Synthesis of Enantiopure Prolines via *exo*-Stereoselective 1,3-Dipolar Cycloadditions to Acetone-Derived Chiral Stabilised Azomethine Ylides

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Abstract: The chiral stabilised azomethine ylide formed from condensation of the dimethyl acetal of acetone with (5*S*)-5-phenylmorpholinone undergoes stereoselective *exo*-cycloaddition reactions with a range of doubly and singly activated dipolarophiles when generated in the presence of excess $MgBr_2 \cdot OEt_2$. The cycloadducts can be degraded to yield enantiomerically pure proline derivatives.

Key words: ketone-derived azomethine ylide, 5,5-disubstituted prolines, Lewis acid, stereoselective cycloaddition

There has been much interest in substituted proline derivatives in recent years. Proline derivatives are important pharmacophores in ACE inhibitors such as captopril and enalaprilat[1] or as residues in peptide sequences, where they have been demonstrated to have a profound effect on *cis/trans* peptide conformation[2] and thus the stabilisation of type 1 geometry in β turns.[3] Recently, it has been demonstrated that functionalized prolines can be used for in situ chemical modification of peptide conformation, a process termed 'proline editing'.[4]

Most substituted proline derivatives are derived from the naturally occurring 4-hydroxyproline (**1**),[5] or by alkylation at the α-carbon of proline derivatives.[6] There have been several total syntheses of highly substituted prolines reported but these have disadvantages of requiring multiple steps[7a–d] or expensive chiral catalysts.[8] Syntheses of 5-substituted prolines are infrequently encountered in the literature; although inclusion of a 5,5-dimethylproline (**2**, Figure 1) residue has been shown to stabilise *cis*-amide conformation and accelerate folding in ribonuclease A.[9]

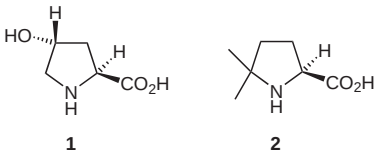
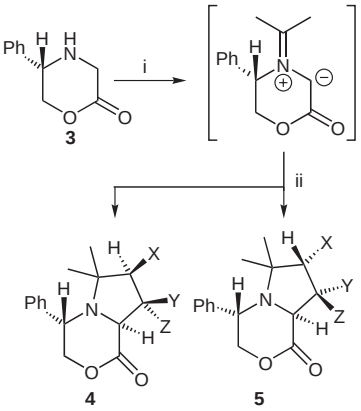


Figure 1

Previous attempts at the synthesis of 5,5-dimethylprolines involved the formation of the racemic product followed by chemical resolution.[10a–c] A recent communication[11] highlighted the catalytic asymmetric synthesis of 5,5-dimethylproline via a ruthenium-catalysed cross-metathesis reaction; however, this route utilises harsh reaction conditions (triflic acid, 100 °C). As such, 5,5-disubstituted prolines continue to be valuable targets for the synthetic chemist.

A previous communication by this group[12] has highlighted an expeditious approach to enantiomerically pure 5,5-dimethylprolines[13] via the 1,3-dipolar cycloaddition of chiral stabilised acetone-derived azomethine ylides generated by Lewis acid catalysed condensation of (5*S*)-5-phenylmorpholinone (**3**) and 2,2-dimethoxypropane with alkene dipolarophiles (Scheme 1). To our knowledge, this was the first report of the generation of chiral stabilised azomethine ylides possessing such substitution and we rationalised our success with 2,2-dimethoxypropane, when 2-methoxypropene and acetone failed to furnish the ylide, by invoking Lewis acid assistance in the rate determining generation of the oxonium electrophile. Although the ylide generation and trapping occurred with excellent diastereocontrol of the stereogenic centre adjacent to nitrogen, mixtures of *endo*-**4** and *exo*-**5** diastereoisomeric cycloadducts were obtained with a preference for the *endo*-products.



Scheme 1 *Reagents and conditions*: (i) Δ, THF, $MgBr_2 \cdot OEt_2$, 2,2-dimethoxypropane; (ii) dipolarophile.

This *endo*-selectivity was in contrast to previous work by our group,[14] which demonstrated that Lewis acid catalysed generation and cycloaddition of aldehyde-derived azomethine ylids derived from **3** showed marked *exo*-stereoselectivity. In that instance, the propensity for the formation of *exo*-adducts was rationalised by invoking a switch from the type 1 cycloaddition observed in

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uncatalysed cycloadditions (HOMO dipole/LUMO dipolarophile) favouring *endo*-cycloadducts to type 3 cycloaddition (LUMO dipole/HOMO dipolarophile) in the catalysed situation. This was proposed to be a consequence of the kinetically active ylide species resulting from complexation of the Lewis acid with the lactone carbonyl of the stabilised ylide. In this situation destabilising secondary orbital interactions combine with steric effects to disfavour *endo* approach of the dipolarophile (Figure 2).

As only one equivalent of Lewis acid had been used in the original protocol for generation of the ketone-derived ylide, it was reasoned that the preference for the *endo* cycloadduct could be a result of O-complexation between the Lewis acid and an acetal methoxy group facilitating elimination of methanol, with the result that there was no Lewis acid available to catalyse the cycloaddition.

With the above in mind it was proposed that adding an excess of Lewis acid would favour a switch to a type 3 interaction as observed in the catalysed cycloaddition of the aldehyde-derived ylides (Figure 2), thus giving *exo* stereoselectivity and access to the minor proline diastereoisomers obtained in the protocol using one equivalent of Lewis acid.

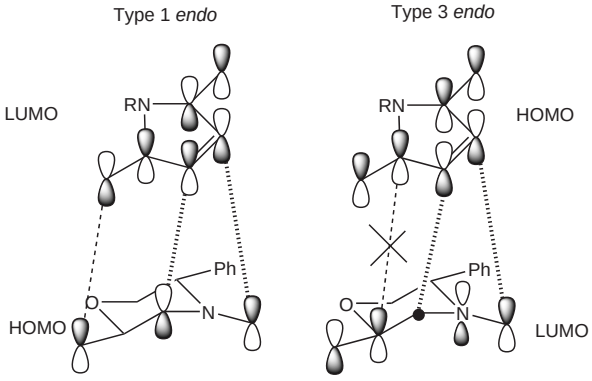
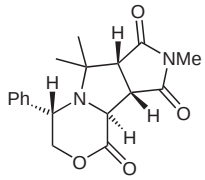
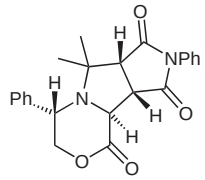
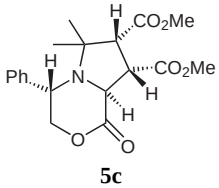
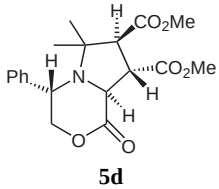
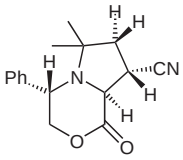
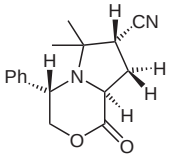


Figure 2

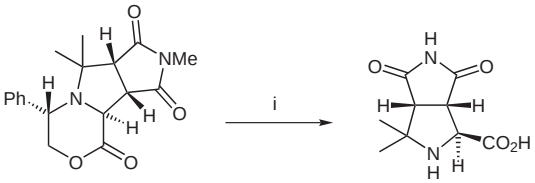
In keeping with our prediction, treatment of (5*S*)-5-phenylmorpholinone and 2,2-dimethoxypropane with ten equivalents of $MgBr_2{\cdot}OEt_2$ and two equivalents of *N*-phenyl maleimide in refluxing THF for 16 hours followed by filtration through Celite® and purification by flash column chromatography on silica furnished only the *exo*-adduct **5a** in 48% yield.[12] It was proposed that the moderate yield might be a result of mechanical losses during workup due to the large excess of Lewis acid. The reaction was therefore repeated with the filtration step being replaced by an aqueous workup furnishing the *exo*-cycloadduct **5a** in 78% yield.[15] The cycloaddition was then repeated with the same range of dipolarophiles as used in our previous study and, in each case, only the *exo*-cycloadduct could be detected in the crude reaction mixtures and the pure adducts were isolated in the yields indicated (Table 1).[16]

Table 1 Cycloaddition with Various Amounts of Magnesium-bromide Etherate

Cycloadduct	*endo*	*exo*	*endo*	*exo*
	Isolated yield (%)			
	1 equiv $MgBr_2{\cdot}OEt_2$[12]		10 equiv $MgBr_2{\cdot}OEt_2$	
 **5a**	43	30	0	78
 **5b**	33	26	0	61
 **5c**	23	16	0	41
 **5d**	0	70	0	70
 **5e**	40	0	0	31[17]
 **5e**,**i**				

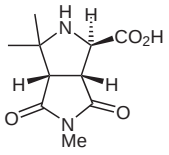
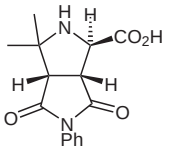
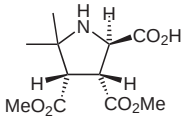
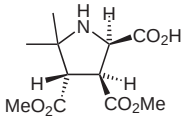
Hydrogenolysis of the cycloadducts (**5a**–**d**) under 5 atm of hydrogen (Pearlman's catalyst, TFA, MeOH, H_2O; Scheme 2) followed by filtration through a pad of Celite®, and purification by dry flash column chromatography, or

by trituration with diethyl ether, furnished the enantiomerically pure proline derivatives (**6a–d**) in excellent to quantitative yield (Table 2).



Scheme 2 MeOH–H_2O, Pearlman's catalyst, TFA, H_2 (5 atm).

Table 2 Hydrogenolysis of Cycloadducts **5a–d**

Cycloadduct	Proline	Yield (%)
5a	 **6a**	70
5b	 **6b**	81
5c	 **6c**	60
5d	 **6d**	Quant.

In conclusion we have demonstrated the *exo*-selective 1,3-dipolar cycloaddition of chiral stabilised acetone-derived azomethine ylides, generated by Lewis acid catalysed condensation of (5*S*)-5-phenylmorpholinone (**1**) and 2,2-dimethoxypropane with alkene dipolarophiles in good to excellent yields, thus lending support to our proposal that Lewis acid facilitates a switch from type 1 to type 3 cycloaddition. This route also provides an expedient entry to enantiomerically pure 5,5-dimethylproline derivatives via the catalytic hydrogenolysis of the template with Pearlman's catalyst. To our knowledge, this is the first report of a completely diastereoselective route to such highly substituted enantiomerically pure prolines.

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(15) **Typical Experimental Procedure.**
2,2-Dimethoxypropane (2 equiv) was added via syringe to a stirred solution of (5*S*)-5-phenylmorpholin-2-one (**3**, 1 equiv), dipolarophile (2 equiv), and $MgBr{\cdot}OEt_2$ (10 equiv) in THF (10 mL per mmol substrate). The resulting mixture was stirred under nitrogen for 6 h, cooled to r.t., then quenched with aq NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with brine, the combined aqueous phases extracted with CH_2Cl_2 (3 × 10 mL) and the organic phases dried ($MgSO_4$) and concentrated in vacuo. The residue was then purified by flash column chromatography, gradient eluting with 3:1 hexane–EtOAc to pure EtOAc.
(16) **Representative Analytical Data.**
***N*-Methyl (2*S*,6*S*,7*S*,8*R*)-9,9-Dimethyl-2-phenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboximide (5b).**
Colourless crystals (61%), mp 160–163 °C; $[\alpha]_D^{25}$ –24.0 (*c* 0.35, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.23 (5 H, m, Ar-H), 4.43 (1 H, t, *J* = 5.7 Hz, 3β-H), 4.38 (1 H, d, *J* = 1.7 Hz, 6α-H), 4.21 (1 H, dd, *J* = 5.7 Hz, *J′* = 11.6 Hz,

2β-H), 4.06 (1 H, dd, *J* = 1.6 Hz, *J′* = 8.5 Hz, 7β-H), 4.00 (1 H, dd, *J* = 5.7 Hz, *J′* = 11.6 Hz, 3α-H), 3.08 (3 H, s, NCH_3), 3.06 (1 H, d, *J* = 8.5 Hz, 8β-H), 1.19 (3 H, s, CH_3), 1.00 (3 H, s, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 178.6, 172.1 (C=O), 139.0, 129.3, 128.5, 126.9 (C-aromatic), 71.2 (C_3), 66.1 (C_9), 60.8 (C_6), 55.2 (C_2), 54.7 (C_8), 44.9 (C_7), 26.2 (CH_3), 25.7 (NCH_3), 23.4 (CH_3). HRMS: *m/z* calcd for $C_{18}H_{20}N_2O_4$: 329.1501; found: 329.1499 [MH^+].

Dimethyl (2*S*,6*S*,7*S*,8*R*)-9,9-Dimethyl-2-phenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylate (5c).

Colourless oil (41%); $[\alpha]_D^{25}$ –71.3 (*c* 0.35, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.25 (5 H, m, Ar-H), 4.79 (1 H, d, *J* = 6.4 Hz, 6α-H), 4.27–4.10 (3 H, m, 2β-3α-3β-H), 3.93 (1 H, dd, *J* = 6.4 Hz, *J′* = 7.8 Hz, 7β-H), 3.72 (3 H, CO_2Me), 3.68 (3 H, CO_2Me), 3.13 (1 H, d, *J* = 7.8 Hz, 8β-H), 1.11 (3 H, s, CH_3) 0.71 (3 H, s, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.7, 172.2 (C=O), 140.8, 129.0, 128.4, 127.3 (C-aromatic), 71.5 (C_3), 65.8 (C_9), 57.8 (C_6), 57.5 (C_2), 56.7 (C_8), 52.9 (C_7), 52.0 (CO_2Me), 45.5 (CO_2Me), 26.2 (CH_3), 21.9 (CH_3). HRMS: *m/z* calcd for $C_{19}H_{24}NO_6$: 362.1603; found: 362.1613 [MH^+].

Dimethyl (2*S*,6*S*,7*S*,8*R*)-9,9-Dimethyl-2-phenyl-1-aza-4-oxa[4.3.0^{1,6}]bicyclononan-5-one-7,8-dicarboxylate (5d).

Colourless crystals (60%); mp 105–107 °C $[\alpha]_d^{25}$ –38.0 (*c* 0.5, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.46–7.29 (5 H, m, Ar-H), 4.43 (1 H, d, *J* = 5.4 Hz, 6α-H), 4.31–4.07 (4 H, m, 2β-3α-3β-7αH), 3.77 (3 H, CO_2Me), 3.74 (3 H, CO_2Me), 3.12 (1 H, d, *J* = 10.8 Hz, 8β-H), 1.11 (3 H, s, CH_3), 0.71 (3 H, s, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 173.7, 173.5 (C=O), 140.2, 129.0, 128.4, 127.3 (C-aromatic), 71.2 (C_3), 65.6 (C_9), 59.3 (C_6), 57.9 (C_8), 56.4 (C_2), 53.7 (C_7), 52.6 (CO_2Me), 44.7 (CO_2Me), 28.8 (CH_3), 16.8 (CH_3): HRMS: *m/z* calcd for $C_{19}H_{24}N_2O_6$: 362.1541; found: 362.1559 [MH^+].

General Procedure for Hydrogenolysis.

The cycloadduct (1 equiv) was dissolved in aq MeOH (2 mL MeOH, 0.1 mL H_2O per mmol substrate) containing TFA (1 equiv). Pearlman's catalyst was added and the suspension was degassed then subjected to H_2 (5 bar) with stirring at r.t. for 48 h. The solution was filtered through a pad of Celite® then the solvent removed in vacuo and the crude material purified by dry flash column chromatography (MeOH–H_2O, 1:1) or by trituration with Et_2O.

(1*S*,3a*R*,6a*S*)-3,3-Dimethyl-4,6-dioxo-5-phenylocta-hydropyrrolo[3,4-*c*]pyrrole-1-carboxylic Acid (6b).

Colourless powder; mp 168–170 °C; $[\alpha]_D^{25}$ +51.3 (*c* 0.30, H_2O). ^1H NMR (250 MHz, MeOH-d_4): δ = 7.56–7.29 (5 H, m, Ar-H), 4.70 (1 H, d, *J* = 4.2 Hz, 2α-H), 4.31 (1 H, dd, *J* = 4.2 Hz, *J′* = 9.3 Hz, 3β-H), 3.59 (1 H, d, *J* = 9.3 Hz, 4β-H), 1.61 (6 H, s, CH_3). ^{13}C NMR (62.5 MHz, MeOH-d_4): δ = 178.6, 176.8, 174.8 (C=O), 133.6, 130.5, 130.3, 128.3 (C-aromatic), 67.9 (C_2), 62.5 (C_5), 54.9 (C_4), 49.0 (C_3), 28.4 (CH_3) 22.8 (CH_3): HRMS: *m/z* calcd for $C_{15}H_{16}N_2O_4$: 289.1188; found: 289.1193 [MH^+].

(2*R*,3*R*,4*S*)-3,4-Bis(methoxycarbonyl)-5,5-dimethyl-pyrrolidine-2-carboxylic Acid (6c).

Colourless powder; mp 168–170 °C; $[\alpha]_D^{25}$ +10.0 (*c* 0.05, H_2O). ^1H NMR (250 MHz, MeOH-d_4): δ = 4.85 (1 H, d, *J* = 8.2 Hz, 2α-H), 4.08 (1 H, t, *J* = 7.0 Hz, 3β-H), 3.76 (3 H CO_2Me), 3.74 (3 H CO_2Me), 3.51 (1 H, d, *J* = 8.1 Hz, 4β-H), 1.51 (3 H, s, CH_3) 1.48 (3 H, s, CH_3). ^{13}C NMR (62.5 MHz, MeOH-d_4): δ = 173.6, 171.9, 170.0 (C=O), 66.9 (C_2), 60.0 (C_5), 56.4 (CO_2Me), 48.0 (CO_2Me), 24.4 (CH_3) 20.9 (CH_3): HRMS: *m/z* calcd for $C_{11}H_{18}NO_6$: 260.1134; found: 260.1123 [MH^+].

(2*R*,3*S*,4*S*)-3,4-Bis(methoxycarbonyl)-5,5-dimethyl-pyrrolidine-2-carboxylic Acid (6d).

Colourless powder; $[\alpha]_D^{25}$ –2.5 (*c* 0.25, H_2O). ^1H NMR (250 MHz, MeOH-d_4): δ = 4.49 (1 H, d, *J* = 7.4 Hz, 2α-H), 3.98 (1 H, dd, *J* = 7.4 Hz, *J′* = 10.3 Hz, 3β-H), 3.79 (3 H CO_2Me), 3.79 (3 H s CO_2Me), 3.31 (1 H, d, *J* = 10.3 Hz, 4α-H), 1.64 (3 H, s, CH_3) 1.30 (3 H, s, CH_3). ^{13}C NMR (62.5 MHz, MeOH-d_4): δ = 173.3, 171.9, 170.0 (C=O), 66.8 (C_2), 60.0 (C_5), 56.4 (CO_2Me), 48.0 (CO_2Me), 24.6 (CH_3), 20.9 (CH_3). HRMS: *m/z* calcd for $C_{11}H_{18}NO_6$: 260.1134; found: 260.1126 [MH^+].

(17) Isolated as an inseparable mixture of *exo*-regioisomers, configuration was assigned by 2D NMR (COSY) experiments and comparison with the known *endo* adduct.