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A NEW AND GENERAL GLYCOSIDATION METHOD FOR PODOPHYLLUM LIGNAN GLYCOSIDES

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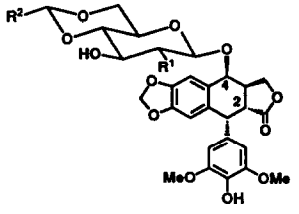
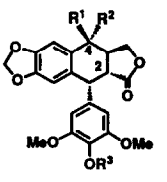
Summary: A facile and stereocontrolled construction of β-glycosidic linkages of podophyllotoxin and 4'-*O*-demethylepipodophyllotoxin D-glucosides or 4'-*O*-demethylepipodophyllotoxin 2-amino-2-deoxy-D-glucoside has been achieved by exploiting glycopyranosyl *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidate and bis(dimethylamido) phosphate as glycosyl donors, respectively.

The rational design and implementation of stereocontrolled glycosidation reactions is one of the classical topics of carbohydrate chemistry. Our efforts in this area have led to the development of new glycosyl donors incorporating diphenyl phospate, diphenylphosphinimidate, or phosphorodiamidimidothioate as leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages.[1] Along this line, we turned our attention to the glycosidation of podophyllum lignans, among a number of glycosides of which etoposide (**1**) and teniposide (**2**) have proven to be effective in the treatment of small cell lung cancer and testicular cancer, either alone or in combination of other drugs such as cisplatin,[2] and 2"-deoxy-2"-dimethylamino-etoposide (**3**)[3] in a clinical study is of great promise. Glycosidation of podophyllotoxin (**4**) and epipodophyllotoxin (**5**) has been a long-standing problem since Kuhn and von Wartburg reported that Koenigs-Knorr method and its variants proved to be less than useful.[4] Although the β-glycosidic linkages of etoposide and its analogues are constructed exclusively by Kuhn's felicitous method[5] via a stereocontrolled attack of 1-OH of glycopyranose derivatives on a common benzyl cation at C-4 generated from 4'-*O*-benzyloxycarbonyl-4'-*O*-demethylpodophyllotoxin (**6**) or the corresponding epipodophyllotoxin derivative (**7**) by use of BF_3·OEt_2, the stereochemistry of the glycosidic linkages is dependent on the anomeric configuration of the glycopyranose, and the stereoselectivity is not necessarily satisfactory even if the β-pure anomer is used. As a matter of course, the method is restricted to the glycosides of epipodophyllotoxin series.

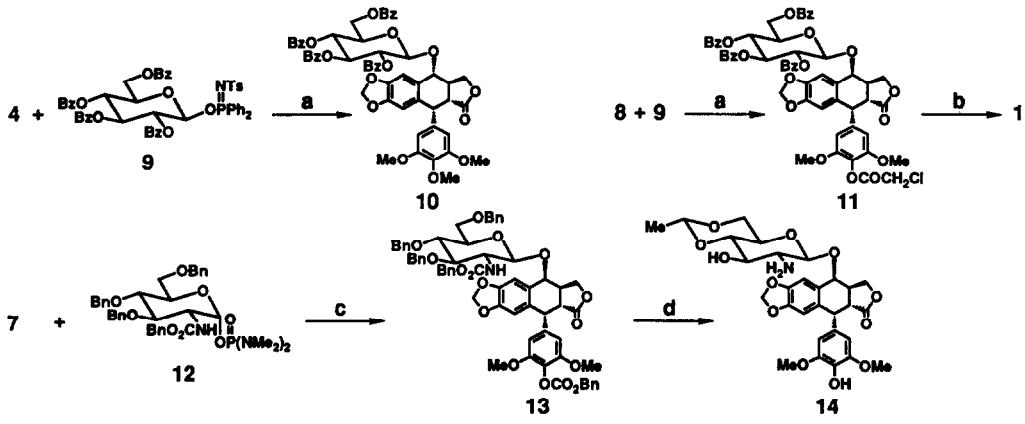
After a number of variations of substituents on the phosphorus atom of the leaving groups of glycosyl donors, we have now found that coupling of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidate (**9**)[1b] (2.0 equiv.) with podophyllotoxin (**4**) (1.0 equiv.) in dichloromethane in the presence of BF_3·OEt_2 (2.5 equiv) and 4Å molecular sieves proceeds smoothly at -5 °C within 0.5 h to give the corresponding β-glucoside **10**[6] as the sole product in 76% yield. It should be noted that no epimerization at C-4 of **4** to epipodophyllotoxin (**5**) took place under the reaction conditions. Furthermore, in spite of the poor nucleophilicity of a pseudoaxial 4-OH of 4'-*O*-demethylepipodophyllotoxin derivatives, the above protocol was



1 R^1 = OH, R^2 = Me
2 R^1 = OH, R^2 = 
3 R^1 = NMe_2, R^2 = Me



4 R^1 = H, R^2 = OH, R^3 = Me
5 R^1 = OH, R^2 = H, R^3 = Me
6 R^1 = H, R^2 = OH, R^3 = CO_2Bn
7 R^1 = OH, R^2 = H, R^3 = CO_2Bn
8 R^1 = OH, R^2 = H, R^3 = $COCH_2Cl$



(a) $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, -5 °C, 0.5 h. (b) $Zn(OAc)_2$ (15 equiv.), MeOH, sealed tube, 70 °C, 12 h; $MeCH(OEt)_2$, TsOH, MeCN, 0.5 h, 71 %. (c) $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, -8 °C, 15 min. (d) H_2, $Pd(OH)_2$/C, MeOH-AcOEt (10:1), 12 h; $MeCH(OEt)_2$, TsOH, CH_3CN, 1 h, 60 %.

also found to be applicable to the synthesis of etoposide (**1**). Thus, glycosidation of **9** (2.5 equiv.) with 4'-*O*-chloroacetyl-4'-*O*-demethylepipodophyllotoxin (**8**) (1.0 equiv.) under the foregoing conditions led to the exclusive formation of the β-glucoside **11** in 74% yield, which underwent methanolysis with zinc acetate and subsequent acetalization to give **1**. Also noteworthy is that zinc acetate[5a] proved to be the reagent of choice for clean methanolysis of even benzoate group without attendant epimerization at C-2 to the *cis*-fused lactone.[2]

On these positive results, we next focused on the synthesis of 2"-deoxy-2"-amino-etoposide (**14**),[3a] a key intermediate for the synthesis of **3** and its derivatives. An initial attempt at glycosidation with 3,4,6-tri-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl *P,P*-diphenyl-*N*-(*p*-toluenesulfonyl)phosphinimidate[7a] met with failure.[8] After considerable experimentation, however, the bis(dimethylamido)phosphate group emerged as the leaving group of choice for this aim.[9] Thus, rapid glycosidation of the phosphate **12**[7b] (1.2 equiv.) with **7** (1.0 equiv.) under the foregoing conditions afforded the corresponding β-glucoside **13** as the sole product in 74% yield, which underwent hydrogenolysis and subsequent acetalization to give **14**.

In conclusion, we have recorded the first successful glycosidation of podophyllum lignans by exploiting diphenylphosphinimidate or bis(dimethylamido)phosphate as the leaving groups of glycosyl donors.[10]

References and Notes

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3. (a) H. Saito, H. Yoshikawa, Y. Nishimura, S. Kondo, T. Takeuchi, and H. Umezawa, *Chem. Pharm. Bull.*, **34**, 3733, 3741 (1986); (b) H. Saito, Y. Nishimura, S. Kondo, and H. Umezawa, *Chem. Lett.*, **1987**, 799.
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6. All new compounds were fully characterized by ^1H NMR (400 MHz), IR, and mass spectral analysis.
7. The glycosyl donor was prepared from 3,4,6-tri-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-D-glucopyranose (T. Inazu and T. Yamanoi, *Chem. Lett.*, **1989**, 69). (a) *n*-BuLi (1.05 equiv.), THF, -78 °C; $TsN{=}P(Ph)_2Cl$[1b] (1.2 equiv.), THF, -78 °C, 0.5 h, 78%; (b) *n*-BuLi (1.05 equiv.), THF, -78 °C; $O{=}P(NMe_2)_2Cl$ (1.1 equiv.), HMPA, -10 °C, 1 h, 85%.
8. The corresponding β-anomer of higher reactivity could not be prepared.
9. Glycosidation of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl bis(dimethylamido)phosphate did not occur below -5 °C.

10. We are grateful to Nippon Kayaku Co. Ltd. for a generous gift of podophyllotoxin and 4'-*O*-demethylepipodophyllotoxin. This research was supported in part by grants from the Japan Research Foundation for Optically Active Compounds, the Japan Science Society, and the Ministry of Education, Science and Culture of Japan.

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