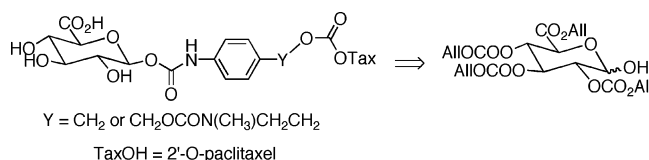


Protecting Groups for Glucuronic Acid: Application to the Synthesis of New Paclitaxel (Taxol) Derivatives

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To prepare two new glucuronide conjugates, allyl ester and allyl carbonates were used as protecting groups of the glucuronic moiety. In this way, an aniline glycosyl carbamate spacer linked to the 2'-OH of paclitaxel was obtained. By using palladium chemistry, an efficient one-step removal of all the allyl groups at the end of the synthesis afforded the desired compounds in good yields.

Introduction

In our ongoing work toward building paclitaxel (Taxol) glucuronyl prodrugs, one major synthetic problem was to introduce a β -D-glucuronic acid moiety in the most efficient possible way. This involved finding a cheap and readily accessible synthon, coupling it to the cytotoxic unit, and importantly, removing the protecting groups. New prodrugs could be obtained in good yields, even in the presence of sensitive groups, such as in the paclitaxel framework. We report here the use of a fully allyl protected glucuronyl derivative and its final deprotection step leading to the planned, tripartite prodrugs which structure is indicated below (Figure 1).

Synthesis of the Allyl Protected D-Glucuronic Acid Derivatives. Glucuronides¹ are oxidized forms of glucosides, often found as metabolites of xenobiotics. They represent a way of obtaining more water-soluble derivatives. Concerning their synthesis, due to their own distinctive chemistry, glucuronides are usually more difficult to prepare than the corresponding glucopyranosides.² Several methods are available for the synthesis of glucuronic acid glycosides, which can be divided into two broad categories involving either oxidation of the corresponding glucosides^{3–8} or direct glycosidation of an

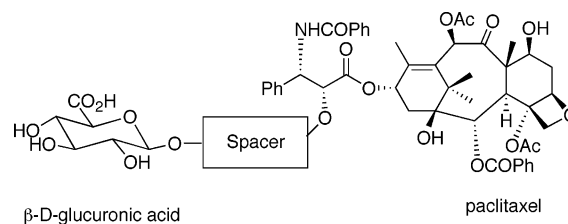


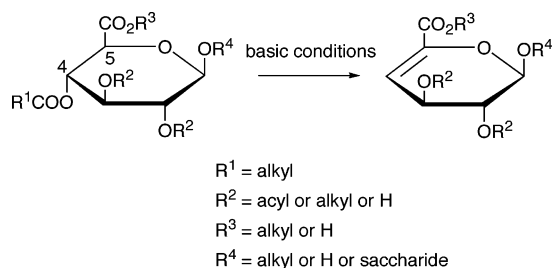
FIGURE 1. Structure of paclitaxel prodrugs.

activated glucuronic acid.^{2,9–11} Uronic acids are less reactive than the corresponding glucopyranosides under glycosidation conditions; moreover, with a leaving group as an acetyl in position 4, they are prone to give the 4,5-unsaturated byproduct by elimination of a molecule of carboxylic acid (R¹CO₂H) under basic conditions (Scheme 1).

Paclitaxel and Targeting Strategies. We are currently involved in the preparation of glucuronide prodrugs of paclitaxel able to release the active compound at the tumor site according to the Tumor Activated Prodrug (TAP) strategy.¹² This consists of using an activating enzyme that will locally cleave a prodrug to deliver the antitumor agent. Controlling the selectivity of cytotoxic drugs like paclitaxel represents a subsidiary advantage. In this context, the activating enzyme β -D-glucuronidase was

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SCHEME 1. β -Elimination of the Glucuronic Esters

selected.¹³ Normally, this endogenous enzyme is exclusively located in lysosomes, thus avoiding premature liberation of the drug in the blood. Moreover, β -D-glucuronidase is highly present in necrotic tumor areas,¹⁴ or can be targeted to the non-necrotic tumor sites via different approaches, such as Antibody Directed Enzyme Prodrug Therapy (ADEPT), Gene Directed Enzyme Prodrug Therapy (GDEPT), or Virus Directed Enzyme Prodrug Therapy (VDEPT), all three involving the use of a conjugate and a targeted enzyme.^{15,16}

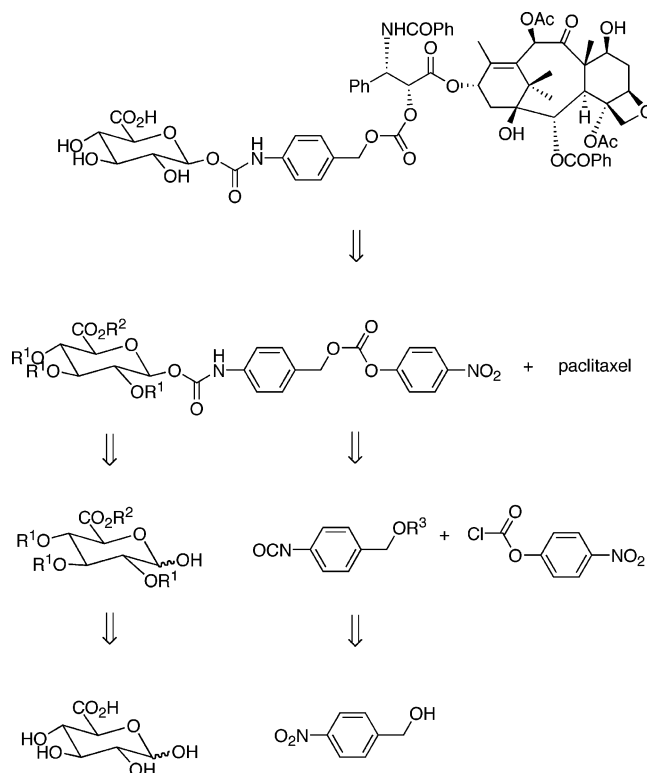
Paclitaxel (Taxol), a potent major anticancer agent that is widely used in clinics, initiates cell death through multiple mechanisms, particularly by binding to tubulin and promoting stable and non-functional microtubule formation.^{17–20} However, the clinical usefulness of this drug is particularly hampered by its poor solubility and lack of selectivity. Improving solubility and selectivity is therefore a very important goal. In this view, we undertook and reported the synthesis of paclitaxel prodrugs designed to be activated by β -D-glucuronidase.^{21,22} The synthetic challenges were the control of the β -glycosidic bond and the choice of the protecting groups of the glucuronic moiety. The protecting groups had to be easy to introduce, able to control a β -glycosidic configuration, and overall easy to remove at the end of the synthesis, especially in the presence of the very sensitive taxane skeleton. All these reactions had to give high yields and be versatile enough to be used in a large variety of different synthetic targets.

Results and Discussion

Retrosynthetic Scheme. For high efficacy, the best choice consisted of coupling the expensive paclitaxel as late as possible to an intermediate composed of a β -D-glucuronic acid linked to a spacer unit.

Synthesis of the Glucuronic Moiety. For the synthesis of the target molecules, the choice of the protecting groups of the

SCHEME 2. Retrosynthetic Analysis



glucuronic moiety was crucial. The ester groups ($R^1 = \text{acetate}$) are most frequently used to protect the 2-, 3-, and 4-hydroxyl of the glucuronyl moiety with a carboxymethyl or ethyl ester ($R^2 = \text{Me or Et}$). In this case, the deprotection step at the end of the synthesis requires the use of basic or nucleophilic conditions for the cleavage of esters. However, whenever a sensitive moiety, like paclitaxel, is present in the molecule, milder conditions are requested.

Another currently used protecting group for the hydroxyls is the benzyl ether.^{23,24} In the case of glucuronic acid derivatives, the most efficient way was to introduce the benzyl ethers into uronic acid prior to the glucose oxidation stage. However, this method, which avoids the classic 4,5-elimination under basic conditions, presents the inconvenience of adding steps to the synthesis.

In a previous work,²² we used *tert*-butyldimethylsilyl ethers (TBS) as hydroxy protecting groups ($R^1 = \text{TBS}$) and a benzyl ester protected carboxyl ($R^2 = \text{Bn}$). The synthetic limitations observed with these protecting groups were the deprotection steps, particularly in the case of the benzyl ester under reductive conditions, when a spacer including a reducible group was present. This procedure is time-consuming and inelegant because ester groups must be introduced first and have to be removed further in the synthesis, and replaced with silyl ester.

Therefore, allyl esters and allyl carbonates were finally chosen for their easy introduction, their mild conditions of removal with palladium, and also for the possibility to simultaneously deprotect hydroxy and carboxylic acid functions. Starting from glucuronic acid, the allyl ester was first prepared by reaction

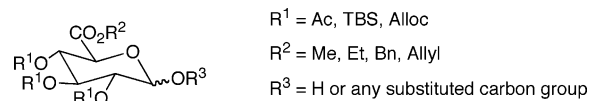


FIGURE 2. Glucuronic acid derivatives.

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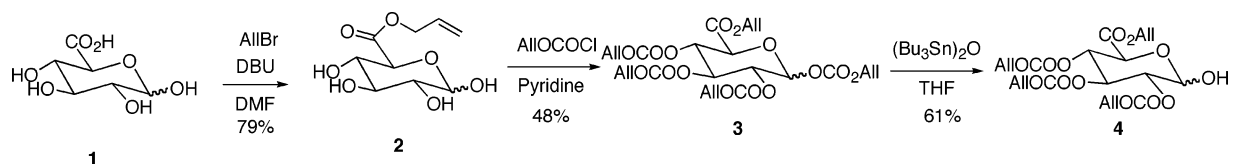
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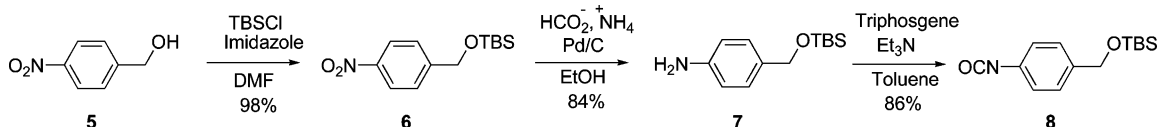
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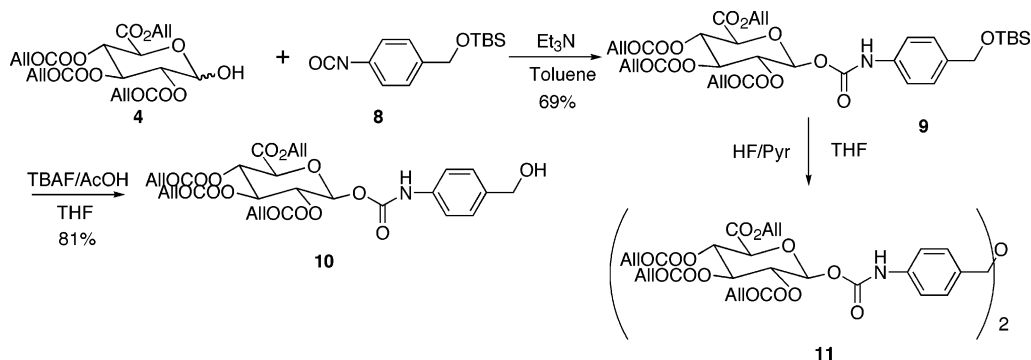
SCHEME 3. Synthesis of the Glucuronic Moiety



SCHEME 4. Synthesis of the Spacer



SCHEME 5. Coupling Between the Glucuronic and the Spacer Moieties



with allyl bromide under basic conditions (DBU).²⁵ The next step was the protection of all the hydroxy groups by treatment with an excess of allyloxycarbonyl chloride. Then, selective cleavage of the anomeric carbonate was performed by treatment with tributyltin oxide giving **4** as a mixture of anomers ($\alpha/\beta = 3.5/1$ according to NMR). These conditions were described for the removal of anomeric acetates,²⁶ but we applied them to allyl carbonates. More classical hydroxyl anomer deacylation conditions, such as hydrazine acetate,²⁷ gave nonselective deprotections of the anomeric allyl-carbonates, thus leading to mixtures of partially protected glucuronic derivatives.

Synthesis of the Spacer Moiety. The *p*-nitrobenzyl alcohol **5** was reacted with TBSCl giving the *O*-silylprotected derivative **6**,^{28,29} and the aromatic nitro group was selectively reduced by hydrogen transfer (H_2 , Pd/C, ammonium formate) to avoid benzylic hydrogenolysis. Next, by using triphosgene,³¹ the amine **7**²⁸ was converted into isocyanate **8**³⁰ which, due to its instability, was immediately engaged in the coupling with the sugar moiety.

Synthesis of the Allyl Protected Aniline β -*O*-Glucuronyl. According to Scheeren et al.,³⁰ aromatic isocyanates react in the presence of Et_3N with anomeric unprotected per-*O*-acetyl glucuronide to highly diastereoselectively afford the corresponding β -*O*-glycosyl carbamates. This high β -stereoselectivity could be explained by the fact that the 1-OH group is known to be more nucleophilic in the β -configuration than in the α -configuration. By using these conditions, compound **9** was obtained, with high β -stereoselectivity as unambiguously determined by NMR analysis, and in a rather good yield (69%) from the allyl protected glucuronic acid **4** and *p*-hydroxybenzyl-silyl isocyanate **8**.

The next step was the deprotection of the silyl ether. The reaction conditions had to be compatible with ester, carbonate, and carbamate functions. Whereas neither TBAF (which proved to be too basic) nor HF/Pyridine (which afforded the dimer **11** as the main product) could be used, the TBAF/AcOH³² couple proved to be the choice reactant to obtain **10** in good yield (81%).

To activate the benzylic alcohol of **10**, it was initially treated with disuccinimidyl carbonate. However, no succinimidyl carbonate was obtained, but the unexpected decarboxylated succinimido derivative **13** was obtained, as is clearly identified by spectroscopic data. Therefore we turned our attention toward an activation with 4-nitrophenyl chloroformate and obtained **12** ready for the coupling reaction with paclitaxel.

A possible mechanism of **13** formation could be the loss of CO_2 by the expected compound, followed by succinimide addition as indicated in Scheme 7.

Couplings with Paclitaxel. To link this glucuronylated spacer to the 2'-OH of paclitaxel, two kinds of carbonates were envisioned. The choice of a carbonate rather than an ester

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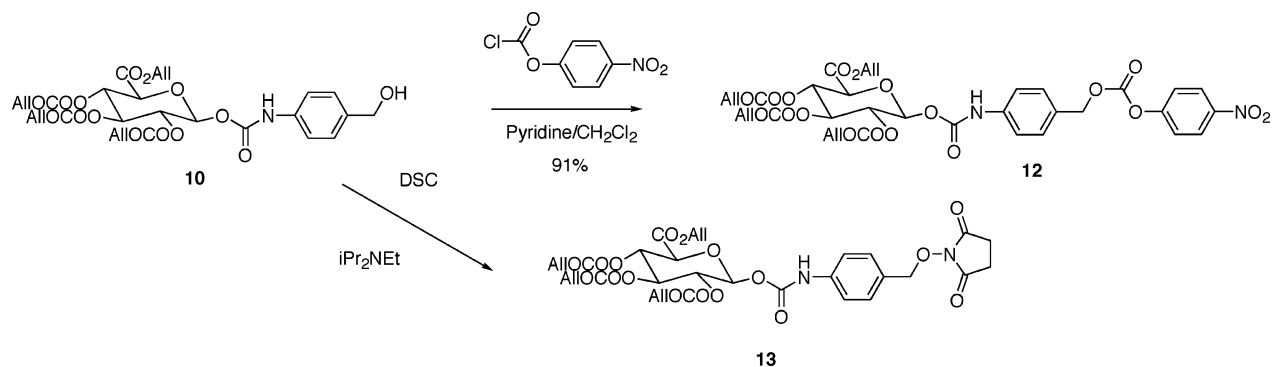
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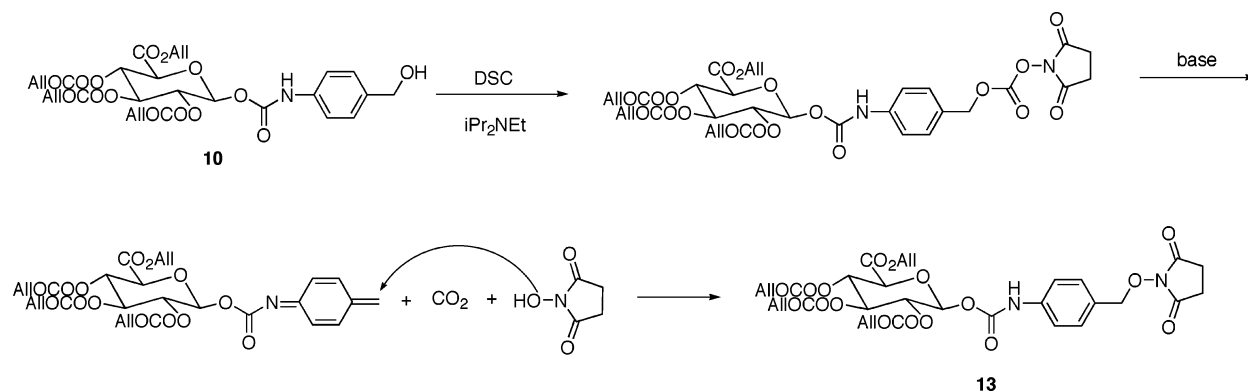
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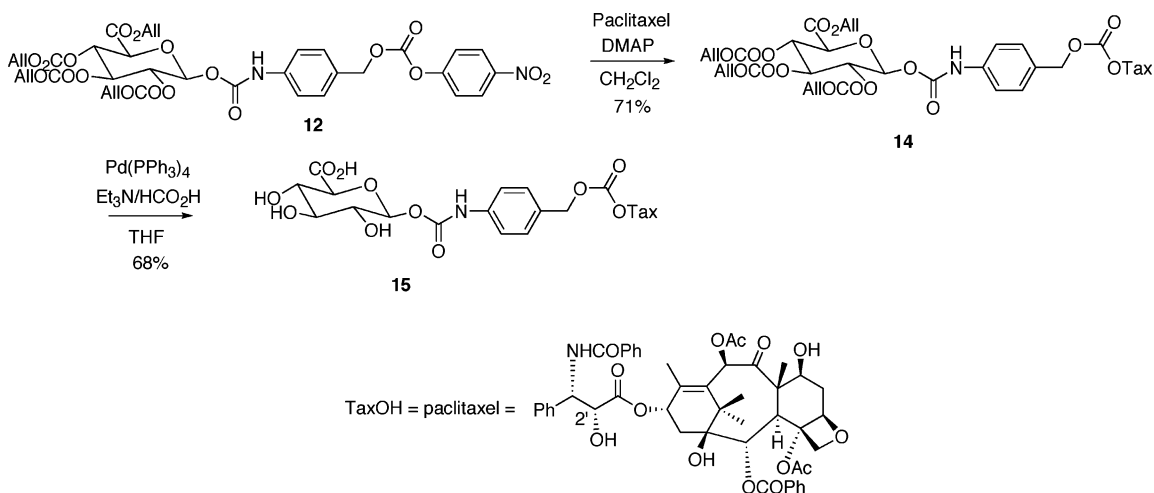
SCHEME 6. Activation of the Glucuronic Spacer Moiety



SCHEME 7. Mechanism of Formation of Compound 13



SCHEME 8. Coupling of Paclitaxel



function was dictated by the fact that carbonates, and particularly paclitaxel-2'-carbonates, are more stable as regards hydrolysis than the corresponding esters.³³ The first carbonate derivative **15** could directly be obtained by coupling **12** with paclitaxel. The second derivative, **19**, bearing an additional 2-methylamino alcohol moiety, was prepared. Its structure was devised according to previous observations by us³⁴ and Scheeren³⁵ et al., which

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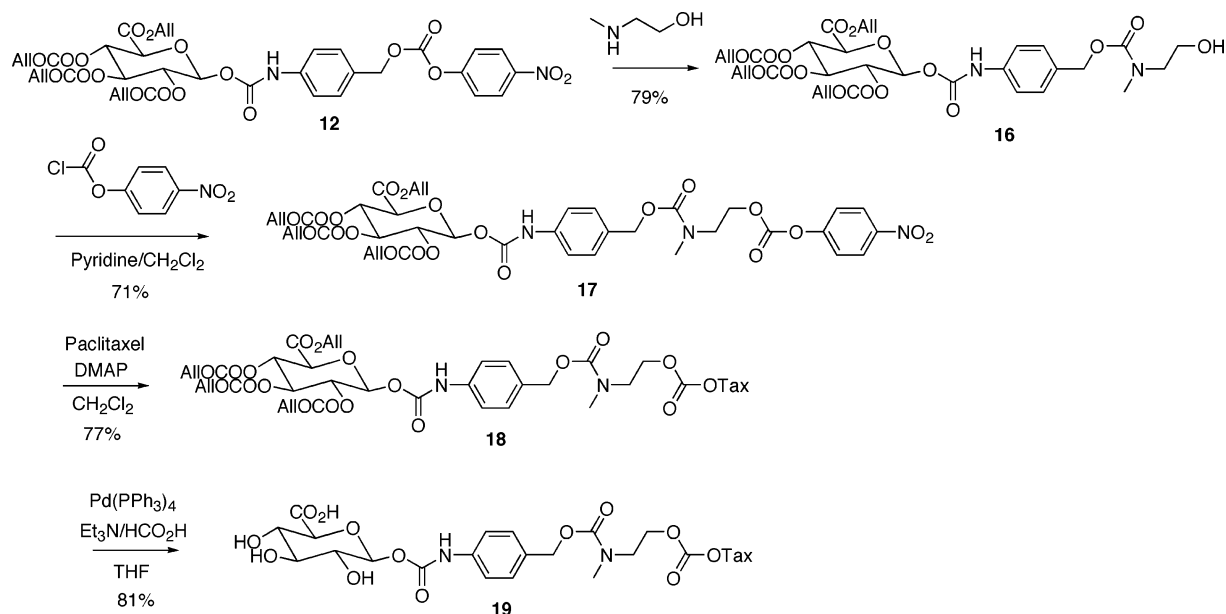
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showed that introducing an additional short spacer such as a diaminoethylene derivative could greatly influence both the stability and kinetics of cleavage of the prodrugs.

To achieve the synthesis of the first prodrug **15**, the activated *p*-nitrophenyl carbonate **12** was condensed (71%) with paclitaxel in the presence of DMAP, followed by simultaneous removal of both allyl ester and allyloxycarbonyl (alloc) that cleanly occurred by reacting **14** with Pd(PPh₃)₄ in the presence of Et₃N/HCO₂H.^{36,37} As these conditions avoided the current formation of byproducts during the classical deprotection of per-*O*-acetyl glucuronides, this could be an interesting alternative to other methods of glucuronide synthesis for base-sensitive compounds.

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SCHEME 9. Synthesis of the Second Prodrug 19



SCHEME 10. Cleavage of Paclitaxel Prodrug

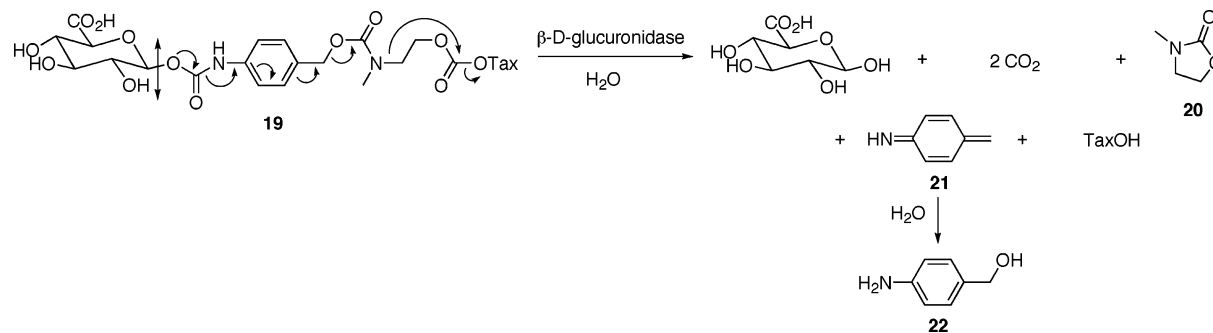


TABLE 1. Decomposition of Prodrug 15

time, h	0	1	2	5	24
decomp with PBS, %	0	5.5	8.9	19.8	40
decomp with PBS + 10% FCS, %	0	6.6	12.6	28.9	64.7

To access to the second prodrug **19**, glucuronyl *p*-nitrophenyl carbonate derivative **12** was reacted with 2-methylamino ethanol to give the carbamate **16**. After activation of the free primary alcohol function as described above for **10**, carbonate **17** was obtained and condensed with paclitaxel; the glucuronyl unit of **18** was then deprotected by Pd(PPh₃)₄ in the presence of Et₃N/HCO₂H.

Stability Tests. The two prodrugs **15** and **19** (190 μM) were dissolved in a phosphate buffer (PBS) containing either no or 10% fetal calf serum (FCS) and the evolution of the solution was followed by HPLC (UV detection) at 37 °C.

In both media, the prodrug **19** proved to be rather stable over 24 h with less than 5% hydrolysis detected, whereas the prodrug **15** was unstable, with spontaneous release of the free paclitaxel. These differences in stability can be explained, since both compounds are paclitaxel-2'-carbonates, but in **15**, it is a benzylic carbonate versus an aliphatic carbonate in **19**. Kinetics of decomposition of **15** (recorded as starting material disappearance) are given in Table 1.

The use of the two prodrugs will be different: the stable prodrug **19** can be used in a TAP strategy, where the prodrug

is specifically transformed into the active paclitaxel by enzymatic cleavage at the tumor site. The unstable prodrug **15** spontaneously releases the active drug, so it could be used as a soluble form of paclitaxel, but without selectivity toward cancer cells.

Cytotoxicity Measurements. Cytotoxicity was measured on HT29 cell lines (colorectal cancer). For the stable prodrug **19**, the IC₅₀ value was 26.3 nM. Under the same conditions, that of paclitaxel was 0.16 nM, meaning that the free drug is 164-fold more cytotoxic than the prodrug. This value is compatible with a TAP strategy where a relatively nontoxic prodrug releases a cytotoxic drug at the tumor site.

As regards the unstable prodrug **15**, the actual value could not be measured due to its decomposition during incubation (72 h) with the cells.

Enzymatic Cleavage. The release of the paclitaxel from its prodrug **19** in the presence of the activating enzyme β-D-glucuronidase was measured by HPLC (UV detection) in either PBS buffer or PBS + 10% FCS.

Prodrug cleavage and release of free paclitaxel were supposed to occur according to Scheme 10. *E. coli* β-D-glucuronidase was used as the activating enzyme. Cleavage of the prodrug was

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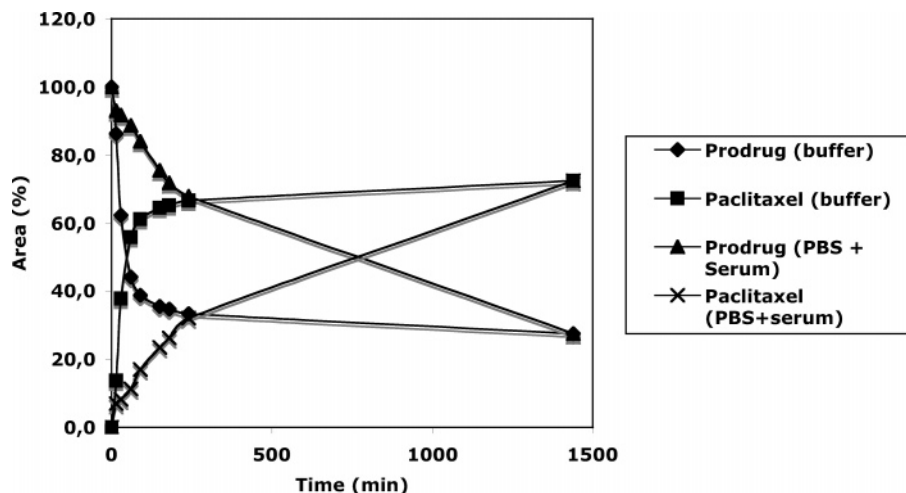


FIGURE 3. Cleavage of prodrug **19** by β -D-glucuronidase.

observed with the simultaneous appearance of paclitaxel (Figure 3). The cleavage was faster in buffer than in PBS + serum.

During the HPLC kinetic analysis, we unexpectedly noticed that no amino alcohol **22** was detected by comparison with an authentic sample. The cleavage seemed to stop after a while and a plateau was reached. Our hypothesis is that imine **21** is not hydrolyzed fast enough, and thus can react first with a nucleophilic residue on the active site of the enzyme, in the same way as quinone methides are reported to react with glucosidases.³⁷ For verification purposes, the enzymatic activity of β -D-glucuronidase was measured after preincubation with prodrug **19** and compared to the native enzyme during the same time. The activity was measured by enzymatic cleavage of 4-nitrophenyl glucuronide. Indeed, the activity was slower after preincubation with the prodrug, thus demonstrating that the enzyme is partially inhibited during preincubation with the prodrug.

Conclusion

Since prodrug therapy based on elevated tumor levels of endogenous or targeted β -glucuronidase (ADEPT, PMT) has been the subject of increasing research for several years, finding an efficient synthesis of glucuronide-containing prodrugs of antitumor agents is a need. So far, the use of conventional protection of the glucuronyl moiety could not be applied whenever acid- or alkali-sensitive groups were present in the drug or reducible functions. In contrast, the use of allyl ester and allyl carbonate, as reported in the paper, proved to be compatible with all these functions and represents a general pathway.

Experimental Section

Allyl D-Glucuronate (2).²⁵ DBU (17.0 mL, 0.11 mol, 1.1 equiv) was added dropwise to a solution of D-glucuronic acid (20 g, 0.103 mol) in DMF (200 mL). After the solution was stirred for 15 min at room temperature, 11 mL (0.12 mmol, 1.2 equiv) of allyl bromide was added dropwise, and the mixture was stirred overnight. After evaporation, the residue was purified over silica gel (eluent: acetone). Compound **2** (19.2 g, 79%) was isolated as an oil: R_f 0.76 (acetone). $[\alpha]_D^{20} +54$ (c 1.0; MeOH) (lit. +55.9°; $^1\text{H NMR}$ (300 MHz, MeOD) (α isomer) δ 5.93 (m, 1H), 5.32 (ddd, 2H, J = 10.4, 3.1, and 1.5 Hz), 5.13 (d, 1H, J = 3.4 Hz), 4.66 (m, 2H),

4.32 (d, 1H, J = 9.7 Hz), 3.68 (t, 1H, J = 9.1 Hz), 3.52 (t, 1H, J = 9.7 Hz), 3.36 (m, 1H); $^1\text{H NMR}$ (300 MHz, MeOD) (β isomer) δ 5.93 (m, 1H), 5.32 (ddd, 2H, J = 10.4, 3.1, and 1.5 Hz), 4.50 (d, 1H, J = 7.6 Hz), 4.66 (m, 2H), 3.85 (d, 1H, J = 9.7 Hz), 3.68 (t, 1H, J = 9.1 Hz), 3.52 (t, 1H, J = 9.7 Hz), 3.18 (m, 1H); $^{13}\text{C NMR}$ (75 MHz, MeOD) δ 171.6, 170.4, 133.1, 118.5, 98.7, 94.4, 77.4, 75.8, 74.3, 73.4, 73.1, 72.6, 66.8, 66.7; MS (FAB+) m/z 257 $[\text{M} + \text{Na}]^+$.

Allyl 1.2.3.4-Tetra-(O-allyloxycarbonyl)-D-glucuronate (3). Compound **2** (9 g, 0.038 mol) was dissolved in anhydrous pyridine (100 mL). Allyl chloroformate (122 mL, 30 equiv) was added dropwise in 15 min at 0 °C (strong gas release). The solution turned brown. After 24 h under stirring, pyridine (30 mL) was added, and the mixture was stirred for another 24 h. The residue was then diluted in dichloromethane (250 mL) and washed twice with water, then three times with a saturated solution of copper sulfate. The last washing with water, drying over MgSO_4 , and evaporation gave a brown oil that was purified over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2). Compound **3** (10.5 g, 48%) was obtained as an oil: R_f 0.66 ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2); $[\alpha]_D^{20} +38$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) (α/β = 2/3) 6.38 (d, 1H, J = 3.5 Hz), 5.99–5.81 (m, 5H), 5.72 (d, 1H, J = 7.3 Hz), 5.54–4.97 (m, 13H), 4.67–4.52 (m, 11H), 4.31 (d, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) 166.2, 165.8, 153.8, 153.5, 153.4, 152.7, 152.6, 131.0, 130.9, 130.8, 130.7, 130.6, 119.8, 119.7, 119.6, 119.4, 119.3, 119.2, 119.1, 119.0, 94.4, 91.9, 75.2, 73.5, 72.6, 72.5, 72.2, 70.0, 69.4, 69.3, 69.2, 69.1, 69.0, 66.8. MS (CI/ NH_3) m/z 588 $[\text{M} + \text{NH}_4]^+$; HRMS (FAB + MB + Na) ($\text{C}_{25}\text{H}_{30}\text{O}_{15}\text{Na}$) m/z calcd 593.1482, found 593.1478.

Allyl 2.3.4-tri-(O-Allyloxycarbonyl)-D-glucuronate (4). Bis(tri-*n*-butyltin) oxide (5.35 mL, 0.01 mol) was added to a solution (6 g, 0.01 mol) of the protected sugar **3** in THF (240 mL), and the mixture was heated to reflux for 6 h. After evaporation of the solvent, the residue was chromatographed twice over silica gel (eluent: first elution $\text{CH}_2\text{Cl}_2/\text{acetone}$ 96/4; second elution $\text{CH}_2\text{Cl}_2/\text{acetone}$ 95/5) to remove the tin derivatives, leading to compound **4** (2.6 g, 61% of conversion). Isolated byproducts were the starting material **3** (1 g) and the diprotected compound (900 mg, 19%): R_f 0.47 ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2); $[\alpha]_D^{20} +45.8$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) (α/β = 3.5/1) δ 5.93–5.77 (m, 4H), 5.57 (d, 1H, J = 3.3 Hz), 5.40 (t, 1H, J = 9.7 Hz), 5.32–5.19 (m, 8H), 5.04 (m, 1H), 4.89 (d, 1H, J = 7.6 Hz), 4.77 (dd, 1H, J = 10.0 Hz and J' = 3.4 Hz), 4.66–4.49 (m, 9H), 4.21 (d, 1H, J = 9.4 Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 167.7, 166.8, 154.2, 154.0, 153.8, 153.7, 153.6, 131.1, 131.0, 130.9, 119.4, 119.3, 119.1, 118.9, 118.8, 95.0, 89.9, 75.9, 75.4, 73.7, 73.1, 72.9, 72.8, 71.9, 69.1, 69.0, 68.9, 67.5, 66.9, 66.7; MS (CI/ NH_3) m/z 504 $[\text{M} + \text{NH}_4]^+$; HRMS (FAB + MB + Na) ($\text{C}_{21}\text{H}_{26}\text{O}_{13}\text{Na}$) m/z calcd 509.1271, found 509.1267.

tert-Butyldimethyl-(4-nitrobenzyloxy)silane (6).^{27,28} To a solution of 4-nitrobenzylic alcohol **5** (5 g, 0.032 mol) and imidazole (4.67 g, 0.068 mol, 2.1 equiv) in anhydrous DMF (35 mL) was added *tert*-butyldimethylsilyl chloride (4.8 g, 0.032 mol) in small portions. After stirring for 2 h at room temperature, the mixture was diluted with EtOAc (250 mL), washed with water (6 × 70 mL), dried over MgSO₄, and evaporated. The crude compound was purified over silica gel (eluent: cyclohexane/EtOAc 8/2). The 8.4 g (98%) yield of product **6** was isolated as an oil: *R*_f 0.51 (cyclohexane/EtOAc 6/4); ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, 2H, *J* = 8.7 Hz), 7.49 (d, 2H, *J* = 8.7 Hz), 4.82 (s, 2H), 0.95 (s, 9H), 0.12 and 0.11 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 149.0, 146.8, 126.1, 123.4, 63.9, 25.7, 18.2, -5.4; MS (CI/NH₃) *m/z* 285 [M + NH₄]⁺.

tert-Butyldimethyl(4-aminobenzyloxy)silane (7).²⁷ Pd/C (10%, 2.5 g) and ammonium formate (8.6 g) were added to a solution of the nitro derivative **6** (8.3 g, 0.031 mol) in absolute ethanol (150 mL). After the solution was stirred for 5 h at room temperature, the catalyst was eliminated by filtration over Celite 545. The filtrate was evaporated and taken up in EtOAc (200 mL), washed with water (200 mL), dried over MgSO₄, and evaporated to dryness. The oil was chromatographed over silica gel (eluent: cyclohexane/EtOAc 8/2). Compound **7** (6.2 g, 84%) was obtained as an oil: *R*_f 0.34 (cyclohexane/EtOAc 6/4); ¹H NMR (300 MHz, CDCl₃) δ 7.14 (d, 2H, *J* = 8.4 Hz), 6.67 (d, 2H, *J* = 8.4 Hz), 4.64 (s, 2H), 3.55 (s, 2H), 0.95 and 0.93 (s, 9H), 0.10 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 145.2, 131.4, 127.6, 114.9, 64.9, 25.9, 25.6, 18.3, -5.1; MS (CI/NH₃) *m/z* 255 [M + NH₄]⁺.

tert-Butyldimethyl(4-isocyanatobenzyloxy)silane (8). To a solution of the amino **7** compound (1.46 g, 6.1 mmol) and triethylamine (0.90 mL, 6.3 mmol, 1.05 equiv) in freshly distilled toluene (40 mL) heated at 70 °C was added triphosgene (0.73 g, 2.4 mmol, 0.4 equiv). The solution became yellow with formation of a precipitate (triethylammonium salts). The mixture was heated for 3 h at 70 °C. After filtration, washing with toluene, and evaporation, isocyanate **8** (1.4 g, 86%) was obtained and directly used for the next step: *R*_f 0.78 (CH₂Cl₂); IR (CHCl₃, cm⁻¹) ν 2220 (NCO); ¹H NMR (300 MHz, CDCl₃) δ 7.28 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.3 Hz), 4.74 (s, 2H), 0.91 (s, 9H), 0.08 (s, 6H); MS (CI/NH₃) *m/z* 264 [M + H]⁺.

***N*-[4-(*tert*-Butyldimethylsilyloxymethyl)phenyl]-*O*-[2,3,4-tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamate (9).** To a sugar **4** solution (1.8 g, 3.70 mmol) in freshly distilled toluene (100 mL) was added triethylamine (0.52 mL, 3.70 mmol) dropwise at 0 °C under argon, then isocyanate **8** (1.26 g, 4.81 mmol, 1.3 equiv) in toluene (10 mL), and the mixture was stirred for 1.5 h at 0 °C. After evaporation, the residue was chromatographed over silica gel (eluent: CH₂Cl₂/acetone 99/1). The coupling product **9** (1.92 g, 69%) was isolated as an oil: *R*_f 0.66 (CH₂Cl₂/acetone 98/2); [α]_D²⁰ -3.8 (c 1.02, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.25 (m, 4H), 6.98 (br s, 1H), 5.94–5.82 (m, 5H), 5.36–5.10 (m, 11H), 4.63 (m, 10H), 4.33 (d, 1H, *J* = 9.4 Hz), 0.92 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.2, 153.8, 153.6, 153.5, 150.4, 136.7, 135.6, 131.1, 130.9, 130.8, 130.7, 130.6, 126.4, 119.2, 119.1, 119.0, 118.9, 118.8, 92.1, 75.0, 72.8, 72.3, 71.9, 69.1, 68.9, 66.7, 64.4, 26.1, 25.8, 25.5, 18.2, -5.3, -5.4; MS (CI/NH₃) *m/z* 767 [M + NH₄]⁺; HRMS (FAB + MB + NaI) (C₃₅H₄₇NNaO₁₅Si) *m/z* calcd 772.2613, found 772.2609.

***N*-[4-(Hydroxymethyl)phenyl]-*O*-[2,3,4-tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamate (10).** Compound **9** (800 mg, 1.067 mmol) and glacial acetic acid (80 μL, 1.387 mmol, 1.3 equiv) were dissolved in anhydrous THF (50 mL) at 0 °C. TBAF (1 M, 420 μL, 1.387 mmol, 1.3 equiv) in THF was added dropwise. After the solution was stirred for 18 h at room temperature, an additional 0.2 equiv of acetic acid and TBAF was added and the stirring was continued for 2 h. After cooling at 0 °C, the mixture was diluted in dichloromethane and washed with a NaHCO₃ saturated solution, then with water. The organic phase was dried over MgSO₄ and evaporated to dryness. After purification over silica

gel (eluent: CH₂Cl₂/acetone 92/8), benzylic alcohol **10** (550 mg, 81%) was obtained as a lacquer: *R*_f 0.24 (CH₂Cl₂/acetone 92/8); [α]_D²⁰ -6.6 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.29 (m, 5H), 5.95–5.79 (m, 5H), 5.37–5.10 (m, 11H), 4.62 (m, 10H), 4.33 (d, 1H, *J* = 9.3 Hz), 1.80 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.3, 153.8, 153.7, 153.5, 150.6, 136.3, 136.2, 130.9, 130.8, 130.7, 127.6, 119.2, 119.1, 119.0, 118.9, 92.1, 75.0, 72.9, 72.3, 71.9, 69.2, 69.0, 66.8, 64.5; MS (FAB + NaI) *m/z* 658 [M + Na]⁺; HRMS (FAB + MB + NaI) (C₂₉H₃₃O₁₅NNa) *m/z* calcd 658.1748, found 658.1742.

Di[[*N*-[2,3,4-tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyl] Oxide (11). HF/pyridine (70%, 0.5 mL) was added to a solution of alcohol **10** (80 mg, 0.106 mmol) in THF (3 mL). The mixture was stirred for 3 h at room temperature. A NaHCO₃ saturated solution (50 mL) was added and extracted with EtOAc (3 × 10 mL). After drying over MgSO₄ and evaporation, the compound was purified over silica gel (eluent: CH₂Cl₂/acetone 98/2). The dimer **11** (84 mg, 63%) was obtained as a lacquer: *R*_f 0.60 (CH₂Cl₂/acetone 98/2); [α]_D²⁰ -6.4 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.23 (m, 5H), 5.92–5.82 (m, 5H), 5.36–5.20 (m, 11H), 4.62 (m, 8H), 4.41 (s, 2H), 4.35 (d, 1H, *J* = 8.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 153.9, 153.7, 153.6, 150.5, 136.3, 133.4, 131.1, 131.0, 130.9, 130.7, 130.6, 128.3, 119.3, 119.2, 119.0, 118.8, 92.3, 75.0, 72.7, 72.3, 71.9, 71.0, 69.3, 69.0, 66.8, 60.3; MS (FAB + NaI) *m/z* 1275 [M + Na]⁺; HRMS (FAB + MB + NaI) (C₅₈H₆₄N₂NaO₂₉) *m/z* calcd 1275.3493, found 1275.3518.

***O*-[[*N*-[2,3,4-Tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonyl]-4-nitrophenol (12).** At 0 °C, anhydrous pyridine (36 μL, 0.44 mmol, 2 equiv) was added to a solution of compound **10** (140 mg, 0.22 mmol) in anhydrous CH₂Cl₂ (5 mL). Then, 4-nitrophenyl chloroformate (89 mg, 0.44 mmol, 2 equiv) was added and the mixture was stirred for 2 h at 0 °C. After evaporation, the residue was chromatographed over silica gel (eluent: CH₂Cl₂/acetone 99/1), giving compound **12** (160 mg, 91%) as a white lacquer: *R*_f 0.56 (CH₂Cl₂/acetone 99/1); [α]_D²⁰ -7.5 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, 2H, *J* = 9.0 Hz), 7.37–7.15 (m, 7H), 5.95–5.77 (m, 5H), 5.37–5.21 (m, 13H), 4.65–4.49 (m, 8H), 4.36 (d, 1H, *J* = 9.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 166.2, 155.4, 153.9, 153.7, 153.6, 152.4, 150.3, 145.3, 137.6, 131.0, 130.9, 130.8, 129.7, 125.3, 121.7, 119.4, 119.2, 119.1, 92.3, 75.2, 73.2, 72.4, 72.2, 70.5, 69.3, 69.2, 69.1, 66.9. MS (MALDI) *m/z* 823 [M + Na]⁺ and 839 [M + K]⁺; HRMS (FAB + MB + NaI) (C₃₆H₃₆N₂NaO₁₉) *m/z* calcd 823.1810, found 823.1793.

1-[[*N*-[2,3,4-Tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyl]pyrrolidine-2,5-dione (13). To a solution of compound **10** (54 mg, 0.085 mmol) in freshly distilled CH₂Cl₂ (5 mL) were added (iPr)₂NEt (37 μL, 0.212 mmol, 2.5 equiv) then DSC (33 mg, 0.127 mmol, 1.5 equiv). The mixture was stirred for 24 h at room temperature. One supplementary equivalent of DSC was added and stirring was continued for an additional 3 h. After evaporation, the residue was chromatographed over silica gel (CH₂Cl₂/acetone 96/4), to obtain the product **13** (20 mg, 40% conversion) as well as 10 mg of starting material: *R*_f 0.63 (CH₂Cl₂/acetone 95/5); [α]_D²⁰ -6.8 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.36 (m, 4H), 7.29 (s, 1H), 5.94–5.82 (m, 5H), 5.36–5.08 (m, 11H), 5.05 (s, 2H), 4.58 (m, 8H), 4.35 (d, 1H, *J* = 9.2 Hz), 2.64 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 171.2, 166.0, 153.8, 153.7, 153.5, 150.2, 138.0, 130.9, 130.8, 129.0, 128.8, 128.2, 119.4, 119.2, 119.1, 118.6, 92.2, 77.9, 75.3, 73.4, 72.4, 72.3, 69.2, 69.1, 66.9, 25.4; MS (FAB + NaI) *m/z* 755 [M + Na]⁺; HRMS (FAB + MB + NaI) (C₃₃H₃₆N₂NaO₁₇) *m/z* calcd 755.1912, found 755.1927.

2'-*O*-[*N*-[2,3,4-tri-(*O*-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonylpaclitaxel (14). 4-Nitrophenyl carbonate **12** (43 mg, 0.053 mmol) and paclitaxel (32 mg, 0.037 mmol, 0.7 equiv) were dissolved in freshly distilled CH₂Cl₂ (7 mL). Then, DMAP (9.8 mg, 0.080 mmol, 1.5 equiv) was

added under argon and the mixture was stirred for 24 h at room temperature. After evaporation, the compound obtained was purified over silica gel (CH₂Cl₂/acetone 9:1), giving the coupled product **14** (40 mg, 71%) as a white solid; mp 188 °C; *R*_f 0.47 (CH₂Cl₂/acetone 9/1); [α]_D²⁰ -31 (*c* 1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, 2H, *J* = 7.2 Hz), 7.72 (d, 2H, *J* = 7.1 Hz), 7.59–7.17 (m, 16H), 6.28 (m, 2H), 5.99–5.79 (m, 6H), 5.69 (d, 1H, *J* = 6.8 Hz), 5.44 (d, 1H, *J* = 2.4 Hz), 5.36–5.17 (m, 10H), 5.12–5.02 (m, 3H), 4.99 (d, 1H, *J* = 9.2 Hz), 4.62 (m, 8H), 4.43 (m, 1H), 4.32 (m, 2H), 4.20 (d, 1H, *J* = 8.3 Hz), 3.81 (d, 1H, *J* = 6.6 Hz), 2.62 (m, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 2.16 (s, 2H), 1.89 (s, 3H), 1.83 (br s, 1H), 1.67 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.8, 171.2, 169.8, 167.8, 167.2, 167.0, 166.3, 166.0, 154.0, 153.9, 153.7, 153.5, 150.2, 142.5, 137.4, 136.6, 133.7, 133.4, 132.8, 132.0, 131.0, 130.9, 130.2, 129.8, 129.7, 129.5, 129.1, 128.7, 128.5, 127.1, 126.5, 126.0, 131.0, 130.9, 119.4, 119.3, 119.0, 119.1, 92.2, 84.4, 81.0, 79.1, 77.2, 76.8, 75.5, 75.3, 75.0, 73.4, 72.4, 72.0, 70.3, 69.4, 69.2, 69.1, 66.9, 58.4, 52.7, 45.6, 43.1, 35.5, 29.6, 26.8, 22.7, 22.1, 20.8, 14.7, 9.6; MS (FAB + MB + Na) *m/z* 1538 [M + Na]⁺; HRMS (C₇₇H₈₂O₂₃N₂Na) *m/z* calcd 1537.4850, found 1537.4812.

2'-O-(N-β-D-Glucopyranosylcarbamoyl-4-oxy)benzyloxycarbonylpaclitaxel (15). The protected prodrug **14** (31 mg, 0.020 mmol) was dissolved in anhydrous THF (2 mL). A solution of NEt₃ (9 μL, 0.061 mmol, 3 equiv)/HCOOH (2 μL, 0.040 mmol, 2 equiv) was added in THF (50 μL) and the mixture was stirred for 10 min under argon, then Pd(PPh₃)₄ (4.6 mg, 0.004 mmol, 0.2 equiv) was added. After the solution was stirred for 30 min at 0 °C, then for 2 h at room temperature, the solvents were evaporated, and the product was purified over silica gel (eluent: CH₃CN/H₂O 95:5). After lyophilisation, prodrug **15** (17 mg, 68%) was obtained as a white solid: mp 198–200 °C; *R*_f 0.32 (CH₃CN/H₂O 9/1); [α]_D²⁰ -31 (*c* 1.2, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 8.11 (d, 2H, *J* = 7.1 Hz), 7.77 (d, 2H, *J* = 7.0 Hz), 7.68–7.26 (m, 16H), 6.44 (s, 1H), 6.03 (m, 1H), 5.82 (d, 1H, *J* = 6.4 Hz), 5.64 (d, 1H, *J* = 7.2 Hz), 5.47 (d, 2H, *J* = 6.5 Hz), 5.15 (s, 2H), 5.01 (d, 1H, *J* = 8.8 Hz), 4.34 (q, 1H, *J* = 10.7 Hz and *J'* = 8.7 Hz), 4.18 (s, 2H), 3.82 (d br, 2H, *J* = 7.1 Hz), 3.68–3.42 (m, 3H), 2.48 (m, 1H), 2.40 (s, 3H), 2.17 (m, 4H), 1.89 (s, 3H), 1.86 (m, 2H), 1.65 (s, 3H), 1.13 and 1.12 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 205.2, 171.7, 171.3, 170.5, 170.2, 167.6, 155.8, 142.2, 138.1, 135.4, 134.9, 134.6, 133.1, 133.0, 132.9, 131.4, 131.2, 130.5, 130.1, 129.9, 129.7, 129.6, 129.5, 129.2, 128.6, 119.9, 96.0, 85.9, 82.2, 79.0, 78.5, 77.5, 76.8, 76.2, 73.7, 73.2, 71.3, 59.2, 56.0, 55.4, 54.8, 47.9, 44.6, 37.5, 36.4, 32.1, 30.7, 29.5, 26.9, 26.5, 23.3, 22.4, 20.8, 15.5, 11.1; MS (ESI+) *m/z* 1246 [M + Na]⁺; MS (ESI-) *m/z* 1222 [M - H]⁺; HRMS (C₆₂H₆₆O₂₄N₂Na) *m/z* calcd 1245.3903, found 1245.3923.

O-[[N-[2,3,4-Tri-(O-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonyl]-2-aminoethanol (16). To a solution of **12** (110 mg, 0.137 mmol) and *N*-methylethanol (12.2 μL, 0.151 mmol, 1.1 equiv) in dichloromethane (7 mL) was added DMAP (20 mg, 0.164 mmol, 1.2 equiv) at 0 °C. The mixture was stirred for 15 min at 0 °C, then for 30 min at room temperature. After evaporation, the product was purified over column (eluent: CH₂Cl₂/acetone 9/1 then 85/15). Compound **16** (80 mg, 79%) was isolated as an oil: *R*_f 0.3 (CH₂Cl₂/acetone 85/15); [α]_D²⁰ -6.7 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.67 (br s, 1H, NH), 7.25 (m, 4H), 5.93–5.80 (m, 5H), 5.35–5.18 (m, 11H), 5.02 (s, 2H), 4.64–4.51 (m, 8H), 4.36 (d, 1H, *J* = 9.1 Hz), 3.74 (br s, 2H), 3.42 (br s, 2H), 2.96 (s, 3H), 2.49 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.3, 157.5, 153.9, 153.8, 153.6, 150.5, 136.8, 132.0, 131.0, 130.9, 130.8, 128.9, 128.7, 119.4, 119.2, 119.0, 92.2, 75.2, 73.1, 72.4, 72.1, 69.2, 69.1, 66.9, 61.0, 60.6, 51.8, 50.9, 35.7, 35.3; MS (MALDI-TOF) *m/z* 759 [M + Na]⁺ and 775 [M + K]⁺; HRMS (FAB + MB + Na) (C₃₃H₄₀N₂NaO₁₇) *m/z* calcd 759.2225, found 759.2212.

O-[[N-[2,3,4-Tri-(O-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonyl]-2-aminoethanol-carbonyl-4-nitrophenol (17). To compound **16** (70 mg, 0.095

mmol) in anhydrous dichloromethane (5 mL) were added pyridine (15 μL, 0.19 mmol, 2 equiv) then 4-nitrophenyl chloroformate (38 mg, 0.19 mmol, 2 equiv) at 0 °C under stirring. Stirring was continued at 0 °C for 2 h, then 24 h at room temperature. The mixture was diluted with dichloromethane and washed with a saturated copper sulfate solution, and with water. After drying on MgSO₄, the solution was evaporated to dryness. Purification over silica gel (eluent: CH₂Cl₂/acetone 97:3) afforded the activated compound **17** (40 mg, 71% conversion) as a white solid. The starting material **16** (24 mg) was also isolated (eluent: CH₂Cl₂/acetone 85/15): mp 78 °C; *R*_f 0.54 (CH₂Cl₂/acetone 95/5); [α]_D²⁰ -6.5 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.26 (d, 2H, *J* = 9.0 Hz), 7.30 (m, 7H), 5.96–5.77 (m, 5H), 5.36–5.14 (m, 11H), 5.06 (s, 2H), 4.64–4.49 (m, 8H), 4.41 and 4.35 (m, 3H, *J* = 9.2 Hz), 3.65 (br s, 2H), 3.0 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 156.3, 153.9, 153.7, 153.6, 152.4, 150.3, 145.4, 136.8, 132.2, 131.0, 130.9, 130.8, 128.8, 128.2, 125.3, 121.8, 121.7, 119.4, 119.2, 119.1, 92.2, 75.2, 75.3, 72.4 and 72.2, 69.2, 69.1, 66.9, 66.8, 47.9, 47.4, 35.7, 35.3; MS (MALDI-TOF) *m/z* 924 [M + Na]⁺ and 940 [M + K]⁺; HRMS (FAB + MB + Na) (C₄₀H₄₃N₃NaO₂₁) *m/z* calcd 924.2287, found 924.2285.

O-[[N-[2,3,4-Tri-(O-allyloxycarbonyl)allylester-β-D-glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonyl]-2-aminoethoxy-carbonylpaclitaxel (18). The activated carbonate **17** (40 mg, 0.044 mmol) and paclitaxel (30 mg, 0.035 mmol, 0.8 equiv) were dissolved in 7 mL of freshly distilled CH₂Cl₂, then DMAP (8 mg, 0.066 mmol, 1.5 equiv) was added under argon. The mixture was stirred at room temperature for 24 h. After evaporation, the compound was purified over silica gel (eluent: CH₂Cl₂/acetone 94/6 then 90/10) to give the coupling product **18** (35 mg, 77%) as a white solid: mp 163 °C; *R*_f 0.34 (CH₂Cl₂/acetone 85/15); [α]_D²⁰ -26 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.13 (d, 2H, *J* = 7.2 Hz), 7.72–7.22 (m, 18H), 6.30 (br s, 2H), 6.00–5.81 (m, 6H), 5.70 (d, 1H, *J* = 6.7 Hz), 5.40–5.14 (m, 11H), 5.09–4.98 (m, 4H), 4.62 (br s, 8H), 4.43 (m, 1H), 4.31–4.18 (m, 5H), 3.83 (d, 1H, *J* = 6.4 Hz), 3.55 (m, 2H), 2.91 (d, 3H, *J* = 8.7 Hz), 2.62 (m, 2H), 2.45 (s, 3H), 2.21 (s, 3H), 1.93 and 1.88 (2s, 5H), 1.68 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.7, 171.2, 169.9, 167.8, 167.2, 167.0, 165.9, 156.3, 156.2, 153.9, 153.8, 153.5, 150.3, 142.5, 136.7, 136.5, 132.8, 133.6, 133.4, 132.0, 131.0, 130.8, 130.2, 129.1, 128.7, 128.5, 127.1, 126.5, 126.1, 119.4, 119.2, 119.1, 118.9, 118.7, 118.6, 92.2, 84.3, 81.0, 79.0, 77.2, 75.5, 75.2, 75.0, 73.4, 72.5, 72.1, 69.2, 69.1, 66.9, 66.8, 66.6, 58.4, 52.6, 48.1, 47.3, 45.6, 43.1, 35.5, 26.7, 22.7, 22.1, 20.8, 14.7, 9.6; MS (FAB+) *m/z* 1638.6 [M + Na]⁺; HRMS (C₈₁H₈₉O₃₂N₃Na) *m/z* calcd 1638.5309, found 1638.5327.

O-[[N-[β-D-Glucopyranosyl]carbamoyl-4-oxy]benzyloxycarbonyl]-2-aminoethoxy-carbonylpaclitaxel (19). The protected prodrug **18** (30 mg, 0.018 mmol) was dissolved in anhydrous THF (2 mL), then a solution of Et₃N (11 μL, 0.074 mmol, 4 equiv)/HCCOH (2 μL, 0.055 mmol, 3 equiv) in THF (50 μL) was added at 0 °C under argon. After the solution was stirred for 10 min under a stream of argon, palladium(tetrakis(triphenyl)phosphine) (4.2 mg, 0.0036 mmol, 0.2 equiv) was added, and stirring was pursued for 30 min at 0 °C, then for 2 h at room temperature. After evaporation of the solvent, the product was purified over silica gel (eluent: CH₃CN/H₂O 95/5), and lyophilisation isolated prodrug **19** (20 mg, 81%) as a white solid: mp 204–206 °C; *R*_f 0.32 (CH₃CN/H₂O 9/1); [α]_D²⁰ -38 (*c* 0.8, MeOH); ¹H NMR (300 MHz, MeOD) δ 9.19 (t, 1H, *J* = 10.0 Hz), 8.12 (d, 2H, *J* = 7.2 Hz), 7.78–7.25 (m, 18H), 6.45 (s, 1H), 6.06 (t, 1H, *J* = 9.1 Hz), 5.84 (d, 1H, *J* = 4.0 Hz), 5.65 (d, 1H, *J* = 6.9 Hz), 5.52 (m, 2H), 5.03 (d, 1H, *J* = 8.3 Hz), 4.94 (s, 2H), 4.31 (m, 3H), 4.18 (s, 2H), 3.83 (d, 2H, *J* = 6.8 Hz), 3.73–3.45 (m, 5H), 2.89 (s, 3H), 2.45 (m, 1H), 2.40 (s, 3H), 2.17 (2 s, 4H), 1.94 (m, 5H), 1.65 (s, 3H), 1.13 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 203.7, 170.5, 170.2, 167.6, 158.2, 157.9, 155.8, 154.0,

142.2, 139.7, 138.1, 135.4, 134.9, 134.6, 133.8, 133.1, 133.0, 132.9, 132.8, 131.4, 131.2, 130.1, 129.9, 129.7, 129.5, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 119.9, 119.5, 96.4, 85.9, 82.3, 79.0, 78.6, 78.5, 77.9, 77.8, 77.7, 77.4, 76.8, 76.2, 73.8, 76.2, 73.8, 73.3, 73.2, 72.3, 68.9, 68.2, 67.5, 59.2, 55.2, 50.1, 49.9, 45.1, 37.1, 35.9, 26.5, 25.0, 22.8, 21.9, 20.4, 14.5, 11.1; MS (MALDI-TOF) m/z 1346 [M + Na]⁺ and 1362 [M + K]⁺; HRMS (C₆₆H₇₃O₂₆N₃Na) m/z calcd 1346.4380, found 1346.4325.

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Supporting Information Available: General experimental information and ¹H and ¹³C NMR spectra for the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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