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# The Catalytically Lignan-Activation-Based Approach for the Synthesis of (*epi*)-Podophyllotoxin Derivatives

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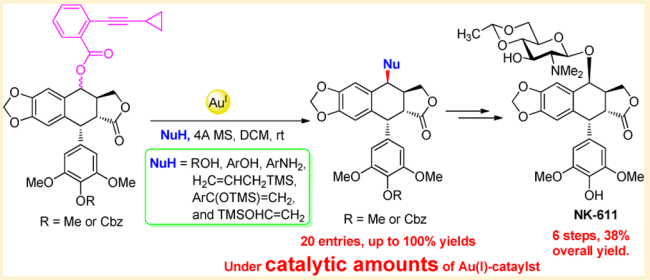
Supporting Information

**ABSTRACT:** Under the effect of a catalytic amount of Au(I) complex, 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxins, easily prepared via dehydrative condensation between (*epi*)-podophyllotoxin and *ortho*-cyclopropylethynylbenzoic acid, could efficiently couple with a variety of nucleophiles including alcohol, phenol, aniline, and carbon nucleophiles, all to provide (*epi*)-podophyllotoxin derivatives. Thus, the first catalytic and lignan-activation-based approach for (*epi*)-podophyllotoxin derivatization was established. Based on the new methodology, as well as the judicious choice of $N_3$, AZMB, and Cbz protecting groups, an efficient approach forward was set. NK-611, an antitumoral agent at a phase II clinical trial was established, featuring an in situ anomerization of the hemiacetal OHs in the critical condensation step. Commencing from easily available starting material, the target molecule was obtained using the longest linear sequence of six steps and a 38% overall yield.




## INTRODUCTION

Great efforts have been devoted to the derivatization of podophyllotoxin (**1**) and (*epi*)-podophyllotoxin (**2**). The endeavor has been rewarded by the discovery of etoposide and teniposide,[1] two widely used clinical antitumoral agents, specifically for the treatment of testicular and small-cell lung cancers, lymphoma, leukemia, and Kaposi's sarcoma.[2] Broad pharmacological applications result in the full recognition of severe undesirable side effects and unsatisfactory pharmaceutical profiles inherent to etoposide and teniposide. Among others, the development of leucopenia and drug resistance, along with overall poor water solubility, are prominent. To overcome these shortcomings and search for more ideal surrogates, further studies of (*epi*)-podophyllotoxin ((E)-PPT) derivatization are urgently needed. In addition, the demand is further intensified by the incompletely understood working mechanism of (E)-PPT derivatives.[3] Based on conventional derivatization methods, many pharmaceutically promising compounds such as NK-611,[4] etopophos,[5] TOP-53,[6] and NPF[7] have been discovered (Figure 1).

Conventional (E)-PPT derivatization methods suffer from moderate-to-low efficiencies and harsh reaction conditions.[8] Recently, the first catalytic glycosylation derivatization of (E)-PPTs was developed by us on the basis of the Yu glycosylation.[9] Nevertheless, this method can only afford anomerically linked (E)-PPT-4-*O*-glycosides.[9b] The appearances of NPF and TOP-53 call on an efficient method which can introduce a broad scope of substituents to (E)-PPTs. Derivatization based on (E)-PPT activation can indeed introduce a variety of substitutes to the (E)-PPT scaffold; however, no efficient catalytic approach has been discovered to date (Figure 2). Under such context, the first catalytically lignan-activation-based approach toward (E)-PPT derivatives was established with (E)-PPT-4-*O*-alkynylbenzoates as the key intermediates and with catalytic amounts of the Au(I) complex as promoter.

## RESULTS AND DISCUSSION

Capitalizing on the appealing low oxophilicity and the excellent functional-group-compatible properties of the gold catalyst, *ortho*-alkynyl benzoate has been widely applied in organic synthesis.[9] Inspired by these precedented works, we assume that (E)-PPT 4-*O*-*ortho*-cyclopropylethynylbenzoates can act as ideal intermediates for a highly efficient derivatization of (E)-PPTs. To reduce this idea to practice, (E)-PPT 4-*O*-*ortho*-cyclopropylethynylbenzoates **4**, **5**, and **7** were synthesized (Scheme 1). Thus, under the conventional dehydrative esterification conditions, (E)-PPT **1** and **2** were esterified with *ortho*-cyclopropylethynylbenzoic acid (ABzOH) to deliver **4** and **5** in high chemical yields (97% and 88%, respectively). 4′-Demethyl-EPPT **6**[10] was converted to compound **7** via successive esterification of the phenolic and alcoholic OHs with CbzCl and ABzOH, respectively (66%, two steps).

With intermediates **4**, **5**, and **7** prepared, the stage was now set for the pivotal condensation with the nucleophiles. The coupling between **4** and primary alcohol **8**[11] was used as a model reaction. When treated with 0.3 equiv of $Ph_3PAuNTf_2$ in the presence of activated 4A molecular sieves at room

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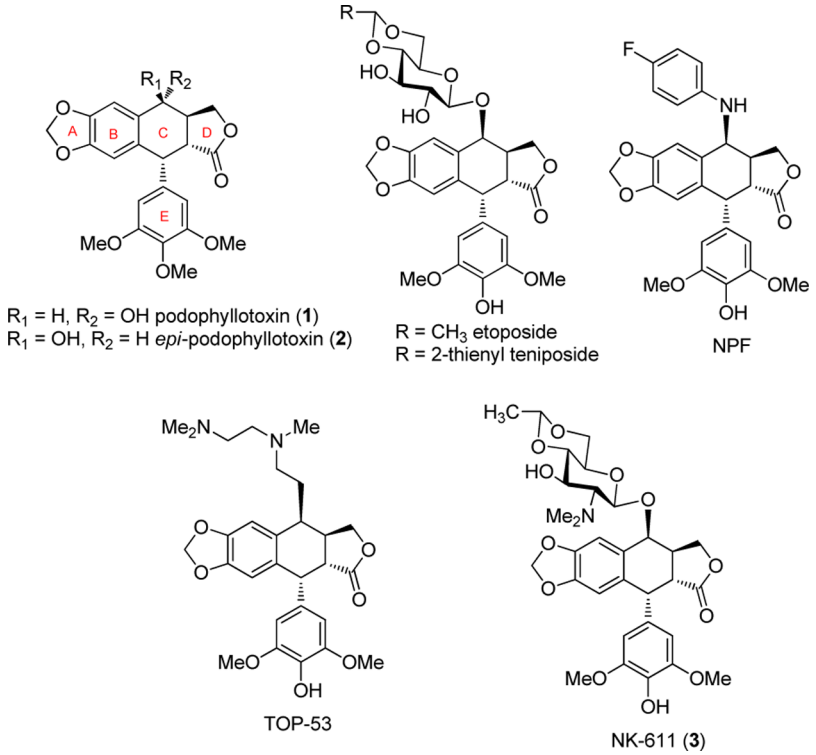


**Figure 1.** Chemical structures of (*epi*)-podophyllotoxin and its derivatives.

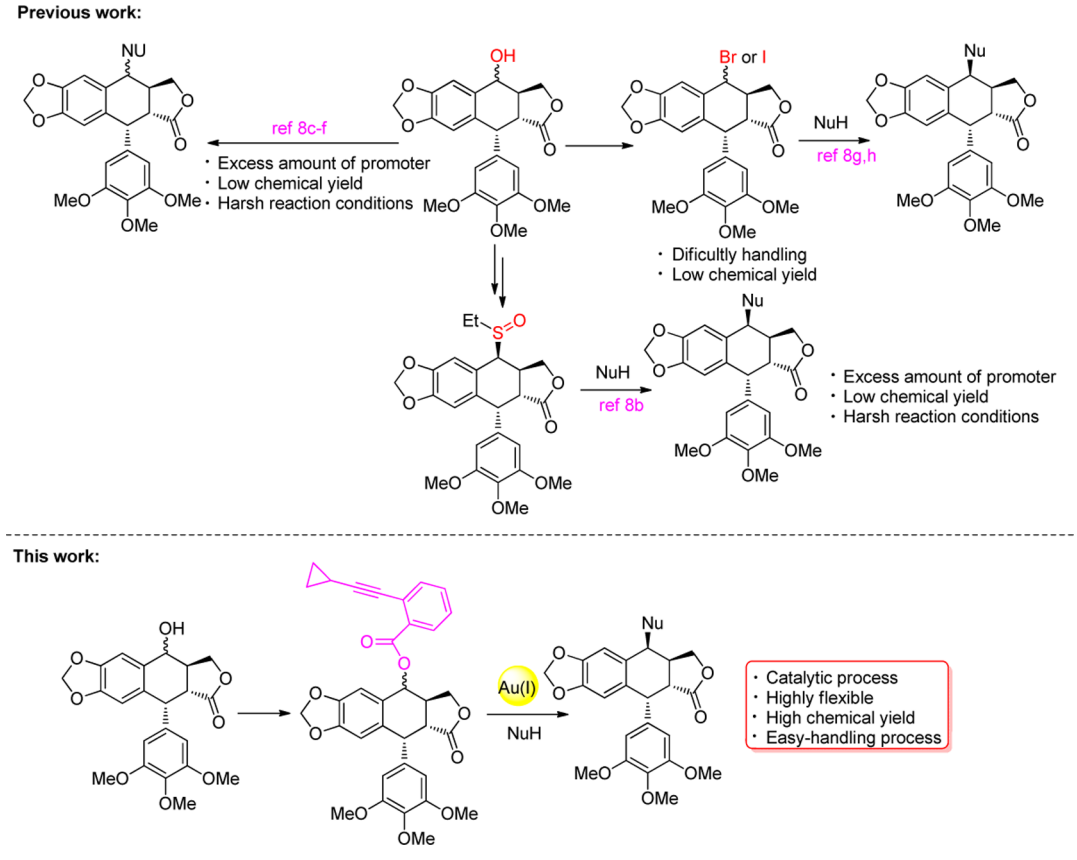


**Figure 2.** Existing (E)-PPT derivatization methods based on lignan activation.

temperature, compound **4** reacted well with **6** to furnish 6-*O*-epodophyllotoxinyl glucoside **16** in a 92% yield (Scheme 2). Encouraged by this promising result, condensation of **4** with the more-reactive alcoholic nucleophile **9**[11] was then attempted under identical conditions. Expectedly, an even better yield of coupling product **17** was obtained (95%). Subsequent study



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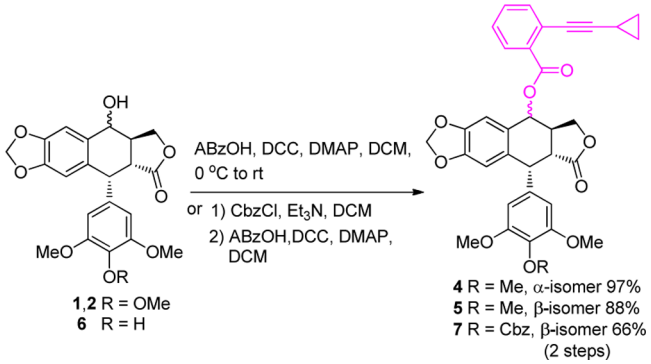
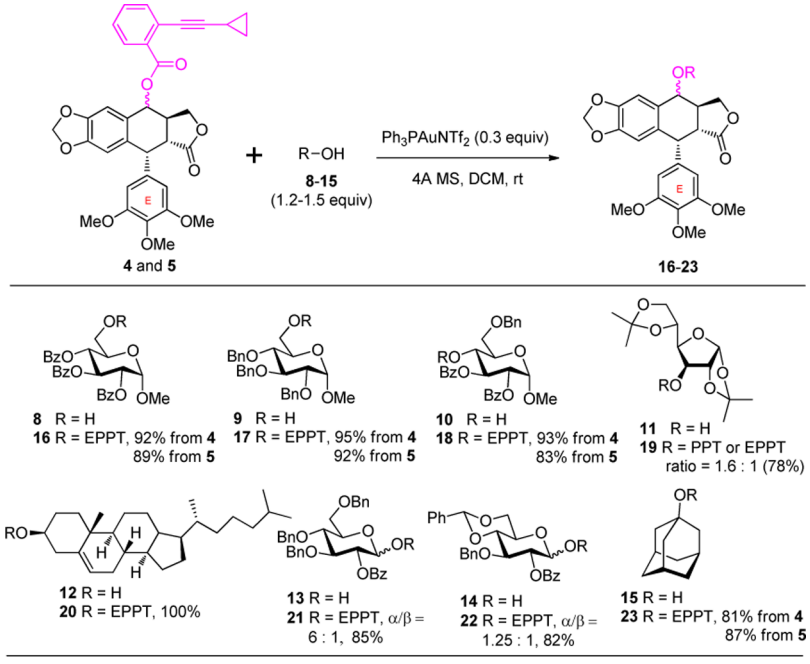
**Scheme 1. Synthesis of *ortho*-Cyclopropylethynylbenzoate 4, 5, and 7**




revealed that more bulky and inert secondary OHs **10**[12], and cholesterol **12** were also viable substrates for the Au(I)-catalyzed coupling reaction, furnishing the desired EPPT derivatives **18** and **20** efficiently (93% and 100% yield, respectively). Surprisingly, when 1,2,5,6-diisopropylidene-α-D-glucofuranoside **11**[13] was selected as a nucleophile to react with **4** under the identical conditions, despite also being a secondary hydroxyl group nucleophile, it delivered the conjugating product **19** nonstereoselectively. A separable mixture of PPT and EPPT isomers marginally favoring the PPT isomer was obtained (78% yield, PPT/ EPPT = 1.6:1). The abnormal stereoselectivity of compound **11** could presumably be attributed to its inert reactivity, which is imposed by the two bulky isopropylidenyl protecting groups. The incorporation of sugar residue through the anomeric OH to C-4 of (E)-PPTs could be realized via the previously established reverse- and direct-glycosylation strategies.[8a] However, it should be noted that the direct combination of sugar residues to the C-4 site of (E)-PPTs via sugar-hydroxyl groups other than anomeric ones through conventinal strategies, to the best of our knowledge, has never been investigated. Therefore, our protocol may find a wide application in the diversity-oriented synthesis of sugar-containing (E)-PPT derivatives. In fact, the anomerically linked EPPT glycosides could also be furnished efficiently via the new condensation method. Thus, when treated with catalytic amounts of Au(I) complex, the conjugation between the anomeric OH of **13**[14] and **4** proceeded without any incident to deliver **21**. Because **13** was used directly as mixture of anomers, the conjugation product **21** was also obtained as a mixture of a pair of diastereoisomers with the α-isomer predominating (85%, $\alpha/\beta$ = 6:1). We attempted to improve the β-selectivity of the anomeric OH nucleophiles via the convenient protecting-group effect, instead of through the laborious acquisition of pure β-hemiacetal OH. The 4,6-*O*-benzylidenyl protecting group was invoked, and hemiacetal **14**[15] equipped with the 4,6-*O*-benzylidenyl group was subsequently checked as a nucleophile. Indeed, under identical conditions, the reaction between **14** and **4** afforded **22** with an enhanced $\beta/\alpha$ ratio of 1:1.25 (82%), pointing out a new and convenient direction for the stereoselective conjugation of hemiacetal nucleophiles. Of particular interest is that even the highly sterically demanding tertiary alcohol **15** could still afford the conjugating product **23** with excellent yield when reacted with **4** under the catalysis of Au(I) complex, which further demonstrated the conjugating potential of the new derivatization protocol.

The effect of the C-4 configuration of (E)-PPT-4-*O*-*ortho*-cyclopropylethynylbenzoate on the coupling potential was subsequently evaluated (Scheme 2). Thus, the condensation of EPPT-4-*O*-ortho-cyclopropylethynylbenzoate **5** with alcoholic nucleophiles **8**, **9**, **10**, and **15**, the representatives of primary, secondary, and tertiary alcohols, were conducted. Good-to-excellent results were obtained (89%, 92%, 83%, and 87%, respectively). The yields are comparable to those obtained with **4**, verifying that the new approach enjoys a broad substrate scope in terms of the lignan partner. It also should be pointed out that when influenced by the α-oriented E phenyl ring, irrespective of the C-4 configuration of *ortho*-cyclopropylethy-

**Scheme 2. Coupling of 4 and 5 with Alcoholic Nucleophiles under the Catalysis of the Au(I) Complex**



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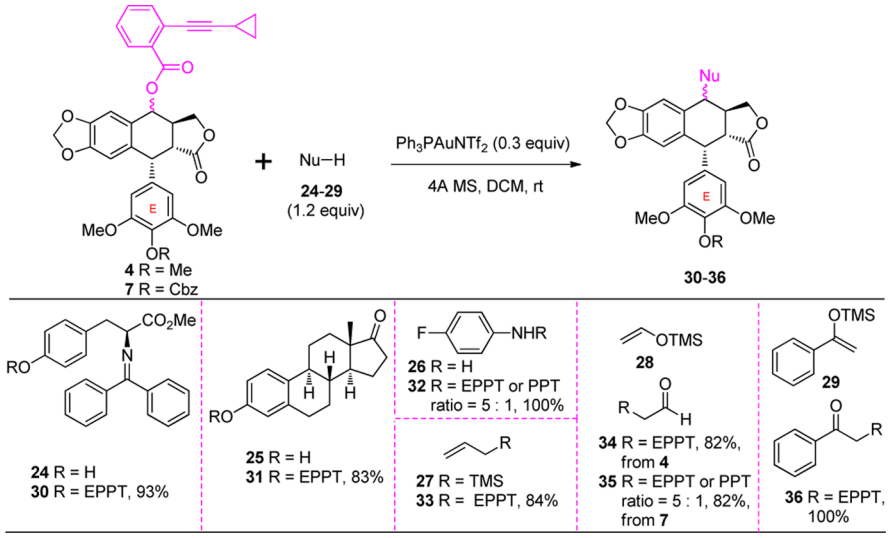
**Scheme 3. Coupling of 4 and 7 with Other Nucleopihles**




nylbenzoates, both **4** and **5** afforded the same coupling products.

As a general (E)-PPT derivatization protocol, the conjugating partners should not be restricted to alcoholic nucleophiles. Other partners including phenol, amine, as well as carbon nucleophiles should also be encompassed (Scheme 3). Tyrosine methyl ester **24**[8b] featuring a highly acid-sensitive benzophenone imine group was chosen as a representative of the highly functionalized phenolic nucleophile. Benefiting from the mild catalysis conditions, the conjugation between **24** and **4** proceeded so efficiently that 93% yield of product **30** was obtained, which is much higher than that obtained with the EPPT 4-sulfoxide as the intermediate.[8b] Under identical condensation conditions, another complex phenolic nucleophile estrone **25** could also smoothly couple with **4** to furnish **31** stereoselectively (83%). Amination of the C-4 position of (E)-PPT derivatives is an extensively investigated (E)-PPT modification reaction.[8d] The involvement of the highly reactive and difficult-handling EPPT 4-Br and I intermediates in precedented methods made the efficiency of amination modifications far from satisfactory. In sharp contrast, as an ideal conjugating intermediate, E-PPT-4-*O*-*ortho*-alkynyl benzoate **4** delivered the NPF analogue **32** in an almost quantitative yield when reacted with 4-fluoroaniline **26**.[8b] The decreased nucleophilicity imposed by the highly electron-withdrawing and *para*-located F atom directed the stereoselectivity of the condensation, and a mixture of epimers favoring the EPPT derivative was isolated (EPPT/PPT = 5:1). The C-4 modification with carbon nucleophiles has been sparsely studied before, and allylation with allyltrimethylsilane as the carbon nucleophile is the only known carbon-substituent modification reaction regarding (E)-PPTs.[8b] To check the application of the present method in the synthesis of carbon-substituent-modified (E)-PPT derivatives, allyltrimethylsilane **27** was investigated to conjugate with **4**. Again, the desired allylated EPPT **33** was isolated in a good 84% yield. Replacing **27** with the more reactive and widely accessible silyl enol ethers **28** and **29** to react with **4** led to the formation of conjugating products **34** and **36** stereoselectively (the *N* values of **27** and **28** are 1.8 and 6.2, respectively), paving the way for the easy accessibility of carbon-substituent-modified (E)-PPTs (82% and 100%, respectively).[16] Nevertheless, the stereoselectivity of the carbon-nucleophiles is highly substrate-sensitive, as exemplified by the condensation between **28** with **7**, which offered **35** as an inseparable mixture of EPPT and PPT derivatives (5:1, favoring the EPPT isomer) with a high combined yield (82%). In view of the fact that EPPT-**35** is a key intermediate for the synthesis of Top-53,[6] this protocol provides an alternative and direct synthetic approach to get this biologically significant compound (conventional detour route was adopted).[8c] The high chemical yields, as well as the good-to-excellent stereoselectivity qualifies the coupling protocol to be an ideal approach for the synthesis of carbon-substituent-modified EPPT derivatives.

The assignment of the C-4 configuration of (E)-PPT residues can be easily made by the *J* values of H-4, which are around 8.0 Hz for PPT derivatives (3,4-protons are *anti* arranged) and 4.0 Hz for EPPT analogues (3,4-protons are *syn*-disposed). The chirality of the sugar anomeric positions can be determined according to the coupling constants of the anomeric protons (for $\beta$ isomers: $J > 7.5$ Hz; for $\alpha$ isomers: $J < 4.5$ Hz). Taking advantages of the H–H COSY (for the assignment of H-4) and the NOE spectra, the C-4 chirality of all the carbon-nucleophile-modified (E)-PPT derivatives can be ascertained.[19]

To check the synthetic application of the protocol, the synthesis of NK-611 (**3**) was subsequently conducted. Compared with etoposide, NK-611 carries a dimethyl amino group at the glucose moiety. The introduction of an amino group can dramatically improve the water solubility of NK-611 and consequently, the corresponding pharmaceutical profiles and efficiency. The superior antitumor activity qualifies NK-611 to be a promising surrogate to etoposide and teniposide and promote it to enter phase-II clinical trial now. The presence of amino group brings about evident improvement in bioactivity; meanwhile, it also makes the synthesis of NK-611 more challenging. With classical reverse glycosylation as the critical step, known synthetic approaches toward NK-611 suffer from tedious or low conjugation stereocontrol, as well as unsatisfactory overall efficiency.[17] To facilitate the following clinical trials, a more efficient approach for NK-611 synthesis is highly desired. Leveraging the Au(I)-catalyzed lignan activation protocol, a new and efficient route to NK-611 was set up.



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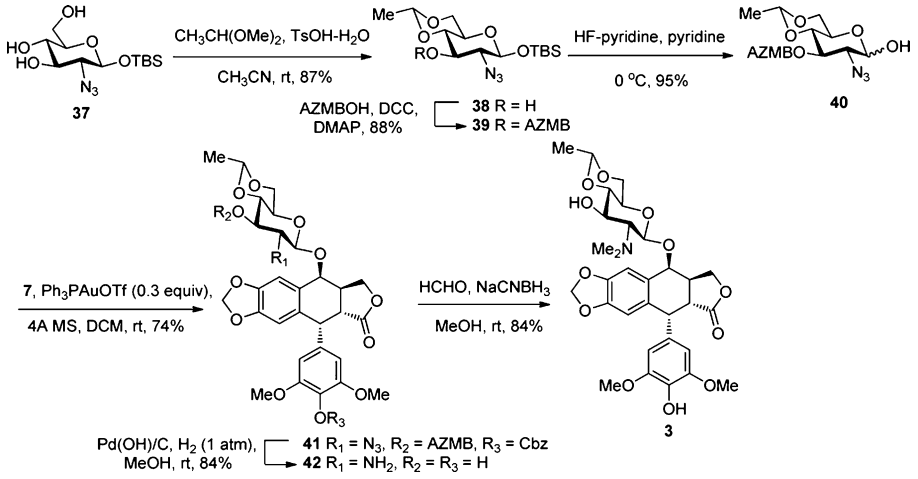
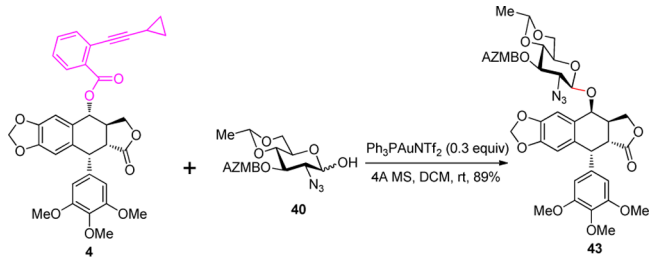
**Scheme 4. Synthesis of NK-611 (3)**




The synthesis commenced with azidoglucoside **37**,[18] prepared from glucosamine in five steps with 34% overall yield. Ethylidenation of **37** under the effect of DME and TsOH was followed by dehydrative esterification with AZMBOH to transform **37** to **39** via intermediate **38** (76%, two steps). Removal of the anomeric TBS with HF/pyridine at a low temperature afforded **40**, which is ready for the subsequent coupling with the lignan moiety (95%). Under the catalysis of $Ph_3PAuNTf_2$, the coupling between **40** and **7** proceeded inefficiently, and only a 50% yield of **41** was isolated. Nevertheless, the stereoselectivity was high and only the $\beta$ condensation product was obtained. Replacing $Ph_3PAuNTf_2$ with the more reactive $Ph_3PAuOTf$ led to a dramatic enhancement in chemical yield (74%); meanwhile, the excellent $\beta$-selectivity was maintained. It also should be pointed out that the originally devised Au(I)-catalyzed glycosylation[9b] could not be applied in this key condensation reaction because glucosyl donors carrying $N_3$ substitute at their 2-position are prone to afford the undesired $\alpha$-glycosylation isomers.[12b] With ample amounts of **41** in hand, $Pd(OH)_2$-catalyzed hydrogenation was then adopted to reduce the azido group and remove the AZMB and the Cbz protecting groups simultaneously, delivering **42** in 85% yield. Finally, reductive amination with 37% formaldehyde solution and $NaBH_3CN$ was applied to incorporate the two methyl groups to $NH_2$ of **42** to complete the synthesis of NK-611 (**3**). Fortunately, the spectra of the synthetic sample were proved to be identical to those reported in literature,[17,19] verifying the correctness of the synthetic **3** (Scheme 4). With **37** as starting material, and the judicious choice of AZMB and Cbz as the protecting groups, which can be removed in the same pot in which the reduction of $N_3$ occurs, the synthetic sequence can be telescoped to six steps. Also, benefiting from the high yield and stereoselectivity of the pivotal conjugating step, the overall yield could reach as high as 38%. The high condensation stereoselectivity, as well as the good overall efficiency, further demonstrated the potential of the new protocol in complex (E)-PPT derivatives synthesis.

It is worth mentioning that to secure the desired $\beta$-selectivity of the condensation between **40** and **7**, neither special cautions nor additional manipulations are required. Moreover, the **40** involved Au(I)-catalyzed condensations could tolerate the structure variation of the lignan moiety well, as exemplified by the conjugation with PPT *ortho*-cyclopropylethynylbenzoate **4** to afford **43** (89%, Scheme 5).

**Scheme 5. Condensation of 43 with 4**




All of the applied nucleophiles can be roughly divided into three categories: the hydroxyl nucleophiles (except for **11**), carbon-type nucleophiles, and special nucleophiles. For the hydroxyl type of nucleophiles, the stereoselectivity of the condensation with 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxins is presumably steered by the $S_N1$ reaction mechanism. Thus, coordination of the gold(I) catalyst to the triple bond of *ortho*-cyclopropylethynylbenzoate elicits the collapse of **4** to generate *p*-oxygen-stabilized benzylic cation species **B** and isochromen-4-yl gold(I) complex **A**. Stereoselectively, constrained by the *trans*-fused D-lactone ring, the species **B** adopts the $^2H_1$ conformation; the bulky E-ring axially occupies the $\alpha$-face of the C-ring. The $^2H_1$ conformer of **B** favors the attack of nucleophiles from the $\beta$-face both stereoelectronically and sterically (route **a** vs route **b**), therefore delivering the EPPT derivatives predominantly, regardless of the chirality of the starting 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxin (Figure 3). For carbon-type nucleophiles such as **27**–**29**,[16] the stereoselectivity of their condensation with 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxins is probably jointly controlled by both $S_N1$ and $S_N2$ reaction mechanisms. In these cases, the chirality of 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxins has a profound effect on the chiral outcome of the condensations: with 4-*O*-(2-cyclopropylethynyl)benzoyl-podophyllotoxin as the starting material, both $S_N1$ and $S_N2$ substitution processes give the same EPPT products, and accordingly, satisfactory stereoselectivity is obtained (for **33**, **34**, and **36**). On the contrary, for 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxin **7**, substitutions via $S_N1$ and $S_N2$ mechanisms lead to EPPT and PPT derivatives, respectively, thus the stereocontrol of conjugation is compromised (**35**). Regarding special nucleophiles **11** and **26**, a competitive trapping of **B** by **A** is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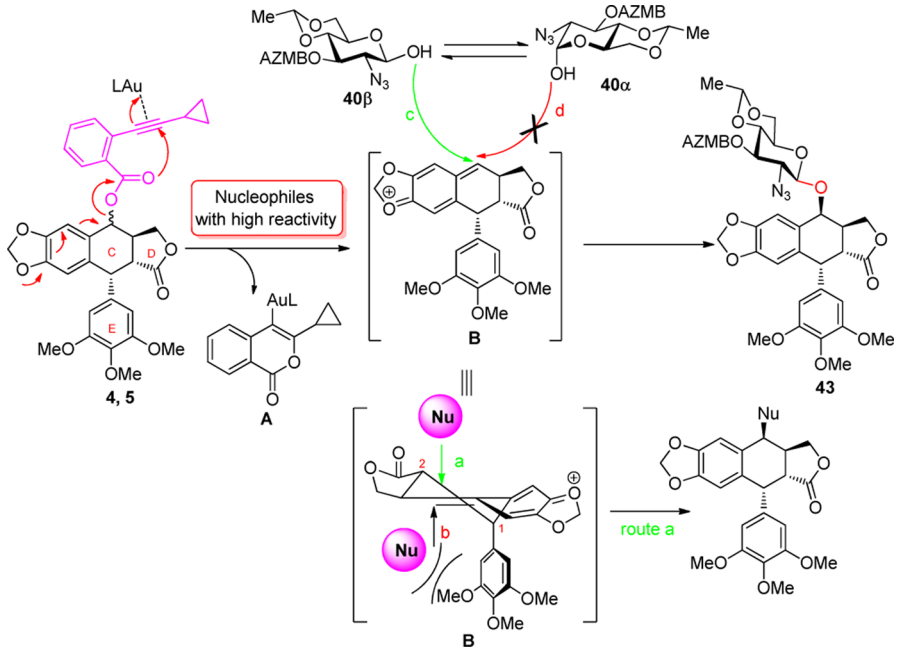


**Figure 3.** Plausible mechanism for the (E)-PPT *ortho*-cyclopropylethynylbenzoate involved stereoselective condensation.

tentatively proposed (Figure 3), which will bring about the in situ formation of 4-*O*-(2-cyclopropylethynyl)benzoyl-(*epi*)-podophyllotoxin because of either the extreme steric hindrance or the weak basicity. Similar to the cases for the carbon-type nucleophiles, the appearance of 4-*O*-(2-cyclopropylethynyl)-benzoyl-(*epi*)-podophyllotoxin will lead to the decrease in conjugation stereoselectivity (**19** and **32**).

Hemiacetals **13**, **14**, and **40** are more challenging substrates, as the stereoselectivities regarding the lignan (PPT/EPPT) and the sugar residues ($\alpha/\beta$) should be simultaneously controlled to guarantee the coupling efficiency. Although the condensation via intermediate **B** could control the PPT/EPPT selectivity, hemiacetals **13** and **14** are used as mixtures of a pair of epimers, affording the coupling products **21** and **22** nonstereoselectively ($\alpha/\beta$ mixtures of glucosides were obtained). In sharp contrast, **40** delivered the condensation product **41** and **43** stereoselectively ($\beta$-glucosides were obtained) because of the considerable nucleophilic difference between **40*α*** and **40*β***. The high reactivity of **40*β*** resulted from the repulsion of lone-pair electrons, exerted by the pyran-ring oxygen atom[20], renders the attack of **40*β*** to **B** to proceed smoothly to give the desirable product **43** (route **c**). On the contrary, influenced by the combined deactivating effects of $N_3$ ($FN_3$ = 0.48)[21] and ethylidenyl groups, the similar attack of **40*α*** to **B** is prohibited (route **d**). As a result, only the $\beta$-condensation product is formed. In fact, during the condensation, an anomerization of **40*α*** to **40*β*** takes place. This ensures the high stereoselectivity regarding the sugar subunit, and the pursuit of pure **40*β*** as a nucleophile, generally a quite difficult and laborious process, to guarantee that the reasonable conjugating stereoselectivity is not necessary.

## CONCLUSIONS

To summarize, under the promotion of catalytic amounts of gold(I) complex, (E)-PPT 4-*O*-*ortho*-cyclopropylethynylbenzoates could react efficiently with a variety of nucleophiles including alcohols, phenols, aniline, and carbon nucleophiles to furnish (E)-PPT derivatives with good-to-excellent yields and stereoselectivity. The new protocol represents the first catalytically lignan-activation-based (E)-PPT modification method, and it will dramatically facilitate the accessibility of (E)-PPT analogues, especially the carbon-substituent modified (E)-PPT derivatives. Leveraging this (E)-PPT modification protocol, the synthetic investigation toward NK-611 was also conducted, through which the most concise and efficient route featuring a kinetic anomerization of the hemiacetal OHs in the key condensation step was established.

## EXPERIMENTAL SECTION

**Podophyllotoxin 4-*O*-*ortho*-Cyclopropylethynylbenzoate (4).** To a solution of podophyllotoxin **1** (3.5 g, 8.5 mmol) and *ortho*-alnynylbenzoic acid (2.4 g, 12.8 mmol) in dry $CH_2Cl_2$ (10 mL) was successively added DMAP (1.6 g, 12.8 mmol) and DCC (3.5 g, 17.0 mmol) at 0 °C. The resultant reaction mixture was warmed to room temperature, and the stirring was continued for another 2 h, at which time TLC showed that all starting material disappeared. $CH_2Cl_2$ was added to dilute the reaction mixture and the resulting solution was washed with water and saturated brine, successively. Evaporation and concentration under reduced pressure gave a residue which was further purified by silica gel chromatography (petroleum ether/ethyl acetate (PE/EA) = 3:1) to afford **4** (4.8 g, 97%) as a white solid: $[\alpha]_D^{25}$ = −169.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.51−7.43 (m, 2 H), 7.35 (dt, *J* = 1.6, 7.6 Hz, 1 H), 6.95 (s, 1 H), 6.57 (s, 1 H), 6.46 (s, 2 H), 6.20 (d, *J* = 8.0 Hz, 1 H), 5.98 (dd, *J* = 1.6, 3.6 Hz, 2 H), 4.65 (d, *J* = 4.0 Hz, 1 H), 4.54 (dd, *J* = 6.0, 8.8 Hz, 1 H), 4.36 (t, *J* = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 6 H), 3.12−3.06 (m, 1 H), 3.03 (dd, *J* = 4.0, 14.4 Hz, 1 H), 1.29−1.24 (m, 1 H), 0.85−0.79 (m, 2 H), 0.78−0.72 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.3, 166.6, 152.2, 147.7, 147.2, 136.6, 134.4, 134.0, 132.0, 131.5, 130.8, 129.4, 128.0, 126.8, 124.1, 109.3, 107.5, 107.1, 101.2, 99.2, 73.9, 73.7, 71.1, 60.3, 55.7, 45.2, 43.4, 38.3, 8.34; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{31}O_9$ 583.1963, found 583.1968.

**(*epi*)-Podophyllotoxin 4-*O*-*ortho*-Cyclopropylethynylbenzoate (5).** A similar procedure as that used for the synthesis of **4** was applied to get **5** from **2** (495 mg, 88%) as a white solid: $[\alpha]_D^{25}$ = −50.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.49 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.45 (td, *J* = 1.6, 7.2 Hz, 1 H), 7.33 (td, *J* = 1.6, 8.0 Hz, 1 H), 7.00 (s, 1 H), 6.58 (s, 1 H), 6.46 (d, *J* = 3.6 Hz, 1 H), 6.32 (s, 2 H), 6.00 (d, *J* = 1.2 Hz, 1 H), 5.96



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(d, $J$ = 1.6 Hz, 1 H), 4.72 (d, $J$ = 5.2 Hz, 1 H), 4.45 (dd, $J$ = 8.0, 8.8 Hz, 1 H), 4.17 (dd, $J$ = 8.8, 10.8 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 6 H), 3.53 (dd, $J$ = 4.8, 14.0 Hz, 1 H), 3.14−3.07 (m, 1 H), 1.40−1.36 (m, 1 H), 0.92−0.89 (m, 2 H), 0.81−0.73 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.0, 165.9, 152.3, 148.5, 147.1, 137.0, 134.3 (2 C), 132.6, 131.7, 130.4, 130.2, 127.5, 126.9, 124.1, 109.7, 109.5, 107.8, 101.2, 99.3, 76.8, 74.3, 68.6, 67.4, 60.4, 55.9, 43.6, 41.5, 36.6, 8.54, 8.50; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{34}H_{31}O_9$ 583.1963, found 583.1968.

**4′-Demethyl-4′-*O*-(benzyloxycarbonyl) (*epi*)-podophyllotoxin 4-*O*-*ortho*-Cyclopropylethynyl Benzoate (7).** To a solution of **6** (500 mg, 1.25 mmol) in dry $CH_2Cl_2$ (6 mL) was added dry $Et_3N$ (0.3 mL, 2.2 mmol) and CbzCl (0.27 mL, 1.9 mmol) at 0 °C. The reaction mixture was warmed to room temperature, and the stirring was continued for another 4 h. Diluted with ethyl acetate, the resultant mixture was washed with water and brine successively. Evaporation under reduced pressure furnished the crude product which was further purified by silica gel chromatography (PE/EA = 2:1) to give the 4′-*O*-Cbz-(*epi*)-podophyllotoxin intermediate.

Subsequently, to a solution of 4′-*O*-Cbz-(*epi*)-podophyllotoxin intermediate (667 mg, 1.25 mmol) and *ortho*-cyclopropylethynylbenzoic acid (516 mg, 1.87 mmol) in dry $CH_2Cl_2$ (4 mL) was added DMAP (229 mg, 1.87 mmol) and DCC (516 mg, 2.5 mmol), successively at 0 °C. After the addition was completed, the reaction mixture was warmed to room temperature, and the stirring was continued for another 3 h. Diluted with ethyl acetate, the resultant mixture was then washed with water and brine successively. Dried with $Na_2SO_4$, the volatile solvent was removed under reduced pressure to give the crude product which was then chromatographed (PE/EA = 4:1) to produce **7** (577.6 mg, 66% for two steps) as a white solid: $[\alpha]_D^{25}$ = −66.9 ($c$ 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (dd, $J$ = 2.4, 7.6 Hz, 1 H), 7.49−7.30 (m, 8 H), 7.01 (s, 1 H), 6.57 (s, 1 H), 6.46 (d, $J$ = 3.6 Hz, 1 H), 6.34 (d, 2 H), 6.01 (d, $J$ = 1.2 Hz, 1 H), 5.97 (d, $J$ = 1.6 Hz, 1 H), 5.27 (s, 2 H), 4.74 (d, $J$ = 5.2 Hz, 1 H), 4.45 (dd, $J$ = 7.6, 8.8 Hz, 1 H), 4.18 (dd, $J$ = 8.8, 10.8 Hz, 1 H), 3.70 (s, 6 H), 3.55 (dd, $J$ = 5.2, 10.4 Hz, 1 H), 3.10−3.01 (m, 1 H), 1.41−1.34 (m, 1 H), 0.92−0.90 (m, 2 H), 0.80−0.76 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.9, 165.9, 152.7, 151.3, 148.6, 147.2, 137.3, 134.7, 134.3, 132.2, 131.7, 130.4, 130.2, 128.1 (3 C), 127.8, 127.6, 126.9, 124.1, 109.8, 109.6, 107.3, 101.3, 99.3, 74.3, 70.0, 68.6, 67.4, 55.9, 43.7, 41.5, 36.6, 8.6, 8.5, −0.0; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{41}H_{35}O_{11}$ 703.2174, found 703.2183.

**Methyl 2,3,4-Tri-*O*-benzoyl-6-*O*-(*epi*)-podophyllotoxyl-α-D-glucopyranoside ( 16).** To a solution of **4** (30 mg, 0.05 mmol) and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **8** (30 mg, 0.06 mmol) in dry $CH_2Cl_2$ (2 mL) was added 4 Å MS under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min, and then $Ph_3PAuNTf_2$ (11 mg, 0.015 mmol) was added. The stirring was continued at room temperature for 4 h (until **4** was consumed, as monitored by TLC). The mixture was filtered, and then the filtrate was concentrated under reduced pressure to yield a residue. This was further purified by silica gel column chromatography (PE/EA = 3:1) to provide **16** (41 mg, 92%) as a white solid: $[\alpha]_D^{25}$ = +7.0 ($c$ 1.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (dd, $J$ = 1.2, 8.0 Hz, 2 H), 7.87 (dd, $J$ = 1.2, 8.0 Hz, 2 H), 7.78 (dd, $J$ = 1.2, 8.0 Hz, 2 H), 7.47−7.39 (m, 2 H), 7.34−7.26 (m, 5 H), 7.21−7.17 (m, 2 H), 6.68 (s, 1 H), 6.42 (s, 1 H), 6.15 (s, 2 H), 6.09 (t, $J$ = 10.0 Hz, 1 H), 5.87 (d, $J$ = 1.6 Hz, 1 H), 5.81 (d, $J$ = 1.6 Hz, 1 H), 5.51 (t, $J$ = 9.6 Hz, 1 H), 5.20 (dd, $J$ = 3.6, 10.0 Hz, 1 H), 5.14 (d, $J$ = 3.6 Hz, 1 H), 4.50 (dd, $J$ = 8.8, 10.8 Hz, 1 H), 4.47 (d, $J$ = 1.6 Hz, 1 H), 4.36 (d, $J$ = 3.2 Hz, 1 H), 4.34 (t, $J$ = 8.0 Hz, 1 H), 4.12−4.08 (m, 1 H), 3.82 (dd, $J$ = 2.4, 10.4 Hz, 1 H), 3.70 (s, 3 H), 3.64 (s, 6 H), 3.62 (dd, $J$ = 4.8, 10.4 Hz, 1 H), 3.38 (dd, $J$ = 5.2, 14.0 Hz, 1 H), 3.35 (s, 3 H), 2.85−2.76 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.9, 164.7 (2 C), 164.3, 151.4, 147.4, 145.5, 136.1, 134.4, 132.5, 132.3, 132.0, 131.5, 128.8, 128.7, 128.6, 128.1, 127.9, 127.8, 127.4 (2 C), 127.3, 127.2, 110.0, 108.4, 107.2, 100.4, 96.0, 74.4, 70.9, 69.3, 68.6, 68.0, 66.5, 59.6, 55.2, 54.6, 43.0, 39.9, 37.3; HRMS (ESI-TOF) $m/z$: $[M-H]^+$ calcd for $C_{50}H_{47}O_{16}$ 903.2870, found 903.2863.

The condensation of **5** and **8** under identical conditions also afforded **16** (39 mg, 89%).

**Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(*epi*)-podophyllotoxyl-α-D-glucopyranoside ( 17).** A similar procedure as that used for the synthesis of **16** was subjected to **4** and **9** to deliver **17** (41 mg, 95%) as a light yellow solid: $[\alpha]_D^{25}$ = −19.8 ($c$ 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.23 (m, 15 H), 6.81 (s, 1 H), 6.52 (s, 1 H), 6.22 (s, 2 H), 6.00 (d, $J$ = 1.6 Hz, 1 H), 5.95 (d, $J$ = 1.6 Hz, 1 H), 5.01 (d, $J$ = 10.8 Hz, 1 H), 4.90 (d, $J$ = 11.2 Hz, 1 H), 4.83 (d, $J$ = 12.0 Hz, 1 H), 4.82 (d, $J$ = 10.4 Hz, 1 H), 4.68 (d, $J$ = 12.4 Hz, 1 H), 4.57 (d, $J$ = 4.4 Hz, 1 H), 4.56 (d, $J$ = 1.2 Hz, 1 H), 4.55 (d, $J$ = 11.2 Hz, 1 H), 4.35 (d, $J$ = 3.2 Hz, 1 H), 4.32−4.24 (m, 2 H), 4.01 (t, $J$ = 9.2 Hz, 1 H), 3.79 (s, 3 H), 3.75 (m, 1 H), 3.73 (s, 6 H), 3.71 (m, 1 H), 3.61−3.51 (m, 1 H), 3.43−3.31 (m, 2 H), 3.34 (s, 3 H), 2.85−2.76 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 152.5, 148.4, 146.7, 138.6, 138.2, 138.1, 137.2, 135.4, 132.5, 129.0, 128.5 (2 C), 128.4, 128.2, 128.1 (2 C), 128.0 (3 C), 127.9, 127.7, 127.6, 110.7, 109.8, 108.3, 101.5, 98.0, 82.0, 80.2, 77.8, 75.8, 75.4, 74.9, 73.5, 70.6, 69.5, 67.5, 60.8, 56.3, 55.3, 43.9, 41.0, 38.5; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{50}H_{52}O_{13}Na$ 883.3300, found 883.3319.

The condensation between **5** and **9** under identical conditions afforded **17** (40 mg, 92%).

**Methyl 2,3-Di-*O*-benzoyl-4-*O*-(*epi*)-podophyllotoxyl-6-*O*-benzyl-α-D-glucopyranoside (18).** Similar procedure as that applied for the synthesis of **16** was adopted for the conjugation between **4** and **10** to afford **18** (41.2 mg, 93%) as a white solid: $[\alpha]_D^{25}$ = −25.3 ($c$ 1.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (m, 2 H), 7.60 (dd, $J$ = 1.2, 8.0 Hz, 2 H), 7.48−7.40 (m, 4 H), 7.37−7.24 (m, 7 H), 6.81 (s, 1 H), 6.03 (s, 2 H), 5.86 (d, $J$ = 1.2, 1 H), 5.82 (d, $J$ = 1.6 Hz, 1 H), 5.69 (dd, $J$ = 9.2, 10.0 Hz, 1 H), 5.60 (s, 1 H), 5.25 (dd, $J$ = 3.6, 10.0 Hz, 1 H), 5.15 (d, $J$ = 4.0 Hz, 1 H), 5.02 (d, $J$ = 12.0 Hz, 1 H), 4.55 (d, $J$ = 12.0 Hz, 1 H), 4.34 (t, $J$ = 9.6 Hz, 1 H), 4.18−4.10 (m, 3 H), 3.90−3.87 (m, 1 H), 3.80−3.73 (m, 2 H), 3.77 (s, 3 H), 3.72 (s, 6 H), 3.68 (dd, $J$ = 2.4, 11.2 Hz, 1 H), 3.44 (dd, $J$ = 5.6, 14.0 Hz, 1 H), 3.41 (s, 3 H), 2.41−2.32 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 165.9, 165.2, 152.3, 147.9, 146.1, 137.1, 136.8, 135.9, 133.3, 132.8, 132.3, 129.8, 129.2 (2 C), 129.1, 129.0, 128.6, 128.5, 128.4, 127.9, 111.0, 109.5, 108.4, 101.2, 97.2, 74.2, 71.8, 71.4, 71.3, 71.1, 70.3, 67.2, 66.8, 60.7, 56.3, 55.5, 43.7, 39.6, 38.1; HRMS (ESI-TOF) $m/z$: $[M+NH_4]^+$ calcd for $C_{50}H_{52}O_{15}N$ 906.3332, found 906.3337.

Compound **5** could also reacted with **10** efficiently to afford **18** (36.8 mg, 83%) under identical reaction conditions.

**1,2,5,6-Diisopropylidene-3-*O*-potophyllotoxyl-α-D-glucofuranoside (PPT-19) and 1,2,5,6-Diisopropylidene-3-*O*-(*epi*)-potophyllotoxyl-α-D-glucofuranoside (EPPT-19).** The condensation of **4** and **11** under identical conditions as those applied for the synthesis of **16** to afforded **PPT-19** (31.3 mg, 48%) and **EPPT-19** (19.7 mg, 30%). For the less polar **PPT-19**: $[\alpha]_D^{25}$ = −80.3 ($c$ 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.87 (s, 1 H), 6.54 (s, 1 H), 6.25 (s, 2 H), 6.00 (d, $J$ = 1.6 Hz, 1 H), 5.99 (d, $J$ = 3.6 Hz, 1 H), 5.98 (d, $J$ = 3.6 Hz, 1 H), 4.60 (d, $J$ = 4.8 Hz, 1 H), 4.59 (d, $J$ = 3.6 Hz, 1 H), 4.54 (d, $J$ = 3.2 Hz, 1 H), 4.44 (dd, $J$ = 8.4, 10.8 Hz, 1 H), 4.36 (t, $J$ = 8.0 Hz, 1 H), 4.27−4.22 (m, 2 H), 3.85 (dd, $J$ = 2.0, 10.0 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 6 H), 3.72−3.61 (m, 2 H), 3.45 (dd, $J$ = 5.2, 14.0 Hz, 1 H), 2.91−2.82 (m, 1 H); 1.49 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 152.5, 148.5, 146.7, 137.2, 135.5, 132.4, 129.0, 112.3, 110.8, 109.7, 108.3, 106.4, 101.5, 101.1, 84.0, 79.5, 75.0 (2 C), 71.9, 70.7, 67.5, 60.7, 56.3, 43.9, 40.9, 38.4, 27.2, 26.5, 24.0; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{34}H_{41}O_{13}$ 657.2542, found 657.2537. For the more polar **EPPT-19**: $[\alpha]_D^{25}$ = −58.2 ($c$ 0.9, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.98 (s, 1 H), 6.55 (s, 1 H), 6.22 (s, 2 H), 6.00 (d, $J$ = 3.6 Hz, 1 H), 5.98 (d, $J$ = 1.2 Hz, 1 H), 5.90 (d, $J$ = 4.0 Hz, 1 H), 4.73 (d, $J$ = 2.8 Hz, 1 H), 4.61 (d, $J$ = 5.6 Hz, 1 H), 4.57 (d, $J$ = 3.6 Hz, 1 H), 4.39 (t, $J$ = 8.0 Hz, 1 H), 4.31 (dd, $J$ = 8.4, 10.8 Hz, 1 H), 4.21 (d, $J$ = 2.8 Hz, 1 H), 4.13−4.06 (m, 2 H), 4.03 (dd, $J$ = 5.6, 8.4 Hz, 1 H), 3.95 (dd, $J$ = 4.4, 5.2 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 6 H), 3.52 (dd, $J$ = 5.6, 14.0 Hz, 1 H), 3.00−2.91 (m, 1 H), 1.52 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.26 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.7, 152.6, 148.6, 146.7,



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137.3, 135.4, 133.0, 128.0, 112.2, 111.0, 110.0, 109.0, 108.3, 105.3, 101.5, 82.8, 81.3, 80.0, 73.3, 72.3, 67.4, 67.2, 60.7, 56.3, 44.0, 40.6, 38.4, 26.8, 26.6, 26.3, 25.1, 24.7; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{34}H_{41}O_{13}$ 657.2542, found 657.2532.

**3-*O*-(*epi*)-podophyllotoxyl-cholesterol (20).** A similar procedure as that used for the synthesis of **16** was adopted to conduct the condensation between **4** and **12** to furnish **20** (54.6 mg, 100%) as a white solid: $[\alpha]_D^{25}$ = −56.8 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.84 (s, 1 H), 6.51 (s, 1 H), 6.27 (s, 2 H), 6.00 (d, *J* = 1.2 Hz, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 5.39 (d, *J* = 5.2 Hz, 1 H), 4.65 (d, *J* = 3.2 Hz, 1 H), 4.60 (d, *J* = 5.2 Hz, 1 H), 4.40 (t, *J* = 8.0 Hz, 1 H), 4.26 (dd, *J* = 8.4, 11.2 Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 6 H), 3.39 (dd, *J* = 5.2, 14.0 Hz, 1 H), 3.28−3.22 (m, 1 H), 2.88−2.80 (m, 1 H), 2.38−2.26 (m, 2 H), 2.07−1.79 (m, 5 H), 1.68−1.42 (m, 8 H), 1.37−1.22 (m, 5 H), 1.01 (s, 3 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 1.6 Hz, 3 H), 0.86 (d, *J* = 2.0 Hz, 3 H), 0.68 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 152.6, 148.2, 147.1, 140.3, 137.2, 135.3, 132.2, 130.5, 122.2, 110.4, 109.3, 108.3, 101.4, 79.2, 71.3, 67.8, 60.7, 56.8, 56.3, 56.2, 50.2, 43.9, 42.4, 41.2, 39.8, 39.5, 39.4, 38.5, 37.2, 36.9, 36.2, 35.8, 31.9 (2 C), 29.7, 29.4, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{49}H_{67}O_8$ 783.4830, found 783.4824.

**(*epi*)-Podophyllotoxin 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-α/β-D-glucopyranoside (21).** A similar procedure as that used for the synthesis of **16** was applied for the coupling between **4** and **13** to produce **21** as a mixture of α/β isomers (81 mg, 85%) as a white solid. An aliquot of pure α-isomer was obtained by silica gel chromatography for detailed characterization: $[\alpha]_D^{25}$ = +54.2 (*c* 0.63, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.62−7.57 (m, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.42−7.31 (m, 5 H), 7.27−7.25 (m, 3 H), 7.20−7.07 (m, 7 H), 6.49 (s, 1 H), 6.21 (s, 2 H), 5.96 (d, *J* = 1.6 Hz, 1 H), 5.92 (d, *J* = 1.2 Hz, 1 H), 5.34 (d, *J* = 4.0 Hz, 1 H), 5.28 (dd, *J* = 3.6, 10.0 Hz, 1 H), 4.80−4.70 (m, 5 H), 4.63 (d, *J* = 5.2 Hz, 1 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 10.4 Hz, 1 H), 4.23 (dd, *J* = 4.4, 10.8 Hz, 1 H), 4.08 (t, *J* = 9.6 Hz, 1 H), 4.01 (t, *J* = *J* = 8.0 Hz, 1 H), 3.84 (t, *J* = 9.2 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 6 H), 3.68−3.60 (m, 3 H), 3.45 (dd, *J* = 5.6, 14.0 Hz, 1 H), 2.86−2.77 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.6, 165.7, 152.6, 148.5, 147.0, 137.9 (2 C), 137.6, 137.3, 135.1, 133.8, 132.5, 129.6, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8 (2 C), 127.7, 110.6, 110.3, 108.3, 101.5, 98.6, 79.7, 77.9, 76.0, 75.6, 75.5, 73.8, 73.7, 71.4, 68.0, 66.6, 60.7, 56.3, 43.9, 40.9, 38.3; HRMS (ESI-TOF) $m/z$: $[M+Cl]^-$ calcd for $C_{56}H_{54}O_{14}Cl$ 985.3197, found 985.3226.

**(*epi*)-Podophyllotoxin 2-*O*-Benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-glucopyranoside (22).** Identical conditions to those used for the synthesis of **16** were applied to the condensation of **4** and **14** to produce **22** as a mixture of α/β isomers (70.3 mg, 82%) as a white solid: $[\alpha]_D^{25}$ = +32.9 (*c* 0.87, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.79 (dd, *J* = 1.2, 8.4 Hz, 1.6 H), 7.64−7.36 (m, 14.4 H), 7.23−7.09 (m, 9 H), 6.94 (s, 1 H), 6.66 (s, 0.8 H), 6.52 (s, 1 H), 6.27 (s, 0.8 H), 6.21 (s, 2 H), 6.13 (s, 1.6 H), 5.984 (d, *J* = 1.6 Hz, 1 H), 5.976 (d, *J* = 1.2 Hz, 1 H), 5.87 (d, *J* = 1.6 Hz, 0.8 H), 5.69 (d, *J* = 1.6 Hz, 0.8 H), 5.64 (s, 0.8 H), 5.60 (s, 1 H), 5.40 (d, *J* = 3.6 Hz, 1 H), 5.26 (dd, *J* = 7.2, 9.2 Hz, 1 H), 5.25 (dd, *J* = 4.0, 9.2 Hz, 0.8 H), 4.89−4.80 (m, 3 H), 4.75−4.69 (m, 2.8 H), 4.66 (d, *J* = 5.2 Hz, 1 H), 4.47−4.39 (m, 1.6 H), 4.32 (d, *J* = 5.2 Hz, 0.8 H), 4.26 (t, *J* = 8.0 Hz, 0.8 H), 4.20−4.06 (m, 3 H), 3.97 (t, *J* = 8.0 Hz, 1 H), 3.91−3.79 (m, 4 H), 3.78 (s, 3 H), 3.76 (s, 2.4 H), 3.71 (s, 6 H), 3.69 (s, 4.8 H), 3.58−3.50 (m, 1 H), 3.42 (dd, *J* = 5.2, 14.0 Hz, 1 H), 3.16 (dd, *J* = 5.6, 14.0 Hz, 0.8 H), 2.86−2.76 (m, 1.8 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.5 (2 C), 165.8, 164.9, 152.6, 152.5, 148.6, 148.4, 146.9, 146.6, 137.9, 137.8, 137.3, 137.2, 137.1, 137.0, 135.2, 135.1, 133.9, 132.9, 132.6, 129.7, 129.6, 129.5, 129.2, 129.1, 128.8 (2 C), 128.3 (3 C), 128.2 (2 C), 128.0, 127.9, 127.8, 127.7, 127.6, 126.0, 125.9, 110.8, 110.5, 109.9, 108.7, 108.3, 108.2, 101.6, 101.4, 101.3 (2 C), 100.0, 99.1, 82.2, 81.7, 75.4, 74.8, 73.9, 73.8, 73.4, 68.6, 68.5, 67.6, 66.5, 66.4, 63.1, 60.7 (2 C), 56.3, 43.9, 43.7, 40.8, 40.7, 38.2, 37.6; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{49}H_{47}O_{14}$ 859.2960, found 859.2948.

**4-*O*-Adamantanyl-(*epi*)-podophyllotoxin (23).** Following the similar procedure as that used for the synthesis of **16**, condensation between **4** and **15** afforded **23** (44.4 mg, 81%) as a white solid: $[\alpha]_D^{25}$ = −53.2 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.96 (s, 1 H), 6.48 (s, 1 H), 6.25 (s, 2 H), 5.98 (d, *J* = 1.6 Hz, 1 H), 5.94 (d, *J* = 1.2 Hz, 1 H), 4.93 (d, *J* = 3.6 Hz, 1 H), 4.59 (d, *J* = 5.6 Hz, 1 H), 4.38 (dd, *J* = 8.0, 10.8 Hz, 1 H), 4.28 (t, *J* = 8.0 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 6 H), 3.41 (dd, *J* = 5.2, 13.6 Hz, 1 H), 2.84−2.75 (m, 1 H), 2.22 (bs, 3 H), 1.86 (s, 6 H), 1.71 (q, *J* = 12.0 Hz, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.3, 152.5, 147.7, 146.9, 137.2, 135.6, 132.6, 131.9, 110.4, 109.6, 108.4, 101.3, 74.7, 69.0, 64.8, 60.7, 56.3, 43.9, 43.4, 41.1, 38.5, 36.2, 30.8; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{32}H_{37}O_8$ 549.2483, found 549.2480.

Compound **5** could also react with **15** under identical conditions to afford **23** in a 87% yield.

**Methyl *N*-Diphenylmethylene-L-(4-*O*-(*epi*)-potophyllotoxyphenyl)-alaninate (30).** Under identical conditions as those applied in the synthesis of **16**, conjugation between **4** and **24** proceeded easily to generate **30** (70.2 mg, 93%) as a white solid: $[\alpha]_D^{25}$ = −124.0 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, *J* = 8.8 Hz, 2 H), 7.42−7.29 (m, 6 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 6.70 (d, *J* = 7.2 Hz, 2 H), 6.64 (s, 1 H), 6.57 (s, 1 H), 6.30 (s, 2 H), 5.96 (d, *J* = 1.2 Hz, 1 H), 5.92 (d, *J* = 1.2 Hz, 1 H), 5.40 (d, *J* = 3.6 Hz, 1 H), 4.69 (d, *J* = 5.2 Hz, 1 H), 4.35 (t, *J* = 8.0 Hz, 1 H), 4.28 (dd, *J* = 4.4, 9.2 Hz, 1 H), 4.13 (dd, *J* = 8.4, 10.8 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 9 H), 3.46 (dd, *J* = 5.2, 14.0 Hz, 1 H), 3.27 (dd, *J* = 4.4, 13.6 Hz, 1 H), 3.20 (m, 1 H), 3.08−3.00 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.5, 172.2, 170.9, 157.0, 152.7, 148.8, 147.2, 139.3, 137.3, 136.0, 134.8, 132.4, 132.2, 131.7, 131.3, 130.4, 130.0, 128.8 (2 C), 128.6, 128.3, 128.2, 128.1, 127.6, 115.7, 110.2, 109.3, 108.2, 101.6, 73.4, 67.5, 67.3, 60.8, 56.3, 52.3, 43.8, 41.6, 38.9, 38.1; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{45}H_{41}NO_{10}Na$ 778.2623, found 778.26218.

**3-*O*-(*epi*)-podophyllotoxyl Estrone (31).** The similar procedure as that adopted for the synthesis of **16** was used to produce **31** via the coupling of **4** and **25** (55.3 mg, 83%) as a white solid: $[\alpha]_D^{25}$ = −42.2 (*c* 1.1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (d, *J* = 7.6 Hz, 1 H), 6.76−6.68 (m, 3 H), 6.58 (s, 1 H), 6.32 (s, 2 H), 5.98 (d, *J* = 1.6 Hz, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 5.47 (d, *J* = 3.6 Hz, 1 H), 4.70 (d, *J* = 4.8 Hz, 1 H), 4.35 (t, *J* = 8.0 Hz, 1 H), 4.16 (dd, *J* = 8.4, 10.8 Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 6 H), 3.48 (dd, *J* = 4.8, 14.0 Hz, 1 H), 3.10−3.03 (m, 1 H), 2.92−2.88 (m, 2 H), 2.55 (dd, *J* = 8.8, 18.8 Hz, 1 H), 2.43−2.38 (m, 1 H), 2.28 (m, 1 H), 2.18−1.96 (m, 4 H), 1.69−1.41 (m, 6 H), 0.93 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.6, 156.4, 152.7, 148.7, 147.2, 138.4, 137.3, 134.9, 133.5, 132.3, 129.0, 126.8, 115.9, 112.9, 110.2, 109.4, 108.3, 101.6, 72.7, 67.7, 60.8, 56.3, 50.4, 48.0, 44.0, 43.8, 41.6, 38.2 (2 C), 35.9, 31.6, 29.7, 26.5, 25.9, 21.6, 13.9; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{40}H_{43}O_9$ 667.2902, found 667.2932.

***N*-(*epi*)-podophyllotoxyl-4-fluoroaniline and *N*-Podophyllotoxyl-4-fluoroaniline (32).** Upon being subjected to the identical conditions to those used for the synthesis of compound **16**, **26** reacted with **4** to afford **32** as a mixture of EPPT and PPT derivatives (50.7 mg, 100%, EPPT/PPT = 5:1) as a light yellow solid: $[\alpha]_D^{25}$ = −104.4 (*c* 0.66, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.15 (s, 0.25 H), 6.96−6.89 (m, 2.5 H), 6.76 (s, 1 H), 6.71 (dd, *J* = 4.0, 8.8 Hz, 0.5 H), 6.53 (s, 0.25 H), 6.52 (2 1 H), 6.50 (dd, *J* = 4.0, 8.8 Hz, 2 H), 6.38 (s, 0.5 H), 6.32 (s, 2 H), 5.96−5.93 (m, 2.5 H), 4.64−4.58 (m, 2.5 H), 4.40 (t, *J* = 8.0 Hz, 1 H), 4.26 (dd, *J* = 7.2, 8.8 Hz, 0.25 H), 4.01 (dd, *J* = 8.4, 10.4 Hz, 1.25 H), 3.80 (s, 3.75 H), 3.77 (s, 1.5 H), 3.75 (s, 6 H), 3.18 (dd, *J* = 4.8, 14.0 Hz, 1 H), 3.04−2.95 (m, 1 H), 2.91 (dd, *J* = 4.8, 14.0 Hz, 0.25 H), 2.75−2.65 (m, 0.25 H), 1.26 (s, 1.25 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.7, 174.3, 157.3, 155.0, 152.6 (2 C), 148.3, 147.7, 147.6, 143.8, 137.5, 137.3, 135.7, 135.1, 131.7, 131.5, 130.6, 129.0, 128.2, 125.3, 116.3, 116.2, 116.1, 116.0, 113.1, 113.0, 110.1, 116.2, 116.1, 116.0, 113.1, 113.0, 110.1, 109.9, 109.1, 108.7, 108.4, 106.9, 101.6, 101.4, 71.2, 68.8, 60.7, 56.4, 56.3, 53.3, 46.4, 44.0, 43.6, 41.8, 38.7; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{28}H_{26}FNO_7$ 508.1766, found 508.1762.



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**4-Deoxy-4-allyl-(*epi*)-podophyllotoxin (33).** A similar procedure as that used for the synthesis of **16** was adopted to get **33** (37 mg, 84%) as a white solid: $[\alpha]_D^{25}$ = −66.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.73 (s, 1 H), 6.47 (s, 1 H), 6.29 (s, 2 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 5.94 (d, *J* = 1.2 Hz, 1 H), 5.84−5.78 (m, 1 H), 5.16−5.10 (m, 2 H), 4.57 (d, *J* = 5.2 Hz, 1 H), 4.28−4.25 (m, 2 H), 3.80 (s, 3 H), 3.74 (s, 6 H), 3.31−3.26 (m, 1 H), 3.10 (dd, *J* = 5.2, 14.0 Hz, 1 H), 3.02−2.94 (m, 1 H), 2.62−2.54 (m, 1 H), 2.46−2.39 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 152.4, 147.1, 146.9, 137.1, 136.7, 136.1, 133.1, 130.9, 116.9, 110.1, 108.7, 108.4, 101.2, 69.0, 60.7, 56.2, 44.1, 42.3, 38.5, 37.7, 36.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{27}O_7$ 439.1751, found 439.1747.

**4-Deoxy-4-(2-formylethyl)-(*epi*)-podophyllotoxin (34).** A similar procedure as that used for the synthesis of **16** was adopted to get **34** (37 mg, 82%) as a white solid: $[\alpha]_D^{25}$ = −55.5 (*c* 0.64, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.88 (s, 1 H), 6.63 (s 1 H), 6.47 (s, 1 H), 6.29 (s, 2 H), 5.96 (d, *J* = 1.2 Hz, 1 H), 5.94 (d, *J* = 1.6 Hz, 1 H), 4.57 (d, *J* = 5.2 Hz, 1 H), 4.33 (dd, *J* = 7.6, 9.6 Hz, 1 H), 3.87−3.84 (m, 1 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.62 (dd, *J* = 9.2, 11.2 Hz, 1 H), 3.06−2.99 (m, 2 H), 2.85−2.77 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.8, 174.5, 152.5, 147.5, 147.2, 137.2, 135.6, 132.3, 131.0, 110.2, 108.4, 101.4, 69.7, 60.8, 56.2, 48.3, 44.0, 41.8, 35.0, 32.7; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{25}O_8$ 441.1544, found 441.15467.

**4′-Demethyl-4′-*O*-(benzyloxycarbonyl)-4-deoxy-4-(2-formylethyl)-(*epi*)-podophyllotoxin (35).** A similar procedure as that used for the synthesis of **16** was adopted to get **35** (23 mg, 82%) as an inseparable mixture of EPPT-**35** and PPT-**35** (5:1) as a white solid: $[\alpha]_D^{25}$ = −80.2 (*c* 0.77, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.86 (s, 1.2 H), 7.43−7.33 (m, 6 H), 6.74 (s, 0.2 H), 6.62 (s, 1 H), 6.54 (s, 0.2 H), 6.46 (s, 1 H), 6.45 (s, 0.2 H), 6.31 (s, 2 H), 5.97 (d, *J* = 1.2 Hz, 0.2 H), 5.96−5.94 (m, 2 H), 5.26 (s, 0.4 H), 5.256 (s, 2 H), 4.62 (d, *J* = 3.6 Hz, 0.2 H), 4.59 (d, *J* = 4.8 Hz, 1 H), 4.36 (m, 0.2 H), 4.32 (dd, *J* = 7.2, 9.2 Hz, 1 H), 4.04 (dd, *J* = 9.2, 10.8 Hz, 0.2 H), 3.85−3.81 (m, 1.2 H), 3.72 (s, 1.2 H), 3.69 (s, 6 H), 3.61 (dd, *J* = 9.2, 10.8 Hz, 1 H), 3.05−2.96 (m, 2.4 H), 2.86−2.75 (m, 2.4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.8, 174.4, 153.1, 151.6, 151.5, 147.6, 147.2, 138.6, 135.1, 132.4, 130.7, 128.5, 128.4, 128.2, 110.3, 108.1, 107.9, 101.4, 70.3, 69.7, 56.2, 48.2, 44.0, 41.8, 35.0, 32.7; HRMS (ESI-TOF) *m*/*z*: $[M+NH_4]^+$ calcd for $C_{31}H_{32}O_{10}N$ 578.2021, found 578.2042.

**4-Deoxy-4-benzoymethyl (*epi*)-Podophyllotoxin (36).** Condensation between **4** and **29** was conducted under the identical conditions as those used for the synthesis of compound **16**, delivering **36** (51 mg, 100%) as a white solid: $[\alpha]_D^{25}$ = −27.9 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (dd, *J* = 1.2, 8.4 Hz, 2 H), 7.63−7.59 (m, 1 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 6.70 (d, 1 H), 6.50 (d, 1 H), 6.32 (s, 2 H), 5.96 (d, *J* = 1.6 Hz, 1 H), 5.94 (d, *J* = 1.2 Hz, 1 H), 4.60 (d, *J* = 4.8 Hz, 1 H), 4.35 (dd, *J* = 7.6, 9.2 Hz, 1 H), 4.07 (qd, *J* = 2.0, 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 6 H), 3.60−3.49 (m, 2 H), 3.24 (dd, *J* = 2.0, 19.2 Hz, 1 H), 3.14−3.04 (m, 1 H), 2.94 (dd, *J* = 4.8, 14.0 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.0, 174.8, 152.5, 147.5, 147.1, 137.1, 135.9, 135.8, 133.9, 133.0, 131.1, 128.9, 128.0, 110.2, 108.4, 108.3, 101.4, 70.2, 60.8, 56.2, 44.1, 42.9, 41.9, 35.2, 34.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{29}O_8$ 517.1857, found 517.1851.

***tert*-Butyldimethylsily 2-Deoxy-2-azido-4,6-di-*O*-ethylidene-*β*-D-glucopyranoside (38).** To a solution of **37** (500 mg, 1.57 mmol) and dimethyl acetal (0.5 mL, 4.71 mmol) in dry acetonitrile (10 mL) was added TsOH (27 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 4 h at which time TLC showed that all starting material was completely consumed. Ethyl acetate was added to dilute the reaction mixture, and the resulting solution was washed successively with saturated $NaHCO_3$, water, and brine, and then dried over $Na_2SO_4$. Filtration and concentration yielded the crude product which was further purified by silica gel chromatography (PE/EA = 4:1) to afford **38** (471 mg, 87%) as a syrup: $[\alpha]_D^{25}$ = −7.0 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.60 (q, *J* = 4.8 Hz, 1 H), 4.45 (d, *J* = 7.6 Hz, 1 H), 3.98 (dd, *J* = 5.2, 10.4 Hz, 1 H), 3.43 (d, *J* = 10.4 Hz, 1 H), 3.38 (d, *J* = 9.2 Hz, 1 H), 3.22 (t, *J* = 9.2 Hz, 1 H), 3.15−3.09 (m, 3 H), 1.23 (d, *J* = 5.2 Hz, 3 H), 0.77 (s, 9 H), 0.00 (s, 3 H), −0.002 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 99.8, 97.5, 80.2, 71.5, 69.1, 68.0, 66.3, 25.5, 20.2, 17.9, −4.4, −5.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{28}N_3O_5Si$ 346.1793, found 346.1796.

***tert*-Butyldimethylsily 2-Deoxy-2-azido-4,6-di-*O*-ethylidene-3-*O*-(2-azidomethyl)benzoyl-*β*-D-glucopyranoside (39).** To a solution of **38** (56 mg, 0.16 mmol) and (2-azidomethyl)benzoic acid (57 mg, 0.32 mmol) in dry $CH_2Cl_2$ (3 mL) was added DMAP (39 mg, 0.32 mmol) and DCC (66 mg, 0.32 mmol) successively at 0 °C. The reaction mixture was warmed to room temperature and was stirred at the same temperature for 4 h. Dilution with ethyl acetate was followed by washing with water and brine successively. Drying over $Na_2SO_4$ and concentrating under reduced pressure gave the crude product which was further purified by silica gel chromatography (PE/EA = 6:1) to deliver **39** (71 mg, 88%) as a syrup: $[\alpha]_D^{25}$ = −21.3 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.43 (td, *J* = 1.2, 7.6 Hz, 1 H), 7.36 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.28 (td, *J* = 1.6, 7.6 Hz, 1 H), 5.10 (t, *J* = 10.0 Hz, 1 H), 4.67−4.56 (m, 2 H), 4.52 (q, *J* = 5.2 Hz, 1 H), 4.00 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.45−3.32 (m, 3 H), 3.26−3.19 (m, 1 H), 1.13 (d, *J* = 5.2 Hz, 3 H), 0.76 (s, 9 H), 0.00 (s, 3 H), −0.01 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.6, 137.3, 132.9, 130.8, 129.8, 128.7, 128.2, 99.8, 97.7, 78.4, 71.8, 68.0, 67.2, 66.6, 53.5, 52.9, 25.5, 20.3, 17.9, −4.4, −5.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{33}N_6O_6Si$ 505.2225, found 505.2227.

**2-Deoxy-2-azido-4,6-di-*O*-ethylidene-3-*O*-(2-azidomethyl)-benzoyl-D-glucopyranose (40).** To a solution of **39** (128.4 mg, 0.26 mmol) in dry pyridine (2 mL) was added HF/pyridine (0.32 mL, 3.57 mmol) dropwise at 0 °C. The resultant mixture was stirred at the same temperature for 3 h, at which time TLC showed that all starting material disappeared. Dilution with ethyl acetate was followed by washing with water, 1 N HCl, aqueous saturated $NaHCO_3$, and brine successively. The organic phase was dried over $Na_2SO_4$, and then filtered. Evaporation to remove volatile solvent gave the crude product which was further purified by silica gel chromatography (PE/EA = 3:1) to give **40** (94.5 mg, 95%) as a mixture of two epimers as a syrup: $[\alpha]_D^{25}$ = +16.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, *J* = 4.4 Hz, 1 H), 8.00 (d, *J* = 4.0 Hz, 1 H), 7.62−7.42 (m, 6 H), 5.81 (t, *J* = 10.0 Hz, 1 H), 5.44 (d, *J* = 3.2 Hz, 1 H), 5.34 (t, *J* = 10.0 Hz, 1 H), 4.89 (d. *J* = 8.0 Hz, 1 H), 4.85−4.70 (m, 6 H), 4.23 (dd, *J* = 4.4, 10.4 Hz, 1 H), 4.17−4.10 (m, 2 H), 3.63−3.45 (m, 6 H), 3.44 (dd, *J* = 3.6, 10.4 Hz, 1 H), 1.34 (d, *J* = 4.8 Hz, 3 H), 1.32 (d, *J* = 4.8 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.9 (2 C), 165.7 (2 C), 137.3, 137.2, 133.0, 132.9, 130.9, 129.9, 129.8, 128.8, 128.6, 128.2 (2 C), 100.0, 99.9, 96.8, 93.2 (2 C), 79.1, 78.3, 72.0 (2 C), 69.9 (2 C), 68.3, 67.9, 66.6 (2 C), 65.9, 62.8 (2 C), 62.3, 52.9, 52.8, 20.2 (2 C); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{18}N_6O_6Na$ 413.1180, found 413.1182.

**4′-Demethyl-4′-*O*-(benzyloxycarbonyl) (*epi*)-Podophyllotoxin 4-*O*-2″-Deoxy-2″-azido-3″-*O*-(azidomethyl)benzoyl-4″,6″-di-*O*-ethylidene-*β*-D-glucopyranoside (41).** Except for the catalyst, the identical conditions for the synthesis of **16** were applied for the reaction between **7** and **40** to furnish **41** (33.6 mg, 74%) as a white solid: $[\alpha]_D^{25}$ = −17.2 (*c* 0.53, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.62 (td, *J* = 1.6, 7.6 Hz, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.46−7.32 (m, 6 H), 6.83 (s, 1 H), 6.57 (s, 1 H), 6.27 (s, 2 H), 6.03 (d, *J* = 1.2 Hz, 1 H), 6.01 (d, *J* = 1.2 Hz, 1 H), 5.29 (t, *J* = 10.0 Hz, 1 H), 5.26 (s, 2 H), 5.00 (d, *J* = 3.2 Hz, 1 H), 4.84−4.70 (m, 4 H), 4.68 (d, *J* = 5.2 Hz, 1 H), 4.44 (dd, *J* = 8.8, 10.8 Hz, 1 H), 4.32−4.23 (m, 2 H), 3.67 (s, 6 H), 3.65−3.55 (m, 3 H), 3.49−3.43 (m, 1 H), 3.40 (dd, *J* = 5.6, 14.0 Hz, 1 H), 2.96−2.88 (m, 1 H), 1.33 (d, *J* = 5.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.4, 165.6, 153.1, 151.6, 149.1, 147.3, 138.1, 137.3, 135.1, 133.0, 132.6, 130.8, 129.9, 128.5 (2 C), 128.4, 128.2 (2 C), 127.2, 111.2, 108.8, 107.7, 101.8, 100.5, 100.0, 78.2, 73.7, 71.6, 70.4, 67.9, 67.4, 66.7, 64.7, 56.2, 52.9, 44.0, 41.0, 37.5, 20.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{45}H_{43}N_6O_{15}$ 907.2781, found 907.2791.

**4′-Demethyl-(*epi*)-podophyllotoxin 4-*O*-2″-deoxy-2″-amino-4″,6″-di-*O*-ethylidene-*β*-D-glucopyranoside (42).** To a solution of **41** (20 mg, 0.022 mmol) in MeOH (2 mL) was added $Pd(OH)_2/C$ (20 mg). After the reaction vessel was immersed in a −78 °C cool bath, the vessel was evacuated and then refilled with $H_2$ (balloon). The process was repeated three times, and then the reaction mixture was


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warmed to room temperature. The stirring was continued for 12 h under an $H_2$ atmosphere (1 atm). Filtration was followed by concentration under reduced pressure to afford the crude product which was further purified by silica gel chromatography ($CH_2Cl_2$/MeOH = 20:1) to yield **42** (10.9 mg, 85%) as a white solic: $[\alpha]_D^{25}$ = −78.4 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $C_5D_5N$) $\delta$ 7.33 (s, 1 H), 6.81 (s, 1 H), 6.79 (s, 2 H), 5.96 (s, 2 H), 5.71 (s, 1 H), 5.05 (d, *J* = 4.0 Hz, 1 H), 5.046 (d, *J* = 7.6 Hz, 1 H), 4.90−4.86 (m, 2 H), 4.72 (dd, *J* = 8.8, 10.8 Hz, 1 H), 4.38−4.33 (m, 2 H), 4.07 (t, *J* = 9.2 Hz, 1 H), 3.77 (s, 6 H), 3.75−3.60 (m, 4 H), 3.30−3.24 (m, 2 H), 1.43 (d, *J* = 4.8 Hz, 3 H); $^{13}$C NMR (100 MHz, $C_5D_5N$) $\delta$ 175.1, 148.6, 148.4, 147.2, 137.0, 133.3, 130.3, 130.1, 110.4, 109.6 (2 C), 105.0, 101.8, 99.6, 81.9, 74.1, 73.4, 68.4, 68.3, 67.2, 59.0, 56.3, 44.1, 41.7, 38.1, 20.5; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{34}NO_{12}$ 588.2076, found 588.2068.

**NK-611 (3).** To a solution of **42** (56 mg, 0.095 mmol) in MeOH (1.5 mL) was added sodium cyanoborohydride (20 mg, 3.34 mmol) and aqueous formaldehyde (37%, 84 μL). The mixture was stirred at room temperature for 4 h, then concentrated in vacuo. Column chromatography ($CH_2Cl_2$/MeOH = 20:1) of the obtained residue on silica gel afforded **3** (52 mg, 84%) as a white solid: $[\alpha]_D^{25}$ = −32.3 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.75 (s, 1 H), 6.58 (s, 1 H), 6.22 (s, 2 H), 6.03−6.02 (m, 2 H), 5.42 (bs, 1 H), 5.01 (d, *J* = 2.8 Hz, 1 H), 4.89 (d, *J* = 8.4 Hz, 1 H), 4.80 (q, *J* = 5.2 Hz, 1 H), 4.66 (d, *J* = 5.6 Hz, 1 H), 4.40 (dd, *J* = 8.8, 10.4 Hz, 1 H), 4.28 (t, *J* = 8.0 Hz, 1 H), 4.21 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.76 (s, 6 H), 3.67−3.59 (m, 2 H), 3.42−3.30 (m, 3 H), 2.96−2.87 (m, 1 H), 2.49−2.44 (m, 1 H), 2.32 (bs, 6 H), 1.42 (d, *J* = 4.8 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.7, 148.8, 147.0, 146.4, 134.2, 133.0, 130.6, 127.5, 111.3, 109.0, 107.8, 101.7, 99.7, 97.8, 80.8, 68.1 (2 C), 67.7, 66.7, 56.5, 43.7, 41.3, 37.4, 20.3; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{31}H_{37}NO_{12}Na$ 638.2208, found 638.2193.

**(*epi*)-Podophyllotoxin 4-*O*-2″-Deoxy-2″-azido-3″-*O*-(azidomethyl)benzoyl-4″,6″-di-*O*-ethylidene-β-D-glucopyranoside (43).** The identical conditions for the synthesis of **16** were applied to the reaction between **4** and **40** to furnish **43** (39.3 mg, 89%) as a white solid: $[\alpha]_D^{25}$ = −67.1 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.62 (td, *J* = 1.6, 7.6 Hz, 1 H), 7.54 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.46 (td, *J* = 1.6, 7.6 Hz, 1 H), 6.82 (s, 1 H), 6.58 (s, 1 H), 6.24 (s, 2 H), 6.03 (d, *J* = 1.2 Hz, 1 H), 6.01 (d, *J* = 1.6 Hz, 1 H), 5.29 (t, *J* = 9.6 Hz, 1 H), 5.02 (d, *J* = 2.8 Hz, 1 H), 4.85 (d, *J* = 7.6 Hz, 1 H), 4.83 (AB, 2 H), 4.74−4.70 (m, 1 H), 4.66 (d, *J* = 5.6 Hz, 1 H), 4.44 (dd, *J* = 8.8, 10.8 Hz, 1 H), 4.32−4.23 (m, 2 H), 3.80 (s, 3 H), 3.73 (s, 6 H), 3.66−3.56 (m, 3 H), 3.49−3.43 (m, 1 H), 3.39 (dd, *J* = 5.6, 14.4 Hz, 1 H), 3.00−2.92 (m, 1 H), 1.33 (d, *J* = 4.8 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.5, 165.6, 152.6, 149.1, 147.2, 137.3 (2 C), 135.1, 133.0 (2 C), 130.9, 129.9, 128.5, 128.2, 127.0, 111.1, 108.8, 108.2, 101.7, 100.4, 100.0, 78.2, 73.7, 71.5, 67.9, 67.4, 66.6, 64.7, 60.8, 56.2, 52.9, 43.9, 40.9, 37.6, 20.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{38}H_{39}N_6O_{13}$ 787.2570, found 787.2565.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00485.

Copies of NMR spectra of all new compounds, including 2D NMR for **33** and **34** (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Botta, B.; Monache, G. D.; Misiti, D.; Vitali, A.; Zappia, G. *Curr. Med. Chem.* **2001**, *8*, 1363.

(2) (a) Aisner, J.; Whitacre, M. Y.; Budman, D. R.; Propert, K.; Strauss, G.; Vanecho, D. A.; Perry, M. *Cancer Chemother. Pharmacol.* **1992**, *29*, 435. (b) Price, B. A.; Peters, N. H. *Eur. J. Cancer* **1992**, *28*, 615. (c) Stadtmauer, E. A.; Cassileth, P. A.; Gale, R. P. *Leuk. Res.* **1989**, *13*, 639. (d) Bostrom, B.; Weisdorf, D. J.; Kim, T.; Kersey, J. H.; Ramsay, N. K.*Bone Marrow Transplant.* **1990**, *5*, 83. https://www.ncbi.nlm.nih.gov/pubmed/2107007.

(3) (a) Wang, Y.; Rea, T.; Bian, J.; Gray, S.; Sun, Y. *FEBS Lett.* **1999**, *445*, 269. (b) Burden, D. A.; Osheroff, N. *Biochim. Biophys. Acta, Gene Struct. Expression* **1998**, *1400*, 139. (c) Gantchev, T. G.; Hunting, D.*Mol. Pharmacol.* **1998**, *53*, 422. http://molpharm.aspetjournals.org/content/53/3/422.short. (d) Froelich-Ammon, S. J.; Osheroff, N. *J. Biol. Chem.* **1995**, *270*, 21429.

(4) Rassmann, I.; Thodtmann, R.; Mross, M.; Huttmann, A.; Berdel, W. E.; Manegold, C.; Fiebig, H. H.; Kaeserfrölich, A.; Burk, K.; Hanauske, A.-R. *Invest. New Drugs* **1998**, *16*, 319.

(5) de Jong, R. S.; Slijfer, E. A. M.; Uges, D. R. A.; Mulder, N. H.; de Vries, E. G. E. *Br. J. Cancer* **1997**, *76*, 1480.

(6) Utsugi, T.; Shibata, J.; Sugimoto, Y.; Aoyagi, K.; Wierzba, K.; Kobunai, T.; Terada, T.; Oh-hara, T.; Tsuruo, T.; Yamada, Y.*Cancer Res.***1996**, *56*, 2809. http://cancerres.aacrjournals.org/content/56/12/2809.short.

(7) Zhang, Y.-L.; Tropsha, A.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 1460.

(8) For review, see: (a) Sun, J.-S.; Liu, H.; Guo, X.-H.; Liao, J.-X. *Org. Biomol. Chem.* **2016**, *14*, 1188. For sulfoxide activation, see: (b) Berkowitz, D. B.; Choi, S.; Bhuniya, D.; Shoe-maker, R. K. *Org. Lett.* **2000**, *2*, 1149. For OH activation, see: (c) Terada, T.; Fujimoto, K.; Nomura, M.; Yamashita, J.-i.; Wierzba, K.; Yamazaki, R.; Shibata, J.; Sugimoto, Y.; Yamada, Y. *J. Med. Chem.* **1993**, *36*, 1689. (d) Xiao, Z.; Bastow, K. F.; Vance, J. R.; Sidwell, R. S.; Wang, H.-K.; Chen, M. S.; Shi, Q.; Lee, K.-H. *J. Med. Chem.* **2004**, *47*, 5140. (e) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Bigatti, E.; Macdonald, P. *J. Org. Chem.* **1993**, *58*, 4175. (f) Silverberg, L. J.; Kelly, S.; Vemishetti, P.; Vipond, D. H.; Gibson, F. S.; Harrison, B.; Spector, R.; Dillon, J. L. *Org. Lett.* **2000**, *2*, 3281. For Br or I activation, see: (g) Wang, Z.-Q.; Kuo, Y.-H.; Schnur, D.; Bowen, P.; Liu, S.-Y.; Han, F.-S.; Chang, J.-Y.; Cheng, Y.-C.; Lee, K.-H. *J. Med. Chem.* **1990**, *33*, 2660. (h) Lee, K.-H.; Beers, S. A.; Mori, M.; Wang, Z.-Q.; Kuo, Y.-H.; Li, L.; Liu, S.-Y.; Chang, J.-Y.; Han, F.-S.; Cheng, Y.-C. *J. Med. Chem.* **1990**, *33*, 1364.

(9) (a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604. (b) Liu, H.; Liao, J.-X.; Hu, Y.; Tu, Y.-H.; Sun, J.-S. *Org. Lett.* **2016**, *18*, 1294. (c) Tang, Y.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396. (d) Zhang, L.; Li, L.; Bai, S.; Zhou, X.; Wang, P.; Li, M. *Org. Lett.* **2016**, *18*, 6030.

(10) Daley, L.; Meresse, P.; Bertounesque, E.; Monneret, C. *Tetrahedron Lett.* **1997**, *38*, 2673.

(11) Kovac, P.; Sklenar, V.; Glaudemans, C. P. J. *Carbohydr. Res.* **1988**, *175*, 201.

(12) (a) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665. (b) Zulueta, M. M. L.; Lin, S.-Y.; Lin, Y.-T.; Huang, C.-J.; Wang, C.-C.; Ku, C.-C.; Shi, Z.; Chyan, C.-L.; Irene, D.; Lim, L.-H.; Tsai, T.-I.; Hu, Y.-P.; Arco, S. C.; Wong, C.-H.; Hung, S.-C. *J. Am. Chem. Soc.* **2012**, *134*, 8988.

(13) Ennis, S. C.; Cumpstey, I.; Fairbanks, A. J.; Butters, T. D.; Mackeen, M.; Wormald, M. R. *Tetrahedron* **2002**, *58*, 9403.

(14) Yang, W.; Sun, J.; Lu, W.; Li, Y.; Shan, L.; Han, W.; Zhang, W.-D.; Yu, B. *J. Org. Chem.* **2010**, *75*, 6879.




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(15) Wang, G.; Lu, Z.; Ding, N.; Zhang, W.; Wang, P.; Li, Y. *Carbohydr. Res.* **2011**, *346*, 2368.
(16) (a) Chen, X.; Wang, Q.; Yu, B. *Chem. Commun.* **2016**, *52*, 12183. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (c) Gu, Z.-Y.; Zhang, X.-T.; Zhang, J.-X.; Xing, G.-W. *Org. Biomol. Chem.* **2013**, *11*, 5017−5022.
(17) (a) Saito, H.; Yoshikawa, H.; Nishimura, Y.; Kondo, S.; Takeuchi, T.; Umezawa, H. *Chem. Pharm. Bull.* **1986**, *34*, 3741. (b) Kolar, C.; Dehmel, K.; Wolf, H. *Carbohydr. Res.* **1990**, *206*, 219.
(18) Li, J.; Yu, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 6618.
(19) See Supporting Information.
(20) (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900. (b) Morris, W. J.; Shair, M. D. *Org. Lett.* **2009**, *11*, 9.
(21) Walvoort, M. T. C.; de Witte, W.; van Dijk, J.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; Codee, J. D. C.; van der Marel, G. A. *Org. Lett.* **2011**, *13*, 4360.



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