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Stereoselective reductions of *N*-Boc-hexahydro-1*H*-indolin-5(6*H*)-ones

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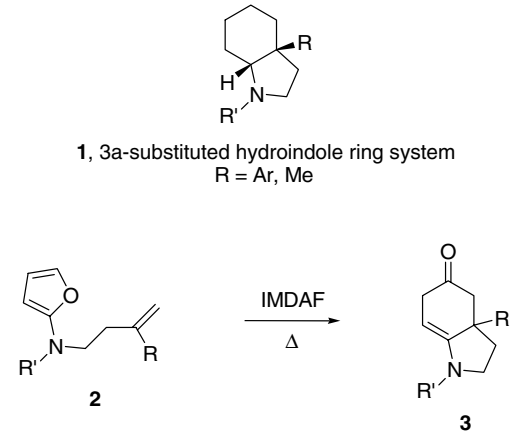
Abstract—We report the divergent effects of a 3a-methyl and 3a-phenyl substituent on the chemoselectivity and stereoselectivity of reduction of the enamide moiety of *N*-Boc-hexahydro-1*H*-indolin-5(6*H*)-ones. Under ionic reduction conditions (triethylsilane/trifluoroacetic acid) the enamide group of 3a-methyl-*N*-Boc-hexahydro-1*H*-indolin-5(6*H*)-one was reduced to afford exclusively a cis ring-fused product. For the 3a-phenyl substituted analogue more forcing conditions (sodium cyanoborohydride at pH 2–2.5) were required and resulted in the selective reduction of the enamide group to give a trans ring-fused product as well as reduction of the ketone group.

The 3a-substituted hydroindole skeleton **1** is a key subunit of the *Sceletium* alkaloids,[1] crinine-type *Amaryllidaceae* alkaloids[2] (R = Ar) and the alkaloid dendrobine (R = Me).[1] In the last few years Padwa et al. have established that the intramolecular Diels–Alder cyclization of alkenyl-substituted 2-amidofuran derivatives **2** (IMDAF) is a convenient method for assembling 3a-substituted hexahydroindolin-5-one species **3** (Scheme 1).[3–7] In order to apply the IMDAF products to the synthesis of 3a-substituted hydroindoles and analogues, the selective reduction of the enamine moiety is required. For the majority of natural product systems there is a cis-relationship between the 3a-substituent and the ring-junction proton. Herein we describe a study involving an improved preparation of 3a-methyl- and 3a-phenyl-hexahydroindolin-5-one and exploration of stereoselectivity in the reductions of these molecules.



Scheme 1.

3a-Methyl-hexahydroindolin-5-one **4** was prepared using the protocol reported by Padwa et al.[5] with optimization at each step to ensure that the process was amenable to larger scale operations (Scheme 2). Furoic acid was converted to the Boc-protected aminofuran **5** using diphenylphosphorazidate in refluxing *tert*-butanol.[3,8,9] We improved the procedure[3] for the formation of **5** by employment of a stoichiometric amount of

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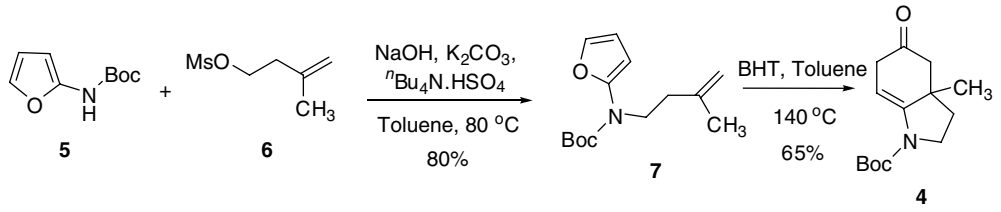
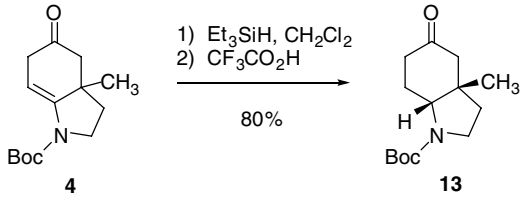


Scheme 2.

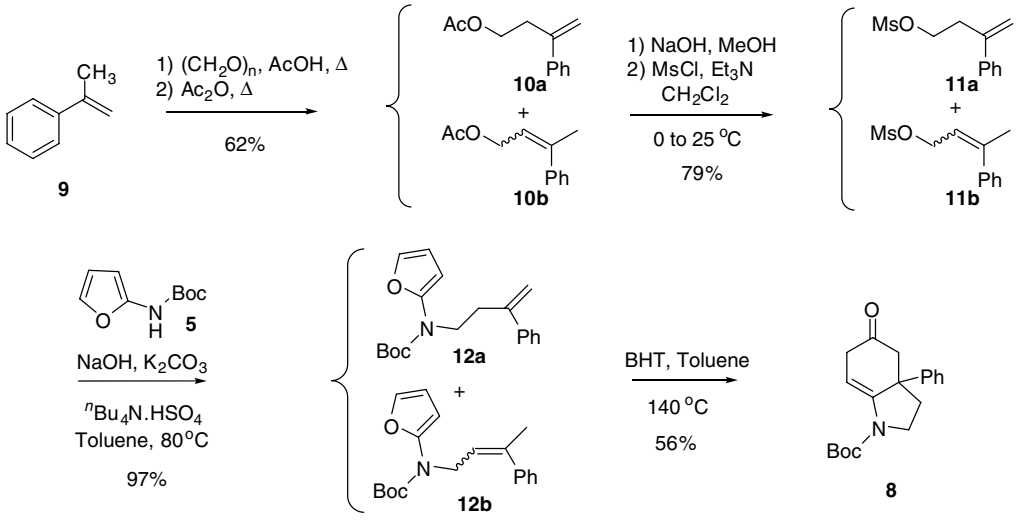
phosphorazidate and use of an alkaline aqueous work-up, rather than chromatography, to remove the diphenylphosphate by-product. Alkylation of freshly prepared carbamate **5** with crude mesylate **6**,[10] afforded the alkenyl-substituted carbamate **7** in high yield after purification through a short column of silica.[12] The intramolecular [4+2]-cycloaddition/rearrangement cascade reaction of **7** was performed in toluene rather than the relatively toxic benzene as first reported.[5] It was found that maintenance of the temperature at 140 °C over 2 days in a sealed tube containing the antioxidant 2,6-di-*tert*-butyl-4-methyl phenol (BHT) gave an optimal yield of the known 3a-methyl-hexahydroindolin-5-one **4**. At higher temperatures (150 °C and above) the reaction was completed in a shorter time; however, the yield of isolated product was lower due to the formation of significant amounts of polymeric side products. For reaction temperatures below 130 °C, the cycloaddition reaction was too sluggish to be practical. Using the optimal conditions, over 70 g of ketoenamide **4** was obtained in 48% overall yield from furoic acid.

3a-Phenyl-hexahydroindolin-5-one **8** was prepared from α-methylstyrene (**9**) (Scheme 3).[13] Styrene **9** was condensed with formaldehyde and acetic anhydride[14] to give acetate **10a** (as a ca. 5:1 mixture with isomer **10b**).[15] Acetate hydrolysis followed by mesylation under standard conditions gave mesylates **11a/b**. N-Alkylation of furanyl carbamate **5** with mesylates **11a/b** afforded excellent yields of the styrenyl-substituted amidofurans **12a/b**. As with the methyl analogue, optimal conditions for the intramolecular [4+2]-cycloaddition/rearrangement cascade reaction of amidofuran **12a** in toluene involved heating crude amidofurans **12a/b** and BHT in a sealed tube at 140 °C for 2 days. This procedure gave a mixture of the hexahydroindolin-5-one **8** and unreacted alkene **12b**. Ketoenamide **8** was isolated in 56% yield after silica gel chromatography. This methodology allowed for efficient production of over 30 g of the required phenyl-substituted ketoenamide **8** in 27% overall yield from α-methylstyrene (**9**).

Chemo- and stereoselective reduction of the enamide moiety of **4** was effected using triethylsilane in the presence of TFA[16,17] to afford a high yield of ketone **13** as a single product (Scheme 4). Interestingly, the order of addition of the reagents was crucial for the success of this reaction. When triethylsilane was added to the substrate prior to the TFA good reproducible yields of **13** resulted. In contrast, when TFA was added before triethylsilane rapid degradation of the starting material



Scheme 4.



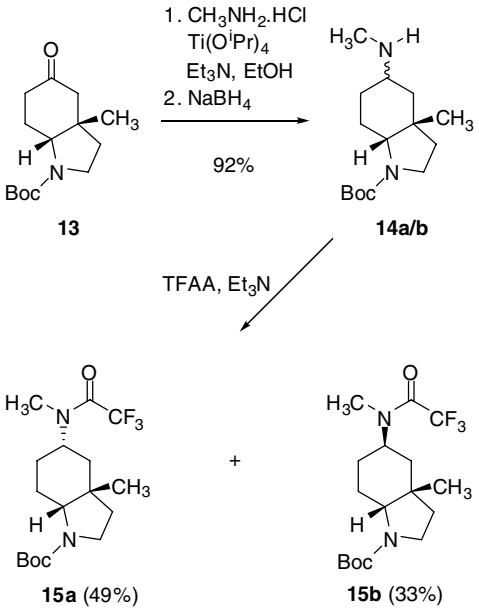
Scheme 3.

was observed resulting in the formation of an intractable material. Neither **4** nor **13** were recovered when the residue was treated with di-*tert*-butyl-dicarbonate in the presence of base indicating that the degradation did not simply involve TFA-promoted loss of the Boc group.[4]

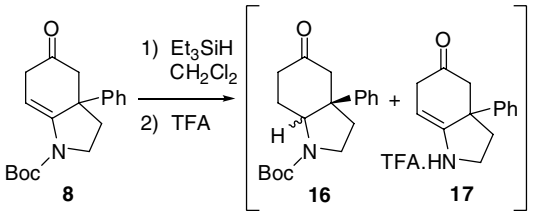
Ketone **13** was initially assigned cis ring fusion stereochemistry based on NMR NOE studies. As the cis-stereoselectivity of the triethylsilane/TFA reduction of the methyl analogue **4** did not correspond to the previous report of trans-stereoselectivity for an aryl-substituted analogue,[6] we sought to confirm the NOE stereochemical assignment by the X-ray structure determination of **13** or a derivative. While the low melting ketone **13** proved unsuitable for such analysis, a crystalline derivative of **13** was obtained (Scheme 5). Thus, reductive methylamination of **13** using the procedure of Bhattacharyya and co-workers[18] gave a 3:2 mixture of diastereomeric methylamines, **14a** and **b**, obtained as an oil in 92% yield. Methylamines **14** were converted to the corresponding trifluoroacetamides **15a** and **b** (ca. 3:2 ratio), which were separated by chromatography. Crystals of minor trifluoroacetamide **15b** suitable for X-ray analysis were obtained. The resultant crystal structure determination of **15b** clearly shows a cis-relationship between the ring-junction substituents (Fig. 1),[19] and therefore confirms the cis ring-fusion stereochemistry of precursor ketone **13**.

In contrast to the methyl-substituted analogue, attempted selective enamide reduction of **8** with triethylsilane and TFA gave poor results. On a single occasion an enamide reduction product **16** (ring-fusion stereochemistry not determined) was isolated in 18% yield (Scheme 6); however, this result could not be repeated. We suspect that a side reaction, involving acid-promoted cleavage of the Boc-group occurs to give **17** (and/or the imine tautomer), predominates over the required enamide reduction. Consistent with this suspicion was the observation that subjection of the crude product, from an attempted triethylsilane/TFA reduction of **8**, to trifluoroacetic anhydride in the presence of base produced a trifluoroacylated derivative of **17**.

Alternative methods for the stereoselective reduction of enamide **8** were explored. Treatment with sodium borohydride in methanol or ethanol or with Raney Nickel resulted in reduction of the ketone and not the enamide. The use of sodium cyanoborohydride in acetic acid[20] resulted in competitive enamide and ketone reductions and a mixture of all four possible diastereoisomers **18** was obtained. In this case, little selectivity was observed, for instance, major isomer **18a** represented only 40% of the mixture of products **18**, as assessed by HPLC analysis. The reduction of **8** with sodium cyanoborohydride in acidic aqueous methanol[21] was explored and the stereoselectivity of the reduction under these conditions



Scheme 5.



Scheme 6.

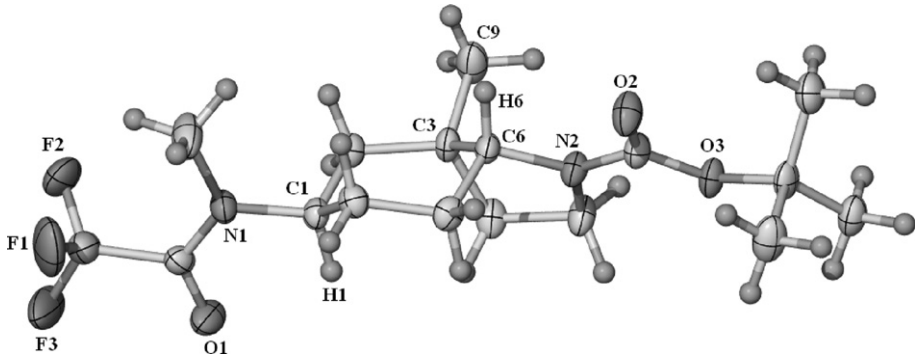
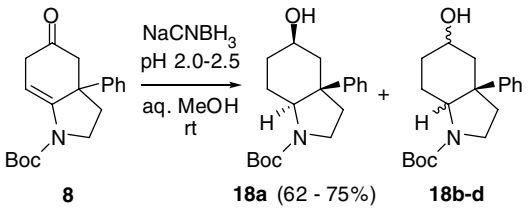


Figure 1. ORTEP diagram of trifluoroacetamide **15b**, illustrating the cis relationship between the ring-junction proton H6 and methyl C9 substituent.



Scheme 7.

was significantly improved (Scheme 7). The effect of pH on conversion rate and stereoselectivity was studied with the optimal conditions for the formation of the major isomer **18a** being pH 2–2.5 (the pH was controlled by addition of 2 M HCl) at room temperature. Attempts to further improve the stereoselectivity by lowering the temperature to 0 °C resulted in unacceptably low conversion rates. Under the optimal conditions, HPLC analysis indicated that the major isomer **18a** represented 80% of the product mixture and could be isolated in 75% yield after chromatography on silica. A larger scale preparation yielded 20 g of analytically pure **18a** in 62% yield after chromatography and recrystallization.

The stereochemistry of major alcohol **18a** was unequivocally determined by single crystal X-ray structure analysis (Fig. 2). The crystal structure clearly shows a trans-relationship between the ring-junction phenyl and hydrogen groups and a cis-relationship between the phenyl group and the alcohol group.[19]

We have found that the ring-junction substituent in **4** (methyl) or **8** (phenyl) has a marked effect on the enamide reactivity and the stereoselectivity of the reduction of the enamide moiety in *N*-Boc-hexahydroindolin-5-ones. The molecular models of compounds **4** and **8** indicate that they are bowl-shaped with the 3a-substituent situated on the convex side of the hexahydroindolinone framework. The shape of the molecule would favour reduction of the enamide from the same face of the molecule as the substituent. Thus for enamide **4**, triethylsilane/TFA reduction (so-called ionic reduction conditions) afforded cis-product **13.** For enamide **8**, the bulkier phenyl substituent hinders reduction from the same face of the molecule as the phenyl group. This results in negligible reduction of the enamide under ionic hydrogenation conditions. Under more forcing conditions (i.e., sodium cyanoborohydride at pH 2–2.5) enamide and ketone reductions both occur, but from the concave face of the molecule to give the trans ring-fused product **18a**.

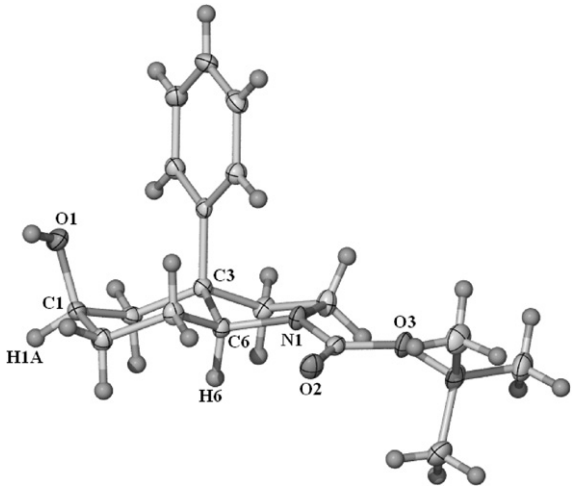


Figure 2. ORTEP diagram of alcohol **18a**, illustrating the trans relationship of the ring-junction proton H6 and phenyl substituent.

In summary, the synthesis of hexahydroindolin-5-ones via IMDAF chemistry has been developed so as to be amenable for large-scale chemistry. Our preliminary results for the reduction of the hexahydroindolin-5-ones show that the ring-junction substituent plays an important role in the reduction of the enamide moiety. The smaller methyl substituent favours formation of the cis ring-fused product, whereas the larger phenyl substituent results in favoured reduction to the trans ring-fused product.

Acknowledgements

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Supplementary data

Experimental procedures and analytical data for all new compounds. X-ray experimental procedures for compounds **15b** and **18a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.078.

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10. Mesylate **6** was prepared from 3-methyl-3-buten-1-ol using standard procedures. The original procedure for the preparation of **7**[5] involved the conversion of **6** into the corresponding bromide[11] for N-alkylation of **5**. The alkylating agent **6** was found to be sufficiently reactive for N-alkylation of **5**.
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12. Chromatographic purification of intermediate **7** facilitated the purification of **4** after the IMDAF reaction.
13. An alternative approach utilizing α-(bromoethyl)styrene was considered, involving acylation of benzene with 3-bromopropionyl chloride followed by methylenation of the aryl ketone product with Tebbe's reagent.[6] The current route was chosen on the basis that it would be less expensive and more amenable to larger scale production.
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19. Crystal data for minor trifluoroacetamide **15b**: $C_{17}H_{27}F_3N_2O_3$, $M = 364.41$, $0.20 \times 0.10 \times 0.10$ mm, triclinic, space group $P\text{-}1$ (No. 2), $a = 6.3551(13)$, $b = 11.069(2)$, $c = 14.080(3)$ Å, $\alpha = 106.72(3)$, $\beta = 95.73(3)$, $\gamma = 92.22(3)°$, $V = 941.5(3)$ Å^3, $Z = 2$, $D_c = 1.285$ g/cm^3, $F_{000} = 388$, Nonius Kappa CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 123(2)$ K, $2\theta_{max} = 55.5°$, 12,716 reflections collected, 4393 unique ($R_{int} = 0.0968$). Final GooF = 1.035, $R_1 = 0.0601$, $wR_2 = 0.1432$, R indices based on 2499 reflections with $I > 2$sigma(I) (refinement on F^2), 231 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.107$ mm^{-1}. Crystal data for major alcohol **18a**: $C_{19}H_{27}NO_3$, $M = 317.42$, colourless flat extended plates, $0.20 \times 0.20 \times 0.10$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 16.434(3)$, $b = 6.2497(12)$, $c = 17.761(4)$ Å, $\beta = 112.36(3)°$, $V = 1687.1(6)$ Å^3, $Z = 4$, $D_c = 1.250$ g/cm^3, $F_{000} = 688$, Nonius Kappa CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 123(2)$ K, $2\theta_{max} = 55.7°$, 15,631 reflections collected, 3969 unique ($R_{int} = 0.0841$). Final GooF = 1.017, $R_1 = 0.0457$, $wR_2 = 0.1008$, R indices based on 2472 reflections with $I > 2$sigma(I) (refinement on F^2), 212 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.084$ mm^{-1}. Crystallographic data (excluding structure factors) for the structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications Nos. CCDC-626810 for compound **15b** and CCDC-626809 for compound **18a**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK {fax: (+44) 1223 336 033; email: deposit@ccdc.cam.ac.uk}.
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