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# Enantioselective synthesis of (*L*)-Fmoc- $\alpha$ -Me-Lys(Boc)-OH via diastereoselective alkylation of oxazinone as a chiral auxiliary

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### 1. Introduction

Optically pure modified amino acids are valuable building blocks for the preparation of biologically active peptidomimetics since they can be utilized to confer stability to peptides against enzymatic degradation.<sup>1</sup> In addition, C<sup> $\alpha$ </sup>-alkylated amino acids are not prone to racemization under basic or acidic conditions due to lack of abstractable or enolizable  $\alpha$ -hydrogen.<sup>2</sup> Furthermore, C<sup> $\alpha$ </sup>-alkylation severely restricts rotation around the N–C<sup> $\alpha$ </sup> ( $\phi$ ) and C<sup> $\alpha$ </sup>–C(O)( $\psi$ ) bonds of the amino acid in a peptide sequence and stabilizes preferred conformations of the peptide backbone.<sup>3</sup>

The quaternization of the  $\alpha$ -carbon of  $\alpha$ -amino acids is rather challenging due to steric constraints. However, several routes to optically pure  $\alpha$ -alkylated  $\alpha$ -amino acids have been developed.<sup>4–8</sup> Most notably, the stereogenic centre is constructed by alkylation of a chiral, nonracemic enolates.<sup>9,10</sup> In these reactions, alkylation occurs from the least-shielded face of the enolate. Furthermore, in successive dialkylation reactions, the second alkyl group comes in from the opposite side of the sterically demanding group(s) present on the chiral auxiliary.<sup>6,8</sup>

The first synthesis of D/L- $\alpha$ -methyllysine was reported in 1978 from alanine derivative (**1**).<sup>11</sup> It has been used to study *L*-lysine uptake in *Escherichia coli* and *Bacillus sphaericus*.<sup>12</sup> Later on, the (*S*)isomer of  $\alpha$ -methyllysine was obtained by Gander-Coquoz and Seebach from (*S*)-lysine derivatives (**2**) by exploiting the principle of self-regeneration of stereocenters (SRS) in rather low yield.<sup>13</sup> Re-

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### ABSTRACT

Benzyl (2*R*,3*S*)-(–)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**4**) was successively alkylated with methyl iodide and 1,4-diiodobutane using a base. In each alkylation step anti-alkylated product formed exclusively. The iodo group was displaced with azide, which served as a precursor for the side-chain amino function. Catalytic hydrogenation with concomitant cleavage of the chiral auxiliary afforded (*L*)- $\alpha$ -Me-Lys-OH (**9**) in a total of four steps in good yield. (*L*)-Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) was obtained from **9** via regioselective benzyloxycarbonylation. Alternately, (*L*)-Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) was obtained via Staudinger reduction of azide (**8**) in a total of six steps in good yield.

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cently, Cativiela et al. have used (1S,2R,4R)-10-(dicyclohexylsulfamoyl)isoborneol as a chiral auxiliary<sup>14</sup> to synthesize (S)- $\alpha$ methyllysine via chiral cyanopropanoate (**3**; Fig. 1) in 10 steps.<sup>15</sup>

In this publication, we report a short and efficient synthesis of (S)- $\alpha$ -methyllysine using William's oxazinone as a chiral auxiliary  $(\mathbf{4})$ .<sup>16</sup> Reasons for 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. Furthermore, the side-chain amino function could be orthogonally protected before cleavage of the chiral auxiliary eliminating the need for regioselective protection of the amino functions in  $\alpha$ -methyllysine.

### 2. Results and discussion

As shown in Scheme 1, benzyl (2*R*,3*S*)-(–)-6-oxo-2,3-diphenyl-4-morpholinecarboxylate (**4**) was alkylated twice; first with methyl iodide and second with 1,4-diiodobutane. Alkylation reactions were optimized in order to achieve highest yields at each step. The first alkylation of **4** with methyl iodide was attempted using sodium bis(trimethylsilyl amide) in THF at -78 °C as reported.<sup>16</sup> However, the yield was low and the product required purification by silica gel column chromatography. The optimum conditions for alkylation with methyl iodide were comprised of dissolving **4** and methyl iodide (5 equiv) in THF/HMPA (10:1), generating enolate at -78 °C with lithium bis(trimethylsilyl amide) (1.5 equiv), and allowing the reaction to warm to ambient temperature over the period of 2 h after 1 h at -78 °C. Aqueous work-up and evaporation yielded a yellow solid in quantitative yield, which



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contained  $\sim$ 3% of the dialkylated product. The mono-alkylated product **5** was obtained in 70% yield as a light yellow solid after recrystallization from 10% EtOAc/hexane.<sup>9</sup>

Next, we optimized the alkylation of (5S)-5-methyloxazinone (**5**) with 1,4-diiodobutane. The best conditions utilized dissolving **5** and 1,4-diiodobutane (10 equiv) in THF/HMPA (10:1) at ambient temperature, adding potassium bis(trimethylsilyl amide) (7 equiv) dropwise at -78 °C, and a reaction time of 4 h at the same temperature. The alkylated product **6** was obtained in quantitative yield as a dark brown solid (flakes) after aqueous work-up. It was recrystallized from 2% methanol/diisopropyl ether to afford off-white solid in 70% yield. It should be mentioned that the use of THF solvent alone with potassium bis(trimethylsilyl amide) as a base resulted in poor yield.<sup>16</sup> Use of lithium bis(trimethylsilyl amide) resulted in only byproducts.

It is important to note that in both alkylation reactions only trans-alkylated product **5** or **6** was formed and no cis-diastereoisomer (i.e., 2R,3S,5R) was detected by HPLC. The high diastereoselectivity of enolate alkylation can be explained by considering the expected twist-boat conformation that disposes the phenyl ring at C-3 of enolate **7** in a pseudoaxial orientation, creating steric shielding of the same face at C-5 position from electrophilic attack as shown in Scheme 1.

The iodo group of dialkylated product **6** underwent nucleophilic substitution with sodium azide smoothly and the azide **8** was obtained in 91% yield as a white solid.<sup>17</sup> The chiral auxiliary was cleaved by hydrogenolysis using palladium chloride and hydrogen gas at 60 psi. The azide group was also reduced under these conditions and (L)- $\alpha$ -Me-Lysine (**9**) was obtained in 84% yield as a dihydrochloride salt.<sup>9</sup>









Scheme 4.

Having obtained  $(L)-\alpha$ -Me-Lysine (**9**), we tried selective protection of the  $\varepsilon$ -amino function via copper complex as shown in Scheme 2. Thus, **9** was treated with basic copper carbonate followed by treatment with (Boc)<sub>2</sub>O. The  $\varepsilon$ -Boc-protected product **10** was obtained in only 25% yield.<sup>18</sup> Cleavage of the copper complex by chelation with 8-hydroxyquinoline afforded (*L*)- $\alpha$ -Me-Lys(Boc)-OH (**11**) in overall 10% yield.<sup>19</sup>

Since the yield form copper complex was poor perhaps due to steric hindrance by  $\alpha$ -methyl group, we decided to try regioselective benzyloxycarbonylation of the  $\varepsilon$ -amino group of **9**. The higher pK<sub>a</sub> of the  $\varepsilon$ -NH<sub>2</sub> (10.5) compared to  $\alpha$ -NH<sub>2</sub> (9.0) renders it more nucle-ophilic and is known to react selectively, albeit in moderate yield.<sup>20</sup>

As shown in Scheme 3, (L)- $\alpha$ -Me-Lys-OH (9) was treated with 1 N ag NaOH (2 equiv) and Cbz-OSu (1.1 equiv) in acetone at 0 °C overnight. As expected (L)-H-α-Me-Lys(Cbz)-OH (12) was obtained in 72% yield. Di-Cbz protected product, Cbz-a-Me-Lys(Cbz)-OH (13) was also obtained in  $\sim$ 11% yield, but it was easily removed by washing the acidic aqueous mixture with ethyl acetate. Compound 12 was then treated with Fmoc-OSu and sodium carbonate in water/dioxane mixture at ambient temperature overnight.<sup>21</sup> (L)-Fmoc-α-Me-Lys(Cbz)-OH (14) was obtained in 60% yield as an offwhite solid after work-up. It was then hydrogenolyzed over 10% Pd/C catalyst to afford (L)-Fmoc- $\alpha$ -Me-Lys-OH (15) in 73% yield, which was subsequently treated with (Boc)<sub>2</sub>O and diisopropylethyl amine in water/dioxane mixture. After work-up and silica gel column chromatography (dichloromethane/methanol), (L)-Fmoc- $\alpha$ -Me-Lys(Boc)-OH (16) was obtained in 64% yield (90% pure) as a white solid. Compound 16 could also be purified by C<sub>18</sub> reversedphase HPLC using 0.1% TFA containing water/acetonitrile buffers.

Using regioselective benzyloxycarbonylation approach (Scheme 3), we obtained Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) in 20% overall yield starting form H- $\alpha$ -Me-Lys-OH (**8**). Our goal was then to improve the yield and reduce the number of steps. Therefore, we adopted an alternative strategy using Staudinger reduction as shown in Scheme 4. Compound **8** was reduced with trimethylphosphine in toluene at 0 °C. The intermediate phosphazene was not isolated but rather reacted with Boc-ON in situ.<sup>22</sup> Compound **17** was isolated in 92% yield after flash silica gel column chromatography (hexane/diethyl ether). The chiral auxiliary was hydrogenolyzed as above with palladium chloride in methanol containing 10% acetic acid/water (1:1) under hydrogen atmosphere at 80 psi pressure. (*L*)-H- $\alpha$ -Me-Lys(Boc)-OH (**11**) was obtained as a gray solid in quantitative yield, which without

further purification was converted into Fmoc-derivative with Fmoc-OSu and sodium carbonate as above. Purification of the crude product as above afforded (*L*)-Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) in 59% isolated yield from azide **8** (three steps). Fmoc- $\alpha$ -Me-Lys(Boc)-OH from both strategies showed identical chromatographic<sup>23</sup> and spectroscopic characteristics.<sup>24</sup>

In conclusion, (*L*)- $\alpha$ -Me-Lys-OH (**9**) was obtained from oxazinone (**4**) as a chiral auxiliary in a total of four steps in 37.4% overall yield. Regioselective protection of **9** afforded Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) in additional four steps. Besides, Fmoc- $\alpha$ -Me-Lys(Boc)-OH (**16**) was obtained via Staudinger reduction of the intermediate azide (**8**) in a total of six steps in overall good yield (26.3%). Both strategies afforded the target compound in excellent optical purity (>95%). The synthesis is short and efficient as the reactions could be monitored by HPLC and the intermediates could be purified simply by recrystallization without the need for column chromatography.

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- 23. Analytical HPLC was performed on a C<sub>18</sub>, reversed-phase column (Vydac,  $150 \times 4.6$  mM, 5  $\mu$ ). A linear gradient from 5% to 95% buffer B in 45 min was used. Buffer A consisted of 0.1% TFA in water and buffer B was 0.1% TFA in acetonitrile. Flow rate was 1.5 mL/min. Compound **16** eluted at 24.4 min under these conditions.
- 24. Maldi-Tof-MS (CCA matrix): 505  $(C_{27}H_{34}N_2O_6)$  (M+Na)<sup>\*</sup> (35%), 382  $(C_{22}H_{26}N_2O_4)$  (M-Boc)<sup>\*</sup> (100%). <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD):  $\delta$  7.80 (2H, d, J = 7.2 Hz), 7.66 (2H, d, J = 7.2 Hz), 7.39 (2H, t, J = 7.2 Hz), 7.31 (2H, t, J = 7.2 Hz), 4.32 (2H, br, s), 4.21 (1H, t, J = 6.6 Hz), 3.02 (2H, br, m), 1.87 (2H, br, m), 1.47 (3H, s), 1.45 (2H, m), 1.41 (9H, m), 1.40 (2H, m).  $[a]_D^{24}$  +1.18 (*c* 0.25, MeOH). Anal. (purified by HPLC using C<sub>18</sub> reversed-phase column and 0.1% TFA containing water/acetonitrile buffers) Calcd for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>-2/3CF<sub>3</sub>CO<sub>2</sub>H: C, 60.92; H, 6.21; N, 5.01. Found: C, 60.78, H, 6.14; N, 5.08.