

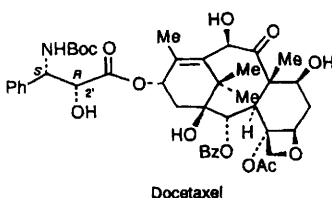
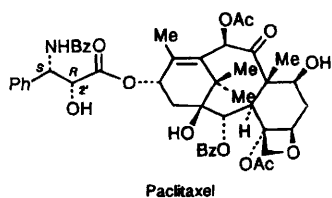
Docetaxel (Taxotere) derivatives: novel NbCl_3 -based stereoselective approach to 2'-methyl docetaxel

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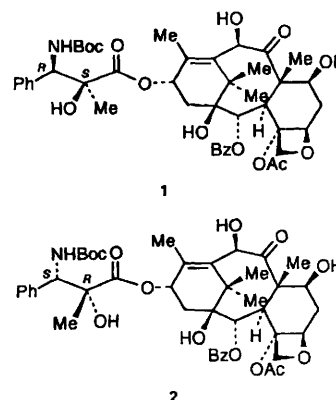
The C-2 methylated 2*S*,3*R* and 2*R*,3*S* side chains of docetaxel have been enantioselectively prepared and esterified with protected 10-deacetylbaccatin III to provide novel analogues of docetaxel.

Paclitaxel (taxol), a complex diterpene from *Taxus brevifolia*, and its semi-synthetic derivative docetaxel (Taxotere) show outstanding activity with various types of cancer.¹ Paclitaxel has already been approved for the treatment of metastatic carcinoma of the ovary and docetaxel, which has been reported to be more active than paclitaxel in certain human-derived cancer cell-line assays and preclinical trials,^{1a} is currently in phase II in Europe and the USA. The major importance of these antineoplastic agents has already occasioned the total synthesis and partial synthesis of numerous structural and stereochemical analogues in the hope of discovering derivatives that are even more effective.^{1,2}

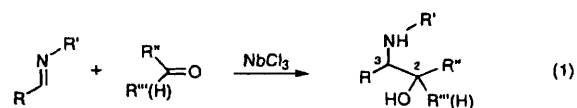


The myriad side chain-modified analogues that have been prepared and evaluated to date allow certain generalizations to be made as to the relative impact on activity of changes in stereochemistry, functional groups, and aliphatic/aromatic substituents. Particularly sensitive to change appears to be the C-2' position: the hydroxy or a latent hydroxy group must be present (deoxy analogues are *ca.* 12 times less cytotoxic than paclitaxel) and the C-2' configuration should be the natural one (*R*) for maximum activity.^{1j,k} Given the key nature of the C-2' position, it is somewhat surprising that no C-2'-alkylated analogues have yet been reported. In fact, more generally, it appears that no alkylated paclitaxel or docetaxel derivatives have been prepared to date. In this paper we describe the enantioselective synthesis of the C-2 methylated 2*S*,3*R* and 2*R*,3*S* side chains of docetaxel and their esterification with protected 10-deacetylbaccatin III to provide the first such analogues (1 and 2, respectively).

Of the various possible approaches to the enantiopure methylated side chain, the vicinal amino alcohol preparation through imine-ketone (or aldehyde) coupling, mediated by



NbCl_3 , seemed to hold particular promise [eqn. (1)].³ This novel reaction, disclosed by Roskamp and Pedersen in 1987, was shown by these authors to be especially effective with *N*-benzylidenebenzylamine and ketones, including ethyl pyruvate. Furthermore, a *syn*-selectivity (with aldehydes) was reported that ranged from 3:1 (*p*-acetoxybenzaldehyde) to 83:1 (pivalaldehyde). With this background and the expectation that the previously noted *syn*-selectivity with aldehydes might also hold for pyruvates,[†] we felt an enantioselective approach to this coupling through the use of a chiral amine as a control element worth examining as a possible means to the desired side chain.



1-Phenylethylamine, commercially available and inexpensive in both enantiomeric forms, was the obvious first choice and, arbitrarily, the *S*-enantiomer was selected. Condensation of this amine with benzaldehyde in the presence of anhydrous magnesium sulfate³ in dichloromethane readily provided the corresponding *N*-benzylidene-1-phenylethylamine 3. To our considerable satisfaction, it was found that addition of this imine to a stirred suspension of niobium(III) chloride in THF at 20 °C followed 0.5 h later at –15 to –20 °C by methyl pyruvate

[†] We had earlier found that the NbCl_3 -promoted coupling reaction between *N*-benzylidenebenzylamine and ethyl glyoxylate provided *syn*-selectively (*syn:anti*, 3.3:1) the expected vicinal amino alcohol. Interestingly, with *N*-(*tert*-butoxycarbonyl)benzylideneamine, the *syn:anti* ratio fell to 1:1 (unpublished results).

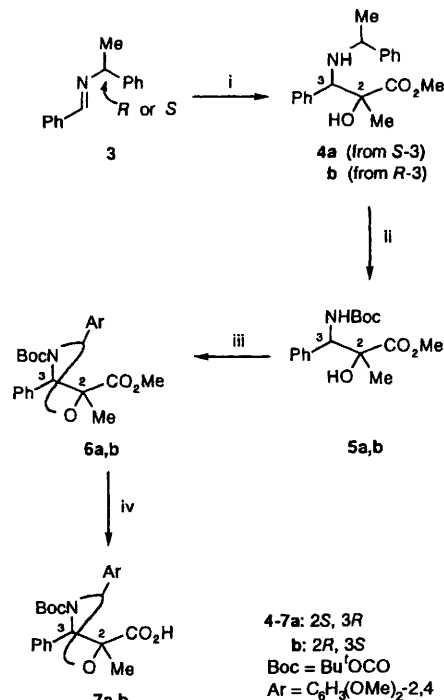
indeed produced a *syn*-diastereoisomer selectively (*syn*:*anti*, ca. 9:1; *syn*:*syn*, ca. 4:1; combined yield, 68% \ddagger). Fortunately, the highly difficult silica gel separation of diastereoisomers could be avoided by recrystallization of the mixture from hexane, which efficiently provided the major diastereoisomer pure in 52% yield from the mixture (35% based on methyl pyruvate). As luck would have it, however, a single-crystal X-ray analysis of **4a** revealed the absolute stereochemistry to be 2*S*,3*R*, gratifyingly *syn*, but enantiomeric with what was thought more highly desirable for correspondence with docetaxel. \S

Repetition of the above starting from the antipodal amine, (*R*)-1-phenylethylamine, led analogously as expected to the pure 2*R*,3*S* isomer **4b**. The enantiomers **4a** and **4b** were then efficiently converted in one pot into the corresponding methylated docetaxel side chain esters **5a** and **5b** through hydrogenation in the presence of Pearlman's catalyst⁴ [Pd(OH)₂], followed by treatment with di-*tert*-butyl dicarbonate (93 and 81%, respectively). Thus, the enantiomeric side-chains can readily be secured in stereochemically pure form in only three operations.

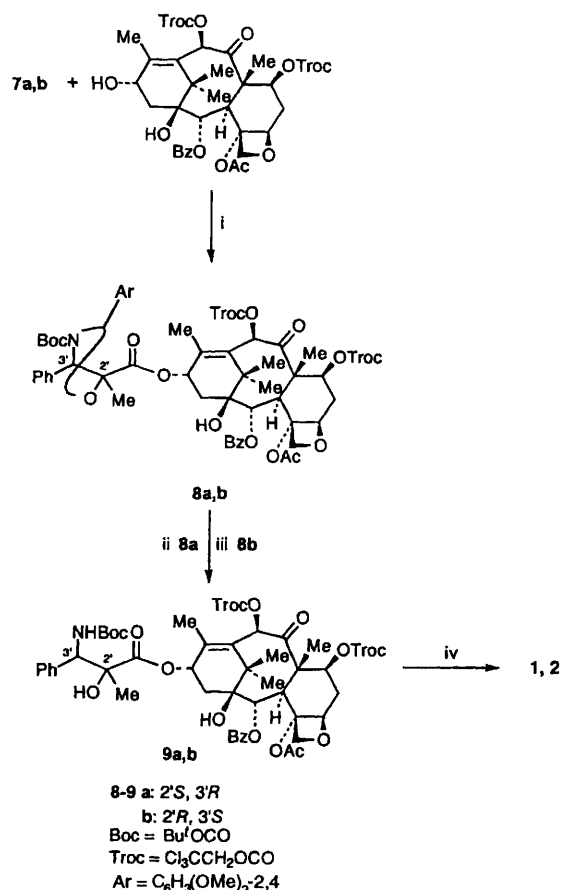
The success previously encountered with *p*-methoxybenzylidene side chain protection⁵ led us initially to transform **5a** and **5b** to the corresponding *p*-methoxybenzylidene-protected compounds [*p*-anisaldehyde dimethyl acetal, pyridinium toluene-*p*-sulfonate (PTS), toluene, 110 °C, 0.5 h, >90%] in anticipation of the subsequent esterification. Ominously, however, even these methyl esters displayed a reluctance to undergo deprotection under acidic conditions. Therefore, in order to enhance the likelihood of successful deprotection at what was envisaged as the penultimate stage of the synthesis, the considerably more acid labile 2,4-dimethoxybenzylidene protecting group was selected.^{5a} Conversion of **5a** and **5b** into the corresponding 2,4-dimethoxyphenyl-substituted oxazolidines **6a** and **6b** (1.5:1 epimeric mixtures) could be achieved in better than 90% yield with 2,4-dimethoxybenzaldehyde dimethyl acetal and PTS in refluxing toluene. Hydrolysis of these derivatives with lithium hydroxide in methanol was uneventful and efficiently furnished the protected, esterification-ready free acids **7a** and **7b** (1.5:1 epimeric mixtures), each in enantiopure form.

Because of the considerable encumbrance in the vicinity of the carboxy group in **7a** and **7b**, there was concern that the key esterification reaction with the 7,10-bis(trichloroethoxycarbonyl) derivative of 10-deacetylbaaccatin III⁶ might be even more challenging than usual. Although the dicyclohexylcarbodiimide-mediated reaction did, in fact, fail to produce any of the desired ester (competitive formation of the *N*-acylurea⁷), fortunately the di-2-pyridyl carbonate variant⁸ was successful and furnished the protected docetaxel derivatives **8a** and **8b** in 72 and 40% yields, respectively. Interestingly, in each of these esterifications the minor diastereoisomer of the 1.5:1 mixture appeared to react appreciably faster than the major one.

In that dimethoxybenzylidene deprotection of **8a** could not be realized without the simultaneous loss of the *tert*-butoxycarbonyl group,⁹ the preparation of the desired ester **9a** necessitated an additional step to regenerate the carbamate



Scheme 1 Reagents and conditions: i, NbCl₅, THF; methyl pyruvate; recrystallization from hexane; ii, H₂, Pd(OH)₂, AcOH–MeOH; Boc₂O, Et₃N; iii, 2,4-dimethoxybenzaldehyde dimethyl acetal, PTS, PhMe; iv, LiOH, MeOH–H₂O



Scheme 2 Reagents and conditions: i, di-2-pyridyl carbonate, DMAP, PhMe; ii, HCO₂H; Boc₂O, Et₃N, CH₂Cl₂; iii, camphorsulfonic acid, MeOH; iv, Zn–Cu, AcOH, MeOH

\ddagger The combined yield is that obtained after filtration (without diastereoisomer separation) of the crude mixture over silica gel. The *syn*:*anti* ratio was determined by high-yield conversion (see text) of the mixture to the separable *syn*- and *anti*-side chain methyl esters; the *syn*:*syn* ratio was established by ¹H NMR of the *syn*-ester in the presence of tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

\S In that the absolute stereochemistry of the starting *N*-benzylidene-1-phenylethylamine was known, the absolute stereochemistry at the C-2 and C-3 asymmetric centres in **4a** was automatically established by the X-ray analysis. Details of the X-ray determination will be published elsewhere.

function. In the natural 2*R*,3*S* series, however, it was found that camphorsulfonic acid in methanol at ambient temperature

smoothly effected the required transformation to give **9b** directly in 72% yield (86% based on recovered **8b**). The carefully chosen dimethoxybenzylidene protecting group thus nicely fulfilled its intended purpose, particularly in the latter series. The final transformation, the concomitant deprotection of the C-7 and C-10 hydroxy groups, was accomplished uneventfully with zinc–copper couple in acetic acid–methanol⁶ to provide in excellent yield the first C-2'-alkylated paclitaxel/docetaxel derivatives, (2'S,3'R)- and (2'R,3'S)-2'-methyl docetaxel.

The 2'S,3'R derivative showed no significant cytotoxicity (P388: IC₅₀ > 10 mg cm⁻³) nor inhibitory activity in microtubule depolymerization (> 100 T). In marked contrast, however, were the results obtained with (2'R,3'S)-2'-methyl docetaxel: cytotoxicity (KB-VI) and inhibitory activity in microtubule depolymerization were each significantly greater than that of docetaxel. A direction for future work is thus clearly indicated.

Experimental

Tetrahydrofuran, toluene, dimethoxyethane and diethyl ether (referred to as ether) were distilled from sodium-benzophenone and dichloromethane and triethylamine were distilled from calcium hydride. Thin-layer chromatography was performed on Merck 60F₂₅₄ (0.2 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70–230 silica gel 60 was employed for column chromatography. A Perkin-Elmer 397 spectrophotometer was used to record IR spectra (neat or as Nujol films). Bruker WPSY 80, AC 200, and AM 300 spectrometers were used for the ¹H and ¹³C NMR spectra (CDCl₃ solutions). *J* values are quoted in Hz. Mass spectra were obtained on an AEI MS-30 mass spectrometer (70 eV, direct insert probe). Optical rotations were measured on a Perkin-Elmer 241 polarimeter; [α]_D values are given in units of 10⁻¹ deg cm² g⁻¹. Mps were obtained with a Buchi-Tottoli apparatus and are uncorrected. Microanalysis were performed by the Central Service of the CNRS.

N-Benzylidene-1-phenylethylamine **3**¹⁰

To a solution of benzaldehyde (4.10 cm³, 40.3 mmol) in dichloromethane (60 cm³) was added (S)-(-)-1-phenylethylamine (5.20 cm³, 40.3 mmol). After the mixture had been stirred for 15 min, an excess of anhydrous magnesium sulfate was added to it and stirring was continued for an additional 5.5 h. The mixture was then filtered and evaporated under reduced pressure. Distillation of the residue provided the imine (S)-**3** (6.16 g, 73%), bp 88 °C (0.05 mmHg); [α]_D²³ + 73 (c 2.3, CHCl₃); ν_{max}(neat)/cm⁻¹ 3060, 3050, 3010, 2960, 2910, 2850, 2825, 1950, 1880, 1810, 1750, 1640, 1600, 1580, 1490, 1450, 1380, 1310, 1300, 1290, 1270, 1210, 1190, 1160, 1150, 1110, 1100, 1080, 1060, 1030, 1015, 1010, 960 and 900; δ_H 1.59 (3 H, d, *J* 6.6), 4.54 (1 H, q, *J* 6.6), 7.19–7.46 (8 H, m), 7.74–7.82 (2 H, m) and 8.37 (1 H, s). The imine (R)-**3**, prepared analogously (77% yield), showed identical properties except for the sign of the optical rotation.

Methyl 2-hydroxy-2-methyl-3-phenyl-3-(1-phenylethylamino)-propanoate **4**

To a stirred suspension of niobium(III) chloride–DME complex **3** (435 mg, 1.5 mmol) in THF (17 cm³) at 20 °C under argon was added dropwise the imine (S)-**3** (313 mg, 1.5 mmol) in THF (6.5 cm³). After 0.5 h, the mixture was cooled to –20 °C and treated over 1 min with methyl pyruvate (91 mm³, 103 mg, 1.0 mmol). The resulting mixture was stirred for 1 h at –15 to –20 °C and for 2 h at 0 °C, after which aq. potassium hydroxide (10%) was added to it. The crude product was isolated with ether in the usual manner and filtered over silica gel with 10% ether–hexane

to give a mixture of diastereoisomers (213 mg, 68%). Recrystallization of the mixture from hexane afforded pure 2*S*,3*R*-isomer **4a** (110 mg, 52% from the mixture or 35% based on methyl pyruvate), mp 99–100 °C; [α]_D²⁵ –119 (c 0.8, CHCl₃); ν_{max}(neat)/cm⁻¹ 3480, 3060, 3050, 3010, 2960, 2950, 2910, 2850, 1730, 1590, 1580, 1480, 1450, 1430, 1360, 1250, 1210, 1195, 1160, 1110, 1060, 1020, 980, 950, 910, 900, 820, 770, 750 and 690; δ_H 0.97 (3 H, s), 1.19 (3 H, d, *J* 6.6), 2.22 (1 H, br s), 3.34 (1 H, q, *J* 6.6), 3.51 (1 H, s), 3.62 (1 H, s), 3.77 (3 H, s) and 7.12–7.39 (10 H, m); δ_C 23.9, 25.3, 52.8, 54.4, 64.6, 77.4, 126.9, 127.2, 127.5, 128.0, 128.2, 129.0, 138.8, 145.4 and 177.6; *m/z* 314 (MH⁺), 210, 124 and 110 (Found: C, 72.75; H, 7.5; N, 4.3. Calc. for C₁₉H₂₃NO₃: C, 72.82; H, 7.40; N, 4.47). The 2*R*,3*S*-isomer **4b**, prepared similarly (19% yield based on methyl pyruvate), showed identical properties except for the sign of the optical rotation.

Methyl 3-(*tert*-butoxycarbonylamino)-2-hydroxy-2-methyl-3-phenylpropanoate **5**

To a solution of the amino alcohol **4a** (360 mg, 1.15 mmol) in methanol–acetic acid (50:1; 7.3 cm³) was added palladium hydroxide (72 mg, 20%) and the resulting mixture was stirred at 20 °C under a hydrogen atmosphere for 17 h. The hydrogen was then replaced with argon and triethylamine (1.0 cm³, 7.2 mmol) and di-*tert*-butyl dicarbonate (488 mg, 2.2 mmol) were added to the mixture. After being stirred at 20 °C for 24 h, the mixture was processed with dichloromethane in the usual way and the crude product was purified by silica gel chromatography with 10% ethyl acetate in hexane to afford the pure 2*S*,3*R*-isomer **5a** (330 mg, 93%), mp 187–188 °C; [α]_D²⁵ +6 (c 0.5, CHCl₃); ν_{max}(neat)/cm⁻¹ 3500, 3380, 2970, 1730, 1685, 1520, 1360, 1245, 1165, 1115, 1040, 1015 and 885; δ_H 1.20 (3 H, s), 1.38 (9 H, s), 3.51 (1 H, br s), 3.84 (3 H, s), 4.95 (1 H, deformed d, *J* 10.0), 5.45 (1 H, deformed d, *J* 9.0) and 7.28–7.35 (5 H, m); *m/z* 310 (MH⁺), 271, 254, 210, 193, 150 and 105 (Found: C, 62.2; H, 7.6; N, 4.2. Calc. for C₁₆H₂₃NO₅: C, 62.12; H, 7.49; N, 4.53). The 2*R*,3*S*-isomer **5b**, prepared analogously (81% yield), showed identical properties except for the sign of the optical rotation.

Methyl 3-*tert*-butoxycarbonyl-2-(2,4-dimethoxyphenyl)-5-methyl-4-phenyloxazolidine-5-carboxylate **6**

A mixture of compound **5a** (855 mg, 2.77 mmol) and 2,4-dimethoxybenzaldehyde dimethyl acetal (1.18 g, 5.57 mmol) in toluene (28 cm³) was heated at 110 °C for 10 min, after which pyridinium toluene-*p*-sulfonate (70 mg, 0.28 mmol) was added to it and heating was continued for an additional 45 min. After being allowed to cool, the reaction mixture was processed with dichloromethane in the usual way and the crude product was purified by silica gel chromatography with 10–20% ether in hexane to give the oxazolidine **6a** (1.22 g, 96%) as a white solid, mp 54–57 °C; [α]_D²⁵ –7 (c 1.3, CHCl₃); ν_{max}(neat)/cm⁻¹ 2980, 2950, 2920, 2900, 2810, 1730, 1700, 1610, 1590, 1500, 1450, 1430, 1390, 1360, 1300, 1260, 1230, 1205, 1140, 1120, 1090, 1035, 935, 830, 760, 730 and 600; δ_H major diastereoisomer [2 rotamers, 4 (major): 1 (minor)]: 1.01 (3 H, s), 1.09 (9 H, s), 3.25 (major) and 3.36 (minor) (3 H, 2 × s), 3.79 (3 H, s), 3.88 (3 H, s), 5.62 (major) and 5.76 (minor) (1 H, 2 × s), 6.39–6.50 (2 H, m), 6.69 (minor) and 6.84 (major) (1 H, 2 × s), 7.01–7.05 (1 H, m) and 7.20–7.40 (5 H, m); minor diastereoisomer: 1.14 (3 H, s), 1.22 (9 H, s), 3.83 (3 H, s), 3.88 (6 H, s), 5.32 (1 H, s), 6.45 (1 H, s), 6.44–6.51 (2 H, m) and 7.20–7.45 (6 H, m); *m/z* 458

|| 2,4-Dimethoxybenzaldehyde dimethyl acetal was prepared by treatment of 2,4-dimethoxybenzaldehyde (1.62 g, 10 mmol) with methyl orthoformate (1.59 g, 15 mmol) and ammonium chloride (15 mg, 0.28 mmol) in refluxing methanol for 72 h, followed by work-up and distillation under reduced pressure (1.29 g, 62%).

(MH⁺), 402, 356, 320, 264, 220 and 166 (Found: C, 65.8; H, 7.1; N, 3.1. Calc. for C₂₅H₃₁NO₇: C, 65.62; H, 6.83; N, 3.06). The 2*R*,3*S*-isomer **6b**, prepared analogously (91% yield), showed identical properties except for the sign of the optical rotation.

3-*tert*-Butoxycarbonyl-2-(2,4-dimethoxyphenyl)-5-methyl-4-phenyloxazolidine-5-carboxylic acid **7**

Compound **6a** (1.10 g, 2.41 mmol) in methanol (62 cm³) was stirred with lithium hydroxide monohydrate (203 mg, 4.83 mmol) at 20 °C under argon for 72 h. The reaction mixture was then processed with dichloromethane in the usual manner to afford the acid **7a** (1.06 g, 99%) as a white solid, mp 94–104 °C; [α]_D²⁵ –21 (c 1.0, CHCl₃); ν_{\max} (neat)/cm^{–1} 3070, 3030, 3000, 2980, 2940, 2890, 1705, 1610, 1590, 1510, 1455, 1440, 1390, 1370, 1300, 1260, 1210, 1155, 1120, 1030, 940, 835, 735 and 700; δ_{H} major diastereoisomer: 1.06 (12 H, s), 3.82 (3 H, s), 3.89 (3 H, s), 5.52 (1 H, s), 6.51 and 6.77 (1 H, 2 × s), 6.46–6.52 (2 H, m), 7.18–7.23 (1 H, m) and 7.23–7.44 (5 H, m); minor diastereoisomer: 1.14 (3 H, s), 1.23 (9 H, s), 3.84 (3 H, s), 3.89 (3 H, s), 5.41 (1 H, s), 6.40 (1 H, s), 6.46–6.54 (2 H, m) and 7.20–7.44 (6 H, m); m/z 444 (MH⁺), 400, 344, 306, 206, 182, 167, 151 and 106 (Found: C, 65.3; H, 6.65; N, 3.2. Calc. for C₂₄H₂₉NO₇: C, 65.00; H, 6.59; N, 3.06). The 2*R*,3*S*-isomer **7b**, prepared analogously (93% yield), showed identical properties except for the sign of the optical rotation.

(2′*S*,3′*R*)-7,10-Bis(trichloroethoxycarbonyl)-2′-methyl derivative of docetaxel **9a**

Di-2-pyridyl carbonate (254 mg, 1.17 mmol) was added in one portion to a solution of the acid **7a** (520 mg, 1.17 mmol) in dry toluene (11.5 cm³) at 20 °C under argon. After being stirred for 5 min, the reaction mixture was treated with dimethylaminopyridine (48 mg, 0.39 mmol) and the 7,10-bis(trichloroethoxycarbonyl) derivative of 10-deacetylbaccatin III⁶ (175 mg, 0.196 mmol) and then heated at 72 °C for 96 h. The crude product was isolated with ethyl acetate in the usual way and purified by silica-gel chromatography with 2% ether in dichloromethane as eluent to give the ester **8a** (186 mg, 72%) as a white solid; ν_{\max} (neat)/cm^{–1} 3480, 3050, 2960, 2940, 2900, 2860, 1760, 1730, 1710, 1615, 1590, 1510, 1470, 1450, 1430, 1370, 1250, 1220, 1210, 1180, 1150, 1110, 1090, 1070, 1030, 970, 940, 820, 770, 720 and 700; δ_{H} (2 diastereoisomers, 2:1) major diastereoisomer: δ_{H} 1.26 (12 H, s), 1.28 (3 H, s), 1.36 (3 H, s), 1.79 (1 H, s), 1.85 (3 H, s), 2.02 (3 H, s), 2.02–2.16 (1 H, m), 2.25–2.62 (3 H, m), 2.40 (3 H, s), 3.71 (3 H, s), 3.83 (1 H, d, J 6.9), 3.84 (3 H, s), 4.10 (1 H, d, J 6.4), 4.29 (2 H, ABq, J_{AB} 8.4, $\delta_{\text{A}} - \delta_{\text{B}}$ 75.5), 4.74 (2 H, ABq, J_{AB} 11.7, $\delta_{\text{A}} - \delta_{\text{B}}$ 94.3), 4.78 (2 H, s), 4.97 (1 H, d, J 9), 5.52–5.59 (1 H, m), 5.59 (1 H, m), 5.76 (1 H, d, J 6.9), 6.10 (1 H, s), 6.28 (1 H, s), 6.28–6.40 (1 H, m), 6.47–6.54 (2 H, m), 7.20–7.51 (8 H, m), 7.63–7.68 (1 H, m) and 8.14–8.17 (2 H, m); minor diastereoisomer (principal resonances): δ_{H} 1.09 (9 H, s), 1.15 (3 H, s), 1.18 (3 H, s), 1.81 (3 H, s), 1.85 (3 H, s), 1.94–2.08 (1 H, m), 2.34–2.44 (2 H, m), 2.50–2.64 (1 H, m), 3.38 (3 H, s), 3.98 (3 H, s), 4.22 (2 H, deformed ABq), 4.71 (2 H, ABq, J_{AB} 12, $\delta_{\text{A}} - \delta_{\text{B}}$ 95.2), 4.75 (2 H, s), 4.92 (1 H, d, J 9), 5.40–5.49 (1 H, m), 5.63–5.67 (1 H, m), 5.73 (1 H, s), 6.16 (1 H, s), 6.24 (1 H, s), 6.38–6.59 (2 H, m), 6.81 (1 H, s), 7.07–7.10 (1 H, m), 7.24–7.70 (8 H, m) and 8.12–8.15 (2 H, m).

The ester **8a** (130 mg, 0.10 mmol) was stirred in formic acid (1.5 cm³) at 20 °C under argon for 72 h. The reaction mixture was processed with ethyl acetate in the usual way and the crude product was purified by dry silica gel chromatography with 0.4% methanol in dichloromethane to give the free amine derivative (74 mg, 70%). The material (70 mg, 0.06 mmol) in dichloromethane (3.4 cm³) under argon was treated with triethylamine (54 mm³, 0.39 mmol) and di-*tert*-butyl dicarbonate (74 mg, 0.34 mmol). After being stirred at 20 °C for

13 h, the mixture was worked-up with dichloromethane in the normal way and the crude product purified by dry silica gel chromatography with 0.2% methanol in dichloromethane as eluent to afford compound **9a** (27 mg, 35%); ν_{\max} (neat)/cm^{–1} 3400, 3050, 2950, 2900, 2860, 1760, 1720, 1600, 1580, 1490, 1450, 1430, 1370, 1245, 1160, 1110, 1090, 1060, 1020, 1000, 970, 960, 820, 770, 720 and 700; δ_{H} 1.22 (3 H, s), 1.26 (9 H, s), 1.30 (3 H, s), 1.32 (3 H, s), 1.87 (3 H, s), 2.00 (3 H, s), 2.06–2.42 (3 H, m), 2.53 (3 H, s), 2.45–2.68 (1 H, m), 3.93 (1 H, d, J 7), 4.26 (2 H, ABq, J_{AB} 8.3, $\delta_{\text{A}} - \delta_{\text{B}}$ 36), 4.72 (2 H, ABq, J_{AB} 11.8, $\delta_{\text{A}} - \delta_{\text{B}}$ 1.1), 4.74 (2 H, ABq, J_{AB} 11.8, $\delta_{\text{A}} - \delta_{\text{B}}$ 61.4), 5.57 (2 H, dd, J 7.2, 10.5), 5.72 (2 H, d, J 7), 6.25 (1 H, s), 6.38 (1 H, t, J 9.0), 7.28–7.46 (5 H, m), 7.50–7.57 (2 H, m), 7.62–7.69 (1 H, m) and 8.07–8.12 (2 H, m); m/z 1172 (M⁺), 1116, 1082, 1072, 1054, 922, 904, 878 and 862.

(2′*R*,3′*S*)-7,10-Bis(trichloroethoxycarbonyl)-2′-methyl derivative of docetaxel **9b**

Di-2-pyridyl carbonate (139.5 mg, 0.65 mmol) was added in one portion to a solution of acid **7b** (260 mg, 0.59 mmol) in dry toluene (5.8 cm³) at 20 °C under argon. After being stirred for 5 min, the reaction mixture was treated with dimethylaminopyridine (24 mg, 0.20 mmol) and the 7,10-bis(trichloroethoxycarbonyl) derivative of 10-deacetylbaccatin III⁶ (87.5 mg, 0.10 mmol) and then heated at 72 °C for 96 h. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography with 2% ether in dichloromethane to give the ester **8b** (51 mg, 40%) as a white solid, mp 171–177 °C; ν_{\max} (neat)/cm^{–1} 3400, 2970, 1760, 1725, 1710, 1640, 1615, 1590, 1510, 1455, 1375, 1250, 1210, 1160, 1150, 1110, 1095, 1065, 1030, 825 and 775; δ_{H} 1.18 (3 H, s), 1.22 (12 H, s), 1.35 (3 H, s), 1.86 (3 H, s), 2.05–2.10 (1 H, m), 2.19–2.31 (2 H, m), 2.25 (3 H, s), 2.31 (3 H, s), 2.58–2.65 (1 H, m), 3.85 (3 H, s), 4.01 (3 H, s), 4.01–4.03 (1 H, m), 4.25 (2 H, ABq, J_{AB} 8.5, $\delta_{\text{A}} - \delta_{\text{B}}$ 76.8), 4.77 (2 H, ABq, J_{AB} 11.8, $\delta_{\text{A}} - \delta_{\text{B}}$ 110.4), 4.80 (2 H, s), 5.03 (1 H, d, J 8.2), 5.53 (1 H, s), 5.68–5.72 (2 H, m), 6.30 (1 H, s), 6.42 (1 H, t, J 9), 6.48 (1 H, s), 6.48–6.51 (2 H, m), 7.26–7.65 (9 H, m) and 8.05–8.07 (2 H, m) (Found: C, 53.5; H, 5.1; N, 1.15. Calc. for C₅₉H₆₅Cl₆NO₂₀: C, 53.65; H, 4.96; N, 1.06).

The ester **8b** (70 mg, 0.05 mmol) in methanol (7 cm³) under argon was treated with camphorsulfonic acid (7 mg, 0.03 mmol). After being stirred for 96 h at 20 °C, the reaction mixture was worked-up with dichloromethane in the normal way and the crude product purified by preparative thin-layer silica-gel chromatography with 4% ether in dichloromethane as eluent to afford recovered **8b** (12 mg, 17%) and the ester **9b** (44.5 mg, 72%); mp 170–173 °C; [α]_D²⁵ –37 (c 0.8, CHCl₃); ν_{\max} (neat)/cm^{–1} 3445, 2975, 1760, 1725, 1600, 1495, 1450, 1375, 1250, 1170, 1110, 1065, 1000, 975, 720 and 710; δ_{H} 1.19 (3 H, s), 1.23 (9 H, s), 1.31 (3 H, s), 1.38 (3 H, s), 1.86 (3 H, s), 1.88 (3 H, s), 2.04–2.10 (1 H, m), 2.23–2.33 (2 H, m), 2.57–2.65 (1 H, m), 2.64 (3 H, s), 3.54 (1 H, s), 3.91 (1 H, d, J 7), 4.26 (2 H, ABq, J_{AB} 8.5, $\delta_{\text{A}} - \delta_{\text{B}}$ 60.6), 4.74 (2 H, ABq, J_{AB} 11.8, $\delta_{\text{A}} - \delta_{\text{B}}$ 124.2), 4.77 (2 H, ABq, J_{AB} 11.9, $\delta_{\text{A}} - \delta_{\text{B}}$ 4.8), 4.96 (1 H, d, J 7.9), 5.02 (1 H, d, J 10.2), 5.47–5.57 (1 H, m), 5.52 (1 H, d, J 10.2), 5.69 (1 H, d, J 7), 6.21 (1 H, s), 6.33 (1 H, t, J 9.4), 7.24–7.40 (5 H, m), 7.47–7.51 (2 H, m), 7.58–7.62 (1 H, m) and 8.11–8.13 (2 H, m); m/z 1173 (MH⁺), 1117, 1072, 977 and 880 (Found: C, 51.0; H, 5.1; N, 1.1. Calc. for C₅₀H₅₇Cl₆NO₁₈: C, 51.21; H, 4.90; N, 1.19).

(2′*S*,3′*R*)-2′-Methyl derivative of docetaxel **1**

A solution of the ester **9a** (120 mg, 0.10 mmol) in acetic acid–methanol (1:1 v/v; 14 cm³) at 66 °C under argon was treated with a zinc–copper couple (600 mg). After being vigorously stirred for 30 min, the mixture was allowed to cool to 20 °C and was then diluted with dichloromethane. The mixture was then filtered through Celite and the crude product isolated with

dichloromethane in the usual way and purified by silica-gel chromatography with 3% ether in dichloromethane as eluent to afford the docetaxel analogue **1** (68 mg, 83%); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3400, 2970, 2920, 2890, 2850, 1735, 1720, 1700, 1600, 1580, 1490, 1450, 1365, 1310, 1270, 1240, 1165, 1130, 1120, 1090, 1065, 1020, 980, 945, 910, 775, 730 and 700; δ_{H} 1.13 (3 H, s), 1.27 (3 H, s), 1.33 (9 H, s), 1.36 (3 H, s), 1.75 (3 H, s), 2.00 (3 H, s), 1.75–1.88 (1 H, m), 2.04–2.23 (2 H, m), 2.18 (3 H, br s), 2.48–2.63 (1 H, m), 3.34 (1 H, br s), 3.89 (1 H, d, J 7), 4.23 (2 H, ABq, J_{AB} 8.5, $\delta_{\text{A}} - \delta_{\text{B}}$ 32.3), 4.15–4.30 (1 H, m), 4.18 (1 H, br s), 4.91 (1 H, deformed d, J 8), 4.83–4.97 (1 H, m), 5.19 (1 H, s), 5.56–5.76 (1 H, m), 5.68 (1 H, d, J 7), 6.25 (1 H, deformed t), 7.31–7.34 (5 H, m), 7.45–7.51 (2 H, m), 7.59–7.64 (1 H, m) and 8.03–8.06 (2 H, m); m/z 821 (M^+), 704, 668, 543 and 339.

(2'R,3'S)-2'-Methyl derivative of docetaxel **2**

A solution of the ester **9b** (39 mg, 0.03 mmol) in acetic acid-methanol (1:1 v/v; 4.6 cm^3) at 65 °C under argon was treated with a zinc-copper couple (196 mg). After being vigorously stirred for 30 min, the mixture was allowed to cool to 20 °C and was then diluted with dichloromethane. The crude product was then isolated with dichloromethane in the usual way and purified by preparative thin-layer silica-gel chromatography with 6% methanol in dichloromethane as eluent to afford the docetaxel derivative **2** (22 mg, 81%); mp 183–186 °C; $[\alpha]_{\text{D}}^{25} -46$ (c 0.5, CHCl_3); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3440, 3065, 2975, 2930, 1710, 1600, 1585, 1495, 1455, 1370, 1315, 1270, 1245, 1165, 1135, 1070, 1020, 985 and 710; δ_{H} 1.14 (3 H, s), 1.24 (9 H, s), 1.29 (3 H, s), 1.39 (3 H, s), 1.78 (6 H, s), 1.75–1.90 (1 H, m), 2.17–2.42 (2 H, m), 2.55–2.67 (1 H, m), 2.62 (3 H, s), 3.53 (1 H, s), 3.93 (1 H, d, J 7.0), 4.10–4.29 (1 H, m), 4.10 (1 H, br s), 4.27 (2 H, ABq, J_{AB} 8.6, $\delta_{\text{A}} - \delta_{\text{B}}$ 36.3), 4.92–5.09 (2 H, m), 5.18 (1 H, s), 5.55 (1 H, d, J 10.0), 5.70 (1 H, d, J 7.0), 6.34 (1 H, deformed t), 7.22–7.62 (8 H, m) and 8.12–8.15 (2 H, m); m/z 822 (MH^+) and 527 [Found: MH^+ (FAB), 822.3730. $\text{C}_{44}\text{H}_{56}\text{NO}_{14}$ requires M , 822.3701].

Acknowledgements

We thank Professor J. Lhomme and Dr E. Fouque for their interest in our work, Professor S. F. Pedersen for advice, and Dr C. Combeau and Dr J-F. Riou for the biological testing. Financial support from the CNRS (URA 332) and Rhône-Poulenc Rorer and a fellowship award from Rhône-Poulenc Rorer (to S. J.) are gratefully acknowledged.

References

- 1 For reviews on the occurrence, biological properties, and syntheses of these compounds and congeners, see: (a) S. Blechert and

- D. Guénard, in *The Alkaloids, Chemistry and Pharmacology*; ed. A. Brossi, Academic Press, San Diego, 1990, vol. 39, pp. 195–238; (b) D. G. I. Kingston, G. Samaranayake and C. A. Ivey, *J. Nat. Prod.*, 1990, **53**, 1; (c) D. G. I. Kingston, *Pharmac. Ther.*, 1991, **52**, 1; (d) C. S. Swindell, *Org. Prep. Proc. Int.*, 1991, **23**, 465; (e) S. Borman, *Chem. Eng. News*, 1991, **69**(35), 11; 1992, **70**(41), 30; (f) P. Potier, D. Guénard and F. Guéritte-Voegelein, *Acc. Chem. Res.*, 1993, **26**, 160; (g) F. Lavelle, F. Guéritte-Voegelein and D. Guénard, *Bull. Cancer*, 1993, **80**, 326; (h) D. G. I. Kingston, A. A. Molinero and J. M. Rimoldi, *Prog. Chem. Org. Nat. Prod.*, 1993, **61**, 1; (i) M. Suffness, in *Ann. Rep. Med. Chem.*, ed. J. A. Bristol, Academic Press, San Diego, 1993; vol. 28, pp. 305–314; (j) K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; (k) G. I. Georg, S. M. Ali, J. Zygmunt and L. R. Jayasinghe, *Exp. Opin. Ther. Patents*, 1994, **4**, 109.
- 2 For total syntheses of paclitaxel, see: K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630; R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1599.
- 3 E. J. Roskamp and S. F. Pedersen, *J. Am. Chem. Soc.*, 1987, **109**, 6551. For related work, see: J. B. Hartung, Jr. and S. F. Pedersen, *J. Am. Chem. Soc.*, 1989, **109**, 5468; E. J. Roskamp, P. S. Dragovich, J. B. Hartung, Jr. and S. F. Pedersen, *J. Org. Chem.*, 1989, **54**, 4736; J. Szymoniak, J. Besançon and C. Moïse, *Tetrahedron*, 1992, **48**, 3867; 1994, **50**, 2841; J. Szymoniak, L. Luque, J. Besançon and C. Moïse, *Bull. Soc. Chim. Fr.*, 1994, **131**, 89.
- 4 W. M. Pearlman, *Tetrahedron Lett.*, 1967, 1663.
- 5 (a) E. Didier, E. Fouque, I. Taillepié and A. Commerçon, *Tetrahedron Lett.*, 1994, **35**, 2349; (b) A. M. Kanazawa, J.-N. Denis and A. E. Greene, *J. Org. Chem.*, 1994, **59**, 1238; (c) A. M. Kanazawa, J.-N. Denis and A. E. Greene, *J. Chem. Soc., Chem. Commun.*, 1994, 2591.
- 6 V. Sènilh, F. Guéritte, D. Guénard, M. Colin and P. Potier, *C. R. Seances Acad. Sci., Ser. 2*, 1984, **299**, 1039.
- 7 See: K. Holmberg and B. Hansen, *Acta Chem. Scand., Ser. A*, 1979, **33**, 410 and references cited therein.
- 8 S. Kim, J. I. Lee and Y. K. Ko, *Tetrahedron Lett.*, 1984, **25**, 4943; J.-N. Denis, A. E. Greene, D. Guénard, F. Guéritte-Voegelein, L. Mangatal and P. Potier, *J. Am. Chem. Soc.*, 1988, **110**, 5917.
- 9 For a related example, see: A. Commerçon, D. Bézard, F. Bernard and J. D. Bourzat, *Tetrahedron Lett.*, 1992, **33**, 5185.
- 10 P. N. Devine, M. Reilly and T. Oh, *Tetrahedron Lett.*, 1993, **34**, 5827.

Paper 5/01486G

Received 10th March 1995

Accepted 29th March 1995