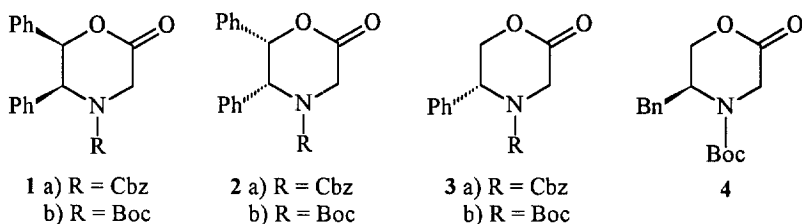


An Expedient Route to the Glycine Templates (R)- or (S)-N-Cbz-5-Phenyl-1,4-oxazin-2-one.

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Abstract: An economical and practical route to the title compounds is described. The three step, essentially "one pot" sequence proceeds in overall yields of up to 80% without the need for chromatography or intermediate isolation. Copyright © 1996 Elsevier Science Ltd

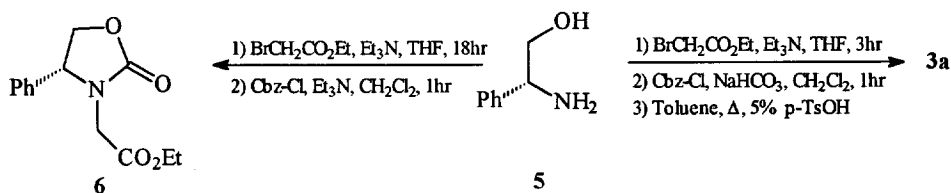
The Williams² cyclic glycine enolate templates **1** and **2** were introduced in 1986 and have been extensively employed. Alternatives **3** and **4**, from Dellaria³ and Baker⁴ respectively, have since been developed. The syntheses of these templates all involve sequential N-alkylation, N-protection and cyclization of the appropriate amino-alcohol starting material. The templates **1a** and **2a** have been synthesized in 66% yield.⁵ Dellaria's synthesis of **3** proceeds in an overall yields of 48% but requires the preparation of phenyl α -bromoacetate for reaction with the amino-alcohol and this step suffers from variable yields (40-83%).³ The synthesis of **4** proceeds, without intermediate isolation, in an overall yield of 67% but is limited to the N-Boc protected template.



As part of an ongoing synthetic programme, template **3a** was chosen (due to the ease of final product release) for the synthesis of a rare α -amino acid. In our hands, the literature procedure³ led only to moderate yields of **3a**.⁶ These difficulties prompted us to develop a refined route to **3a** and a recent reference⁷ to this template encouraged us to report our findings.

The initial alkylation of (R)-phenylglycinol **5** with ethyl α -bromoacetate proceeded readily, but subsequent N-protection afforded only the oxazolidinone **6** in 93% yield (Scheme 1). This product⁸ evidently arose from alternative nucleophilic substitution at the carbamate carbonyl. Fortunately, employment of Schotten-Baumann conditions circumvented this undesired cyclization. Moreover, these N-acylation conditions may reliably be applied directly to the alkylation product mixture, hence obviating a work-up. The

final step was accomplished quantitatively by distillation of a toluene solution of the hydroxy-ester at atmospheric pressure to give **3a** (73-80% overall yield).⁹ The enantiomeric (S)-template was similarly obtained from (S)-phenylglycinol.¹⁰



Scheme 1

Now that a reliable and economical route to the attractive template **3a** exists, it is hoped that its further use will be encouraged.

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1. Author to whom correspondence should be addressed, e-mail dastlik@chem.murdoch.edu.au
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9. **(5R)-2,3,5,6-Tetrahydro-5-phenyl-N-(benzyloxycarbonyl)-4H-1,4-oxazin-2-one (3a)**. (R)-phenylglycinol (1.37g, 10 mmol) was suspended in dry THF (20ml) and dry triethylamine (1.65ml, 1.21g, 12 mmol) at 0 °C under an atmosphere of N₂. To this stirred solution was added ethyl α-bromoacetate (1.30ml, 0.86g, 12 mmol, Al₂O₃ filtered) and the reaction stirred to room temperature over 3hr (*stirring for 24hr only marginally increases the final yield*). The reaction mixture was cooled to 0 °C, filtered and the filter cake washed with THF (20ml). The combined THF fractions were evaporated to dryness (bath temp. <45 °C) and the residue was dissolved in CH₂Cl₂ (20ml). NaHCO₃ (5%, 40ml) was added and the stirred solution cooled to 0 °C. Cbz-Cl (1.65ml, 1.09g, 11 mmol, 95%) was added and stirring continued for 1hr. The layers of the reaction mixture were separated and the NaHCO₃ fraction extracted with further CH₂Cl₂ (3x20 ml). The combined CH₂Cl₂ fractions were washed (H₂O, 20 ml), dried (Na₂SO₄) and concentrated to dryness (bath temp. <45 °C). The residue was taken up in toluene (100 ml), p-TsOH (100mg, 0.05 equiv.) added and the excess toluene distilled to near dryness at atmospheric pressure. Any remaining toluene was removed on the rotavap. The reaction products were dissolved in Et₂O (100ml), washed (H₂O, 20 ml), dried (Na₂SO₄) and concentrated to ~5ml. The product then crystallized by the addition of hexanes with cooling to yield 2.48g (80%, range 73%-80%) of white solid. The product may be recrystallized from CH₂Cl₂/Et₂O as granular crystals: mp 122.5-123.5 (Lit³ mp 97-98°C), [α]_D²³ -56.6 (c = 1.0, CH₂Cl₂); IR (KBr) 1773 (lactone), 1665 (carbamate) cm⁻¹; ¹H NMR (300MHz, CDCl₃, 60°C) δ_H 7.14-7.36 (m, 10H, Ph), 5.22 (dd, 1H, H₅, J_{5,6} = 4.5, 4.7Hz), 5.14 (d, 1H, J = 12Hz, CH₂Ph), 5.08 (d, 1H, J = 12Hz, CH₂Ph), 4.63 (d, 1H, H₃, J_{3,3} = 18Hz), 4.59 (dd, 1H, H₆, J_{6,5} = 4.5 Hz, J_{6,6} = 12 Hz), 4.50 (dd, 1H, H₆, J_{6,5} = 4.5 Hz, J_{6,6} = 12 Hz), 4.18 (d, 1H, H₃, J_{3,3} = 18Hz); ¹³C NMR (75.5 MHz, CDCl₃, 60°C) δ_C 166.6, 154.7, 137.2, 135.9, 129.2, 128.6, 128.4, 128.3, 128.0, 126.3, 69.9, 68.2, 54.1, 44.8.
10. See reference 9. [α]_D²¹ +56.4 (c = 1.0, CH₂Cl₂)