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Synthesis of enantiomerically pure α-amino acids via chemo- and diastereoselective alkylation of (5*S*)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one

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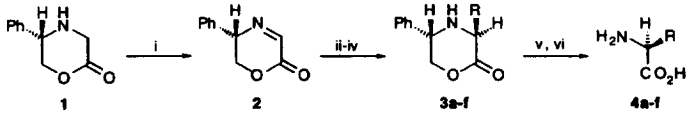
Abstract: (5*S*)-5-Phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **2** undergoes Lewis acid-mediated chemo- and diastereoselective nucleophilic addition of Grignard reagents to furnish adducts **3** which can be dismantled to allow ready access to enantiomerically pure (*S*)-α-amino acids **4**. © 1997 Elsevier Science Ltd. All rights reserved.

Synthesis of enantiomerically pure α-amino acids, particularly unnatural analogues,[1] continues to challenge the organic chemist. A plethora of approaches towards these compounds has been established, of which the use of chiral glycine equivalents has proved extremely profitable.[2a–e] Williams has used chiral oxazin-2-one templates possessing two stereogenic centres to achieve asymmetric induction by diastereocontrolled alkylation via α-brominated intermediates[2b,c] and there is a healthy literature precedent for the concept of alkylation of acyclic imines to prepare optically active amines.[3a–i] Undeterred by the moderate levels of stereoselectivity often observed with the latter systems,[3a,c,f,i] we decided to investigate the level of stereocontrol available using the isolable cyclic imine (5*S*)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **2**, which we have already employed as a heterodienophile.[4] Diastereoselective alkylation of **2** and subsequent template cleavage through our established protocol[5] would then provide access to enantiomerically pure α-amino acids **4** (Scheme 1).



1 **2** **3a-f** **4a-f**

Reagents and conditions: (i) NBS, propylene oxide, DCM, r.t., 4h; (ii) $BF_3.OEt_2$ (1.1 eq.), THF, –40 °C, 2h; (iii) RMgX (1.3 eq.), THF, –30 °C, 30 min; (iv) aq. $NaHCO_3$; (v) H_2 (5 bar), 20% $Pd(OH)_2/C$, TFA, aq. MeOH, 24h; (vi) ion-exchange chromatography.

Scheme 1.

We have reported the application of such an approach to the formation of α-substituted alanine derivatives, in which the cyclic imine was prepared by cyclisation of (2*S*)-2-phenylglycinol with α-keto ester derivatives, and alkylated with Grignard reagents using a Lewis acid to facilitate chemoselection between the imine and lactone functionalities.[6] This chemoselectivity is complementary to that observed by Molinski in the absence of a Lewis acid, when phenylmagnesium bromide attacks the ester function of (5*S*)-5-isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one with subsequent intramolecular addition of the liberated alkoxide to the imine.[7] The parent system **2**, lacking 3-substitution, cannot be prepared by the direct approach and is known to be readily isomerised to 5-phenyl-3,6-dihydro-

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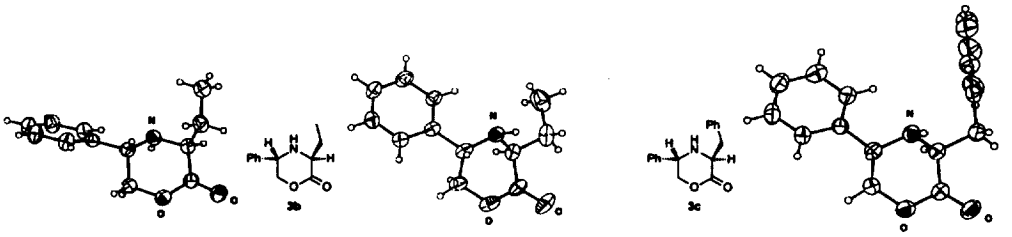

Figure 1.

Table 1.

Entry	R	Product	Isolated yield (%) 3	4
1	Me	**a**	34	91
2	Et	**b**	57	94
3	Bn	**c**	46	84
4	*i*-Bu	**d**	46	98
5	*i*-Pr	**e**	43	78
6	*t*-Bu	**f**	33	95

2*H*-1,4-oxazin-2-one with concomitant loss of chirality. It was therefore open to question whether the chemoselective alkylation procedure could be applied to this substrate.

Imine **2** was prepared via a one-pot bromination–dehydrobromination of tetrahydrooxazin-2-one **1** with NBS in the presence of propylene oxide,[4] providing **2** of sufficient purity to be used directly. Optimal conditions for the alkylation procedure used low temperature pre-complexation with the Lewis acid at −40°C, followed by slow addition of the Grignard reagent at −30°C (Scheme 1).[8]

Scrutiny of the crude product mixtures indicated a single 3,5-*anti*-disubstituted oxazin-2-one **3** to be present. Our stereochemical rationale,[5] invoking nucleophilic attack on the imine carbon in a *quasi*-axial approach to a flattened chair which is conformationally locked by the 5-phenyl substituent yielding the 3,5-*anti*-oxazin-2-one, once again holds good and was supported by X-ray analysis of **3b** and **3c** which were shown to be single enantiomers (Figure 1).[9,14–16]

It should be noted that there is clearly a delicate balance of the conformational energies in this 3,5-*anti*-oxazin-2-one system. There are two conformations adopted by **3b** in the asymmetric unit, the former being a flattened chair thereby giving the 3-ethyl group a *pseudo*-axial position, the latter being a boat conformation, allowing both the 3-ethyl and 5-phenyl groups *pseudo*-equatorial positions. However, the greater steric demand of the 3-benzyl group forces **3c** to adopt solely the boat conformation.

Yields of purified adducts **3** over the two steps are consistent and acceptable for addition of primary and secondary Grignard reagents (Table 1, entries 2–5); although using more hindered reagents resulted in a decrease in overall yield (Table 1, entry 6). This two step process permits expedient chemo- and diastereoselective nucleophilic addition to the imine **2** to furnish oxazin-2-ones **3a–f**,[10,17] in an approach which is diastereocomplementary to hydrogenation of dihydro-2*H*-1,4-oxazin-2-ones to furnish 3,5-*syn*-adducts.[5,11] Degradation of the template by the one-pot hydrogenolysis–hydrolysis procedure[12] afforded the amino acids **4a–f** as colourless powders in high yield after ion-exchange chromatography (Scheme 1, Table 1).[13,18,19]

Since either antipode of **1** can be obtained with equal facility,[11] this protocol allows the synthesis of α-amino acids in both enantiomeric series. Extension of this methodology towards the construction of specific targets will be reported in due course.

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8. General two-step procedure for synthesis of adducts **3**: (5*S*)-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one **1** (0.71 mmol) was prepared as described previously[4] and the crude product immediately dissolved in anhydrous tetrahydrofuran (6 mL) under nitrogen and the solution cooled to −40°C. Boron trifluoride etherate (0.10 mL, 0.79 mmol, 1.1 eq.) was added in a single portion and the reaction mixture stirred at −40°C for 2 h, whereupon the requisite Grignard reagent (0.90 mmol, 1.3 eq.) was added dropwise over 15 min. The reaction mixture was stirred for a further 15 min, while the temperature was allowed to rise to −30°C, and then quenched by the addition of sat. aq. $NaHCO_3$ solution. The organic phase was removed, brine added (15 mL) and the aqueous phase further extracted with diethyl ether (2×20 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification of the residue by flash column chromatography, eluting with diethyl ether:light petroleum (2:5), followed by recrystallisation from diethyl ether–light petroleum furnished adducts **3** as colourless crystalline solids.
9. Crystal data for **3b**: $C_{12}H_{15}NO_2$, M=205.26, monoclinic, space group $P2_1$, a=12.949 (12), b=6.109 (8), c=14.558 (14) Å, β=98.224 (10)°, U=1140 Å^3, Z=4, D_c=1.196 gcm^{-3}, F(000)=440. 3685 Reflections, 3643 independent (R_{int}=0.0307), were collected with MoK_α radiation using the MARresearch Image Plate System. Final residuals above background were $R1$=0.0557 and $wR2$=0.1446. Crystal data for **3c**: $C_{17}H_{17}NO_2$, M=267.33, orthorhombic, space group $P2_12_12_1$, a=6.518 (8), b=8.476 (8), c=27.21 (2) Å, U=1503 Å^3, Z=4, D_c=1.177 gcm^{-3}, F(000)=564. 3948 reflections, 2429 independent (R_{int}=0.0344), were collected with MoK_α radiation using the MARresearch Image Plate System. Final residuals above background were $R1$=0.0555 and $wR2$=0.1622. In each case the crystals were positioned at 70 mm from the Image Plate and 95 frames were measured at 2° intervals with a counting time of 2 min. Data analysis was carried out

with the XDS program.[14] The structures were determined by direct methods using SHELX86.[15] Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms bonded to carbon were included in geometric positions with isotropic thermal parameters and the hydrogen atom bonded to nitrogen was located in a difference Fourier map and refined independently. The structures were then refined by full-matrix least-squares on F^2 using SHELXL.[16]

10. Adducts **3a–f** gave spectroscopic data, microanalytical and/or high resolution mass spectrometric data in accordance with their assigned structures. Typical data: **3c**: mp 108–111°C; Found C: 76.2, H: 6.43, N: 5.23%, $C_{17}H_{17}NO_2$ requires C: 76.4, H: 6.41, N: 5.24%; ν_{max} (KBr) 3347, 2912, 1734, 1491, 1450, 1204, 1164, 1134, 1042, 757 and 701 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.46–7.17 (10H, m), 4.45–4.26 (3H, m), 4.09 (1H, dd, *J* 9.4, *J'* 4.3 Hz), 3.31 (1H, dd, *J* 13.9, *J'* 4.3 Hz), 3.19 (1H, dd, *J* 13.9, *J'* 9.5 Hz) and 1.84 (1H, br s); δ_C (100.4 MHz, $CDCl_3$) 170.62, 137.97, 136.93, 129.34, 128.92, 128.88, 128.46, 127.11, 126.94, 73.65, 57.23, 52.51 and 37.96; *m/z* (CI, NH_3) 268 (24%, MH^+), 176 (100), 117 (24), 104 (73), 91 (71) and 77 (10); $[\alpha]_D^{25}$ −70.5 (*c* 1.27, $CHCl_3$), lit.[17] $[\alpha]_D^{22}$ −55.8 (*c* 3.00, $CHCl_3$).
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12. General procedure for synthesis of α-amino acids **4**: the requisite oxazin-2-one **3** (100 mg, 0.37 mmol) was dissolved in methanol (5 mL) in a Fischer–Porter bottle containing Pearlman's catalyst (100 mg), trifluoroacetic acid (0.1 mL) and water (0.5 mL). The bottle was pressurised with hydrogen to 5 bar and the mixture stirred rapidly for 24 h. After depressurisation the mixture was filtered through Celite® and the solvent evaporated *in vacuo*. The residue was purified by ion-exchange chromatography (Dowex® 50WX8-100) and triturated with diethyl ether to furnish α-amino acids **4** as colourless powders.
13. α-Amino acids **4a–f** gave spectroscopic data in accordance with their assigned structures. Specific rotations: **4a**: $[\alpha]_D^{24}$ +2.4 (*c* 0.29, H_2O), lit.[18] $[\alpha]_D^{25}$ +2.4 (*c* 10.00, H_2O). **4b**: $[\alpha]_D^{27}$ +7.3 (*c* 0.30, H_2O), lit.[18] $[\alpha]_D^{19}$ +8.4 (*c* 4.00, H_2O). **4c**: $[\alpha]_D^{23}$ −32.2 (*c* 0.32, H_2O), lit.[18] $[\alpha]_D^{20}$ −35.1 (*c* 1.94, H_2O). **4d**: $[\alpha]_D^{24}$ −9.2 (*c* 0.36, H_2O), lit.[18] $[\alpha]_D^{25}$ −10.8 (*c* 2.20, H_2O). **4e**: $[\alpha]_D^{24}$ +10.7 (*c* 0.30, H_2O), lit.[18] $[\alpha]_D^{20}$ +13.9 (*c* 0.90, H_2O). **4f**: $[\alpha]_D^{24}$ −6.7 (*c* 0.30, H_2O), lit.[19] $[\alpha]_D^{20}$ −9.5 (*c* 3.00, H_2O).
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