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N-Methylation of the C3′ Amide of Taxanes: Synthesis of *N*-Methyltaxol C and *N*-Methylpaclitaxel

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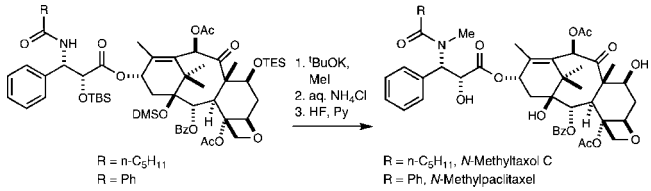

A method has been developed for the methylation of the C3′ amide of taxol C and paclitaxel. Taxol C and paclitaxel were sequentially silylated at the 2′, 7, and 1-hydroxyl groups with *tert*-butyldimethylsilyl chloride, triethylsilyl chloride, and dimethylsilyl chloride, respectively. Subsequent reaction with potassium *tert*-butoxide and methyl iodide provided the corresponding *N*-methylated taxane derivatives. Removal of the silyl protecting groups furnished *N*-methyltaxol C and *N*-methylpaclitaxel.

Tubulin-binding taxanes such as paclitaxel and docetaxel are important cancer chemotherapeutic agents. However, these drugs suffer from limitations such as poor aqueous solubility and oral bioavailability,[1,2] emerging drug resistance,[3] and the lack of blood−brain barrier permeability.[4] For these reasons, there is a continuous need for the development of novel taxanes that can overcome the limitations of the first-generation taxanes.[5]

Methods for producing taxane anticancer agents include isolation from the bark of *Taxus brevifolia* and other taxus species, plant tissue culture, and the semisynthesis of the taxanes using naturally occurring baccatin III and related analogues as building blocks for the diterpene part of the taxanes.[6]

Taxane anticancer agents that are isolated from natural sources and from cell culture production have to be separated from structurally closely related taxanes that represent impurities. Such impurities, if and when present, need to be characterized in New Drug Applications (NDA) to the FDA. Depending on the source of the natural taxane, one such impurity is *N*-methyltaxol C (Scheme 1). *N*-methyltaxol C was first reported by Ma et al. as a constituent of a cell culture of *T. baccata* in 0.00022% of the biomass and also from the roots of *Taxus x media* Rehd. cv Hicksii.[7,8] Later, 7-(β-xylosyl)-*N*-methyltaxol C was isolated from *T. yunnanensis*.[9] *N*-Methyltaxol C was found to possess similar activity in a tubulin assembly assay compared to paclitaxel.[7]

The presence of *N*-methyltaxol C as a potential impurity in clinically used taxanes, produced from natural sources and cell culture, and its low availability from natural sources, prompted us to investigate the synthesis of this compound via *N*-alkylation of the more readily available natural product taxol C. Although the C13 phenyl isoserinate side chain of paclitaxel has been the focus of intense structure−activity relationship investigations,[5] to the best of our knowledge, there are no reports involving *N*-alkylation studies at the C-3′ amide of the taxane C13 side chain.

In order to avoid undesirable reactions at the C2′ and C7 hydroxy groups of taxol C during the proposed *N*-alkylation studies, the prior protection of the above hydroxyl groups was necessary. Following a known protocol,[10] taxol C was converted to the corresponding 7-TES-2′-TBS derivative **1a** in high overall yield. Subsequent attempts to methylate the 3′-amide of 7-TES-2′-TBS-taxol C under a variety of conditions did not result in the formation of any *N*-alkylated product. Alkylation attempts were made using different bases such as NaH, LDA, NaHMDS, LiHMDS, and silver oxide (Ag_2O) and methylating agents MeI or dimethyl sulfate (Me_2SO_4). The two different solvents used in these attempts were THF and DMF. The above reactions were carried out in temperature ranges from −78 °C to room temperature.

In order to eliminate the possible interference of the (typically unreactive) free tertiary hydroxyl group at C1 during the attempted *N*-deprotonation/alkylation sequence, protection of the C1 hydroxyl group followed by *N*-alkylation studies of the resulting triprotected taxol C was next investigated. Therefore, the tertiary hydroxyl group at the C1-position of 7-TES-2′-TBS-taxol C was protected as its dimethylsilyl ether derivative **3** (Scheme 1).[11] Subsequent potassium *tert*-butoxide-assisted deprotonation at the amide functionality of **3**, followed by quenching of the resulting anion with excess methyl iodide led to the formation of the corresponding *N*-methyl derivative **5** in

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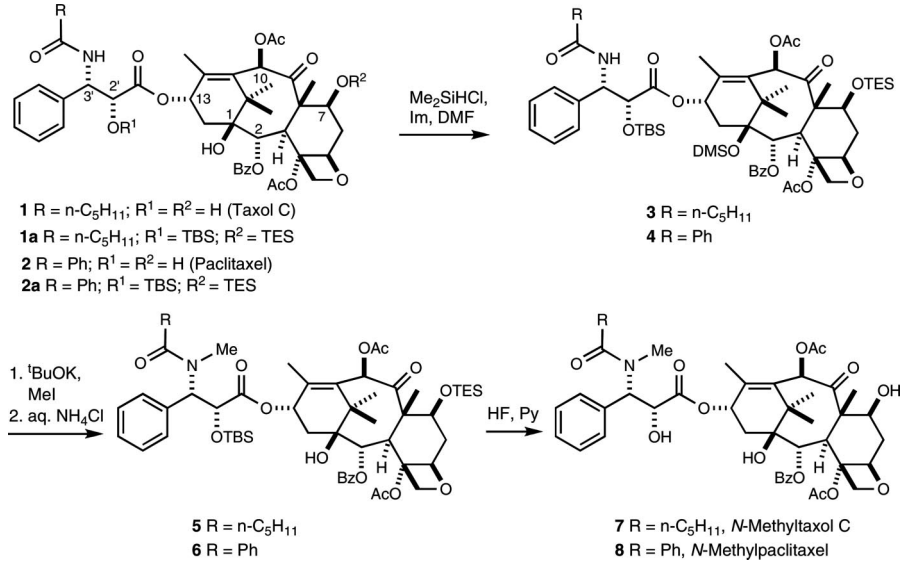
SCHEME 1. Synthesis of *N*-Methyltaxol C (7) and *N*-Methylpaclitaxel (8)



60%. Standard aqueous acidic workup of the above reaction mixture resulted in clean deprotection of the labile dimethylsilyl protecting group at C1, directly providing *N*-Me-7-TES-2′-TBS-taxol C (**5**). Simultaneous removal of the TBS and TES protecting groups with HF in pyridine completed the synthesis of *N*-methyltaxol C (**7**). Multiple gram quantities of *N*-methyltaxol C were easily synthesized using the above method. The optical rotation of our product was higher ($[\alpha]^{D}_{25}$ −61 ($CHCl_3$, *c* 0.27) than what has been reported for the natural product ($[\alpha]^{D}_{25}$ −53 ($CHCl_3$, *c* 1.0)[8] and $[\alpha]^{D}_{25}$ −16.5 (MeOH, *c* 0.103).[9] In addition, we found that the melting point of our product (146−148 °C, amorphous solid) was different from the reported melting points of 225−228 °C (dec from MeOAc/hexane)[8] and 134 °C (dec from MeOH). We therefore recrystallized a sample of *N*-methyltaxol C (**7**) from MeOAc/hexane and found the same melting point of 146−148 °C that we had observed for the amorphous material.

Having developed an efficient route to a 3′-*N*-methyl taxane, it was considered of interest to also extend the above method toward synthesizing the hitherto unreported *N*-methylated paclitaxel. Following the same procedure as described above, initial conversion of paclitaxel (**2**) to the corresponding trisilyl protected derivative **4**, followed by potassium *tert*-butoxide mediated deprotonation and subsequent *N*-methylation resulted in the formation of the desired 7-TES-2′-TBS-*N*-methylpaclitaxel derivative **6** (Scheme 1) in 40% yield (determined by ^{1}H NMR analysis) accompanied by 20% of 2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (**2a**), obtained from deprotection of the labile dimethylsilyl protecting group at C1 of unreacted intermediate **4**. We found that it was difficult to separate *N*-methylated **6** from **2a** by silica gel chromatography. Removal of the silyl protecting groups of a purified sample of **6** completed the synthesis of *N*-methylpaclitaxel (**8**).

In conclusion, a reaction protocol has been developed for the syntheses of 3′-*N*-methylated taxanes. During these studies, prior protection of the C1 tertiary hydroxyl group at the taxane core was found to be a critical requirement to achieve the desired alkylation. The new method is providing access to a new class of *N*-alkyltaxanes.

Experimental Section

2′-*tert*-Butyldimethylsilyl-7-triethylsilyltaxol C (1a). A solution of taxol C (3.39 g, 4 mmol), TBSCl (3.02 g, 20 mmol), imidazole (1.9 g, 28 mmol), and DMAP (25 mg, cat.) in anhydrous CH_2Cl_2 (125 mL) was stirred at room temperature for 18 h. The mixture was diluted via addition of anhydrous CH_2Cl_2 (125 mL) followed by addition of pyridine (2.4 mL, 30 mmol), DMAP (25 mg, cat.) and TESCl (3.4 mL, 20 mmol). The resulting mixture was stirred at room temperature for another 3 h and then quenched by the addition of water (50 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residual oily liquid on trituration with hexane afforded the pure product **1a** as a colorless solid (4 g, 93%): mp 130−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.28 and −0.09 (2s, 6H), 0.58−0.62 (m, 6H), 0.78 (s, 9H), 0.83 (t, J = 4.5 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 1.22−1.27 (m, 12H), 1.54−1.58 (m, 1H), 1.71 (s, 1H), 1.85 (s, 1H), 1.88−1.92 (m, 1H), 2.04 (s, 3H), 2.12−2.17 (m, 1H), 2.19 (s, 3H), 2.21−2.25 (m, 2H), 2.32−2.41 (m, 1H), 2.47−2.53 (m, 1H), 2.56 (s, 3H), 3.84 (d, J = 7.0 Hz, 1H), 4.20, 4.31 (ABq, J = 8.4 Hz, 2H), 4.48 (dd, J = 10.5, 6.6 Hz, 1H), 4.57 (d, J = 2.2 Hz, 1H), 4.95 (br d, J = 8.3 Hz, 1H), 5.56 (d, J = 9.5 Hz, 1H), 5.71 (d, J = 7.1 Hz, 1H), 6.27 (t, J = 8.9 Hz, 1H), 6.34 (d, J = 9.1 Hz, 1H), 6.47 (s, 1H), 7.25−7.61 (series of m, 8H), 8.12 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.7, 171.4, 170.2, 169.3, 167.1, 140.3, 138.5, 133.6, 130.3, 129.2, 128.8, 128.6, 127.8, 126.5, 84.2, 81.2, 78.9, 75.2, 74.97, 72.2, 58.4, 55.0, 46.7, 43.4, 36.6, 31.3, 26.6, 25.5, 25.4, 23.1, 22.3, 20.9, 18.2, 14.3, 13.9, 10.2, 6.8, 5.3, −5.4, −5.8. HRMS (FAB-POS) *m/e* calcd for $C_{58}H_{86}NO_{14}Si_2$ [M^+ + 1]: 1076.5587, found 1076.5607.

1-Dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol C (3). To an ice-cold solution of 2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol C (**1a**) (7.76 g, 7.22 mmol) and imidazole (3.44 g, 50.54 mmol) in DMF (70 mL) was added very slowly dimethylchlorsilane (4.01 mL, 36.09 mmol). The reaction mixture was allowed to warm to 20 °C and was stirred overnight. The reaction mixture was quenched with crushed ice, and extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo and the residue was charged onto a silica gel column. Elution with ethyl acetate/hexane (1:4) furnished 1-dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol-C (6.54 g, 80%) as a colorless solid: mp 116−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.28 (s, 3H), −0.24 (d, J = 2.8

Hz, 3H), −0.11 (s, 3H), 0.09 (d, J = 2.7 Hz, 3H), 0.64−0.50 (m, 6H), 0.77 (s, 9H), 0.88−0.79 (m, 2H), 0.93 (t, J = 7.9 Hz, 9H), 1.18 (s, 3H), 1.24 (s, 3H), 1.21−1.28 (m, 4H), 1.52−1.60 (m, 2H), 1.70 (s, 3H), 1.77 (s, 1H), 1.84−1.98 (m, 1H), 2.01 (s, 3H), 2.18 (s, 3H), 2.22 (t, J = 7.4 Hz, 2H), 2.35−2.55 (m, 3H), 2.57 (s, 3H), 3.84 (d, J = 7.0 Hz, 1H), 4.27 (s, 2H), 4.45 (dd, J = 10.6, 6.6 Hz, 1H), 4.52−4.62 (m, 2H), 4.94 (d with st, J = 7.9 Hz, 1H), 5.66 (d, J = 9.3 Hz, 1H), 5.77 (d, J = 7.0 Hz, 1H), 6.26 (t, J = 9.4 Hz, 1H), 6.31 (d, J = 9.3 Hz, 1H), 6.45 (s, 1H), 7.22−7.42 (series of m, 5H), 7.44−7.62 (m, 3H), 8.14 (d, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.58, 171.5, 170.3, 169.4, 165.6, 139.9, 138.5, 133.6, 133.4, 130.4, 130.1, 128.7, 127.9, 126.5, 84.4, 81.6, 81.4, 75.5, 75.4, 75.0, 72.3, 71.4, 58.4, 54. 9, 46.5, 44.4, 37.3, 36.5, 34.1, 31.4, 27.5, 25.6, 25.3, 23.2, 22.4, 22.2, 21.0, 18.3, 14.3, 13.9, 10.1, 6.8, 5.4, 0.5, −0.04, −5.4, −5.9; IR (KBr) 2956, 2133, 1728, 1684, 1493, 1370, 1245, 1114, 1067, 1025, 989, 904, 838, 809, 782, 745, 710, 618 cm^{-1}; HRMS (FAB-POS) *m/e* calcd for $C_{60}H_{92}NO_{14}Si_3$ [M$^+$ + 1]: 1134.5826, found 1134.5861.

***N*-Methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol C (5).** In a flame-dried RB flask, 1-dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilytaxol C (**2**) (5.3 g, 4.68 mmol) was placed under an argon blanket. THF (50 mL, dried over benzophenone ketyl) was added and cooled to −78 °C. Potassium *tert*-butoxide (7.02 mL, 7.02 mmol, 1.0 M solution in THF) was added very slowly and stirred for 30 min at −78 °C. Excess MeI (7.28 mL, 117 mmol) was added and stirred for an additional 2 h at −78 °C. The reaction mixture was warmed slowly to 0 °C over 1 h, and quenched with saturated NH_4Cl solution. The mixture was stirred at 20 °C for 30 min and extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was charged onto a silica gel column, and gradient elution with ethyl acetate/hexane (1:9 to 1:5) furnished *N*-methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol C (3.06 g, 60%): mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.52−0.62 (m, 6H), 0.84 (t, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.94 (t, J = 7.9 Hz, 9H), 1.19 (s, 3H), 1.22 (s, 3H), 1.20−1.32 (m, 4H), 1.52−1.62 (m, 2H), 1.70 (s, 3H), 1.64−1.76 (m, 3H), 1.82−2.00 (m, 3H), 2.17 (s, 3H), 2.32 (t, J = 7.6 Hz, 2H), 2.30−2.40 (m, 1H), 2.46 (s, 3H), 2.45−2.60 (m, 1H), 2.94 (s, 3H), 3.82 (d, J = 7.0 Hz, 1H), 4.18, 4.28(ABq, J = 8.3 Hz, 2H), 4.45 (dd, J = 10.4, 6.7 Hz, 1H), 4.95 (d, J = 8.3 Hz, 1H), 5.07 (br d, J = 5.1 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 6.15 (t, J = 8.8 Hz, 1H), 6.32 (br s, 1H), 6.41 (s, 1H), 7.25−7.39 (series of m, 5H), 7.48 (m, 2H), 7.60 (m, 1H), 8.12 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 202.1, 174.2, 171.8, 170.5, 169.3, 167.0, 140.7, 136.5, 133.6, 133.2, 130.3, 129.4, 128.7, 128.6, 128.1, 128.0, 84.4, 80.8, 78.8, 76.7, 75.2, 75.0, 73.5, 72.3, 71.1, 58.5, 46.7, 43.3, 37.3, 35.4, 33.8, 31.7, 26.5, 25.7, 24.8, 22.8, 22.5, 21.3, 20.9, 18.1, 14.2, 14.0, 10.1, 6.8, 5.4, −4.4, −5.2; IR (KBr) 3452, 2956, 1727, 1651, 1452, 1392, 1370, 1238, 1110, 1018, 987, 884, 837, 822, 780, 730, 709, 619 cm^{-1}; HRMS (FAB-POS) *m/e* calcd for $C_{59}H_{88}NO_{14}Si_2$ [M$^+$ + 1]: 1090.5743, found 1090.5726.

***N*-Methyltaxol C (7).** *N*-Methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol C (**4**) (5.50 g, 5.05 mmol) was dissolved in pyridine (35 mL) and cooled to 0 °C. Then, HF•pyridine (6 mL) was added very slowly, and the resulting mixture was stirred for 18 h at 20 °C. The reaction mixture was poured into a mixture of ethyl acetate (500 mL) and a saturated $NaHCO_3$ solution (100 mL). The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was charged onto a silica gel column. Elution with ethyl acetate/hexane (1:1) furnished *N*-methyltaxol C (4.20 g, 97%) as a colorless amorphous solid: mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−0.92 (m, 3H), 1.15 (s, 3H), 1.27 (s, 3H), 1.22−1.28 (m, 4H), 1.53−1.63 (m, 2H), 1.67 (s, 3H), 1.80−1.90 (m, 2H), 1.88 (s, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 2.25−2.42 (m, 4H), 2.48 (d, J = 4.0 Hz, 1H), 2.48−2.60 (m, 1H), 2.89 (s, 3H), 3.79 (d, J = 7.0 Hz, 1H), 4.16, 4.28 (ABq, J = 8.4 Hz, 2H), 4.35 (d, J = 8.0 Hz, 1H), 4.42 (m, 1H), 4.89 (dd, J = 8.0, 3.9 Hz, 1H), 4.93 (d, J = 9.5 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 5.76 (d, J = 3.5 Hz, 1H), 6.16 (t, J = 8.7 Hz, 1H), 6.30 (s, 1H), 7.30−7.45 (series of m, 5H), 7.48 (dd, J = 7.7, 7.7 Hz, 1H), 7.61 (dd, J = 7.3, 7.3 Hz, 2H), 8.10 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 175.1, 173.5, 171.2, 170.2, 166.8, 142.6, 136.6, 133.6, 132.8, 130.2, 129.3, 128.9, 128.6, 128.1, 84.4, 80.8, 78.9, 76.4, 75.7, 75.0, 72.7, 72.1, 72.0, 61.3, 58.5, 45.6, 43.2, 35.7, 35.6, 35.2, 34.0, 31.5, 26.7, 24.7, 22.4, 22.2, 21.9, 20.9, 14.8, 13.9, 9.6; IR (KBr) 3434, 2935, 1726, 1636, 1451, 1371, 1244, 1115, 1025, 982, 619 cm^{-1}; HRMS (FAB-POS) *m/e* calcd for $C_{47}H_{60}NO_{14}$ [M$^+$ + 1]: 862.4014, found 862.4027. $[\alpha]^D_{25}$ −61 ($CHCl_3$, *c* 0.27).

1-Dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (4). To an ice-cold solution of 2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel[10] (10.34 g, 9.57 mmol) and imidazole (4.55 g, 66.96 mmol) in DMF (90 mL) was added very slowly dimethylchlorosilane (5.31 mL, 47.83 mmol). The reaction mixture was allowed to warm to 20 °C and was stirred overnight, quenched with crushed ice, and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, and the residue was charged onto a silica gel column. Elution with ethyl acetate/hexane (1:4) furnished 1-dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (10.35 g, 95%) as a colorless solid: mp 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.44 (d, J = 2.8 Hz, 3H), −0.29 (s, 3H), −0.14 (d, J = 2.7 Hz, 3H), −0.03 (s, 3H), 0.50−0.60 (m, 6H), 0.77 (s, 9H), 0.93 (t, J = 7.9 Hz, 9H), 1.12 (s, 3H), 1.20 (s, 3H), 1.56−1.62 (m, 1H), 1.69 (s, 3H), 1.86−1.96 (m, 1H), 2.03 (s, 3H), 2.17 (s, 3H), 2.26−2.60 (series of m, 2H), 2.63 (s, 3H), 3.83 (d, J = 7.1 Hz, 1H), 4.26 (s, 2H), 4.33 (t, J = 2.8 Hz, 1H), 4.45 (dd, J = 10.6, 6.6 Hz, 1H), 4.70 (d, J = 2.3 Hz, 1H), 4.94 (d, J = 7.7 Hz, 1H), 5.73 (d, J = 7.1 Hz, 1H), 5.86 (dd, J = 9.3, 2.0 Hz, 1H), 6.30 (t, J = 8.7 Hz, 1H), 6.43 (s, 1H), 7.02 (d, J = 9.3 Hz, 1H), 7.27−7.64 (series of m, 11H), 7.74 (d, J = 7.1 Hz, 2H), 8.15 (d, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 171.4, 170.4, 169.4, 166.8, 165.6, 139.8, 138.1, 134.0, 133.6, 133.3, 131.7, 130.4, 130.1, 128.7, 128.6, 127.9, 127.1, 126.5, 84.4, 81.6, 81.3, 76.7, 75.5, 75.3, 74.9, 72.3, 71.1, 58.7, 55.4, 46.5, 44.4, 37.3, 34.2, 27.5, 25.5, 23.2, 22.3, 20.9, 18.2, 14.3, 10.1, 6.8, 5.3, 0.3, −0.3, −5.2, −5.9; IR (KBr) 3330, 2951, 2877, 2125, 1757, 1724, 1665, 1515, 1483, 1454, 1368, 1262, 1178, 1112, 1067, 986, 911, 899, 837, 797, 780, 747, 714, 698, 619 cm^{-1}; HRMS (FAB-POS) *m/e* calcd for $C_{61}H_{86}NO_{14}Si_3$ [M$^+$ + H]: 1140.5356, found 1140.5403.

***N*-Methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (6).** To a cooled (−78 °C) solution of 1-dimethylsilyl-2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (**4**) (9.0 g, 7.9 mmol) in anhydrous THF (100 mL, dried over benzophenone ketyl) was slowly added potassium *tert*-butoxide (11.85 mL, 11.85 mmol, 1.0 M solution in THF) and allowed to stir for 30 min at the same temperature. Excess of MeI (12.3 mL, 197.5 mmol) was added, and the reaction mixture was stirred for an additional 2 h at −78 °C. The reaction mixture was slowly warmed to 0 °C over 1 h and quenched with a saturated aq NH_4Cl solution (100 mL). The mixture was stirred at 20 °C for 30 min and extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was charged onto a silica gel column. Elution with ethyl acetate/hexane (1:9) furnished a 5.20 g mixture (60% total yield of a 2:1 mixture as determined by ^{1}H NMR) of the desired *N*-methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilyltaxol (**6**, 40% by ^{1}H NMR analysis) along with 2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (**2a**, 20% by ^{1}H NMR analysis). A sample of pure *N*-methyl derivative **6** was obtained by additional flash silica gel chromatographic purification [long column, eluted with ethyl acetate/hexanes (1:10)] and used for analytical purposes and in the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.22 (s, 3H), 0.50−0.68 (m, 6H), 0.94 (s, 9H), 0.95 (t, J = 7.9 Hz, 9H),

1.17 (s, 3H), 1.21 (s, 3H), 1.70 (s, 3H), 1.72 (s, 3H), 1.80 (s, 1H), 1.84−1.98 (m, 2H), 2.17 (s, 3H), 2.31−2.41 (m, 1H), 2.50 (s, 3H), 2.48−2.60 (m, 1H), 2.87 (s, 3H), 3.82 (d, J = 7.0 Hz, 1H), 4.19, 4.29 (ABq, J = 8.3 Hz, 2H), 4.46 (dd, J = 10.4, 6.7 Hz, 1H), 4.95 (d, J = 8.7 Hz, 1H), 5.24 (d, J = 5.1 Hz, 1H), 5.67 (d, J = 7.0 Hz, 1H), 6.21 (t, J = 8.9 Hz, 1H), 6.38 (br s, 1H), 6.41 (s, 1H), 7.26−7.54 (series of m, 12H), 7.59 (dd, J = 7.4, 7.4 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 172.6, 171.9, 170.5, 169.3, 166.9, 140.6, 136.6, 135.7, 133.6, 133.3, 130.2, 129.6, 129.4, 128.8, 128.6, 128.5, 128.3, 126.7, 84.4, 80.9, 78.7, 76.7, 75.2, 74.9, 73.4, 72.3, 71.1, 58.5, 46.7, 43.2, 37.3, 35.5, 26.5, 25.7, 22.8, 21.2, 20.9, 18.2, 14.2, 10.1, 6.8, 5.4, −4.4, −5.0; HRMS (FAB-POS) *m*/*e* calcd for $C_{60}H_{82}NO_{14}Si_2$ [M^+ + H]: 1096.5274, found 1096.5255.

***N*-Methylpaclitaxel (8).** *N*-Methyl-2′-*tert*-butyldimethylsilyl-7-triethylsilylpaclitaxel (**6**) (30 mg, 0.03 mmol) was dissolved in pyridine (1.0 mL) and cooled to 0 °C. To this solution, HF·pyridine (6 drops) was added slowly, and the resulting mixture was stirred for 24 h at 20 °C. The reaction mixture was poured into an ethyl acetate (10 mL) and saturated $NaHCO_3$ solution (2 mL) mixture. The layers were separated, and the organic layer was washed with a saturated $NaHCO_3$ solution, water, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was charged onto a silica gel column. Elution with ethyl acetate/hexane (1:1) furnished *N*-methylpaclitaxel (20 mg, 85%) as a colorless amorphous solid: mp 186−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.27 (s, 3H), 1.68 (s, 3H), 1.82−1.92 (m, 2H), 1.89 (s, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 2.34−2.42 (m, 2H), 2.49−2.62 (m, 2H), 2.84 (s, 3H), 3.82 (d, J = 6.8 Hz, 1H), 4.18, 4.3 (ABq, J = 8.4 Hz, 2H), 4.40−4.46 (m, 2H), 4.95 (d, J = 9.4 Hz, 1H), 5.02 (dd, J = 6.8, 3.8 Hz, 1H), 5.69 (d, J = 6.9 Hz, 1H), 5.90 (s, 1H), 6.25 (t, J = 8.4 Hz, 1H), 6.30 (s, 1H), 7.37−7.57 (series of m, 12H), 7.62 (dd, J = 7.2, 7.0 Hz, 1H), 8.10 (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 173.6, 173.4, 171.4, 170.3, 166.9, 142.7, 136.2, 136.0, 133.7, 132.9, 130.3, 130.1, 129.3, 129.1, 128.7, 128.7, 128.5, 126.9, 84.1, 81.0, 79.1, 76.5, 75.4, 75.1, 72.9, 72.2, 61.5, 58.6, 45.7, 43.3, 37.6, 35.9, 35.6, 26.9, 22.4, 22.0, 21.0, 15.0, 9.6; IR (KBr) 3467, 2940, 1731, 1617, 1451, 1371, 1239, 1114, 1070, 1025, 708, 613 cm^{-1}; HRMS (FAB-POS) *m*/*e* calcd for $C_{48}H_{54}NO_{14}$ [M^+ + H]: 868.3544, found 868.3566. $[\alpha]^D_{20}$ −42 ($CHCl_3$, *c* 0.12).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, methods for UPLC analysis and HPLC purification, and UPLC traces for compounds **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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