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Unusual oxidative rearrangement of 1,5-diazadecalin

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Abstract—Upon treatment with $(PhIO)_n$ or $PhI(OAc)_2$, 1,5-diaza-*cis*-decalin undergoes oxidation at the more hindered position along with fragmentation to yield the ring-expanded bislactam. The *cis* and *trans* 1,5-diazadecalins both undergo the same elimination indicating a potential stereoelectronic preference for oxidation at the more substituted carbon alpha to the nitrogen. Oxidation at the less hindered positions of 1,5-diaza-*cis*-decalin was accomplished on the Boc-protected derivative to provide an intermediate for the synthesis of 2,6-substituted-1,5-diaza-*cis*-decalins.

Previous efforts in our laboratories have identified the 1,5-diaza-*cis*-decalins as useful ligands for asymmetric synthesis.[1,2] One drawback to employing these compounds with weakly coordinating species such as alkyl lithiums, is the presence of an equilibrium between two conformational forms **1-in** and **1-out** (Fig. 1). These conformers readily interconvert by a chair–chair inversion and the position of the equilibrium between **1-in** and **1-out** progressively favors the latter upon substitution with increasingly larger R groups.[3] In an effort to generate compounds disposed toward the conformational arrangement found in **1-in**, we have undertaken the synthesis of substituted 1,5-diaza-*cis*-decalins **2**.[4] The addition of alkyl groups at C2 and C6 with the illustrated relative stereochemistry should shift the position of the equilibrium in these species toward **2-in**.

Bislactam **7** has been identified as a common intermediate which would allow the synthesis of derivatives of **2** with various R′ groups. First, the reported synthesis of lactam **7** from pyrrolidinone was reexamined (Scheme 1).[5] Photodimerization of pyrrolidinone provided a ~1:1 ratio of racemic **3a** and *meso* **3b**. Yields for this reaction were low, consistent with prior reports,[6] but large scale reactions with the inexpensive starting material easily allowed for the synthesis of 20–50 g quantities. On the other hand, purification of the racemic **3a** was laborious since recrystallization did not result in satisfactory enrichment and water needed to be employed in the silica chromatography of this very polar compound. With pure **3a** in hand, we did find that formation of **7** could be optimized. Treatment of **3a** with 6N HCl provided an equilibrium mixture of **4**–**7**. When the course of this reaction was monitored by ^{1}H NMR spectroscopy, the ratio in Scheme 1 was achieved after 10 h and did not change substantially thereafter. In contrast to the work of Rapoport,[5] we subjected the mixture of **4**–**7** directly to esterification and cyclization to provide 63% of **7** in three steps from **3a** (3.5 g scale).

Since the route from pyrrolidinone did not allow the facile production of large quantities, a more efficient entry to bislactam **7** was sought. We had a simple and rapid method for the preparation of quantities of resolved **10**,[1] so the oxidation of 1,5-diazadecalin to the corresponding lactam was investigated (Scheme 2).

Based upon the precedent for the oxidation of **11** and **13** to the respective lactams **12** and **14** with iodosobenzene (Eqs. (1) and (2)),[7] it was anticipated that oxida-

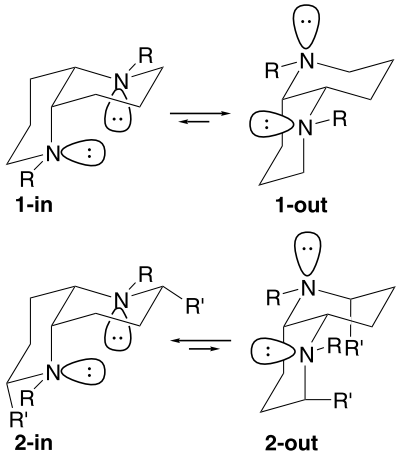

Figure 1.

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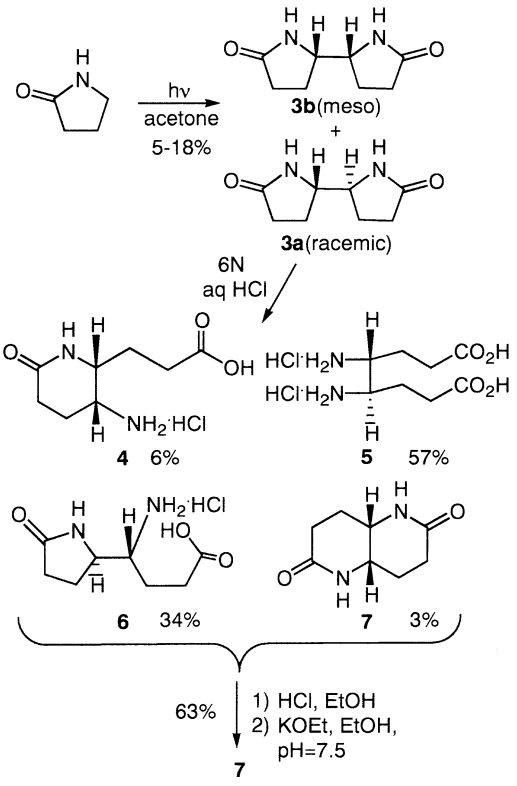
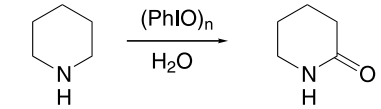
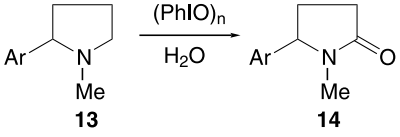


Scheme 1.

tion of 1,5-diaza-*cis*-decalin (**10**) would yield bislactam **7**.

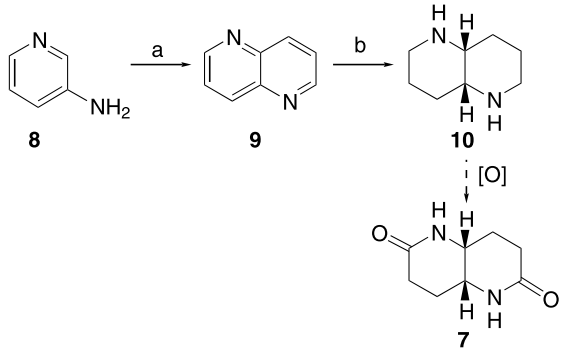


(1)

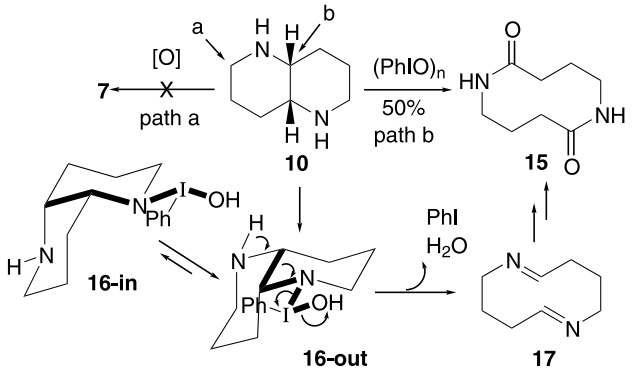


(2)

When 1,5-diaza-*cis*-decalin (**10**) was treated with $(PhIO)_n$ in the presence of water only the ring expanded macrocyclic bislactam **15**[8] was isolated (Scheme 3). From this result it appears that oxidation occurs at the more hindered position ***b*** alpha to nitrogen rather than at the expected less hindered position ***a***. Stereoelectronic control in the elimination of the iodoso species serves to explain this phenomenon. If an iodosoamine intermediate **16** is formed with the iodoso group residing in the less hindered equatorial position, then a clear pathway for a *syn* or *anti* hydrogen elimination is not available. Rather, the orbitals of the ring fusion bond are well aligned for elimination in **16-out**. In this unusual Grob-type variant, the leaving group resides on nitrogen and a second nitrogen functions as an electron donor causing the formation of a bisimine (**17**).[9] This reaction may proceed via direct cleavage of the N–H bond or via fragmentation to a nitrogen-stabilized cation that is subsequently deprotonated. Regardless,



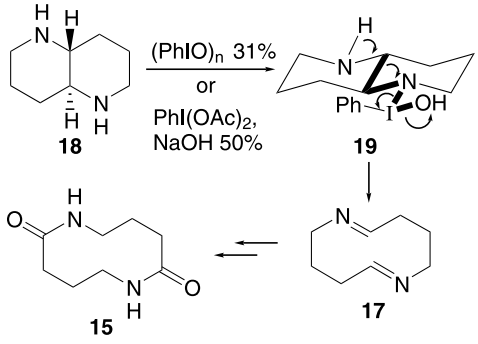
Scheme 2. (a) *m*-NO_2PhSO_3Na, glycerol, H_2SO_4, 140°C, 64%; (b) (i) Rh/Al_2O_3, 1000 psi H_2, rt, 90:10 *cis*:*trans* mixture produced, 95%, (ii) recrystallization.



Scheme 3.

further oxidation of the hydrate of bisimine **17** results in oxidation at position ***b*** to furnish bislactam **15**.

The 1,5-diaza-*cis*-decalins are conformationally mobile such that another conformation **16-in** may also be present. This species, with the large iodoso group(s) on nitrogen, is expected to be less stable than the **16-out** form and also does not provide a stereoelectronically favorable pathway to oxidation at position ***a***.[3] The 1,5-diaza-*trans*-decalin (**18**) undergoes a similar fragmentation/oxidation reaction although better yields are obtained when $(PhIO)_n$ is generated in situ (Scheme 4). In this case, conformational exchange is absent and the two nitrogens are in an *anti* relationship. In the resultant iodoso intermediate **19**, the orbitals of the ring fusion bond are similarly aligned for a fragmentation to



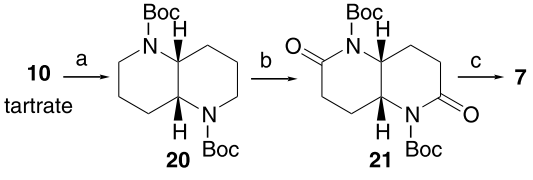
Scheme 4.

yield bisimine **17** whereas none of the alpha hydrogens are oriented periplanar to the N–I bond.

Other oxidants were examined to see if the regiochemical results might be reversed. The use of $RuO_2/NaIO_4$[10] or CrO_3·pyridine[11] led only to decomposition. As such, an approach towards **7** was undertaken in which free diamine **10** was protected in the form of bis-Boc carbamate **20** (Scheme 5). Protection of the amines as carbamates was anticipated to lessen the electron rich character of the nitrogen making it a poorer initiator for the fragmentation. Subsequent oxidation with $RuO_2/NaIO_4$ generated bislactam **21** cleanly in 84% yield with oxidation taking place at the less hindered centers. Deprotection of **21** afforded **7** in quantitative yield. The regiochemistry of the oxidation and the stereochemistry of the ring fusion in **7** was secured from the X-ray crystal structure (Fig. 2).[12]

The X-ray structure also reveals several unusual features for **7**. The conformation of **7** is assigned as **7-in** since the two nitrogens are in a *gauche* arrangement (Fig. 2). Each lactam ring of this strained bicyclic compound adopts a half-chair conformation. This structure is surprisingly bent with a ~75° angle between the two carbonyl groups. Apparently, the 1,4-interactions of **7-out** are more severe than the $A^{1,3}$-interactions arising from the endocyclic amides of **7-in**. This stands in contrast to **20** which contains exocyclic amide bonds and adopts the 'out' conformation in solution[3a,13] and in the X-ray structure (Fig. 2).[12] In this case, the $A^{1,3}$-interactions of **20-in** are more severe than the 1,4-interactions of **20-out**.

With the required intermediate **21** in hand, compounds such as **2** could be prepared (Scheme 6). For example, enolization of **21** and trapping with *N*-(5-chloro-2-pyridyl)triflimide was readily performed to yield bistriflate **22** in 93% yield.[14] Suzuki coupling then provided bisenamide **23** in 97% yield. Removal of the Boc protecting groups was accompanied by isomerization of the double bond into the internal position to afford bisimine **24**. Stereoselective reduction of this bisimine from the *exo* face of the fused bicyclic ring system provided the 2,6-diphenyl derivative **2a**. The stereochemistry of the reduction was very sensitive to the reducing agent with a rhodium-catalyzed hydrogenation proving the most effective in providing the indicated diastereomer.



Scheme 5. (a) Boc_2O, NaOH, 94%; (b) RuO_2, $NaIO_4$, 84%; (c) TFA.

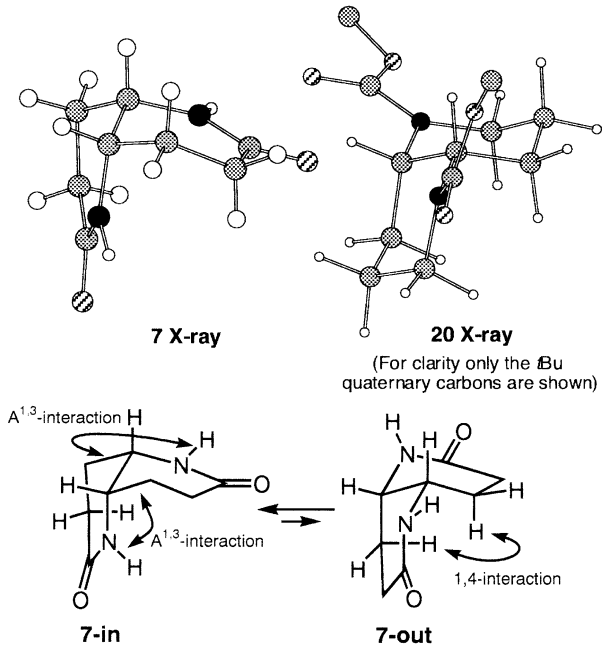
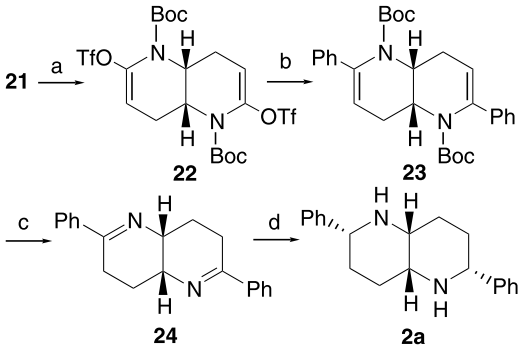


Figure 2.



Scheme 6. (a) (i) LiHMDS, –78°C, (ii) $ArNTf_2$, 93%; (b) $(Ph_3P)_2PdCl_2$, $PhB(OH)_2$, Na_2CO_3, 50°C, 97%; (c) TFA; (d) H_2, Rh/Al_2O_3, HOAc, 43% from **23**.

Acknowledgements

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8. 1,5-Diaza-*cis*-decalin (**10**, 35 mg, 0.25 mmol) was added to a stirred suspension of $(PhIO)_n$ (230 mg, 1.04 mmol) in distilled water (5 mL) in an ice-water bath. After stirring for 1 h at 9°C and 24 h at rt, the slurry was filtered. The filtrate was extracted with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$. After filtration and concentration, the crude product was purified by chromatography (SiO_2, 10% $MeOH/CH_2Cl_2$) to yield **15** in 50% yield (21 mg, 0.12 mmol) as an oil. 1,5-Diaza-*trans*-decalin (**18**, 138 mg, 0.98 mmol) was oxidized in a similar manner to provide **15** in 31% yield (52.7 mg, 0.31 mmol) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (br, 2H, 2N**H**), 3.36 (t, $J=7.1$ Hz, 4H, 2COC$\mathbf{H}_2$CH$_2$), 2.25 (t, $J=7.1$ Hz, 4H, 2NHC$\mathbf{H}_2$CH$_2$), 2.08 (quintet, $J=7.1$ Hz, 4H, 2CH$_2$C$\mathbf{H}_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 42.7, 30.5, 21.2; IR ($CDCl_3$ soln) 3220–3440 (br), 2965, 2899, 1640–1680 cm^{-1}.
9. For a related Grob fragmentation from a 1-aza-*cis*-decalin, see: LeBel, N. A.; Caprathe, B. W. *J. Org. Chem.* **1985**, *50*, 3940–3942.
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12. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 178870 (**7**) and 178871 (**21**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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