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Direct Glycosylation of Bioactive Small Molecules with Glycosyl Iodide and Strained Olefin as Acid Scavenger

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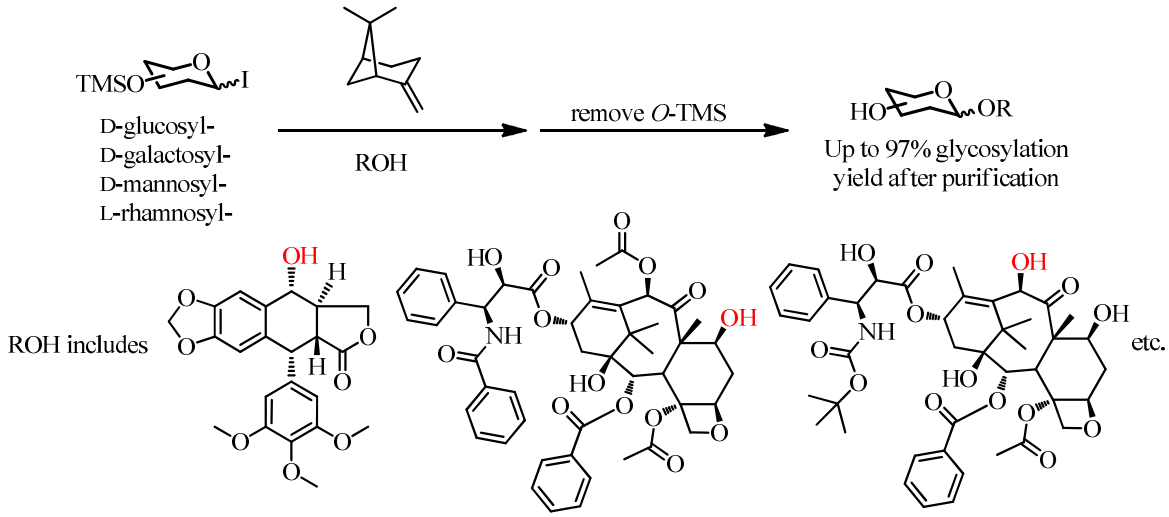
Abstract



A new strategy for diversity-oriented direct glycosylation of bioactive small molecules was developed. This reaction features (-)-*β*-pinene as acid scavenger and work with glycosyl iodides under mild conditions. With the aid of RP-HPLC and chiral SFC separation techniques, the new direct glycosylation proved effective at gram scale on bioactive small molecules including AZD6244, podophyllotoxin, paclitaxel and docetaxel. Interesting glycoside derivatives were efficiently created with good yields and 1,2-*cis* selectivity.

Introduction

From small molecule nature products to complex proteins, attachment of carbohydrates at the final synthetic stage [1] is a common practice by Mother Nature. Such glycosylated products often display unique targeting effect, improved stability, and altered activity, when compared to the original scaffolds. [2] Convenient construction of glycosylated libraries from known bioactive small molecules is of particular interest for medicinal chemists. However, such efforts are often hampered by the synthetic challenge in direct glycosylation on bioactive structures. This challenge can be exemplified by the fact that only a handful of paclitaxel glycosides have been prepared to date, [3] even though 7-*β*-xylopyranosyl paclitaxel, which was discovered along along with taxol from plant extracts, displays similar activity to paclitaxel. [4] Also due to the lack of direct glycosylation methods, total syntheses of some glycosylated nature products typically involve incorporating the sugar moiety in the mid-stage, rendering variation of sugar moiety unpractical.[5] With the rapid advancement of carbohydrate chemistry, various enzymatic [6] or chemical [7] conjugation methods have been developed to circumvent the synthetic problem. However, to carry out diversity-oriented [8] direct chemical glycosylation on many labile bioactive compounds is still difficult, and convenient chemical access

to glycosylated libraries with native glycosyl bonds between carbohydrates and bioactive small molecules remains inviting.

The synthetic challenge of direct glycosylation is manifold: 1) Glycosylation reactions often require the participation of acid, base, heavy metal or oxidating reagents,[9] which are not always compatible with structures of higher complexity; 2) removal of protecting groups on carbohydrates frequently employs similarly harsh condition; 3) precise synthesis of a particular isomer (often an anomer) is laborious and contradictory to the practice of diversity-oriented synthesis. The solutions for the first two problems reside in the continuous development of carbohydrate chemistry, while the third one admittedly could not be easily solved with current synthetic methods. During our research, we have found from various cases that isomers or side products from glycosylation reaction mixture are efficiently isolated by preparative reverse phase (RP) HPLC and chiral supercritical fluid chromatography (SFC) techniques. Therefore, we believe that the third problem can be partially circumvented by modern separation techniques, which could turn an otherwise unsuccessful glycosylation with imperfect anomeric selectivity into a productive conversion with desired diversified output structures. That is, when high glycosylation yield remains essential, compromised anomeric (or regio-) selectivities may contribute to the product diversity, as long as the isomers are separable.

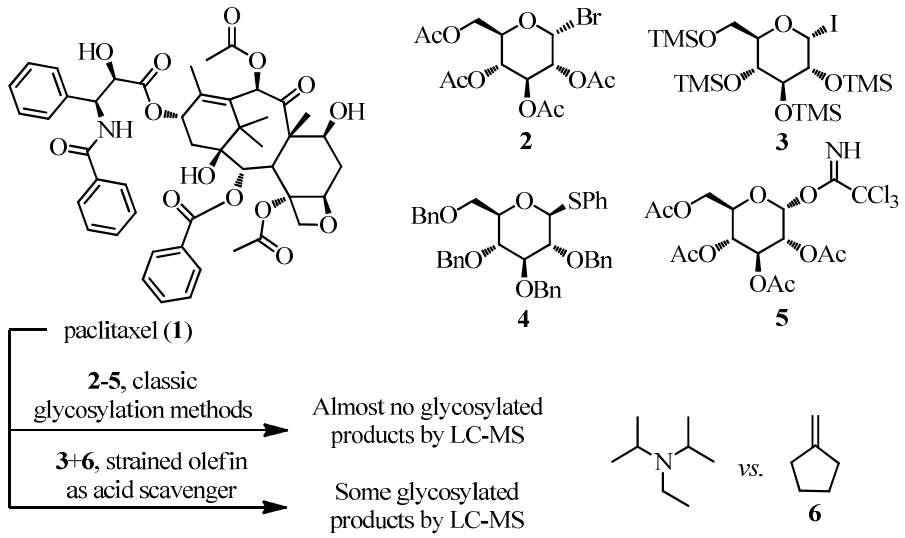
Thus, we propose that a practical strategy for diversity-oriented glycosylation of bioactive small molecules should have the following features: 1) very mild reaction and deprotection conditions, 2) high glycosylation yield, and 3) offering separable regioisomers or anomers.

Results and Discussion

To realize this strategy, the preliminary study was carried out by screening classic glycosylation methods on paclitaxel **1** as a model compound (Scheme 1). These methods include the glycosyl halide method with compound **2** [10] and **3**, [11] glycosyl sulfide method with compound **4**, [12] and trichloroacetimidate method with compound **5**. [13] With the donors **2** and **3**, using standard reaction conditions, [10b, 11o] almost no conversion was observed. With compound **4**, [12b] about half of compound **1** was consumed but the product was a complex mixture. With compound **5**, [13b] compound **1** was completely converted into an inseparable mixture. For all four cases, very little glycosylated products could be observed by LC-MS ananlysis.

Among all the reactions, compound **3** gave the cleanest result and the large amount of remaining intact **1** indicated that the condition is mild enough. Compound **3** is a typical glycosyl iodide, which has been demonstrated largely by Gervay-Hague *et al* as a powerful glycosylating reagent.[11] We found that glycosyl iodides could be efficiently prepared in large scale with a combination of the protection method by Wang *et al* [14] and the iodination method by Gervay-Hague *et al*. [11d] Typical 1,2-*cis* glycosylation condition using *O*-TMS protected glycosyl iodides is very mild and involves only TBAI as a halide-ion catalyst[15] and DIPEA as an acid scavenger. [11j] 1,2-*trans* Glycosylation with *O*-TMS protected glycosyl iodides can also be achieved using neighbouring-group participation along with silver salts as promoters.[11g, l, m] Besides, the removal of *O*-TMS protection is effortless. The fact that standard glycosylation with compound **3** failed to convert paclitaxel **1** may have multiple reasons: the *O*-TMS migration to the acceptor, DIPEA or TBAI induced decomposition of acceptor, or insufficient glycosylating activity of the system. We believe that the glycosyl iodide method could be further modified. Since it is known that strained olefins are reactive to protons, [16] we speculate that it might be possible to use olefin as a surrogate for DIPEA in the glycosylation

reaction with glycosyl iodides.[17] To test this idea, we carried out a glycosylation with compound **3** using methylidene cyclopentane **6** and TBAI. Much to our delight, the amount of glycosylated product in the reaction mixture increased significantly as measured by LC-MS.



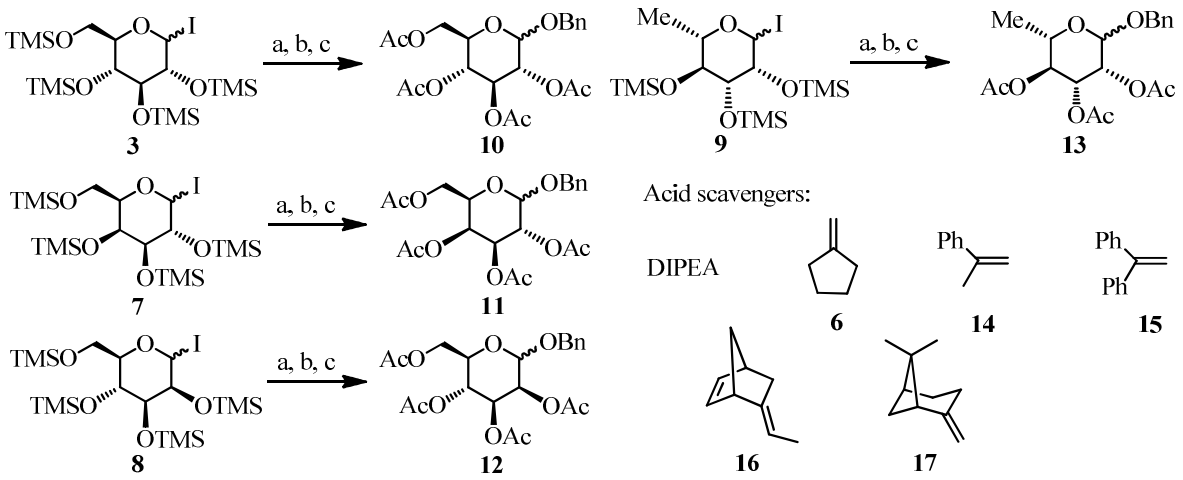
Scheme 1. Initial screening of glycosylation on paclitaxel **1** using classic methods. Reaction conditions: Using donor **2**: Ag_2CO_3 and DCM, RT; Using donor **3**: DIPEA or compound **6**, TBAI and DCM, RT; Using donor **4**: Tf_2O, NIS, MS 3 Å and DCM, -20 ^oC to RT; Using donor **5**: BF_3 etherate and DCM, -20 ^oC to RT. The reactions were monitored by TLC and LC-MS.

With this encouraging discovery, we decided to expand the glycosyl iodide chemistry and implement our strategy of diversity-oriented glycosylation. Details of this research will be elaborated in the following.

First, we systematically inspected this new glycosylation reaction using strained olefin as acid scavenger. We chose benzyl alcohol as the acceptor and screened readily available strained olefins (**6** and **14**-**17**). Following Gervay-Hague's protocol with the exception of using compound **6** instead of

DIPEA, our initial experiment with *O*-TMS protected D-glucopyranosyl iodide (**3**) and benzyl alcohol did yield the desired product which was identified by the following deprotection of *O*-TMS and re-acetylation (Table 1, entry 2). Compared to the original reaction with DIPEA [18] (Table 1, entry 1), the yield with compound **6** was slightly higher, albeit with inferior stereoselectivity. [19] As demonstrated in Table 1, entry 3-6, the yield and stereoselectivity vary with the olefin structures. Although the underlying reason was not clear, significantly improved yield for donor **1** was recorded with (-)-*β*-pinene (**17**, Table 1, enrty 6) when compared to entry 1, demonstrating a reactivity enhancement for glucosyl iodides [11j] previously known as less reactive species. Also, the stereoselectivity in Table 1, entry 6 was improved over those in entry 2-5. Under similar conditions, *O*-TMS protected D-galactopyranosyl iodide **7** was reacted with BnOH in the presence of olefin **16** or **17**. Again, better yield and selectivity were found with **17** (Table 1, entry 7 and 8). To identify a set of even milder conditions, we further investigated the possibility of removing the stoichimetric TBAI, since it is known that high concentration of iodide is reactive. For compounds **3** and **7**, with (-)-*β*-pinene (**17**), the yields were similar with or without TBAI. However, the stereoselectivities were poor in the absence of TBAI (Table 1, entry 9 and 10). Moreover, although the stereoselectivities were not ideal, D-mannopyranosyl iodide (**8**) and L-rhamnopyranosyl iodide (**9**) gave good glycosylation yields under TBAI free condition, too (Table 1, entry 11 and 12).

Table 1. Initial screening with different glycosyl donors and olefins.[a]

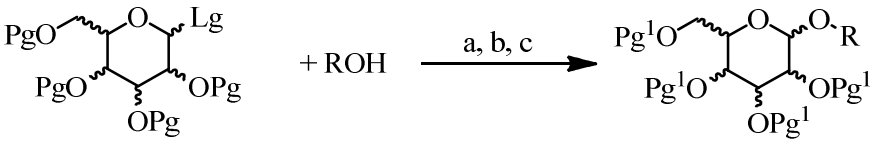


No.	Glycosyl iodide	Acid scavenger	Additive	Product No., Yield (α:β) [b]
1	**3**	DIPEA	TBAI, 3 Å MS	**10**, 37% (15:1)
2	**3**	**6**	TBAI, 3 Å MS	**10**, 44% (2.3:1)
3	**3**	**14**	TBAI, 3 Å MS	**10**, 45% (1.6:1)
4	**3**	**15**	TBAI, 3 Å MS	**10**, 44% (1.2:1)
5	**3**	**16**	TBAI, 3 Å MS	**10**, 67% (3.0:1)
6	**3**	**17**	TBAI, 3 Å MS	**10**, 68% (7.0:1)
7	**7**	**16**	TBAI, 3 Å MS	**11**, 52% (4.0:1)
8	**7**	**17**	TBAI, 3 Å MS	**11**, 69% (8.0:1)
9	**3**	**17**	3 Å MS	**10**, 70% (1.7:1)
10	**7**	**17**	3 Å MS	**11**, 64% (1:2.0)
11	**8**	**17**	3 Å MS	**12**, 52% (1:1.3)
12	**9**	**17**	3 Å MS	**13**, 75% (1:1.5)

[a] Reaction conditions: a) benzyl alcohol, acid scavenger, additives, and DCM, RT; b) MeOH, reflux; c) Ac_2O, and Py. [b] Yields were determined after flash chromatography and based on glycosyl donors. Anomeric ratio was determined by NMR.

According to the aforementioned strategy, we were not particularly discouraged by the imperfect stereoselectivity resulting from the absence of TBAI. Instead, we decided to use the TBAI free condition described in Table 1, entry 9-12 to further define the reaction scope, since this condition constitutes probably one of the mildest known chemical glycosylation reactions. In table 2, entry 1-6, donor **3** was reacted with acceptors of different hindrance levels. Except for entry 4 and 6, the yields were similar and generally satisfying while the stereoselectivities ascended with the increasing steric hindrance of the alcohols. For alcohol **22** in entry 4, although the yield was low, the double bond was identified intact in the product and the acetylated **22** could be recovered. In entry 6, sugar alcohol **26** was too hindered to react with **3**. In entry 7, D-galactopyranosyl donor (**7**) was used with alcohol **22** and demonstrated very good selectivity, though again with compromised yield. We further explored the reaction between *O*-Bn protected D-glucopyranosyl iodide **28** or *O*-Bn protected D-mannopyranosyl iodide **30** and BnOH. While the yields were satisfying, the stereoselectivities were anticipatively modest (Table 2, entry 8 and 9). Interestingly, under the catalysis of iodine, disarmed *O*-Ac protected D-glucopyranosyl bromide (**2**) failed to react with BnOH (table 2, entry 10). This indicates that high reactivity of donor is important for glycosylation under our condition. It is also important to note that 1) glycal formation is still observed even without the presence of a nitrogen base; and 2) side reactions related to the carbocations formed by addition of proton to olefin have not been identified.

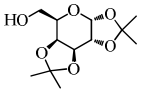
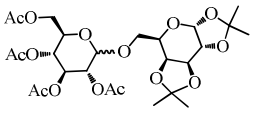
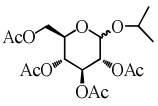
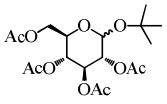
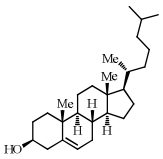
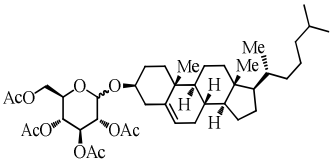
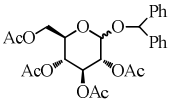
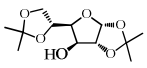
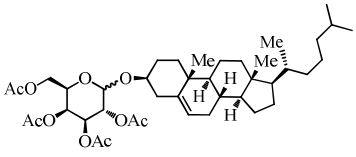
Table 2. Mapping the glycosylation scope with different glycosyl donors and acceptors. [a]

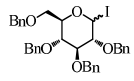
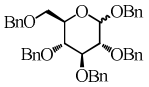
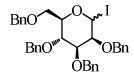
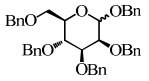


Glycosyl donor
Lg = leaving group
Pg = protecting group

Glycosyl acceptor

Product
Pg' = protecting group

No.	Glycosyl Donor	Glycosyl acceptor (ROH)	Product No., Yield (α:β) [b]
1	**3**	 **18**	 α-**19**, 48%; β-**19**, 18%; (2.7:1)
2	**3**	*i*-PrOH	 α-**20**, 35%; β-**20**, 22%; (1.6:1) [c]
3	**3**	*t*-BuOH	 **21**, 70% (2.7:1)
4	**3**	 **22**	 α-**23**, 23%; β-**23**, 4%; (5.1:1) [c]
5	**3**	 **24**	 **25**, 78% (7.3:1)
6	**3**	 **26**	*n.d.*
7	**7**	**22**	

			27, 32% (17:1)
8	 **28**	BnOH	 **29**, 76% (1:5.3)
9	 **30**	BnOH	 **31**, 56% (1:2.5)
10	**2**	BnOH	*n.d.* [d]

[a] Reaction conditions: a) glycosyl acceptor, (-)-*β*-pinene, 3 Å MS, and DCM, RT; for TMS protected sugar starting materials (entry 1-7), the following two steps were performed: b) MeOH, reflux; c) Ac_2O, and Py. [b] Unless otherwise mentioned, yields were determined after flash chromatography and based on glycosyl donors. Anomeric ratio was determined by NMR. See supporting information for details of experiments in table 2. [c] Anomers were separated by flash chromatography and the ratio was determined based on pure products. [d] No reaction could be observed with additional cat. I_2.

According to experiments in table 1 and 2, the new glycosylation method generally gives satisfying yields for different types of glycosyl donors and acceptors, albeit with compromised stereoselectivities in certain cases. It is reasonable to conclude that this new condition has improved reactivity compared to the original DIPEA/TBAI/DCM system. From the stereochemistry outcomes, it also appears justified to propose that glycosyl iodide donors experience rapid anomerization, even without TBAI. With less hindered alcohol acceptor, the different reactivities of *α*- and *β*-glycosyl

iodides could not be reflected, and low stereoselectivity was observed. However, when hindered acceptors were used, more reactive anomer will lead to higher selectivity, and the yield could remain unchanged due to the anomerization of the glycosyl iodides.

At this stage, we consider that the new glycosylation condition meets the criteria for diversity-oriented glycosylation of bioactive small molecules. Therefore, we did not carry out further reaction optimization, and directly applied the condition to more complex bioactive small molecule acceptors. (Scheme 2) We chose anti-tumour small molecules as our glycosylation targets due to their ever-increasing clinical significance.

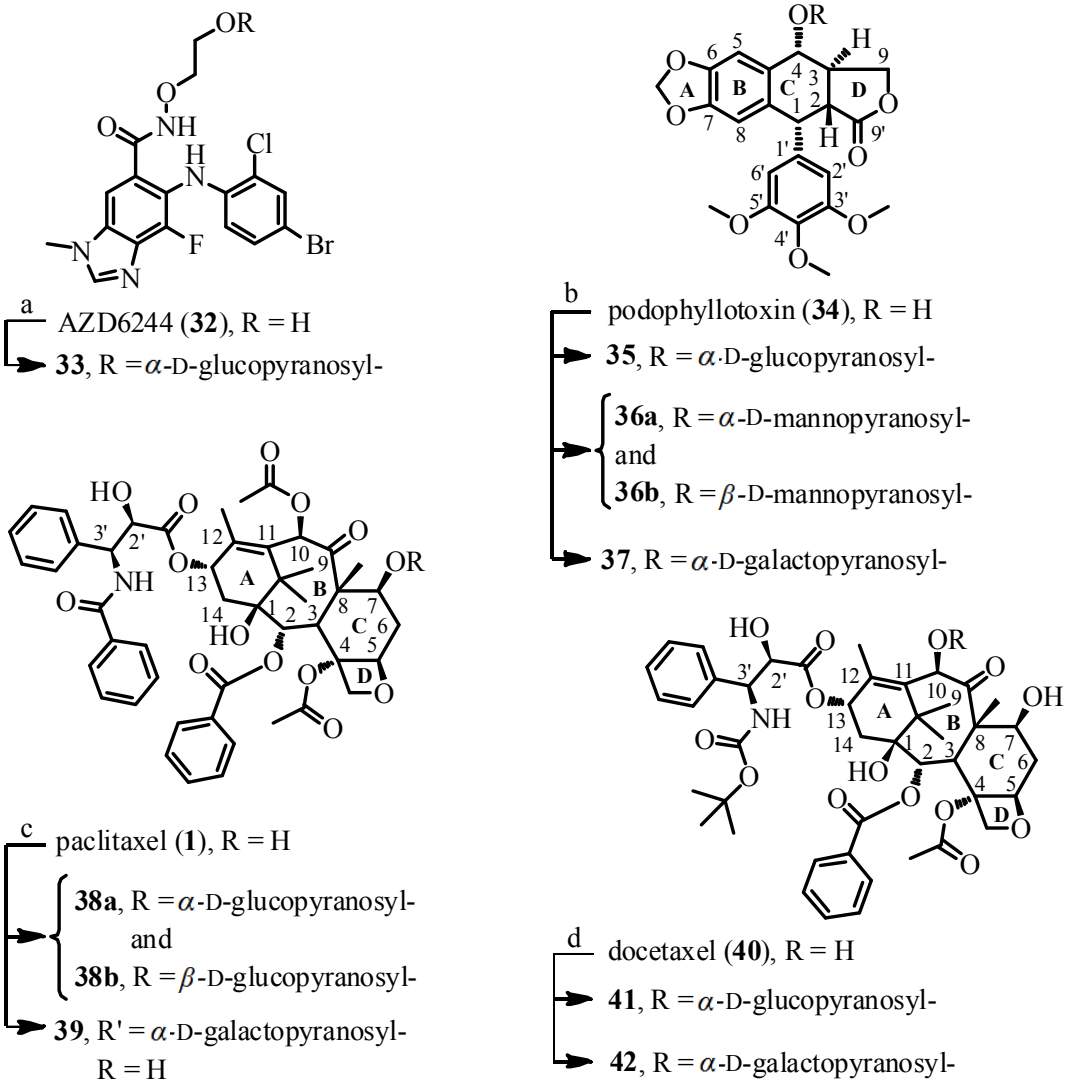
First, AZD6244 (**32**), an MEK inhibitor with low water solubility issue,[20] was glycosylated with donor **3**.[21] After the removal of *O*-TMS protection by heating the product mixture with MeOH, glycosylated prodrug **33** with improved water solubility was obtained (60% after FC on silica gel and 28% after RP-HPLC).[22] This example demonstrated that nitrogen rich heterocyclic structure can be used with our glycosylation condition.

The second case begins with podophyllotoxin (**34**), a well-known anti-tumour leading structure with unwanted high toxicity. Podophyllotoxin glycosides are known for better activity and less toxicity. Although the synthetic difficulties have been partially reduced by the invention of reverse glycosylations, types of podophyllotoxin glycosides are still quite limited.[23] Nevertheless, with our method, we have successfully accessed hitherto unknown podophyllotoxin α-D-glucopyranoside **35** (44% after FC on silica gel and 20% after RP-HPLC. β-Anomer was not observed in the crude product),[22] both podophyllotoxin α- and β-D-mannopyranoside **36a** and **36b** (98% for a anomeric mixture after FC on silica gel; 71% for **36a** after SFC and 26% for **36b** after SFC), as well as podophyllotoxin α-D-galactopyranoside **37** (96% after FC on silica gel and 32% after RP-HPLC and

SFC. β-Anomer was not observed in the crude product). For podophylloxin based glycosides, the removal of *O*-TMS protection should be carried out with HF-pyridine complex to achieve good yields.

The third case involves taxanes, which are one of the most important classes of antitumor agents despite the poor water solubility and low selectivity profile for its cytotoxicity. Upon the early discovery of paclitaxel, 7-β-D-xylopyranosyl paclitaxel was also separated from plant extracts and found with similar activity to paclitaxel.[4, 24] Probably due to synthetic difficulties, paclitaxel glycosides were later rarely prepared and investigated.[3] Excitingly, with our method, paclitaxel (**1**) was reacted with donor **3** followed by deprotection to give two anomers **38a** and **38b** (70% for the crude mixture after FC on silica gel; 18% for **38a** after RP-HPLC and 21% for **38b** after RP-HPLC). In a similar manner, paclitaxel was reacted with donor **7** to give the α-D-galactoside **39** (74% after FC on silica gel and 43% after RP-HPLC. β-Anomer was not observed in the crude product). The regioselectivity of this reaction was exclusively on 7-OH of paclitaxel according to NMR study, and this glycosylation site is interestingly coincident with the natural 7-xyloside. Also, it should be noted here, that in the early patent, 7-*O*-glycosylation has to be done with the prior 2'-*O*-protection.[3b] Deprotection of *O*-TMS for paclitxel series were carried out with HF-pyridine complex. For docetaxel (**40**), there are currently no glycosides reported.[25] Nevertheless, with our method, glycosylated docetaxels were easily prepared: From donor **3**, α-D-glucoside **41** was obtained after deprotection (90% after FC on silica gel and 55% after RP-HPLC.[22] β-Anomer was not observed in the crude product). With donor **7**, α-D-galactoside **42** was obtained after deprotection (63% after FC on silica gel and 32% after RP-HPLC. β-Anomer was not observed in the crude product). NMR Analysis indicated that our glycosylation took place only on 10-OH. AcOH-MeOH System was used

to remove the *O*-TMS protection for glycosylated docetaxel series. All above taxane glycosides were previously unknown.



Scheme 2. Applications of the glycosylation method on various bioactive small molecules. Reaction conditions: a) compounds **3** and **17**, TBAI, 3 Å MS, and DCM; then MeOH, reflux; b) donor **3**, **7**, or **8**, compound **17**, 3 Å MS, and DCM; then HF-pyridine complex; c) donor **3** or **7**, compound **17**, 3 Å MS, and DCM; then HF-pyridine complex; d) donor **3** or **7**, compound **17**, 3 Å MS, and DCM; then HOAc and MeOH. Different from Table 1 and 2, yields here were based on the glycosyl acceptors.

Conclusion

In conclusion, a very mild glycosylation reaction using different glycosyl iodides and (-)-*β*-pinene as acid scavenger was developed. Based on this method, we have performed direct glycosylation on anti-tumour small molecules including AZD6244, podophyllotoxin, paclitaxel and docetaxel, using per-*O*-TMS protected glucosyl, mannosyl and galactosyl iodides as donors. The glycosylation yields were generally satisfying and the removal of *O*-TMS protection was efficient. With modern purification techniques including RP-HPLC and chiral SFC, anomers from the glycosylation step were separated. As a result, 10 highly valuable glycosides of bioactive molecules were produced from 8 two-step, one-pot reactions, manifesting the power of the new glycosylation method, and a successful implementation of the strategy for diversity-oriented glycosylation of bioactive small molecules. It should be noted that most of the products are 1,2-*cis* glycosides, which are not easily prepared by other methods. We hope that this direct glycosylation method on bioactive small molecules will contribute to advancing the research on carbohydrate based medicinal chemistry.

Experimental Section

All solvents were dried and purified prior to use: Toluene was distilled from sodium, Et_2O and THF were distilled from potassium, and CH_2Cl_2 was distilled from CaH_2. All other commercially available reagents were used as received. Reactions at −78 °C were performed in a dry ice/acetone bath. All moisture sensitive reactions were performed under N_2 (ca. +1.1 bar) in heating-gun (500-600 °C)/vacuum dried glassware sealed with rubber septa. Flash chromatography was performed on silica gel (300-400 mesh ASTM), and monitored by thin layer chromatography (TLC)

on HSGF-254 (10-40 μm) TLC plates. NMR data from solutions in $CDCl_3$ (δC = 77.0 ppm) are calibrated relative to TMS (δH = 0.00 ppm). Peaks on ^{1}H-NMR and ^{13}C-NMR are assigned with the aid of COSY, HSQC and HMBC methods. HRMS data were collected with ESI-Q-TOF method. Unless otherwise mentioned, HPLC analysis was performed on a YMC-ODS column (4.6 x 50 mm, 5 μm). HPLC conditions: solvent A = H_2O containing 0.1% (v/v) TFA, solvent B = MeCN containing 0.1% (v/v) TFA; flow rate = 2.5 mL/min; Gradient (B%): 0-0.5 min (4% isostatic), 0.5-4.5 min (4% - 95%); peaks were identified at 254 nm and 214 nm.

General procedure A for the syntheses of compounds 10, 11, 12, and 13 in Table 1 and the syntheses of compounds 19, 20, 21, 23, 25, and 27 in Table 2

Activated 3 Å molecular sieves (0.1 g), TBAI (optional, according to the instruction in the tables), acid scavenger (DIPEA, compounds **6**, **14**, **15**, **16**, or **17**, 2 eq.) and the alcohols were mixed and dissolved in DCM (0.5 mL). A solution of the glycosyl donor [11c, d] (0.11 g, 0.19 mmol, 1 eq.) in DCM (0.5 mL) was added to the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, and stirred overnight. The mixture was then evaporated to dryness, and the residue was refluxed for 2 h with MeOH (4 mL). Upon completion by TLC, the mixture was again evaporated to dryness, treated with pyridine (0.3 mL, 3.8 mmol, 20 eq.) and Ac_2O (0.17 mL, 1.9 mmol, 10 eq.), stirred at RT overnight, and quenched with MeOH. The mixture was distributed in 1 N aq. HCl and ethyl acetate. The organic phase was separated and the aqueous phase was washed by ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and purified with flash chromatography on silica gel (ethyl acetate / 60 – 90 °C petroleum ether) to give compounds **10**, **13**, **19**, **20**, **21**, **23**, **25**, and **27**.

General procedure B for the syntheses of compounds 29 and 31 in Table 2

Activated 3 Å molecular sieves (0.2 g), compound **17** (2 eq.) and BnOH (0.69 mmol, 2 eq.) were mixed and dissolved in DCM (1 mL). A solution of glycosyl donor **28** or **30** [11c, d] (0.34 mmol, 1 eq.) in DCM (1 mL) was added to the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, and stirred overnight. The resulting mixture was dried and purified directly by flash chromatography on silica gel (ethyl acetate / 60 – 90 °C petroleum ether) to give compounds **29** and **31**.

Preparation of benzyl 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranoside (10)

Table 1，Entry 1：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and DIPEA (0.07 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained as an inseparable anomeric mixture (light yellow oil, 31 mg, α:β = 15:1, 37%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on α-**10**: δ 5.54 (t, J = 9.8 Hz, 1 H), 4.73 (d, J = 12.2 Hz, 1 H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on β-**10**: δ 4.63 (d, J = 12.3 Hz, 1 H), 3.68 (ddd, J = 9.7, 4.7, 2.5 Hz, 1 H). NMR data of compound **10** matches the literatures.[26]

Table 1，Entry 2：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and methylene cyclopentane (**6**, 0.04 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 37 mg, α:β = 2.3:1, 44%).

Table 1，Entry 3：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and 2-phenyl propene (**14**, 0.05 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 38 mg, α:β = 1.6:1, 45%).

Table 1，Entry 4：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and 1,1-diphenyl ethylene (**15**, 0.07 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 37 mg, α:β = 1.2:1, 44%).

Table 1，Entry 5：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and 5-ethylidene-2-norbornene (**16**, 0.05 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 56 mg, α:β = 3.0:1, 67%).

Table 1，Entry 6：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and β-(-)-pinene (**17**, 0.06 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 57 mg, α:β = 7.0:1, 68%).

Table 1，Entry 9：From compound **3** (0.11 g, 0.19 mmol, 1 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and β-(-)-pinene (**17**, 0.06 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **10** was obtained (light yellow oil, 59 mg, α:β = 1.7:1, 70%).

Preparation of benzyl 2, 3, 4, 6-tetra-*O*-acetyl-D-galactopyranoside (11)

Table 1，Entry 7：From compound **7** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and 5-ethylidene-2-norbornene (**16**, 0.05 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **11** was obtained as an inseparable anomeric mixture (light yellow oil, 44 mg, α:β = 4.0:1, 52%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on α-**11**: δ 5.47 (d, J = 3.1 Hz, 1H), 4.74 (d, J = 12.2 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on β-**11**: δ 4.99 (dd, J = 10.4, 3.4 Hz, 1H), 4.92 (d, J = 12.3 Hz, 1H), 4.64 (d, J = 12.3 Hz, 1H), 3.90 (t, J = 6.7 Hz, 1H). NMR data of compound **11** matches the literatures. [27]

Table 1，Entry 8：From compound **7** (0.11 g, 0.19 mmol, 1 eq.), TBAI (0.14 g，0.37 mmol，2 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.06 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **11** was obtained (light yellow oil, 58 mg, *α:β* = 8.0:1, 69%).

Table 1，Entry 10：From compound **7** (0.11 g, 0.19 mmol, 1 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.06 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **11** was obtained (light yellow oil, 54 mg, *α:β* = 1:2.0, 64%).

Preparation of benzyl 2, 3, 4, 6-tetra-*O*-acetyl-D-mannopyranoside (12)

Table 1，Entry 11：From compound **8** (0.11 g, 0.19 mmol, 1 eq.), BnOH (0.04 mL, 0.37 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.06 mL, 0.37 mmol, 2 eq.), according to general procedure A, compound **12** was obtained as an inseparable anomeric mixture (light yellow oil, 44 mg, *α:β* = 1:1.3, 52%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**12**: δ 4.07 – 3.97 (m, 2H, H-5,H-6); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**12**: δ5.46 (d, *J* = 3.3 Hz, 1H, H-2), 5.00 (dd, *J* = 10.0, 3.3 Hz, 1H, H-3), 4.19 (dd, *J* = 12.2, 2.5 Hz, 1H, H-6), 3.61 (ddd, *J* = 10.0, 5.6, 2.5 Hz, 1H, H-5). NMR data of compound **12** matches the literature. [28]

Preparation of benzyl 2, 3, 4-tri-*O*-acetyl-L-rhamnopyranoside (13)

Table 1，Entry 12：From compound **9** (0.11 g, 0.22 mmol, 1 eq.), BnOH (0.05 mL, 0.44 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.07 mL, 0.44 mmol, 2 eq.), according to general procedure A, compound **13** was obtained as an inseparable anomeric mixture (light yellow oil, 63 mg, *α:β* = 1:1.5, 75%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**13**: δ 3.92 (dq, *J* = 9.8, 6.3 Hz, 1H, H-5); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**13**: δ 3.51 (dq, *J* = 9.5, 6.1 Hz, 1H, H-5). NMR data of known compound **13** matches the literature. [29]

Preparation of 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranosyl-(1→6) -1, 2 : 3, 4 -di-*O*-isopropylidene-*α*-D-galactopyranose (19)

Table 2，Entry 1：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), compound **18** (0.29 g, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, *α*-**19** (colorless oil, 157 mg, 48%) and *β*-**19** (colorless oil, 59 mg, 18%) were obtained. *α*:*β* = 2.7:1. *α*-**19**: R_f 0.26 (ethyl acetate : 60 – 90 °C petroleum ether, 1:3); $[\alpha]_D^{25}$ +32.80 (*c* 0.5 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 – 5.45 (m, 2H, H-1, H- 3′), 5.10 (d, *J* = 3.7 Hz, 1H, H-1′), 5.07 (t, *J* = 9.8 Hz, 1H, H-4′), 4.90 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2′), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H, H-3), 4.33 (dd, *J* = 5.0, 2.5 Hz, 1H, H-2), 4.33 – 4.26 (m, 1H, H-6′a), 4.23 (dd, *J* = 7.9, 1.9 Hz, 1H, H-4), 4.15 – 4.07 (m, 2H, H-5′, H-6′b), 3.99 (td, *J* = 6.6, 2.0 Hz, 1H, H-5), 3.81 (dd, *J* = 10.5, 6.7 Hz, 1H, H-6a), 3.70 (dd, *J* = 10.6, 6.5 Hz, 1H, H-6b), 2.10 (s, 3H, C$\underline{H}_3$C=O), 2.06 (s, 3H, C$\underline{H}_3$C=O), 2.03 (s, 3H, C$\underline{H}_3$C=O), 2.01 (s, 3H, C$\underline{H}_3$C=O), 1.56 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.42 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.34 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.32 (s, 3H, C(C$\underline{H}_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.16 (C=O), 169.55 (C=O), 169.45 (C=O), 169.07 (C=O), 108.86 (C(CH$_3$)$_2$), 108.18 (C(CH$_3$)$_2$), 95.73 (C-1), 95.41 (C-1′), 70.39 (C-4), 70.11 (C-2′), 70.09 (C-3), 69.93 (C-2), 69.64 (C-3′), 67.93 (C-4′), 66.76 (C-5′), 66.63 (C-6), 65.31 (C-5), 61.28 (C-6′), 25.54 (CH$_3$C=O), 25.44 (CH$_3$C=O), 24.39 (CH$_3$C=O), 24.05 (CH$_3$C=O), 20.20 (C(CH$_3$)$_2$), 20.16 (C(CH$_3$)$_2$), 20.11 (C(CH$_3$)$_2$), 20.08 (C(CH$_3$)$_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{38}O_{15}Na$ 613.2108; Found 613.2103. *β*-**19**: [30] R_f 0.25 (ethyl acetate : 60 – 90 °C petroleum ether, 1:3); $[\alpha]_D^{25}$ -42.23 (*c* 0.5 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, *J* = 5.0 Hz, 1H, H-1), 5.21 (t, *J* = 9.5 Hz, 1H, H-3′), 5.08 (t, *J* = 9.7 Hz, 1H, H-4′), 5.00 (dd, *J* = 9.7, 8.0 Hz, 1H, H-2′), 4.62 (d, *J* = 8.0 Hz, 1H, H-4), 4.59 (dd, *J* = 7.9, 2.4 Hz, 1H, H-3), 4.31 – 4.24 (m, 2H, H-2, H-6′a), 4.18 (dd, *J* = 7.9, 1.9 Hz, 1H, H-4), 4.13 (dd, *J* = 12.3, 2.4 Hz, 1H, H-6′b), 4.02 (dd, *J* = 11.4, 3.5 Hz, 1H, H-6a),

3.93 (ddd, J = 7.7, 3.4, 1.8 Hz, 1H, H-5), 3.73 – 3.65 (m, 2H, H-6b, H-5′), 2.09 (s, 3H, C$\underline{H}_3$C=O), 2.07 (s, 3H, C$\underline{H}_3$C=O), 2.02 (s, 3H, C$\underline{H}_3$C=O), 2.00 (s, 3H, C$\underline{H}_3$C=O), 1.50 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.44 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.32 (s, 6H, C(C$\underline{H}_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.18 (C=O), 169.73 (C=O), 169.03 (C=O), 168.93 (C=O), 108.88 (C(CH$_3$)$_2$), 108.15 (C(CH$_3$)$_2$), 100.95 (C-1′), 95.69 (C-1), 72.23 (C-3′), 71.21 (C-5′), 70.73 (C-4), 70.54 (C-2), 70.13 (C-3), 69.93 (C-2), 69.03 (C-6), 67.99 (C-4′), 67.29 (C-5), 61.42 (C-6′), 25.53 (CH$_3$C=O), 25.43 (CH$_3$C=O), 24.53 (CH$_3$C=O), 23.81 (CH$_3$C=O), 20.23 (C(CH$_3$)$_2$), 20.18 (C(CH$_3$)$_2$), 20.13 (C(CH$_3$)$_2$), 20.10 (C(CH$_3$)$_2$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{26}H_{38}O_{15}Na$ 613.2108; Found 613.2107.

Preparation of isopropyl 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranoside (20)

Table 2，Entry 2：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), *i*-PrOH (0.08 mL, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, *α*-**20** (light yellow oil, 76 mg, 35%) and *β*-**20** (light yellow oil, 48 mg, 22%) were obtained. *α:β* = 1.6:1. Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**20**: δ 5.52 (d, J = 19.6 Hz, 1H), 4.85 (dd, J = 10.3, 3.8 Hz, 1H), 1.29 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**20**: δ 4.95 (dd, J = 9.7, 8.0 Hz, 1H), 3.69 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H). NMR data of compounds *α*- and *β*-**20** matches the literatures. [31]

Preparation of *tert*-butyl 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranoside (21)

Table 2，Entry 3：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), *t*-BuOH (0.11 mL, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, compound **21** was obtained as an inseparable anomeric mixture (light yellow oil, 163 mg, *α:β* = 2.7:1, 70%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**21**: δ 5.35 (d, J = 3.8 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**21**: δ 5.23 (t, J = 9.5 Hz, 1H). NMR data of compound **21** matches the literatures. [32]

Preparation of (3*β*)-cholest-5-en-3-yl 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranoside (23)

Table 2，Entry 4：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), cholesterol **22** (0.43 g, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, *α*-**23** (light yellow oil, 91 mg, 23%) and *β*-**23** (light yellow oil, 16 mg, 4%) were obtained. *α:β* = 5.1:1. Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**23**: δ 4.80 (dd, *J* = 10.2, 3.8 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**23**: δ 4.58 (d, *J* = 8.0 Hz, 1H). NMR data of compound **23** matches the literature. [33]

Preparation of diphenylmethyl 2, 3, 4, 6-tetra-*O*-acetyl-D-glucopyranoside (25)

Table 2，Entry 5：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), diphenyl carbinol (0.20 g, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**24**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, compound **25** was obtained as an inseparable anomeric mixture (light yellow oil, 223 mg, *α:β* = 7.3:1, 78%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**25**: δ 4.93 (dd, *J* = 10.3, 3.8 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**25**: δ 4.53 (d, *J* = 7.4 Hz, 1H). NMR data of compound **25** matches the literature. [34]

Reaction between compound 3 and 26

Table 2，Entry 6：From compound **3** (0.33 g, 0.56 mmol, 1 eq.), compound **26** (0.29 g, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, no reaction could be observed by TLC inspection.

Preparation of (3*β*)-cholest-5-en-3-yl 2, 3, 4, 6-tetra-*O*-acetyl-D-galactopyranoside (27)

Table 2，Entry 7：From compound **7** (0.33 g, 0.56 mmol, 1 eq.), cholesterol **22** (0.43 g, 1.11 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.18 mL, 1.11 mmol, 2 eq.), according to general procedure A, compound **27** was obtained as an inseparable anomeric mixture (light yellow oil, 127 mg, *α:β* = 17:1, 32%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**27**: δ 4.33 (t, *J* = 6.6 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$,

400 MHz) on *β*-**27**: δ 4.44 (d, *J* = 7.9 Hz, 1H). NMR data of known compound **27** matches the literature. [11b]

Preparation of 1, 2, 3, 4, 6-penta-*O*-benzyl-D-glucopyranose (29)

Table 2，Entry 8：From compound **28** (0.22 g, 0.34 mmol, 1 eq.), BnOH (0.07 mL, 0.69 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.11 mL, 0.69 mmol, 2 eq.), according to general procedure B, compound **29** was obtained (light yellow oil, 165 mg, *α:β* = 1:5.3, 76%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**29**: δ 4.18 (t, *J* = 9.3 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**29**: δ 3.60 (ddd, *J* = 9.0, 4.5, 1.9 Hz, 1H). NMR data of known compound **29** matches the literature. [35]

Preparation of 1, 2, 3, 4, 6-penta-*O*-benzyl-D-mannopyranose (31)

Table 2，Entry 9：Table 2，Entry 8：From compound **30** (0.22 g, 0.34 mmol, 1 eq.), BnOH (0.07 mL, 0.69 mmol, 2 eq.), and *β*-(-)-pinene (**17**, 0.11 mL, 0.69 mmol, 2 eq.), according to general procedure B, compound **31** was obtained as an inseparable anomeric mixture (light yellow oil, 121 mg, *α:β* = 1:2.5, 56%). Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *α*-**31**: δ 4.02 (t, *J* = 9.4 Hz, 1H); Selected ^{1}H-NMR ($CDCl_3$, 400 MHz) on *β*-**31**: δ 3.51 – 3.42 (m, 2H). NMR data of compound **31** matches the literatures. [36]

Reaction between compound 2 and BnOH with compound 17

Table 2，Entry10：Activated 3 Å molecular sieves (0.1 g), compound **17** (0.04 mL, 0.24 mmol, 2 eq.) and BnOH (0.04 mL, 0.36 mmol, 3 eq.) were mixed and dissolved in DCM (0.5 mL). A solution of glycosyl donor **2** (0.05 g, 0.12 mmol, 1 eq.) in DCM (0.5 mL) was added to the above suspension. The resulting mixture was stirred overnight at RT. No reaction could be detected by TLC. Catalytic amount of iodine was added to this mixture, which was stirred for 24 h at RT. Again, no reaction was observed by TLC inspection.

Preparation of 6-(4-bromo-2-chloroanilino)-7-fluoro-*N*-[2-(*α*-D-glucopyranosyloxy)-ethoxy]-3-methylbenzimidazole-5-carboxamide (33)

Under N_2 atomosphere, activated 3 Å molecular sieves (0.7 g), *β*-(-)-pinene (**13**, 0.41 mL, 2.62 mmol, 6 eq.), TBAI (0.97 g, 2.62 mmol, 6 eq.), and AZD6244 (0.2 g, 0.44 mmol, 1 eq.) were dissolved in DCM (3.5 mL). A solution of compound **3** [11c, d] (0.78 g，1.31 mmol, 3 eq.) in DCM (3.5 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred overnight, and then evaporated to dryness. The residue was refluxed for 2 h with MeOH (8 mL). Upon completion by TLC, the mixture was again evaporated to dryness and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **33** (light yellow glass, 163 mg, 60%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) to give the pure product **33** after lyophilization (amorphous white powder, 76 mg, 28%). R_f 0.36 (CH_2Cl_2 : CH_3OH, 5 : 1); $[\alpha]_D^{25}$ +46.79 (*c* 0.5 MeOH); HPLC t_R 2.40 min; ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H, Ar), 7.71 (s, 1H, Ar), 7.49 (d, *J* = 2.2 Hz, 1H, Ar), 7.18 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar), 6.41 (dd, *J* = 8.8, 3.9 Hz, 1H, Ar), 4.82 (d, *J* = 3.8 Hz, 1H, H-1), 4.14 – 4.01 (m, 2H, O(C$\underline{H}_2$)$_2$O), 3.97 (s, 3H, NC$\underline{H}_3$), 3.96 – 3.86 (m, 1H, O(C$\underline{H}_2$)$_2$O), 3.86 – 3.77 (m, 1H, H-6a), 3.73 – 3.59 (m, 4H, H-3, H-6b, H-5, O(C$\underline{H}_2$)$_2$O), 3.39 (dd, *J* = 9.7, 3.8 Hz, 1H, H-2), 3.25 (t, *J* = 9.3 Hz, 1H, H-4). ^{13}C NMR (101 MHz, CD_3OD) δ 167.2 (C=O), 148.4 (Ar), 142.7 (Ar$_q$), 135.4 (Ar$_q$), 135.3 (Ar$_q$), 132.5 (Ar), 131.6 (Ar), 126.5 (Ar$_q$), 122.5 (Ar$_q$), 122.34 (Ar$_q$), 122.2 (Ar$_q$), 116.5 (Ar), 111.1 (Ar$_q$), 108.1 (Ar), 100.4 (C-1), 76.3 (O(C$\underline{H}_2$)$_2$O), 75.2 (C-5), 73.8 (C-3), 73.6 (C-2), 71.9 (C-4), 66.9 (O(C$\underline{H}_2$)$_2$O), 62.8 (C-6), 32.0 (NC$\underline{H}_3$); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{23}H_{25}BrClFN_4O_8H$ 619.0601; Found 619.0600.

General procedure for the syntheses of compounds 35, 36a, 36b, and 37

Under N_2 atomosphere, activated 3 Å molecular sieves, *β*-(-)-pinene (**17**, 0.68 mL, 4.34 mmol, 6 eq.), and podophyllotoxin (0.3 g, 0.73 mmol, 1 eq.) were dissolved in DCM (5.0 mL). A solution of compound **3**, [11c, d] **7**, [11c, d] or **8** [11c, d] (1.29 g, 2.17 mmol, 3 eq.) in DCM (5.0 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred overnight, and then filtered. The filtrate was treated with HF-pyridine complex (70% HF, 1.95 mL, 10 eq.) and stirred at RT for 30 min. Upon completion by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **35**, **36a**, **36b**, and **37**, which was then purified by RP-HPLC or SFC to give the pure product **35**, **36a**, **36b**, and **37**.

Preparation of 7-(*α*-D-glucopyranosyloxy)-3', 4', 5'-trimethoxy-4, 5-methylenedioxy-2, 7'-cyclolignan-9', 9-lactone (35) [37]

From compound **3** [11c, d] (1.29 g，2.17 mmol, 3 eq.), activated 3 Å molecular sieves (1.1 g), *β*-(-)-pinene (**17**, 0.68 mL, 4.34 mmol, 6 eq.), and podophyllotoxin (0.3 g, 0.73 mmol, 1 eq.), according to general procedure, crude product **35** was obtained (light yellow glass, 184 mg, 44%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) to give the pure product **38** after lyophilization (amorphous white powder, 83 mg, 20%). R_f 0.53 (CH_2Cl_2 : CH_3OH, 7 : 1); $[\alpha]_D^{25}$ -19.45 (*c* 0.5 MeOH); HPLC t_R 5.34 min; ^{1}H NMR (500 MHz, CD_3OD) δ 7.60 (s, 1H, Ar), 6.45 (s, 1H, Ar), 6.43 (s, 2H, OC$\underline{H}_2$O), 5.95 – 5.87 (m, 2H, OC$\underline{H}_2$O), 5.08 (d, *J* = 3.8 Hz, 1H, H-1″), 4.93 (dd, *J* = 8.9, 7.1 Hz, 1H, H-9a), 4.78 (d, *J* = 9.3 Hz, 1H, H-4),

4.55 (d, *J* = 4.8 Hz, 1H, H-1), 4.18 (dd, *J* = 10.5, 8.9 Hz, 1H, H-9b), 3.82 – 3.76 (m, 1H, H-6″a), 3.72 (d, *J* = 1.6 Hz, 9H, 3×OC$\underline{H}_3$), 3.72 – 3.60 (m, 3H, H-6″b, H-3″, H-4″), 3.54 (dd, *J* = 9.9, 3.8 Hz, 1H, H-2″), 3.33 – 3.25 (m, 1H, H-5″, mixed with methanol peak), 3.06 (dd, *J* = 14.4, 4.8 Hz, 1H, H-2), 2.90 – 2.77 (m, 1H, H-3). ^{13}C NMR (126 MHz, CD_3OD) δ 177.1 (C=O), 153.8 (2C, Ar_q), 149.2 (Ar_q), 148.8 (Ar_q), 138.1 (Ar_q), 137.7 (Ar_q), 133.1 (Ar_q), 132.8 (Ar_q), 110.0 (Ar), 109.6 (2C, Ar), 109.4 (Ar), 103.2 (C-1″), 102.7 (O$\underline{C}H_2$O), 83.5 (C-4), 75.1 (C-5″), 74.6 (C-9), 73.9 (C-2″), 73.6 (C-3″), 71.9 (C-4″), 62.8 (C-6″), 61.1(O$\underline{C}H_3$), 56.7 (2C, 2×O$\underline{C}H_3$), 46.5 (C-2), 45.1 (C-1), 40.8 (C-3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{32}O_{13}Na$ 599.1735; Found 599.1727.

Preparation of 7-(*α*-D-mannopyranosyloxy)-3', 4', 5'-trimethoxy-4, 5-methylenedioxy-2, 7'-cyclolignan-9', 9-lactone (36a) [37] **and 7-(*β*-D-mannopyranosyloxy)-3', 4', 5'-trimethoxy-4, 5-methylenedioxy-2, 7'-cyclolignan-9', 9-lactone (36b)** [37]

From compound **8** [11c, d] (1.29 g，2.17 mmol, 3 eq.), activated 3 Å molecular sieves (1.1 g), *β*-(-)-pinene (**17**, 0.68 mL, 4.34 mmol, 6 eq.), and podophyllotoxin (0.3 g, 0.73 mmol, 1 eq.), according to general procedure, crude product **36a**,**b** was obtained (light yellow glass, 409 mg, 98%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) to give a mixture of **36a**,**b** and again by SFC (CO_2/MeOH = 60/40 (v/v), 20 mL/min, Chemegachiral CCA, 2 cm× 25 cm) to give pure **36a** (white foam, 296 mg, 71%) and **36b** (white foam, 109 mg, 26%). Compound **36a**：R_f 0.34 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ -42.15 (*c* 0.3 MeOH); HPLC t_R 2.57 min; ^{1}H NMR (500 MHz, CD_3OD) δ 6.98 (s, 1H, Ar), 6.47 (s, 1H, Ar), 6.41 (s, 2H, Ar), 5.96 – 5.93 (m, 2H, OC$\underline{H}_2$O), 5.09 (d, *J* = 2.0 Hz, 1H, H-1″), 4.95 (dd, *J* = 8.9, 7.1 Hz, 1H, H-9a), 4.85(m, 1H, H-4, mixed with water peak), 4.55 (d, *J* = 4.6 Hz, 1H, H-1), 4.18 (dd, *J* = 10.5, 8.9 Hz, 1H, H-9b), 4.07 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2″), 3.82 (dd, *J* = 11.9, 2.0 Hz, 1H, H-6″a),

3.77 – 3.73 (m, 1H, H-3″), 3.72 (s, 3H, OC<u>H</u>$_3$), 3.71 (s, 6H, 2×OC<u>H</u>$_3$), 3.70 – 3.58 (m, 3H, H-6″b, H-4″, H-5″), 3.05 (dd, *J* = 14.4, 4.6 Hz, 1H, H-2), 2.88 – 2.73 (m, 1H, H-3); ^{13}C NMR (101 MHz, CD_3OD) δ 177.0 (C=O), 153.8 (2C, Ar$_q$), 149.2 (Ar$_q$), 148.9 (Ar$_q$), 138.0 (Ar$_q$), 137.5 (Ar$_q$), 133.1 (Ar$_q$), 132.8 (Ar$_q$), 110.2 (Ar), 109.4 (2C, Ar), 108.3 (Ar), 104.1 (C-1″), 102.8 (O<u>C</u>H$_2$O), 82.8 (C-4), 76.1 (C-5″), 73.6 (C-9), 72.5 (C-2″), 72.3 (C-3″), 68.6 (C-4″), 63.0 (C-6″), 61.1 (O<u>C</u>H$_3$), 56.6 (2C, 2×O<u>C</u>H$_3$), 46.5 (C-2), 45.0 (C-1), 40.7 (C-3) . HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. For $C_{28}H_{32}O_{13}Na$ 599.1741, found 599.1739. Compound **36b**：R_f 0.34 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ -76.73 (*c* 0.5 MeOH); HPLC t_R 2.52 min; ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (s, 1H, Ar), 6.45 (s, 1H, Ar), 6.43 (s, 2H, Ar), 5.93 (dd, *J* = 5.3, 1.1 Hz, 2H, OC<u>H</u>$_2$O), 5.18 (d, *J* = 9.6 Hz, 1H, H-4), 4.70 – 4.61 (m, 2H, H-9a, H-1″), 4.56 (d, *J* = 4.8 Hz, 1H, H-1), 4.25 (dd, *J* = 10.5, 8.6 Hz, 1H, H-9b), 3.94 – 3.87 (m, 2H, H-2″, H-6″a), 3.76 (dd, *J* = 11.9, 6.1 Hz, 1H, H-6″b), 3.71 (d, *J* = 1.3 Hz, 9H, 3×OC<u>H</u>$_3$), 3.62 (t, *J* = 9.5 Hz, 1H, H-4″), 3.48 (dd, *J* = 9.5, 3.2 Hz, 1H, H-3″), 3.23 (ddd, *J* = 9.5, 6.1, 2.3 Hz, 1H, H-5″), 3.06 (dd, *J* = 14.4, 4.8 Hz, 1H, H-2), 2.93 – 2.77 (m, 1H, H-3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.3 (C=O), 152.4 (2C, Ar$_q$), 147.6 (Ar$_q$), 147.3 (Ar$_q$), 136.8 (Ar$_q$), 136.4 (Ar$_q$), 131.7 (Ar$_q$), 131.2 (Ar$_q$), 108.7 (Ar), 108.2 (2C, Ar), 108.0 (Ar), 101.3 (O<u>C</u>H$_2$O), 98.1 (C-1″), 77.3 (C-4), 76.9 (C-5″), 73.8 (C-3″), 71.5 (C-9), 71.4 (C-2″), 67.1 (C-4″), 61.4 (C-6″), 59.7 (O<u>C</u>H$_3$), 55.3 (2C, 2×O<u>C</u>H$_3$), 45.0 (C-2), 43.7 (C-1), 38.9 (C-3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{32}O_{13}Na$ 599.1741; Found 599.1747.

Preparation of 7-(*α*-D-galactopyranosyloxy)-3', 4', 5'-trimethoxy-4, 5-methylenedioxy-2, 7'-cyclolignan-9', 9-lactone (37) [37]

From compound **7** [11c, d] (1.29 g，2.17 mmol, 3 eq.), activated 3 Å molecular sieves (1.1 g), *β*-(-)-pinene (**17**, 0.68 mL, 4.34 mmol, 6 eq.), and podophyllotoxin (0.3 g, 0.73 mmol, 1 eq.),

according to general procedure, crude product **37** was obtained (light yellow glass, 401 mg, 96%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) and again by SFC (CO_2/MeOH = 70/30 (v/v), 20 mL/min, chiralcel OJ-H, 2 cm x 25 cm) to give pure **37** (white foam, 134 mg, 32%). R_f 0.27 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ -14.77 (*c* 0.5 MeOH); HPLC t_R 2.56 min; ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (s, 1H, Ar), 6.44 (s, 1H, Ar), 6.43 (s, 2H, Ar), 5.92 (dd, *J* = 5.8, 1.1 Hz, 2H, OC$\underline{H}_2$O), 5.12 (d, *J* = 3.9 Hz, 1H, H-1″), 4.94 (dd, *J* = 8.9, 7.1 Hz, 1H, H-9a), 4.77 (d, *J* = 9.4 Hz, 1H, H-4), 4.54 (d, *J* = 4.7 Hz, 1H, H-1), 4.17 (dd, *J* = 10.5, 8.9 Hz, 1H, H-9b), 3.95 (dd, *J* = 10.3, 3.9 Hz, 1H, H-2″), 3.91 – 3.87 (m, 2H, H-6″a, H-4″), 3.81 (dd, *J* = 10.3, 3.2 Hz, 1H, H-3″), 3.73 -3.68 (m, 11H, 3×OC$\underline{H}_3$, H-5″, H-6″b), 3.04 (dd, *J* = 14.4, 4.7 Hz, 1H, H-2), 2.90 – 2.77 (m, 1H, H-3). ^{13}C NMR (126 MHz, CD_3OD) δ 177.2 (C=O), 153.8 (2C, Ar_q), 149.1 (Ar_q), 148.8 (Ar_q), 138.0 (Ar_q), 137.8 (Ar_q), 133.3 (Ar_q), 132.7 (Ar_q), 110.0 (Ar), 109.5 (2C, Ar), 109.4 (Ar), 103.8 (C-1″), 102.6 (O$\underline{C}H_2$O), 83.5 (C-4), 73.7 (C-5″), 73.6 (C-9), 71.1 (C-4″), 71.1 (C-3″), 70.5 (C-2″), 62.8 (C-6″), 61.1 (O$\underline{C}H_3$), 56.6 (2C, 2×O$\underline{C}H_3$), 46.5 (C-2), 45.0 (C-1), 40.8 (C-3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{32}O_{13}Na$ 599.1741; Found 599.1745.

Preparation of (2*α*,4*α*,5*β*,7*β*,10*β*,13*α*)-4,10-bis(acetyloxy)-7-(*α*-D-glucopyranosyloxy)-13-{[(2*R*,3*S*)- 3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}- 1-hydroxy-9-oxo-5, 20-epoxytax-11-en-2-yl benzoate (38a) and (2*α*,4*α*,5*β*,7*β*,10*β*,13*α*)-4,10-bis(acetyloxy)-7-(*β*-D-glucopyranosyloxy)- 13-{[(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}- 1-hydroxy-9-oxo-5, 20-epoxytax-11-en-2-yl benzoate (38b)

Under N_2 atomosphere, activated 3 Å molecular sieves (1.0 g), *β*-(-)-pinene (**17**, 1.1 mL, 7.03 mmol, 6 eq.), and paclitaxel (1.0 g, 1.17 mmol, 1 eq.) were dissolved in DCM (9.0 mL). A solution of

compound **3** [11c, d] (1.89 g, 3.51 mmol, 3 eq.) in DCM (9.0 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred overnight, and then filtered. The filtrate was concentrated to a volume of ca. 5 mL, treated with HF-pyridine complex (70% HF, 1.57 mL, 15 eq.) and stirred at RT for 30 min. Upon completion by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **38** (light yellow glass, 833 mg, 70%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) to give the pure product **38a** after lyophilization (amorphous white powder, 214 mg, 18%) and pure product **38b** after lyophilization (amorphous white powder, 250 mg, 21%). Compound **38a:** R_f 0.44 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ +18.06 (*c* 0.4 MeOH); HPLC t_R 2.90 min; ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 – 8.07 (m, 2H, Ar), 7.91 – 7.84 (m, 2H, Ar), 7.59 – 7.24 (m, 11H, Ar), 6.67 (s, 1H, H-10), 6.13 – 6.05 (m, 1H, H-13), 5.78 (d, *J* = 3.0 Hz, 1H, H-3′), 5.58 (d, *J* = 5.4 Hz, 1H, H-2), 5.31 (t, *J* = 2.9 Hz, 1H, H-5), 4.67 (d, *J* = 3.1 Hz, 1H, H-2′), 4.65 (d, *J* = 3.8 Hz, 1H, H-1″), 4.61 (brs, 1H, NH), 4.17 (dd, *J* = 11.6, 4.7 Hz, 1H, H-7), 3.87 (d, *J* = 5.4 Hz, 1H, H-3), 3.76 (d, *J* = 11.5 Hz, 1H, H-20a), 3.54 (d, *J* = 11.5 Hz, 1H, H-20b), 3.37 – 3.25 (m, 2H, H-6″a, H-3″), 3.25 (dd, *J* = 9.7, 3.7 Hz, 1H, H-2″), 3.22 – 3.10 (m, 3H, H-6″b, H-4″, H-14a), 2.80 (ddd, *J* = 10.0, 3.9, 2.4 Hz, 1H, H-5″), 2.28 (dd, *J* = 15.5, 9.9 Hz, 1H, H-14b), 2.23 (d, *J* = 1.4 Hz, 3H, C=CCH_3), 2.18 (d, *J* = 1.2 Hz, 6H, 2×CH_3), 2.16 – 1.94 (m, 2H, H-6), 1.30 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.11 (s, 3H, CH_3). ^{13}C NMR (126 MHz, CD_3OD) δ 205.2 (C-9), 173.7 (C=O), 172.3 (C=O), 171.4 (C=O), 170.2 (C=O), 168.4 (C=O), 141.3 ($C=C_q$), 141.0 (Ar_q), 136.3 ($C=C_q$), 136.1 (Ar_q), 134.5 (Ar), 132.8 (Ar), 131.6 (2C, Ar), 131.1 (Ar_q), 129.7 (Ar),

129.7 (2C, Ar), 129.7 (2C, Ar), 128.9 (3C, Ar), 128.7 (3C, Ar), 101.9 (C-1″), 78.3 (C-4), 77.4 (C-2), 76.7 (C-10), 75.6 (C-1), 75.5 (C-5), 74.65 (C-2′), 74.55 (C-3″), 73.7 (C-2″), 73.5 (C-5″), 73.4 (C-13), 71.7 (C-20), 70.8 (C-4″), 69.7 (C-7), 61.6 (2C, C-8, C-6″), 57.0 (C-3′), 49.7 (C-3), 44.5 (C-15), 36.5 (C-14), 33.3 (C-6), 27.6 ($\underline{C}H_3$), 22.5 ($\underline{C}H_3$), 20.9 ($\underline{C}H_3$), 20.7 ($\underline{C}H_3$), 16.1 ($\underline{C}H_3$), 11.6 ($\underline{C}H_3$). Selected NOE (400 MHz, CD_3OD, 298 K): δ (^{1}H) / δ (^{1}H) = 4.65 / 5.31, 3.54, 2.16 - 1.94 (H-1″ / H-5, H-20b, H-6), 2.80 / 3.76 (H-5 / H-20a). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{53}H_{61}NO_{19}H_2ONa$ 1056.3841; Found 1056.3856. Compound **38b**：R_f 0.44 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ +7.56 (*c* 0.3 MeOH); HPLC t_R 3.10 min; ^{1}H NMR (500 MHz, CD_3OD) δ 8.13 – 8.08 (m, 2H, Ar), 7.88 – 7.82 (m, 2H, Ar), 7.69 – 7.26 (m, 11H, Ar), 6.35 (s, 1H, H-10), 6.17 – 6.09 (m, 1H, H-13), 5.67 (d, *J* = 7.1 Hz, 1H, H-2), 5.64 (d, *J* = 5.4 Hz, 1H, H-3′), 4.99 (dd, *J* = 9.7, 2.0 Hz, 1H, H-5), 4.88 (s, 1H, H-1″, mixed with water peak), 4.73 (d, *J* = 5.4 Hz, 1H, H-2′), 4.61 (brs, 1H, N$\underline{H}$), 4.32 (dd, *J* = 10.4, 6.7 Hz, 1H, H-7), 4.20 (s, 2H, H-20), 3.83 (d, *J* = 7.0 Hz, 1H, H-3), 3.74 – 3.64 (m, 2H, H-6″), 3.52 – 3.46 (m, 1H, H-4″), 3.35 (d, *J* = 5.1 Hz, 2H, H-3″, H-5″), 3.34 – 3.27 (m, 1H, H-2″, mixed with methanol peak), 2.77 (ddd, *J* = 14.5, 9.8, 6.6 Hz, 1H, H-6a), 2.36 (s, 3H, C$\underline{H}_3$), 2.24 (dd, *J* = 15.4, 9.4 Hz, 1H, H-14a), 2.17 (s, 3H, C$\underline{H}_3$), 2.01 -1.94 (m, 4H, C$\underline{H}_3$, H-14b), 1.88 (ddd, *J* = 14.6, 10.7, 2.3 Hz, 1H, H-6b), 1.77 (s, 3H, C$\underline{H}_3$), 1.18 (s, 3H, C$\underline{H}_3$), 1.11 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (126 MHz, CD_3OD) δ 204.5 (C-9), 174.5 (C=O), 171.9 (C=O), 171.5 (C=O), 170.4 (C=O), 167.6 (C=O), 142.1 (C=C_q), 140.0 (Ar_q), 135.6 (C=C_q), 134.6 (Ar), 134.4 (Ar_q), 132.9 (Ar), 131.4 (Ar_q), 131.2 (2C, Ar), 129.78 (2C, Ar), 129.75 (Ar), 129.6 (3C, Ar), 129.0 (Ar), 128.5 (4C, Ar), 97.9 (C-1″), 85.1 (C-5), 82.2 (C_q), 78.9 (C_q), 77.7 (C-10), 77.5 (C-20), 77.2 (C-7), 76.1 (C-2), 74.9 (C-2′), 74.8 (C-3″), 74.2 (C-4″), 73.2 (C-2″), 72.2 (C-13), 71.2 (C-5″), 61.9 (C-6″), 59.3 (C_q), 57.8 (C-3′), 48.0 (C-3), 44.6 (C_q), 36.4 (C-14), 34.0 (C-6), 26.7 ($\underline{C}H_3$), 23.3 ($\underline{C}H_3$), 22.0 ($\underline{C}H_3$), 21.0 ($\underline{C}H_3$), 14.8 ($\underline{C}H_3$), 11.6 ($\underline{C}H_3$). Selected NOE

(500 MHz, CD_3OD, 298 K): δ (^1H) / δ (^1H) = 4.88 / 4.32, 2.77, 1.88 (H-1″/H-7, H-6a, H-6b), 3.35 / 6.35 (H-3″ / H-10). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{53}H_{61}NO_{19}Na$ 1038.3735; Found 1038.3741.

Preparation of (2*α*,4*α*,5*β*,7*β*,10*β*,13*α*)-4,10-bis(acetyloxy)-7-(*α*-D-galactopyranosyloxy)-13-{[(2*R*,3*S*)- 3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}- 1-hydroxy-9-oxo-5, 20-epoxytax-11-en-2-yl benzoate (39)

Under N_2 atomosphere, activated 3 Å molecular sieves (0.6 g), *β*-(-)-pinene (**17**, 0.33 mL, 2.10 mmol, 6 eq.), and paclitaxel (0.3 g, 0.35 mmol, 1 eq.) were dissolved in DCM (3.0 mL). A solution of compound **7** [11c, d] (0.57 g, 1.05 mmol, 3 eq.) in DCM (3.0 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred overnight, and then filtered. The filtrate was concentrated to a volume of ca. 3 mL, treated with HF-pyridine complex (70% HF, 0.32 mL, 15 eq.) and stirred at RT for 30 min. Upon completion by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **39** (light yellow glass, 264 mg, 74%), which was then purified by RP-HPLC (water/MeCN gradient, 5 mL/min, Waters Sunfire C18, 1 cm x 10 cm, 5 μM) to give the pure product **39** after lyophilization (amorphous white powder, 153 mg, 43%). R_f 0.50 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ +5.33 (*c* 0.1 MeOH); HPLC t_R 3.09 min; ^1H NMR (500 MHz, CD_3OD) δ 8.13 – 8.08 (m, 2H, Ar), 7.87 – 7.83 (m, 2H, Ar), 7.69 – 7.64 (m, 1H, Ar), 7.61 – 7.36 (m, 9H, Ar), 7.31 – 7.26 (m, 1H, Ar), 6.42 (s, 1H, H-10), 6.13 (t, *J* = 8.7 Hz, 1H, H-13), 5.67 (d, *J* = 7.1 Hz, 1H, H-2), 5.63 (d, *J* = 5.4 Hz, 1H, H-3′), 5.00 (dd, *J* = 9.8, 2.0 Hz, 1H, H-5), 4.95 (d, *J* = 4.0 Hz, 1H, H-1″),

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Preparation of (5*β*,7*β*,10*β*,13*α*)-4-Acetoxy-1, 7-dihydroxy-10-(*α*-D-glucopyranosyloxy)-13-{[(2*R*,3*S*)-2-hydroxy-3-({[(2-methyl-2-propanyl)oxy]carbonyl}amino)-3-phenylpropanoyl]oxy}-9-oxo-5,20-epoxytax-11-en-2-yl benzoate (41)

Under N_2 atomosphere, activated 3 Å molecular sieves (0.6 g), *β*-(-)-pinene (**17**, 0.35 mL, 2.23 mmol, 6 eq.), and docetaxel (0.3 g, 0.37 mmol, 1 eq.) were dissolved in DCM (3.0 mL). A solution of compound **3** [11c, d] (0.60 g, 1.12 mmol, 3 eq.) in DCM (3.0 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred

overnight, and then filtered. The filtrate was concentrated to dryness, treated with MeOH (6 mL) and AcOH (0.32 mL, 5 eq.), and stirred at RT for 1 h. Upon completion by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **41** (light yellow glass, 324 mg, 90%), which was then purified by RP-HPLC (water/MeCN gradient, 10 mL/min, Epic C18, 2 cm x 25 cm) to give the pure product **41** after lyophilization (amorphous white powder, 198 mg, 55%). R_f 0.22 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ +31.43 (*c* 0.5 MeOH); HPLC t_R 3.14 min; ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (d, *J* = 7.6 Hz, 2H, Ar), 7.69 – 7.22 (m, 9H, Ar), 6.15 (t, *J* = 8.9 Hz, 1H, H-13), 5.63 (d, *J* = 7.1 Hz, 1H, H-2), 5.36 (s, 1H, H-10), 5.14 – 5.07 (m, 1H, H-3′), 5.00 (dd, *J* = 10.2, 1.8 Hz, 1H, H-5), 4.94 (d, *J* = 3.7 Hz, 1H, H-1″), 4.57 (brs, 1H, N<u>H</u>), 4.49 (d, *J* = 5.0 Hz, 1H, H-2′), 4.27 (dd, *J* = 11.3, 6.5 Hz, 1H, H-7), 4.18 (s, 2H, H-20), 3.83 (d, *J* = 7.1 Hz, 1H, H-3), 3.74 – 3.66 (m, 3H, H-6″, H-3″), 3.62 -3.56 (m, 1H, H-5″), 3.44 (dd, *J* = 9.6, 3.7 Hz, 1H, H-2″), 3.37 (t, *J* = 9.5 Hz, 1H, H-4″), 2.44 (ddd, *J* = 14.3, 9.7, 6.4 Hz, 1H, H-6a), 2.32 (s, 3H, C<u>H</u>$_3$), 2.26 – 2.15 (m, 1H, H-14a), 2.07 – 1.98 (m, 1H, H-14b), 1.94 (s, 3H, C<u>H</u>$_3$), 1.83 (ddd, *J* = 13.9, 11.2, 2.3 Hz, 1H, H-6b), 1.67 (s, 3H, C<u>H</u>$_3$), 1.40 (s, 9H, 3×C<u>H</u>$_3$), 1.19 (s, 3H, C<u>H</u>$_3$), 1.17 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (126 MHz, CD_3OD) δ 210.6 (C-9), 174.5 (C=O), 171.8 (C=O), 167.7 (C=O), 157.9 (C=O), 140.6 (C-12), 136.7 C-11), 134.6 (Ar), 131.4 (Ar$_q$), 131.2 (2C, Ar), 129.7 (2C, Ar), 129.6 (3C, Ar, Ar$_q$), 128.8 (Ar), 128.3 (2C, Ar), 100.8(C-1″), 86.1(C-5), 82.4(C$_q$), 80.7 (C$_q$), 80.5 (C-10), 79.2 (C$_q$), 77.5 (C-20), 76.3 (C-2), 75.6 (C-3″), 75.4 (C-2′), 74.6 (C-5″), 73.8 (C-2″), 72.8 (C-7), 72.5 (C-13), 71.2 (C-4″), 62.4 (C-6″), 58.8 (C$_q$), 58.6 (C-3′), 48.4 (C-3), 44.6 (C$_q$), 37.6 (C-6), 36.8 (C-14), 28.8 (3C, 3×<u>C</u>H$_3$), 27.4 (<u>C</u>H$_3$), 23.3 (<u>C</u>H$_3$), 22.6 (<u>C</u>H$_3$), 14.6 (<u>C</u>H$_3$), 10.3 (<u>C</u>H$_3$). Selected NOE (500 MHz,

CD_3OD, 298 K): δ (^{1}H) / δ (^{1}H) = 4.94 / 5.36 (H-1″ / H-10). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{49}H_{63}NO_{19}Na$ 992.3892; Found 992.3902.

Preparation of (5*β*,7*β*,10*β*,13*α*)-4-Acetoxy-1, 7-dihydroxy-10-(*α*-D-galactopyranosyloxy)-13-{[(2*R*,3*S*)-2-hydroxy-3-({[(2-methyl-2-propanyl)oxy]carbonyl}amino)-3-phenylpropanoyl]oxy}-9-oxo-5,20-epoxytax-11-en-2-yl benzoate (42)

Under N_2 atomosphere, activated 3 Å molecular sieves (0.6 g), *β*-(-)-pinene (**17**, 0.35 mL, 2.23 mmol, 6 eq.), and docetaxel (0.3 g, 0.37 mmol, 1 eq.) were dissolved in DCM (3.0 mL). A solution of compound **7** [11c, d] (0.60 g, 1.12 mmol, 3 eq.) in DCM (3.0 mL) was added into the above suspension under ice bath. The resulting mixture was stirred under ice bath for 3 h, slowly warmed to RT, stirred overnight, and then filtered. The filtrate was concentrated to dryness, treated with MeOH (6 mL) and AcOH (0.32 mL, 5 eq.), and stirred at RT for 1 h. Upon completion by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate for several times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, evaporated to dryness, and the residue was purified with flash chromatography on silica gel (MeOH / DCM) to give the crude product **42** (light yellow glass, 227 mg, 63%), which was then purified by RP-HPLC (water/MeCN gradient, 5 mL/min, Waters Sunfire C18, 1 cm x 10 cm, 5 μM) to give the pure product **42** after lyophilization (amorphous white powder, 115 mg, 32%). R_f 0.25 (CH_2Cl_2 : CH_3OH, 10 : 1); $[\alpha]_D^{25}$ +14.33 (*c* 0.1 MeOH); HPLC t_R 3.16 min; ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.09 (d, *J* = 7.7 Hz, 2H, Ar), 7.66 (t, *J* = 7.4 Hz, 1H, Ar), 7.56 (t, *J* = 7.8 Hz, 2H, Ar), 7.42 – 7.35 (m, 4H, Ar), 7.29 – 7.23 (m, 1H, Ar), 6.16 (t, *J* = 8.7 Hz, 1H, H-13), 5.62 (d, *J* = 7.2 Hz, 1H, H-2), 5.36 (s, 1H, H-10), 5.12 – 5.08 (m, 1H, H-3′), 5.00 (dd, *J* = 9.6, 2.1 Hz, 1H, H-5), 4.96 (d, *J* = 3.8 Hz, 1H, H-1″), 4.61 (brs, 1H, NH), 4.49 (d, *J* = 3.8 Hz, 1H, H-2′), 4.27 (dd, *J* = 11.2, 6.5 Hz, 1H, H-7), 4.17 (s, 2H, H-20), 3.93 (dd, *J* = 3.2, 1.3

Hz, 1H, H-4″), 3.88 – 3.80 (m, 3H, H-3, H-2″ and H-5″), 3.77 (dd, *J* = 10.0, 3.2 Hz, 1H, H-3″), 3.70 (dd, *J* = 11.2, 6.2 Hz, 1H, H-6″a), 3.64 (dd, *J* = 11.2, 6.4 Hz, 1H, H-6″b), 2.44 (ddd, *J* = 14.2, 9.7, 6.4 Hz, 1H, H-6a), 2.32 (s, 3H, C$\underline{H}_3$), 2.24 – 2.16 (m, 1H, H-14a), 2.24 – 2.16 (m, 1H, H-14b), 1.95 (s, 3H, C$\underline{H}_3$), 1.83 (ddd, *J* = 13.9, 11.1, 2.3 Hz, 1H, H-6b), 1.67 (s, 3H, C$\underline{H}_3$), 1.40 (s, 9H, C$\underline{H}_3$), 1.18 (s, 3H, C$\underline{H}_3$), 1.15 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (126 MHz, MeOD) δ 209.4 (C-9), 173.0 (C=O), 170.4 (C=O), 166.2 (C=O), 156.4 (C=O), 139.3 (C-12), 139.1 (C-11), 135.2 (Ar$_q$), 133.2 (Ar), 130.0 (Ar$_q$), 129.8 (2C, Ar), 128.3 (2C, Ar), 128.2 (2C, Ar), 127.4 (Ar), 126.9 (2C, Ar), 99.7 (C-1″), 84.6 (C-5), 80.9 (C$_q$), 79.4 (C-10), 77.7 (C$_q$), 76.1 (C-20), 74.8 (C-2), 74.0 (C-2′), 71.7 (C-5″), 71.3 (C-7), 71.0 (C-13), 70.7 (C-3″), 69.3 (C-4″), 69.1 (C-2″), 60.8 (C-6″), 57.3 (C-3′), 57.2 (C$_q$), 46.9 (C-3), 36.2 (C-6), 35.3 (C-14), 27.3 (3C, 3×C$\underline{H}_3$), 26.0 (C$\underline{H}_3$), 21.9 (C$\underline{H}_3$), 21.2 (C$\underline{H}_3$), 13.2 (C$\underline{H}_3$), 8.9 (C$\underline{H}_3$). Selected NOE (500 MHz, Methanol-d_4, 298 K): δ (^{1}H) / δ (^{1}H) = 4.96 / 5.36, 2.44 (H-1″ / H-10). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd. for $C_{49}H_{63}NO_{19}Na$ 992.3892; Found 992.3892.

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Dedication

We would like to dedicate this work to Prof. Dr. Hartmut Redlich.

Supporting information

Supporting Information: Copies of ^{1}H-NMR, ^{13}C-NMR, 2D-NMR. This material is available free of charge via the Internet at http://pubs.acs.org/.

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