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An Enantioselective Route to Pyrrolidines: Removal of the Chiral Template from Homochiral Pyrroloimidazoles

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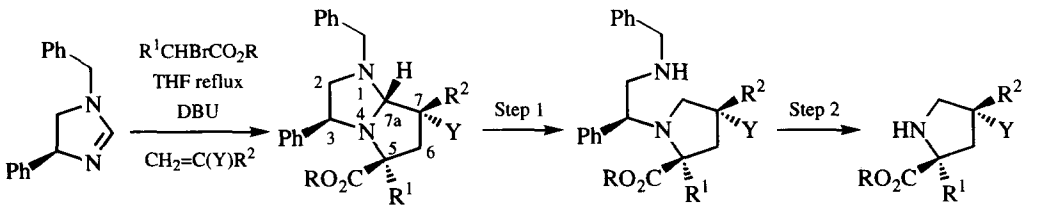
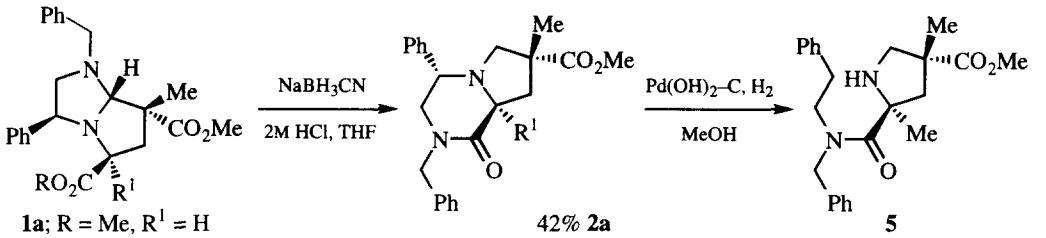
Abstract: Two-step reductive removal of the chiral template from optically active pyrroloimidazoles, available from 1,3-dipolar cycloaddition of homochiral imidazolinium ylides, gives optically active substituted pyrrolidines. Selective manipulation of the substituents affords, e.g. naturally occurring proline derivatives and homochiral pyrrolizidines.

We have recently discovered a new route to homochiral pyrroloimidazoles **1a-l** by the 1,3-dipolar cycloaddition of imidazolinium ylides, whereby three of the five bonds in the new pyrrolidine ring are formed in 'one-pot', and now report extension of this work to the production of homochiral pyrrolidines.[2] Removal of the templating atoms from the pyrrolidine ring requires cleavage of the C(7a)–N1) and C(3)–N(4) bonds of the pyrroloimidazole, Scheme 1. It was envisaged that this could be accomplished by a two-step reductive sequence. Previous studies indicated that step 1, reduction of the aminal function ($NaBH_3CN$, pH 1), should occur exclusively with C(7a)–N(1) bond cleavage.[3] It was anticipated that step 2, removal of the benzylic N-substituent, could be effected by hydrogenolysis.



1a-l **Scheme 1**

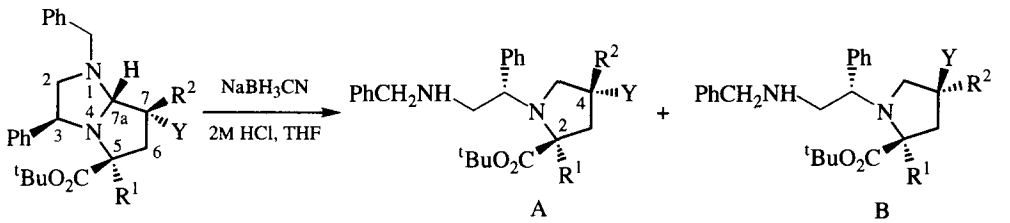
Aminal reduction ($NaBH_3CN$, 2M HCl, EtOH) of the C-5 methoxycarbonyl pyrroloimidazole **1a** or its enantiomer **1b** resulted solely in lactamisation to pyrrolopyrazines **2a** and **2b**, respectively, Scheme 2; the C-5 ethoxycarbonyl pyrroloimidazole **1c** similarly cyclised to **2c**. Although in certain cases these pyrrolopyrazines may be employed in the hydrogenolysis reaction, *vide infra*, the cyclisation is undesirable and complicates template removal. Earlier work had demonstrated that lactamisation could be suppressed by performing the reduction in acetic acid with inclusion of acetic anhydride to acylate the incipient secondary amine.[4] However, it was necessary to employ a large excess of acetic anhydride, and the resulting multi-component product mixture complicated purification. Reduction in TFA/TFAA also proved unsuccessful.



Scheme 2

Increasing the steric hindrance of the C-5 ester was found to suppress completely the undesired lactamisation. Thus C-5 *t*-butoxycarbonyl cycloadducts **1d-l** were reduced in near quantitative yield ($NaBH_3CN$, 2M HCl, THF) to the N-substituted pyrrolidines **3a-m**, Scheme 3. Attempted purification by column chromatography proved difficult, resulting in extensive loss of material; fortunately the crude pyrrolidines could be employed directly in the hydrogenolysis step. An unexpected difficulty was that pyrroloimidazoles mono-substituted at C-7 (R^2 = H) yielded pyrrolidines partially epimerised at C-4. It was found that use of a large excess (10 mol equiv.) of acid, followed immediately by rapid addition of exactly one mol equiv. of $NaBH_3CN$ gave acceptable epimer ratios in favour of the 2,4-*trans* isomers.[5] Thus reduction of **1h** produced a 5:1 *trans:cis* mixture of C-4 epimers **3e** and **3f**, respectively, whilst adducts **1j** and **1k**, from *t*-butyl acrylate, afforded **3i** and **3j** in an isomer ratio of 3:1 in favour of *trans*. Due to the difficulties encountered in purifying these N-substituted pyrrolidines the epimer mixture was carried directly through to the hydrogenolysis step.

Cleavage of the benzylic C–N bond in **3** completes template removal to reveal the homochiral pyrrolidines **4a-m**. Hydrogenolysis of **3a** [Pd-C, H_2 (1 atm.), AcOH] or treatment with ACE-Cl[6] resulted in extensive decomposition and none of the expected product. Changing to Pearlman's catalyst [$Pd(OH)_2$, with



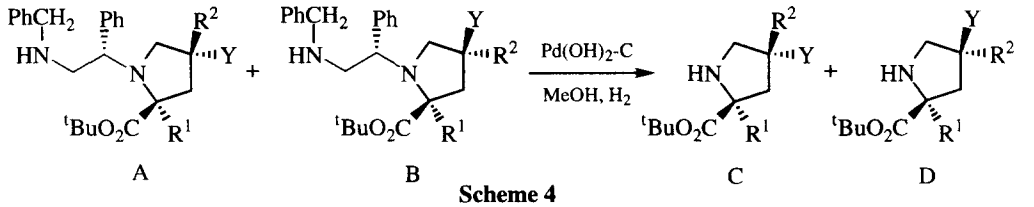
Scheme 3

Pyrroloimidazole	Pyrrolidine A	Pyrrolidine B
1d R^1 = H, R^2 = Me, Y = CO_2Me	73% **3a** (from enantiomer **1e**, 76% **3b**)	
1f R^1 = H, R^2 = Me, Y = CN	80% **3c** (from enantiomer **1g**, 51% **3d**)	
1h R^1 = R^2 = H, Y = CO_2Me	83% **3e**† (from enantiomer **1i**, 83% **3g**)†	17% **3f**† (from enantiomer **1i**, 17% **3h**)†
1j R^1 = R^2 = H, Y = $CO_2{}^tBu$	72% **3i**† (from enantiomer **1k**, 73% **3k**)†	24% **3j**† (from enantiomer **1k**, 24% **3l**)†
1l R^1 = R^2 = Me, Y = CO_2Me	99% **3m**†	

†unpurified yield

H_2 (60 psi), MeOH, TFA (1 mol equiv.)] as standard conditions smoothly cleaved the benzylic N-substituent in **3** to give pyrrolidines **4a-m**, Scheme 4. In the nitrile series (**3c,d**) the hydrogenolysis was poor, e.g. **3d** giving **4d** in 15% crude yield; further purification was not possible. Alternative reductive (Na, liq. NH_3) or oxidative [$Pb(OAc)_4$] protocols for cleavage were unsuccessful.

Hydrogenolysis of crude epimer mixtures **3e-l** afforded epimeric pyrrolidines **4e-l**. It was pleasing to observe a considerable improvement in epimer ratio in the products over the starting materials in all but one case, suggesting that the 2,4-*cis*-substituted pyrrolidines are less stable to the reaction conditions than the 2,4-*trans*. Separation of the epimeric pyrrolidines proved straightforward by column chromatography. Lactam **2c** was also subjected to hydrogenolysis and cleanly yielded amide **5**, Scheme 2, although problems associated with cleavage of the amide moiety meant that we did not pursue this route further.

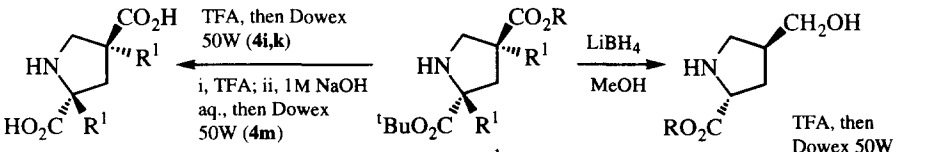


Scheme 4

Pyrrolidine	A	B	C	D
R^1 = H, R^2 = Me, Y = CO_2Me	**3a** enantiomer **3b**		**4a** 90% **4b** 53%	
R^1 = H, R^2 = Me, Y = CN	**3c** enantiomer **3d**		**4c** 30% **4d** 15%	
R^1 = R^2 = H, Y = CO_2Me	**3e** enantiomer **3g**	**3f** enantiomer **3h**	**4e** 24% enantiomer **4g** 45%	**4f** 31% enantomer **4h** 6%
R^1 = R^2 = H, Y = $CO_2{}^tBu$	**3i** enantiomer **3k**	**3j** enantiomer **3l**	**4i** 57% enantiomer **4k** 60%	**4j** 5% enantiomer **4l** 4%
R^1 = R^2 = Me, Y = CO_2Me	**3m**		**4m** 61%	

The crystalline p-bromobenzamide of **4a** (p-bromobenzoyl chloride, Et_3N, DCM, 86%) enabled an absolute stereochemical determination by single-crystal X-ray analysis.[7] The pyrrolidine had the expected 2*S*, 4*R* configuration, confirming the retention of stereochemical integrity throughout the synthesis.

Deprotection of pyrrolidines **4i** and **4k** (i, TFA, 0°C; ii, Dowex 50W) provided amino diacids **7a** (89%) and **7b** (80%), respectively, Scheme 5. Data for **7a**, a potent competitive glutamate transport inhibitor,[8] were in good agreement with those of the natural material.[9] Our synthesis of **7a** is shorter than the reported



R^1 = H **7b** 80%
enantiomer **7a** 89%
R^1 = Me, enantiomer **7c** 81%

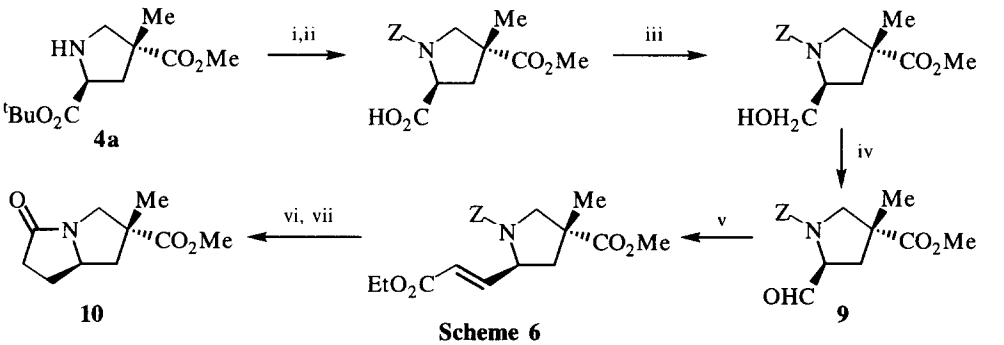
R = Me, R^1 = H **4g**
R = ^{t}Bu, R^1 = H **4k**
enantiomer **4i**
R = R^1 = Me, enantiomer **4m**

R = ^{t}Bu
8 ; R = H 21% (2 steps)

Scheme 5

route,[8] and easily modified to provide analogues of **7a**. Thus deprotection of **4m** (i, TFA, 0°C; ii, 1M NaOH aq., then Dowex 50W; 81%) led to the 2,4-dimethyl analogue **7c**.

Differentially protected pyrrolidines permit manipulation at either the C-2 or C-4 substituent. Thus reduction of the C-4 methyl ester in **4g** was achieved selectively (i, $LiBH_4$, MeOH, 41%; ii, TFA, 0°C, then Dowex 50W, 51%) to afford the naturally ocurring pyrrolidine **8**[10] in two steps. Selective manipulation at the C-2 substituent led to the aldehyde **9**, Scheme 6, which on chain extension followed by cyclisation onto nitrogen, provides an entry into pyrrolizidine and indolizidine ring systems present in a wide range of natural products. The synthesis of pyrrolizidine **10**, summarised in Scheme 6, was undertaken as an illustration.



Scheme 6

Reagents and Conditions: i, $PhCH_2OCOCl$, Et_3N, DCM, 97%; ii, TFA, quant.; iii, DCCI, HOSu, THF; then $NaBH_4$, THF, 68%; iv. TPAP, NMO, DCM, 4A sieves, 75%; v, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 57%; vi, Pd-C, H_2 (60 psi), MeOH, quant.; vii, xylene, reflux, 50%.

References and Notes

1. Current address: Chemistry Department, Open University, Walton Hall, Milton Keynes MK7 6AA.
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5. Epimerisation at C-4 most probably occurs by deprotonation-reprotonation at C-4 of the intermediate iminium ion, before hydride trapping. Excess $NaBH_3CN$ was found to promote epimerisation, possibly due to the basic nature of the cyanoborohydride anion.
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9. Data for **7a**: $[\alpha]_D^{20}$ – 46.6 (*c* 0.09, H_2O) {lit.: $[\alpha]_D^{20}$ – 46.0 (*c* 1, H_2O); Impellizzeri, G.; Piattelli, M.; Sciuto, S.; Fattorusso, E. *Phytochem.*, **1977**, *16*, 1601}; δ_H (400 MHz; D_2O) 2.16 (1H, m, CHC*H*HCH), 2.68 (1H, m, CHCH*H*CH), 3.20 (1H, m, CH_2CHCH_2), 3.54 (2H, d, *J* 8.2, $NHCH_2$) and 4.17 (1H, t, *J* 8.7, NHC*H*); δ_C (68 MHz; D_2O) 33.00 (C-3), 44.98 (C-4), 48.19 (C-5), 61.60 (C-2), 174.10 and 178.17 (2 x CO); δ_H (400 MHz; D_2O and TFA) 2.54 (1H, m, CHC*H*HCH), 2.79 (1H, m, CHCH*H*CH), 3.48 (1H, m, CH_2CHCH_2), 3.66 (2H, dd, *J* 8.4 and 12.2, NHC*H*H), 3.88 (1H, d, *J* 12.2 and 6.0, NHCH*H*) and 4.59 (1H, dd, *J* 7.6 and 8.5, NHC*H*); δ_C (68 MHz; D_2O and TFA) 33.69 (C-3), 44.26 (C-4), 50.22 (C-5), 62.19 (C-2), 173.47 and 177.64 (2 x CO).
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