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A new approach to the synthesis of L-3-hydroxy-4-methoxy-5-methyl-phenylalanine derivatives from L-tyrosine

Ruijiao Chen, Deguang Zhu, Zuoqiang Hu, Zhiming Zheng, Xiaochuan Chen *

Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

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ABSTRACT

A practical procedure to regioselectively install a methyl group and a phenolic hydroxyl group onto L-tyrosine was developed. By using this approach, protected L-3-hydroxy-4-methoxy-5-methyl-phenylalanine and L-3-hydroxy-4-methoxy-5-methyl-phenylalanol, which are utilized in efficient syntheses of the relevant tetrahydroisoquinoline alkaloids, were prepared conveniently with high yield.

1. Introduction

Tetrahydroisoquinoline alkaloids and their derivatives,[1] notably exemplified by ecteinascidin 743 **1** (Et 743)[2–5] which is a highly promising antitumor drug, have attracted particular attention in synthetic chemistry due to their biological activities. As an important sector contained in quite a few members of the tetrahydroisoquinoline family including ecteinascidins, renieramycins and saframycins **1–4** (Fig. 1), L-3-hydroxy-4-methoxy-5-methyl-phenylalanine derivatives might be conveniently used to asymmetric total syntheses of these alkaloids. For example, L-3-hydroxy-4-methoxy-5-methyl-phenylalanol **5** was a common intermediate in the quite efficient syntheses of Et 743 **1**[3c] and Et 597 **2**[6] developed by Zhu et al., while its corresponding amino acids **6** were the important coupling partners in the convergent syntheses of cribrostatin 4 **3**[7] and Et 743.[4b] Therefore, a highly efficient synthesis for the preparation of moieties **5** and **6** is necessary for the related total syntheses.

Two synthetic routes to L-3-hydroxy-4-methoxy-5-methyl-phenylalanine derivatives, based on a diastereoselective alkylation and an enantioselective alkylation, respectively, have been reported by Williams et al.[8] and Zhu et al.[9] Subsequently, the Schmidt protocol which employs L-tyrosine **7** to prepare **5** and **6** seems more economic and has received more attention.[10] Unfortunately, the low yield in the Riemer–Tiemann reaction (25–30%) decreases the overall efficiency of the attractive approach. Very recently Zhu described a more efficient conversion of L-tyrosine to **5**.[11] Herein, we report an alternative route to **5** and **6** from L-tyrosine, in which the key methylation was achieved by a sequence involving selective hydroxymethylation/ionic hydrogenation instead of the procedures via iodination/Stille or Suzuki reaction in the two former syntheses.[10,11] Therefore, this strategy removes

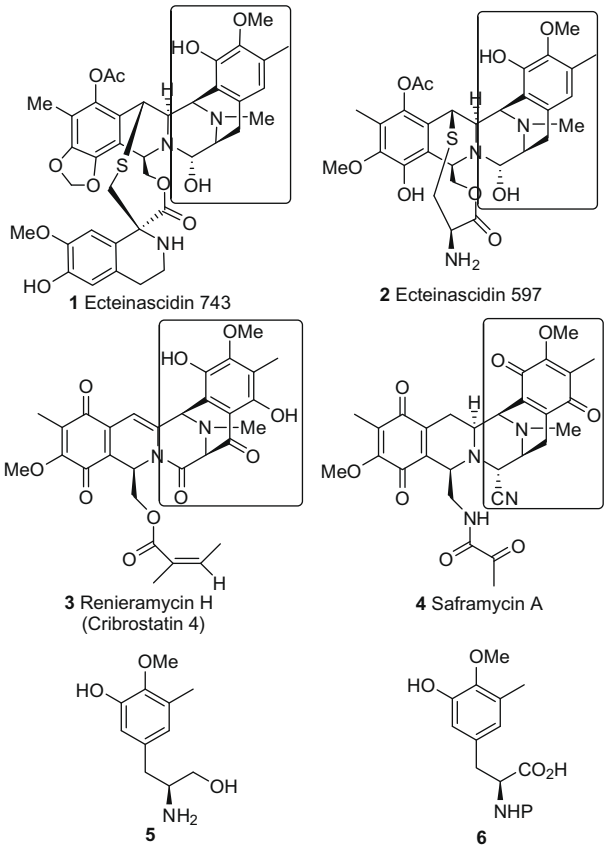

Figure 1. Several tetrahydroisoquinoline alkaloids **1–4** and their common structural sectors **5–6**.

* Corresponding author. Tel./fax: +86 28 85413712.
E-mail address: chenxc@scu.edu.cn (X. Chen).

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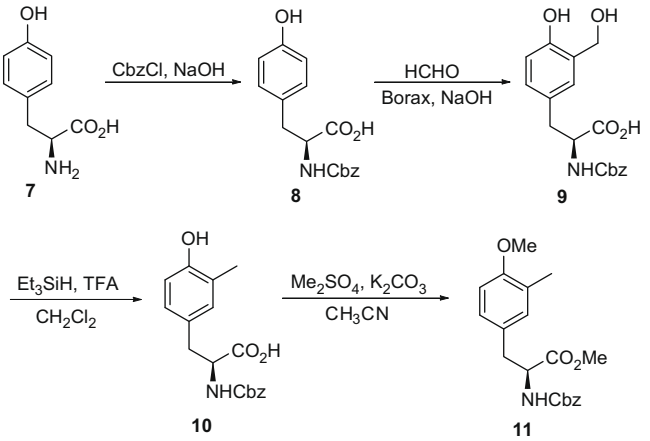


Scheme 1. Synthesis of **11** from L-tyrosine via the primary methylation procedure.

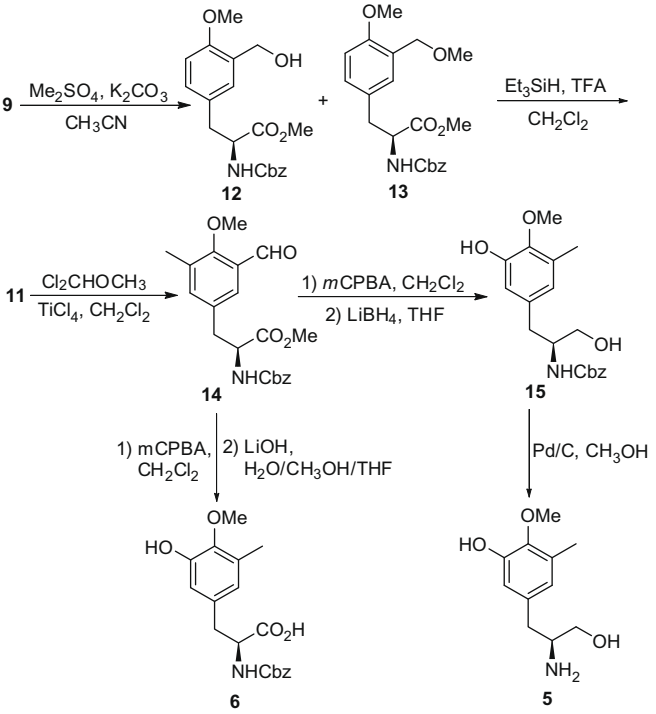
the need for expensive reagents and harsh reaction conditions. This will greatly improve the ease of synthesis and the overall yield of these complex natural alkaloids.

2. Results and discussion

Our initial attempts at the methylation of L-tyrosine are outlined in Scheme 1. L-Tyrosine **7** was N-protected with CbzCl in aqueous NaOH solution affording L-*N*-Cbz-tyrosine **8**[12] in 80% yield. The base-promoted phenolic aldol condensation between **8** and formaldehyde in the presence of $Na_2B_4O_7$ was achieved smoothly to generate the desired *mono*-hydroxymethylated product **9** in 85% yield. Here $Na_2B_4O_7$ is necessary for the reaction to prevent considerable bishydroxymethylation of **8** by chelating with **9**.[13] Ionic hydrogenation,[14] a widely used method for the hydrogenation of benzyl alcohols with electron-rich aromatic ring was then employed in the conversion of the hydroxymethyl group in **9** to its corresponding methyl group. After investigation of various reagents and conditions, the optimized hydrogenation was carried out in CH_2Cl_2 using TFA (12 equiv) and Et_3SiH (3 equiv) for 16–24 h to furnish L-*N*-Cbz-3-methyl-tyrosine **10** in 70–80% yield. Compound **10** was subjected to the esterification and the etherification in one-pot to produce L-*N*-Cbz-3-methyl-4-methoxy-phenylalanine methyl ester **11**. However, the presence of a free carboxylic acid in **9** and **10** complicated the TLC detection and chromatographic purification.

Thus, we switched the reaction sequence in the methylation as shown in Scheme 2. Treatment of **9** with excessive Me_2SO_4 and K_2CO_3 generated a mixture of L-*N*-Cbz-3-hydroxymethyl-4-methoxy-phenylalanine methyl ester **12** and its corresponding methyl ether **13** in a ratio of 1:3. Both **12** and **13** showed higher activity than **9** in the subsequent hydrogenation. In particular, the hydrogenation of **13** was easily accomplished within 6 h and gave the desired **11** in 97% yield under the same conditions as that of **9**. This improvement in the reaction velocity and yield is attributed to the benzylic methoxy group in **13** being a better leaving group than the hydroxyl group in **9** under the hydrogenation conditions. To simplify the experimental procedures, the crude products **13** and **12** were utilized in the next reduction without any further purification to generate compound **11** in an excellent yield of 92%.

The phenol group *ortho* to the methoxyl in **11** was then functionalized via formylation followed by Baeyer–Villiger oxidation. Treatment of **11** under Vilsmeier–Haack conditions[15] led only to the decomposition of the reactants and we failed to observe any trace amounts of the formylation products. Fortunately, the formylation of **11** with α,α-dichloromethyl methyl ether in the presence



Scheme 2. Modified methylation approach to **11** and its conversion to **5** and **6**.

of $TiCl_4$[16] worked well with high regioselectivity to produce L-*N*-Cbz-3-formyl-4-methoxy-5-methyl-phenylalanine methyl ester **14** in 92% yield. By stirring a mixture of the formylation product **14** and *m*CPBA in CH_2Cl_2 for only 12 h, we observed a complete and clean conversion of **14** to the resulting formate ester, which was partly hydrolyzed to the corresponding phenol in situ. In contrast, for the acetylation counterpart of **14**, the Baeyer–Villiger oxidation required 5–7 days to proceed thoroughly.[11] Without further purification, the mixture of the formate ester and the phenol was reduced with lithium borohydride to its amino alcohol **15** in 80% yield after two steps. Following Zhu's procedure, removal of the Cbz- protecting group in **15** by Pd-catalyzed hydrogenolysis produced L-3-hydroxy-4-methoxy-5-methyl-phenylalanol **5**, whose physical and spectroscopic characteristics ($[\alpha]_D$, IR, $^1H/^{13}C$ NMR) were consistent with that of the authentic sample in the literature.[11] Treatment of **14** with *m*CPBA followed by hydrolysis in aqueous LiOH[17] gave the corresponding amino acid **6**.

3. Conclusion

In conclusion, we have developed a novel and short access to L-3-hydroxy-4-methoxy-5-methyl-phenylalanine derivatives, by which the two representative compounds, **5** and **6** were obtained from L-tyrosine in eight steps with an overall 46% yield and in seven steps with an overall 51% yield, respectively. This economically efficient and robust synthesis may promote its employment to the total syntheses of related natural alkaloids and their analogues accordingly.

4. Experimental

4.1. General

IR spectra were recorded on a NEXUS 670 spectrophotometer. ^1H NMR spectra were recorded on Bruker AV II-400 (400 MHz), and AV II-600 (600 MHz) with TMS as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity

(s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz). ^{13}C NMR data were collected on Bruker AV II-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million (ppm) from the tetramethylsilane with the solvent resonance as an internal standard. Optical rotations were measured on AUTOPOL V automatic polarimeter at room temperature. Anhydrous CH_2Cl_2 and anhydrous CH_3CN were distilled from CaH_2 before use. All reagents were obtained from commercial suppliers unless otherwise stated.

4.2. L-*N*-Benzyloxycarbonyl-3-hydroxymethyl-tyrosine 9

A mixture of L-*N*-benzyloxycarbonyl-tyrosine (5.30 g, 16.70 mmol), borax (12.80 g), 1 M sodium hydroxide (33 mL) solution, and H_2O (111 mL) was stirred for 30 min at room temperature, and aqueous formaldehyde (5 mL, 37% solution, 67 mmol) was added in one portion. After the reaction was stirred at 40 °C for 5 days, the cooled reaction mixture was acidified with 3 M hydrochloric acid to pH 2. The suspension was extracted with ethyl acetate (3 × 100 mL). The latter organic phases were combined, and dried (Na_2SO_4). After concentration under reduced pressure, the residue was purified by column chromatography on silica gel to give **9** (4.90 g, 85%); $[\alpha]_D^{27} = +11$ (*c* 0.99, AcOH); ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.80 (1H, br. s), 9.20 (1H, s), 7.58 (1H, d, *J* = 8.3 Hz), 7.24–7.43 (5H, m), 7.18 (1H, s), 6.92 (1H, d, *J* = 7.9 Hz), 6.66 (1H, d, *J* = 8.1 Hz), 4.99 (1H, d, *J* = 12.7 Hz), 4.96 (1H, d, *J* = 12.7 Hz), 4.45 (2H, s), 4.10 (1H, m), 2.95 (1H, dd, *J* = 13.8, 4.2 Hz), 2.72 (1H, dd, *J* = 13.8, 10.3 Hz).

4.3. L-*N*-Benzyloxycarbonyl-3-methyl-4-methoxy-phenylalanine methyl ester 11

To a solution of compound **9** (0.56 g, 1.62 mmol) in dry CH_3CN were added $(CH_3)_2SO_4$ (0.46 mL, 4.85 mmol) and anhydrous K_2CO_3 (0.67 g, 4.85 mmol), and the resulting mixture was stirred at 60 °C for 5 h. The solvent removed in vacuo, and the water (20 mL) was added. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated in vacuo affording a mixture of **12** and **13**. The mixture was dissolved in dry CH_2Cl_2 (16 mL), and Et_3SiH (0.78 mL, 4.86 mmol) and CF_3COOH (1.20 mL) were added under argon atmosphere. The resulting mixture was stirred overnight at room temperature, basified with the diluted aqueous solution of sodium bicarbonate to pH 7, and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford **11** as a yellow oil (0.58 g, 92% over two steps); $[\alpha]_D^{26} = +49$ (c 0.99, $CHCl_3$); IR (neat) ν_{max}: 3355, 2956, 1724, 1506, 1446, 1392, 1255, 1009, 827, 753, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25–7.37 (5H, m), 6.87 (2H, m), 6.71 (1H, d, *J* = 8.1 Hz), 5.20 (1H, d, *J* = 8.0 Hz), 5.12 (1H, d, *J* = 12.3 Hz), 5.07 (1H, d, *J* = 12.3 Hz), 4.60 (1H, m), 3.79 (3H, s), 3.72 (3H, s), 3.02 (2H, m), 2.16 (3H, s); MS (ESI^+) *m/z*: $(M+Na)^+$ 380.1.

4.4. L-*N*-Benzyloxycarbonyl-3-formyl-4-methoxy-5-methyl-phenylalanine methyl ester 14

To a solution of compound **11** (1.04 g, 2.91 mmol) in dry CH_2Cl_2 (11 mL), $TiCl_4$ (0.77 mL, 6.98 mmol) and Cl_2CHOCH_3 (0.32 mL, 3.49 mmol) were added at −30 °C under an argon atmosphere. After stirring for 1 h, ice-cold water (30 mL) was added and stirred at rt for 1 h. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried with Na_2SO_4, filtered, and the solvent evaporated in vacuo. The crude material was purified by column chromatography on silica gel to afford **14** as a yellow oil (1.03 g, 92%); $[\alpha]_D^{27} = +63$ (*c* 1.1, $CHCl_3$); IR (neat) ν_{max}: 3314, 2954, 2866, 1748, 1692, 1541, 1259, 1214, 1058, 1006, 749, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.32 (1H, s), 7.42 (1H, s), 7.25–7.37 (5H, m), 7.19 (1H, s), 5.31 (1H, d, *J* = 8.0 Hz), 5.12 (1H, d, *J* = 12.2 Hz), 5.07 (1H, d, *J* = 12.3 Hz), 4.63 (1H, m), 3.85 (3H, s), 3.73 (3H, s), 3.13 (1H, dd, *J* = 13.9, 5.5 Hz), 3.03 (1H, dd, *J* = 13.9, 6.0 Hz), 2.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.5, 37.4, 52.5 54.8, 63.1, 67.0, 126.9, 128.1, 128.2, 128.5, 129.0, 132.1, 132.6, 136.2, 138.4, 155.6, 160.9, 171.7, 190.0; MS (ESI^+) *m/z*: $(M+Na)^+$ 408.1; HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{23}NO_6Na$: 408.1423; found: 408.1418.

4.5. L-*N*-Benzyloxycarbonyl-3-hydroxy-4-methoxy-5-methyl-phenylalanol 15

To a solution of the compound **14** (0.42 g, 1.10 mmol) in CH_2Cl_2 (10 mL), *m*CPBA (98.4%; 0.28 g, 1.65 mmol) was added. After the reaction was stirred overnight at rt, the reaction mixture was diluted with aqueous solution of sodium bicarbonate and extracted with ethyl acetate (3 × 40 mL). The combined extracts were washed with aqueous solution of sodium bicarbonate, brine, dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude was taken up in anhydrous THF (11 mL), and $LiBH_4$ (92 mg, 2.20 mmol) was added under argon atmosphere. The resulting mixture was stirred overnight at rt, and methanol (1 mL) was added. Then the solvent was evaporated and the residue was diluted with H_2O (50 mL), extracted with ethyl acetate (3 × 30 mL), and dried (Na_2SO_4). After concentration and column chromatography, the amino alcohol **15** (0.32 g, 80%, over two steps) was isolated as a pale yellow oil; $[\alpha]_D^{27} = -23$ (*c* 1.1, $CHCl_3$); IR (neat) ν_{max}: 3340, 2933, 1696, 1501, 1452, 1264, 1233, 1052, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25–7.37 (5H, m), 6.64 (1H, s), 6.52 (1H, s), 6.00 (1H, s), 5.12 (1H, d, *J* = 7.4 Hz), 5.07 (2H, s), 3.88 (1H, s), 3.76 (3H, s), 3.60 (2H, m), 2.71 (2H, d, *J* = 2.7 Hz), 2.23 (3H, s); MS (ESI^+) *m/z*: $(M+Na)^+$ 368.1.

4.6. L-*N*-Benzyloxycarbonyl-3-hydroxy-4-methoxy-5-methyl-phenylalanine 6

To a solution of compound **14** (0.24 g, 0.61 mmol) in CH_2Cl_2 (6 mL), *m*CPBA (98.4%; 0.16 g, 0.92 mmol) was added. After the reaction was stirred overnight at rt, the reaction mixture was diluted with aqueous solution of sodium bicarbonate and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with aqueous solution of sodium bicarbonate, brine, dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude was taken up in a mixture of $H_2O/CH_3OH/THF$ (1:3:1, 6 mL), and LiOH (77 mg, 1.84 mmol) was added. The resulting mixture was stirred overnight at room temperature. Then the solvent was evaporated and the residue was diluted with H_2O (50 mL), extracted with ethyl acetate (3 × 30 mL), and dried (Na_2SO_4). After concentration and column chromatography, the compound **6** (0.22 g, 88% over two steps) was isolated as a red oil; $[\alpha]_D^{27} = +41$ (*c* 1.1, $CHCl_3$); IR (neat) ν_{max}: 3339, 3032, 2394, 1712, 1500, 1447, 1233, 1055, 1001, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21–7.34 (5H, m), 6.59 (1H, s), 6.46 (1H, s), 5.45 (1H, d, *J* = 8.1 Hz), 5.10 (1H, d, *J* = 12.2 Hz), 5.05 (1H, d, *J* = 12.4 Hz), 4.62 (1H, m), 3.70 (3H, s), 3.03 (1H, dd, *J* = 14.0, 5.3 Hz), 2.94 (1H, dd, *J* = 14.0, 6.4 Hz), 2.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.8, 37.2, 54.7, 60.5, 67.3, 114.4, 123.5, 128.1, 128.2, 128.5, 131.2, 132.0, 136.1, 144.7, 148.9, 156.2, 175.7; MS (ESI^+) *m/z*: $(M+Na)^+$ 382.1; HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}NO_6Na$: 382.1267; found: 382.1278.

4.7. L-3-Hydroxy-4-methoxy-5-methyl-phenylalanol 5

A mixture of compound **15** (0.13 g, 0.38 mmol) and 10% Pd/C (17 mg) in anhydrous methanol (3.80 mL) was stirred at rt under an H_2 atmosphere. After completion of the reaction (monitoring

by TLC), the catalyst was removed by filtration over Celite. After concentration in vacuo, the residue was purified by flash column chromatography to afford the compound **5** (77 mg, 97%); $[\alpha]_D^{27} = -17$ (*c* 0.99, CH_3OH); IR (neat) ν_{max}: 3347, 2925, 1589, 1456, 1330, 1234, 1144, 1050, 1006, 863 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ (ppm) 6.57 (1H, s), 6.53 (1H, s), 3.74 (3H, s), 3.55 (1H, dd, J = 10.8, 4.3 Hz), 3.38 (1H, dd, J = 10.8, 6.9 Hz), 3.03 (1H, br. m), 2.65 (1H, dd, J = 13.5, 6.2 Hz), 2.44 (1H, dd, J = 13.5, 7.7 Hz), 2.23 (3H, s); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 149.6, 144.5, 134.3, 131.2, 122.0, 114.6, 65.0, 59.0, 54.0, 38.5, 14.6; MS (ESI^+) *m/z*: $(M+Na)^+$ 234.1; HRMS (ESI^+): *m/z* $[M+Na]^+$ calcd for $C_{11}H_{17}NO_3Na$: 234.1106; found: 234.1100.

Acknowledgments

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