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An efficient asymmetric synthesis of Fmoc-L-cyclopentylglycine via diastereoselective alkylation of glycine enolate equivalent

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Abstract—Stereoselective alkylation of the enolate derived from benzyl (2*R*,3*S*)-(−)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**1**) with cyclopentyl iodide afforded anti-α-monosubstituted product, benzyl (2*R*,3*S*,5*S*)-(−)-6-oxo-2,3-diphenyl-5-cyclopentyl-4-morpholinecarboxylate (**3**) in 60% yield. Catalytic hydrogenolysis over $PdCl_2$ cleaved the auxiliary ring system to give L-cyclopentylglycine (**4**) in 84% yield. Subsequent protection of the α-amino function with Fmoc-OSu gave Fmoc-L-cyclopentylglycine (**5**) in high yield.

1. Introduction

Nature has afforded us 22 naturally occurring coded amino acids commonly found in proteins isolated from eukaryotic and prokaryotic sources. A host of enzymes are present in nature to extend this repertoire much further by utilizing post-translational modification.[1] A variety of synthetic means have also been established to produce a plethora of non-proteinogenic amino acids as tools to investigate enzymatic mechanisms, extend biological half-life, establish a specific conformational determinant or increase potency of therapeutically interesting peptides.[2] Of these, stereoselective homologation of readily available chiral auxiliaries, such as cyclic glycine enolate equivalents derived from bis-lactim ethers,[3] imidazolidinones,[4] and oxazinones[5] are particularly useful. Besides, glycylsultam[6] and pseudoephedrine glycinate hydrate[7] are also useful α-amino acid templates.

Cyclopentylglycine (Cpg) is a competitive inhibitor of isoleucine uptake in *E. coli*[8] and also has been used in designing angiotensin II antagonists.[9] It has been synthesized via S_N2 displacement of bromoglycinate with an organometallic reagent followed by epimerization.[10] Syntheses of racemic 2-cyclopentenylglycine,[11] cyclopentylglycine,[8] and 2-cyclopentadieneylglycine[12] have also been reported. In this publication, we wish to report a short and efficient asymmetric synthesis of Fmoc-L-cyclopentylglycine (**5**) by using benzyl (2*R*,3*S*)-(−)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**1**) as a template. The reasons behind choosing this chiral auxiliary were: (1) commercial availability, (2) excellent optical purity of the final product, (3) high reactivity towards unactivated electrophiles and (4) scalability.

2. Results and discussion

As shown in Scheme 1, chiral auxiliary **1** was alkylated with cyclopentyl iodide in the presence of lithium bis(trimethylsilyl)amide base. Enolate generation at −78°C followed by quenching with alkylating agent at the same temperature did not result in any reaction. Optimum conditions utilized dissolving **1** and cyclopentyl iodide in THF/HMPA (10:1) by heating to ~35°C, generating enolate at −78°C and allowing the reaction mixture to warm to room temperature over a period of 2 h. Under these conditions, alkylated product **3** was obtained in 60% yield.[†]

Variations in experimental conditions, such as longer reaction time, increasing the amount of base (>1.5

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[†] **Compound 3**: ESI-MS: 456 ($C_{29}H_{30}NO_4$) $(M+H)^+$. ^1H NMR (600 MHz, $CDCl_3$): δ 7.26–7.07 (13H, m), 6.52 (2H, d, $J=6.8$ Hz), 6.00 (1H, d, $J=3.0$ Hz), 5.13 (1H, d, $J=3.0$ Hz), 4.91 (1H, d, $J=12.0$ Hz), 4.85 (1H, d, $J=12.0$ Hz), 3.74 (1H, m), 2.44 (1H, m), 1.90–1.80 (4H, m), 1.65–1.55 (4H, m); mp 216–217°C; $[\alpha]_D^{24}$ −44.88° (*c* 0.5, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) calcd for $C_{29}H_{29}NO_4$: C, 76.48; H, 6.37; N, 3.07. Found: C, 76.58, H, 6.29; N, 3.28.

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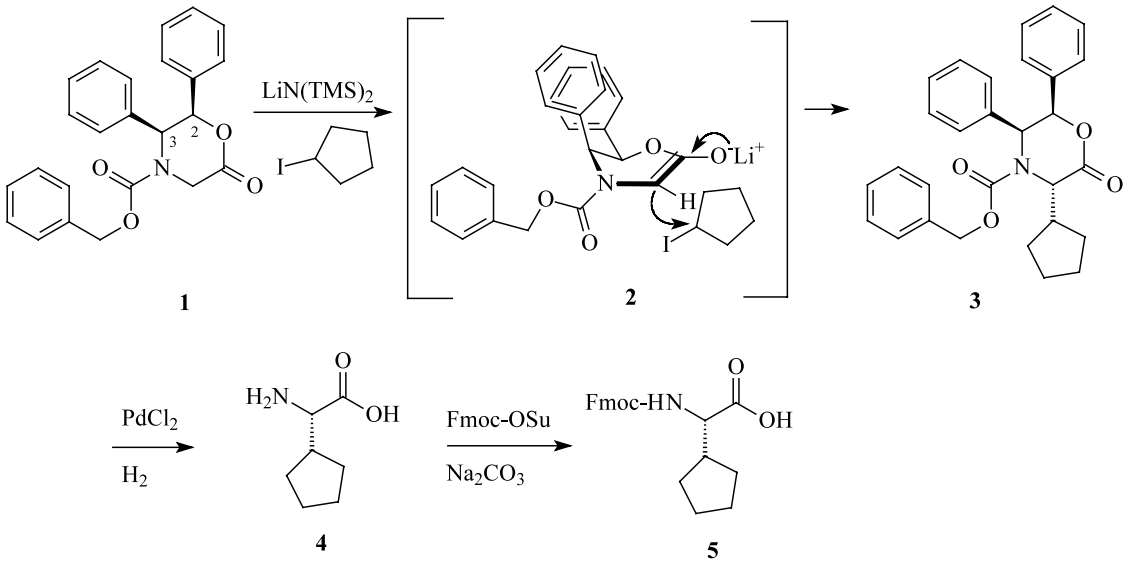

Scheme 1.

equiv.) or cyclopentyl iodide (>5 equiv.) and substituting the solvating agent HMPA with DMPU either did not result in any improvements or lowered the yield of the alkylation product **3**. Since cyclopentyl iodide is an unactivated electrophile, raising the reaction temperature to 40°C was expected to improve the yield of alkylation product **3**. However, reaction at 40°C for 1 h resulted in the formation of 10–15% of side product **6** (Fig. 1), in addition to alkylation product **3**.

It is important to note that no dialkylation product was formed. Furthermore, only *trans*-alkylated product (**3**) formed and no *cis*-diastereoisomer (i.e. 2*R*,3*S*,5*R*) was detected by HPLC. The high diastereoselectivity of the enolate alkylation can be explained by considering the expected boat conformation of **2** that disposes the phenyl ring at C-3 in a pseudoaxial orientation, creating steric shielding of the same face at C-5 position from electrophilic attack as shown in Scheme 1.

No purification by column chromatography was necessary. The *trans*-alkylated product **3** was easily crystallized out as a white solid from EtOAc/hexane in 60% of isolated yield (>99% de by HPLC) after standard work-up (cf. *syn*-alkylated product is usually an oil).[10] Additional evidence of stereoselectivity was apparent from ^{1}H NMR as the methine protons (CH) at C-2 and C-3 appeared at δ 6.00 and 5.13 ppm, respectively (0.87 ppm apart, characteristic of *anti*-alkylation product; cf. 0.6–0.7 ppm apart for the *syn*-alkylated product).[10]

Cleavage of the auxiliary ring system **3** was performed using H_2 and $PdCl_2$ as a catalyst in THF/MeOH (2:1) solvent mixture at 60 psi for 48–60 h. After removing the catalyst (pyrophoric), the solvent was removed and the residue was triturated with ether to afford Cpg **4** in almost quantitative yield. The contaminating byproduct, 1,2-diphenylethane was easily removed by extracting the dilute aqueous HCl solution of **4** with EtOAc. Removal of aqueous solvent followed by crystallization of the syrup from MeOH/EtOAc afforded **4** in 84% yield.‡

Protection of the α-amino function of Cpg **4** was accomplished by treating it with Fmoc-OSu in the presence of Na_2CO_3 overnight in dioxane/H_2O (1.5:1) solvent mixture. Fmoc-Cpg-OH (**5**) was obtained in quantitative yield after crystallization from EtOAc/hexane.

Thus, an efficient asymmetric synthesis of Fmoc-Cpg-OH (**5**) from a commercially available chiral auxiliary was successfully accomplished on multigram scale. Synthesis was easy to perform, as no chromatographic purification was required at any step. Furthermore, excellent optical purity (>99%) and high yield (50% overall) was obtained.

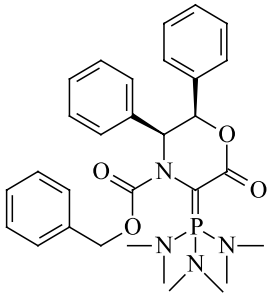

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Figure 1.

‡ **Compound 4:** ESI-MS: 144 ($C_7H_{13}NO_2$) $(M+H)^+$. ^{1}H NMR (600 MHz, DMSO-d^6): δ 4.74 (1H, m), 2.48 (1H, m), 1.78–1.69 (2H, m), 1.53–1.42 (4H, m), 1.39–1.25 (2H, m); mp 245–247°C (dec.); $[\alpha]_D^{24}$ +12.34° (*c* 0.5, MeOH); (lit.[10], +11.6°, *c* 0.49, 1N HCl)). Anal. (recrystallized from MeOH/EtOAc) calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.70, H, 8.85; N, 9.99.

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