Synthesis and Biological Evaluation of 2-*epi*-Paclitaxel

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Studies both in our laboratories[1] and in those of others[2] have demonstrated convincingly that the presence of an aroyl substituent at the C-2 position of paclitaxel (**1**) is necessary for full biological activity and that the nature of the aroyl substituent can cause profound changes (both positive and negative) in the extent of this activity. The reasons for this requirement of a 2-aroyl group are not fully understood, although one intriguing hypothesis is based on the observation that a "hydrophobic collapse" of the C-3′ phenyl, the C-2 benzoyl, and the C-4 acetate occurs in polar solvents.[3] It is proposed that the occurrence of this collapse is related to the bioactivity of paclitaxel, but it is not clear why there is an apparent linkage between bioactivity and hydrophobic collapse.

Although a number of different aroyl groups have been substituted for the benzoyl group at the C-2 position of paclitaxel,[1,2] all the substitutions to date have retained the original 2α stereochemistry of paclitaxel. The synthesis of 2-*epi*-paclitaxel would provide further insight into the structural and stereochemical requirements for activity, and we herein report such a synthesis.

The synthesis of 2-*epi*-paclitaxel proceeded through the key 2-debenzoylpaclitaxel intermediate **3**. Various methods for the preparation of 2-debenzoylpaclitaxels have been reported,[1b,2] including reduction with Red-Al,[2e] electroreduction,[2g] and treatment with potassium *tert*-butoxide.[2h] In our original report,[1b] we described the use of phase transfer catalysis, but we have subsequently developed a more convenient procedure involving the reaction of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-paclitaxel (**2**) with Triton B (40% trimethylbenzylammonium hydroxide in MeOH) in CH_2Cl_2 at −78 to −10 °C. This procedure gave the 2-debenzoyl derivative **3** in 75% yield. Oxidation of **3** with tetrapropylammonium perruthenate(VII)/*N*-methylmorpholine *N*-oxide (TPAP/NMO) in CH_2Cl_2 at room temperature then gave a good yield of the 2-oxo compound **4** (Scheme 1). Compound **4** was characterized primarily on the basis of its ^{1}H and ^{13}C-NMR spectra; in its ^{1}H-NMR spectrum the signal for H-2 was missing and H-3 appeared as a singlet at 4.12 ppm, while in its ^{13}C-NMR spectrum the resonance for C-2 appeared at 199.9 ppm.

Reduction of **4** with $NaBH_4$ in THF/MeOH at room temperature gave exclusive formation of a single new compound **5** more polar than the 2-debenzoyl compound **3**. The ^{1}H-NMR spectrum of **5** showed the resonance of H-2α as a doublet (J = 2.4Hz; coupling to the OH proton) at 3.62 ppm and that of H-3α as a singlet at 3.41 ppm, consistent with a dihedral angle of approximately 90° between H-2α and H-3α. The ^{13}C-NMR spectrum of **5** included a resonance for C-2 at 83.1 ppm in place of the carbonyl carbon of **4**. The stereochemistry of C-2 was confirmed by a NOESY spectrum, which showed correlations between H-2α and H-3α and H-14α. The possibility that epimerization had occurred at C-3 prior to reduction was eliminated by the observation of NOESY correlations in **5** or its benzoate **6** between H-3α and H-7α and H_3-18; *no* correlation was observed between H-3α and H_3-19.

The stereoselectivity of the reduction can be explained by changes in the conformation of the eight-membered B ring that favored attack of hydride ion from the less hindered α-face of the molecule. The low energy conformation of **4** as obtained from the Chem3D program is shown in Figure 1 and indicates that the expected complexation of borohydride with the C-1 OH group would favor attack from the bottom face of the molecule, and not from the top face as might be expected. Attack from the top face is also hindered by the C-17 and the C-19 methyl groups, which project over the approach vector for β-attack; although the bottom face is also hindered, the hindering groups on this face can rotate away from the approach vector for α-attack.

Benzoylation of **5** under standard conditions (benzoic acid/DCC/PP) gave the protected 2-*epi*-paclitaxel **6**, and deprotection of **6** with HF/pyridine furnished 2-*epi*-paclitaxel **7**. The ^{1}H-NMR spectrum of **7** was similar to that of paclitaxel, except that the signals for H-2α and H-3α appeared as singlets at 5.41 and 3.69 ppm, respectively. A NOESY spectrum of **7** showed correlations between H-2α and H-20α, H-20β, H-3α, and H-14α, as well as between H-3α and H-7α; this latter correlation excluded the possibility that epimerization of H-3α of ketone **4** had taken place. An additional prominent correlation was observed between the *ortho* protons of the C-2β benzoyloxy group and the C-17 and C-19 methyl protons. All these correlations confirm the structural assignment of **7** as 2-*epi*-paclitaxel.

Bioassay of **7** in a tubulin-assembly assay and an HCT 116 cytotoxicity assay indicated that the compound was inactive in both assays. This result thus provides further evidence for the importance of the nature and stereochemistry of the 2-aroyl group for the bioactivity of paclitaxel.

Experimental Section

General Methods. All chemicals were procured from Aldrich Chemical Co. and were used without further purification. All anhydrous reactions were performed under argon. THF was dried over sodium/benzophenone. All reactions were monitored

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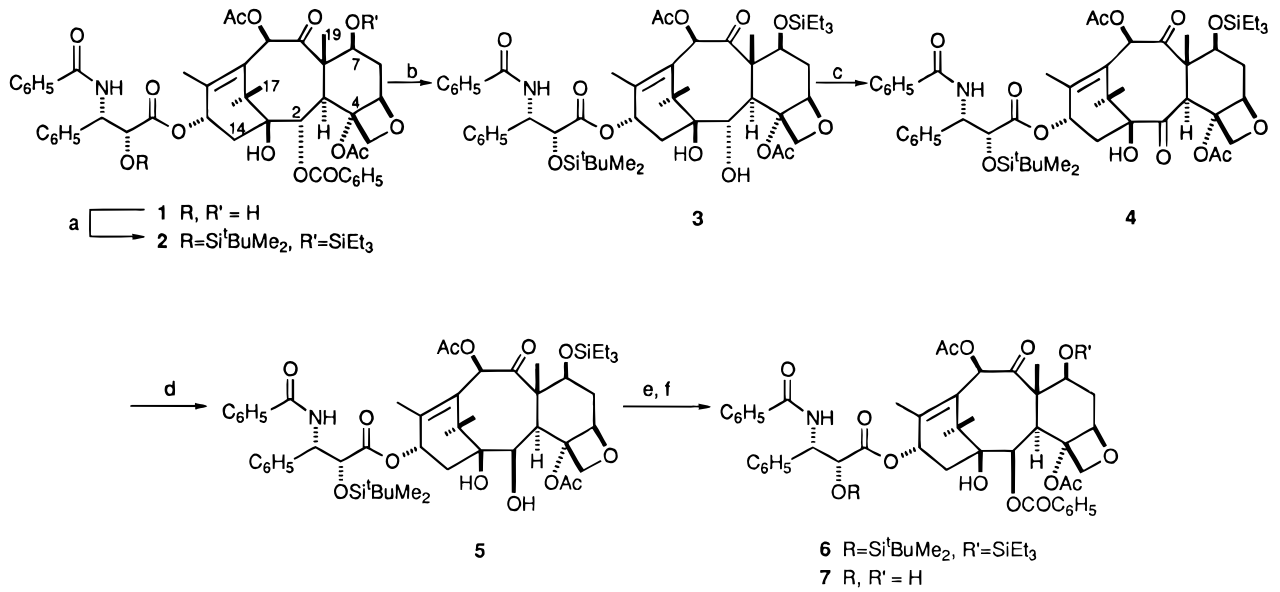
(2) (a) Chen, S.-H.; Wei, J.-M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205−3206. (b) Chen, S.-H.; Huang, S.; Gao, Q.; Golik, J.; Farina, V. *J. Org. Chem.* **1994**, *59*, 1475−1484. (c) Boge, T. C.; Himes, R. H.; Vander Velde, D. G.; Georg, G. I. *J. Med. Chem.* **1994**, *37*, 3337−3343. (d) Georg, G. I.; Ali, S. M.; Boge, T. C.; Datta, A.; Falborg, L.; Himes, R. H. *Tetrahedron Lett.* **1994**, *35*, 8931−8934. (e) Chen, S.-H.; Farina, V.; Wei, J.-M.; Long, B.; Fairchild, C.; Mamber, S. W.; Kadow, J. F.; Vyas, D.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 479−482. (f) Nicolaou, K. C.; Couladouras, E. A.; Nantermet, P. G.; Renaud, J.; Guy, R. K.; Wrasidlo, W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1581−1583. (g) Pulicani, J.-P.; Bézard, D.; Bourzat, J.-D.; Bouchard, H.; Zucco, M.; Deprez, D.; Commerçon, A. *Tetrahedron Lett.* **1994**, *32*, 9717−9720. (h) Georg, G. I.; Ali, S. M.; Boge, T. C.; Datta, A.; Falborg, L.; Park, H.; Mejillano, M.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 259−264.

(3) (a) Paloma, L. G.; Guy, R. K.; Wrasidlo, W.; Nicolaou, K. C. *Chem. Biol.* **1994**, *1*, 107−112. (b) Vander Velde, D. G.; Georg, G. I.; Grunewald, G. L.; Gunn, C. W.; Mitscher, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 11650−11651. (c) Dubois, J.; Guénard, D.; Guéritte-Voegelein, F.; Guerida, N.; Potier, P.; Gillet, B.; Beloeil, J.-C. *Tetrahedron* **1993**, *49*, 6533−6544. (d) Williams, H. J.; Scott, A. I.; Dieden, R. A.; Swindell, C. S.; Chirlian, L. E.; Francl, M. M.; Heerding, J. M.; Krauss, N. E. *Tetrahedron* **1993**, *49*, 6545−6560.

0022-3263/96/1961-0799$12.00/0

Scheme 1[a]



[a] Key: (a) ^{t}BuMe$_2$SiCl, imidazole, DMF, 60 °C, 1 h, and then Et$_3$SiCl, imidazole, rt; (b) Triton B, CH_2Cl_2, −78 to −10 °C; (c) TPAP, NMO, CH_2Cl_2, rt, 3 h; (d) $NaBH_4$, THF, MeOH, rt, 1 h; (e) PhCOOH, DCC, pyrrolidinopyridine, toluene, 60 °C; (f) HF/pyridine, THF, rt, 2 h.

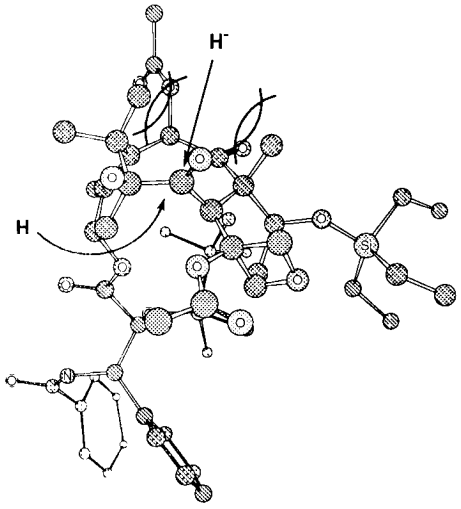


Figure 1.

by TLC (silica gel, GF) and analyzed with UV light and developed with vanillin spray. FTIR spectra were recorded on a Nicolet Impact 400 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at 270 and 400 MHz for proton spectra and assigned primarily by comparison of chemical shifts and coupling constants with those of related compounds and by appropriate 2D NMR techniques. Coupling constants are reported in Hz. ^{13}C NMR spectra were assigned with the aid of HETCOR and DEPT spectra. Some ^{1}H NMR spectra showed the presence of traces of ethyl acetate; paclitaxel and its derivative retain ethyl acetate very tightly, and it cannot be removed completely even on prolonged treatment in vacuo at 38 °C. FAB mass spectra and exact mass measurements were obtained at the Nebraska Center for Mass Spectrometry. Biological evaluation was carried out at the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (2). To a stirred solution of paclitaxel **1** (270 mg, 0.316 mmol) in 2.5 mL of anhydrous DMF were added imidazole (107 mg, 1.58 mmol) and *tert*-butyldimethylsilyl chloride (238 mg, 1.58 mmol). The solution was heated at 60 °C for 2 h. The mixture was cooled to room temperature, and additional amounts of imidazole (107 mg, 1.58 mmol) and triethylsilyl chloride (150 μL, 1.34 mmol) were added. After being stirred at room temperature for 1 h, the reaction mixture was diluted with ethyl acetate and washed successively with water and brine. Drying of the organic layer over Na_2SO_4 and evaporation under reduced pressure yielded crude material, which was purified by column chromatography over silica gel (EtOAc:hexanes, 1:2) to give 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (**2**) (325 mg, 95%) as an amorphous solid: mp 130−131 °C; ^{1}H-NMR δ −0.20 (s, 3H), −0.02 (s, 3H), 0.62 (q, J = 7.8, 6H), 0.79 (s, 9H), 0.92 (t, J = 7.8, 9H), 1.17 (s, 3H), 1.21 (s, 3H), 1.70 (s, 3H), 2.02 (bs, 3H), 2.16 (s, 3H), 2.40 (m, 1H), 2.55 (m, 1H), 2.58 (s, 3H), 3.83 (d, J = 7.0, 1H), 4.19 (d, J = 8.3, 1H), 4.30 (d, J = 8.3, 1H), 4.48 (dd, J = 9.4,6.6, 1H), 4.67 (d, J = 2.1, 1H), 4.94 (bd, J = 8.8, 1H), 5.69 (d, J = 7.0, 1H), 5.74 (dd, J = 9.0,2.1, 1H), 6.26 (bt, 1H), 6.45 (s, 1H), 7.10 (d, J = 8.9, 1H), 7.30−7.60 (m, 11H), 7.74 (dd, J = 8.5,1.5, 2H), 8.13 (dd, J = 8.5,1.4, 2H). ^{13}C-NMR δ −5.86, −5.20, 5.27, 6.73, 10.11, 14.24, 18.11, 20.85, 21.50, 23.10, 25.49, 26.54, 35.55, 37.21, 43.31, 46.64, 55.63, 58.39, 71.36, 72.19, 74.92, 74.95, 75.10, 76.55, 78.82, 81.17, 84.22, 126.40, 126.97, 127.92, 128.68, 128.70, 128.71, 129.19, 130.20, 131.76, 133.60, 133.66, 134.03, 138.26, 140.14, 166.88, 167.03, 169.28, 170.13, 171.38, 201.67; MS m/z (rel int) $[M + Na]^+$ 1104 (5), 705 (3) 422 (40), 354 (12), 105 (100); HRMS calcd for $C_{59}H_{79}NO_{14}Si_2Na$ $[M + Na]^+$ m/z 1104.4937, found 1104.4936.

2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)-paclitaxel (3). To a solution of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (**2**) (110.4 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (5mL) was added benzyltrimethylammonium hydroxide (100 mL, 40% w/w solution in methanol) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min, and the reaction flask was transferred to a −10 °C bath (diethylene glycol, dry ice) and stirred at −10 °C for 10−15 min. During this time, the progress of the reaction was monitored by TLC, which indicated the formation of a more polar compound. The mixture was then diluted with cold CH_2Cl_2 (−78 °C, 10 mL) and quenched with 5 mL of 0.1 N HCl. The organic layer was washed successively with water, dilute $NaHCO_3$, and brine and dried over Na_2SO_4. Concentration under reduced pressure gave crude residue, which was purified by preparative TLC (silica gel, 1000 μm, EtOAc:hexanes, 2:3) to yield compound **3** (73.0 mg, 75%) and starting material (11.0 mg, 10%). Compound **3**: mp 133−35 °C; ^{1}H-NMR δ −0.28 (s, 3H), −0.04 (s, 3H), 0.57 (q, J = 7.8, 6H), 0.80 (s, 9H), 0.92 (t, J = 7.8, 9H), 1.07 (s, 3H), 1.15 (s, 3H), 1.62 (s, 3H), 1.96 (bs, 3H), 2.14 (s, 3H), 2.40 (m, 1H), 2.51 (m, 1H), 2.42 (s, 3H), 2.79 (d, J = 5.9, 1H), 3.46 (d, J = 7.0, 1H), 3.92 (t, J = 6.3, 1H), 4.41 (dd, J = 9.4, 6.6, 1H), 4.60 (d, J = 1.6, 1H), 4.63 (bs, 2H), 4.95 (bd, J = 8.6, 1H), 5.67 (dd, J = 9.2, 1.6, 1H), 6.24 (bt, 1H), 6.37 (s, 1H), 7.05 (d, J = 9.2, 1H), 7.30−7.54 (m, 8H), 7.74 (dd, J = 8.3, 1.5, 2H); MS m/z (rel int) $[M + Na]^+$ 1000 (3), 400 (22)

354 (84), 105 (100); HRMS calcd for $C_{52}H_{75}NO_{13}Si_2Na$ [M + Na]$^+$ *m/z* 1000.4675, found 1000.4632.

Oxidation of 2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel (3) with TPAP/NMO. To a solution of 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel (**3**) (49.0 mg, 0.05 mmol) in dry CH_2Cl_2 were added tetrapropylammonium perruthenate (5.0 mg, 0.014 mmol, catalytic) and *N*-methylmorpholine *N*-oxide (23.0 mg, 0.196 mmol). The mixture was stirred at room temperature for 3 h. The mixture then diluted with CH_2Cl_2 and filtered through a short column of Celite and silica gel. The crude compound thus obtained was purified by column chromatography over silica gel to give compound **4** as a colorless glassy solid (42.0 mg, 86%): FTIR ($CHCl_3$) 1751, 1740, 1736, 1724, 1700, 1663 cm^{-1}; ^{1}H NMR δ −0.32 (s, 3H), −0.04 (s, 3H), 0.57 (q, *J* = 7.8, 6H), 0.80 (s, 9H), 0.92 (t, *J* = 7.8, 9H), 1.20 (s, 3H), 1.58 (s, 3H), 1.94 (m, 1H), 1.94 (s, 3H), 1.99 (bs, 3H), 2.03 (dd, *J* = 9.2,15.2, 1H), 2.14 (s, 3H), 2.31 (dd, *J* = 8.8, 15.2, 1H), 2.43 (s, 3H), 2.52 (m, 1H), 4.12 (s, 1H), 4.35 (dd, *J* = 6.8, 10.4, 1H), 4.43 (d, *J* = 8.8, 1H), 4.62 (d, *J* = 1.6, 1H), 4.69 (s, 1H), 4.96 (bd, *J* = 8.0, 1H), 5.46 (d, *J* = 8.8, 1H), 5.69 (dd, *J* = 1.6, 9.2, 1H), 6.35 (bt, *J* = 8.0, 1H), 6.45 (s, 1H), 7.02 (d, *J* = 9.2, 1H), 7.24−7.54 (m, 8H), 7.75 (dd, *J* = 8.3, 1.5, 2H); ^{13}C-NMR δ −5.88, −5.19, 5.20, 6.74, 10.68, 14.53, 18.11, 20.76, 22.64, 22.96, 25.18, 25.50, 34.51, 38.03, 43.00, 49.75, 55.38, 58.33, 70.62, 72.25, 74.81, 75.21, 75.77, 82.15, 82.77, 83.36, 126.35, 127.00, 127.93, 128.70, 128.80, 131.86, 134.04, 134.64, 138.22, 140.50, 166.89, 169.18, 170.38, 171.14, 199.94, 210.94; MS *m/z* (rel int) [M + Na]$^+$ 998.4 (40), 599 (14) 422 (100), 354 (21), 172 (17); HRMS calcd for $C_{52}H_{73}NO_{13}Si_2Na$ [M + Na]$^+$*m/z* 998.4518, found 998.4523.

Reduction of 2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-2-oxo-7-(triethylsilyl)paclitaxel (4) with Sodium Borohydride. To a solution of the 2-oxo compound **4** (35.0 mg, 0.036 mmol) in THF (1.0 mL) and MeOH (100 μL) was added $NaBH_4$ (6.0 mg, 0.15 mmol), and the mixture was stirred at room temperature for 1 h. TLC analysis indicated the formation of a more polar spot (R_f 0.2 in EtOAc:hexane, 40:60). The mixture was diluted with EtOAc (5 mL) and washed successively with water, and the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material obtained as syrup was purified by preparative TLC (silica gel, 500 μm, EtOAc:hexane, 40:60, double elution) to yield 2-*epi*-2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel (**5**) (27.5 mg, 78%) as an amorphous white solid: ^{1}H-NMR δ −0.28 (s, 3H), −0.02 (s, 3H), 0.57 (q, *J* = 7.8, 6H), 0.79 (s, 9H), 0.92 (t, *J* = 7.8, 9H), 1.05 (s, 3H), 1.27 (s, 3H), 1.68 (dd, *J* = 9.2, 15.6, 1H), 1.78 (s, 3H), 1.93 (bs, 3H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (m, 1H), 2.51 (m, 1H), 3.14 (s, 1H), 3.41 (s, 1H), 3.46 (bs, 1H), 3.62 (d, *J* = 2.4, 1H), 4.40 (dd, *J* = 6.4, 10.0, 1H), 4.49 (d, *J* = 7.2, 1H), 4.60 (d, *J* = 1.6, 1H), 4.99 (m, 2H), 5.64 (dd, *J* = 9.2, 1.6, 1H), 6.25 (bt, *J* = 7.6, 1H), 6.35 (s, 1H), 7.07 (d, *J* = 9.2, 1H), 7.30−7.51 (m, 8H), 7.71 (dd, *J* = 6.8, 1.6, 2H); ^{13}C-NMR δ −5.83, −5.16, 5.30, 6.76, 12.84, 14.06, 18.11, 20.88, 22.56, 22.86, 25.49, 26.08, 37.56, 40.49, 43.72, 44.25, 55.32, 58.28, 71.02, 73.07, 74.77, 75.05, 75.14, 76.75, 81.77, 83.12, 83.61, 126.33, 126.95, 128.02, 128.72, 128.87, 132.01, 133.77, 135.31, 137.97, 138.64, 167.42, 169.41, 169.00, 171.14, 202.15; MS *m/z* (rel int) [M + Li]$^+$ 984 (28), 585 (10), 406 (100), 177 (16); HRMS calcd for $C_{52}H_{75}NO_{13}Si_2Li$ [M + Li]$^+$ *m/z* 984.4937, found 984.4934.

Benzoylation of 2-*epi*-2′-(*tert*-Butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel (5). To a mixture of the title compound **5** (22.0 mg, 0.022 mmol), dicyclohexylcarbodiimide (45.3 mg, 0.22 mmol), benzoic acid (24.1 mg, 0.20 mmol), and pyrrolidinopyridine (1.0 mg, catalytic) was added dry toluene (0.1 mL), and the resulting heterogenous mixture was stirred at 80 °C for 8 h. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a pad of Celite and silica gel to remove a white solid. The filtrate was concentrated and purified by preparative TLC (silica gel, 500 μm, EtOAc:hexane, 1:4, 3-fold elution) to yield compound **6** (20.0 mg, 82%): ^{1}H-NMR δ −0.28 (s, 3H), −0.02 (s, 3H), 0.58 (q, *J* = 7.8, 6H), 0.80 (s, 9H), 0.93 (t, *J* = 7.8, 9H), 1.14 (s, 3H), 1.42 (s, 3H), 1.71 (s, 3H), 1.99 (bs, 3H), 2.19 (s, 3H), 2.40 (dd, *J* = 9.2, 15.4, 1H), 2.50 (s, 3H), 3.73 (s, 1H), 4.25 (d, *J* = 8.0), 4.47 (dd, *J* = 6.4, 10.4, 1H), 4.49 (d, *J* = 8.0, 1H), 4.64 (d, *J* = 2.0, 1H), 5.01 (bd, *J* = 8.4, 1H), 5.36 (s, 1H), 5.72 (dd, *J* = 9.2, 2.0, 1H), 6.25 (bt, *J* = 9.2, 1H), 6.49 (s, 1H), 7.05 (d, *J* = 9.2, 1H), 7.30−7.60 (m, 8H), 7.78 (dd, *J* = 1.6, 7.2, 2H), 8.01 (dd, *J* = 1.6, 7.2, 2H); ^{13}C-NMR δ −5.84, −5.18, 5.35, 6.73, 12.46, 14.29, 18.11, 20.85, 22.98, 24.91, 25.50, 26.22, 37.56, 40.83, 43.34, 44.24, 55.38, 58.35, 71.00, 73.25, 74.59, 75.05, 75.27, 77.83, 80.41, 81.55, 83.33, 126.41, 127.00, 127.92, 128.68, 128.78, 128.97, 130.17, 131.83, 133.62, 134.09, 134.72, 138.19, 139.77, 166.93, 167.00, 169.35, 169.92, 171.31, 202.71; MS *m/z* (rel int) [M + Na]$^+$ 1104 (11); HRMS calcd for $C_{59}H_{79}NO_{14}Si_2Na$ [M + Na]$^+$ *m/z* 1104.4937, found 1104.4928.

2-*epi*-Paclitaxel (7). To a solution of 2-*epi*-2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (**6**) (18.0 mg, 0.017 mmol) in dry THF (0.5 mL) was added HF/pyridine (0.1 mL) in a Teflon vial. The mixture was stirred at room temperature for 2 h. The mixture was then diluted with EtOAc (10 mL) and washed throughly with dilute $NaHCO_3$, dilute HCl, H_2O, and finally brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to yield crude product, which was purified by preparative TLC (silica gel, 500 μm, EtOAc:hexane, 1:1, double elution) to yield compound **7** (11.4 mg, 80%): FTIR (Nujol) 1739, 1735, 1718, 1458, 1376, cm^{-1}; ^{1}H-NMR δ 1.19 (s, 3H), 1.36 (s, 3H), 1.68 (s, 3H), 1.77 (bs, 3H), 1.87 (m, 2H), 2.21 (s, 1H), 2.25 (s, 3H), 2.27 (s, 3H), 2.52 (m, 1H), 2.56 (d, *J* = 4.4, 1H), 2.68 (dd, *J* = 9.2, 15.2, 1H), 3.69 (s, 1H), 3.71 (d, *J* = 5.2, 1H), 4.24 (d, *J* = 8.4, 1H), 4.39 (m, 1H), 4.47 (d, *J* = 8.4, 1H), 4.77 (dd, *J* = 2.4, 5.2, 1H), 4.99 (d, *J* = 8.4, 1H), 5.41 (s, 1H), 5.76 (dd, *J* = 1.6, 9.2, 1H), 6.20 (bt, *J* = 8.0, 1H), 6.32 (s, 1H), 7.02 (d, *J* = 9.2, 1H), 7.35−7.62 (m, 8H), 7.75 (dd, *J* = 7.2, 1.5, 2H), 7.99 (dd, *J* = 7.2, 1.2, 2H); ^{13}C-NMR δ 11.92, 14.88, 20.85, 22.48, 23.14, 26.41, 36.03, 41.19, 42.62, 43.97, 54.76, 58.44, 72.03, 72.91, 73.30, 74.61, 75.75, 77.71, 80.23, 81.55, 83.42, 127.03, 127.06, 128.33, 128.72, 128.78, 128.85, 128.98, 130.10, 131.99, 133.58, 133.74, 134.38, 137.96, 141.25, 166.92, 167.12, 170.18, 171.17, 172.60, 204.25; MS *m/z* (rel int) [M + Li]$^+$ 860 (40), 669 (57), 281 (41), 221 (65), 147 (100); HRMS calcd for $C_{47}H_{51}NO_{14}Li$ [M + Li]$^+$ *m/z* 860.3469, found 860.3458.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **4**−**7**, NOESY spectra of compounds **5** and **7,** and a listing of ^{1}H-NMR peak assignments of compounds **2**−**7** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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