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A Highly Efficient Approach To Construct (*epi*)-Podophyllotoxin-4-*O*-glycosidic Linkages as well as Its Application in Concise Syntheses of Etoposide and Teniposide

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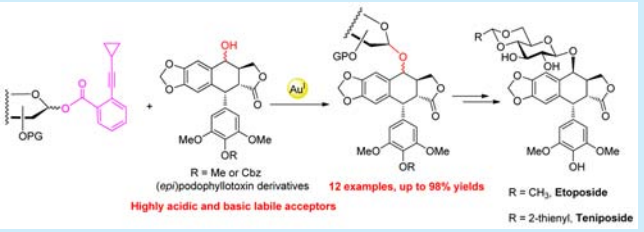
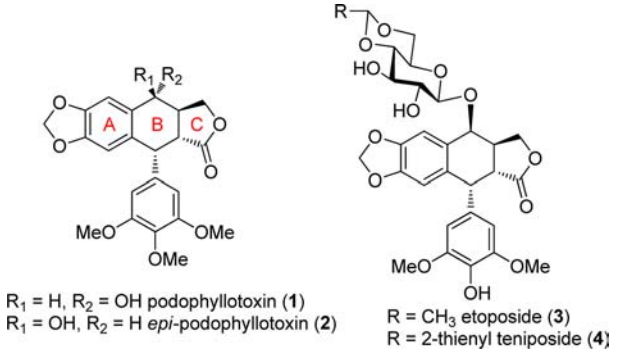
Supporting Information

ABSTRACT: By taking full advantage of the mild promotion conditions of an *ortho*-alkynylbenzoate glycosylation protocol, a highly efficient approach to construct the challenging (*epi*)-podophyllotoxin 4-*O*-glycosidic linkages was devised under the activation of a catalytic amount of a Au(I) complex. The novel method enjoys a quite broad substrate scope in terms of both glycosyl donors and podophyllotoxin derivative acceptors, providing the desired glycosides in excellent yields. Based on the new approach, concise syntheses of clinically used anticancer reagents etoposide and teniposide were accomplished, and the overall yields counting from easily available starting materials could reach as high as 18% and 9%, respectively.



Intrigued by the great clinical success of etoposide and teniposide, which are now widely used as the first-line antitumoral reagents to treat small cell lung carcinoma,[1] testicular cancer,[2] and leukemia[3] either alone or in combination with other drugs, tremendous efforts have been devoted to searching for highly efficient approaches to synthesize aryltetralin 4-*O*-glycosides (Figure 1). In fact, the synthetic

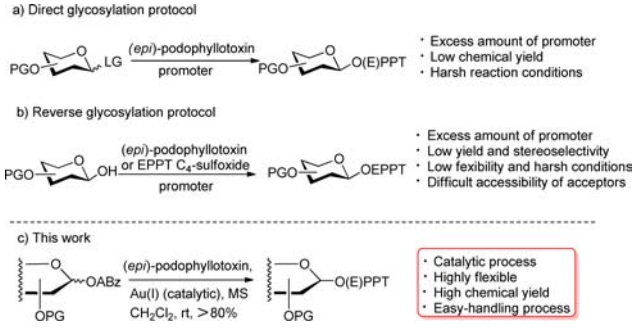


R1 = H, R2 = OH podophyllotoxin (**1**)
R1 = OH, R2 = H *epi*-podophyllotoxin (**2**)

Figure 1. Chemical structures of (*epi*)-podophyllotoxin, etoposide, and teniposide.

endeavor could date back as early as 1968, at which time Kuhn and Wartburg established two fundamental protocols, direct glycosylation and reverse glycosylation protocols, for the synthesis of (*epi*)-potophyllotoxin 4-*O*-glycosides (Scheme 1).[4] Due to the low efficiency and inherent shortcomings, attempts to improve them from both Kuhn's[5] and other groups[6] were made thereafter. Nevertheless, only marginal improvements have been achieved, and most of the associated drawbacks of the established approaches, including a large

Scheme 1. Methods To Construct (*epi*)-Podophyllotoxin 4-*O*-Glycosidic Linkages



excess amount of promoters, low to moderate chemical yields, inefficient stereocontrol of the glycosidic linkage, and unsatisfying flexibility, could not be thoroughly eliminated. This situation can be attributed to either the lack of an efficient glycosylation method specific for (*epi*)-podophyllotoxin 4-OH acceptors (for direct glycosylation protocol) or the relatively low glycosylation capacity of aryltetralin 4-OHs as glycosylation donors (for reverse glycoylation protocol). In constrast, the continuing emergence of aryltetralin 4-*O*-glycosides such as etopophos[7] and NK-611[8] with more promising pharmaceutical applications than etoposide and teniposide, as well as the incompletely understood functional mechanism of etoposide and teniposide, calls for a highly efficient method to construct the pivotal aryltetralin 4-*O*-glycosidic linkages.

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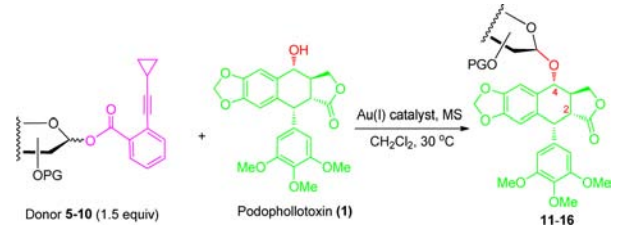
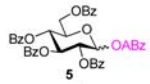
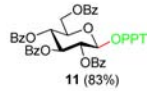
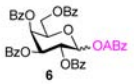
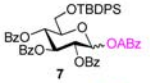
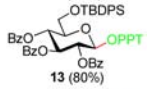
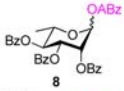
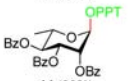
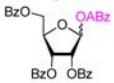
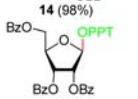
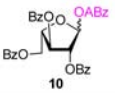
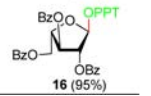
The challenges associated with aryltetralin 4-*O*-glycosidic linkage construction mainly originate from the acid sensitivity of benzylic aryltetralin 4-OHs and base vulnerability of the trans-fused B/C ring architecture of (*epi*)-podophyllotoxins. To solve this problem, we decided to apply the conceptually new Au(I)-catalyzed glycosylation method[9] to the field of aryltetralin 4-*O*-glycoside synthesis, and the investigation has resulted in not only the establishment of a highly efficient, flexible, and catalytic protocol to produce aryltetralin 4-*O*-glycosides but also the discovery of more concise and efficient routes to obtain etoposide and teniposide (Scheme 1).

The glycosylation of podophyllotoxin (**1**) was tried with perbenzoylated glucosyl *ortho*-cyclopropylethynylbenzoate donor **5**,[10] under the effect of $Ph_3PAuNTf_2$ (0.2 equiv to acceptor) in the presence of activated 4 Å MS at 30 °C. Fortunately, after 4 h of stirring, an excellent yield of the desired podophyllotoxin 4-*O*-glucoside **11** was isolated (83%, Table 1, entry 1). The stereoselectivity of the glycosylation was

Table 1. Glycosylation of Podophyllotoxin 4-OH with Glycosyl *ortho*-Cyclopropylethynylbenzoate as Donors



Entries	Donor	Au(I) (equivalent)	MS	Product (yield)[a]
1	 5	PPh_3AuNTf_2 (0.2)	4A	 11 (83%)
2	 6	PPh_3AuNTf_2 (0.2)	4A	 12 (83%)
3	 7	PPh_3AuNTf_2 (0.2)	4A	 13 (80%)
4	 8	PPh_3AuNTf_2 (0.2)	4A	 14 (98%)
5	 9	PPh_3AuNTf_2 (0.2)	4A	 15 (82%)
6	 10	PPh_3AuNTf_2 (0.2)	4A	 16 (95%)

[a]Isolated yield.

thoroughly controlled, as elucidated by the anomeric proton of **11** (4.99 ppm, J = 7.6 Hz). The chiral integrity of C-4 in **11** was also maintained under the mild glycosylation conditions, as verified by H-4 signal which resided at 4.99 ppm as a doublet signal with a J value of 10.0 Hz. Encouraged by the promising result of donor **5**, its galactosyl counterpart **6**[11] and 6-*O*-TBDPS protected glucosyl donor **7**[12] was then tested to condense with podophyllotoxin (**1**) under the above-mentioned glycosylation conditions; again, excellent yields of desired glycosides **12** and **13** were obtained (83% and 80%, respectively, entries 2 and 3). As the representative of L-series donors, rhamnosyl donor **8**[13] was demonstrated to be a vital substrate for the new podophyllotoxins 4-*O*-glycoside synthesis method, and a near-quantitative yield of podophyllotoxin 4-*O*-rhamnoside **14** was recorded (98%, entry 4). Besides pyranosyl donors, sugar furanosyl donors including D-ribofuranosyl donor **9**[13] and L-arabinosyl donor **10**[22] could also be used in podophyllotoxin 4-*O*-glycoside synthesis, yielding glycosides **15** and **16** in 82% and 95% yields, respectively (entries 5 and 6). Moreover, it also should be noted that, due to the mild glycosylation conditions, no attendant epimerization at C-2 to the *cis*-fused lactone was detected, which could be easily determined by the diagnostic signals of H-1 and H-2 in the ^{1}H NMR spectrum, which appeared at around 4.50 ppm in a doublet form (J = 4.0 Hz) and around 2.70 ppm as a doublet of doublets form (J = 4.0, 14.4 Hz), respectively.

After the optimal conditions for podophyllotoxin 4-*O*-glycosides synthesis has been fixed, our attention was then turned to *epi*-podophyllotoxin 4-*O*-glycosides synthesis. In comparison to podophyllotoxin, the *epi*-podophyllotoxin 4-OH orients axially and thus has poor nucleophility;[6a] in turn its glycosylation becomes more challenging. Direct adoption of conditions applied for podophyllotoxin 4-OH glycosylation to the condensation between donor **5** and *epi*-podophyllotoxin (**2**)[14] met with some problems, and only a moderate yield of **17** was isolated (45%), with the remaining material balance for glycosyl acceptor being recovered as well as decomposed *epi*-podophyllotoxin, which further verify the low reactivity of *epi*-podophyllotoxin 4-OH. Changing the MS form basic 4 Å to acidic 5 Å,[15] diminishing the catalyst amount from 0.2 to 0.13 equiv, and increasing the donor amount to 3.0 equiv could enhance the yield of **17** dramatically to 74% (Table 2, entry 1). The chemical structure of **17** was determined by the ^{1}H NMR spectrum in which the H-4 (4.96 ppm, J = 2.8 Hz, axially oriented 4-*O*-glycoside) as well as the anomeric H″-1 (5.06 ppm, J = 8.8 Hz, β-configuration of the glycosidic linkage) is easily discriminated. When the slightly modified glycosylation conditions were applied to donors **6** and **7** to couple with *epi*-podophyllotoxin (**2**), an 80% yield of **18** and a 73% yield of **19** were produced (entries 3 and 4). Rhamnosyl donor **8** could also react with **2** under the same conditions, yielding the desired rhamnosyl glycoside **20** in 77% yield (entry 4). Similarly, upon treatment with **2** under identical conditions, furanosyl donor **9** provided a 72% yield of **21** (entry 8). Surprisingly, the performance of the L-arabinosyl donor **10** was so impressive that an 88% yield of product **22** was obtained (entry 10). Although the modified glycosylation conditions could afford the desired glycosides, in most cases only moderate yields (around 70%, for entries 1, 4, 6, and 8) were recorded; therefore, further optimization is required. Finally, we resort to the more reactive Au(I) catalyst $Ph_3PAuOTf$ (0.2 equiv),[9a,16] and under otherwise identical conditions, donors **5**, **7**, **8**, and **9** could afford excellent yields of glycosylation products when reacted with **2** (entries 2, 5, 7, and 9). In spite of the enhanced activity of $Ph_3PAuOTf$, the glycosylation conditions were so mild that no unwanted epimerization at C-2 was detected, as verified by the H-2 signal (appear at around 3.0 ppm in a doublet of doublets form, J = 5.6, 14.0 Hz).

All chemical structures of the glycosylation products from **11** to **22** were determined by ^{1}H and ^{13}C NMR spectra. Fortunately, for *epi*-podophyllotoxin 4-*O*-glucoside **19** and *epi*-podophyllotoxin 4-*O*-rhamnoside **20**, suitable crystals for X-

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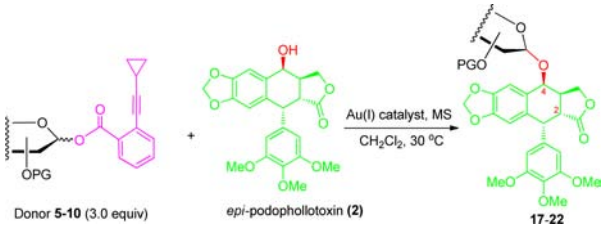
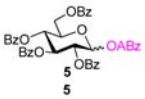
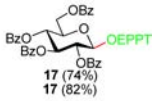
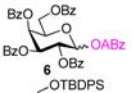
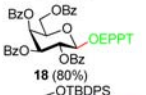
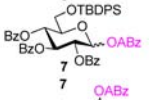
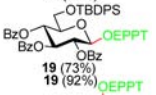
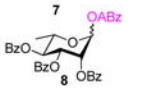
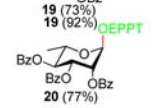
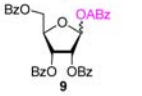
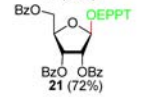
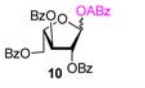
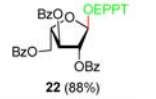
Table 2. Glycosylation of *epi*-Podophyllotoxin 4-OH with Glycosyl *ortho*-Cyclopropylethynylbenzoate as Donors



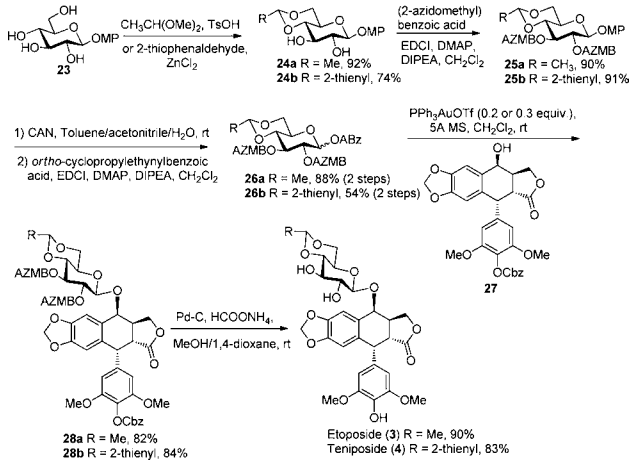
Entries	Donor	Au(I) (equivalent)	MS	Product (yield)[a]
1		$Ph_3PAuNTf_2$ (0.13)	5A	 17 (74%)
2	5	$Ph_3PAuOTf$ (0.2)[b]	5A	17 (82%)
3		$Ph_3PAuNTf_2$ (0.13)	5A	 18 (80%)
4		$Ph_3PAuNTf_2$ (0.13)	5A	 19 (73%)
5	7	$Ph_3PAuOTf$ (0.2)[b]	5A	19 (92%)
6		$Ph_3PAuNTf_2$ (0.13)	5A	 20 (77%)
7	8	$Ph_3PAuOTf$ (0.2)[b]	5A	20 (99%)
8		$Ph_3PAuNTf_2$ (0.13)	5A	 21 (72%)
9	9	PPh_3AuOTf (0.2)[b]	5A	21 (98%)
10		PPh_3AuNTf_2 (0.13)	5A	 22 (88%)

[a]Isolated yield. [b]Prepared by combination of PPh_3AuCl and AgOTf in CH_2Cl_2 in the presence of activated 5 Å MS.

ray diffraction were cultivated, and the structures were further corroborated by single crystal diffraction analysis.[17,18]

With the optimal conditions for synthesis of both podophyllotoxin 4-*O*-glycosides and *epi*-podophyllotoxin 4-*O*-glycosides being fixed, we then decided to employ them in the syntheses of etoposide (**3**) and teniposide (**4**) so as to check the synthetic potential as well as to find more concise and efficient routes to obtain these two clinically important anticancer medicines. So far, at least six synthetic routes to generate etoposide have been established.[4−6] However, all existing methods suffer from either low glycosylation yield and stereoselectivity or inefficient as well as inconvenient deprotection process and exhibits difficulty in handling. To solve these problems, a new and highly concise approach to obtain etoposide (**3**) was devised (Scheme 2). Thus, easily accessible 4-methoxylphenyl glucoside **23**, derived from cheap D-glucose through three steps of conventional conversions,[19] was treated with 1,1-dimethoxyethane in the presence of TsOH to afford **24a** efficiently, realizing the installation of a 4″,6″-*O*-ethylidenyl group on the sugar residue (92%). To control the stereoselectivity in the glycosylation step and facilitate the deprotection process in the final stage, the (2-azidomethyl)-benzoyl (AZMB)[20] group which has been proven to possess good orthogonality with other ester groups was selected to block C-2,3 OHs of glucose. The method of introduction of AZMB via AZMBCl in the presence of pyridine is widely employed,[20] but an additional step to generate AZMBCl is required. We found that, under standard dehydrative conditions

Scheme 2. Synthesis of Etoposide (3) and Teniposide (4)



(EDCI, DMAP), AZMBs could be efficiently introduced using AZMB acid directly, affording **25a** in 90% yield. CAN mediated regioselective release of the anomeric OH was followed by esterification with *ortho*-cyclopropylethynylbenzoic acid to produce donor **26a** (88%, 2 steps). The pivotal glycosylation between **26a** and *epi*-podophyllotoxin derivative **27**[21] proceeded without any event under the optimized conditions for *epi*-podophyllotoxin acceptors, furnishing the fully protected etoposide **28a** (82%). Finally, simultaneous removal of two AZMB groups and one Cbz group was efficiently achieved under palladium-catalyzed hydrogen transfer conditions (Pd−C, HCO_2NH_4),[20a] without the need to resort to difficult-to-handle hydrogen gas, to generate etoposide in a yield as high as 90%. Counting from easily available starting material **23**, only six steps are required to obtain etoposide, and the overall yield could reach as high as 18%. The analytic data are in good agreement with those reported in literature.[6,18]

Different from etoposide, the synthesis of teniposide was scarcely investigated presumably due to synthetic challenges associated with it. We encountered a problem at the outset of the synthesis when attempts were made to incorporate the 2-thiophenylidene group on **23** (Scheme 2). Both 2-thenaldehyde dimethyl acetal and 2-thenaldehyde as thiophenylidenation reagents under the catalysis of TsOH were checked,[22] but no desired product was detected. Further investigation revealed that anhydrous $ZnCl_2$ was the best acid to use, and a 74% yield of 2-thiophenylidene **24b** was isolated with dry 2-thenaldehyde acting as both reagent and solvent. With **24b** in hand, the following introduction of AZMBs proceeded fluently via direct dehydrative esterification, yielding **25b** efficiently (91%, yield). Subsequent removal of the anomeric MP (*p*-methoxyphenyl) group with CAN in the presence of a thienyl group is a risky task since it is well-known that CAN is an efficacious reagent to oxidize thioethers to sulfoxide either stoichiometrically or catalytically. This concern was borne out by the fact that the simultaneous dethiophenylidenated product was isolated when the same conditions as those used for MP removal of compound **25a** was applied to **25b**. The dethiophenylidenation side reaction probably was not induced by the acidic property of CAN because even a large excess amount of $NaHCO_3$ (10.0 equiv to CAN) could not suppress it; instead, the oxidative character should be responsible for the side reaction. Finally, the side reaction was completely prevented by shortening the reaction time (15 min), decreasing the reaction temperature (0

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°C), and adjusting the pH value of the reaction medium with $NaHCO_3$ (1.0 equiv), providing the desired lactol in a good 72% yield (100% BRSM). Dehydrative esterification of resultant lactol with *ortho*-alkynylbenzoic acid gave donor **26b** (74%), which was then subjected to glycosylation with **27** under the optimal conditions screened for *epi*-podophyllotoxin to furnish **28b** efficiently (84%) with no noted adverse effect exerted by the sulfur atom. At this junction, what remained to complete the synthesis of teniposide is palladium-catalyzed AZMBs and Cbz removal. Before conducting this transformation, we were concerned that the sulfur atom contained in the thiophene ring may poison the palladium catalyst, retarding the deprotection process. However, the concern proved to be superfluous and under the catalysis of Pd−C the ester protecting groups were globally removed in 83% yield to afford teniposide (**4**). The analytic data for the synthetic compound are identical to those reported in literature.[23,18] With easily available **23** as starting material, only six steps are required to synthesize teniposide with an overall yield of 9%.

In summary, a highly efficient method to construct the challenging (*epi*)-podophyllotoxin 4-OH glycosidic linkages was established, featuring the employment of glycosyl *ortho*-alkynylbenzoates as donors and catalytic amounts of a Au(I) complex as the promoter. The mild promotion conditions ensure that the both acid- and base-sensitive acceptors, (*epi*)-podophyllotoxin derivatives, remain intact during the glycosylation reactions, while donors equipped with acyl groups on 2-OH guarantee efficient stereoselective control of the glycosidic linkages via anchimeric assistance, rendering the described method as the most effective approach for aryltetralin 4-*O*-glycoside synthesis. Based on the devised method and appropriate choice of AZMB and Cbz as protecting groups, highly concise and efficient routes to synthesize etoposide and teniposide were also discovered.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00216.

Synthetic procedures, characterization data including X-ray diffraction spectra and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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