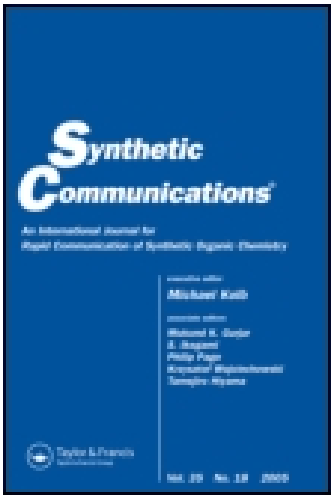

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Alternative Synthesis and the Determination of Absolute Configuration of Docetaxel, an Anticancer Drug

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ALTERNATIVE SYNTHESIS AND THE DETERMINATION OF ABSOLUTE CONFIGURATION OF DOCETAXEL, AN ANTICANCER DRUG

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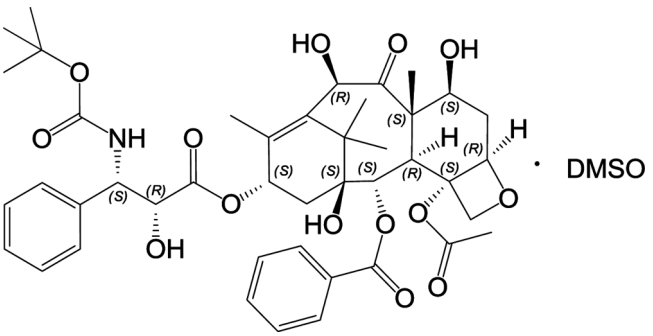
GRAPHICAL ABSTRACT



Abstract *A simple, efficient, and alternative synthetic route for docetaxel with better control on the protection–deprotection sequence has been developed. The process is easily scalable and commercially viable, and critical impurities can be controlled efficiently. For the first time, absolute configuration of docetaxel was determined unambiguously by single-crystal x-ray diffraction.*

Keywords Absolute configuration; anticancer; 10-deacetyl baccatin III; docetaxel and non-small cell lung cancer (NSCLC)

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INTRODUCTION

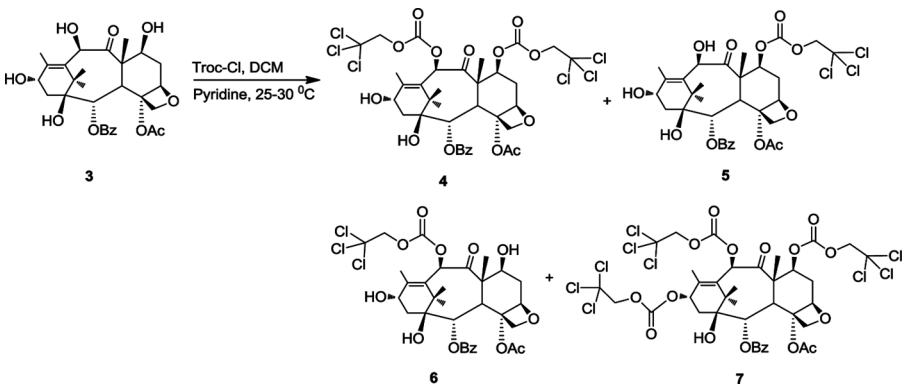
Docetaxel (**1**), an analog of paclitaxel (**2**), was obtained by semisynthesis from 10-deacetyl baccatin III (**3**), which was extracted from the needles of the European yew tree *Taxus baccata* L.[1,2] Docetaxel (**1**) is an antineoplastic agent that acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly, which leads to a marked decrease of free tubulin and eventually to cancer cell death. The binding of docetaxel (**1**) to microtubules does not alter the number of protofilaments.[3,4] Docetaxel (**1**) has better bioavailability[3] than paclitaxel (**2**) and hence is extensively used in the treatment of cancer, specifically breast cancer and non-small-cell lung cancer (NSCLC). See Fig. 1.

There are several synthetic routes reported in the literature for the synthesis of paclitaxel analog, docetaxel (**1**).[5–15] These synthetic routes involve mostly semisynthetic procedures starting from 10-deacetyl baccatin III (10-DAB III) (**3**) The most practical synthesis[14,15] of the paclitaxel analog docetaxel (**1**) involves introduction of a side chain through selective protection and deprotection methodology.

Selective protection of 7,10-hydroxy groups of 10-DAB III (**3**) by 2,2,2-trichloroethyl chloroformate (Troc-Cl) as per reported procedure generates several side products [viz., 7-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III (7-troc 10-DAB III) (**5**), 10-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III (10-troc 10-DAB III) (**6**), 7,10,13-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III (7,10,13-troc 10-DAB III) (**7**), and 7,10-di-(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III (7,10-ditroc 10-DAB III) (**4**)] as shown in Scheme 1. These side products should be controlled in the initial stages of the synthesis to avoid competitive reactions in further sequence of reactions.

A tedious downstream process was involved during deprotection at the advanced stage of the synthesis of docetaxel (**1**). The deprotection of the acetonide group in coupled product (**9**), followed by protection of amino group using di-tert-butyldicarbonate [$(BOC)_2O$] as reported in literature, generates several impurities, specifically epimers of docetaxel.

Docetaxel (**1**) is a complex molecule that is sensitive to acid, base and heat.[2,16,17] It is therefore important to reduce the cycle time during downstream



Scheme 1. Synthesis of 7,10-ditroc 10-DAB-III **(4)**.

process and also to avoid formation of side products that otherwise may carry forward to the final product. Thus, the major disadvantage in the previously reported synthetic schemes is extensive purification of the final product by column chromatography to control the impurities. The present synthetic scheme controls the formation of critical impurities in addition to simplifying purification methods.

Herein, we report an alternative synthetic route for the synthesis of docetaxel (**1**) using a modified protection–deprotection sequence. Further, we have determined the absolute configuration of docetaxel (**1**) by single-crystal x-ray diffraction.

RESULTS AND DISCUSSION

The selective protection of 7,10-hydroxy groups of 10-deacetyl baccatin III (**3**) by 2,2,2-trichloroethyl chloroformate (Troc-Cl) is challenging because of the presence of other hydroxyl groups. There is a reactivity difference among the hydroxyl groups present at different centers ($7 > 10 > 13 > 1$)[18,19] but the generation of impurities out of unselective protection cannot be ruled out. Thus, there is a possibility of formation of side products (**5–7**) along with 7,10-ditroc 10-deacetyl baccatin III (**4**). Hence, there is an unmet need to design a process that can lead to the product in a better yield by avoiding the formation of impurities. Strategically, we were able to control the undesired compounds by limiting the molar equivalents of Troc-Cl to 3.5. Temperature and rate of addition of reagent (1.5–2 ml/min) were also critical factors to obtain good results as shown, in Table 1.

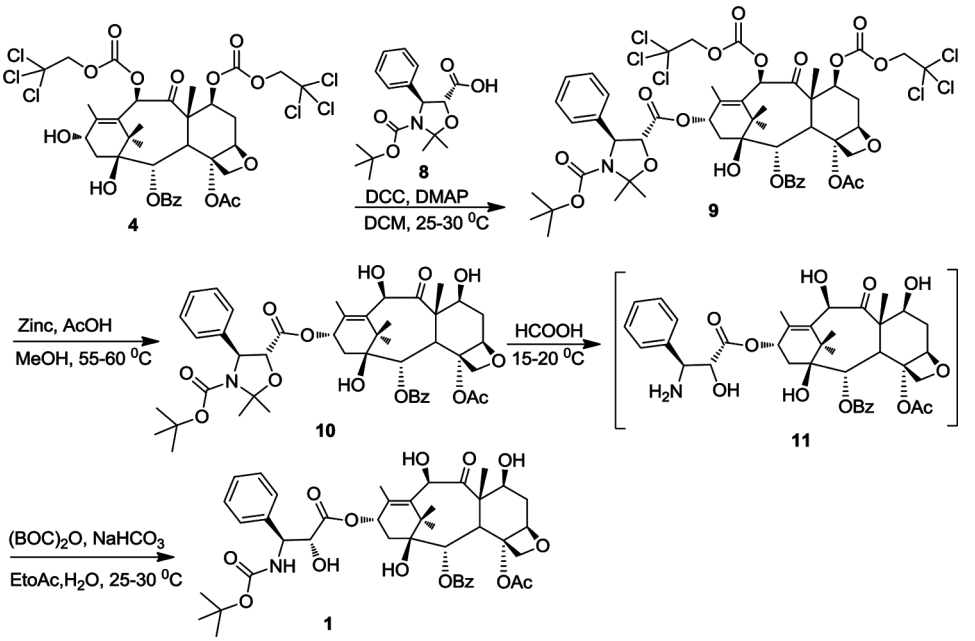
The synthesis of 7,10,13-protected 10-DAB III (**9**) from protected 10-DAB III (**4**) has been reported in the literature.[14,15] Esterification of the side chain (**8**) with protected 10-DAB III (**4**) has been well optimized to afford the desired purity and good yield.[20] In contrast to the literature procedures, the Troc protecting groups in compound **9** were first deprotected using zinc–acetic acid (AcOH) in methanol (MeOH) to afford 13-protected 10-DAB III (**10**) in significantly good yields.

Treatment of **10** with formic acid (HCOOH) gave the corresponding amino alcohol derivative of docetaxel (**11**), which was then taken up directly for the subsequent protection with ditert butyldicarbonate [$(BOC)_2O$] to afford docetaxel (**1**)[20] as shown in Scheme 2. The product thus obtained was subjected to purification

Table 1. Effect of 2,2,2-trichloroethyl chloroformate (Troc-Cl) and temperature

Entry	Troc-Cl (Eq.)	Temperature (°C)	HPLC (%) 4	5	6	7	3
1	2.0	25–30	17.7	24.6	33.6	ND[a]	21.8
2	3.0	25–30	24.4	30.2	34.6	0.2	8.6
3	3.5	20–25	94.5	0.5	0.8	0.9	0.5
4	3.5	25–30	96.2	0.1	0.2	1.3	0.2
5	3.5	30–35	90.2	0.05	0.1	7.7	ND
6	3.5	35–40	87.4	ND	ND	9.9	ND
7	4.0	25–30	86.5	ND	ND	11.4	0.1
8	4.5	25–30	33.3	ND	ND	64.2	ND

[a]ND, not detected.



Scheme 2. Alternative synthesis of docetaxel.

to afford the product **1** in good yield and quality, far superior compared to the previous method reported and practiced. In addition, the reduced downstream process could also reduce significantly the formation of critical impurities. This alternative process has also helped in reducing the epimers of docetaxel as the acetonide deprotcetion was carried out in the last stage of the synthesis. The docetaxel (**1**), thus obtained has excellent purity and is suitable for the preparation of dosage forms as per regulatory agencies.[21]

Several attempts have been made to generate single crystals of docetaxel (**1**) using different single and binary solvents by the slow evaporation method. Few crystals of compound **1** were obtained by slow evaporation crystallization from dimethyl sulfoxide (DMSO). The crystal structure reveals that the asymmetric unit consists of one molecule of docetaxel (**1**) and one dmethylsulfoxide (DMSO) molecule. Hence the crystal is DMSO solvate of docetaxel (**1**) with 1:1 stoichiometry; ORTEP is shown in Fig. 2. Because the crystal consists of one heavy atom (sulfur), the absolute

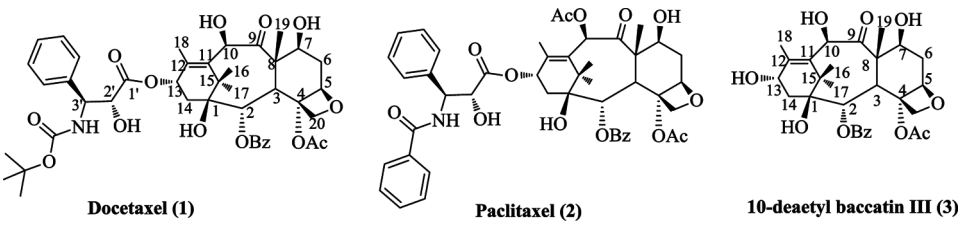


Figure 1. Structures of 10-deacetyl baccatin III (10-DAB III) derivatives.

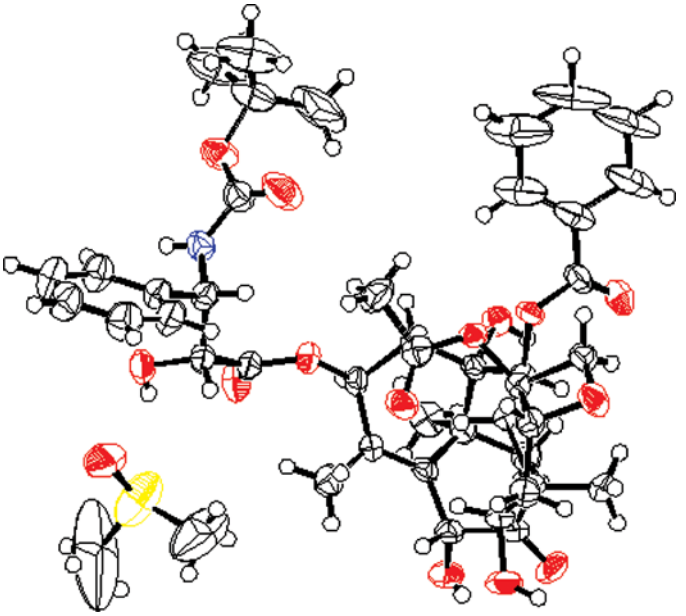


Figure 2. ORTEP of docetaxel (1)•DMSO with displacement ellipsoids drawn at the 50% probability level for nonhydrogen atoms. H atoms are represented by circles of arbitrary size. Atoms are not labeled for clarity. Ellipsoids with black color are carbons, red are oxygens, blue is nitrogen, and yellow is sulfur. (Figure is provided in color online.)

configurations of 11 chiral centers in docetaxel (**1**) were determined. The configurations are the same as those reported for docetaxel (**1**). The absolute configuration of the chiral centers in docetaxel has not been reported in the literature.[22–25] To the best of our knowledge, we report the determination of the absolute configuration of docetaxel (**1**) by the single-crystal x-ray diffraction for the first time. The crystal

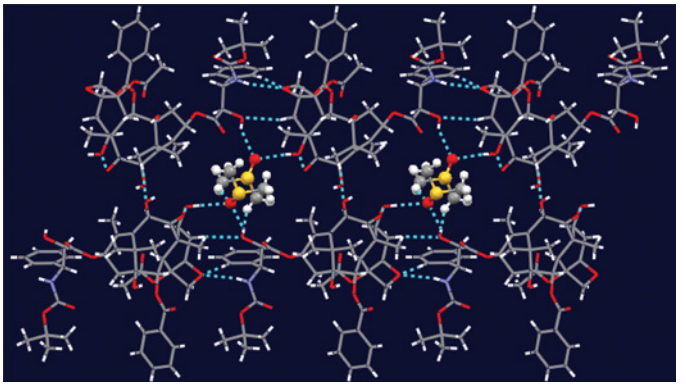


Figure 3. Crystal packing of docetaxel (1)•DMSO inclusion complex, view down [010]. Notice that docetaxel molecules form the host framework and DMSO molecules (shown with ball and stick model) occupy the channels. *Note*: Carbons are in grey, oxygens in red, nitrogens in blue hydrogens in white, and Sulfurs in yellow. (Figure is provided in color online.)

structure shows that docetaxel (**1**) molecules are forming the host framework through hydrogen bonds with channels (approximate size 8.7×7.5 Å) along [010], similar to our previously reported inclusion complexes.[22] The DMSO guest solvent molecules reside in the channels and hydrogen is bonded to the docetaxel (**1**) host framework through strong O–H···O=S hydrogen bonds as shown in Fig. 3.

CONCLUSION

In conclusion, an alternative synthetic route for the preparation of docetaxel has been reported. The new process is simple and scalable and involves a modified protection–deprotection strategy to control the critical process-related substances. The product could also be obtained in good yield with excellent purity and is suitable for the preparation of dosage forms as required by regulatory agencies. For the first time, absolute configuration of docetaxel has been determined unambiguously by single-crystal x-ray diffraction.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus and Unity Inova at 400 and 500 MHz. High-resolution mass spectrographic (HRMS) studies were performed on a Waters LCT Premier XE. The Fourier transform–(FT-IR) infrared spectrum was recorded in the solid state KBR medium using a Shimzdzu IR Prestige 21 FT-IR spectrophotometer. The optical rotation was carried out on a Jasco DIP-370 polarimeter. Single-crystal x-ray data was collected on a Rigaku AFC-7S diffractometer equipped with a Mercury CCD detector using Mo-Kα radiation. The solvents and reagents were used without further purification.

7,10-Di(2,2,2-trichloroethoxycarbonyl)-10-deacetyl baccatin III (4)

10-Deacetyl baccatin III (100.0 g, 0.183 mol) was dissolved in pyridine (0.5 L). A solution of 2,2,2-trichloroethyl chloroformate (87.4 mL, 0.635 mol) in dichloromethane (2.0 L) was added at 25–28 °C for 45–60 min under a nitrogen atmosphere and stirred at 25–30 °C for 5–10 min at moderate speed. After checking the completion of reaction by thin-layer chromatography (TLC), the reaction mixture was quenched with water (1.0 L). The organic layer was separated and washed with 10% hydrochloric acid ($2.0 \text{ L} \times 3$), saturated sodium bicarbonate solution (2.0 L), and water (1.0 L). The organic layer was evaporated to less than three volumes, precipitated with 4.5 L of *n*-heptane, and stirred for 1 h at 25–30 °C. The crude material was filtered and crystallized with ethyl acetate / *n*-heptane (0.5 L/1.65 L). The crystallized material was filtered and dried under vacuum at 45–50 °C to obtain pure 7,10-ditroc 10-deactyl baccatin III (**4**) (148 g, yield: 90%, purity: 99% by HPLC). Spectral data of the obtained compound are well in agreement with the reported spectral data.[15]

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 3H, C-17H_3), 1.0 (s, 3H, C-16H_3), 1.7 (s, 3H, C-19H_3), 1.84 (m, 1H, C-6H_a), 2.0 (s, 3H, C-18H_3), 2.24 (s, 3H, Ac), 2.2 (m, 1H, C-14H_a), 2.3 (m, 1H, C-14H_b), 2.54 (m, 1H, C-6H_b), 3.83 (d, 1H, $J = 7.0$ Hz, Hz, C-3H), 4.04 (d, 1H, $J = 8.5$ Hz, C-20H_a), 4.11 (d, 1H, $J = 8.5$ Hz, C-20H_b), 4.68

(m, 1H, C-13H), 4.68 (s, 1H, C-1 OH, D_2O exchangeable), 4.77 (d, 1H, $J = 12.5$, C-10 –OCOO$\underline{CH_a}CCl_3$), 4.94 (d, 1H, $J = 12.5$, C-10 –OCOO$\underline{CH_b}CCl_3$), 4.97 (d, 1H, $J = 12.5$, C-7 –OCOO$\underline{CH_a}CCl_3$), 5.0 (d, 1H, $J = 12.5$, C-7–OCOO$\underline{CH_b}CCl_3$), 5.02 (d, 1H, $J = 5.0$ Hz, C-5H), 5.1 (br, 1H, C-13 OH, D_2O exchangeable), 5.46 (d, 1H, $J = 7.0$ Hz, C-7H), 5.48 (d, 1H, $J = 5.0$ Hz, C-2H), 6.17 (s, 1H, C-10 H), 7.58 (t, 2H, $J = 7.5$ Hz, m-Bz-H), 7.68 (t, 1H, $J = 7.5$ Hz, p-Bz-H), 8.03 (d, 2H, $J = 7.5$ Hz, o-Bz-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 10.34 (C-19), 15.05 (C-18), 20.57 (C-17), 22.17 (CH_3 of Ac), 26.55 (C-16), 32.76 (C-6), 38.55 (C-14), 42.54 (C-15), 46.60 (C-3), 55.47 (C-8), 66.0 (C-13), 73.89 (C-7), 75.18 (C-20), 76.24 (C-10 –OCOO$\underline{CH_2}CCl_3$), 76.48 (C-2), 76.57 (C-7 –OCOO$\underline{CH_2}CCl_3$), 76.69 (C-1), 79.35 (C-4) 79.56 (C-10), 82.62 (C-5), 94.36 (C-7 –OCOOCH$_2\underline{C}Cl_3$), 94.61 (C-10 –OCOOCH$_2\underline{C}Cl_3$), 128.66 (C-m-Bz), 129.52 (C-o-Bz), 129.91 (C1-Bz), 133.31 (C-p-Bz), 129.25 (C-11), 148.27 (C-12), 152.27 (C-7 –O$\underline{CO}$OCH$_2$CCl$_3$), 152.61 (C-10 -O$\underline{CO}$OCH$_2$CCl$_3$) 165.15 (C=O of Bz), 170.05 (C=O of Ac), 201.63 (C-9). HRMS (EI) m/z calcd. for $C_{35}H_{38}O_{14}NaCl_6$ $(M + Na)^+$: 915.0290; found: 915.0285. IR (KBr) cm^{-1}: 3532, 3487, 2957, 2905, 1765, 1730, 1717, 1379, 1288, 1250, 1179, 1111, 1067, 721, 706. SOR: $[\alpha]_D^{25}$ −12.20° (c = 1.0, DMSO).

10-Deacetylbaccatin III-13-O-[(4S,5R)-4-Phenyl-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-5-carboxylate] (10)

To the acetic acid (1.25 L, 10 vol) taken in a round-bottom flask, compound **9** (125 g, 0.104 mol) was added and stirred for 5–10 min, and subsequently methanol (1.25 L, 10 vol) was added to the solution. Zinc dust (54.3 g, 0.83 mol) was charged to the solution, heated to 55–60 °C, and stirred for 30 min. After completion of the reaction, it was filtered and washed with methanol (125 mL). The filtrate was slowly added to 8.75 L of water over a period of 5–10 min, and then the suspension was stirred for 1 h at 25–30 °C. The white solid precipitate was filtered and washed with water (250 mL). The solid was dissolved in ethyl acetate (1.25 L) and washed with water (250 mL) and saturated sodium bicarbonate solution (250 mL). The organic layer was concentrated under vacuum at 45–50 °C to a minimum volume (500 mL) and crystallized with *n*-heptane (2.5 L) to afford title compound **10** (76.6 g, yield: 86.7%, purity: 94% by HPLC).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 [s, 3H, C-17H$_3$), 1.08 (s, 3H, C-16H$_3$), 1.08 (s, 9H, -C($\underline{CH_3}$)$_3$ of Boc], 1.52 (s, 3H, C-19H$_3$), 1.63 [m, 1H, C-6H$_a$], 1.65 [s, 3H, C(C$\underline{H_3}$)$_2$), 1.74 (s, 3H, C(C$\underline{H_3}$)$_2$], 1.77 (s, 3H, Ac), 1.82 (s, 3H, C-18H$_3$), 2.07 (m, 1H, C-14H$_a$), 2.25 (m, 1H, C-6H$_b$), 2.26 (m, 1H, C-14H$_b$), 3.71 (d, 1H, $J = 6.6$ Hz, C-3H), 3.97 (d, 1H, $J = 8.1$ Hz, C-20H$_a$), 4.02 (d, 1H, $J = 8.1$ Hz, C-20H$_b$), 4.06 (m, 1H, C-7H), 4.59 (d, 1H, $J = 6.5$ Hz, C-2′H), 4.69 (s, 1H, C-1 OH, D_2O exchangeable), 4.86 (dd, 1H, $J = 9.2$, 2.0 Hz, C-5H), 4.96 (br, 1H, C-10 OH, D_2O exchangeable), 5.0 (br, 1H, C-7 OH, D_2O exchangeable), 5.05 (br, 1H, C-3′H), 5.13 (br, 1H, C-10H), 5.45 (d, 1H, $J = 7.1$ Hz, C-2), 6.08 (t, 1H, $J = 9.2$ Hz, C-13H), 7.36 (m, 2H, m-Ph-H), 7.41 (m, 2H, o-Ph-H), 7.43 (m, 1H, p-Ph-H), 7.60 (t, 2H, $J = 7.8$ Hz, m-Bz-H), 7.70 (t, 1H, $J = 7.2$ Hz, p-Bz-H), 7.98 (d, 2H, $J = 6.94$ Hz, o-Bz-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 9.72 (C-19), 13.80 (C-18), 20.74 (C-17), 21.16 (CH_3 of Ac), 25.80 [CH_3 of C($\underline{C}H_3$)$_2$], 26.51 [CH_3 of C($\underline{C}H_3$)$_2$[, 26.51 [C-16), 27.58 (-C($\underline{CH_3}$)$_3$ of Boc], 35.44 (C-14), 36.46 (C-6), 42.95 (C-15), 45.99 (C-3), 57.05 (C-8),

63.57 (C-3′), 70.74 (C-7), 71.78 (C-13), 73.74 (C-10), 74.74 (C-2), 75.39 (C-20), 76.85 (C-1), 79.46 (C-*t*-Bu), 80.24 (C-4), 80.24 (C-2′), 83.75 (C-5), 95.82 [C-C(CH_3)$_2$], 126.60 (C-m-Ph), 127.49 (C-p-Ph), 128.58 (C-o-Ph), 128.58 (C-m-Bz), 129.55 (C-o-Bz), 130.06 (C1-Bz), 133.33 (C-p-Bz), 135.69 (C-11), 136.93 (C-12), 140.49 (C-1-Ph), 150.82 (C=O of carbamate), 165.16 (C=O of Bz), 169.74 (C=O of C-1′), 169.74 (C=O of Ac), 209.42 (C-9). HRMS (EI) m/z calcd. for $C_{46}H_{58}NO_{14}$ $(M+H)^+$: : 848.3857; found: 848.3846. IR (KBr) cm^{-1}: 3499, 2983, 1706, 1369, 1246, 1138, 1071, 773, 709. SOR: $[\alpha]_D^{25}$ −50.2° (c = 1.0, MeOH).

Docetaxel (1)

Compound **10** (50 g, 0.0589 mol) was added to the formic acid (500 mL) taken in a round-bottom flask at 15–20 °C and stirred for 1–1.5 h. After completion of the reaction, the formic acid was distilled under high vacuum below 20 °C to obtain a syrupy mass of compound **11**. Water (0.5 L) was added to the mass and washed with ethyl acetate (0.5 L × 2) and separated. To the aq. layer, ethyl acetate (0.5 L) was added and stirred for 5 min. The pH of the reaction mixture was adjusted to 7.5–8.5 using solid sodium bicarbonate (~54 g, 0.64 mol), and di-tert-butyldicarbonate (19.3 g, 0.091 mol) was added immediately in a single lot at 25–30 °C and stirred for 1–1.5 h. After completion of the reaction, the organic layer was separated, washed with water (0.5 L), and distilled to minimum volume. Acetonitrile (100 mL) was added to the mass, followed by diisopropyl ether (0.75 L), and stirred for 1 h. The obtained solid was filtered and dried for 2 h to afford the crude title compound **1** (30 g, yield: 63%, purity: > 96% by HPLC). Thus obtained, crude compound **1** was purified by column chromatography using 230 to 400-mesh silica gel and 40–50% ethyl acetate / petroleum ether as eluent. The fractions were distilled to minimum and precipitated with petroleum ether to obtain 22 g of docetaxel (**1**) with purity > 99% by HPLC. The column of purified docetaxel was optionally crystallized in acetone / disioproyl ether to afford anhydrous crystalline docetaxel (**1**) with purity > 99.8% by HPLC.

Spectral Data of N-De-*tert*-butoxycarbonyl Docetaxel (11)

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 3H, C-17H_3), 1.02 (s, 3H, C-16H_3), 1.51 (s, 3H, C-19H_3), 1.64 (m, 1H, C-6H_a), 1.68 (m, 1H, C-14H_a), 1.74 (s, 3H, C-18H_3), 1.82 (m, 1H, C-14H_b), 1.85 (br, 1H, C-1 OH, D_2O exchangeable), 2.11 (s, 3H, Ac), 2.26 (m, 1H, C-6H_b), 3.3 (br, 1H, C-2′ OH, D_2O exchangeable), 3.4 (br, 1H, C-7 OH, D_2O exchangeable), 3.64 (d, 1H, J = 6.5 Hz, C-3H), 3.99 (m, 1H, C-20H_a), 4.02 (m, 1H, C-3′H), 4.04 (m, 1H, C-20H_b), 4.05 (m, 1H, C-7H), 4.08 (m, 1H, C-2′H), 4.53 (br, 1H, C-10 OH, D_2O exchangeable), 4.89 (d, 1H, J = 10 Hz, C-5H), 4.95 (br, 2H, NH_2, D_2O exchangeable), 5.08 (s, 1H, C-10H), 5.40 (d, 1H, J = 7.5 Hz, C-2), 5.87 (t, 1H, J = 8.5 Hz, C-13H), 7.20 (m, 1H, p-Ph-H), 7.36 (m, 2H, m- Ph-H), 7.39 (m, 2H, o-Ph-H), 7.63 (t, 2H, J = 7.5 Hz, m-Bz-H), 7.72 (t, 1H, J = 7.5 Hz, p-Bz-H), 7.95 (d, 2H, J = 6.5 Hz, o-Bz-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 9.81 (C-19), 13.71 (C-18), 20.81 (C-17), 22.34 (CH_3 of Ac), 26.54 (C-16), 35.04 (C-14), 36.47 (C-6), 42.91 (C-15), 45.97 (C-3), 57.00 (C-8), 58.08 (C-3′), 69.75 (C-13), 70.80 (C-7), 73.79 (C-10), 74.77 (C-2), 75.43 (C-20), 76.87 (C-1), 76.87 (C-2′), 80.29 (C-4), 83.73 (C-5), 127.47 (C-p-Ph), 128.04 (C-m-Ph),

128.32 (C-o-Ph), 128.69 (C-m-Bz), 129.53 (C-o-Bz), 130.06 (C-1 Bz), 133.44 (C-p-Bz), 135.91 (C-12), 136.81 (C-11), 139.41 (C-1 Ph), 165.22 (C=O of Bz), 169.67 (C=O of Ac), 172.62 (C=O of C1′), 209.38 (C-9). IR (KBr) cm^{-1}: 3422, 2984, 2955, 1722, 1583, 1452, 1371, 1271, 1244, 1177, 1107, 1070, 985, 773, 708. HRMS (EI) m/z calcd. for $C_{38}H_{46}NO_{12}$ $(M+H)^+$: 708.3555; found: 708.3018. SOR: $[\alpha]_D^{25}$ −50.1°(c = 1.0, MeOH).

Spectral Data of Docetaxel (1)

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (s, 3H, C-17H_3), 1.24 (s, 3H, C-16H_3), 1.34 [s, 9H, -C(CH_3)$_3$ of Boc], 1.52 (br, 1H, C-7 OH, D_2O exchangeable), 1.65 (br, 1H, C-1 OH, D_2O exchangeable), 1.76 (s, 3H, C-19H_3), 1.81 (m, 1H, C-6H_a), 1.86 (s, 3H, C-18H_3), 2.27 (m, 2H, C-14H_2), 2.37 (s, 3H, Ac), 2.58 (m, 1H, C-6H_b), 3.37 (br s, 1H, C-2′ OH, D_2O exchangeable), 3.91 (d, 1H, J = 7.5 Hz, C-3H), 4.19 (d, 1H, J = 8.5 Hz, C-20H_a), 4.21 (br, 1H, C-10 OH, D_2O exchangeable), 4.23 (dd, 1H, J = 11.0, 6.5 Hz, C-7H), 4.31 (d, 1H, J = 8.5 Hz, C-20H_b), 4.62 (br s, 1H, C-2′H), 4.94 (dd, 1H, J = 11.5, 2.0 Hz, C-5H), 5.20 (s, 1H, C-10H), 5.26 (br d, 1H, J = 6.0 Hz, Hz, C-3′H), 5.43 (d, 1H, J = 9.0 Hz, NH, D_2O exchangeable), 5.68 (d, 1H, J = 8.5 Hz, C-2H), 6.21 (t, 1H, J = 8.5 Hz, C-13H), 7.32 (m, 1H, p-Ph-H), 7.38 (m, 2H, m-Ph-H), 7.39 (m, 2H, o-Ph-H), 7.50 (t, 2H, J = 8.0 Hz, m-Bz-H), 7.61 (t, 1H, J = 8.0 Hz, p-Bz-H), 8.10 (d, 2H, J = 8.0 Hz, o-Bz-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 9.84 (C-19), 14.32 (C-18), 20.64 (C-17), 22.53 (CH_3 of Ac), 26.44 (C-16), 28.18 [-C(CH_3)$_3$ of Boc], 35.71 (C-14), 36.88 (C-6), 43.06 (C-15), 46.47 (C-3), 56.22 (C-3′), 57.67 (C-8), 71.92 (C-7), 72.37 (C-13), 73.69 (C-2′), 74.53 (C-10), 74.87 (C-2), 76.61 (C-20), 78.78 (C-1), 80.19 [-C(CH_3)$_3$ of Boc)], 81.10 (C-4), 84.21 (C-5), 126.75 (C-m-Ph), 128.0 (C-p-Ph), 128.67 (C-m-Bz), 128.78 (C-o-Ph), 129.19 (C1-Bz), 130.14 (C-o-Bz), 133.66 (C-p-Bz), 135.95 (C-11), 138.43 (C-12), 138.43 (C-1Ph), 155.39 (C=O of carbamate), 166.99 (C=O of Bz), 170.31 (C=O of Ac), 172.70 (C=O of C-1′), 211.27 (C-9). IR (KBr) cm^{-1}: 3536, 3459, 3432, 2979, 2904, 1723, 1706, 1492, 1369, 1264, 1249, 1167, 1098, 1072, 710. HRMS (EI) m/z calcd. for $C_{43}H_{53}NO_{14}Na$ $(M+Na)^+$: 830.3364; found: 830.3383. SOR: $[\alpha]_D^{25}$ −40°(c = 1.0, MeOH); lit.[26] $[\alpha]_D^{25}$ −38.5 to −41.5°(c = 1.0, MeOH)

Preparation of Docetaxel Dimethylsulfoxide (DMSO) Single Crystal

About 1.0 g of docetaxel (**1**) was dissolved in 5 mL of dimethylsulfoxide (DMSO) and stirred for about 10 min. The solution was allowed to stand without disturbance at ambient conditions for slow evaporation. A few crystals were observed after 15 days, which were filtered carefully, collected and used for single-crystal x-ray diffraction.

Crystal Data of 1

$(C_{43}H_{53}NO_{14})\bullet(C_2H_6SO)$, M = 886.02, monoclinic, space group $P2_1$, a = 12.763(5) Å, b = 8.830(3) Å, c = 20.503(8) Å, β = 101.378(4)°, V = 2265.3(15) Å^3, T = 298 K, Z = 2, D_c = 1.299 g cm^{-3}, μ(Mo-Kα) = 0.14 mm^{-1}, 25105 reflections measured, 9322 unique reflections, 7561 observed reflections [I > 2.0σ(I)], R1_obs = 0.064, wR2_all = 0.101. CCDC 769072 contains the supplementary crystallographic

data for this article. These data can be obtained free of charge via http:\\www.ccdc.cam.ac.uk\conts\retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

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