $LiBH_4$.

Keywords: Aminocyclopropane; Cyclobutane; Piperazine; Imidazolidinone; Rearrangement

Piperazines are versatile heterocycles in medicinal chemistry, for example, as solubilizing or hydrophobic groups, or as scaffolds that can orient substituents in a rigid fashion.[1] A recent search of the MDL drug report database listed over 70 marketed drugs containing a piperazine,[2] with examples including the active ingredients in *Viagra*™, *Januvia*™, and *Crixivan*™. However, piperazines are also prone to metabolism through imine formation, a process that can occasionally be prevented with substitution about the ring.[3] Imidazolidinones are somewhat less popular, *Tanatril*™ being recently launched for the treatment of hypertension. As part of a medicinal chemistry program we became interested in cyclopropyl piperazine **5**.

We planned to prepare piperazine **5** by the reduction of diketopiperazine **4**, a well-established approach for the synthesis of substituted piperazines.[4] Commercially available *N*-Cbz cyclopropyl amino acid **1** was coupled to glycine methyl ester using HOBt and EDC giving dipeptide **2** in 68% yield. Hydrogenolysis followed by heating oily **3** to 150 °C neat for 10 min cleanly provided **4** as a white solid. However, numerous attempts at reduction of the bislactam rendered unreacted substrate and/or complex mixtures containing **5**.

Concerned about the sensitivity of the aminocyclopropane moiety to the typically harsh reaction conditions required for amide reduction, we considered a milder two-step reduction process via Boc diimide **6**; prepared from **4** by treatment with Boc_2O and DMAP at ambient temperature. A solution of **6** in THF was treated at −78 °C with 4 equiv of DIBAL-H for 1 h giving diol **7** in 84% yield as a 3:1 mixture of diastereomers after an aqueous work-up. Next, a solution **7** in DCM was treated at −78 °C with 4 equiv each of $BF_3{\cdot}OEt_2$ and Et_3SiH for 2 h.[5] To our surprise, the white solid product isolated was not the planned cyclopropyl piperazine derivative but instead the rearranged cyclobutyl piperazine **8**.[6]

Bicycle **8** is a new piperazine which rigidifies the conformation of the piperazine scaffold and may also hinder metabolism. The symmetry of **8** however complicates stereochemical analysis, and so derivative **9**[7] was prepared to desymmetrize the piperazine, which was then subjected to NOESY experiments. The lack of any observed NOE

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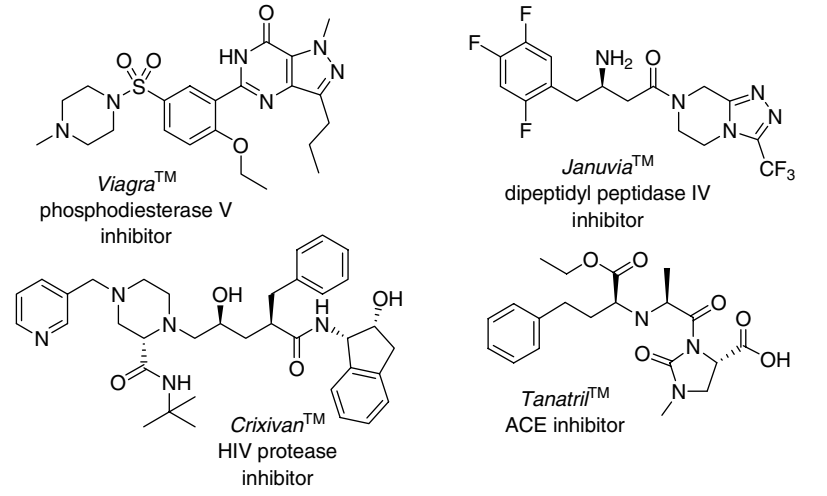
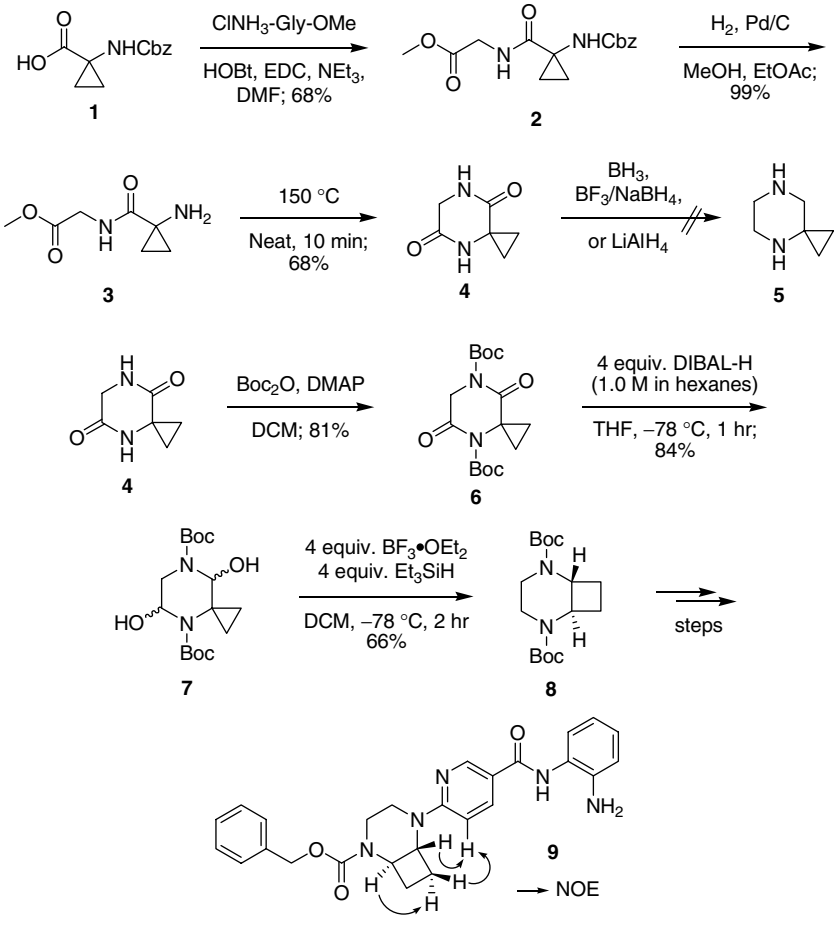


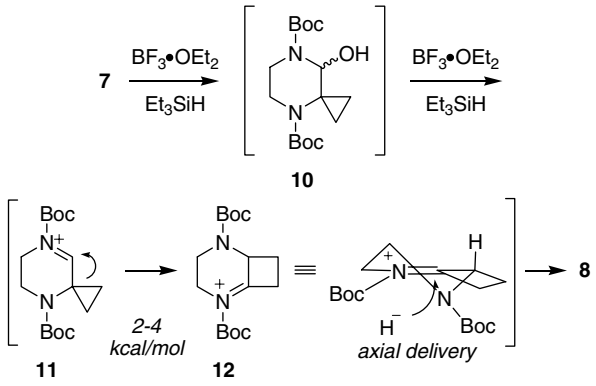


at either methine when the other is inverted, coupled with transannular effects around cyclobutane and with the adjacent pyridine ring clearly indicates that the bicycle is *trans*-fused. The coupling constant of ~7 Hz between methine protons is consistent with this assignment.

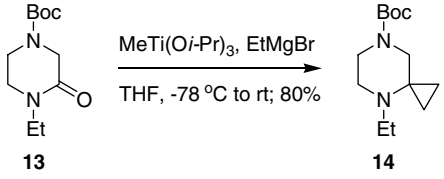
Reduction of diol **7** was nearly as effective using $EtMe_2SiH$ (50% yield) but not with $CyMe_2SiH$ (29% yield), while $(MeO)_3SiH$ gave an uncharacterized mixture of products. Efforts to combine the separate reduction steps in a single pot from **6** failed to yield product **8** in good yield.[8]

It is reasonable that the more accessible alcohol of **7** is reduced first, giving intermediate **10**. A second ionization would then lead to iminium ion **11** which would rearrange to a more stable iminium ion **12**, followed by triethylsilane reduction that would follow an axial trajectory. We estimate that iminium ion **12** is 2–4 kcal/mol lower in energy

than iminium ion **11**, based on DFT and HF calculations at the B3LYP/6-31G* and RHF/6-31++G** levels of theory, respectively.[9] This is consistent with the ring strain energy of a cyclopropane being ~3 kcal/mol greater than that of a cyclobutane.[10]



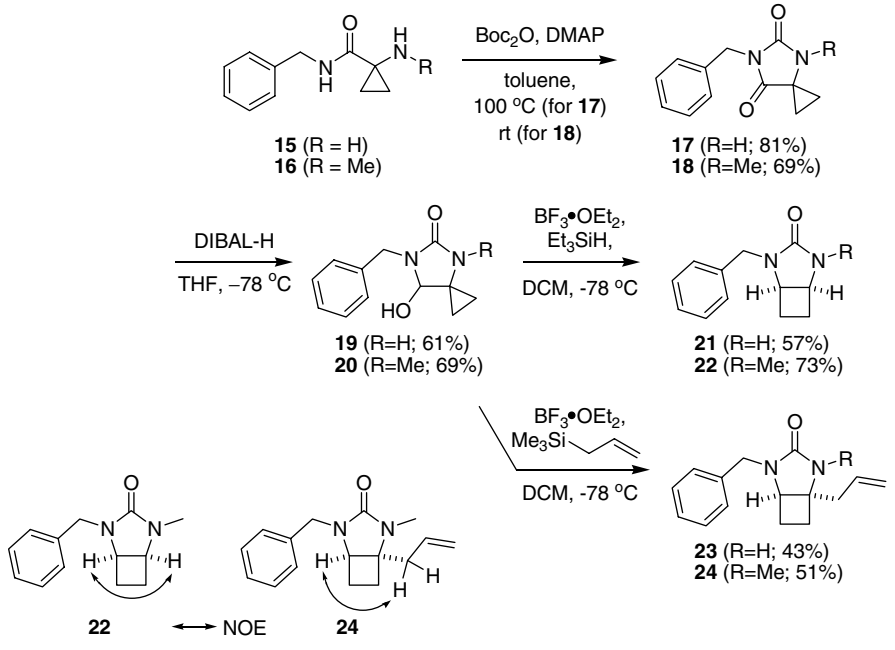
While the rearrangement to form novel bicyclic piperazine **8** is of interest, there remained a need to access cyclopropyl piperazine. Lactam cyclopropanation using a modified Kulinkovich reaction with $MeTi(OiPr)_3$/EtMgBr is a well-established method for the preparation of cyclopropyl amines.[11] Lactam **13** derived from the commercially available phenylpiperazinone undergoes clean cyclopropanation to give **14**.

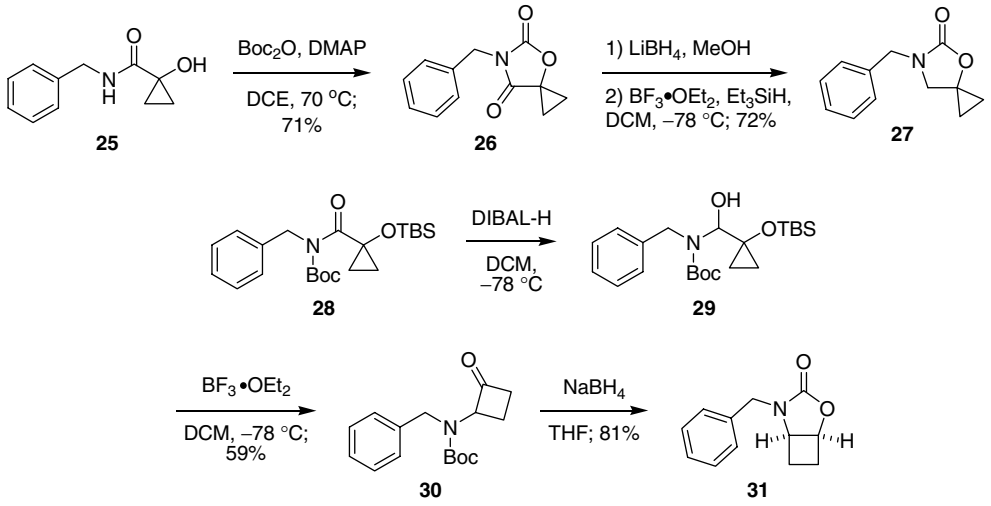


Over the course of exploring this sequence with various imides, we turned to imidazolidinediones such as **17** formed from cyclopropyl aminoamide **15** by treatment with Boc_2O and DMAP at elevated temperature. In contrast, methylamine **16** cyclized rapidly to **18** at ambient temperature.[12] Imidazolidinediones **17** and **18** both react cleanly with DIBAL-H at −78 °C to give hydroxyimidazolidinones **19** and **20** in 61% and 69% yield, respectively. Then as expected treatment with 2 equiv each of $BF_3{\cdot}OEt_2$ and Et_3SiH at −78 °C gave rearrangement to the bicyclic imidazolidinones **21** and **22** in 57% and 73% yields, respectively. Alternatively, trapping the intermediate iminium ions with 2 equiv of allyl trimethylsilane giving **23** and **24** in 43–51% yield is promising for more general carbon incorporation.[13] In contrast to piperazine **8**, NOESY experiments with **22** and **24** indicate a *cis*-fused bicycle.

Oxazolidinedione **26** was prepared in an analogous fashion from amide **25** and reduced with $LiBH_4$ at ambient temperature to give the intermediate hydroxyoxazolidinone. Then in stark contrast to the imidazolidinone series, exposure to 3 equiv each of $BF_3{\cdot}OEt_2$ and Et_3SiH at −78 °C gave clean reduction to **27** in 72% overall yield; this time with the cyclopropane intact. It is likely that the nitrogen in the imidazolidinone series is a better donor than the oxygen in the oxazolidinone.

An alternative route to bicyclic oxazolidinones is from the acyclic silyloxy cyclopropane **28**. Treatment with DIBAL-H at −78 °C gave the acyclic aminal **29** following an aqueous work-up.[14] When a solution of crude aminal **29** in DCM was treated at −78 °C with $BF_3{\cdot}OEt_2$, a rearrangement and concommitant loss of the silyl protective group gave cyclobutanone **30** in 59% overall two-step yield.[15] The addition of triethylsilane had no effect in this transformation. Finally, reduction with $NaBH_4$ provides





25 26 27 28 29 30 31

access to the bicyclic oxazolidinone **31**. This represents a novel route to 2-aminocyclobutanones which are useful substrates for the preparation of various 1,2-disubstituted cyclobutanes.[16]

In conclusion, cyclopropyl ketopiperazinyl and imidazolinedionyl imides undergo reductive rearrangement to the corresponding bicyclic *trans*- or *cis*-fused cyclobutyl derivatives, respectively, by sequential treatment with DIBAL-H and $BF_3{\cdot}OEt_2/Et_3SiH$. The incorporation of an allyl group upon the replacement of Et_3SiH with TMS–allylsilane suggests a more general use for this transformation. The extensive utility of piperazines and imidazolidinones and their derivatives in medicinal chemistry will render these unique analogs of interest in drug discovery.[17]

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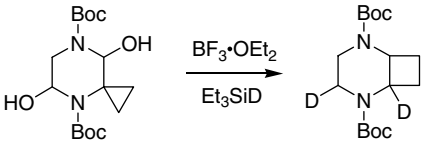
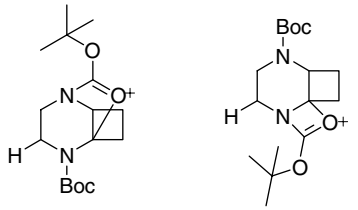
8. As expected, the treatment of diol **7** with $BF_3{\cdot}OEt_2$ and Et_3SiD gave deuterium incorporation:



7 32

9. Participation by either of the Boc protective groups (**33** and **34** below) would not be long-lived species as both were calculated to be of high energy. In addition, **34** was found to be unstable during QM geometry optimization, converting directly to **12**.



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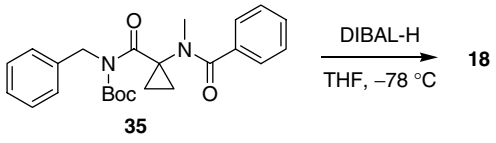
12. Attempted reduction of imide **35** with DIBAL-H induced cyclization giving cyclic urea **18** as the only isolable product. Likewise, Cbz-protected amine **36** was bisprotected as Boc imides at elevated temperature with excess Boc anhydride. However, hydrogenolysis of the Cbz protective group led to rapid cyclization giving **37**.



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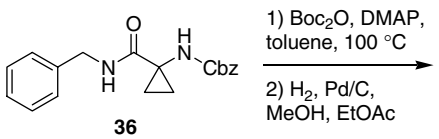

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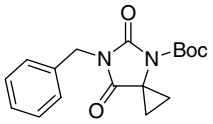

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17. *Representative procedure*: di-*tert*-butyl (1*R*,6*R* and 1*S*,6*S*)-2,5-diazabicyclo[4.2.0]octane-2,5-dicarboxylate (**8**). A stirred solution of di-*tert*-butyl 5,8-dioxo-4,7-diazaspiro[2.5]octane-4,7-dicarboxylate **6** (150 mg, 0.441 mmol) in 2 mL of THF was treated at −78 °C with a 1.0 M solution of DIBAL-H in hexane (1.80 mL, 1.80 mmol) and stirred for 1 h. The reaction mixture was quenched with 2 N Rochelle's salt solution and extracted with DCM. The organic layer was dried (Na_2SO_4), filtered, and concentrated leaving 128 mg (84%) of diol **7** as a 3:1 mixture of diastereomers. Diol **7** (91 mg, 0.26 mmol) was next dissolved in 1.5 mL of DCM and treated at −78 °C with $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) and Et_3SiH (0.20 mL, 1.25 mmol) and stirred for 2 h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The white solid residue was triturated with hexanes to provide 57 mg of **8** (66%). ^1H NMR (600 MHz, DMSO-d_6): 4.22 (br s, 2H), 3.55 (br s, 2H), 3.35 (br s, 2H), 2.08 (br s, 4H), 1.45 (s, 18H); ^{13}C NMR (150 MHz, DMSO-d_6): 155.5, 80.6, 49.8, 41.3, 28.7, 24.7; MS ($M+Na^+$) calculated for $C_{16}H_{28}N_2O_4Na$ 335.2, found 335.3.