Iodine-mediated Ring Closing Alkene Iodoamination with N-Debenzylation for the Asymmetric Synthesis of Polyhydroxylated Pyrrolidines

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Abstract: An iodine-mediated ring closing alkene iodoamination with N-debenzylation protocol provides a direct route for the asymmetric synthesis of polyhydroxylated pyrrolidines from homochiral β-amino acid derivatives.

Key words: conjugate addition, iodoamination, debenzylation, cyclisation, pyrrolidine

The stereoselective syntheses of pyrrolidines and piperidines are of widespread academic and pharmaceutical interest, both as natural product targets and for potential applications in asymmetric synthesis. Within this expanding field, the synthesis of polyhydroxylated derivatives of these nitrogen heterocycles is of particular interest, as these sugar mimics exhibit a diverse range of biological activities, including potential as anti-HIV candidates[1] and as glycosidase inhibitors.[2] As a result, a range of methodologies for their synthesis has been developed, including manipulation of carbohydrates[3] and the application of asymmetric synthesis.[4] Previous work from this laboratory has shown that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters provides a general methodology for the asymmetric synthesis of β-amino acids.[5] As an extension of this versatile methodology we report herein a stereoselective iodine-mediated ring closing alkene iodoamination with concomitant N-debenzylation for the asymmetric synthesis of polyhydroxylated pyrrolidine β-amino acid derivatives.[6]

Conjugate addition of homochiral lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to the α,β-unsaturated acceptor (4*S*,5*R*)-**1**[7] gave β-amino ester (3*S*,4*S*,5*R*)-**2** in 88% de, and after purification in 70% isolated yield with >98% de.[8] Treatment of β-amino ester (3*S*,4*S*,5*R*)-**2** with iodine in MeCN in the presence of $NaHCO_3$ gave a chromatographically separable 81:19 mixture of *N*-benzyl pyrrolidines **4**:**5** in 63% and 17% isolated yield respectively and as single diastereoisomers in each case, in which ring closure to the pyrrolidine and chemoselective N-deprotection had been effected in a single reaction step. Furthermore, *N*-α-methylbenzylacetamide (**6**) was also isolated, whose specific rotation {$[\alpha]_D^{25}$ –3.8 (*c* 0.7, $CHCl_3$); lit.,[9] $[\alpha]_D^{25}$ +129.5 (*c* 1.0, $CHCl_3$)} indicated that essentially complete racemisation of the *N*-α-methylbenzyl stereocentre had occurred during the Ritter reaction. This N-deprotection protocol shows remarkable chemoselectivity, with the selective removal of the *N*-α-methylbenzyl group in the presence of the N-benzyl group being in direct contrast to the previously reported chemoselective N-debenzylations under oxidative[10] or hydrogenative[11] conditions that have been developed upon similar systems from within this laboratory. The isolation of racemic *N*-α-methylbenzylacetamide (**6**) and pyrrolidines **4** and **5** from this reaction manifold is consistent with the mechanism of this transformation involving iodonium ion formation and intramolecular trapping by the tethered tertiary amine to give quaternary ammonium species **3**. Preferential S_N1 loss of the *N*-α-methylbenzyl protecting group from **3** accounts for the remarkable chemoselectivity observed in this reaction, with trapping of the resultant carbocation with MeCN and subsequent hydrolysis giving (*RS*)-*N*-α-methylbenzylacetamide (**6**) (Scheme 1). This protocol of cyclisation and N-debenzylation therefore offers a simple direct stereoselective entry to polyhydroxylated pyrrolidines.[12,13]

With the pyrrolidine skeleton in hand from this novel debenzylation protocol, functionalisation of the primary iodide was investigated. Treatment of iodide **4** (>98% de) with AgOAc in toluene gave the acetate **7** as a single diastereoisomer in 79% yield after purification. However, similar exposure of the diastereoisomeric iodide **5** to identical conditions gave an inseparable 45:55 mixture of the pyrrolidine and piperidine acetates **9**:**10** in 82% overall yield. The possible intermediacy of an aziridinium ion in these transformations from participation of the adjacent N-atom is well precedented,[14] with mechanistic studies indicating that the regioselectivity of aziridinium opening is dependent upon the nature of the nucleophile[15] and solvent[16] and both steric and electronic substituent effects.[17] To probe the involvement of an aziridinium ion in this protocol, treatment of iodide **4** with $AgBF_4$ gave the isolable aziridinium **8** in quantitative yield, which upon treatment with NaOAc in toluene gave acetate **7** as a single diastereoisomer in 70% yield. Treatment of the diastereoisomeric iodide **5** with $AgBF_4$ similarly gave a quantitative yield of aziridinium **11**, which upon treatment with NaOAc in toluene gave a 45:55 mixture of the pyrrolidine and piperidine acetates **9**:**10** in 62% isolated yield, confirming the intermediacy of an aziridinium ion in each AgOAc promoted displacement (Scheme 2).

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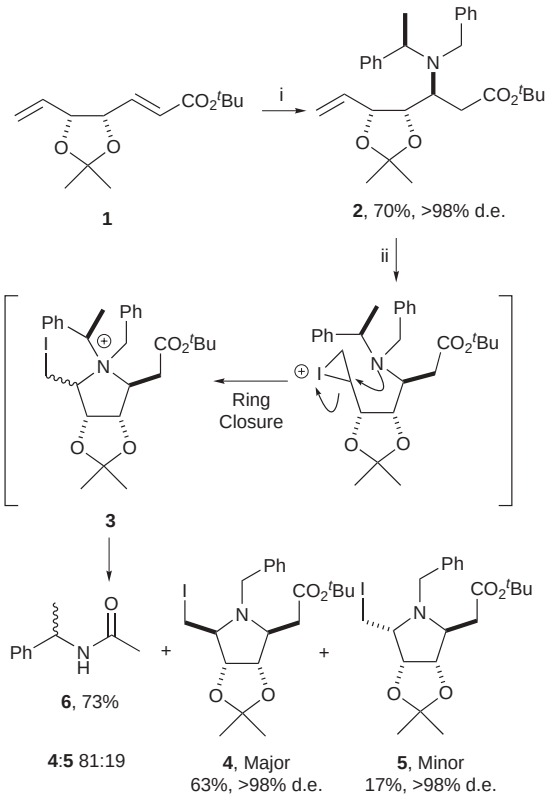
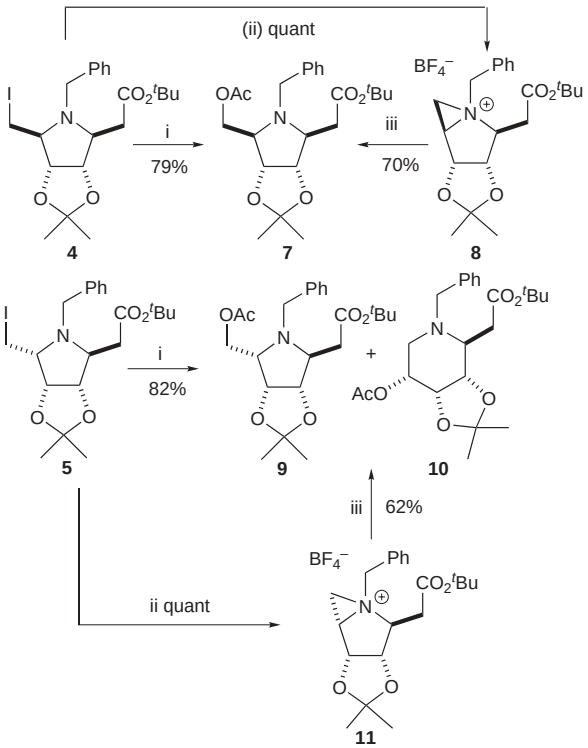
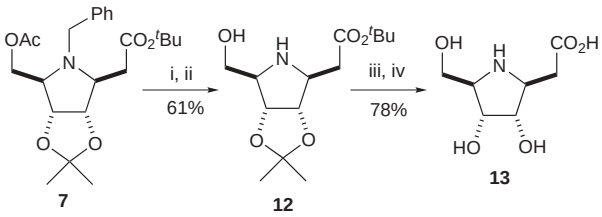


Scheme 1 *Reagents and conditions:* (i) Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, Et_2O, –20 °C; (ii) I_2, $NaHCO_3$, MeCN.



Scheme 2 *Reagents and conditions:* (i) AgOAc, toluene, r.t.; (ii) $AgBF_4$, CH_2Cl_2, r.t.; (iii). NaOAc, toluene, r.t.

In the major diastereoisomeric series, N-debenzylation of **7** followed by basic hydrolysis of the acetate gave the alcohol **12** in good yield and as a single diastereoisomer, the absolute configurations within which were established unambiguously by X-ray crystallographic analysis, relative to the known absolute configurations of the (3*R*,4*S*)-stereocentres derived from D-ribose (Figure 1).[18] Subsequent acidic hydrolysis and ion exchange gave the desired β-amino acid **13** in 78% yield as a single diastereoisomer (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) $Pd(OH)_2$ on C, MeOH, H_2 (1 atm); (ii) K_2CO_3, MeOH; (iii) TFA then H_2O; (iv) Dowex 50W-X8.

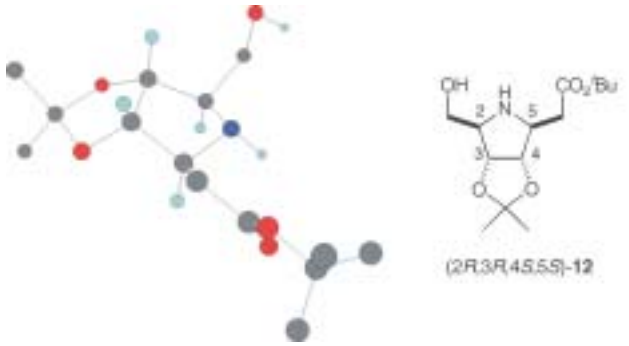


Figure 1 Chem 3D representation of the X-ray crystal structure of (2*R*,3*R*,4*S*,5*S*)-**12**.

In conclusion, the protocol described herein delineates a rapid and efficient route for the asymmetric synthesis of polyhydroxylated pyrrolidines. The generality of this transformation and its application to natural product synthesis is currently under investigation.

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(18) The crystal structure of the hemi-hydrate of **12** was solved; crystal data for **12**, $C_{14}H_{25}NO_5 \cdot 0.5\ (H_2O)$, colourless plate, M = 296.36, monoclinic, space group C121, a = 23.8038 (15) Å, b = 5.9100 (5) Å, c = 12.0009 (9) Å, U = 1654.3 (2) Å^3, Z = 4, μ = 0.091, crystal dimensions 0.05 × 0.1 × 0.5 mm. A total of 2081 unique reflections were measured for 5<θ<30 and 1705 reflections were used in the refinement. The final parameters were wR_2 = 0.053 and R_1 = 0.045 [I>3σ(I)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre (CCDC 225944).