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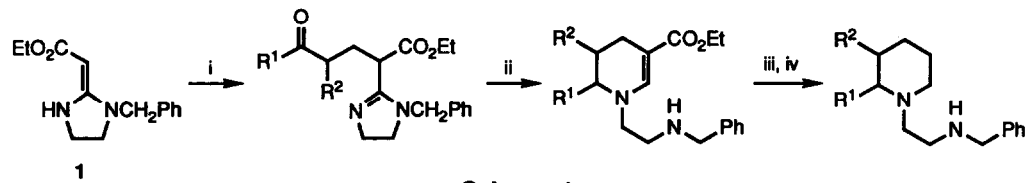
A New Route To Homochiral Piperidines

Raymond C F Jones *, Ian Turner, and Kevin J Howard
(Chemistry Department, Nottingham University, Nottingham NG7 2RD, UK)

Abstract: The synthesis of an enantiomeric pair of enaminoesters from phenylglycine is described. Conjugate addition to α,β-enones, reductive cyclization–fragmentation to octahydroimidazopyridines and further reduction to remove the auxiliary atoms, completes a new route to homochiral piperidines in which the enaminoesters function as homochiral 'ethanal enamines'.

We have recently reported a new approach to tetrahydropyridines and hence to piperidines *via* a novel reductive cyclization–fragmentation of the adducts formed from the enaminoester **1** and α,β-unsaturated ketones, Scheme 1.[1]

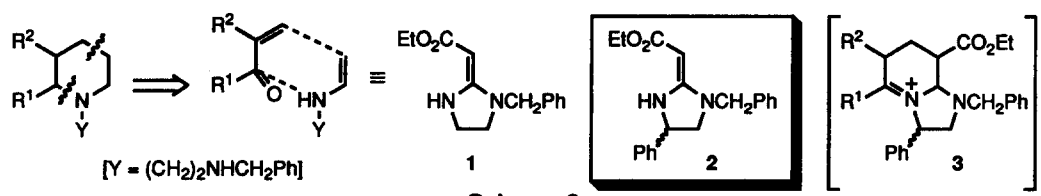


1

Scheme 1

Reagents: i, $R^1COCR^2{=}CH_2$, MeCN reflux; ii, H_2, PtO_2; or BH_3-THF; iii, 50% aq. H_2SO_4; iv, $NaBH_3CN$, H^+.

This approach is characterised retrosynthetically as a C_2N+C_3 assembly, as shown in Scheme 2; the heterocyclic enaminoester **1** acts as the synthetic equivalent of an enamine of ethanal. We report here the extension of this approach to the construction of homochiral piperidines by the use of the optically active enaminoesters **2** as homochiral C_2N components. Homochiral piperidines are found in a wide range of natural products, many having important biological properties.[2]



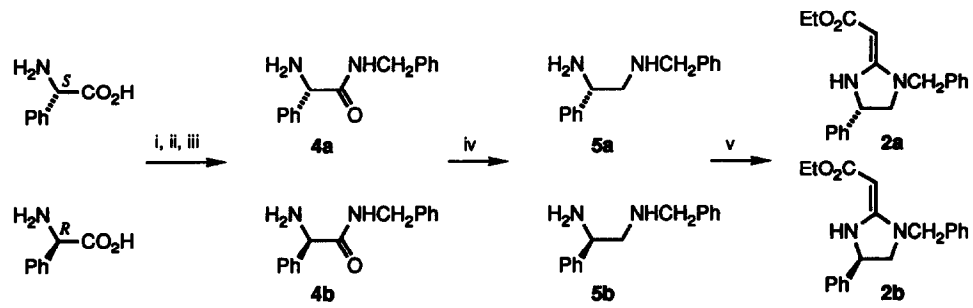
[Y = $(CH_2)_2NHCH_2Ph$]

1 **2** **3**

Scheme 2

An obvious approach to an optically active 'ethanal enamine' requires a chiral auxiliary on nitrogen but rotational freedom around the N-to-auxiliary bond is a problem for predictable asymmetric induction. We reasoned that the conformational restraint of the heterocycle (with its 'extra' C–N bond) in **2** would allow predictable facial discrimination and hence asymmetric induction *via* presumed intermediate **3** in the reductive cyclization–fragmentation.[1] The choice of 'backbone' substituent was defined by the need for (i) ready availability in both enantiomeric series, and (ii) easy removal of the auxiliary by hydrogenolytic C–N cleavage.[3,4]

Key intermediates in our synthesis were the (*S*-) and (*R*)-1-phenyl-N-benzyldiaminoethanes **5a** and **5b** prepared from commercial (*S*-) and (*R*)-phenylglycine, respectively, as shown in Scheme 3.[5] The amino-acid enantiomers were separately converted to their N-benzylamides **4a** and **4b** *via* the benzyloxycarbonyl derivatives (NaOH, $PhCH_2OCOCl$; *S* 85%, *R* 88%), mixed anhydride coupling to benzylamine (Bu^iOCOCl, N-methyl-morpholine; $PhCH_2NH_2$; *S* 82%, *R* 83%) and deprotection by hydrogenolysis (H_2, Pd–C, MeOH; *S* or *R* 100%). Reduction of **4** by diborane–THF provided the key diamines **5** (*S* or *R* 80%), which were treated with ethyl ethoxycarbonylethanimidate hydrochloride (EtOH reflux)[6] to furnish the homochiral enaminoesters **2a** (44%) and **2b** (87%).[7]

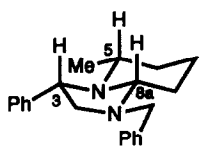


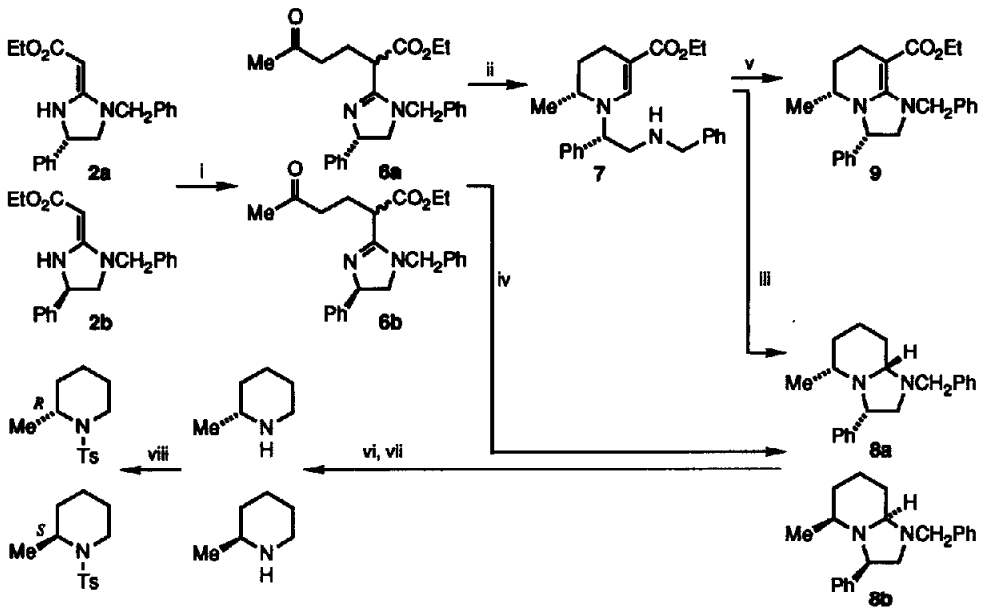
Scheme 3

Reagents: i, $PhCH_2OCOCl$, aq. NaOH; ii, N-methylmorpholine, $ClCO_2Bu^i$; $PhCH_2NH_2$; iii, H_2, Pd–C, MeOH; iv, BH_3.THF; v, $EtO_2CCH_2C(OEt)=NH_2^+Cl^-$.

Conjugate addition of **2a** and **2b** to but-3-en-2-one (MeCN reflux) gave the 1,4-adducts **6a** and **6b** (87, 76%), Scheme 4, which were initially subject to hydrogenation as previously reported (H_2, 1 atm., PtO_2)[1] but rather than the products of cyclization–fragmentation, inseparable mixtures were observed. However our alternative reduction protocol using diborane–THF (2M aq. HCl workup)[1] was successful, affording the tetrahydropyridine **7** (77%) from **6a** as a single diastereoisomer.[8] The relative stereochemistry of **7** was assigned by n.O.e. measurements. For this purpose the tetrahydropyridine was converted to less conformationally flexible bicyclic derivatives. Thus treatment of **7** with 50% sulphuric acid afforded the octahydroimidazopyridine **8a** (58%);[1,9] alternatively **8a** and **8b** were prepared directly from **6a** and **6b** (46, 43%) by following the diborane reduction with workup using 50% sulphuric acid. Titration of **7** with bromine, followed by excess triethylamine, gave the hexahydroimidazopyridine **9** (64%).[9] The latter showed a 4% enhancement of the signal for H-5 (δ 3.21) on irradiation of the benzylic methine proton H-3 at δ 4.30, suggesting the *syn*-disposition of H-3 and H-5, whilst for **8a** enhancements were observed of the signals for H-5 (δ 2.43; 4.5%) and H-8a (δ 2.78), also on irradiation of the benzylic methine proton H-3, implying a structure such as **10** in which the three protons H-3, 5, 8a are pseudoaxial and all the substituents are pseudoequatorial. The stereochemical assignments were further confirmed by conversion to piperidines of known absolute configuration.

10



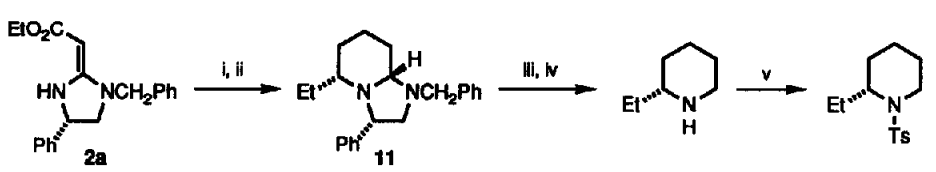


Scheme 4

Reagents: I, $MeCOCH{=}CH_2$, MeCN reflux; ii, BH_3.THF, 2M aq. HCl workup; iii, 50% aq. H_2SO_4; iv, BH_3.THF, 50% aq. H_2SO_4 workup; v, Br_2, then Et_3N; vi, $NaBH_3CN$, pH 3; vii, H_2 Pd–C, MeOH; viii, TsCl, pyridine.

To remove the auxiliary atoms the octahydroimidazopyridines **8a** and **8b** were subjected successively to sodium cyanoborohydride in acidic conditions to reduce the aminal (81% from **8a**; 77% from **8b**) and hydrogenolysis of the benzylic C–N bond (H_2, Pd–C, MeOH)[10] to produce the enantiomers of the volatile 2-methylpiperidine, which were isolated for convenience directly as their crystalline N-tosyl derivatives [*R* 63%: m.p. 68-69°C, $[\alpha]_D^{19}$ –43.5° (*c* 0.96 in EtOH); *S* 61%: m.p. 68-69°C, $[\alpha]_D^{21}$ +46.5° (*c* 0.98 in EtOH)]. These data were in accord with those reported for (*S*)-N-tosyl-2-methylpiperidine [m.p. 68-70°C, $[\alpha]_D^{21}$ +41.0° (*c* 0.98 in EtOH)] obtained by sulphonation of the natural product isolated from pine needles.[11]

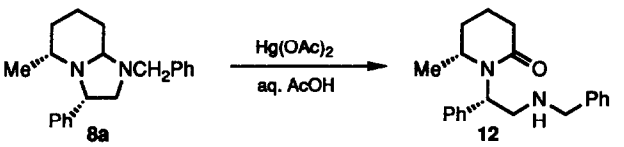
In a further demonstration of the methodology, (*R*)-2-ethylpiperidine was prepared from **2a**, Scheme 5. Reaction with pent-1-en-3-one (MeCN reflux; 79%) followed by diborane reduction with the H_2SO_4 workup, gave the octahydroimidazopyridine **11** (45%), again as a single diastereoisomer. The reduction-derivatization protocol ($NaBH_3CN$, H^+; 47%; H_2, Pd–C, MeOH, then TsCl, pyridine; 54%) led to *R*-2-ethylpiperidine as the N-tosyl derivative [m.p. 73-75°C, $[\alpha]_D^{23}$ –32.0° (*c* 0.36 in MeOH); lit.[12] m.p. 74-75°C, $[\alpha]_D^{25}$ –35.0° (*c* 0.30 in MeOH)].



Scheme 5

Reagents: i, $EtCOCH{=}CH_2$, MeCN reflux; ii, BH_3.THF, 50% aq. H_2SO_4 workup; iii, $NaBH_3CN$, pH 3; iv, H_2, Pd–C; v, TsCl, pyridine.

A number of the naturally occurring piperidines have a 2,6-disubstitution pattern[2] and introduction of a 6-substituent into these 2-substituted piperidines, with control of relative stereochemistry, is possible by existing methods.[13] The bicyclic aminals **8** or **11** have also been converted oxidatively into 6-substituted-2-piperidones, e.g. **12** from **8a** [$Hg(OAc)_2$, aq. AcOH; 44%][14] which have the potential for elaboration at C-2 by reported methods.[15]



8a **12**

We have thus demonstrated the value of the homochiral enaminoesters **2** in the synthesis of optically active six-membered nitrogen heterocycles. Further applications of this methodology, and of the uses of heterocycles derived from the diamines **5** in asymmetric synthesis, are under development. The support of SERC and Glaxo Group Research (studentship to I.T.) and Nottingham University (studentship to K.J.H.) is gratefully acknowledged.

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1. Jones, R.C.F.; Hirst, S.C. *Tetrahedron Lett.*, **1989**, *30*, 5365-5368.
2. For example: Fodor, G.B.; Colasanti, B The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. In '*Alkaloids: Chemical and Biological Perspectives*'; Pelletier, S.W. Ed.; John Wiley & Sons, Inc.: New York, vol. 3, 1983; pp. 1-90; Pinder, A.R., *Nat. Prod. Reports*, **1992**, *9*, 17-23, and earlier reports in this series.
3. Exploratory work with 4-isopropyl- rather than 4-phenyl-tetrahydroimidazole enaminoesters was discontinued as the auxiliary could not easily be removed. The 4,5-diphenyl enaminoester was also prepared in racemic form; the synthesis was less convenient than that described in Scheme 3, and would necessitate a resolution to access homochiral material.
4. For use of a related oxazolidinopyridine in asymmetric piperidine synthesis: Bonin, M.; Grierson, D.S.; Royer, J.; Husson, H.-P. *Org. Synth.*, **1991**, *70*, 54-59; Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.*, **1992**, *57*, 4211-4214.
5. Route to diamines **5a,b** modified from that reported for analogous proline-based diamines: Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 1869-1873.
6. *Cf.* Anderson, M.W.; Begley, M.J.; Jones, R.C.F.; Saunders, J. *J. Chem. Soc., PerkinTrans. 1*, **1984**, 2599-2602; Jones, R.C.F.; Smallridge, M.J. *Tetrahedron Lett.*, **1988**, *29*, 5005-5008.
7. All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
8. No other diastereoisomer could be isolated from the crude reaction mixture.
9. Selected data: for **8a**: white solid, m.p. 59-60°C (Found: C, 82.1; H, 8.9; N 8.75%; M^+ 306.214. $C_{21}H_{26}N_2$ requires C, 82.3; H, 8.55; N, 9.15%; *M* 306.210); $[\alpha]_D^{20} = +32.8°$ (*c* 1.38 in MeOH); δ_H (400 MHz; $CDCl_3$) 0.67 (3H, d, *J* 6.3, *Me*CH), 1.29 (1H, m, $CH_aH_bCH_aH_bCH_aH_b$), 1.38 (1H, m, $CH_aH_bCH_aH_bCH_aH_b$), 1.50 (2H, m, $CH_aH_bCH_aH_bCH_aH_b$), 1.81 (1H, m, $CH_aH_bCH_aH_bCH_aH_b$), 1.96 (1H, m, $CH_aH_bCH_aH_bCH_aH_b$), 2.43 (1H, m, MeC*H*), 2.68 (1H, dd, *J* 9.6, 9.3, $CHCH_aH_bN$), 2.72 (1H, dd, *J* 9.6, 4.9, $CHCH_aH_bN$), 2.78 (1H, dd, *J* 10.0, 2.0, NCHN), 3.24 (1H, d, *J* 13.1, NCH_aH_bPh), 3.66 (1H, dd, *J* 9.3, 4.9, $CHCH_aH_bN$), 4.03 (1H, d, *J* 13.1, NCH_aH_bPh) & 7.10–7.50 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 22.3 (Me), 23.2 ($CH_2CH_2CH_2$), 29.6 ($CH_2CH_2CH_2$), 35.2 ($CH_2CH_2CH_2$), 56.9 ($CHCH_2N$), 58.4 (MeCHN), 61.6 (NCH_2Ph), 64.6 (NCHPh), 86.1 (NCHN), 126.3, 126.7, 127.1, 128.0, 128.1, 128.7 (all ArCH) and 139.0, 147.5 (ArC); for **9**: (Found: C, 76.35; H, 7.6; N 7.55%. $C_{24}H_{28}N_2O_2$ requires C, 76.6; H, 7.45; N, 7.45%); δ_H (250 MHz; $CDCl_3$) 0.70 (3H, d, *J* 6.6, *Me*CH), 1.21 (3H, t, *J* 7.1, CH_2CH_3), 1.55 (1H, m, $CHCH_aH_bCH_aH_b$), 1.69 (1H, m, $CHCH_aH_bCH_aH_b$), 2.32 (1H, m, $CHCH_aH_bCH_aH_b$), 2.52 (1H, m, $CHCH_aH_bCH_aH_b$), 3.14 (1H, dd, *J* 10.5, 8.5, $CHCH_aH_bN$), 3.21 (1H, m, MeC*H*), 3.54 (1H, dd, *J* 10.5, 9.2, $CHCH_aH_bN$), 4.04 (2H, q, *J* 7.1, CH_2CH_3), 4.30 (1H, dd, *J* 9.2, 8.5, $CHCH_aH_bN$), 4.46 (1H, d, *J* 14.8, NCH_aH_bPh), 4.65 (1H, d, *J* 14.8, NCH_aH_bPh) & 7.10–7.40 (10H, m, ArH).
10. This two-step reductive removal of the auxiliary atoms proved more effective than any one-pot procedures.
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