DOI: 10.1002/cjoc.201201142

An Efficient Semi-Synthetic Method to Construct Docetaxel via Sterically Crowded Linear Side Chain Esterification†

Xin Shen,*[,a] Jidong Yang,[a] Huaxing Zhan,[a] Hu Wang,[a] Shaohong Wu,[b] and Zili Chen*[,c]

[a] *Shanghai Parling PharmaTech Co., Ltd., Suite 2, No. 868 Zhenchen Road, Baoshan District, Shanghai, 200444, China*

[b] *Fujian South Pharmaceutical Co., Ltd., 98#, Dong-Xin Road, Xuefeng Town, Mingxi County, Fujian 365200, China*

[c] *Department of Chemistry, Renmin University of China, Beijing 100872, China*

An efficient semi-synthetic method was developed to construct docetaxel **1** by using *N*,*N*-di-Boc protected linear isoserine derivative **5** as the side chain source, in which, bulky protecting group on the nitrogen atom blocked C-2' position and prohibited unavoidable racemization in previous studies.

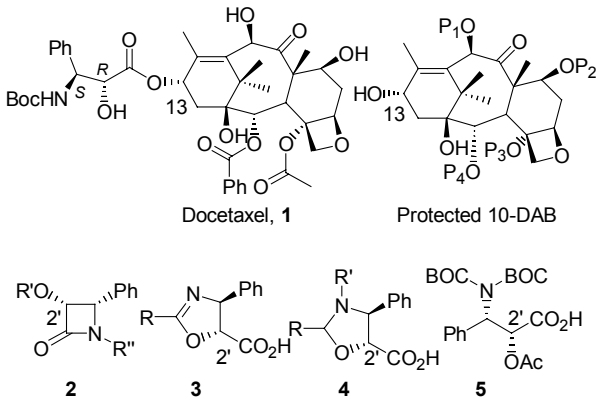
Keywords Docetaxel, semi-synthesis, 10-deacetylbaccatin III, esterification

Introduction

Docetaxel (Taxotere, **1**), an important antitumor pharmaceutical from Taxol family, was approved by FDA for the treatment of breast cancer in 1996.[1,2] The clinical importance of this drug and its analogs, coupled with their structural complexity has stimulated intensive research toward their total synthesis and their commercial semi-synthesis. 10-Deacetylbaccatin III (10-DAB), a structurally similar natural product extracted from yew leaves, was proved to be an efficient semi-synthetic precursor for Docetaxel's commercial scale production, in which, the key step involved with C-13 esterification of the protected 10-DAB with (*2R*,*3S*)-phenyl isoserine derivatives.

In previous results, Docetaxel's phenyl isoserine side chain section, as indicated in Scheme 1, was derived from the cyclic surrogates, such as 4-member β-lactam **2**[3] or 5-member oxazoline **3**[4] and its analog **4**.[5,6] Synthetic application of these methods was therefore limited by the tedious preparation of these subunits. Developing new approach of esterification by using linear side chain equivalents can enhance the flexibility to construct these important bioactive molecules.[7] However, efforts to employ linear isoserine units directly failed because of side chain racemization (C-2' position, Scheme 1) and the difficulty in diastereomer separation.[8] We envisioned that a bulky protecting group would block the C-2' hydrogen atom from the outside base, and eliminate the undesired side chain enolization and subsequent racemization. Considering the steric protecting group on oxygen atom (C-2' hydroxyl group) might prohibit the side chain esterification reaction, the use of a bulky protecting group on nitrogen atom would be a feasible choice. Herein, we will report a convenient, and efficient new semi-synthetic method to construct docetaxel **1** by using *N*,*N*-di-Boc protected linear surrogate **5** as the side chain source. This is the first report in taxel's semi-synthesis, to the best of our knowledge, of employing linear side chain equivalent in C-13 esterification step without any racemization.

Scheme 1 Docetaxel and its synthetic subunits



* E-mail: shenx1972@hotmail.com, zilichen@ruc.edu.cn
Received November 18, 2012; accepted December 12, 2012; published online January 8, 2013.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201201142 or from the author.
† Dedicated to the Memory of Professor Weishan Zhou.

Experimental

General information

PE (chromatography solvent) refers to petroleum ether. Anhydrous toluene was freshly distilled over Na/benzophenone under N_2 prior to use. Anhydrous CH_2Cl_2 was distilled over CaH_2 under N_2 before use. Melting points are uncorrected. NMR spectra were obtained on a Varian Inova system using $CDCl_3$ or DMSO-d_6 as solvent, respectively.

(2*R*,3*S*)-*N*-Boc-3-phenylisoserine (**7**): To a solution of (2*R*,3*S*)-3-phenyl-isoserine (217.6 g, 1.0 mol) in acetone (1 L) and water (1 L) was added solid $NaHCO_3$ (336 g, 4.0 mol) and Boc_2O (327 g, 1.5 mol) carefully. After the starting material disappeared, the reaction mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was washed with ethyl acetate. The aqueous phase was then acidified to pH＝3.0. The precipitate was filtered and dried *in vacuo* to give compound **7** (250 g, yield 89.0%) as a white crystalline material. Data for compound **7**: m.p.: 123.7－124.9 ℃; $[\alpha]_D^{25}$ ＋24.9 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.74 (s, 1H), 7.30 (s, 4H), 7.22 (s, 1H), 7.04－7.02 (m, 1H), 5.25 (brs, 1H), 4.93 (d, *J*＝9.0 Hz, 1H), 4.18 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 173.8, 155.3, 141.0, 128.3, 127.2, 127.1, 78.6, 74.0, 57.1, 28.4; ESI: 304.2 (M＋Na^+); FT-IR (KBr) *v*: 3450, 1730, 1715 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{19}NNaO_5$ 304.1161, found 304.1156.

(2*R*,3*S*)-*N*-Boc-3-phenylisoserine benzyl ester (**8**): A solution of **7** (28.0 g, 0.100 mol), BnCl (15.2 g, 0.120 mol), Et_3N (30.3 g, 0.300 mol) and Bu_4NI (2.8 g, cat.) in anhydrous acetone (250 mL) was heated to reflux. After the reaction finished, the acetone was removed and the residue was dissolved in ethyl acetate and water. The organic phase was separated and washed with water and brine, dried over $MgSO_4$. The compound **8** (34.5 g, yield 93.0%) was obtained as a white crystalline material after recrystallized from ethyl acetate and PE. Data for compound **8**: m.p.: 116－118 ℃; $[\alpha]_D^{25}$ ＋17.1 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38－7.25 (m, 10H), 5.46－5.44 (m, 1H), 5.25 (s, 2H), 5.28－5.16 (m, 1H), 4.48 (s, 1H), 3.30 (brs, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 155.1, 134.8, 128.7, 128.6, 128.5, 127.7, 126.7, 79.8, 73.6, 68.1, 56.1, 28.2; ESI: 394.3 (M＋Na^+); FT-IR (KBr) *v*: 3430, 1750, 1710 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{25}NNaO_5$ 394.1630, found 394.1622.

(2*R*,3*S*)-*N*-Boc-2-acetyl-3-phenylisoserine benzyl ester (**9**): To a solution of compound **8** (30.0 g, 80.9 mmol) and acetic anhydride (9.90 g, 97.0 mmol) in CH_2Cl_2 were added Et_3N (20.2 g, 200 mmol) and 4-dimethylamino pyridine (DMAP, 1.22 g, 10 mmol). When no starting material was detected, the reaction mixture was washed with saturated aq. citric acid solution, saturated aq. $NaHCO_3$ solution, and brine. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give the compound **9** (31.8 g, yield 95.0%) as colorless oil. Data for compound **9**: $[\alpha]_D^{25}$ −4.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35－7.25 (m, 10H), 5.55－5.40 (m, 2H), 5.35 (s, 1H), 5.24 (s, 2H), 2.05 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 167.6, 154.7, 134.9, 128.5, 128.4, 128.3, 128.2, 127.7, 126.3, 79.9, 74.7, 67.5, 54.5, 53.3, 31.0; FT-IR (film) *v*: 2900, 1740, 1710 cm^{-1}; ESI: 436.3 (M＋Na^+); ESI-HRMS calcd for $C_{23}H_{27}NNaO_6$ 436.1736, found 436.1755.

(2*R*,3*S*)-*N*,*N*-di-Boc-2-acetyl-3-phenylisoserine benzyl ester (**10**): A solution of **9** (4.13 g, 10.0 mmol) and Boc_2O (4.36 g, 20.0 mmol) in acetonitrile (80 mL) was heated at short reflux. To this solution was added a solution of 4-dimethylaminopyridine (2.44 g, 20.0 mmol) in acetonitrile (20 mL) dropwise. The reaction mixture was then stirred under reflux until starting material disappeared on TLC. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 and washed with 1 mol/L aqueous citric acid solution, saturated aq. $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated by rotary evaporator. The residue was purified by silica gel chromatography to give compound **10** (4.11 g, yield 80.0%) as pale yellow oil. Data for compound **10**: $[\alpha]_D^{25}$ ＋40.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.46－7.44 (m, 2H), 7.30－7.21 (m, 6H), 7.02－7.00 (m, 2H), 6.09 (d, *J*＝10.5 Hz, 1H), 5.70 (d, *J*＝10.5 Hz, 1H), 4.98 (d, *J*＝12.5 Hz, 1H), 4.91 (d, *J*＝12.5 Hz, 1H), 2.11 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.4, 168.5, 152.6, 135.2, 134.8, 128.8, 128.5, 128.2, 128.1, 128.0, 127.9, 82.6, 72.1, 66.9, 59.3, 27.7, 20.4; FT-IR (film) *v*: 2910, 1745, 1710 cm^{-1}; ESI: 536.4 (M＋Na^+); ESI-HRMS calcd for $C_{28}H_{35}NNaO_8$ 536.2260, found 536.2243.

(2*R*,3*S*)-*N*,*N*-Di-Boc-2-acetyl-3-phenylisoserine (**5**): A solution of **10** (4.00 g, 7.79 mmol) and Pd/C (5%, 400 mg) in ethyl acetate (50 mL) was hydrogenated at atmospheric pressure until no more hydrogen was absorbed. The mixture was filtered. The filtrate was then concentrated *in vacuo* to give compound **5** (3.20 g, yield 97.0%) as a white crystalline material. Data for compound **5**: m.p.: 146.5－147.8 ℃; $[\alpha]_D^{25}$ ＋55.5 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.26 (s, 1H), 7.40－7.30 (m, 5H), 5.80 (d, *J*＝10.7 Hz, 1H), 5.53 (d, *J*＝10.7 Hz, 1H), 2.07 (s, 3H), 1.36 (s, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.4, 169.1, 152.3, 135.4, 128.4, 128.3, 128.2, 82.4, 71.7, 58.7, 27.3, 20.2; FT-IR (KBr) *v*: 3400, 2900, 1750, 1710 cm^{-1}; ESI: 446.3 (M＋Na^+); ESI-HRMS calcd for $C_{21}H_{29}NNaO_8$ 446.1791, found 446.1778.

7,10-Di-Troc-*N*′-Boc-2'-acetyl-docetaxel (**12**) and 7,10-di-Troc-13-acetyl-10-DAB (**13**):[9] To a suspension of **11** (10 g, 11.2 mmol) and **5** (20.0 g, 47.2 mmol) in anhydrous toluene (100 mL) was added a solution of DMAP (2.5 g, 20.5 mmol) and DCC (20.0 g, 97.0 mmol) in anhydrous toluene (20 mL) in one portion at 15－20 ℃. The reaction mixture was stirred at room tempera-

ture until starting material (**11**) disappeared on TLC. Water was added and the mixture was stirred for 0.5 h. The reaction mixture was then filtered, and the cake was washed with toluene. The combined organic layer was washed with water, brine, dried over anhydrous $MgSO_4$. Chromatography gave **12** (10.5 g, yield 72.1%) and **13** (2.62 g, yield 25.0%) as white solids. Data for compound **12**: m.p.: 152－154 ℃; $[\alpha]_D^{25}$ −38.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.08 (d, *J*＝8.0 Hz, 2H), 7.68 (t, *J*＝7.5 Hz, 1H), 7.56 (t, *J*＝7.5 Hz, 2H), 7.51 (d, *J*＝8.0 Hz, 2H), 7.32 (t, *J*＝7.5 Hz, 2H), 7.16 (t, *J*＝7.5 Hz, 1H), 6.22－6.18 (m, 1H), 6.01 (d, *J*＝10.8 Hz, 1H), 5.88 (t, *J*＝10.8 Hz, 1H), 5.62 (dd, *J*＝10.8, 15.0 Hz, 2H), 5.55 (dd, *J*＝10.8, 11.8 Hz, 1H), 4.96 (d, *J*＝10.8 Hz, 1H), 4.89 (d, *J*＝15.0 Hz, 1H), 4.78－4.72 (m, 2H), 4.58 (d, *J*＝11.8 Hz, 1H), 4.29 (d, *J*＝8.5 Hz, 1H), 4.13 (d, *J*＝8.5 Hz, 1H), 3.84 (d, *J*＝7.1 Hz, 1H), 2.65－2.59 (m, 1H), 2.42 (s, 3H), 2.17 (s, 3H), 2.04－1.99 (m, 1H), 1.89 (s, 3H), 1.88－1.86 (m, 1H), 1.81 (s, 3H), 1.45 (s, 18H), 1.19 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 200.9, 170.2, 169.5, 169.3, 166.8, 153.1, 153.0, 152.9, 143.4, 135.6, 133.9, 131.4, 130.1, 129.2, 129.0, 128.8, 128.6, 128.5, 94.2, 83.8, 82.9, 80.3, 79.1, 78.7, 77.3, 76.3, 76.2, 74.4, 72.7, 71.1, 60.2, 56.1, 46.8, 42.9, 34.5, 33.2, 27.9, 26.2, 22.4, 21.0, 20.3, 14.6, 10.7; FT-IR (KBr) *v*: 2910, 1775, 1750, 1735, 1710 cm^{-1}; ESI: 1320.1; $(M+Na^+)$; ESI-HRMS calcd for $C_{56}H_{65}Cl_6NNaO_{21}$ 1320.2078, found 1320.2067.

Data for compound **13**: m.p.: 163－164 ℃; $[\alpha]_D^{25}$ −56.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.07 (dd, *J*＝0.75, 8.0 Hz, 2H), 7.62 (t, *J*＝7.5 Hz, 1H), 7.49 (t, *J*＝7.5 Hz, 2H), 6.26 (s, 1H), 6.20 (t, *J*＝4.5 Hz, 1H), 5.68 (d, *J*＝7.0 Hz, 1H), 5.57 (dd, *J*＝7.0, 10.5 Hz, 1H), 4.98 (d, *J*＝8.0 Hz, 1H), 4.90 (d, *J*＝11.5 Hz, 1H), 4.80－4.75 (m, 2H), 4.60 (d, *J*＝11.8 Hz, 1H), 4.33 (d, *J*＝8.5 Hz, 1H), 4.17 (d, *J*＝8.5 Hz, 1H), 3.93 (d, *J*＝7.0 Hz, 1H), 2.66－2.60 (m, 1H), 2.35 (s, 3H), 2.26 (dd, *J*＝3.5, 9.0 Hz, 2H), 2.21 (s, 3H), 2.06－2.02 (m, 1H), 2.02 (s, 3H), 1.85 (s, 3H), 1.73 (brs, 1H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 200.8, 170.1, 169.9, 166.8, 153.2, 153.1, 143.2, 133.8, 131.8, 130.0, 129.1, 128.7, 94.2, 83.7, 80.7, 79.2, 78.8, 77.4, 77.1, 76.5, 76.2, 74.2, 69.5, 56.2, 47.1, 43.0, 35.5, 33.2, 26.3, 22.4, 21.2, 20.6, 14.9, 10.7; FT-IR (KBr) *v*: 2905, 1770, 1755, 1715 cm^{-1}; ESI calcd for $C_{56}H_{65}Cl_6NNaO_{21}$ 1320.2, found 1320.4 $(M+Na^+)$.

N′-Boc-2′-acetyl-docetaxel (**14**): To a solution of **12** (1.00 g, 0.77 mmol) in acetic acid (5 mL) and methanol (50 mL) was added zinc power (1.5 g, activated before use). The mixture was refluxed for 0.5 h. After cooling and filtration, the filtrate was concentrated under the reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate, water, brine and dried over anhydrous $MgSO_4$. Chromatography gave **14** (620 mg, yield 84.8%) as a white solid. Data for compound **14**: m.p.: 144－146 ℃; $[\alpha]_D^{25}$ −45.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.07 (d, *J*＝8.0 Hz, 2H), 7.67 (t, *J*＝7.5 Hz, 1H), 7.56 (t, *J*＝7.5 Hz, 2H), 7.49 (d, *J*＝8.0 Hz, 2H), 7.30 (t, *J*＝7.5 Hz, 2H), 7.12 (t, *J*＝7.5 Hz, 1H), 5.99 (d, *J*＝10.8 Hz, 1H), 5.85 (t, *J*＝8.5 Hz, 1H), 5.61 (d, *J*＝11.0 Hz, 1H), 5.57 (d, *J*＝7.0 Hz, 1H), 5.14 (s, 1H), 4.93 (d, *J*＝8.5 Hz, 1H), 4.27 (d, *J*＝8.5 Hz, 1H), 4.25－4.20 (m, 1H), 4.15－4.13 (m, 2H), 3.84 (d, *J*＝7.0 Hz, 1H), 2.56－2.51 (m, 1H), 2.39 (s, 3H), 2.17 (s, 3H), 1.85 (dd, *J*＝9.0, 15.0 Hz, 1H), 1.81－1.78 (m, 1H), 1.83 (s, 3H), 1.74 (s, 2H), 1.69 (s, 3H), 1.56 (s, 1H), 1.45 (s, 18H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 211.5, 170.1, 169.4, 166.9, 152.9, 139.2, 135.3, 133.8, 130.1, 129.4, 129.0, 128.8, 128.6, 128.4, 84.3, 82.9, 80.6, 78.8, 76.5, 75.0, 74.4, 72.7, 71.7, 71.4, 60.3, 57.5, 46.4, 42.8, 36.8, 34.9, 27.9, 26.3, 22.4, 20.6, 20.3, 14.2, 9.9; FT-IR (KBr) *v*: 3420, 2900, 1770, 1755, 1730 cm^{-1}; ESI: 973.0 $(M+Na^+)$; ESI-HRMS calcd for $C_{50}H_{63}NNaO_{17}$ 972.3994, found 972.4014.

2′-Acetyl-docetaxel (**15**):[10] To a solution of **14** (500 mg, 0.53 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (72.5 mg, 0.64 mmol, 1.2 equiv.) at room temperature. After the reaction finished, the mixture was washed with saturated aq. $NaHCO_3$ solution, water, brine and dried over anhydrous $MgSO_4$. Chromatography gave **15** (400 mg, yield 88.9%) as a white solid. Data for compound **15**: m.p.: 176－177 ℃; $[\alpha]_D^{25}$ −39.5 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.11 (d, *J*＝7.5 Hz, 2H), 7.60 (t, *J*＝7.5 Hz, 1H), 7.50 (t, *J*＝7.5 Hz, 2H), 7.41－7.38 (m, 2H), 7.32－7.27 (m, 3H), 6.24 (brs, 1H), 5.69 (d, *J*＝3.0 Hz, 1H), 5.51 (d, *J*＝10.0 Hz, 1H), 5.49－5.55 (m, 1H), 5.40 (brs, 1H), 5.22 (d, *J*＝9.2 Hz, 1H), 5.22 (s, 1H), 4.96 (d, *J*＝9.1 Hz, 1H), 4.31 (d, *J*＝9.0 Hz, 1H), 4.28－4.25 (m, 2H), 4.20 (d, *J*＝9.0 Hz, 1H), 3.92 (d, *J*＝7.1 Hz, 1H), 2.58－2.55 (m, 1H), 2.43 (s, 3H), 2.08 (s, 3H), 2.04 (s, 2H), 1.93 (s, 3H), 1.88－1.83 (m, 2H), 1.74 (s, 3H), 1.33 (s, 9H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 211.4, 171.2, 170.1, 168.3, 167.0, 155.2, 139.0, 137.4, 135.6, 133.6, 130.1, 129.3, 128.8, 128.7, 128.1, 126.3, 84.2, 81.0, 80.4, 78.8, 76.5, 75.0, 74.4, 72.0, 71.7, 60.4, 57.6, 46.4, 43.1, 36.8, 35.6, 28.1, 26.3, 22.6, 21.0, 20.9, 20.3, 14.1, 9.9; FT-IR (KBr) *v*: 3410, 2900, 1740, 1710 cm^{-1}; ESI: calcd for $C_{45}H_{55}NNaO_{15}$ 872.3, found 872.7 $(M+Na^+)$.

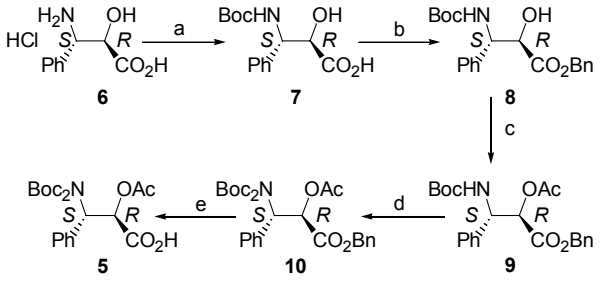
Docetaxel (**1**): To a solution of **15** (340 mg, 0.40 mmol) in THF (5.0 mL) was added saturated aq. $NaHCO_3$ solution (1.0 mL) and hydrogen peroxide (30%, 1.0 mL). The reaction mixture was stirred at room temperature until starting material **15** disappeared on TLC. The mixture was acidified to pH＝6－7 by adding 1 mol/L aqueous citric acid solution and then introduced into water (100 mL). The precipitation was filtered, washed with cold water and dried to give the product－Docetaxel **1** (300 mg, yield 92.8%). Data for compound **1**: m.p.: 232－234 ℃; $[\alpha]_D^{25}$ −36.2 (*c* 1.0, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.15－8.10 (m, 2H), 7.62－7.58 (m, 1H), 7.53－7.49 (m, 2H), 7.40－7.37 (m, 5H), 6.22 (t, *J*＝9.0 Hz, 1H), 5.68 (d, *J*＝7.0 Hz, 1H), 5.46 (d,

J=9.0 Hz, 1H), 5.26 (d, *J*=9.0 Hz, 1H), 5.22 (s, 1H), 4.94 (d, *J*=9.0 Hz, 1H), 4.65−4.60 (m, 1H), 4.32 (d, *J*=9.0 Hz, 1H), 4.28−4.25 (m, 1H), 4.19 (d, *J*=9.0 Hz, 1H), 3.91 (d, *J*=7.0 Hz, 1H), 2.60−2.55 (m, 1H), 2.37 (s, 3H), 2.35−2.30 (m, 2H), 1.88 (s, 3H), 1.75 (s, 3H), 1.35 (s, 9H), 1.23 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.1, 172.7, 170.3, 167.0, 155.5, 138.6, 138.5, 136.0, 133.0, 130.2, 129.3, 128.7, 127.9, 127.4, 126.9, 84.4, 81.1, 80.2, 78.9, 77.3, 75.1, 74.5, 73.9, 72.3, 71.8, 57.7, 56.6, 46.6, 43.1, 36.7, 35.8, 28.2, 26.5, 22.5, 20.7, 14.3, 9.9; FT-IR (KBr) ν: 3400, 2900, 1710 cm^{-1}.

Results and Discussion

Our synthetic effort started from (2*R*,3*S*)-phenylisoserine hydrochloride **6**. As shown in Scheme 2, amino group protection of isoserine **6** with Boc_2O under the standard condition afforded acid **7** in 89% yield, which was then transformed into benzyl ester **8** in a yield of 93%. Esterification of the hydroxyl group with acetic anhydride and Et_3N in CH_2Cl_2 (**9**, 95%), followed by the second Boc protection on the nitrogen atom readily provided compound **10** in 80% yield. Hydrogenative debenzylation then produced the desired linear side chain synthetic subunit **5** in a high yield (97%).

Scheme 2 Preparation of the linear chain isoserine synthetic subunit **5**



Reagents and conditions: (a) Boc_2O, acetone, $NaHCO_3$ (aq.), r.t., 89.0%; (b) BnCl, NEt_3, acetone, reflux, 93.0%; (c) Ac_2O, NEt_3, CH_2Cl_2, r.t., 95.0%; (d) Boc_2O, DMAP, acetonitrile, reflux, 80.0%; (e) Pd/C, H_2, ethyl acetate, r.t., 97.0%.

With compound **5** in hand, we then turned our attention to the esterification of C-13 hydroxy group. When 10-di-Troc-10-DAB **11** (1 mmol) was treated with *N*, *N*-di-Boc phenyl isoserine **5** (2.3 equiv.) in the condition of DCC (8.5 equiv.) and DMAP (4 equiv.),[3,4] the normal coupling product **12** was obtained in 51% yield. To our surprise, an unexpected acetyl migration by-product **13** was also separated from the reaction mixture in 45% yield.

A series of experiments were then performed to optimize the coupling step, and the results were summarized in Table 1. It was found that 8.5 equiv. of DCC should be added. Reducing the amount of DCC will prolong the reaction time and lead to some side products. As shown in Table 1, the ratio of 10-DAB **11**/side chain **5**/DMAP and the reaction temperature were examined. When 4.6 equiv. of compound **5** was added, an improved **12/13** ratio was obtained (Table 1, Entry 2, total yield=96%, **12**/**13**=1.9/1). Further improvement of **5**'s equivalent (Table 1, Entry 3) was proved fruitless. The effect of DMAP's amount on the reaction yield was then investigated. When 3.0 equiv. of DMAP was added, the **12/13** ratio was improved to 2.0/1 (Table 1, Entry 4), while 2.0 equiv. of DMAP gave a ratio of 2.2/1 (Table 1, Entry 5). 1.0 equiv. of DMAP led to a long reaction time (Table 1, Entry 6). Further increasing DMAP's equivalence would lead to a lower yield (Table 1, Entry 6, 7). When the reaction temperature fell to 15 ℃, the ratio of **12/13** was improved to 3/1. When the temperature was below 10 ℃, no reaction occurred. Therefore, the optimal reaction condition should be 1.0 equiv. 10-DAB **11**, 4.6 equiv. of side chain **5** and treatment with 8.5 equiv. DCC and 2.0 equiv. of DMAP in toluene at 15 ℃ for 3 h.

Two scale-up experiments were performed. When 10 mmol 10-DAB **11** was used, product **12** was obtained in a yield of 72 % with a ratio of **12/13** equal to 2.9/1, while 100 mmol 10-DAB **11** gave **12** in 73% yield with **12/13**=3/1.

Based on the optimal condition obtained in Table 1, the coupling product **12** was obtained in 73% yield. After removal of the Troc protecting group by using Zn powder and acetic acid in methanol,[11] compound **14** was treated with trifluoro acetic acid to remove one Boc protecting group (Scheme 3). Compound **15** was obtained in 89% yield.[12] Further deprotection of the C-2' hydoxyl group in the condition of $NaHCO_3$ (aq.), H_2O_2 in THF afforded docetaxol (**1**) in 93% yield.[13] Thus, four steps synthetic route provided docetaxel in 51% overall yield, of which, the optical rotation was $[\alpha]_D^{25}$ −36.2 (*c* 1.0, EtOH) [Ref. data: $[\alpha]_D^{25}$ −36 (*c* 0.74, EtOH)].[14]

In order to improve the synthetic efficiency, by-product **13** can be reused. Direct C-13 deprotection was proved unsuccessful. The feasible route included three steps conversion. C-10 and C-13 deprotection, followed by the reaction with TrocCl in pyridine provided 7,10-di-Troc-10-DAB **10** in 70% yield.

Conclusions

In conclusion, we have developed An efficient semi-synthetic method to construct docetaxel **1** in a total yield of 51% after four steps. Different from the cyclic surrogates utilized before, the bulky protected linear side chain derivative **5**, obtained from (2*R*,3*S*)-phenylisoserine hydrochloride **6**, was directly employed in C-13 esterification step to provide the coupling product **12** in a moderate yield. The presence of the bulky protecting group blocked side chain C-2' hydrogen and prohibited C-2' enolization and racemization, which is unavoidable in previous studies. A series of experiments were performed to optimize the unexpected acetyl mi-

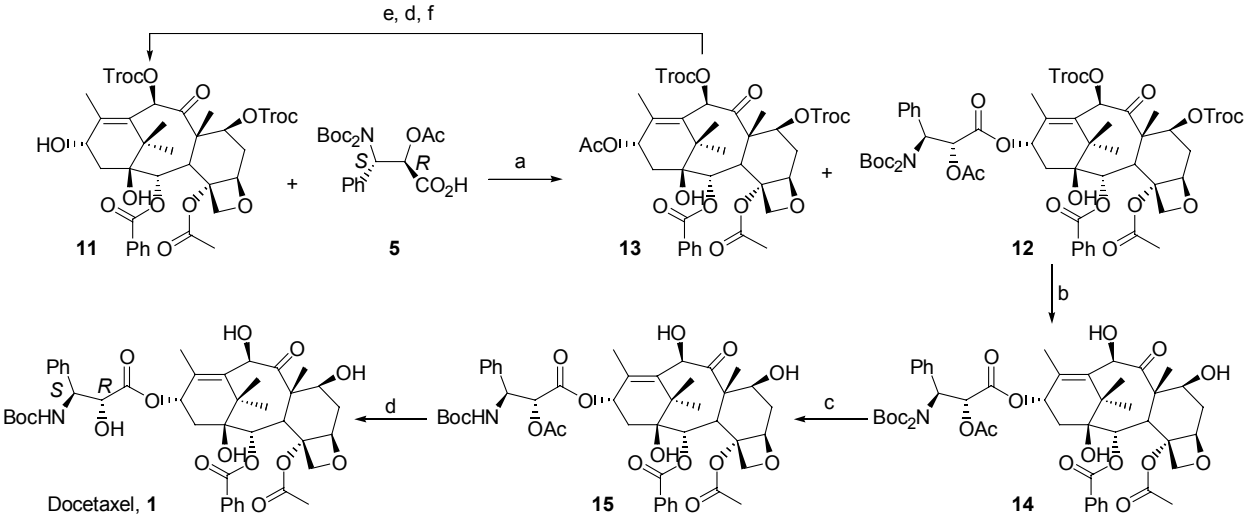
CHINESE JOURNAL OF CHEMISTRY

Table 1 condensation reaction of the compounds **11** and **5** under different conditions[a]

Entry	**11**/mmol	**5**/equiv.	DMAP/equiv.	Temp./℃	Reaction time/h	Ratio (**12**/**13**)[b]	Yield (**12**+**13**)[c]/%
1	1.0	2.3	4.0	25	1.0	1.1/1	95.3
2	1.0	4.6	4.0	25	1.0	1.9/1	96.3
3	1.0	6.9	4.0	25	1.0	1.6/1	97.8
4	1.0	4.6	3.0	25	2.0	2.0/1	95.2
5	1.0	4.6	2.0	25	2.5	2.2/1	94.7
6	1.0	4.6	1.0	25	10	2.2/1	93.0
7	1.0	4.6	8.0	25	0.75	0.6/1	93.5
8	1.0	4.6	16.0	25	0.25	0.33/1	96.4
9	1.0	4.6	2.0	15	3.0	3/1	98.0
10	1.0	4.6	2.0	10	12.0		NR
11	10	4.6	2.0	15	3.0	2.9/1	97.1
12	100	4.6	2.0	15	3.0	3/1	97.4

[a] Unless noted, the reaction was performed in 1 mmol scale, 1 equiv. of 10-DAB **11** and 8.5 equiv. of DCC were used, DMAP＝*N*,*N*-dimethyl pyridine; [b] HPLC data; [c] separated yield; [d] NR＝no reaction.

Scheme 3 An efficient synthetic route to construct Docetaxol



Reagents and conditions: (a) DCC, DMAP, toluene, 15 ℃, 73%; (b) Zn (powder), AcOH, Methanol, 55 ℃, 85%; (c) TFA, CH_2Cl_2, r.t., 89%; (d) $NaHCO_3$ (aq.), H_2O_2, THF, r.t., 93%; (e) Zn (powder), AcOH, methanol, 55 ℃, 85%; (f) TrocCl, Pyr., 0 ℃, 70%.

gration side product in the esterification step. Further work directed to the new method's synthetic application in the semi-synthesis of taxol and its analogs is still in progress.

Acknowledgement

Support of this work by the Fundamental Research Funds for the Central Universities and the Research Funds of Renmin University of China (No. 11XNI003) is gratefully acknowledged.

References

[1] Ojima, I.; Lin, S.; Slater, J. C. *Bioorg. Med. Chem.* **2000**, *8*, 1619.
[2] Chen, S. H.; Farina, V.; Vyas, D. M. *J. Org. Chem*. **1996**, *61*, 2065.
[3] (a) Holton, R. A. *EP-A-400971*, **1990** [*Chem. Abstr*. **1991**, *114*, 164568q]; Holton, R. A. *US 5015744*, **1991** [*Chem. Abstr.* **1992**, *115*, 159485b]; Holton, R. A. *EP-428376*, **1991** [*Chem. Abstr.* **1992**, *115*, 114817]; Holton, R. A. *WO 93/06079*, **1993** [*Chem. Abstr.* **1993**, *119*, 139574]; Holton, R. A. *US 5430160*, **1995** [*Chem. Abstr.* **1995**, *123*, 286341]; Holton, R. A. *US 5717115*, **1998** [*Chem. Abstr.* **1998**, *128*, 180554]; (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem*. **1991**, *56*, 1681; (c) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985; (d) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett*. **1993**, *34*, 4149; (e) Ojima, I. *WO 94/18164*, **1994** [*Chem. Abstr.* **1995**, *123,* 83095]; Ojima, I. *US 20020087013*, **2002** [*Chem. Abstr.* **2002**, *137*, 79100]; (f) Holton, R. A.; Rengan, K.; Nadizadeh, H. *US 5283253*, **1994** [*Chem. Abstr.* **1994**, *121*, 134497].
[4] (a) Kingston, D. G. I.; Chaudhary, A. G.; Gunatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett*. **1994**, *35*, 4483; (b) Poss, M. A.; Moniot, J. L.; Trifunovich, I. D.; David, J.; Thottahil, J. K.; Chen, S.-H.; Wei, J. (Bristol-Myers Squibb) *US 5808102*, **1998** [*Chem.*

Abstr. **2008**, *149*, 246674]; (c) Chen, S.-H.; Huang, S.; Roth, G. P. *Tetrahedron Lett*. **1995**, *36*, 8933; (d) Chen, S.-H.; Farina, V.; Vyas, D. M.; Doyle, T. W.; Long, B. H.; Fairchild, C. *J. Org. Chem*. **1996**, *61*, 2065; (e) For the synthesis of the oxazoline acid intermediate, see: Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem*. **1993**, *58*, 1287; (f) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc*., *Perkin Trans. 1* **1993**, 1375.

[5] (a) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc*. **1988**, *110*, 5917; (b) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F. *EP 336840*, **1989** [*Chem. Abstr.* **1990**, *112*, 158670]; (c) Commercon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett*. **1992**, *33*, 5185; (d) Denis, J. N.; Kanazawa, A. M.; Greene, A. E. *Tetrahedron Lett.* **1994**, *35*, 105; (Rhone-Poulenc Rorer S. A.), *WO 94/10169*, **1994**; *FR Appl. 92*/*13000*, **1992** [*Chem. Abstr.* **1993**, *121,* 280917]; (e) Kanazawa, A. M.; Denis, J. N.; Greene, A. E. *J. Chem. Soc*., *Chem. Commun*. **1994**, 2591.

[6] For applications after 1993, see: (a) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Soresen, E. J. *J. Am. Chem. Soc*. **1995**, *117*, 624; (b) Holton, R. A.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc*. **1994**, *116*, 1597; (c) Ojima, I.; Park, Y. H.; Sun, C.-M.; Fenoglio, I.; Appendino, G.; Pera, P.; Bernacki, R. J. *J. Med. Chem*. **1994**, *37*, 1408; (d) Holton, R. A.; Somoza, C.; Chai, K.-B. *Tetrahedron Lett*. **1994**, *35*, 1665; (e) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J.; *Nature* **1994**, *367*, 30; (f) Kant, J.; O'Keeffe, W. S.; Chen, S.-H.; Farina, V.; Fairchild, C.; Johnston, K.; Kadow, J. F.; Long, B. H.; Vyas, D. *Tetrahedron Lett*. **1994**, *35*, 5543; (g) Chen, S.-H.; Farina, V.; Fairchild, C.; Johnston, K.; Kadow, J. F. *J. Org. Chem*. **1994**, *59*, 6156; (h) Boge, T. C.; Himes, R. H.; Vander Velde, D. G.; Georg, G. I. *J. Med. Chem*. **1994**, *37*, 3337; (i) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc*. **1995**, *117*, 2409; (j) Young, W. B.; Masters, J. J.; Danishefsky, S. *J. Am. Chem. Soc*. **1995**, *117*, 5228; (k) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem*., *Int. Ed. Engl*. **1995**, *34*, 1723; (l) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vander Velde, D. G.; Himes, R. H. *J. Org. Chem*. **1996**, *61*, 2664; (m) Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Langley, D. R.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495; (n) Park, H.; Hepperle, M.; Boge, T. C.; Himes, R. H.; Georg, G. I. *J. Med. Chem*. **1996**, *39*, 2705.

[7] Recent examples: (a) Heo, J. H.; Park, S. J.; Kang, J. H.; Lee, I. S.; Lee, J. S.; Park, Y. J.; Kim, K. S.; Lee, J. Y. *Bull. Korean Chem. Soc*. **2009**, *30*, 25; (b) Zhou, H.; Chen, D.; Gao, H.; Li, Q. *Lett. Org. Chem*. **2010**, *7*, 450; (c) Nan, P.-J.; He, W.; Wang, Q.-F.; Jing, L.-L.; Sun, X.-L. *Chin. Pharm. J*. **2007**, *42*, 709.

[8] Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem*., **1994**, *59*, 1238.

[9] (a) Gueritte-Voegelein, F.; Senilh, V.; David, B.; Guenard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451; (b) Py, S.; Pan, J. W.; Khuong-Huu, F. *Tetrahedron* **1994**, *50*, 6881.

[10] Dubois, J.; Guenard, D.; Gueritte-Voegelein, F.; Guedira, N.; Potier, P.; Gillet, B.; Beloeil, J.-C. *Tetrahedron* **1993**, *49*, 6533.

[11] (a) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett*. **1967**, *8*, 2555; (b) Imoto, M.; Kusunose, N.; Kusumoto, S.; Shiba, T. *Tetrahedron Lett*. **1988**, *29*, 2227.

[12] (a) van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1992**, *57*, 6083; (b) Papageorgiou, G.; Ogden, D.; Corrie, J. E. T. *J. Org. Chem*. **2004**, *69*, 7228.

[13] Zheng, Q. Y.; Darbie, L. G.; Cheng, X.; Murray, C. K. *Tetrahedron Lett*. **1995**, *36*, 2001.

[14] Mangatal, L.; Adeline, M.-T.; Mangatal, L.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177.

(Zhao, X.)

