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SYNTHESIS OF ETOPOSIDE LACTAM VIA A MITSUNOBU REACTION SEQUENCE

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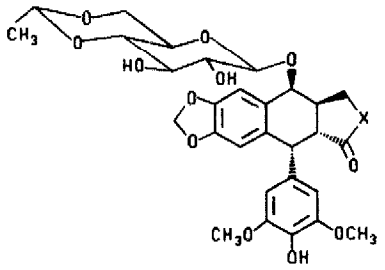
Abstract: A novel chemical sequence for the conversion of a lactone antitumor agent **1** (etoposide) to the corresponding lactam **2** is described. The key steps involve a Mitsunobu cyclization (Ph_3P, DEAD) of the γ-hydroxymethyl acyl benzaldehyde hydrazone **6** to a lactam derivative **7** followed by reductive cleavage (Ra-Ni) to lactam **2**.

Etoposide (1) is an antitumor agent which is currently in clinical use for the treatment of testicular cancer and small cell lung cancer.[1] Metabolism studies have shown that *in-vivo* the strained *trans* lactone of **1** can be hydrolyzed and epimerized to the corresponding hydroxyacid and *cis* lactone;[2] derivatives which display greatly diminished biological activity. Other D ring analogs have therefore been synthesized in an attempt to provide resistance to such deactivating processes.[3]



1, X=O, ETOPOSIDE

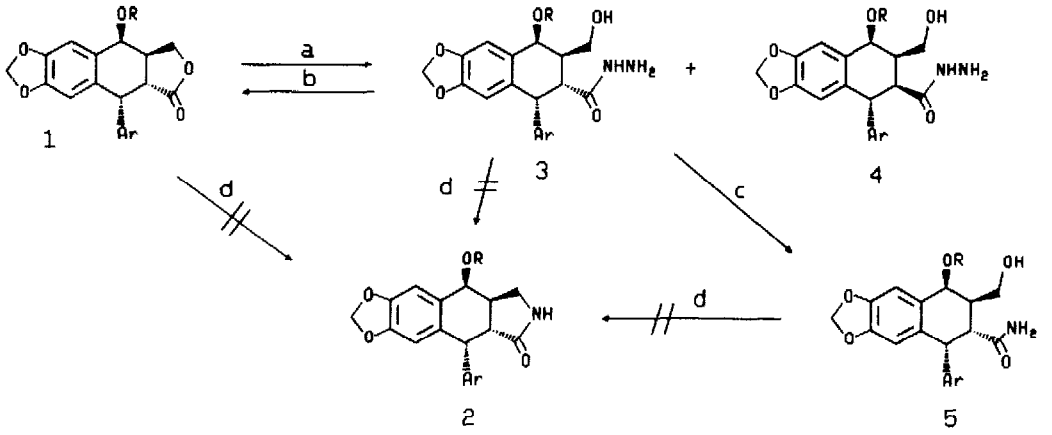
2, X=NH

In this communication, we report a mild approach to convert the readily epimerizable, *trans* lactone moiety present in the highly functionalized compound **1**, to a *trans* lactam via a sequence of reactions which should find utility in organic synthesis. We felt the lactam analog **2** would be resistant to hydrolysis and epimerization while hopefully retaining the antitumor activity of **1**.

Our initial attempts to directly convert the lactone moiety of **1** to a lactam using NH_3 and heat were unsuccessful.[4] Ring opening of **1** with either LiI or ammonia was never useful in our hands. However reaction with hydrazine in refluxing MeOH/AcOH provided a mixture of the desired *trans* hydrazide **3** (50%) along with nearly equivalent amounts of the epimerized *cis* hydrazide **4** (40%) (Scheme 1).[5] Although the two hydrazides appeared quite

amenable to chromatographic separation, cis hydrazide **4** was, fortuitously, essentially insoluble in the reaction medium and could be easily removed by filtration.[6] The trans stereochemistry of the desired hydrazide **3** was confirmed by reacting the compound with 1.1 eq. $NaNO_2$ in THF/AcOH to regenerate **1** in nearly quantitative yield (Scheme 1).[7]

SCHEME 1



R=β-D-4,6-O-ethylidene glucose. Ar= 3,5-dimethoxy-4-hydroxy phenyl
a) NH_2NH_2, AcOH, MeOH, reflux, 2h (see ref. 6). b) 1.1eq. $NaNO_2$, THF, AcOH, 2° to 25° 16h. c) Raney Nickel (W-2), EtOH, reflux. d) see text.

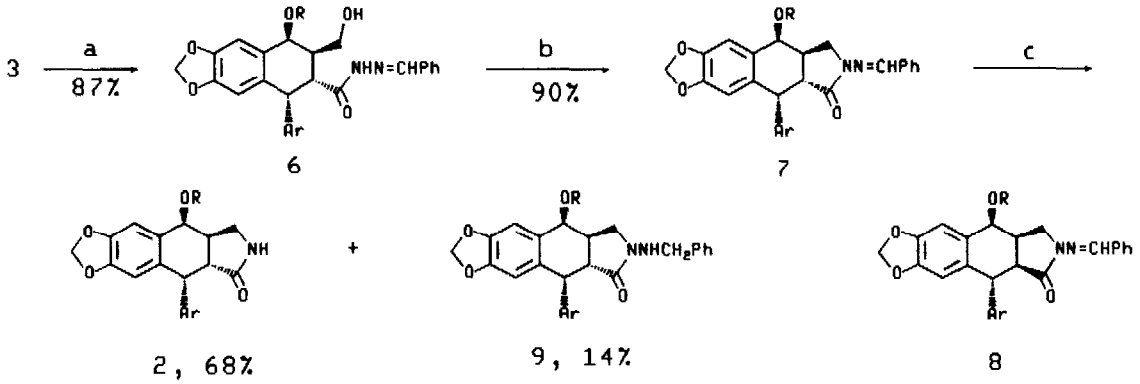
Our efforts to convert trans hydrazide **3** directly to a cyclized lactam were unsuccessful and limited by the compound's poor solubility. The corresponding trans amide **5** or fully protected counterparts also failed to provide a lactam using a variety of strategies.[8] The direct Mitsunobu reactions on either hydrazide **3** or amide **5** failed to provide the desired cyclized products.[9]

However, the earlier report of the cyclization of β-hydroxy hydroxamates used by Miller and coworkers[10] for the synthesis of β-lactam intermediates suggested that protection of the hydrazide moiety in **3** would facilitate a Mitsunobu cyclization. [To our knowledge, the preparation of five membered ring lactams via such a cyclization has not been reported.] A suspension of **3** was reacted with excess benzaldehyde in 4:1 CH_2Cl_2/MeOH at 25° to provide the trans hydroxymethyl acyl benzaldehyde hydrazone **6** in 87% yield (Scheme 2). Addition of DEAD (1.8 eq) to a THF solution (22mL/mmol substrate) of Ph_3P (3 eq) and **6** followed by stirring for 20 min at 25° provided the desired cyclized product **7** in 90% yield after aqueous workup and flash chromatographic purification. Traces of products resulting from O-cyclization could only occasionally be detected in the crude product in contrast to ketone hydrazones or amidine analogs of hydrazide **3**.[11,12]

Epimerization of **7** (KOtBu, DMF, 70°) provided the more stable cis substituted lactam **8** thereby confirming the stereochemical assignment of the cyclization product. Synthesis

of 8 from the cis hydrazide 4 using the same sequence described above for the corresponding trans hydrazide proceeds without complication in similar overall yield.

SCHEME 2



R=β-D-4,6-O-ethylidene glucose. Ar= 3,5-dimethoxy-4-hydroxy phenyl.
a) excess PhCHO, 4:1 CH_2Cl_2, 25°. b) 1.8eq. DEAD, 3eq. PPh_3, THF, 25°, 20min.
c) Raney Nickel (W-2), EtOH reflux.

Reduction of 7 in ethanol at reflux for 6 h with an excess of Raney Nickel (Aldrich, W-2), which had been previously washed with water [until the washes were no longer basic], provided a 68% yield of the target lactam analog 2 and 14% of the incompletely reduced benzyl hydrazide 10 after flash chromatography (eq.3). However, hydrogenation of 7 with 10% Pd/C in ethanol at 25° for 3h provides benzyl hydrazide 9 in 55% yield without further reduction. Subjecting 8 to the same Raney-Nickel reduction used above for 7, produces the corresponding cis lactam.

To summarize, using the sequence described above (hydrazine ring opening, Schiff base formation, cyclization, and N-N bond cleavage) the lactone moiety of etoposide has been efficiently converted to a lactam ring. Both cis and trans fused γ-lactam rings were formed with equal effectiveness from γ-hydroxymethyl acyl benzaldehyde hydrazones under Mitsunobu conditions. Work to define the generality of this sequence on unrelated substrates and the scope of this cyclization procedure is in progress. The biological activity of the compounds described herein will be reported elsewhere.

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147. d) Ref. 3b and references therein.

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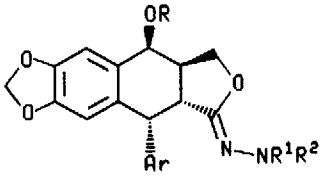
4. Anjanamurthyl, C.; Lokanantha Rai, K.M. **Ind. J. Chem.**, 1987, **26B**, 131.
5. Ring opening of a similar lignan aglycone has been reported to occur without epimerization: a) Rutschmann, J.; Renz, J. **Helv. Chim. Acta.** 1959, **42**, 890-907. b) Rutschmann, J. U.S. 2,984,674; May 16, 1961.
6. The reaction is run using the following quantities of reagent: 10g of etoposide, 100 mL of Methanol, 10 mL of hydrazine, and 10 mL of glacial acetic acid. The cis and trans hydrazides are distinct by TLC on SiO_2 using 10%MeOH/CH_2Cl_2 as eluent.
7. All new compounds have been fully characterized spectroscopically and by elemental analysis. High field ^1H and ^{13}C NMR spectra of lactam analogs corresponded well to those of the lactone series.
8. For example: heat or [TsCl,Pyr] or [$SOCl_2$/Pyr] or [Ph_3P, CCl_4] or [i) PPh_3, DEAD, $(PhO)_2PON_3$, ii) azide reduction and cyclization]. Fully or partially silyated **5** as well as carbonate derivatives were also explored without success.
9. For a review of the use of DEAD/PPh_3 see: Mitsunobu, O. **Synthesis** 1981, 1.
10. Miller, M.J. **Acc. Chem. Res.** 1986, **19**, 49; and references therein.
11. The conditions for this reaction have been determined empirically and have not been exhaustively explored. When aldehydes were used to form the Schiff bases, only traces of products tentatively identified as arising from O-cyclization have been detected. However preliminary results using ketone Schiff bases or N,N-dialkyl amidines similar to **6** have shown that appreciable amounts of stable O-cyclization products **10** may be isolated.



10

12. Since the completion of this work the synthesis of β-lactams via Mitsunobu cyclization of β-hydroxy acyl benzophenone hydrazones has been reported: Curran, W.V.; Ross, A.A; Lee, V.J. **J. of Antibiotics** 1988, **XLI**, 1419.

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