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Novel "Reverse Kahne-Type Glycosylation": Access to O-, N-, and C-Linked Epipodophyllotoxin Conjugates

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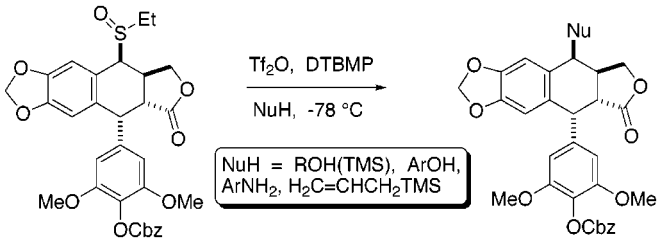
ABSTRACT



Exposure of epipodophyllotoxin C_4-sulfoxides to triflic anhydride, followed by a silyl glycoside, provides a glycoconjugate of the etoposide variety via formal "reverse Kahne glycosylation." To our knowledge, this is the first example of this variant of the Kahne activation method wherein the activating functionality is positioned on the aglycon, rather than on the sugar. Phenols, anilines, or allyl silanes are also efficiently captured at C_4, producing the corresponding O-, N-, and C-linked lignan conjugates.

Etoposide (**1**), a semisynthetic glucoconjugate of epipodophyllotoxin, has found widespread clinical application as an antineoplastic agent for over two decades.[1] Its clinical success, as well as its incompletely understood mechanism of action,[2] have stimulated interest in structural modification of the drug. Several congeners with altered carbohydrate sectors have emerged as promising drug candidates, including etopophos (**2**),[3] NK-611 (**3**),[4] TOP-53 (**4**),[5] NPF (**5**),[6] and GL-331 (**6**) (Figure 1).[7]

We have developed the first catalytic, asymmetric synthesis of (−)-podophyllotoxin.[8] Our route is designed to be modular in ring E, and so permits for SAR studies in that potentially mechanistically important sector of the molecule.[2c,9] To examine possible synergy between modifications in ring

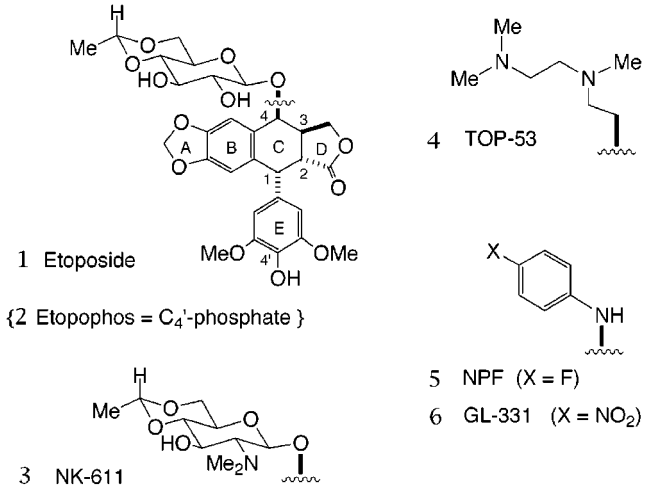


Figure 1. Epipodophyllotoxin conjugates with anticancer activity.

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(2) (a) Wang, Y.; Rea, T.; Bian, J.; Gray, S.; Sum, Y. *FEBS Lett.* **1999**, *445*, 269−273. (b) Burden, D. A.; Osheroff, N. *Biochim. Biophys. Acta* **1998**, *1400*, 139−154. (c) Gantchev, T. G.; Hunting, D. J. *Mol. Pharmacol.* **1998**, *53*, 422−428. (d) Froelich-Ammon, S. J.; Osheroff, N. *J. Biol. Chem.* **1995**, *270*, 21429−21432.

(3) 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*, 1480−1483.

(4) Rassmann, I.; Thodtmann, R.; Mross, M.; Huttmann, A.; Berdel, W. E.; Manegold, C.; Fiebig, H. H.; Kaeserfrolich, A.; Burk, K.; Hanauske, A. R. *Invest. New Drugs* **1998**, *16*, 319−324.

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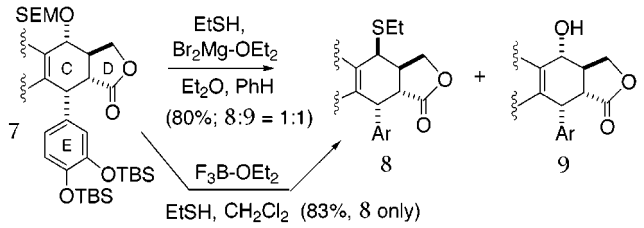
E and those in the "carbohydrate sector," we sought a glycosylation method that would efficiently interface with our synthetic route to scalemic aglycon.

Though Koenigs−Knorr glycosylation was originally used to make podophyllotoxin conjugates,[10,11] most current approaches rely upon a "reverse glycosylation" approach due to Kuhn and von Wartburg, wherein the aglycon serves as the "reverse glycosyl donor" and the sugar as "reverse glycosyl acceptor."[12] The reaction is normally run at −20 to 0 °C, under $F_3B{-}Et_2O$ promotion. An important modification by Allevi, wherein a silyl sugar is employed, facilitates control of the anomeric stereochemistry.[13]

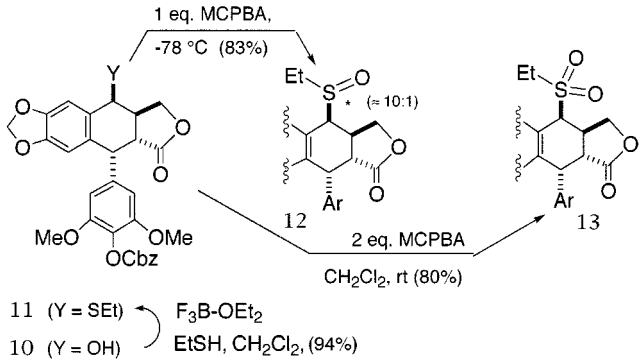
Our approach to the aglycon employs a C_4-*O*-SEM protecting group. Fortuitously, we observed that, under the SEM deprotection conditions of Kim,[14] a significant amount of C_4-thioether may be formed. More recently, we have found that substitution of $F_3B{-}OEt_2$ for $Br_2Mg{-}OEt_2$ improves conversion to the thioether (Scheme 1).

Scheme 1. Removal of the C_4-*O*-SEM Protecting Group with Direct Thioether Installation



This synthetic move would serve as a simultaneous SEM deprotection/aglycon activation procedure, were it possible to develop a sulfur-based reverse glycosylation method here. Toward this end, we chose the natural product as our model system. $C_{4'}$-O-Cbz-protected epipodophyllotoxin **10** was efficiently converted to the thioether, as for **7**. Subsequent

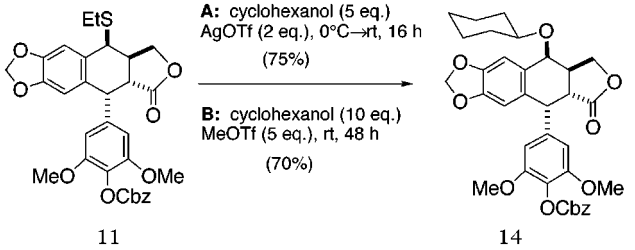
Scheme 2. Installation of the Epipodophyllotoxin C_4-Sulfide, Sulfoxide, or Sulfone



controlled oxidation provided either the corresponding sulfoxide(s) (**12**) or sulfone (**13**). A 10:1 ratio of readily separable diastereomeric sulfoxides was obtained. The pure major diastereomer was carried on for lignan conjugate synthesis.

Whereas initial attempts to activate **11** with NBS, $SnCl_4$, or $Hg(CN)_2$ led largely to decomposition products, activation with AgOTf or MeOTf was quite successful (Scheme 3).

Scheme 3. Use of an Epipodophyllotoxin C_4-Thioether for Lignan Conjugation



With cyclohexanol as intercepting nucleophile, the lignan conjugate **14** was obtained in good yields and with complete control of stereochemistry (exclusively C_4-*S*). The stereochemical outcome is certainly suggestive of an S_N1-like process, though in both cases, effective conversion requires warming to room temperature.

These observations provided the first evidence that a sulfur-based reverse glycosylation strategy would be feasible in the epopodophyllotoxin family. We next turned our attention to sulfoxide **12**, anticipating that activation might be more efficiently achieved in this system. After all, **12** may be viewed as a doubly vinylogous analogue of an anomeric sulfoxide. And Kahne has nicely demonstrated that highly reactive glycosyl donors are obtained upon treatment of *anomeric sulfoxides* with triflic anhydride.[15,16] More recently, Gin has shown that placement of the sulfoxide functionality *in solution*, can also lead to a reactive glycosylating species, in the presence of an unprotected anomeric hydroxyl or a glycal, upon addition of triflic anhydride.[17]

We present here, to our knowledge, the first example of the third logical variant of the Kahne-type activation

(5) 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*, 2809−2814.

(6) Zhang, Y.-L.; Tropsha, A.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **1994**, 37, 1460−1464.

(7) Huang, T.-S.; Lee, C.-C.; Chao, Y.; Shu, C.-H.; Chen, L.-T.; Chen, L.-L.; Chen, M.-H.; Yuan, C.-C.; Whang-Peng, J. *Pharm. Res.* **1999**, *16*, 997−1002.

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(9) (a) Loike, J. D.; Horwitz, S. B. *Biochemistry* **1976**, *15*, 5443−5448. (b) Long, B. H.; Musial, S. T.; Brattain, M. G. *Biochemistry* **1984**, *23*, 1183−1188.

(10) Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1968**, *51*, 163−168.

(11) For an alternative glycosylation of (epi)podophyllotoxin, in which a glucosyl phosphinimidate or phosphate serves as glycosyl donor, see: Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1991**, *32*, 1653−1654.

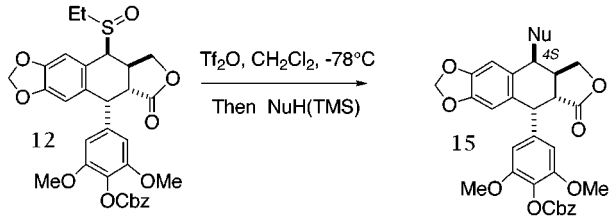
(12) (a) Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1968**, *51*, 1631−1640. (b) Kolar, C.; Moldenhauer, H.; Kneissl, G. *J. Carbohydr. Chem.* **1990**, 571−583. (c) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M.; Macdonald, P. *Tetrahedron Lett.* **1992**, *33*, 4831−4834.

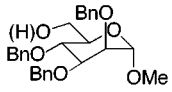
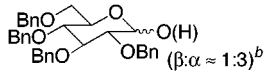
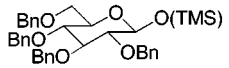
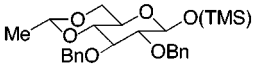
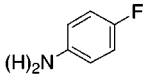
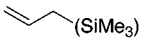
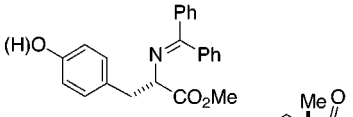
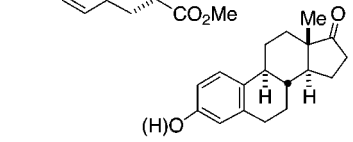
(13) (a) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Bigatti, E.; Macdonald, P. *J. Org. Chem.* **1993**, *58*, 4175−4178. (b) Vogel, K.; Sterling, J.; Herzig, Y.; Nudelman, A. *Tetrahedron* **1996**, *52*, 3049−3056. (c) Daley, L.; Guminski, Y.; Demerseman, P.; Kruczynski, A.; Etievant, C.; Imbert, T.; Hill, B. T.; Monneret, C. *J. Med. Chem.* **1998**, *41*, 4475−4485.

(14) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183−184.

chemistry; namely *placement of the sulfoxide on the aglycon*. Thus, exposure of **12** to triflic anhydride and an appropriate O-, N-, or C-nucleophile provides efficient access to the corresponding lignan conjugate (Table 1). This new procedure offers a convenient, lower temperature alternative to the traditional Kuhn−von Wartburg glycosylation procedure.[11a]

Table 1. Sulfoxide-Mediated Aglycon Activation: Access to Novel Epipodophyllotoxin C_4-Conjugates



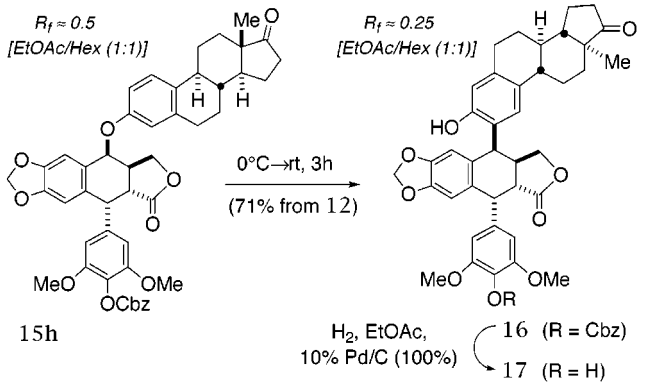
entry	NuH(TMS)	% yield[a]
a		91%
b	 (β:α ≈ 1:3)[b]	68%[c] (β:α ≈ 1:2)
c		65%[c] (β only)
d		74%[c] (β only)
e		72%[c] {2:1; (*4S*):(*4R*)}
f		85%
g		64%
h		75%

[a] All yields are for isolated, chromatographically purified compounds giving satisfactory spectral data. All reactions were run at −78 °C, for 3−4 h, unless otherwise noted. In the product structures, the atom/group in parentheses is replaced by C_4 of the aglycon. Products have the C_4-*(S)* ("epi") stereochemistry unless noted. [b] The β/α ratio here was measured in $CDCl_3$, by integration of the anomeric carbon signals. The glycosylation was run in CH_2Cl_2. [c] Reaction was run at −78 → −40 °C for 3−5 h.

With the exception of the 4-fluoroaniline case, all nucleophiles enter anti to the pseudoaxial pendant ring E, presumably via attack upon a *p*-oxygen-stabilized, C_4-carbocationic intermediate.[18] Nonetheless, entry **e** is of interest as it represents an especially mild route to NPF and related aniline conjugates. Lee has published extensively on members of this family. They are generally synthesized by incubation of the aniline with the C_4-bromide or iodide of the lignan at room temperature in the presence of anhydrous $BaCO_3$.[19]

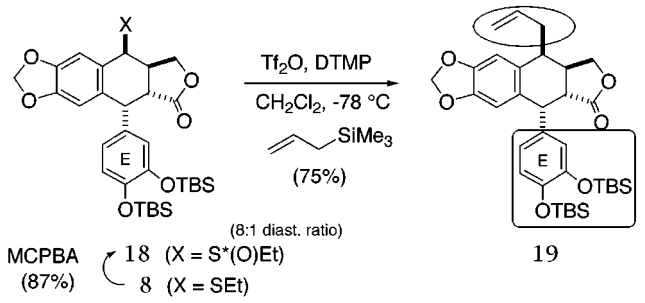
The last two entries highlight the effectiveness of this new conjugation protocol vis-à-vis phenolic nucleophiles. Thus, at −78 °C, two highly functionalized phenols, estrone and the benzophenone imine of tyrosine methyl ester, cleanly and stereoselectively couple with the lignan at C_4. Moreover, if desired, the O-linked estrone adduct may be transformed to the corresponding C-linked derivative upon warming, analogous to the known rearrangement of aryl glycosides under appropriate conditions (Scheme 4).[20]

Scheme 4. Estrone Adduct Undergoes O- to C-Rearrangement



The efficient capture of activated lignan−sulfoxide with $H_2C{=}CHCH_2TMS$ represents an alternative route into the promising TOP-53 family. Indeed, as is illustrated in Schemes 1 and 5, we now have a direct linkage between our ring E modular aglycon synthesis (which delivers C_4-*O*-SEM protected aglycons) and this new glycosylation protocol. Thus, C-linked lignan conjugate **19** (formally three steps from the actual TOP-53 analogue)[21] is available in three steps from the protected, ring E-modified aglycon (**7**) itself.

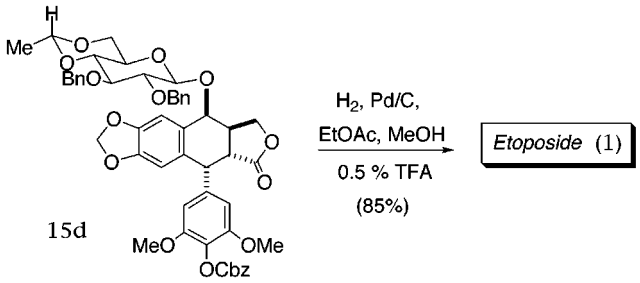
Scheme 5. Melding Unnatural "Carbohydrate Sectors" with Unnatural Rings E



(15) (a) Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 6176−6182. (b) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961−5969 (c) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239−9248. (d) Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. *Science* **1996**, *274*, 1520−1522 (e) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1992**, *114*, 4518−4529. (f) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *11*, 6881−6882.

Perhaps most importantly, entries **b**−**d** demonstrate that glycoside synthesis can be achieved with Kahne-type aglycon activation. "Armed" sugars[22] perform well as reverse glycosyl acceptors here. Moreover, anomeric O-silylation apparently serves the dual purpose of arming the sugar nucleophile and providing for control of anomeric stereochemistry (entries **c** and **d** vs **b**).[13a] Employing trimethylsilyl 4,6-*O*-ethylidene-2,3-*O*-benzyl-β-D-glycopyranoside as nucleophile, for example, provides a nicely convergent route to the etoposide family of chemotherapeutics, in good yield, and with complete control of both anomeric and C_4-stereochemistry (Table 1, entry **d**). The glycosylation product, **15d**, can then be smoothly deprotected at both the phenolic Cbz group, and the benzyl ethers, to provide etoposide itself (Scheme 6).

Scheme 6. Global Deprotection to Etoposide



The application of this new, aglycon-centered variant of the Kahne glycosylation to the synthesis of other unnatural podophyllotoxin-type lignan conjugates is currently under active investigation. Furthermore, we expect that the methodology described herein will be extendible to glycosylation/conjugation in other systems employing electron-rich aglycons.

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Supporting Information Available: Descriptions of experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For both complementary mechanistic studies and the application of Kahne glycosylation chemistry to β-mannopyranosides, see: (a) Crich, D.; Li, H. *J. Org. Chem.* **2000**, *65*, 801−805. (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(17) (a) Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204−207. (b) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515−13516. (c) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

(18) Note: In the Kahne and Gin glycosylations, potential glycosyl donors include the following: (i) an open oxocarbenium ion (refs 15a, 16c, and 17c); (ii) an anomeric triflate (ref 16c); (iii) a triflated sulfoxide (refs 15a and 16c); and (iv) an anomeric sulfenate ester (at higher temperatures; ref 15b). Though we certainly favor an S_N1-like transition state, all of the analogous, aglycon-based electrophiles are conceivable activated intermediates here.

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