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Synthesis of Homochiral α–Amino Acids by Reductive Amination of α–Ketoacids *via* 3–Substituted– 5–Phenyl–3,4–dehydromorpholin-2-ones: Synthesis of (*S*)– and (*R*)–2–Aminobutanoic Acid

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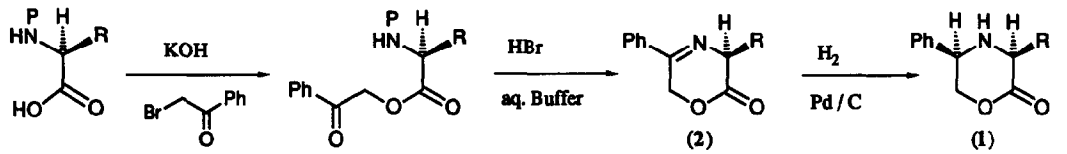
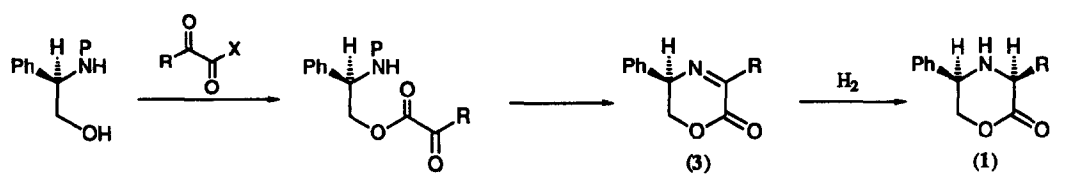
Abstract: 2–Oxobutanoic acid has been converted to (*R*)– or (*S*)–2-aminobutanoic acid *via* highly diastereocontrolled hydrogenation of the corresponding homochiral 3–ethyl–5–phenyl–3,4–dehydromorpholin–2–one derivatives.

We have made extensive use of 3–substituted 5–phenylmorpholin–2–ones (**1**) as chiral templates for the synthesis of substituted proline derivatives, by relaying the chiral infomation at C–3 through the sequence of azomethine ylid formation and trapping.[1] The morpholin–2–one templates are prepared by the method of Caplar,[2] commencing with the requisite *N*–protected α-amino acid and proceeding *via* imines (**2**), diastereoselective hydrogenation of which furnishes the desired morpholin-2-one templates (**Scheme 1**).



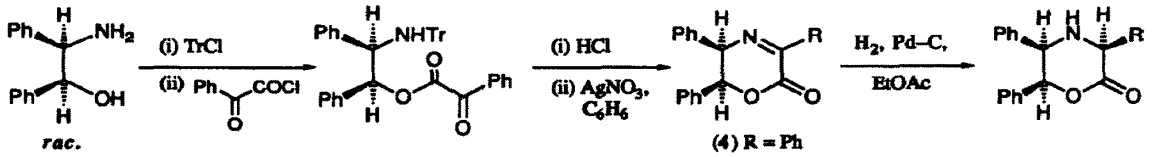
Scheme 1

An alternative construction of the morpholin-2-one template (**1**) might be envisaged to proceed *via* cyclocondensation of (*R*)– or (*S*)–phenylglycinol and α–ketoacid derivatives, with the key step being diastereoselective reduction of the imine system (**3**) which is regioisomeric with (**2**) above (**Scheme 2**).



Scheme 2

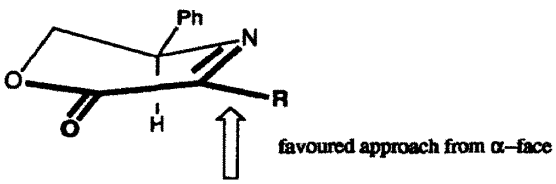
Such a template has been considered previously, but it was reasoned that a single phenyl group at C–5, occupying a *quasi*–equatorial environment, would provide insufficient diastereofacial distinction.[3] Moreover, these workers were able to demonstrate diastereospecific hydrogenation of the 5,6–*syn*–diphenyl template (**4**) derived from racemic *erythro*–2–amino–1,2–diphenylethanol, judging the complete stereocontrol to be a consequence of one of the phenyl groups occupying a *quasi*–axial position. (**Scheme 3**).



Scheme 3

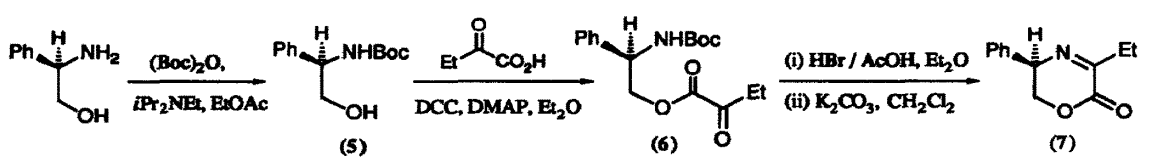
Recently, reduction of the homochiral template (4, R = $CH_2CH_2P(O)(OEt)_2$) derived from *erythro*–(1*S*, 2*R*)–2–amino–1,2–diphenylethanol has been reported using aluminium amalgam. Subsequent modification furnished (*S*)–2–amino–4–phosphonobutanoic acid in 67% e.e. indicating moderate diastereocontrol of the aluminium amalgam reduction step. In this case, Raney nickel or heterogeneous catalytic hydrogenation was found to cause simultaneous disruption of the ring, leading to racemic material.[4]

In our formalism[1c] for predicting the diastereocontrol during trapping of azomethine ylids derived from (1) we also consider the C–5 phenyl group to be in a *quasi*– equatorial environment, in accord with the earlier proposal.[3] However, we rationalise the high diastereocontrol observed by proposing that the group exerts its stereodirecting influence by acting as a conformational locking group (rather than a steric block) with the dipolarophile subsequently approaching the ylid in an axial manner. Consequently we decided to investigate the possibility that hydrogenation of (3) could be carried out in a diastereoselective manner as a consequence of approach of hydrogen to the double bond of the conformationally locked imine (4) to afford the desired *syn*–3,5–disubstituted morpholin–2–one system (**Figure**).



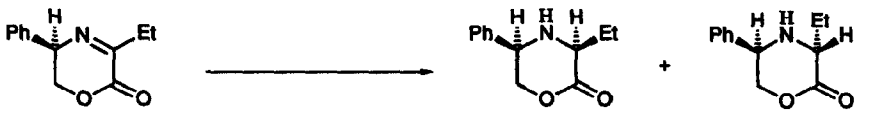
Figure

In this communication, we illustrate the efficacy of the overall process outlined in **Scheme 2** by describing the conversion of 2–oxobutanoic acid to homochiral 2–aminobutanoic acid and thereby effecting an enantiocontrolled reductive amination. (*R*)–Phenylglycinol[5] was protected as its *N*–Boc derivative (*R*)–(5) in 85% yield {(t–BuOCO)$_2$O, iPr$_2$NEt, EtOAc; $[\alpha]_D^{23}$ –41.9 (c = 1.00, $CHCl_3$) [(*S*)–(5), $[\alpha]_D^{23}$ +38.7 (c = 1.06, $CHCl_3$)]}. Condensation with 2–oxobutanoic acid gave the ester (*R*)–(6) in yields varying between 60–80% {DCC / DMAP, Et_2O; $[\alpha]_D^{23}$ –32.4 (c = 1.00, $CHCl_3$) [(*S*)–(6), $[\alpha]_D^{23}$ +29.5 (c = 1.12, $CHCl_3$)]}.[6] Subsequent *N*–deprotection with hydrogen bromide in acetic acid gave the amine hydrobromide which was immediately neutralised (K_2CO_3, CH_2Cl_2, r.t.), resulting in spontaneous cyclisation to furnish (5*R*)–3–ethyl–5–phenyl–3,5–dehydromorpholin–2–one (7) in 91% yield over the two steps {$[\alpha]_D^{23}$ –243 (c = 1.04, $CHCl_3$) [(5*S*)–(7), $[\alpha]_D^{23}$ +233 (c=1.07, $CHCl_3$)]} (**Scheme 4**).



Scheme 4

Although stable to silica, the crude product was sufficiently pure to examine the diastereoselectivity of the hydrogenation step. However, (7) was found to undergo hydrogenation slowly under the conditions previously employed successfully with substrates (4)[3] and regioisomeric substrates (2) (10% Pd/C, H_2, EtOAc)[1,2]. Even more significantly, the reaction evolved to furnish a mixture of the desired product (8) together with the C–3 epimeric material (9) (Scheme 5). Subsequently, a variety of reduction conditions was investigated to improve the diastereomeric ratio. The representative sample shown in Scheme 5 shows that the desired material (8) is formed in disappointing diastereomeric excess with those conditions that result in hydrogenation with the exception of Adams' catalyst in CH_2Cl_2, which gave a satisfactory diastereomeric ratio of >15 : 1 (8) : (9).



Conditions	Ratio 8 : 9[a]
$NaBH_3CN$, EtOH	–[b]
$(Ph_3P)_2RhCl$, CH_2Cl_2	–
Pd / C, CH_2Cl_2	3.6 : 1.0
Rh / C, CH_2Cl_2	1.5 : 1.0
Ru / C, CH_2Cl_2	–
Pt / C, CH_2Cl_2	3.2 : 1.0
PtO_2, CH_2Cl_2	> 15 : 1.0

[a] Diastereomeric ratios determined by 500 MHz NMR analysis of the crude reaction mixture.
[b] No reduction products isolated.

Scheme 5

Recrystallisation of the material derived by hydrogenation over Adams' catalyst gave the desired (3*S*,5*R*)–3–ethyl–5–phenylmorpholin–2–one (8) in 100% d.e. and 53% yield from (7); {$[\alpha]_D^{23}$ –111.5 (c = 1.14, $CHCl_3$) [(3*R*,5*S*)–(8), $[\alpha]_D^{23}$ +103.3 (c = 1.13, $CHCl_3$)]}. Subsequent hydrogenolysis of (8) to furnish 2–aminobutanoic acid (10) also proved to be more problematical than in our previous work, but was eventually achieved in 55–59% yield using Pearlman's catalyst under elevated hydrogen pressure [$Pd(OH)_2$, H_2 (6 atm.), MeOH : H_2O (10 : 1), CF_3CO_2H (1 equiv.)] followed by trituration of the product with ether and ion exchange chromatography of the ether insoluble material{(*S*)–(10) $[\alpha]_D^{23}$ +7.82 (c = 1.10, H_2O); (*R*)–(10), $[\alpha]_D^{23}$ –7.84 (c = 1.11, D_2O)}, lit.[7] (*R*)–(10) $[\alpha]_D^{20}$ –7.94 (c = 4, H_2O)}.

In conclusion, we have shown that homochiral *syn*–3–ethyl–5–phenylmorpholin–2–one (7) can be synthesised with equal facility in either enantiomeric series from phenylglycinol in 5 steps and 32.5% overall yield without the need for chromatographic purification. Subsequent stepwise hydrogenation and hydrogenolysis furnishes the homochiral 2–aminobutanoic acid. We are currently investigating the scope and generality of this route for the synthesis of unnatural amino acids.

Acknowledgements

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5 Purchased from Aldrich Chemical Company.

6 All novel compounds gave spectroscopic data in accordance with their assigned structures. All except (**7**), gave satisfactory microanalytical data. Selected data: (5*S*)–(**5**) M.p.= 136–138°C; found C, 65.65, H, 8.13, N, 5.80 $C_{13}H_{19}NO_3$ requires C, 65.8, H, 8.02, N, 5.91; δ_H (200 MHz, $CDCl_3$) 7.43–7.21 (m, 5 H), 5.43–5.18 (bs, 1 H), 4.93–4.71 (bs, 1 H), 3.90–3.72 (bs, 2 H), 2.65–2.45 (bs, 1 H), 1.42 (s, 9 H); $[\alpha]_D^{23}$ +38.7 (c 1.06, $CHCl_3$). (5*R*)–(**5**) M.p.=138-139°C, $[\alpha]_D^{23}$ –41.9 (c 1.0, $CHCl_3$). (5*S*)–(**6**) M.p.= 86–88°C; found C, 63.41, H, 7.45, N, 4.76, $C_{17}H_{23}NO_5$ requires C, 63.55, H, 7.17, N, 4.36; ν_{max} (KBr) 3387, 3087, 3066, 2979, 1736, 1688 cm^{-1}; δ_H(500 MHz, $CDCl_3$) 7.39–7.30 (m, 5 H), 5.10 (bs, 2 H), 4.51–4.42 (m, 2 H), 2.85-2.81 (q, *J* 7.2, 2 H), 1.11 (t, *J* 7.2, 3 H); $[\alpha]_D^{23}$ +29.5 (c 1.12, $CHCl_3$); (5*R*)–(**6**) M.p.= 89-91°C, found C, 63.32, H, 7.15, N, 4.08; $[\alpha]_D^{23}$ –32.4 (c 1.82, $CHCl_3$). (5*S*)–(**7**) M.p.= 67-69°C; δ_H (500 MHz, $CDCl_3$) 7.46-7.29 (m, 5 H), 4.91-4.87 (m, 1 H), 4.61–4.57 (dd, *J* 11.57 & 4.52, 1 H), 4.25–4.20 (t, *J* 11.2, 1 H), 2.90–2.73 (m, 2 H), 1.26 (t, *J* 7.4, 3 H); δ_C (125.7 MHz, $CDCl_3$) 163.9, 151.1, 137.0, 128.9, 128.3, 127.1, 71.4, 59.4, 27.8, 10.2; ν_{max} (KBr) 3065, 3028, 2937, 1725, 1651, 700, 664 cm^{-1}; $[\alpha]_D^{23}$ +233 (c 1.07, $CHCl_3$). (5*R*)–(**7**) M.p.= 65-67°C, $[\alpha]_D^{23}$ –243 (c 1.04, $CHCl_3$). (3*R*,5*S*)–(**8**) M.p.= 44–45°C; found C, 70.00, H, 7.37, N, 6.69 $C_{12}H_{15}NO_2$ requires C, 70.24, H, 7.36, N, 6.83; δ_H (500 MHz, $CDCl_3$) 7.45–7.33 (m, 5 H), 4.36–4.23 (m, 3 H), 3.81–3.79 (dd, *J* 7.0, 4.1, 1 H), 3.81–1.88 (m, 3 H), 1.10–1.07 (t, *J* 7.4, 3 H); δ_C (125.7 MHz, $CDCl_3$) 169.8, 137.9, 128.9, 128.7, 127.1, 74.7, 60.0, 57.4, 26.2, 10.0; $[\alpha]_D^{23}$ +103.3 (c 1.13, $CHCl_3$). (3*S*, 5*R*)–(**8**) M.p.= 41-44°C, found C, 70.54, H, 7.68, N, 6.82; $[\alpha]_D^{23}$ –111.5 (c 1.14, $CHCl_3$). (*S*)–(**10**) δ_H (500 MHz, D_2O) 3.68–3.65 (t, *J* 5.9, 1 H), 1.89–1.81 (m, 2 H), 0.94–0.92 (t, *J* 7.5, 3 H); $[\alpha]_D^{23}$ +7.82 (c 1.10, H_2O); (*R*)–(**10**) $[\alpha]_D^{23}$ –7.84 (c 1.11, D_2O) lit.[7] $[\alpha]_D^{20}$ –7.94 (c 4.0, H_2O).

7 As quoted for (*R*)-(**10**) by Aldrich Chemical Company.

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