Tetrahedron Letters, Vol.32, No.47, pp 6927-6930, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A Short and Simple Synthesis of the Thioglucose Analog of the Antitumor Agent Etoposide [1]

Pietro Allevi*, Mario Anastasia, and Pierangela Ciuffreda

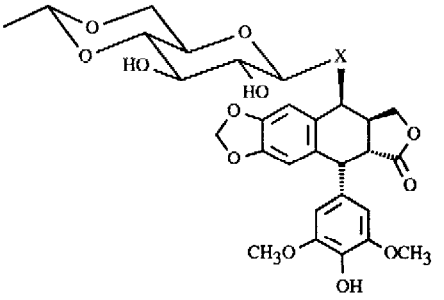
Department of Chemistry and Biochemistry, University of Milan, Via Saldini 50, I-20133 Milan, Italy

Key Words: etoposide; antitumor; anticancer; glycosilation; thioglucose

Abstract: *the thioglucose-derived analogue of the antitumor agent etoposide has been synthesized from unprotected 4'-demethylepipodophyllotoxin.*

Etoposide (**1**) is a semisynthetic podophyllotoxin derivative widely used alone [2] or in combination with other drugs[3,4]as an antitumor agent. Its clinical efficacy has stimulated the synthesis of various analogues with enhanced activity or active against etoposide-resistent tumor cells.[5]

In the course of studies aimed at the synthesis of analogues of (**1**), differing in the linkage between the sugar and the aglycone moieties, we have discovered a very simple route to the thioglucose-derived analogue (**2**).



1, X = O, Etoposide

2, X = S

3, X = SO (*R* and *S* isomers)

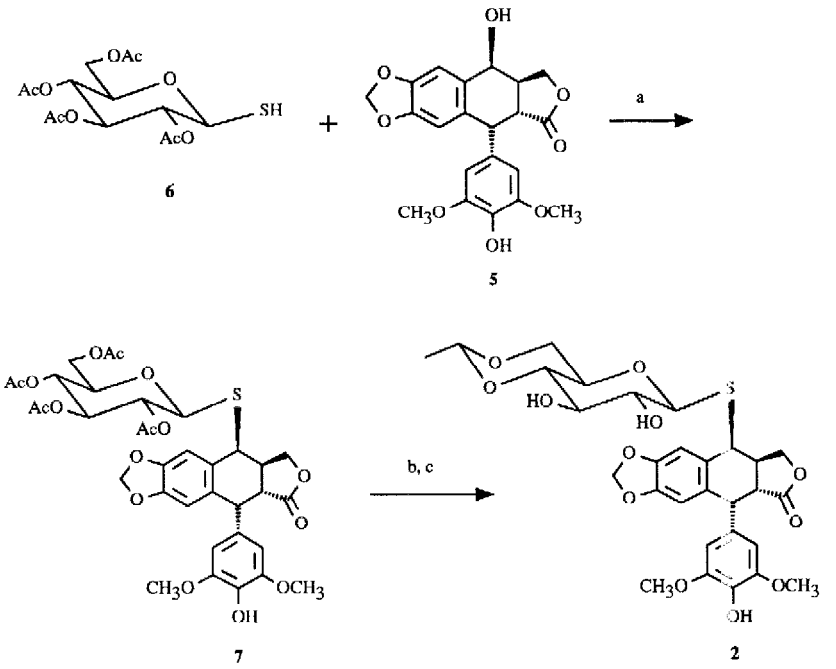
4, X = SO_2

The recent report[6] concerning the synthesis of (**2**), which turns out to be also a valuable intermediate for obtaining the oxidized sulfur compounds (**3** and **4**), prompted us to publish our results which permit the synthesis of compound (**2**) in three steps starting from commercially available 2,3,4,6-tetra-O-acetyl-1β-thio-D-glucopyranose (**6**) and 4'-demethylepipodophyllotoxin (**5**) which, under the conditions described, does not require any selective protection of the phenolic hydroxy group.

The key step for the synthesis is the simple direct glucosidation of (**5**) (1 eq) by reaction with (**6**) (1 eq) in the presence of $BF_3 . Et_2O$ (1 eq) (Scheme).

The glycosidation occurs in a short time, at room temperature and affords the C-4 β-diastereomer (7) in nearly quantitative yields (96%) and in a completely regio- and stereoselective manner.

Scheme



(a) $BF_3.Et_2O$, CH_2Cl_2 (70 ml/mmol), 25°C, 15 min; 96%. (b) 2 eq $Zn(OAc)_2$, MeOH (6 ml/mmol), reflux 40 h; 70%. (c) 21 eq $MeCH(OMe)_2$, 0.3 eq TsOH, $MeNO_2$ (12 ml/mmol), 25°C, 2 h; 68%.

The stereochemistry of compound (7) was derived from the inspection of its ^{1}H-NMR spectrum (500 MHz),[7] in particular the β-configuration at the anomeric center in a $^4C_1$ conformation of the pyranosidic ring, showed by a complete assignment of all pyranosidic proton signals, was evident from the axial-axial relationship of the anomeric proton and the adjacent glucosidic proton ($J_{1'',2''}$ 10 Hz) and the β-configuration at C-4 was derived from the value of the coupling constant (3.7 Hz) observed for H-3 and H-4 protons which are in a *cis* relationship[8] [these protons show an higher (9.0-10.0 Hz) coupling constant in the 4α configuration where are in a *trans* geometry].[8] On the other hand the observed coupling constant values of the proton at C-3 and the adjacent protons ($J_{2,3}$ 14.0 Hz, $J_{3,11a}$ 10.0 Hz, $J_{3,11b}$ 7.5 Hz) show that no epimerization of the lactonic function of (7), to afford a picropodophyllotoxin analogue, has occurred. The observed values are typical[9,10] for podophyllotoxin series and are quite different from those observed for picropodophyllotoxin ($J_{2,3}$ 9.0 Hz, $J_{3,11a}$ 6.0 Hz, $J_{3,11b}$ 1.5 Hz).

This result suggests that the condensation is a SN_1 type process that involves the attack of the glucosidic sulfur atom to the benzylic carbon ion at C-4 of the aglycone moiety generated by $BF_3 . Et_2O$. This

is remarkable since the glycosidation is performed on compound (**5**) without any protection of its phenolic hydroxy group. Previously reported glucosidations of (**5**) have always[11-13] carried out with selective protection of the phenolic hydroxy group, which on turn requires its successive regeneration.

Saponification of the acetate groups of (**7**) occurs in mild conditions without epimerization of the lactonic function and successive acetalization afford the target thioetoposide (**2**) in 45 % total yield from (**5**).

In conclusion our synthetic route to the thioanalogue of etoposide (**2**) represent the first direct regio- and stereoselective glycosidation of the podophyllum lignan 4'-demethylepipodophyllotoxin (**5**) and complements the reported[6] approach which also obviates the use of a protecting group for the phenolic hydroxy group by starting from the unstable[6] 4-bromo-4-deoxy-4'-demethylepipodophyllotoxin. Our method has the merit of a relative simplicity, almost quantitative yields in the key glycosidation, and utilizes the readily available and stable compound (**5**).[14,15]

REFERENCES AND NOTES

1. This paper is dedicated to the memory of Prof. Alberto Fiecchi.
2. For review: Jardine, I. *Podophyllotoxin in Anticancer Agents Based on Natural Products Models*, Academic Press, Inc., New York **1980**, pp. 319-351.
3. Stähelin, H.; von Wartburg, A. *Prog. Drug. Res.*, **1989**, *33*, 169-181.
4. Rose, W. C.; Basier, C. A.; Mamber, S. W.; Sauinier, M.; Casazza, A. M.; Carter, S K. *Proc. Am. Assoc. Cancer Res.* Annu. Meet., **1988**, *29*, 353.
5. Wang, Z. Q.; Kuo, Y. H.; Schnur, D.; Bowen, J. P.; Liu, S. Y.; Han, F. S.; Chang, J. Y. Cheng, Y. C.; Lee, K. H. *J. Med. Chem.*, **1990**, *33*, 2660-2666.
6. Hollis Showalter, H. D.; Winters, R. T.; Sercel, A. D.; Michal, A. *Tetrahedron Lett.*, **1991** *32*, 2849.
7. All new compounds have satisfactory elemental analyses and spectroscopic data confirming the assigned structure. (**2**): mp 180-186 °C (dec); $[\alpha]_D^{27}$ = - 114° (c 1, $CHCl_3$); ^{1}H-NMR 500 MHz, $CDCl_3$: δ 6.89 (1 H, s, H-5), 6.40 (1 H, s, H-8), 6.25 (2 H, s, H-2' and H-6'), 5.94, 5.92 (2 H, 2 x d, O-C$\underline{H}_2$-O), 5.43 (1 H, s, 4'-OH), 4.71 (1 H, q, J 4.9 Hz, CH_3-C$\underline{H}O_2$), 4.53-4.49 (3 H, overlapping, H-1", H-1 and H-11a), 4.43 (1 H, d, J 4.2 Hz, H-4), 4.12 (1 H, dd, J 6.3 and J 8.4 Hz, H-11b), 4.12 (1 H, dd, J 4.9 and J 10.5 Hz, H-6"a), 3.75 (6 H, s, 3'- and 5'-OCH_3), 3.71 (1 H, ddd, J 2.8, J 9.1, and J 9.1 Hz, H-3"), 3.51 (1 H, dd, J 10.5 and J 10.5 Hz, H-6"b), 3.42 (1 H, ddd, J 2.8, J 9.1, and J 9.1 Hz, H-2"), 3.32 (1 H, dd, J 9.1 and J 9.1 Hz, H-4"), 3.26 (1 H, ddd, J 4.9, J 9.8 and J 10.5 Hz, H-5"), 3.15-3.06 (2 H, overlapping, H-2 and H-3), 3.04 (1 H, d, J 2.8 Hz, 3"-OH), 3.02 (1 H, d, J 2.8 Hz, 2"-OH), and 1.35 (3 H, d, J 4.9 Hz, C$\underline{H}_3$CHO$_2$). (**7**): mp 140-150 °C (dec); $[\alpha]_D^{27}$ = - 70° (c 1, $CHCl_3$); ^{1}H-NMR 500 MHz, $CDCl_3$: δ 6.81 (1 H, s, H-5), 6.42 (1 H, s, H-8), 6.26 (2 H, s, H-2' and H-6'), 5.95, 5.93 (2 H, 2 x d, O-C$\underline{H}_2$-O), 5.39 (1 H, s, 4'-OH), 5.22 (1 H, dd, J 10.0 and J 10.0 Hz, H-3"), 5.03 (1 H, dd, J 10.0 and J 10.0 Hz, H-4"), 4.96 (1 H, dd, J 10.0 and J 10.0 Hz, H-2"), 4.64 (1 H, d, J 10.0 Hz, H-1"), 4.52 (1 H, d, J 5.0 Hz, H-1), 4.52 (1 H, dd, J 7.0 and J 10.0 Hz, H-11a), 4.41 (1 H, d, J 3.7 Hz, H-4), 4.24 (1 H, dd, J 7.0 and J 7.5 Hz, H-11b), 4.17 (1 H, dd, J 3.5 and J 12.5 Hz, H-6"a), 4.13 (1 H, dd, J 5.5 and J 12.5 Hz, H-6"b), 3.75 (6 H, s, 3'- and 5'-OCH_3), 3.62 (1 H, ddd, J 3.5, J 5.5, and J 10.0 Hz, H-5"), 3.11 (1 H, dddd, J 3.7, J 7.0, J 10.0, and J 14.0 Hz, H-3), 3.07 (1 H, dd, J 5.0 and J 14.0 Hz, H-2), 2.07, 2.06, 2.02 and 1.99 (12 H, 4 x s, 4 x C$\underline{H}_3$COO). Hydrolisys of (**6**) afforded the corresponding alcohol: mp 263-266 °C; $[\alpha]_D^{27}$ = - 110° (c 0.5, MeOH); ^{1}H-NMR 500 MHz, CD_3OD (structurally diagnostic signals): 4.66 (1 H, dd, J 9.0 and J 9.5 Hz, H-11a), 4.63 (1 H, d, J 3.5 Hz, H-4), 4.55 (1 H, d, J 9.5 Hz, H-1"), 4.51 (1 H, d, J 5.5 Hz, H-1), and 4.41 (1 H, dd, J 7.0 and J 9.0 Hz, H-11b).
8. Lee, K. H; Imakura, Y.; Haruna, M.; Beers, S. A.; Thurston, L. S.; Dai, H. J.; Chen, C. H.; Liu, S. Y.; cheng, Y. C. *J. Nat. Prod.*, **1989**, *52*, 606-613.

9. Jardine, I.; Strife, R. J.; Kozlowski, J. *J. Med. Chem.*, **1982**, *25*, 1077-1081.
10. Glinski, M. B.; Freed, J. C.; Durst, T. *J. Org. Chem.*, **1987**, *52*, 2749-2753.
11. Saito, I.; Njshimura, K.; Kondo, S.; Umezawa, H. *Chem. Lett.*, **1987**, pp. 799-802.
12. Thurston, L. S.; Iamakura, Y.; Haruna, M.; Li, D.; Lin, Z.; Lin, S.; Chen, Y.; Lee, K. *J. Med. Chem.*, **1989**, *32*, 604-608.
13. Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.*, **1991**, *32*, 1653-1654.
14. Kuhn, M.; Keller-Juslén, C.; von Wartburg, A. *Helv. Chim. Acta*, **1969**, *52*, 944-947
15. This work was supported by the Italian Research Council (CNR Progetto Finalizzato "Chimica Fine II" Unità Operativa N° 115.04515).

(Received in UK 12 September 1991)