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

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ABSTRACT

Benzyl (*2R,3S*)-(−)-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*)-α-Me-Lys-OH (**9**) in a total of four steps in good yield. (*L*)-Fmoc-α-Me-Lys(Boc)-OH (**16**) was obtained from **9** via regioselective benzyloxycarbonylation. Alternately, (*L*)-Fmoc-α-Me-Lys(Boc)-OH (**16**) was obtained via Staudinger reduction of azide (**8**) in a total of six steps in good yield.

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.[1] In addition, C^{α}-alkylated amino acids are not prone to racemization under basic or acidic conditions due to lack of abstractable or enolizable α-hydrogen.[2] Furthermore, C^{α}-alkylation severely restricts rotation around the N–C^{α} (φ) and C^{α}–C(O) (ψ) bonds of the amino acid in a peptide sequence and stabilizes preferred conformations of the peptide backbone.[3]

The quaternization of the α-carbon of α-amino acids is rather challenging due to steric constraints. However, several routes to optically pure α-alkylated α-amino acids have been developed.[4–8] Most notably, the stereogenic centre is constructed by alkylation of a chiral, nonracemic enolates.[9,10] 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.[6,8]

The first synthesis of D/L-α-methyllysine was reported in 1978 from alanine derivative (**1**).[11] It has been used to study *L*-lysine uptake in *Escherichia coli* and *Bacillus sphaericus*.[12] Later on, the (*S*)-isomer of α-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.[13] Recently, Cativiela et al. have used (*1S,2R,4R*)-10-(dicyclohexylsulfamoyl)isoborneol as a chiral auxiliary[14] to synthesize (*S*)-α-methyllysine via chiral cyanopropanoate (**3**; Fig. 1) in 10 steps.[15]

In this publication, we report a short and efficient synthesis of (*S*)-α-methyllysine using William's oxazinone as a chiral auxiliary (**4**).[16] 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 α-methyllysine.

2. Results and discussion

As shown in Scheme 1, benzyl (*2R,3S*)-(−)-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.[16] 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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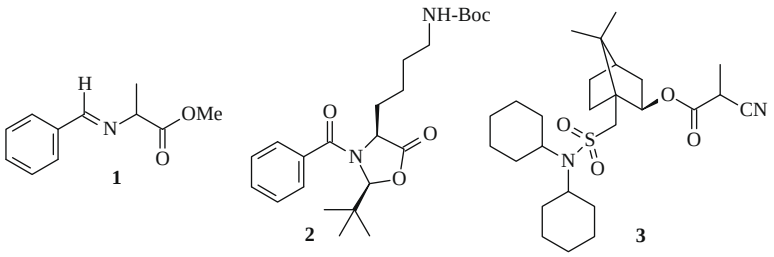
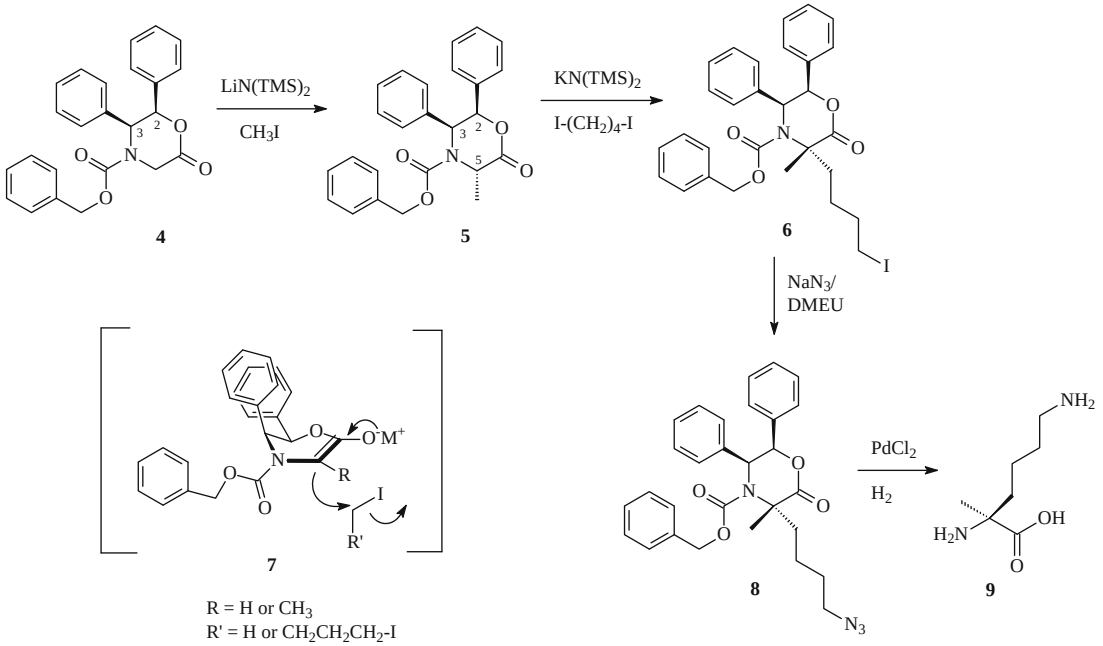


Figure 1.



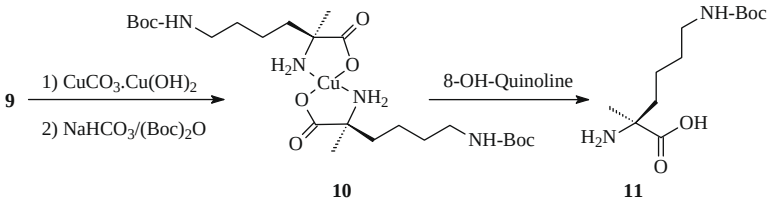
Scheme 1.

contained ~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.[9]

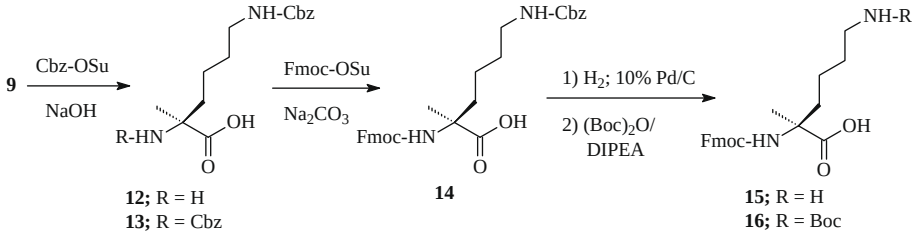
Next, we optimized the alkylation of (*5S*)-5-methyloxazinone (**5**) with 1,4-diiodobutane. The best conditions utilized dissolving **5** and 1,4-diiodobutane (10 equiv) in THF/HMPA (10:1) at ambient temperature, adding potassium bis(trimethylsilyl amide) (7 equiv) dropwise at −78 °C, and a reaction 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.[16] 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.

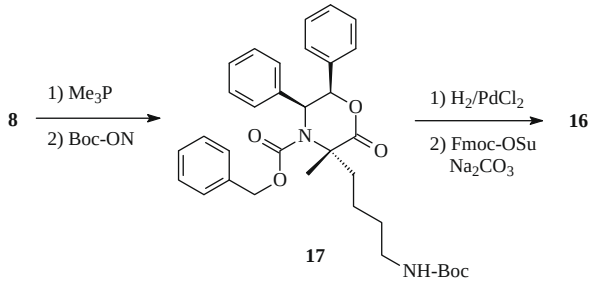
The iodo group of dialkylated product **6** underwent nucleophilic substitution with sodium azide smoothly and the azide **8** was obtained in 91% yield as a white solid.[17] The chiral auxiliary was cleaved by hydrogenolysis using palladium chloride and hydrogen gas at 60 psi. The azide group was also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



Scheme 2.



Scheme 3.



Scheme 4.

Having obtained (*L*)-α-Me-Lysine (**9**), we tried selective protection of the ε-amino function via copper complex as shown in Scheme 2. Thus, **9** was treated with basic copper carbonate followed by treatment with $(Boc)_2O$. The ε-Boc-protected product **10** was obtained in only 25% yield.[18] Cleavage of the copper complex by chelation with 8-hydroxyquinoline afforded (*L*)-α-Me-Lys(Boc)-OH (**11**) in overall 10% yield.[19]

Since the yield form copper complex was poor perhaps due to steric hindrance by α-methyl group, we decided to try regioselective benzyloxycarbonylation of the ε-amino group of **9**. The higher pK_a of the ε-NH_2 (10.5) compared to α-NH_2 (9.0) renders it more nucleophilic and is known to react selectively, albeit in moderate yield.[20]

As shown in Scheme 3, (*L*)-α-Me-Lys-OH (**9**) was treated with 1 N aq 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-α-Me-Lys(Cbz)-OH (**13**) was also obtained in ~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.[21] (*L*)-Fmoc-α-Me-Lys(Cbz)-OH (**14**) was obtained in 60% yield as an off-white solid after work-up. It was then hydrogenolyzed over 10% Pd/C catalyst to afford (*L*)-Fmoc-α-Me-Lys-OH (**15**) in 73% yield, which was subsequently treated with $(Boc)_2O$ and diisopropylethyl amine in water/dioxane mixture. After work-up and silica gel column chromatography (dichloromethane/methanol), (*L*)-Fmoc-α-Me-Lys(Boc)-OH (**16**) was obtained in 64% yield (90% pure) as a white solid. Compound **16** could also be purified by C_{18} reversed-phase HPLC using 0.1% TFA containing water/acetonitrile buffers.

Using regioselective benzyloxycarbonylation approach (Scheme 3), we obtained Fmoc-α-Me-Lys(Boc)-OH (**16**) in 20% overall yield starting form H-α-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.[22] 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-α-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-α-Me-Lys(Boc)-OH (**16**) in 59% isolated yield from azide **8** (three steps). Fmoc-α-Me-Lys(Boc)-OH from both strategies showed identical chromatographic[23] and spectroscopic characteristics.[24]

In conclusion, (*L*)-α-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-α-Me-Lys(Boc)-OH (**16**) in additional four steps. Besides, Fmoc-α-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_{18}, reversed-phase column (Vydac, 150 × 4.6 mM, 5 μ). 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 ($C_{27}H_{34}N_2O_6$) $(M+Na)^+$ (35%), 382 ($C_{22}H_{26}N_2O_4$) $(M-Boc)^+$ (100%). ^1H NMR (600 MHz, CD_3OD): δ 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). $[\alpha]_D^{24}$ +1.18 (*c* 0.25, MeOH). Anal. (purified by HPLC using C_{18} reversed-phase column and 0.1% TFA containing water/acetonitrile buffers) Calcd for $C_{27}H_{34}N_2O_6{\cdot}2/3CF_3CO_2H$: C, 60.92; H, 6.21; N, 5.01. Found: C, 60.78, H, 6.14; N, 5.08.