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# FACILE SYNTHESIS OF THIOGLUCOSE ANALOGS OF THE ANTICANCER AGENT ETOPOSIDE[1]

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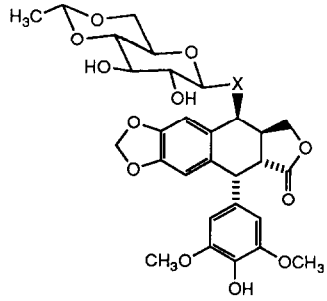
Abstract: Thioglucose-derived analogs of the clinical anticancer agent etoposide have been synthesized via a novel strategy of coupling the sugar and aglycone moieties.

Etoposide (**1**) is widely utilized clinically as a single agent in the treatment of refractory testicular cancer, and in combination for the front-line treatment of small cell lung cancer. In recent years, burgeoning interest in drugs of this class has led to the synthesis of several potentially superior congeners, including the clinical agent etopophos,[2] the clinical candidate NK-611,[3] and a number of 2-azapodophyllotoxins which await further structural elaboration.[4]

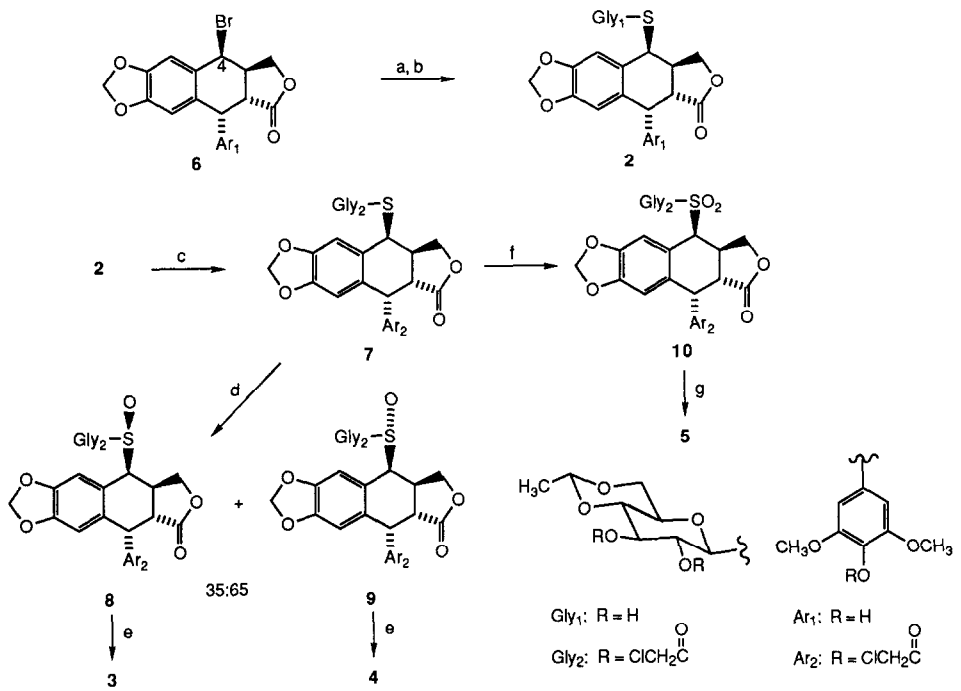


**1**, X=O, Etoposide
**2**, X=S
**3**, X=SO (*S*-isomer)
**4**, X=SO (*R*-isomer)
**5**, X=$SO_2$

In this Letter, we report on a novel strategy resulting in a short synthesis of the thioglucose congener (**2**) of etoposide, and detail further elaboration of this to the *S*- and *R*- sulfoxides (**3** and **4**, respectively) and sulfone (**5**). In these analogs, we expected that substitution of sulfur in various oxidation states for the glycosidic oxygen of etoposide would not only alter lipophilicity, but also vary the geometrical disposition of the sugar moiety about the aglycone. Such changes should markedly affect biological activity.

Our synthetic route is shown in Scheme 1. Contrary to traditional approaches in this area, we coupled the sugar and aglycone moieties via SN1 displacement chemistry on the unstable 4-bromo precursor (**6**), a strategy which obviates the use of protecting groups. Thus, reaction of **6**[5] with commercially available 1-thio-*R*-D-glucose, sodium salt, in DMF at -10° resulted in an inseparable mixture of C-4 epimeric thiosugar adducts in 80% yield and an unfavorable 1:4 ratio, suggesting a mixed SN1 and SN2 mechanism under these conditions. This ratio was improved to 1:1 when carrying out the reaction in refluxing $CH_3CN$ on the $(n\text{-}Bu)_4N^+$ salt. Complete stereoselection for the desired C-4 ß-diastereomer was achieved by utilizing a "soft" organomercaptide sugar[6] and a medium more favorable for an SN1-type process.[7] Hence, treatment of the thiosugar with n-$Bu_3SnCl$ in 2,2,2-trifluoroethanol (TFE) followed by the addition of bromo substrate (**6**) gave a single adduct that

SCHEME 1




(a) 1-Thio-*R*-D-glucose sodium salt, 1.02 eq n-$Bu_3SnCl$, 2,2,2-TFE, 25°, 2 h; add compound **6**, 25°, overnight; 56%. (b) Excess 1,1-DME, CSA, 25°, 20 h, then 4:1 HOAc:$H_2O$, 45°, 1 h; 75%. (c) Excess chloroacetyl chloride, pyridine, $CH_2Cl_2$, 0°, 1 h; 65%. (d) 1 eq MCPBA, $CH_2Cl_2$, -10°, 1.25 h, flash sg chromatography; 90%. (e) 3.2 eq $NH_2CH_2CH_2NH_2$, pyridine, 5°, 1 h; 74-77%. (f) 2 eq MCPBA, $CH_2Cl_2$, 5°, 2 h; 70%. (g) Excess $NH_2CH_2CH_2NH_2$, $CH_2Cl_2$, -78°, 3 h; 63%.

was then 4-6-*O*-ethylidenated with 1,1-dimethoxyethane to provide the thioglucose congener (**2**)[8] of etoposide in 42% yield. Other combinations of solvent (TFE or $CH_3CN$) with the stannylated or silylated derivatives, or sodium salt, of the thiosugar led in some cases to equivalent stereoselection, but in all cases to sluggish reactivity and lower yields.

The elaboration of **2** to its sulfoxide and sulfone congeners was carried out as follows: Acylation of **2** with an excess of chloroacetyl chloride at 0° gave the tris(chloroacetyl) intermediate **7** that was oxidized with one equivalent of MCPBA at -10° to give a 35:65 mixture of diastereomeric sulfoxides, **8** and **9** respectively, following flash sg chromatography. Each isomer was then treated with an excess of ethylenediamine in pyridine at 5° to afford target sulfoxides **3** and **4**, respectively. The assignment of sulfoxide stereochemistry was made by x-ray analysis of **4** (Fig. 1).[9] Similarily, treatment of **7** with an excess of MCPBA followed by ethylenediamine

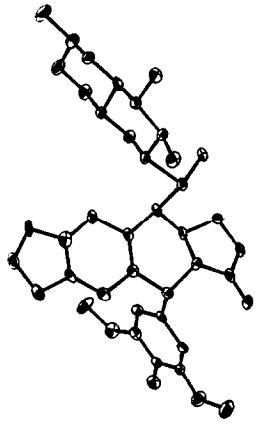


FIGURE 1. Single Crystal X-ray Structure of *R*-sulfoxide **4**

deacylation of **10** in $CH_2Cl_2$ at -78° gave the target sulfone **5**.

In summary, we have devised a simple and highly convergent route to the thioglucose analog of etoposide utilizing a novel strategy to couple sugar and aglycone moieties. The further application of this methodology to the synthesis of straight-chain ether and thioether congeners along with detailed nmr studies, molecular modeling, and biological evaluation of this class will be the subject of a future report.

## References and Notes


1. This paper is dedicated to Professor Ernest Wenkert on the occasion of his 65th birthday.

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3. Ekimoto, H.; Okamoto, K.; Nakamori, K.; Takahashi, K.; Takeuchi, T., *Proc. Am. Assoc. Cancer Res. Annu. Meet.*, **1990**, *31*, 449.

4. (a) Van der Eycken, J.; Bosmans, J.-P.; Van Haver, D.; Vandewalle, M., *Tetrahedron Lett.*, **1989**, *30*, 3873; (b) Tomioka, K.; Kubota, Y.; Koga, K., *Ibid.*, **1989**, *30*, 2953; (c) Pearce, H.L.; Bach, N.J.; Cramer, T.L., *Ibid.*, **1989**, *30*, 907.

5. We have developed a much improved process to this compound in 45% isolated yield by the addition of a controlled amount of anhydrous HBr to a 10:1 1,2-dichloroethane:ether solution of podophyllotoxin at -20°, followed by prolonged storage. Details will be reported in our full paper.

6. For the application of organotin mercaptides in SN2 processes, see Harpp, D.N.; Aida, T.; and Chan, T.H., *Tetrahedron Lett.*, **1983**, *24*, 5173, and references cited therein.

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8. All new compounds have satisfactory elemental analyses and spectroscopic data supporting their structures. (**2**): mp ~200°C; $[\alpha]_D^{23}$ = -120° (c 1.25, $CHCl_3$). (**3**): mp 173-176°C; $[\alpha]_D^{23}$ = -149°C (c 1.03, $CHCl_3$). (**4**): mp 209-212°C; $[\alpha]_D^{23}$ = -106° (c 0.995, DMF). (**5**): mp 187-189°C (d); $[\alpha]_D^{23}$ = -63° (c 0.94, DMSO). (**7**): mp 155-165°C; $[\alpha]_D^{23}$ = -66° (c 1.19, $CHCl_3$). (**8**): mp 154-158°C; $[\alpha]_D^{23}$ = -78° (c 1.08, $CHCl_3$). (**9**): mp 178-180°C; $[\alpha]_D^{23}$ = -140° (c 1.02, $CHCl_3$). (**10**): mp 208°C (d); $[\alpha]_D^{23}$ = -49° (c 1.09, $CHCl_3$).

9. All inquiries regarding x-ray data should be directed to A. Michel. Coordinates have been filed in the Cambridge Structural Database.

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