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Synthesis of C-3′ Methyl Taxotere (Docetaxel)

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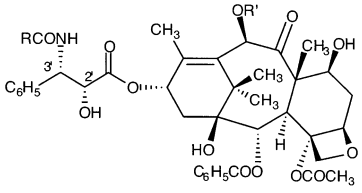
Received September 19, 2002

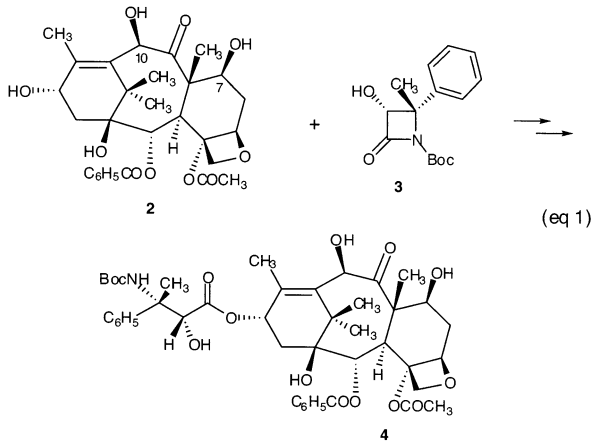
Abstract: Protected (3*R*,4*S*)-*N*-Boc-3-hydroxy-4-methyl-4-phenylazetidin-2-one has been synthesized stereoselectively and used to esterify protected 10-desacetylbaccatin III to give, following removal of the protecting groups, novel C-3′ methyl taxotere (docetaxel).

Taxol (paclitaxel, **1a**), found naturally in different species of *Taxus*, and taxotere (docetaxel, **1b**), a semi-synthetic analogue first prepared at ICSN in France, are remarkable broad-spectrum cancer chemotherapeutic agents that act by stabilizing microtubules, thus thwarting mitosis.[1]



1a, R = C_6H_5 ; R' = CH_3CO (Taxol)
b, R = $(CH_3)_3CO$; R' = H (Taxotere)

The success of these two worldwide-marketed compounds has been accompanied by a major search for analogues with improved properties (inter alia: simpler structures, higher water solubility, increased activity, less tendency to induce multi-drug resistance). We have previously reported[2] the synthesis of C-2′ methyl taxotere and the favorable effect of this methyl substituent on the biological activity of the molecule in microtubule stabilization and KB and KB-VI cytotoxicity assays. In this paper, the synthesis of C-3′ methyl taxotere (**4**) from protected 10-desacetylbaccatin III (**2**) and protected (3*R*,4*S*)-*N*-Boc-3-hydroxy-4-methyl-4-phenylazetidin-2-one (**3**) is described (eq 1).[3] The latter has been prepared in enantiopure form through a novel Staudinger ketene-ketimine cycloaddition reaction.



(eq 1)

β-Lactams have proven highly popular as side-chain equivalents for the synthesis of taxol and taxotere, as well as numerous analogues,[1] and therefore, extension of this methodology for the synthesis of C-3′ methyl taxotere was envisaged. The planned preparation of the appropriate β-lactam was, however, uncertain since it required a relatively unusual ketene-ketimine pairing in a [2 + 2] Staudinger cycloaddition; moreover, it assumed that the cycloaddition would proceed with a useful level of asymmetric induction with a readily cleavable imine chiral auxiliary, which was unprecedented for the creation of a C-4 quaternary stereogenic center.[4,5]

Our successful route to the desired β-lactam, inspired in part by the work of Commerçon[6] and Lawrence,[7] began with commercially available (*S*)-(−)-1-(4-methoxyphenyl)-ethylamine,[8,9] which was smoothly converted with acetophenone and *p*-toluenesulfonic acid in refluxing tolu-

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(1) For reviews on the occurrence, biological properties, and syntheses of taxol, taxotere, and congeners, see: (a) Nicolaou, K. C.; Dai W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (b) Georg, G. I.; Ali, S. M.; Zygmunt, J.; Jayasinghe, L. R. *Exp. Opin. Ther. Pat.* **1994**, *4*, 109−120. (c) *The Chemistry and Pharmacology of Taxol and Its Derivatives*; Farina, V., Ed.; Elsevier: Amsterdam, 1995. (d) *Taxol: Science and Applications*, Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995. (e) Jenkins, P. *Chem. Britain* **1996**, *32* (11), 43−46. (f) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726−734. (g) Kingston, D. G. I. *J. Chem. Soc., Chem. Commun.* **2001**, 867−880.

(2) Denis, J.-N.; Fkyerat, A.; Gimbert, Y.; Coutterez, C.; Mantellier, P.; Jost, S.; Greene, A. E. *J. Chem Soc., Perkin Trans. 1* **1995**, 1811−1815. See also: Génisson, Y.; Massardier, C.; Gautier-Luneau, I.; Greene, A. E. *J. Chem Soc., Perkin Trans. 1* **1996**, 2869−2872. Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495−6498. Ojima, I.; Wang, T.; Delaloge, F. *Tetrahedron Lett.* **1998**, *39*, 3663−3666. Barboni, L.; Lambertucci, C.; Ballini, R.; Appendino, G.; Bombardelli, E. *Tetrahedron Lett.* **1998**, *39*, 7177−7180.

(3) In view of the large number of diverse taxol and taxotere derivatives published to date, it is surprising that this is apparently the first example of substitution at C-3′.

(4) (a) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; pp 295−368. (b) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Román, P.; Luque, A.; Server-Carrió, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070−2079. (c) Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235.

(5) For general reviews on asymmetric methods to create quaternary centers and use of these methods in natural product synthesis, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401 and references therein.

(6) Bourzat, J. D.; Commerçon, A. *Tetrahedron Lett.* **1993**, *34*, 6049−6052.

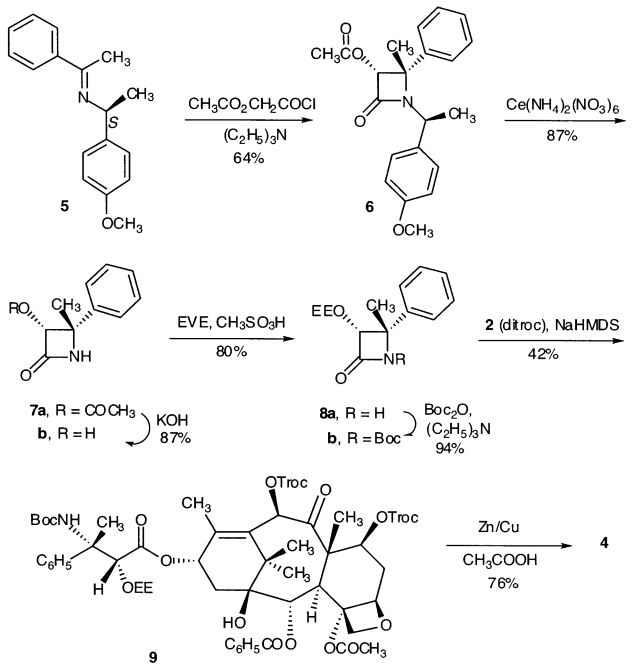
(7) (a) Brown, S.; Jordan, A. M.; Lawrence, N. J.; Pritchard, R. G.; McGown, A. T. *Tetrahedron Lett.***1998**, *39*, 3559−3562. (b) See also: Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem Soc., Perkin Trans. 1* **2001**, 3106−3111.

(8) Lancaster Synthesis, Bischheim-Strasbourg, France.

(9) Our earlier efforts with 1-phenylethylamine and 1-(2,6-dichlorophenyl)ethylamine were unsuccessful: the β-lactam resulting from the former could not be cleanly freed of the α-methylbenzyl group and the acetophenone imine derived from the latter proved a poor ketene partner in the Staudinger reaction.

10.1021/jo026460n CCC: $22.00
Published on Web 11/22/2002

SCHEME 1



ene to the known[10] imine derivative **5** (Scheme 1). The Staudinger reaction[4] of this imine with acetoxyacetyl chloride and triethylamine in dichloromethane produced in high yield a separable 70:30 mixture[11] of the 2*S*,3*R* and the 2*R*,3*S* diastereomers, respectively, to the exclusion of the 2 other possible isomers.[12,13] That the major isomer was in fact the 2*S*,3*R* (**6**) was established by X-ray diffraction analysis of the corresponding alcohol,[14,15] obtained by saponification.

Selective oxidative cleavage of the exocyclic nitrogen-benzylic carbon bond could be cleanly effected by using cerium ammonium nitrate (CAN) in aqueous acetonitrile to provide in 87% yield the enantiopure β-lactam **7a**. This material was next treated with potassium hydroxide in aqueous THF to obtain the corresponding alcohol **7b** (87% yield), which was converted into the ethoxyethyl (EE) derivative **8a** with ethyl vinyl ether and a catalytic amount of methanesulfonic acid in THF (80% yield). The β-lactam **8b** for the upcoming esterification was easily prepared from **8a** in 94% yield by treatment with Boc anhydride in the presence of triethylamine and DMAP.

The esterification of the 7,10-ditroc derivative[16] of 10-desacetylbaccatin III (**2**) with β-lactam **8b** to give ester **9** proved particularly challenging, undoubtedly due to the additional steric impediment present in **8b**, but was finally achieved in moderate yield with sodium hexamethyldisilazide according to the Ojima protocol.[17] Triple deprotection of this ester with zinc−copper couple in acetic acid[16] then afforded C-3′ methyl taxotere (**4**) in 76% yield following silica gel purification.

C-3′ methyl taxotere at 10 and 20 μM concentrations displayed no activity in microtubule stabilization assays (taxotere at 5 μM = 100%). This surprising result indicates that the C-3′ methyl may act to destabilize certain favorable hydrophobically collapsed conformations, but caveats have been sounded on this type of interpretation.[1f,g]

In summary, a Staudinger reaction has been used in the preparation of the first example of a C-3′-substituted taxol or taxotere derivative. While the biological results with this derivative are disappointing, the present work does serve to broaden the scope of the Staudinger reaction by demonstrating it is possible to access valuable[4b,5] enantiopure 4,4-disubstituted β-lactams through the use of imines with cleavable chiral controllers.

Experimental Section

The reaction mixture was generally poured into water, and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhydrous Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium-benzophenone and pentane, dichloromethane, pyridine, and triethylamine were distilled from calcium hydride.

***N*-[(1*S*)-1-(4-Methoxyphenyl)ethyl]-*N*-[(1*E*)-1-phenylethylidene]amine (5).**[10] A solution of 4.00 g (26.5 mmol) of (*S*)-(−)-1-(4-methoxyphenyl)ethylamine, 3.20 g (26.6 mmol) of acetophenone, and 0.015 g (0.08 mmol) of *p*-toluenesulfonic acid in 50 mL of toluene was stirred at reflux with removal of water for 72 h. The cooled reaction mixture was treated with 4 mL of an aqueous solution of saturated Na_2CO_3 and then extracted with ether, which was washed with brine, dried over Na_2SO_4, and filtered. Removal of the solvents and the small excess of acetophenone under reduced pressure left 6.60 g of essentially pure imine **5**. The analytical sample was prepared by evaporative distillation (ca. 130 °C, 0.1 Torr) of a small amount of this material: mp 43−45 °C; $[\alpha]^{26}_D$ +39.4 (*c* 1.0, $CHCl_3$); IR 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, J = 6.5 Hz, 3 H), 2.14 (s, 3 H), 3.66 (s, 3 H), 4.67 (q, J = 6.5 Hz, 1 H), 6.74−7.70 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.9, 25.5, 55.7, 59.6, 114.2, 127.2, 128.0, 128.5, 129.7, 138.9, 142.0, 158.6, 163.6.

(2*S*,3*R*)-1-[(1*S*)-1(4-Methoxyphenyl)ethyl]-2-methyl-4-oxo-2-phenylazetidin-3-yl Acetate (6). To a stirred solution of 4.80 g (19.0 mmol) of the above imine **5** and 6.80 mL (4.94 g, 48.8 mmol) of triethylamine in 60 mL of dichloromethane at 0 °C was added dropwise 2.80 g (20.5 mmol) of acetoxyacetyl chloride, and stirring was continued for 3 h at 0 °C and 12 h at 20 °C. Water was then added, and the crude reaction product was isolated with dichloromethane in the usual way and purified by

(10) Gauthrie, R. D.; Hedrick, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 2971−2977.

(11) For comparison, the imine from benzaldehyde and 1-phenylethylamine with acetoxyacetyl chloride has been reported to give diastereomeric ratios of 60:40 and 75:25 (60 and 74% yields).[6,7a]

(12) For a recent discussion of the stereochemical outcome of the Staudinger reaction, see: Arrieta, A.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 5869−5876. See also ref 4a,c.

(13) In THF, the ratio was higher, but the yield was considerably lower (83:17, 43%). Solvent effects on the ratio of diastereomers in the Staudinger reaction have previous been noted. See, for example, ref 7a.

(14) Crystal data for $C_{19}NO_3H_{21}$: orthorhombic, $P2_12_12_1$, a = 8.787(2) Å, b = 10.580(1) Å, c = 21.090(3) Å, V = 1960.8(5) Å^3, Z = 4, d_{calcd} = 1.197 mg/m^3, F(000) = 752, θ range 2.10−72°, 2229 measured reflections, 2229 independent reflections, $R(1)$ [$I > 1.5\sigma(I)$] = 0.044, wR2 [all data] = 0.0468, GoF (all data) = 1.887.

(15) The minor isomer was assigned the alternative "cis" configuration (2*R*, 3*S*) from X-ray diffraction analysis. Crystal data for $C_{21}NO_4H_{23}$: monoclinic, $P2_1$, a = 7.2889(7) Å, b = 7.5705(6) Å, c = 15.566(2) Å, β = 96.4(4)°, V = 853.6(5) Å^3, Z = 2, d_{calcd} = 1.211 mg/m^3, F(000) = 332, θ range 2.63−30°, 10 043 measured reflections, 4544 [R(int) = 0.09] independent reflections, R(1) [$I > 3\sigma(I)$] = 0.0496, wR2 [all data] = 0.0664, GoF (all data) = 1.903.

(16) Sénilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Seances Acad. Sci., Ser. 2* **1981**, *293*, 501−503 (troc = 2,2,2-trichloroethoxycarbonyl).

(17) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149−4152.

medium-pressure chromatography on silica gel with 5−10% ethyl acetate in pentane to afford 1.90 g (28%) of the minor diastereomer, followed by 4.30 g (64%) of the major diastereomer **6**: $[\alpha]^{25}_D$ −15.2 (*c* 1.0, $CHCl_3$); IR 3012, 1752, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3 H), 1.54 (d, J = 7.2 Hz, 3 H), 1.76 (s, 3 H), 3.70 (s, 3 H), 4.40 (q, J = 7.2 Hz, 1 H), 5.23 (s, 1 H), 6.72−7.24 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3, 21.3, 22.6, 54.1, 55.8, 68.3, 83.4, 114.4, 128.3, 128.4, 128.5, 129.3, 134.0, 137.7, 159.6, 164.6, 170.0. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.45; H, 6.57; N, 4.03.

(3*R*,4*S*)-3-Hydroxy-4-methyl-4-phenyl-1-[(1*S*)-1-phenylethyl]azetidin-2-one (6′) (6, OH Replaces CH_3CO_2). A solution of 1.48 g (4.19 mmol) of acetate **6** in 245 mL of THF was treated with 25 mL (25 mmol) of 1 M aqueous potassium hydroxide and then stirred for 12 h at 20 °C. The crude product was isolated with ethyl acetate in the usual manner and purified by dry silca gel chromatography with 50% ethyl acetate in hexane to afford 1.15 g (88%) of the corresponding alcohol **6′** as a white solid: mp 193−195; $[\alpha]^{25}_D$ +141.2 (*c* 1.0, $CHCl_3$); IR 3282, 1730 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 1.48 (d, J = 7.0 Hz, 3 H), 3.29 (s, 3 H), 3.73 (s, 3 H), 4.41 (q, J = 7.0 Hz, 1 H), 4.52 (d, J = 6.8 Hz, 1 H), 5.81 (d, J = 6.8 Hz, 1 H), 6.86−7.38 (m, 9 H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$) δ 22.4, 23.3, 53.2, 55.9, 69.2, 84.3, 114.4, 127.5, 128.2, 128.3, 129.2, 135.9, 140.8, 159.0, 169.0. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.56; H, 6.76; N, 4.55.

(2*S*,3*R*)-2-Methyl-4-oxo-2-phenylazetidin-3-yl Acetate (7a). A solution of 580 mg (1.64 mmol) of acetate **6** in 35 mL of 3:2 water−acetonitrile at 0 °C was treated with 2.70 g (4.92 mmol) of cerium ammonium nitrate and then stirred for 4 h at this temperature. The crude product was isolated with ethyl acetate in the usual way and purified by dry silica gel chromatography with 40% ethyl acetate in pentane to give 314 mg (87%) of lactam **7a** as a yellow oil: $[\alpha]^{25}_D$ −14.5 (*c* 1.0, $CHCl_3$); IR 3265, 1787, 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3 H), 1.90 (s, 3 H), 5.52 (s, 1 H), 7.34 (s, 5 H), 7.62 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3, 25.7, 64.2, 83.4, 126.8, 128.3, 128.6, 139.1, 165.3, 167.0. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 6.07; N, 6.27.

(3*R*,4*S*)-3-Hydroxy-4-methyl-4-phenylazetidin-2-one (7b). A solution of 395 mg (1.80 mmol) of acetate **7a** in 20 mL of THF was treated with 3.5 mL (3.5 mmol) of 1 M aqueous potassium hydroxide and then stirred for 12 h at 20 °C. The crude product was isolated with ethyl acetate in the usual way to afford 277 mg (87%) of alcohol **7b** as a white solid: mp 182 °C; $[\alpha]^{25}_D$ +15.3 (*c* 1.0, $CHCl_3$); IR 3278, 1744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3 H), 4.69 (s, 1 H), 6.78 (s, 1 H), 7.34−7.42 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.5, 66.3, 84.6, 126.9, 128.4, 129.1, 164.2. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.31; H, 6.26; N, 7.90.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-methyl-4-phenylazetidin-2-one (8a). To a solution of 100 mg (0.56 mmol) of alcohol **7b** in 8.0 mL of THF at 0 °C was added 0.125 mL (94 mg, 1.31 mmol) of ethyl vinyl ether and a catalytic amount of methanesulfonic acid. The reaction mixture was stirred for 6 h, whereupon the crude product was isolated with ethyl acetate in the normal way and purified by dry silica gel (pretreated with 2.5% triethylamine, v/v) chromatography with 30% ethyl acetate in pentane to afford 112 mg (80%) of acetal **8a** as a yellow oil: $[\alpha]^{25}_D$ +56.7 (*c* 1.0, $CHCl_3$); IR 3273, 1763 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 1.08 (m, 6 H), 1.77 (s, 3 H), 3.35 (m, 2 H), 4.69 (m, 2 H), 7.31 (s, 5 H). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.02; H, 7.70; N, 5.43.

***tert*-Butyl (2*S*,3*R*)-3-(1-Ethoxyethoxy)-2-methyl-4-oxo-2-phenylazetidine-1-carboxylate (8b).** To a solution of 110 mg (0.44 mmol) of acetal **8a**, 0.400 mL (290 mg, 2.87 mmol) of triethylamine, 450 mg (2.06 mmmol) of di-*tert*-butyl dicarbonate, and a catalytic amount of DMAP in 4.0 mL of ethyl acetate was stirred for 36 h. The reaction mixture was then processed with ethyl acetate in the usual way and the crude product was purified by dry silica gel (pretreated with 2.5% triethylamine v/v) chromatography with 30% ethyl acetate in pentane to give 145 mg (94%) of acetal **8b** as a yellow oil: $[\alpha]^{25}_D$ +71.3 (*c* 1.0, $CHCl_3$); IR 1812, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93−1.09 (m, 6 H), 1.32 (s, 9 H), 1.92 (s, 3 H), 3.16−3.65 (m, 3 H), 4.47−4.75 (m, 1 H), 7.30 (s, 5 H). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.53; H, 7.86; N, 4.13.

2′-*O*-Ethoxyethyl-3′-methyl-7,10-ditroc Taxotere (9). To a solution of 51 mg (0.057 mmol) of 7,10-ditroc-10-deacetylbaccatin III in 0.105 mL of THF at −50 °C was added dropwise a solution of 1 M NaHMDS in THF (0.063 mL, 0.063 mmol). The reaction mixture was stirred for 0.5 h while the temperature was allowed to reach −35 °C at which time a solution of 30 mg (0.086 mmol) of β-lactam **8b** was added. The reaction mixture was allowed to warm to 0 °C over 0.5 h and was then processed with ethyl acetate in the usual way. The crude product was purified by dry silica gel (pretreated with 2.5% triethylamine v/v) chromatography with 20% ethyl acetate in pentane to give 30 mg (42%) of ester **9** as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.07−1.29 (m, 8 H), 1.52 (m, 3 H), 1.75 (m, 3 H), 1.84 (m, 5 H), 1.91 (s, 2 H), 2.24 (s, 1.5 H), 2.31 (s, 1.5 H), 2.51 (m, 1 H), 3.22−3.53 (m, 1 H), 3.74 (m, 1 H), 4.06 (m,1 H), 4.22 (m, 2 H), 4.50 (m, 1 H), 4.69 (s, 2 H), 4.84 (m, 2 H), 5.41−5.65 (m, 2 H), 5.91 (br s, 1 H), 6.12 (d, J = 4.7 Hz, 1 H), 7.11−8.09 (m, 10 H); mass spectrum (ES^+), m/z 1266 $(M + Na)^+$.

3′-Methyl Taxotere (4). A mixture of 30 mg (0.024 mmol) of ester **9** and 240 mg (ca. 3.7 mmol) of Zn/Cu couple in 3.0 mL of 1:1 methanol-acetic acid was stirred for 1.5 h at 65 °C. The reaction mixture was then processed with ethyl acetate in the normal manner and the crude product was purified by preparative silica gel TLC with 5% methanol in dichloromethane to give 15 mg (76%) of 3′-methyl taxotere (**4**) as a white amorphous solid: $[\alpha]^{25}_D$ −30.4 (*c* 1.0, $CHCl_3$); IR 3436, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.42 (s, 9 H), 1.67−2.04 (m, 12 H), 2.28 (s, 3 H), 2.56 (m, 1 H), 3.83 (d, J = 6.6 Hz, 1 H), 4.14−4.30 (m, 3 H), 4.62 (br s, 1 H), 4.92 (d, J = 8.8 Hz, 2 H), 5.16 (s, 1 H), 5.52 (m, 1 H), 5.64 (d, J = 6.9 Hz, 1 H), 5.97 (m, 1 H), 7.38 (m, 5 H), 7.51 (t, J = 7.2 Hz, 2 H), 7.64 (t, J = 7.2 Hz, 1 H), 8.07 (d, J = 7.4 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.9, 13.2, 14.2, 19.8, 21.2, 25.5, 27.3, 28.6, 34.8, 35.9, 41.9, 45.3, 56.5, 60.9, 64.8, 70.4, 70.9, 73.4, 73.9, 76.7, 76.9, 77.9, 78.2, 79.7, 79.7, 83.1, 124.8, 126.6, 128.2, 129.1, 132.7, 134.5, 137.7, 141.0, 165.9, 169.3, 170.4, 210.4; mass spectrum (ES^+), m/z 822 $(M+H)^+$; HRMS (ES^+) m/z calcd for $C_{44}H_{55}NO_{14}Na$ $(M + Na)^+$ 844.3520, found 844.3521.

Acknowledgment. We thank Dr. C. Philouze for the X-ray structure determination, Drs. A. Commerçon and C. Combeau for the bioassays, and Dr. C. Fontaine for help with NMR interpretations. Financial support from Université Joseph Fourier and the CNRS (UMR 5616) and a fellowship award from the MESR to C.L. are gratefully acknowledged.

Supporting Information Available: X-ray data for compounds **6′** and **6** (2*R*, 3*S*). This material is available free of charge via the Internet at http://pubs.acs.org.

JO026460N