A Novel Method to Synthesize Docetaxel and its Isomer With High Yields

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Received March 6, 2004

Side chains of docetaxel and its isomer were obtained through Staudinger cycloaddition and catalytic hydrogenation of chlorophenyl intermediates, using chlorobenzaldehyde as starting material. Syntheses of three novel chiral azetidinone derivatives through the Staudinger cycloaddition reaction of chlorophenyl chiral amine Schiff base with different substituted positions were described and their ring-opening reaction under the catalysis of $Pd/MgCO_3$ or Pd/C to afford side chains of docetaxel and its isomer in high yields was investigated. Finally, docetaxel and its isomer were obtained. Single crystal of (3*S*,4*R*)-3-hydroxy-*N*-[(*S*)-(1-phenyl)ethyl]-4 -(2'-chlorophenyl) -2-azetidinone (**4c**) was obtained, the configuration of which was determined by X-ray diffraction. Because of the mild cyclization reaction condition and convenient asymmetric resolution operation when *p*-chlorobenzaldehyde was employed instead of benzaldehyde, the yield of cyclization and hydrogenation increased dramatically and the total yield of docetaxel was higher than the result in literature. When *o*-chlorobenzaldehyde was employed instead of benzaldehyde an isomer of docetaxel was obtained by the same way.

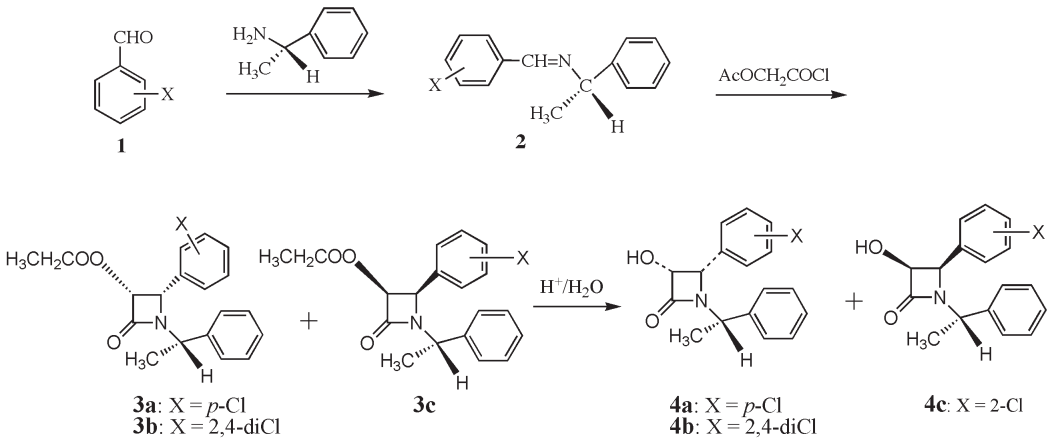
J. Heterocyclic Chem., **42**, 679 (2005).

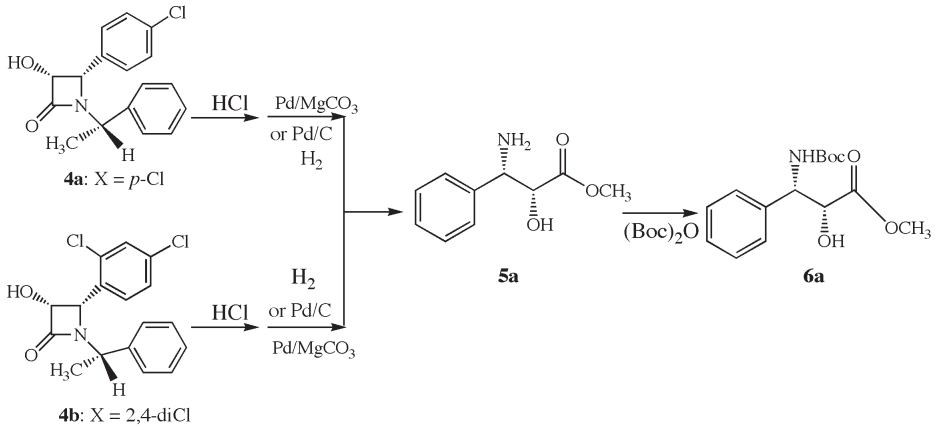
Docetaxel has been thought as one of as an anticancer pharmaceutical with the most remarkable curative effects, and passed clinical trials of mammary gland cancer, lung cancer, stomach cancer and crown cancer at the end of 1990's. In 1996, it was authorized by Food and Drug Administration (FDA) and applied in clinic [1,2]. Due to its complex structure, great difficulty exists in the total synthesis of docetaxel. Since 10-deacetylbaccatin □ (10-DAB□), with a ring structure similar to docetaxel, was extracted in large scale from European *Taxus baccata*, effective semisynthesis were started to reduce synthetic difficulty and cost of docetaxel dramatically [3-5]. Considering that the key procedure, synthesis of the side chain that joined with 10-DAB□ and (3*R*,4*S*)-3-hydroxy-4-(*p*-chlorophenyl)-2-(α-phenylethyl)azetidinone can proceed in high yield, it would become an effective and cheap way to synthesize docetaxel if the chlorine atom can be reduced to a hydrogen atom. Hence, the following reaction route was designed for the synthesis of docetaxel and its isomer (Scheme).

Results and Discussion.

Configurations of β-Lactams and Side Chain Compounds.

Chiral Schiff bases were employed to afford two diastereoisomers containing the β-amide ring *via* the Staudinger cycloaddition reaction. The structure of **4c** has been proven by X-ray diffraction (Figure), and the configuration found to be 3*S*,4*R*. The (3*S*,4*R*)-β-propiolactam (**4c**), which was obtained *via* the Staudinger cycloaddition reaction using the Schiff base of the chiral amine and aromatic aldehyde was deposited in the Cambridge date base (CCDC 252696). Compounds **4a** and **4b** were determined to be 3*R*,4*S* configuration on the basis of ^{1}H-NMR, H-HCOSY, optical activity and comparison with the structure of **4c**. In the ring-opening and hydrogenation reactions, the products retain their original configuration hence the side chain compounds have the same configurations as that of the corresponding β-lactams.

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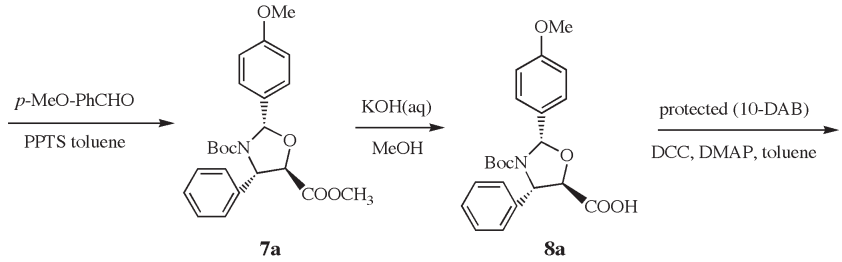
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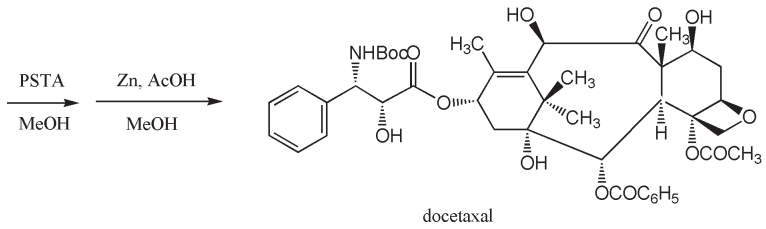
7a
8a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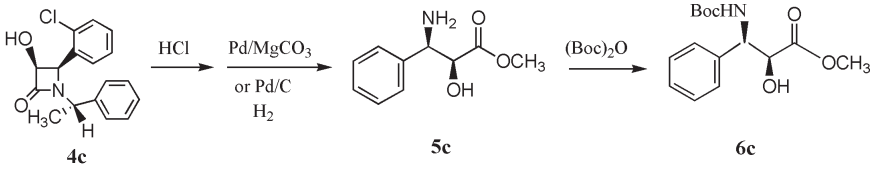
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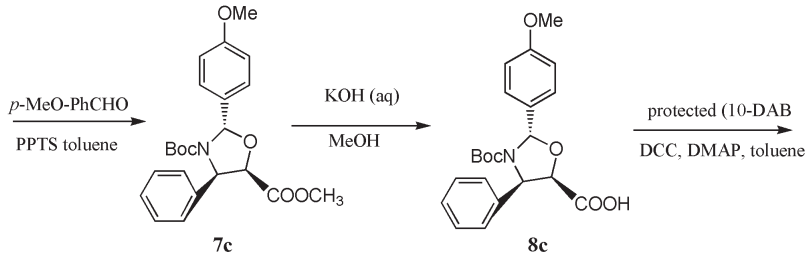
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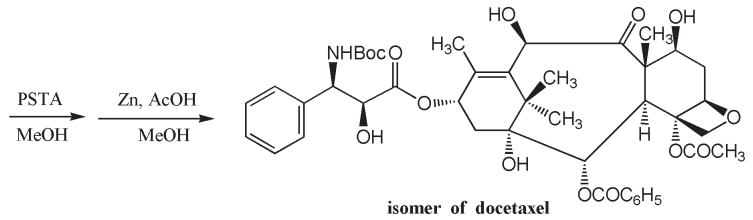
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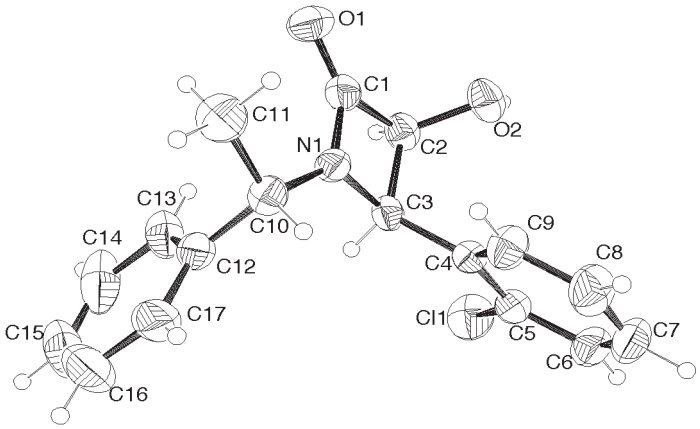

Figure. X-ray crystal structure of (3*S*,4*R*)-3-hydroxy-4-(2'-chlorophenyl)-2-(α-phenylethyl)azetidinone.

Hydrogenation.

The Pd content in the catalyst plays a key role in the reduction of the chlorine atom. When Pd/$MgCO_3$ or Pd/C containing 3% Pd was employed, only *N*-phenylethyl was reduced to ethylbenzene after reacting for 8 h at 50 °C. As the reaction time is increased, the formation of by-products also greatly increased with only partial reduction of chlorine atoms. Both phenylethyl groups and chlorine atoms can be reduced if the content of Pd increased to 10% under the same reaction conditions. The reaction is complete in 3 h and Pd/$MgCO_3$ or Pd/C containing 8-20% Pd was employed for catalytic hydrogenation. The optimum temperature of catalytic hydrogenation is 35-45 °C with alcohol as solvent. When methanol and ethanol are used, good catalytic effects are observed.

Synthesis.

The acetoxyacetyl chloride, used in the preparation of β-lactams adopting benzaldehyde as starting materials, is very sensitive to water. Considering that dropwise addition of the acyl chloride/chloroform solution is a long procedure, trace amounts of water in chloroform can react with the acyl chloride to afford the corresponding carboxylic acid, which was precipitates out and does not react further. This results in dramatically lower yields therefore the chloroform must be adequately dried with anhydrous $CaCl_2$ before use.

In this reaction, as far as the mechanism was concerned, the acyl chloride reacts first with triethylamine to form the ketene like intermediate *via* loss of HCl followed by Stautinger cycloaddition with the Schiff base to form the β-lactam. According to the literature method [7], we found that the optimum temperature for dropwise addition of the acyl chloride is -20 °C followed by raising the temperature above 0 °C, for a reaction time of 4-6 hours. However, when *p*-chlorobenzaldehyde is used instead benzaldehyde a cyclization temperature of -5-10 °C was appropriate and the reaction time was shortened, evidently to simplify the operation.

Due to the viscosity of the intermediate propiolactam **3a**, its isomers cannot be resolved by recrystallization. We used the way that the hydroxy group is released through hydrolysis to resolve the propiolactam, then recrystallized in mixture of ethyl acetate and *n*-hexane (7:1) to afford **4a** (3*R*,4*S*)-3-hydroxy-4-(*p*-chlorophenyl)-2-(α-phenylethyl)-azetidinone in high yield (the total yield of the preceding three steps was about 76%). Compared with the corresponding product using benzaldehyde as starting material, this method not only gave higher yields than the literature method [4], but also with a convenient and quick recrystallization operation. The total yield of **4c** (3*S*,4*R*)-3-hydroxy-4-(2'-chlorophenyl)-2-(α-phenylethyl)azetidinone was about 22%.

After the treatment of **4a**, **4b** and **4c** with HCl, the ring-opening products underwent catalytic hydrogenation directly by Pd/$MgCO_3$ or Pd/C with nearly 100% yields. The yields of **5a** and **5c** were 69.8% and 66.5% respectively.

Both of the side chain of docetaxel (**8a)** and its isomer (**8c**), obtained through hydrolysis of the ester directly, reacted with the parent ring without purification. Side chain **8a** and the parent ring reacted according to the literature [7] to give the docetaxel. Similarly, side chain (**8c**) of the isomer reacted with the parent ring to afford docetaxel isomer.

Because of the mild cyclization reaction conditions and the convenient asymmetric resolution operation when employing *p*-chlorobenzaldehyde instead of benzaldehyde, the yields of cyclization and hydrogenation increased dramatically. The total yield of docetaxel was higher than that reported in the literature [7]. Considering the high yields and convenient operation, the cost of docetaxel synthesis decreased greatly by this method and will be suitable for

substantive commercial production and provides the foundation for further efforts to increase access to it.

EXPERIMENTAL

Melting points were determined on RY-1 melting point apparatus and uncorrected. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H-NMR spectra were measured with a Brucker-500 MHz spectrometer using TMS as an internal standard. Optical activity was performed using a Perkin-Elmer 241 MC polarimeter. Schiff base of the substituted benzaldehyde was synthesized according to the literature method [6].

Preparation of $Pd/MgCO_3$ or Pd/C Catalyst.

To a 50 mL flask was added active carbon or $MgCO_3$ and 0.1% $PdCl_2$ and stirred for 2 h at room temperature until the solution became clear and the color of $MgCO_3$ turned from white to red. After the resulting mixture was filtered, the solid obtained was washed with water and dried to afford fresh Pd^{2+} catalyst loaded with $MgCO_3$ or carbon black. Then the catalyst was added in 30 mL methanol and pre-activated in the hydrogen atmosphere. The target $Pd/MgCO_3$ or Pd/C catalyst obtained after filtration and drying is red before pre-activation black after pre-activation.

Synthesis of new azetidinone derivatives **4a**, **4b** and **4c**.

To a 100 mL three-necked flask were added Schiff base **2** dissolved in 20 mL trichloromethane and triethylamine (0.021 mol, 2.9 mL). The mixture was stirred and cooled to -5-0 °C, followed by dropwise addition of acetoxyacetyl chloride (0.012 mol, 1.6 mL) in 15 mL of trichloromethane. Then the reaction continued for 2-4 h at room temperature and acidified with 20 mL 2.7 *M* HCl. The resulting solution was washed twice with water (20 mL) and the organic layer was separated and dried with $MgSO_4$. After removal of solvent, 3-ester-4-(substitutedphenyl)-2-(α-phenylethyl) azetidinone was obtained as a brown viscous solution.

To a 100 mL three-necked flask were added 3 *M* KOH (13 mL) and THF (15 mL), then a mixture of 3-ester-4-(substitutedphenyl)-2-(α-phenylethyl) azetidinone and THF (9 mL) was added dropwise at -1-3 °C. After stirring for 2.5 h, the pH of the resulting solution was adjusted to 9 by addition of 30 mL saturated $NaHCO_3$, and the organic layer was extracted with ethyl acetate (20 mL x 3) and dried using $MgSO_4$. After removal of solvent, a yellow solid was obtained. The target product and its isomer were resolved by recrystallization.

(3*R*,4*S*)-3-Hydroxy-4-(*p*-chlorophenyl)-2-(α-phenylethyl) azetidinone (**4a**).

White crystal (1.63 g) was obtained in 50.3% total yield by recrystallization in a mixture of ethyl acetate and *n*-hexane (5:1). $[\alpha]^{20}_D$ +158 (c1.0, MeOH); mp 141-142.5 °C; IR (KBr) 3260, 2991, 2989, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.16-7.58 (m, 9H, Ar), 5.06 (d, 1H, J=4.3Hz, CHOH), 4.95 (d, 1H, J=4.3Hz, CHN), 4.55 (q, 1H, J=7.17Hz, N*CH*CH_3), 3.51 (bs, 1H, OH), 1.45 (d, 3H, J=7.17Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 500MHz): β 169.7, 139.7, 134.9, 134.1, 130.4, 129.2, 129.0, 128.5, 127.6, 77.7, 77.5, 62.0, 52.7.

Anal. Calcd for $C_{17}H_{16}NO_2Cl$: C, 67.66; H, 5.34; N, 4.64. Found C, 67.39; H, 5.22; N 4.71.

(3*R*,4*S*)-3-Hydroxy-4-(2', 4'-dichlorophenyl)-2-(α-phenylethyl) azetidinone (**4b**).

White crystal (2.29 g) was obtained in 68.1% total yield by recrystallization a mixture of ethyl acetate and *n*-hexane (8:1). $[\alpha]^{20}_D$ +212 (c1.0, MeOH); mp 154-157 °C; IR (KBr) 3259, 2991, 2900, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.26-7.42 (m, 9H, Ar), 5.10 (d, 1H, J=4.7Hz, C*H*OH), 5.03 (d, 1H, J=4.7Hz, C*H*N), 4.94 (q, 1H, J=7.17Hz, C*H*CH_3), 1.50 (d, 3H, J=7.17Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 500MHz): δ 169.9, 140.9, 134.3, 132.4, 130.2,129.7, 129.2, 129.2, 128.4, 127.3, 127.1, 77.7, 77.5, 59.5, 55.0.

Anal. Calcd for $C_{17}H_{16}NO_2Cl$: C, 67.66; H, 5.34; N, 4.64. Found C, 67.51; H, 5.30; N, 4.57.

(3*S*,4*R*)-3-Hydroxy-4-(2'-chlorophenyl)-2-(α-phenylethyl)azetidinone (**4c**).

White crystal (0.71 g) was obtained in 21.9% total yield by recrystallization a mixture of ethyl acetate and *n*-hexane (4:1). $[\alpha]^{20}_D$ –153 (c1.0, MeOH); mp 157-158 °C; IR (KBr) 3322, 2992, 2987, 1732 cm^{-1}, ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.26-7.39 (m, 9H, Ar), 5.09 (s, 2H, C*H*OH and C*H*N), 4.54 (dd, 1H, J=7.17Hz, C*H*CH_3), 3.48 (bs, 1H, OH), 1.90 (d, 3H, J=7.17Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 500MHz): δ 169.9, 140.9, 134.3, 132.4, 130.2,129.7, 129.2, 129.2, 128.4, 127.3, 127.1 77.7, 77.5, 59.5, 55.0.

Anal. Calcd for $C_{17}H_{16}NO_2Cl$: C, 67.66; H, 5.34; N, 4.64. Found C, 67.51; H, 5.30; N, 4.57.

The Catalytic Ring-opening Reaction and Hydrogenation of β-Lactams to Obtain Compounds **5a** and **5c**.

To a 100 mL flask were added **4** (12 mmol) and 45 mL of a saturated solution of HCl in methanol. After the mixture was stirred for 3-8 h and the solvent was removed, the resulting solid was dissolved in water and neutralized by 7.5 *M* NaOH in an ice-water bath. The organic layer obtained by extracting with CH_2Cl_2 (35 mL x 3). After removal of solvent, (2*,3*)-2-hydroxy-3-[(*S*)-(1'-phenyl)]amino-3- substituted phenyl-methyl propionate was obtained in 85-95% yield as yellow liquid.

The catalyst was swollen in 20 mL methanol and 8 mL glacial acetic acid and pre-activated in a hydrogen atmosphere, followed by addition of the ring-opened products **5a** or **5c** (6 mL). After stirring for 8-12 h at room temperature and in hydrogen atmosphere, the catalyst and solvent were removed, then water and CH_2Cl_2 were added. The resulting mixture was neutralized with 3 *N* NaOH under stirring in the ice-water bath. Removal of the solvent, from the organic layer, affords a light yellow solid. Recrystallizion with ethyl acetate/isopropyl ether (2/1) gave white lamellar crystal.

(2*R*,3*S*)-Methyl 2-Hydroxy-3-amino-3-phenylpropionate (**5a**).

This compound was obtained in 51.3% yield; $[\alpha]^{20}_D$= -22 (C=1.0, MeOH); mp 103-106 °C (lit. [8] mp:106-108 °C); $[\alpha]^{20}_D$= -22 (C=1.0, MeOH)]; IR (KBr) 3345, 3293 (N-H), 3065 (O-H), 2912 (C-H), 1742 (C=O), 1604 (C=C), 1214, 1171, 1089 (C-O); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.20-7.42 (m, 5H, Ar), 4.35 (d, 1H, C*H*N/C*H*OH), 4.33 (d, 1H, C*H*N/C*H*OH), 3.80 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125MHz): δ 174.17 (C=O), 142.22, 128.98, 128.13, 127.12 (6C, Ar), 75.28, 58.23, 53.07.

(2*S*,3*R*)-Methyl 2-Hydroxy-3-amino-3-phenylpropionate (**5c**).

This compound was obtained in 46.5% yield; $[\delta]^{20}_D$= +30 (C=1.0, MeOH); mp 112-114 °C; IR (KBr) 3345, 3293 (N-H), 3039 (O-H), 2912 (C-H), 1742 (C=O), 1605 (C=C), 1215, 1171, 1089 (C-O); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.28-7.43 (m, 5H,

Ar), 4.36 (d, 1H, C*H*N/C*H*OH), 4.35 (d, 1H, C*H*N/C*H*OH), 3.81 (s, 3H, OCH_3), ^{13}C NMR (125MHz, $CDCl_3$): δ 174.17 (C=O), 142.23, 128.99, 128.14, 127.12 (6C, Ar), 75.27, 58.23, 53.08.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.18. Found C, 61.83; H, 6.79; N 7.20.

Protection of Amino Group to Synthesis of Compounds **6a** and **6c** [7,9].

(2*R*,3*S*)-Methyl 2-Hydroxy-3-(*N*-tert-butoxycarbonyl)amino-3-phenylpropionate (**6a**).

This compound was obtained in 93% yield; $[\alpha]^{20}_D$= -7.5 (C=1.0, $CHCl_3$); mp: 132-133 °C (lit. [7,9] mp: 135 °C); $[\alpha]^{20}_D$= -7 (C=1.0, $CHCl_3$)]; IR (KBr) 3508 (N-H), 3381 (O-H), 2973 (C-H), 1733 (O=$COCH_3$), 1688 (O=CNH), 1518 (N-C), 1249, 1099.93 (C-O); ^1H NMR ($CDCl_3$, 500MHz): δ (s, 1H, NH), 3.87 (s, 3H, OCH_3), 3.15 (bs, 1H, OH), 1.44 (s, 9H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 125MHz): δ 173.83, 155.21, 139.49, 129.04, 128.16, 127.12, 81.15, 73.92, 56.45, 53.52, 28.66.

(2*S*,3*R*)-Methyl 2-Hydroxy-3-(*N*-tert-butoxycarbonyl)amino-3-phenylpropionate (**6c**).

This compound was obtained in 91% yield; $[\alpha]^{20}_D$= 21 (C=1.0, $CHCl_3$); mp: 119-121 °C; IR (KBr) 3509 (N-H), 3381 (O-H), 2972 (C-H), 1733 (O=$COCH_3$), 1689 (O=CNH), 1517 (N-C), 1249, 1099 (C-O); ^1H NMR ($CDCl_3$, 500MHz): δ 7.29-7.39 (m, 5H, Ar), 5.41(d, 1H, J=9Hz, C*H*N/C*H*OH), 5.24 (d, 1H, J=9Hz, C*H*N/C*H*OH), 4.50 (s, 1H, NH), 3.87 (s, 3H, OCH_3), 1.44 (s, 9H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 125MHz): δ 173.8, 155.5, 139.5, 129.0, 128.2, 127.1, 80.7, 73.9, 56.5, 53.5, 28.7.

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.02; H, 7.12; N, 4.75. Found C, 61.27; H, 7.31; N 4.93.

Cyclization Protection of Amino and Hydroxy Group [7].

(2*,4*S*,5*R*)-Methyl *N*-*tert*-Butoxycarbonyl-2-(4'-methoxy)-phenyl-4-phenyl-1,3-oxazolidine-5- methionate (**7a**).

For recrystallization a mixture of ethyl acetate and *n*-hexane was used to go give **7a** in 94% yield; $[\alpha]^{20}_D$= -59 (C=1.0, $CHCl_3$); mp:100-102 °C (lit. [7] No data); IR (KBr) 2977 (C-H), 1743 (O=$COCH_3$), 1699 (O=CN), 1613 (C=C), 1245, 1132 (C-O); ^1H NMR (DMSO, 500MHz): δ 7.41, 7.32, 6.97 (m, 9H, Ar), 6.34 (bs, 1H, PhC*H*/O=CC*H*), 5.22 (bs, 1H, PhC*H*/O=CC*H*), 4.67 (bs, 1H,NCHO), 3.78 (s, 3H, O=$COCH_3$), 3.55 (bs, 3H, $PhOCH_3$), 0.97 (s, 9H, $(CH_3)_3C$).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found C, 66.96; H, 6.59; N 3.26.

(2*,4*R*,5*S*)-Methyl *N*-*tert*-Butoxycarbonyl-2-(4'-methoxy)-phenyl-4-phenyl-1,3-oxazolidine-5-methionate (**7c**).

For recrystallization a mixture of toluene and isopropyl ether was used to give **7c**; mp: 96-98 °C; $[\alpha]^{20}_D$= 61 (C=1.0, $CHCl_3$); yield: 91%; IR (KBr) 2977 (C-H), 1742 (O=CO), 1699 (O=CN), 1613 (C=C), 1245, 1132 (C-O); ^1H NMR (DMSO, 500MHz): δ 7.41, 7.32, 6.97(m, 9H, Ar), 6.34 (bs, 1H, PhC*H*/O=CC*H*), 5.22 (bs, 1H, PhC*H*/O=CC*H*), 4.67 (bs, 1H, NCHO), 3.78 (s, 3H, O=$COCH_3$), 3.55 (bs, 3H, $PhOCH_3$), 0.97 (s, 9H, $(CH_3)_3C$).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found C, 69.02; H, 6.61; N 3.18.

Preparation of Docetaxel and its Isomer.

The side chains of docetaxel and its isomer were synthesized by the hydrolysis of the ester group according to literature method [7] The authors need to put in a detailed procedure for the preparation here. The reference is not enough. Two crude products, (2*,4*S*,5*R*) *N*-*tert*-butoxycarbonyl-2-(4'-methoxy)phenyl-4-phenyl-1,3-oxazolidine-5-formic acid (**8a**) and (2*,4*R*,5*S*) *N*-*tert*-butoxycarbonyl-2-(4'-methoxy)phenyl-4-phenyl-1,3-oxazolidine-5-formic acid (**8c**), were obtained. These crude products can be directly reacted in the following steps without purification.

The reaction of the side chain **8a** with the parent ring was carried out according to literature procedure [7]. The docetaxel was obtained and the result was consistent with that in the corresponding reference. The side chain (**8c**) of the isomer was reacted with the parent ring in a similar manner to afford the docetaxel isomer in higher yield.

(2*,4*S*,5*R*) *N*-*tert*-Butoxycarbonyl-2-(4'-methoxy)phenyl-4-phenyl-1,3-oxazolidine-5-formic Acid (**8a**).

This compound has mp 134~138 °C; IR (KBr): 3135 (COO-H), 2977 (C-H), 1754 (O=COH), 1679 (O=CN); ^1H NMR (DMSO, 500 MHz): δ 11.46 (br, 1H, COOH), 7.38- 6.83 (m, 9H, Ar), 6.32 (bs, 1H, PhC*H*/O=CC*H*), 5.14 (bs, 1H, PhC*H*/O=CC*H*), 4.69 (bs, 1H, NCHO), 3.75 (bs, 3H, $PhOCH_3$), 0.96 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2 (HOC=O), 160.2 (t-BuOC=O), 154.6 (=$CHOCH_3$), 139.2, 132.0, 129.3, 128.3, 127.6, 121.8, 114.9, (6C, Ar), 91.4, 82.3, 81.2, 63.2, 56.5 ($ArOCH_3$), 38.6(($CH_3)_3C$).

(2*,4*R*,5*S*) *N*-*tert*-Butoxycarbonyl-2-(4'-methoxy)phenyl-4-phenyl-1,3-oxazolidine-5-formic Acid (**8c**).

This compound has mp 129~132 °C; IR (KBr): 3134 (COOH), 2977 (C-H), 1753 (O=COH), 1679 (O=CN); ^1H NMR (DMSO, 500 MHz): δ 11.48 (br, 1H, COOH), 7.37- 6.80 (m, 9H, Ar), 6.29 (bs, 1H, PhC*H*/O=CC*H*), 5.11 (bs, 1H, PhC*H*/O=CC*H*), 4.70 (bs, 1H,NCHO), 3.73 (bs, 3H, $PhOCH_3$), 0.95 (s, 9H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2 (HOC=O), 160.2 (t-BuOC=O), 154.6 (=$CHOCH_3$), 139.2, 132.0, 129.3, 128.3, 127.6, 121.8, 114.9, (6C, Ar), 91.4, 82.3, 81.2, 63.2, 56.5 ($ArOCH_3$), 38.6(($CH_3)_3C$).

Protection of 10-DAB **9** (Preparation of **10)**.

10-DAB (2 mmol, 1.09 g) was dissolved in pyridine (16 ml) under an N_2 atmosphere, 2,2,2-trichloroethyl chloroformate (6.7 mmol, 0.85 ml) was added dropwise at temperature of 0 to -3 °C then place the flask was placed in a water bath at 20 to 30 °C, the reaction ended with stirring at 25 °C for one hour. The reaction mixture was then poured into ice (33 g) after cooling by ice-salt bath, an appropriate quantity of acid was added to neutralize the pyridine, then the mixture was extracted with dichloromethane (3 x 30 ml), the organic phase was dried with magnesium sulfate and recrystallized in ethyl acetate to afford pure protected 10-DAB; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.13 (d, 2H, J=7.5Hz), 7.64 (t, 1H, J=7.5Hz), 7.52 (t, 2H, J=7.5Hz), 6.31 (s, 1H), 5.66 (d, 1H, J=7.5Hz), 5.61 (m, 1H), 5.00 (d, 1H), 4.93 (m, 1H), 4.82 and 4.78 (2d, 2H, J=12Hz), 4.92 and 4.63 (2d, 2H, J=12Hz), 4.35 and 4.18 (2d, 2H, J=9Hz), 4.00 (d, 1H, J=7Hz), 2.65 (m, 1H), 2.33 (m, 2H), 2.33 (s, 3H), 2.19 (s, 3H), 2.10 (m, 1H), 2.05 (m, 1H), 1.87 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H).

Connection of Side Chain and Master Ring (Preparation of **11**).

To a 25 ml flask, **10** (0.3 mmol, 0.265 g), **8a** or **8c** (0.32 mmol, 0.132 g), DCC (0.9 mmol) and DMAP (0.06 mmol) were added

consecutively, followed by 3 ml toluene to dissolve the solid , the reaction was complete after 2 h stirring at room temperature. The mixture then was washed with water (2 x 2 ml) and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure to afford a pale yellow oil that can be used in the next reaction.

Deprotection of Acetal (Preparation of **12**).

Compound **11** (0.3 mmol) PTSA (0.33 mmol) and 15 ml methanol were added to a 25 ml flask and stirred at 25 °C for 2 h at which time the reaction is complete. Removal of the solvent by distillation gave a white solid, which was then dissolved in 10 ml ethyl acetate, washed with both water and saturated sodium carbonate and dried with anhydrous magnesium sulfate. Crude product **12** was obtained as yellow oil after distillation of solvent. The oil was purified by flash chromatography (acetate:petrol ether = 1:3) to give **12** as a white solid.

Deprotection of Hydroxyl (Preparation of Docetaxel and Isomer of Docetaxel).

First, the zinc granules were treated with dilute hydrochloric acid, washed with methanol and dried for further use. Then, compound **17** (0.3 mmol) was dissolved in 2 ml methanol followed by addition of 0.5 ml acetic acid and three grains of the granulated zinc. The reaction was allowed to proceed at 65 °C for about 1.5 h. The reaction mixture was filtered to remove the zinc and solid that had formed and the crude product, which was obtained after removal of solvent by distillation, was purified by flash chromatography (elute: acetate:petrol ether = 1:1) to afford a white solid in 59% overall yield.

Docetaxel.

This compound has mp 174~177 °C; IR (KBr): 3434.8 (OH- and NH_2), 2978.2 and 2933.5 (C-H), 1713.3 (O=C), 1245.6; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (d, 2H, J=7.5Hz, Ar), 7.64 (t, 1H, J=7.5Hz, Ar), 7.52 (t, 2H, J=7.5Hz, Ar), 7.43-7.39 (m, 4H, Ar), 7.35-7.34 (m, 1H, Ar), 6.23 (m, 1H), 5.69 (d, 1H, J=7Hz), 5.49 (br d, 1H), 5.29 (br d, 1H), 5.24 (s, 1H), 4.96 (d, 1H J=9.3Hz), 4.64 (br, 1H), 4.33 and 4.20 (dd, 2H, J=8.5Hz), 4.25 (dd, 1H), 3.93 (d, 1H, J=7Hz), 3.45 (bs, 1H), 2.63-2.56 (m, 1H), 2.40 (s, 3H), 1.89 (s, 3H), 1.86 (m, 1H), 1.77 (s, 3H), 1.36 (s, 9H, $C(CH_3)_3$), 1.30 (s, 3H),1.15(s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 211.4 (C=O), 172.8,170.3 (C=O), 167.1, 155.4 (C=O), 138.5, 135.9, 133.7, 130.2, 129.2, 128.8, 128.7, 128.1, 126.8 (13C of Cl-Ph, Bz and C=C), 84.2, 81.1, 78.8, 74.8,74.5,73.7,72.4,72.0,57.7, 56.2, 46.5, 43.1, 37.0,35.7,28.2 (3C, t-Bu), 26.5, 22.6, 20.7, 14.4, 9.9.

Isomer of Docetaxel.

(2*S*,3*R*)-*N*-Carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-12α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate was obtained as an eluant from ethyl acetate/petroleum ether (7:10) in 43% yield, mp 169~171 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (d, 2H, J=7.5Hz, Ar), 7.64 (t, 1H, J=7.5Hz, Ar), 7.50 (t, 2H, J=7.5Hz, Ar), 7.28-7.44 (m, 5H, Ar), 6.24 (m, 1H), 5.70 (d, 1H, J=7Hz), 5.40 (d, 1H, J=9Hz), 5.28 (s, 1H), 5.27 (br d, 1H), 5.00 (d, 1H, J=9Hz), 4.51 (bs, 1H), 4.33 and 4.20 (2d, 2H, J=8.5Hz), 4.30 (dd, 1H), 3.99 (d, 1H, J=7Hz), 3.40 (bs, 1H), 2.65 (m, 1H), 2.29 (s, 3H), 2.07 (s, 3H), 1.88 (m, 1H), 1.79 (s, 3H), 1.42 (s, 9H, $C(CH_3)_3$), 1.27 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125NHz, DMSO): δ 211.5 (C=O), 173.0, 170.2 (C=O), 166.5, 155.6 (C=O), 141.1, 138.0, 137.3, 134.1, 130.5, 130.1, 129.2, 129.1, 128.4 (13C of Cl-Ph, Bz and C=C), 84.8, 81.6, 79.1, 77.0, 76.5, 75.2, 71.9, 58.0, 57.2, 47.8, 47.1, 43.5, 34.5, 28.9 (3C, t-Bu), 27.4, 25.2, 21.5, 14.8, 10.2; MS(m/z,%): 807(M^+, 37).

Acknowledgments.

We thank the National Natural Science Foundation of China (Project 20171008 and 20371009) for the financial support.

REFERENCES AND NOTES

[1] I. Ojima, S. Lin and J. C. Slater, *Bioorganic and Medicinal Chemistry*, **8**, 1619 (2000).

[2] S. H. Chen, V. Farina and D. M. Vyas, *J. Org. Chem.*, **61**, 2065 (1996).

[3] E. Didier and E. Fouque, *Tetrahedron Lett.*, **35**, 2349 (1994).

[4] C. M. Qi, L. C. Yang and L. Y. Wang, *Chin. J. Chem*., **21**, 1536 (2003).

[5] I. Ojima, S. Lin and S. Chakravarty, *J. Org. Chem.*, **63**, 1637 (1998); F. Gueritte-Voegelein, D. Guenard, F. Lavelle, M. T. Le Goff, L. Mangatal and P. Potier, *J. Med. Chem.*, **34**, 992 (1991).

[6] C. M. Qi, G. X. Zhang and X. F. Guo, *Chinese Journal of Beijing Normal University*, **37**, 535 (2001).

[7] D. B. Jean and C. Alain, *Tetrahedron Lett*., **34**, 6049 (1993).

[8] R. C. Kelly and H. I. Skulnick, *US 5965739* (1999); *Chem. Abstr.*, **131**, 272040w (1999).

[9] J. N. Dean, A. Cornea and A. E. Greene, *J. Org. Chem.*, **55**, 1957 (1990).