Semisynthesis of Flexible 5,7-Dideoxypaclitaxel Derivatives from Taxine B

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Two new 5,7-dideoxypaclitaxel derivatives with flexible C-rings have been prepared starting from Taxine B, an alkaloid isolated from the leaves of *Taxus baccata*. Both derivatives lack the oxetane ring present in the antitumor agent paclitaxel, but possess an oxygenated 4β-substituent as a substitute for the oxetane ring oxygen atom. These derivatives provide additional information about the importance of this oxygen atom for cytotoxic activity.

Introduction

Paclitaxel (**1a**), first isolated from the bark of *Taxus brevifolia* in the late 1960s, is considered one of the most promising chemotherapeutic agents at the moment. It acts by stabilizing microtubules, thereby blocking mitosis, and triggering apoptosis, and has been approved by the American Food and Drug Administration (FDA) for the treatment of advanced ovarian cancer, metastatic breast cancer, non-small cell lung cancer, and Kaposi's sarcoma.[1]

Thanks to its high cytotoxic activity and unique mechanism of action, and also because of its drawbacks (poor water solubility and induction of multi-drug resistance), paclitaxel has become the subject of extensive structure-activity relationship (SAR) studies, in order to obtain better insight into its mechanism of action at the molecular level and to prepare new, more active analogues with better pharmacological properties.

The level of importance of the oxetane D-ring for cytotoxic activity has not yet been established by SAR studies. It has been proposed that the ring might serve two functions: (i) the oxygen atom in the oxetane ring may have an important stabilizing dipolar or hydrogen-bonding interaction with an amino acid residue inside the binding pocket on polymerized tubulin heterodimers, and (ii) the inflexible oxetane ring may promote the biologically important conformation of paclitaxel because of its rigidifying effect on the whole taxane skeleton.

Several derivatives with modified D-rings have been synthesized (Figure 1), and all were shown to be less active than paclitaxel against cancer cell lines. Kingston and colleagues[2,3] synthesized D-secopaclitaxel **2**, which showed considerably less activity against a KB cell culture assay. They also prepared thietane analogue **3a**, which displayed a more than 500-fold reduction in activity with respect to its oxetane ring containing counterpart **3b**.[4] Dubois and co-workers[5] prepared two azetidine derivatives of docetaxel (**1b**). Derivative **4a** showed no inhibitory activity of microtubule disassembly, whereas **4b** showed a 16-fold drop with respect to docetaxel. Both derivatives were inactive against a KB cell line. 5(20)-Deoxydocetaxel (**5**) has recently been prepared by Dubois and co-workers.[6] Its microtubule disassembly inhibitory activity was half of that of docetaxel. No cytotoxicity data were presented.

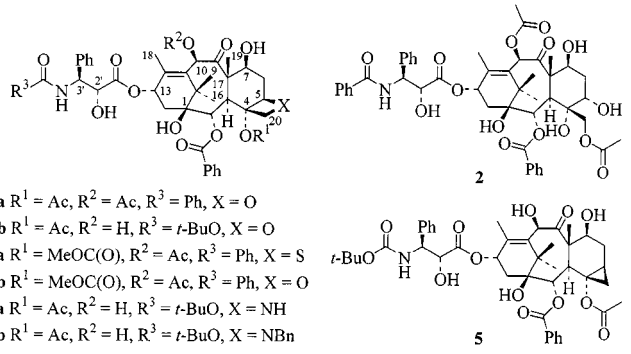

Figure 1. Paclitaxel (**1a**), docetaxel (**1b**), and D-ring modified derivatives

The low cytotoxic activity of derivatives **3a**, **4a**, and **4b** does not disallow one of the two alleged functions of the oxetane ring, as all derivatives are both flexible and without an oxygen atom. The high microtubule disassembly inhibitory activity of **5**, however, seems to imply that rigidity alone is sufficient for induction of inhibitory activity.

Recent calculations using a minireceptor approach and a refined model of the paclitaxel–β-tubulin binding pocket have shown that flexible derivatives with oxygenated substituents at C-4 and C-5 can also be well accommodated inside the β-tubulin binding pocket.[7] The relatively polar hydroxy groups at C-4 and C-5 on D-secopaclitaxel **2** are the probable cause of its low tubulin polymerization activity, due to unfavorable desolvation energies. Conversion of these alcohol groups to less polar groups, or complete removal of some alcohol groups, reduces the desolvation energy and should afford flexible derivatives that stabilize microtubules.[7]

Here, we wish to report the synthesis of two flexible C-ring derivatives that lack a C-5 oxygen substituent, but pos-

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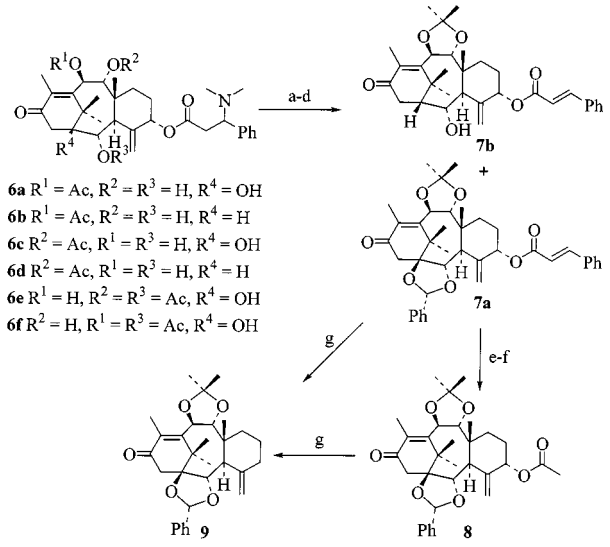
sess an oxygenated 4β-substituent that might substitute for the oxetane ring oxygen atom. Both derivatives also differ from paclitaxel at C-7, C-9, and C-10. Modifications at these three positions, however, have been shown to have only minor effects on biological activity. The derivatives have been prepared from taxine (**6**), an alkaloid mixture isolated from the leaves of the European Yew, *Taxus baccata*.

Results and Discussion

Taxine B (**6a**) and 5 related taxanes **6b**−**6f** form the major proportion (ca. 40%) of an alkaloid mixture from *T. baccata*, easily obtained in 0.5−1% yield by acid extraction of dried leaves.[8] Although the structures of taxines **6a**−**6f** are quite distinct from paclitaxel, several groups have used these alkaloids to prepare 7-deoxypaclitaxel derivatives in a reasonable number of steps.[9−14]

The crude alkaloid mixture was purified and converted into a mixture of compounds 7**a** and 7**b** by iodomethylation, saponification of the acetate groups with concomitant elimination of the trimethylammonium group, protection of the 9- and 10-hydroxy groups with an isopropylidene bridge, and protection of the 1- and 2-hydroxy groups with a benzylidene bridge as previously described (Scheme 1).[14]

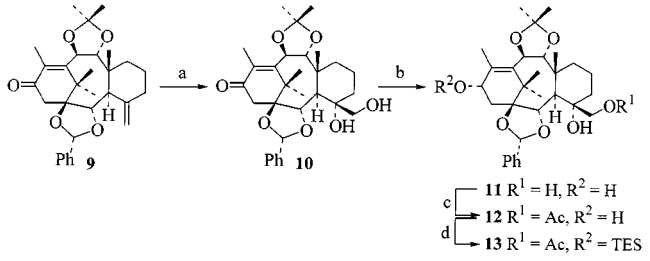


Scheme 1. Preparation of taxane **9**; reagents and conditions: (a) MeI, Et_2O; (b) K_2CO_3, $EtOH/H_2O$; (c) 2,2-dimethoxypropane, PTS, CH_2Cl_2; (d) benzaldehyde dimethyl acetal, PTS, CH_2Cl_2; (e) 20 N NaOH in H_2O, THF, Δ; (f) Ac_2O, pyridine; (g) $Pd(dba)_2$, PBu_3, HCOOH, NEt_3, THF, Δ

In order to remove the C-5 ester group, we focused on allylic substitution. Mukaiyama and co-workers have been able to substitute the allylic C-5 acetate group in a related taxane by hydride, using a palladium-catalyzed substitution reaction with triethylammonium formate as the hydride donor.[15,16] Acetate **8** was therefore prepared by hydrolysis of **7a** under strongly basic conditions, followed by acetylation of the secondary hydroxy group. Allylic substitution using bis(dibenzylideneacetone)palladium(0) as the pre-catalyst afforded the desired deoxygenated taxane **9** in almost quantitative yield. When the same reaction was carried out with **7a**, taxane **9** was obtained in excellent yield, the reaction time being almost equal to that for acetate **8**. This seems understandable, as the palladium catalyst has to approach the allylic system from the side opposite to the allylic ester group in order to be able to expel it.[17] The bulkiness of the ester group is therefore of minor importance for the reaction rate. Changing the phosphorus ligand from tri(*n*-butyl)phosphane to triphenylphosphane induced a 3-fold reduction in the reaction rate.

We next set out to convert **9** into a 5,7-dideoxypaclitaxel derivative doubly substituted at C-4, by dihydroxylation of the exocyclic double bond and acetylation of the two hydroxy groups. Dihydroxylation of **9**, using a catalytic amount of osmium tetroxide, proceeded with complete facial selectivity to afford **10** in moderate yield. The stereochemical outcome of this reaction is the same as for the 5α-hydroxy analogue of **9**,[14] which indicates that it is not determined by the presence and orientation of the 5-hydroxy group but solely by the conformation of the molecule, which causes steric shielding of the β-face of the double bond by the 8-methyl group.

In order to circumvent concomitant reduction of the primary acetate group at C-20 when reducing the 13-carbonyl group, this reduction was carried out prior to acetylation. Reduction with DIBALH afforded the desired α-isomer **11** in good yield (Scheme 2). Acetylation of the primary hydroxy group at C-20, affording **12**, and triethylsilyl protection of the secondary hydroxy group at C-13 gave taxane **13**.



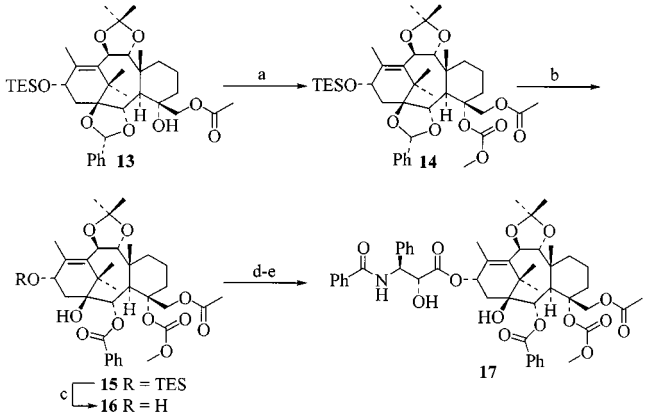
Scheme 2. Preparation of taxane **13**; reagents and conditions: (a) OsO_4, NMMO, THF/H_2O; (b) DIBALH, CH_2Cl_2, −20°C; (c) Ac_2O, pyridine, 4°C; (d) TESCl, imidazole, DMF

Acetylation of the tertiary hydroxy group on **13** proved troublesome. None of the usual acetylation methods, such as acetic anhydride/pyridine, acetyl chloride/LDA, acetyl chloride/LHMDS, afforded the desired product. Treatment of **13** with methyl chloroformate and lithium hexamethyldisilazide, however, afforded carbonate **14**, albeit in low yield.

A similarly low 4-hydroxy group reactivity was encountered by Kingston and colleagues in the synthesis of derivative **3a**.[4] Possibly, the relatively large thietane ring and the acetoxymethyl group shield the tertiary hydroxy group more effectively than the oxetane ring does. Alternatively, a

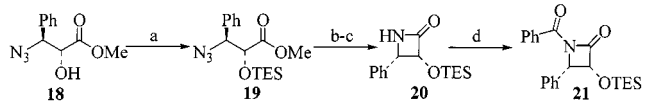
different conformation, situating the tertiary hydroxy group in a more crowded environment, might be involved.

The benzylidene bridge of carbonate **14** was oxidatively opened with palladium(II) acetate and *tert*-butyl hydroperoxide[14] to afford taxane **15** (Scheme 3). Deprotection of the 13-hydroxy group gave **16**, which was then coupled to β-lactam **21** using standard coupling procedures. Taxane **15** was observed as a side product in this reaction, as a consequence of a silyl shift from **21** to **16**. Derivative **17** was obtained upon fluoride-assisted desilylation.



Scheme 3. Preparation of derivative **17**; reagents and conditions: (a) MeOC(O)Cl, LHMDS, CH_2Cl_2, −78°C; (b) $Pd(OAc)_2$, *t*BuOOH, toluene, 60°C; (c) TBAF, THF; (d) **21**, NaHMDS, CH_2Cl_2, −78°C; (e) TBAF, THF

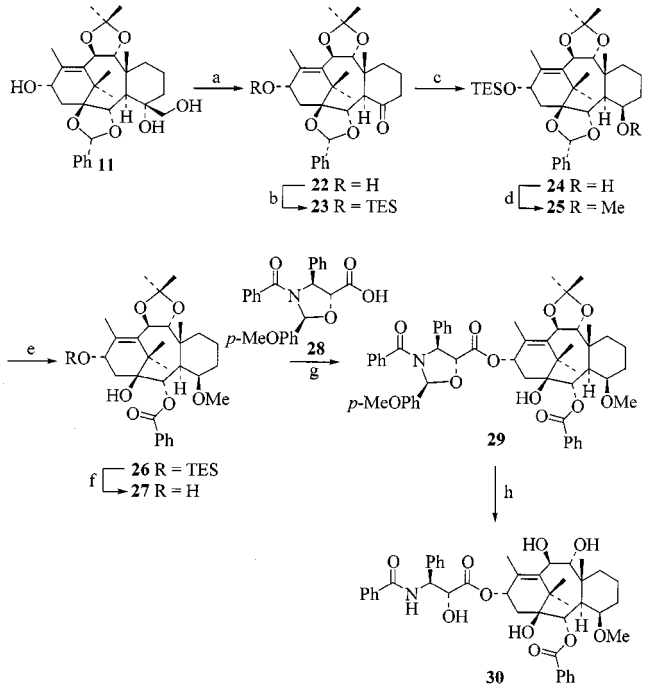
β-Lactam **21** was prepared in 8 steps starting from methyl (*E*)-cinnamate, in 27% overall yield. Asymmetric dihydroxylation, tosylation, epoxide formation and nucleophilic epoxide opening afforded **18** as described previously.[18,19] Following a new route, **18** was converted into β-lactam **21** in 4 steps. Silyl protection of the secondary hydroxy group gave **19** (Scheme 4). Reduction of the azido group to an amino group was followed by ring-closure, affording β-lactam **20**. *N*-benzoylation eventually afforded β-lactam **21**.



Scheme 4. Preparation of β-lactam **21**; reagents and conditions: (a) TESCl, NEt_3, THF; (b) H_2, Pd/C, EtOAc; (c) TMSCl, Et_3N, Et_2O, then *t*BuMgCl; (d) BzCl, DMAP, NEt_3, CH_2Cl_2

In our approaches towards paclitaxel derivatives, this 8-step preparation of β-lactam **21**[20] has been preferred over the Staudinger approach towards β-lactams like **21**,[21] as the former method offers intermediates which can easily be converted into other differently protected side chains such as **28** (vide infra). In some cases, these are the reagents of choice in the coupling step to baccatin III derivatives, as they provide higher reaction yields.

The synthesis of a derivative with only an oxygenated 4β-substituent was envisaged as starting with an oxidative cleavage of the vicinal diol unit on **11**. Oxidation with sodium periodate provided 4-oxotaxane **22** in almost quantitative yield (Scheme 5). Protection of the secondary hydroxy group, affording **23**, was followed by reduction of the ketone function with sodium borohydride. The reduction proved completely facial-selective, the hydride approaching the carbonyl group from the α-face to give **24**. This reaction again demonstrates complete steric blocking of the β-face of an exocyclic π-system at C-4 by the 8-methyl group.



Scheme 5. Preparation of derivative **30**; reagents and conditions: (a) $NaIO_4$, H_2O/THF; (b) TESCl, imidazole, DMF; (c) $NaBH_4$, MeOH, 0°C; (d) MeI, BuLi, THF; (e) *t*BuOOH, $Pd(OAc)_2$, toluene, 50°C; (f) TBAF, THF; (g) **28**, DCC, DMAP, CH_2Cl_2; (h) PTS, MeOH

The 4β-hydroxy group proved to be sterically highly encumbered, as no reaction was observed when **24** was treated with acetic anhydride/DMAP or acetyl chloride/BuLi. Methylation of the hydroxy group was accomplished, but only when large excesses of butyllithium and methyl iodide were used, the yield being low. The stereochemistry of 4β-methoxytaxane **25** was confirmed by NOE data. These showed contacts between 4-H/3-H and 4-H/14α-H, which clearly proves an α-orientation of 4-H.

The benzylidene bridge on **25** was oxidatively opened with *tert*-butyl hydroperoxide and palladium(II) acetate to afford **26**. Removal of the triethylsilyl protecting group, giving **27**, was followed by a DCC coupling with **28**, which proceeded in good yield to afford **29**.[22] Deprotection of the side chain led to concomitant deprotection of the 9- and 10-hydroxy groups to give D-ring modified derivative **30**.

The biological activities of taxanes **17** and **30** were determined in vitro in a range of well defined cancer cell lines. Both derivatives proved virtually inactive against all cell lines, the IC_{50} values being 1,000−10,000 times higher than those of paclitaxel. A logical line of reasoning would be to attribute this lack of activity to the flexible C-ring. Alternatively, the combination of the 4β-acetoxymethyl group and the 4α-methoxycarbonyloxy group may be too bulky to en-

able **17** to fit well inside the binding pocket on polymerized tubulin heterodimers. The low cytotoxic activity of **30** may be attributed to the absence of an apolar 4α-substituent on **30**, as it has been shown that the 4α-H derivative of paclitaxel exhibits a greatly reduced tubulin polymerization activity.[23] New, flexible C-ring derivatives possessing a small, apolar 4α-substituent and a relatively small, oxygenated 4β-substituent should divulge the true reason for the low activity of derivatives **17** and **30**. Preparation of such compounds is currently under investigation.

Experimental Section

General Remarks: All solvents were, if necessary, distilled and dried prior to use, following standard procedures. − ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and 2D NMR experiments were performed with a Bruker AC300 spectrometer in $CDCl_3$, using TMS as the internal standard unless otherwise stated. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). − Mass spectra were recorded with an MAT 9005, using FAB and EI modes. − Elemental analyses were carried out with a Carlo Erba Instruments CHNSO EA 1108 element analyzer. − Thin layer chromatography was carried out on Merck precoated 60 F-254 silica gel plates (thickness: 0.25 mm). − Column chromatography was carried out using Baker silica gel (63−200 mesh).

1,2-Benzylidene-9,10-isopropylidene-5α-acetyltaxicin-I (8): Aqueous NaOH (20 N, 25 mL) was added to a solution of **7a** (5.00 g, 8.00 mmol) in THF (60 mL). The reaction mixture was stirred at reflux temperature for 2 d, diluted with water (50 mL), and extracted twice with dichloromethane (150 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptanes, 1:1), yielding the saponified product (3.00 g, 6.07 mmol, 76%). This was dissolved in dry pyridine (25 mL), and acetic anhydride (8 mL) was added. The reaction mixture was stirred for 4 d at room temperature. The mixture was then diluted with ethyl acetate (75 mL), washed with a 0.5 M aqueous $KHSO_4$ solution, a saturated aqueous Na_2CO_3 solution, and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/heptanes, 1:3), yielding **8** (4.00 g, 7.45 mmol, 93%) as a white, amorphous solid. − ^{1}H NMR: δ = 1.13 (s, 3 H, 19-H), 1.37 (s, 3 H, 17-H), 1.47 (s, 3 H, acetonide), 1.54 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.94 (s, 3 H, 18-H), 2.10 [s, 3 H, $CH_3C(O)$], 2.65 (d, 1 H, J_{gem} = 19.6 Hz, 14-H), 2.72 (d, 1 H, J_{gem} = 19.6 Hz, 14-H), 3.05 (d, 1 H, J_{3-2} = 5.3 Hz, 3-H), 4.32 (d, 1 H, J_{9-10} = 9.2 Hz, 9-H), 4.37 (d, 1 H, J_{2-3} = 5.3 Hz, 2-H), 4.91 (d, 1 H, J_{10-9} = 9.2 Hz, 10-H), 5.27 (m, 2 H, 20-H + 5-H), 5.66 (br. s, 1 H, 20-H), 5.78 (s, 1 H, Ph-CH), 7.36−7.44 (m, 5 H, Ph). − FAB-MS; *m*/*z*: 559 [M + Na]$^+$. − $C_{32}H_{40}O_7$ (536.7): calcd. C 71.62, H 7.51; found C 71.34, H 7.63.

1,2-Benzylidene-9,10-isopropylidene-5-deoxytaxicin-I (9): Tri(*n*-butyl)phosphane (80 μL, 0.32 mmol) was added to a solution of bis(dibenzylideneacetone)palladium(0) (36.8 mg, 0.0640 mmol) in dry THF (50 mL). Triethylamine (1.78 mL, 12.8 mmol), formic acid (491 μL, 12.8 mmol), and **7a** (3.99 g, 6.38 mmol) were added successively at 0°C. The reaction mixture was stirred at reflux temperature for 3 d. It was then diluted with ethyl acetate (80 mL), washed with a saturated aqueous NH_4Cl solution, water, a saturated aqueous $NaHCO_3$ solution, and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/heptanes, 8:1), yielding **9** (2.76 g, 5.76 mmol, 90%) as a white, amorphous solid. − ^{1}H NMR: δ = 1.14 (s, 3 H, 19-H), 1.36 (s, 3 H, 17-H), 1.46 (s, 3 H, acetonide), 1.52 (s, 3 H, acetonide), 1.68 (s, 3 H, 16-H), 2.03 (s, 3 H, 18-H), 2.47 (d, 1 H, J_{3-2} = 5.5 Hz, 3-H), 2.67 (d, 1 H, J_{gem} = 19.6 Hz, 14-H), 2.74 (d, 1 H, J_{gem} = 19.6 Hz, 14-H), 4.32 (d, 1 H, 9-H), 4.34 (d, 1 H, 2-H), 4.87 (d, 1 H, J_{10-9} = 9.27 Hz, 10-H), 4.98 (br. s, 1 H, 20-H), 5.47 (br. s, 1 H, 20-H), 5.79 (s, 1 H, Ph-CH), 7.35−7.46 (m, 5 H, Ph). − FAB-MS; *m*/*z*: 479 [M + H]$^+$. − $C_{30}H_{38}O_5$ (478.6): calcd. C 75.28, H 8.00; found C 75.09, H 8.17.

1,2-Benzylidene-4α,20-dihydroxy-9,10-isopropylidene-5-deoxytaxicin-I (10): NMMO (1.40 g, 10.4 mmol) and OsO_4 (7.6 mL, 0.61 mmol; 2.5 wt-% in *tert*-butyl alcohol) were added to a solution of **9** (2.91 g, 6.08 mmol) in THF (78 mL) and water (18 mL). The reaction mixture was stirred for 6 d at room temperature, with 2 mL of water being added every day. The reaction was quenched by addition of $Na_2S_2O_4$ (320 mg, 1.84 mmol) and Florisil (2.5 g). After 20 min, the reaction mixture was filtered through Celite and diluted with ethyl acetate (100 mL) and water (30 mL). The aqueous layer was separated from the organic layer and washed with ethyl acetate (50 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/heptanes, 3:2), yielding **10** (2.08 g, 4.06 mmol, 67%) as a glassy solid. − ^{1}H NMR: δ = 1.16 (s, 3 H, 19-H), 1.40 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.49 (s, 3 H, acetonide), 1.67 (s, 3 H, 16-H), 2.00 (s, 3 H, 18-H), 2.10 (d, 1 H, J_{3-2} = 5.1 Hz, 3-H), 2.31 (dd, 1 H, J_{OH-20} = 2.2 Hz, $J_{OH-20'}$ = 9.4 Hz, 20-OH), 2.79 (d, 1 H, J_{gem} = 19.3 Hz, 14-H), 3.29 (s, 1 H, 4-OH), 3.34 (d, 1 H, J_{gem} = 19.3 Hz, 14-OH), 3.71 (pseudo-t, 1 H, *J* = 10.2 Hz, 20′-H), 3.96 (br. d, 1 H, J_{gem} = 10.8 Hz, 20-H), 4.24 (d, 1 H, J_{9-10} = 9.3 Hz, 9-H), 4.35 (d, 1 H, J_{2-3} = 5.1 Hz, 2-H), 4.77 (d, 1 H, J_{10-9} = 9.3 Hz, 10-H), 5.87 (s, 1 H, Ph-CH), 7.41 (m, 5 H, Ph). − FAB-MS; *m*/*z*: 513 [M + H]$^+$, 535 [M + Na]$^+$. − $C_{30}H_{40}O_7$ (512.6): calcd. C 70.29, H 7.86; found C 69.90, H 7.82.

Reduction of Diol 10 to Triol 11: DIBALH (5.9 mL, 8.8 mmol; 25 wt-% solution in toluene) was added slowly at −20°C to a solution of **10** (1.00 g, 1.95 mmol) in dichloromethane (30 mL). After 30 min, a 10% aqueous solution of citric acid (30 mL) was added. The two layers were separated and the aqueous layer was extracted twice with dichloromethane (20 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/heptanes, 3:2), yielding **11** (612 mg, 1.19 mmol, 61%) as a white solid. − ^{1}H NMR: δ = 1.12 (s, 3 H, 19-H), 1.20 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.46 (s, 3 H, acetonide), 1.58 (s, 3 H, 16-H), 2.01 (s, 3 H, 18-H), 2.28 (dd, 1 H, J_{gem} = 16.0 Hz, J_{14-13} = 2.4 Hz, 14-H), 2.37 (br. d, 1 H, J_{OH-20} = 7.0 Hz, 20-OH), 2.52 (d, 1 H, J_{3-2} = 4.5 Hz, 3-H), 2.65 (dd, 1 H, J_{gem} = 15.9 Hz, J_{14-13} = 10.0 Hz, 14-H), 2.92 (br. d, J_{OH-13} = 8.0 Hz, 13-OH), 3.56 (s, 1 H, 4-OH), 3.63 (pseudo-t, 1 H, *J* = 9.7 Hz, 20′-H), 4.07 (br. d, 1 H, 20-H), 4.08 (d, 1 H, J_{9-10} = 9.3 Hz, 9-H), 4.18 (d, 1 H, J_{2-3} = 4.5 Hz, 2-H), 4.47 (pseudo-t, *J* = 9.2 Hz, 13-H), 4.74 (d, 1 H, J_{10-9} = 9.3 Hz, 10-H), 5.81 (s, 1 H, Ph-CH), 7.37−7.48 (m, 5 H, Ph). − FAB-MS; *m*/*z*: 537 [M + Na]$^+$. − $C_{30}H_{42}O_7 \cdot 0.5\ H_2O$ (523.7): calcd. C 68.80, H 8.27; found C 68.53, H 8.04.

Acetylation of Triol 11 To Give Acetate 12: Acetic anhydride (600 μL, 6.40 mmol) was added at 0°C to a solution of **11** (2.02 g, 3.92 mmol) in dry pyridine (80 mL). The reaction mixture was

stirred overnight at 4°C. The reaction was quenched with a 1 N aqueous HCl solution (100 mL) and the resulting mixture was extracted twice with ethyl acetate (100 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (EtOAc/heptanes, 1:1) yielded **12** (1.54 g, 2.78 mmol, 70%) as a white solid. − ^{1}H NMR: δ = 1.19 (s, 3 H, 19-H), 1.20 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.59 (s, 3 H, 16-H), 2.01 (s, 3 H, 18-H), 2.06 [s, 3 H, C(O)CH_3], 2.23 (br. d, 1 H, J = 16.2 Hz, 14-H), 2.53 (d, 1 H, J_{3-2} = 4.5 Hz, 3-H), 2.61 (dd, 1 H, J_{gem} = 16.3 Hz, J_{14-13} = 10.2 Hz, 14-H), 4.10 (d, 1 H, J_{9-10} = 9.4 Hz, 9-H), 4.14 (d, 1 H, J_{2-3} = 4.4 Hz, 2-H), 4.42 (br. d, 1 H, J = 9 Hz, 13-H), 4.44 (d, 1 H, J_{gem} = 13 Hz, 20-H), 4.74 (d, 1 H, J_{10-9} = 9 Hz, 10-H), 4.78 (d, 1 H, J_{gem} = 13 Hz, 20-H), 5.84 (s, 1 H, Ph-CH), 7.37−7.52 (m, 5 H, Ph). − FAB-MS; *m/z*: 579 [M + Na]$^+$. − $C_{32}H_{42}O_8$·0.25 H_2O (561.2): calcd. C 68.49, H 7.99; found C 68.25, H 7.54.

Protection of Acetate 12 To Give Silyl Ether 13: Chlorotriethylsilane (2.10 mL, 12.5 mmol) was added to a solution of imidazole (2.21 g, 32.5 mmol) in DMF (10 mL). The mixture was stirred for 20 min at room temperature, after which a solution of **12** (1.39 g, 2.49 mmol) in DMF (10 mL) was added. After 1.5 h, the reaction mixture was diluted with ethyl acetate (100 mL) and water (100 mL). The layers were separated and the aqueous layer was washed three times with ethyl acetate. The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:2) yielded **13** (1.33 g, 1.97 mmol, 79%) as a white solid. − ^{1}H NMR: δ = 0.62 [q, 6 H, J = 7.9 Hz, Si(CH_2CH_3)$_3$], 0.96 [t, 9 H, J = 7.8 Hz, Si(CH_2CH_3)$_3$], 1.22 (s, 6 H, 17-H + 19-H), 1.41 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.59 (s, 3 H, 16-H), 1.94 (s, 3 H, 18-H), 2.05 [s, 3 H, C(O)CH_3], 2.29 (m, 2 H, 3-H + 14-H), 2.73 (dd, 1 H, J_{gem} = 15.2 Hz, J_{14-13} = 4.2 Hz, 14-H), 4.11 (d, 1 H, J_{9-10} = 10 Hz, 9-H), 4.46 (d, 1 H, J_{gem} = 11.9 Hz, 20-H), 4.67 (d, 1 H, J_{gem} = 12.0 Hz, 20-H), 4.73 (m, 2 H, 10-H + 13-H), 5.77 (s, 1 H, Ph-CH), 7.35−7.39 (m, 3 H, Ph), 7.46−7.51 (m, 2 H, Ph). − FAB-MS; *m/z*: 693 [M + Na]$^+$. − $C_{38}H_{58}O_8Si$·0.25 H_2O (675.5): calcd. C 67.57, H 8.73; found C 67.41, H 8.26.

Methoxycarbonylation of Silyl Ether 13 To Give Carbonate 14: A solution of lithium bis(trimethylsilyl)amide (3.4 mmol) [prepared from butyllithium (2.1 mL, 3.4 mmol; 1.6 M solution in *n*-hexane) and hexamethyldisilazane (789 μL, 3.74 mmol) in THF (2 mL) at 0°C] was added at −78 °C to a solution of **13** (765 mg, 1.14 mmol) in THF (10 mL). After 10 min, methyl chloroformate (885 μL, 11.4 mmol) was added, and the reaction mixture was then stirred for 15 min at −78 °C. The reaction mixture was diluted with ethyl acetate (50 mL) and washed successively with a saturated aqueous NH_4Cl solution and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:7) yielded **14** (325 mg, 0.446 mmol, 39%) as a white solid, together with recovered **13** (110 mg, 0.164 mmol, 14%). − ^{1}H NMR: δ = 0.60 [q, 6 H, J = 7.8 Hz, Si(CH_2CH_3)$_3$], 0.94 [t, 9 H, J = 7.8 Hz, Si(CH_2CH_3)$_3$], 1.26, (s, 3 H, 19-H), 1.29 (s, 3 H, 17-H), 1.41 (s, 3 H, acetonide), 1.46 (s, 3 H, acetonide), 1.63 (s, 3 H, 16-H), 1.90 [s, 3 H, C(O)CH_3], 1.94 (s, 3 H, 18-H), 2.25 (dd, 1 H, J_{gem} = 15 Hz, J_{14-13} = 9.7 Hz, 14-H), 2.28 (d, 1 H, J_{3-2} = 4.7 Hz, 3-H), 2.84 (dd, 1 H, J_{gem} = 15.0 Hz, J_{14-13} = 5.7 Hz, 14-H), 3.75 (s, 3 H, OCH_3), 4.10 (d, 1 H, J_{2-3} = 4.7 Hz, 2-H), 4.19 (d, 1 H, J_{9-10} = 9.4 Hz, 9-H), 4.64 (d, 1 H, J_{gem} = 14.1 Hz, 20-H), 4.74 (d, 1 H, J_{gem} = 14 Hz, 20-H), 4.75 (d, 1 H, J_{10-9} = 9 Hz, 10-H), 4.88 (m, 1 H, 13-H), 5.76 (s, 1 H, Ph-CH), 7.31−7.35 (m, 3 H, Ph), 7.41−7.45 (m, 2 H, Ph). − FAB-MS; *m/z*: 751 [M + Na]$^+$. − $C_{40}H_{60}O_{10}Si$·0.25 H_2O (733.5): calcd. C 65.50, H 8.31; found C 65.27, H 7.81.

Oxidative Opening of the Benzylidene Acetal on 14 To Give Benzoate 15: Palladium(II) acetate (17 mg, 0.076 mmol) and *tert*-butyl hydroperoxide (84 μL, 5.0−6.0 M solution in decane) were added to a solution of **14** (300 mg, 0.412 mmol) in toluene (10 mL). The reaction mixture was stirred at 60 °C for 24 h and then filtered through Celite, which was rinsed afterwards with ethyl acetate (25 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (CH_2Cl_2/heptanes/EtOAc, 10:5:2) yielded **15** (132 mg, 0.177 mmol, 43%) as a white solid. − ^{1}H NMR: δ = 0.67 [q, 6 H, J = 7.8 Hz, Si(CH_2CH_3)$_3$], 1.00 [t, 9 H, J = 7.8 Hz, Si(CH_2CH_3)$_3$], 1.22, (s, 3 H, 19-H), 1.24 (s, 3 H, 17-H), 1.42 (s, 3 H, acetonide), 1.49 (s, 3 H, acetonide), 1.77 (s, 3 H, 16-H), 1.98 (s, 3 H, 18-H), 2.21 [s, 3 H, C(O)CH_3], 2.64 (d, 1 H, J_{3-2} = 4.8 Hz, 3-H), 3.14 (dd, 1 H, J_{gem} = 14.8 Hz, J_{14-13} = 6.0 Hz, 14-H), 3.64 (s, 3 H, OCH_3), 4.21 (d, 1 H, J_{gem} = 13.5 Hz, 20-H), 4.33 (d, 1 H, J_{9-10} = 9.6 Hz, 9-H), 4.55 (d, 1 H, J_{gem} = 13.5 Hz, 20-H), 4.82 (d, 1 H, J_{10-9} = 9.6 Hz, 10-H), 4.99 (m, 1 H, 13-H), 5.75 (d, 1 H, J_{2-3} = 4.7 Hz, 2-H), 7.46 (pseudo-t, 2 H, J = 7.4 Hz, Ph), 7.58 (pseudo-t, 1 H, J = 7 Hz, Ph), 7.98 (d, 2 H, J = 7.3 Hz, Ph). − FAB-MS; *m/z*: 1512 [2 M + Na]$^+$, 767 [M + Na]$^+$. − $C_{40}H_{60}O_{11}Si$·2H_2O (781.0): calcd. C 61.51, H 8.26; found C 61.87, H 7.76.

Desilylation of Carbonate 15 To Give Alcohol 16: Tetrabutylammonium fluoride (300 μL, 0.3 mmol; 1 M solution in THF) was added to a solution of **15** (185 mg, 0.248 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 10 min and the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted twice with ethyl acetate (15 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 2:1) yielded **16** (114 mg, 0.181 mmol, 73%) as a white solid. − ^{1}H NMR: δ = 1.14, (s, 3 H, 19-H), 1.24 (s, 3 H, 17-H), 1.43 (s, 3 H, acetonide), 1.50 (s, 3 H, acetonide), 1.65 (s, 3 H, 16-H), 2.03 (s, 3 H, 18-H), 2.25 [s, 3 H, C(O)CH_3], 2.48 (dd, 1 H, J_{gem} = 15.1 Hz, J_{14-13} = 10.1 Hz, 14-H), 2.77 (dd, 1 H, J_{gem} = 15 Hz, J_{14-13} = 3.4 Hz, 14-H), 2.82 (d, 1 H, J_{3-2} = 4.9 Hz, 3-H), 3.65 (s, 3 H, OCH_3), 4.22 (d, 1 H, J_{gem} = 13.6 Hz, 20-H), 4.30 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.57 (d, 1 H, J_{gem} = 13.6 Hz, 20-H), 4.68 (m, 1 H, 13-H), 4.81 (d, 1 H, J_{10-9} = 9.5 Hz, 10-H), 5.77 (d, 1 H, J_{2-3} = 4.7 Hz, 2-H), 7.47 (pseudo-t, 2 H, J = 7.6 Hz, Ph), 7.60 (pseudo-t, 1 H, J = 7.4 Hz, Ph), 7.98 (d, 2 H, J = 7.2 Hz, Ph). − FAB-MS; *m/z*: 1284 [2 M + Na]$^+$, 653 [M + Na]$^+$. − $C_{34}H_{46}O_{11}$ (630.7): calcd. C 64.75, H 7.35; found C 64.66, H 7.34.

Coupling of Alcohol 16 with β-Lactam 21 and Desilylation To Give Derivative 17: β-Lactam **21** (18.1 mg, 0.0495 mmol) was added to a solution of **16** (20.9 mg, 0.0331 mmol) in THF (2 mL). The reaction mixture was cooled to −78 °C, after which sodium bis(trimethylsilyl)amide (79 μL, 0.079 mmol; 1 M solution in THF) was added. The reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL), and the mixture was diluted with ethyl acetate (5 mL). The layers were separated and the aqueous fraction was extracted twice with ethyl acetate (5 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. This afforded crude 2′-TES-protected **17** (23 mg, 0.023 mmol, 70%), which was deprotected without prior purification as follows. Tetrabutylammonium fluoride (28 μL,

0.028 mmol; 1 M solution in THF) was added to a solution of 2′-TES-protected **17** (23 mg, 0.023 mmol) in THF (1.5 mL). The reaction mixture was stirred at room temperature for 10 min. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous fraction was extracted twice with ethyl acetate (5 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification by means of PLC (preparative layer chromatography) on alumina (EtOAc/heptanes, 2:1) yielded **17** (15 mg, 0.017 mmol, 72%) as a white solid. − ^{1}H NMR: δ = 1.22, (s, 3 H, 19-H), 1.24 (s, 3 H, 17-H), 1.40 (s, 3 H, 16-H), 1.49 (s, 3 H, acetonide), 1.53 (s, 3 H, acetonide), 1.68 (s, 3 H, 18-H), 2.19 [s, 3 H, C(O)CH_3], 2.45 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 10.2 Hz, 14-H), 2.60 (d, 1 H, J_{3-2} = 4.8 Hz, 3-H), 3.10 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 5.4 Hz, 14-H), 3.42 (d, 1 H, $J_{OH-2'}$ = 6.5 Hz, 2′-OH), 3.64 (s, 3 H, OCH_3), 4.24 (d, 1 H, J_{gem} = 13.4 Hz, 20-H), 4.32 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.48 (d, 1 H, J_{gem} = 13.4 Hz, 20-H), 4.69 (d, 1 H, J_{10-9} = 9.5 Hz, 10-H), 4.71 (dd, 1 H, 2′-H), 5.70 (dd, 1 H, J = 8.8 Hz, J = 3.1 Hz, 3′-H), 5.78 (d, 1 H, J_{2-3} = 4.8 Hz, 2-H), 6.05 (m, 1 H, 13-H), 7.33−7.59 (m, 11 H, Ph), 7.82 (d, 2 H, J = 7.0 Hz, Ph), 7.97 (d, 2 H, J = 7.2 Hz, Ph). − FAB-MS; *m/z*: 1818 [2 M + Na]$^+$, 920 [M + Na]$^+$. − $C_{50}H_{59}NO_{14}$·$2H_2O$ (934.0): calcd. C 64.30, H 6.80, N 1.50; found C 64.42, H 6.56, N 1.64.

Silylation of Alcohol 18 To Give Silyl Ether 19: Triethylamine (7.75 mL, 55.3 mmol) and chlorotriethylsilane (4.65 mL, 27.7 mmol) were added to a solution of methyl (2*R*,3*S*)-3-azido-2-hydroxy-3-phenylpropanoate (**18**) (2.04 g, 9.22 mmol) in THF (60 mL). The resulting suspension was stirred overnight. It was diluted with ethyl acetate (150 mL) and then washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:8) yielded **19** (2.96 g, 8.82 mmol, 96%) as an oil. − ^{1}H NMR: δ = 0.55 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.90 [t, 9 H, J = 7.89 Hz, Si(CH$_2$CH_3)$_3$], 3.61 (s, 3 H, OCH_3), 4.32 (d, 1 H, J_{2-3} = 5.93 Hz, 2-H), 4.80 (d, 1 H, J_{3-2} = 5.93 Hz, 3-H), 7.29−7.37 (m, 5 H, Ph). − FAB-MS; *m/z*: 306 [M − N_2 − H]$^+$, 293 [M − N_3]$^+$. − $C_{16}H_{25}N_3O_3$ (335.5): calcd. C 57.28, H 7.51, N12.53; found C 56.87, H 7.66, N12.27.

Reduction of 19 and Ring-Closure To Give β-Lactam 20: Pd/C (10% Pd on C, 150 mg) was added to a solution of **19** (2.90 g, 8.64 mmol) in ethyl acetate (30 mL). The resulting suspension was hydrogenated for 20 h using a Parr apparatus. The reaction mixture was filtered through Celite, which was thoroughly rinsed with ethyl acetate. The combined organic fractions were concentrated in vacuo, affording methyl (2*R*,3*S*)-3-amino-3-phenyl-2-(triethylsilyloxy)propanoate (2.58 g, 8.34 mmol) as an oil. − ^{1}H NMR: δ = 0.46 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.82 [t, 9 H, J = 7.9 Hz, Si(CH$_2$CH_3)$_3$], 3.68 (s, 3 H, OCH_3), 4.28 (d, 1 H, J_{2-3} = 4.1 Hz, 2-H), 4.30 (d, 1 H, J_{3-2} = 4.1 Hz, 3-H), 7.22−7.35 (m, 5 H, Ph). − Triethylamine (1.51 mL, 10.8 mmol) and trimethylsilyl chloride (1.27 mL, 10.0 mmol) were added at 0°C to a solution of the crude product in diethyl ether (100 mL). The solution was stirred at room temperature for 1 h and then cooled to 0°C. A solution of *tert*-butylmagnesium chloride (12.5 mL, 25.0 mmol; 2.0 M solution in diethyl ether) was added slowly. The reaction mixture was stirred at room temperature for 3 h, diluted with ether (100 mL), and extracted with a saturated aqueous NH_4Cl solution. The aqueous fraction was extracted with diethyl ether and the combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:1) yielded **20** (1.43 g, 5.17 mmol, 62%) as a white solid. − ^{1}H NMR: δ = 0.44 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.76 [t, 9 H, J = 7.88 Hz, Si(CH$_2$CH_3)$_3$], 4.79 (d, 1 H, J_{2-3} = 4.7 Hz, 2-H), 5.08 (dd, 1 H, J_{3-2} = 4.7 Hz, $J_{3\text{-NH}}$ = 2.68 Hz, 3-H), 6.17 (br. s, 1 H, NH), 7.28−7.38 (m, 5 H, Ph). − EI-MS; *m/z*: 277 [M]$^+$. − $C_{15}H_{23}NO_2Si$ (277.4): calcd. C 64.94, H 8.36, N 5.05; found C 65.17, H 8.43, N 5.08.

Benzoylation of 20 To Give β-Lactam 21: Triethylamine (1.04 mL, 7.49 mmol), 4-(dimethylamino)pyridine (9.2 mg, 0.075 mmol), and freshly distilled benzoyl chloride (655 μL, 5.64 mmol) were added at 0°C to a solution of **20** (1.04 g, 3.75 mmol) in dichloromethane (40 mL). The reaction mixture was stirred for 20 h at room temperature, diluted with dichloromethane (30 mL), and then washed with a saturated aqueous NH_4Cl solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 2:5) yielded **21** (1.24 g, 3.27 mmol, 87%) as an oil. − ^{1}H NMR: δ = 0.48 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.80 [t, 9 H, J = 7.88 Hz, Si(CH$_2$CH_3)$_3$], 5.15 (d, 1 H, J_{2-3} = 6.12 Hz, 2-H), 5.41 (d, 1 H, J_{3-2} = 6.12 Hz, 3-H), 7.29−7.38 (m, 5 H, Ph), 7.48 (t, 2 H, J = 7.9 Hz, Bz), 7.60 (m, 1 H, Bz), 8.03 (m, 2 H, Bz). − EI-MS; *m/z*: 496 [M + TES]$^+$, 382 [M + 1]$^+$; peak match: calcd. for $C_{22}H_{27}NO_3Si$: 381.17602; found 381.17584.

Oxidative Cleavage of Triol 11 To Give Ketone 22: A solution of **11** (809 mg, 1.57 mmol) and sodium periodate (1.34 g, 6.28 mmol) in THF/water (40 mL, 11:9 v/v) was stirred for 72 h at room temperature. The reaction mixture was then diluted with ethyl acetate (25 mL) and water (25 mL). The layers were separated and the aqueous layer washed with ethyl acetate (25 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (CH_2Cl_2/EtOAc, 10:1) afforded **22** (748 mg, 1.55 mmol, 99%) as a white solid. − ^{1}H NMR: δ = 1.11 (s, 3 H, 19-H), 1.16 (s, 3 H, 17-H), 1.45 (s, 3 H, acetonide), 1.48 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.91 (dd, 1 H, J_{gem} = 15.8 Hz, J_{14-13} = 4.1 Hz, 14-H), 2.06 (s, 3 H, 18-H), 2.26−2.42 (m, 3 H, 14-H + 2 × 6-H/7-H/8-H), 3.34 (d, 1 H, J_{3-2} = 5.8 Hz, 3-H), 4.10 (d, 1 H, J_{9-10} = 9 Hz, 9-H), 4.11 (d, 1 H, J_{2-3} = 6 Hz, 2-H), 4.71 (m, 1 H, 13-H), 4.88 (d, 1 H, J_{10-9} = 9.4 Hz, 10-H), 5.85 (s, 1 H, Ph-CH), 7.30−7.37 (m, 3 H, Ph), 7.48−7.51 (m, 2 H, Ph). − FAB-MS; *m/z*: 505 [M + Na]$^+$, 987 [2 M + Na]$^+$. − $C_{29}H_{38}O_6$·0.5 H_2O (491.6): calcd. C 70.85, H 7.99; found C 71.14, H 7.86.

Silylation of 22 To Give Silyl Ether 23: A solution of imidazole (368 mg, 5.41 mmol) and chlorotriethylsilane (349 μL, 2.08 mmol) in DMF (15 mL) was stirred for 15 min at room temperature, after which **22** (200 mg, 0.414 mmol) was added. The mixture was stirred for 5 h at room temperature, diluted with ethyl acetate (40 mL), and extracted with water (40 mL). The water/DMF layer was washed with ethyl acetate (40 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/hexanes, 1:5) afforded **23** (227 mg, 0.380 mmol, 92%) as a white solid. − ^{1}H NMR: δ = 0.55 [q, 6 H, J = 7.9 Hz, Si(CH_2CH$_3$)$_3$], 0.92 [t, 9 H, J = 7.9 Hz, Si(CH$_2$CH_3)$_3$], 1.12 (s, 3 H, 19-H), 1.15 (s, 3 H, 17-H), 1.44 (s, 3 H, acetonide), 1.47 (s, 3 H, acetonide), 1.56 (s, 3 H, 16-H), 1.88 (dd, 1 H, J_{gem} = 15.6 Hz, J_{14-13} = 3.9 Hz, 14-H), 2.01 (s, 3 H, 18-H), 2.22−2.38 (m, 3 H, 14-H + 2 × 6-H/7-H/8-H), 3.36 (d, 1 H, J_{3-2} = 5.8 Hz, 3-H), 4.07 (m, 2 H, 2-H + 9-H), 4.60 (m, 1 H, 13-H), 4.88 (d, 1 H, J_{10-9} = 9.4 Hz, 10-H), 5.86 (s, 1 H, Ph-CH), 7.30−7.36 (m, 3 H, Ph), 7.45−7.49 (m, 2 H, Ph). − FAB-MS; *m/z*: 596 [M]$^+$, 619 [M + Na]$^+$, 711 [M + TES]$^+$. − $C_{35}H_{52}O_6Si$ (596.9): calcd. C 70.43, H 8.78; found C 70.43, H 8.73.

Reduction of 23 To Give Alcohol 24: $NaBH_4$ (57.9 mg, 1.53 mmol) was added in small portions at 0°C to a solution of **23** (300 mg,

0.503 mmol) in methanol (10 mL). After stirring for 20 min at 0°C, the reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (5 mL). Next, ethyl acetate (10 mL) and water (10 mL) were added and the layers were separated. The aqueous layer was washed twice with ethyl acetate (10 mL). The combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 2:3) afforded **24** (265 mg, 0.442 mmol, 88%) as a white solid. − ^{1}H NMR: δ = 0.59 [q, 6 H, *J* = 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$], 0.95 [t, 9 H, *J* = 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 1.17 (s, 3 H, 17-H), 1.41 (s, 3 H, 19-H), 1.42 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.57 (s, 3 H, 16-H), 1.90 (s, 3 H, 18-H), 2.02 (dd, 1 H, J_{gem} = 15.2 Hz, J_{14-13} = 4.2 Hz, 14-H), 2.09 (m, 1 H, 3-H), 2.38 (dd, 1 H, J_{gem} = 15.2 Hz, J_{14-13} = 9.3 Hz, 14-H), 2.69 (br. s, 1 H, 4-OH), 4.07 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.13 (d, 1 H, J_{2-3} = 4.4 Hz, 2-H), 4.34 (br. s, 1 H, 4-H), 4.68 (m, 1 H, 13-H), 4.69 (d, 1 H, J_{10-9} = 9.5 Hz, 10-H), 5.82 (s, 1 H, Ph-CH), 7.35−7.40 (m, 3 H, Ph), 7.45−7.49 (m, 2 H, Ph). − FAB-MS; *m*/*z*: 598 [M]$^+$, 621 [M + Na]$^+$. − $C_{35}H_{54}O_6Si{\cdot}H_2O$ (616.9): calcd. C 68.14, H 9.15; found C 68.41, H 9.00.

Methylation of Alcohol 24 To Give Methyl Ether 25: *n*-Butyllithium (3.4 mL, 5.4 mmol; 1.6 M solution in *n*-hexane) was added to a solution of **24** (218 mg, 0.364 mmol) in THF (10 mL). The solution was stirred for 30 min at 0°C, after which methyl iodide (454 μL, 7.3 mmol) was added carefully. The mixture was allowed to warm to room temperature and was stirred for 20 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) and the mixture was then diluted with ethyl acetate (20 mL) and water (10 mL). The layers were separated and the combined organic fractions were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:4) afforded **25** (127 mg, 0.207 mmol, 57%) as a white solid. − ^{1}H NMR: δ = 0.57 [q, 6 H, *J* = 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$], 0.94 [t, 9 H, *J* = 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 1.16 (s, 3 H, 17-H), 1.35 (s, 3 H, 19-H), 1.41 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide), 1.56 (s, 3 H, 16-H), 1.90 (s, 3 H, 18-H), 1.93 (dd, 1 H, J_{14-13} = 4.5 Hz, 14-H), 2.07 (m, 1 H, 3-H), 2.28 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 9.7 Hz, 14-H), 3.21 (s, 3 H, OCH$_3$), 3.67 (br. s, 1 H, 4-H), 4.08 (m, 2 H, 9-H + 2-H), 4.64 (m, 1 H, 13-H), 4.71 (d, 1 H, J_{10-9} = 9.4 Hz, 10-H), 5.89 (s, 1 H, Ph-CH), 7.33−7.37 (m, 3 H, Ph), 7.50−7.52 (m, 2 H, Ph). − FAB-MS; *m*/*z*: 635 [M + Na]$^+$. − $C_{36}H_{56}O_6Si$ (612.9): calcd. C 70.55, H 9.21; found C 70.38, H 9.07.

Oxidative Opening of the Benzylidene Acetal on 25 To Give Benzoate 26: The same procedure was followed as for **15**, except that the reaction mixture was stirred at 50°C for 3 d. In this way, 100 mg (0.163 mmol) of taxane **25** afforded 49 mg (0.078 mmol, 48%) of **26** after column chromatography (EtOAc/heptanes, 1:5). − ^{1}H NMR: δ = 0.70 [q, 6 H, *J* = 7.9 Hz, Si(C*H*$_2$CH$_3$)$_3$], 1.05 [t, 9 H, *J* = 7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 1.14 (s, 3 H, 17-H), 1.34 (s, 3 H, 19-H), 1.41 (s, 3 H, acetonide), 1.48 (s, 3 H, acetonide), 1.60 (s, 3 H, 16-H), 1.92 (s, 3 H, 18-H), 2.32 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 4.0 Hz, 14-H), 2.46 (dd, 1 H, J_{14-13} = 9.2 Hz, 14-H), 2.48 (m, 1 H, 3-H), 2.61 (s, 3 H, OCH$_3$), 3.62 (br. s, 1 H, 4-H), 4.24 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.75 (d, 1 H, J_{10-9} = 9.5 Hz, 10-H), 5.56 (d, 1 H, J_{2-3} = 5.3 Hz, 2-H), 7.44 (pseudo-t, 2 H, *J* = 7.5 Hz, Ph), 7.55 (t, 1 H, *J* = 7.3 Hz, Ph), 8.06 (d, 2 H, *J* = 7.1 Hz, Ph). − FAB-MS; *m*/*z*: 652 [M + Na + H]$^+$. − $C_{36}H_{56}O_7Si{\cdot}H_2O$ (646.9): calcd. C 66.84, H 9.04; found C 66.91, H 8.87.

Desilylation of 26 To Give Alcohol 27: The same procedure was followed as for **16**. In this way, 38 mg (0.060 mmol) of taxane **26** afforded 28 mg (0.078 mmol, 91%) of **27** after column chromatography (EtOAc/heptanes, 1:2). − ^{1}H NMR: δ = 1.16 (s, 3 H, 17-H), 1.36 (s, 3 H, 19-H), 1.42 (s, 3 H, acetonide), 1.49 (s, 3 H, acetonide), 1.62 (s, 3 H, 16-H), 1.99 (s, 3 H, 18-H), 2.32 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 4.2 Hz, 14-H), 2.44 (dd, 1 H, J_{3-2} = 5.4 Hz, J_{3-4} = 1.0 Hz, 3-H), 2.53 (dd, 1 H, J_{gem} = 15.3 Hz, J_{14-13} = 9.7 Hz, 14-H), 2.62 (s, 3 H, OCH$_3$), 3.68 (br. s, 1 H, 4-H), 4.27 (d, 1 H, J_{9-10} = 9.5 Hz, 9-H), 4.74 (d, 1 H, J_{10-9} = 9.5 Hz, 10-H), 4.84 (m, 1 H, 13-H), 5.59 (d, 1 H, J_{2-3} = 5.4 Hz, 2-H), 7.46 (pseudo-t, 2 H, *J* = 7.7 Hz, Ph), 7.52 (t, 1 H, *J* = 7.3, Ph), 8.10 (d, 2 H, *J* = 7.3 Hz, Ph). − FAB-MS; *m*/*z*: 537 [M + Na]$^+$, 1051 [2M + Na]$^+$. − $C_{30}H_{42}O_7{\cdot}2H_2O$ (550.7): calcd. C 65.43, H 8.42; found C 65.32, H 8.72.

Coupling of Alcohol 27 with Oxazolidine 28 To Give the Protected Derivative 29: 4-Pyrrolidinopyridine (7.3 mg, 0.049 mmol), **28** (24 mg, 0.060 mmol), and dicyclohexyl carbodiimide (13 mg, 0.063 mmol) were added at 0°C to a solution of **27** (23 mg, 0.045 mmol) in toluene/CH_2Cl_2 (1.5 mL, 30:1 v/v). The reaction mixture was allowed to warm to room temperature and was stirred for 45 min. Diethyl ether (5 mL) was added and the resulting suspension was filtered through Celite. The filtrate was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:2) afforded **29** (29 mg, 0.032 mmol, 71%) as a white solid. − ^{1}H NMR: δ = 1.23 (s, 3 H, 19-H), 1.34 (s, 3 H, 17-H), 1.43 (s, 3 H, acetonide), 1.49 (s, 3 H, acetonide), 1.65 (s, 3 H, 16-H), 1.92 (s, 3 H, 18-H), 2.24 (dd, 1 H, J_{gem} = 15.5 Hz, 14-H), 2.37 (dd, 1 H, J_{3-2} = 5.4 Hz, J_{3-4} = 3.4 Hz, 3-H), 2.57 (s, 3 H, OCH$_3$), 2.66 (dd, 1 H, J_{gem} = 15.5 Hz, 14-H), 3.62 (m, 1 H, 4-H), 3.80 (s, 3 H, C$_6$H$_4$OC*H*$_3$), 4.29 (d, 1 H, J_{9-10} = 9.4 Hz, 9-H), 4.74 (d, 1 H, J_{10-9} = 9.4 Hz, 10-H), 5.02 (d, 1 H, 2′-H), 5.60 (d, 1 H, J_{2-3} = 5.4 Hz, 2-H), 5.72 (br. s, 1 H, 3′-H), 6.06 (br. d, 1 H, 13-H), 6.73 (br. s, 1 H, *p*-MeOC$_6$H$_4$C*H*), 6.80 (d, 2 H, *J* = 8.3 Hz, Ph), 7.22−7.39 (m, 14 H, Ph), 7.50 (t, 1 H, *J* = 7.4 Hz, Ph), 8.10 (d, 2 H, *J* = 7.1 Hz, Ph). − FAB-MS; *m*/*z*: 900 [M]$^+$, 922 [M + Na]$^+$.

Deprotection of 29 To Give Derivative 30: A solution of **29** (26 mg, 0.029 mmol) and *p*-toluenesulfonic acid (4.4 mg, 0.025 mmol) in methanol (10 mL) was stirred for 5 d at room temperature. The reaction mixture was diluted with ethyl acetate (15 mL) and the resulting solution was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography (EtOAc/heptanes, 1:1) afforded **30** (18 mg, 0.023 mmol, 81%) as a white solid. − ^{1}H NMR: δ = 1.10 (s, 3 H, 19-H), 1.16 (s, 3 H, 17-H), 1.45 (s, 3 H, 16-H), 1.86 (s, 3 H, 18-H), 2.01 (dd, 1 H, J_{3-4} = 2.4 Hz, J_{3-2} = 7.5 Hz, 3-H), 2.14 (dd, 1 H, J_{gem} = 14.8 Hz, J_{14-13} = 7.0 Hz, 14-H), 2.42 (dd, 1 H, J_{gem} = 14.8 Hz, J_{14-13} = 7.0 Hz, 14-H), 2.58 (s, 3 H, OCH$_3$), 3.60 (br. d, 1 H, *J* = 2.3 Hz, 4-H), 4.08 (d, 1 H, J_{9-10} = 9.6 Hz, 9-H), 4.35 (d, 1 H, J_{10-9} = 9.6 Hz, 10-H), 4.74 (d, 1 H, $J_{2'-3'}$ = 2.0 Hz, 2′-H), 5.70 (pseudo-t, 1 H, *J* = 7.0 Hz, 13-H), 5.83 (dd, 1 H, $J_{3'-NH}$ = 9.3 Hz, $J_{3'-2'}$ = 2.0 Hz, 3′-H), 5.92 (d, 1 H, J_{2-3} = 7.5 Hz, 2-H), 7.01 (d, 1 H, $J_{NH-3'}$ = 9.3 Hz, NH), 7.21−7.49 (m, 11 H, Ph), 7.78 (d, 2 H, *J* = 7.2 Hz, Ph), 7.98 (d, 2 H, *J* = 7.2 Hz, Ph). − FAB-MS; *m*/*z*: 764 [M + Na]$^+$. − $C_{43}H_{51}NO_{10}{\cdot}1.5H_2O$ (768.9): calcd. C 67.17, H 7.08, N 1.82; found C 67.03, H 6.97, N 1.99.

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