Tetrahedron Letters,Vol.30,No.8,pp 907-910,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

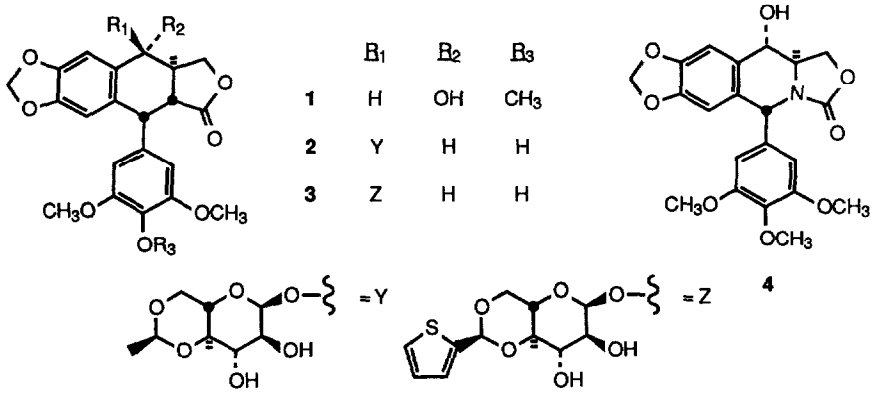
SYNTHESIS OF 2-AZAPODOPHYLLOTOXIN

H. L. Pearce*, N. J. Bach, and T. L. Cramer

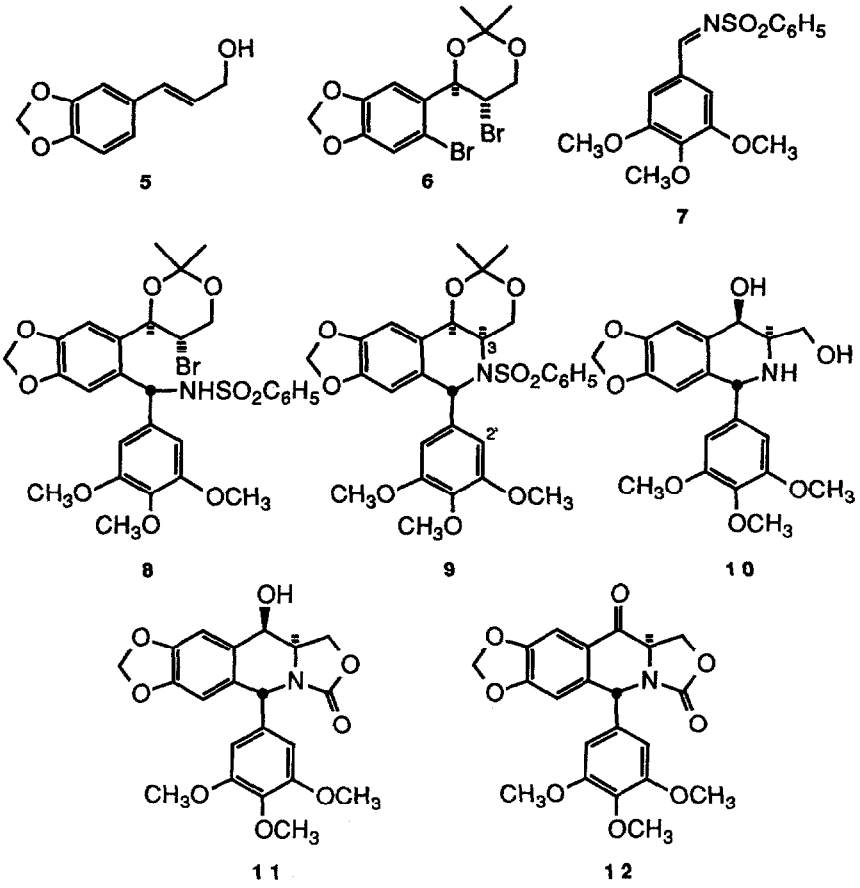
Lilly Research Laboratories
Lilly Corporate Center, Indianapolis, IN 46285

Abstract: 2-Azapodophyllotoxin was prepared by addition of an aryllithium to an appropriately substituted benzesulfonimine followed by intramolecular ring closure.

Podophyllotoxin (**1**) is the major cytotoxic constituent of several members of the plant species *Podophyllum peltatum*. The compound has attracted considerable attention as a target for total synthesis,[1] and it's biological properties have been exploited in several medicinal preparations.[2] The semisynthetic derivatives of **1**, etoposide (**2**) and teniposide (**3**), are now used in the treatment of several human tumors.[3] The clinical utility of **2** and **3** may be compromised by the highly reactive nature of the trans-fused γ-lactone moiety present in these compounds since the products of epimerization at C-2 and/or hydrolysis of the lactone ring have been identified as circulating metabolites in man and are devoid of antitumor (or cytotoxic) activity.[4] We reasoned that 2-azapodophyllotoxin (**4**) would be an interesting target for synthesis since the oxazolidone moiety present in parallel derivatives would be considerably more stable to hydrolytic cleavage and immune to epimerization. A detailed molecular mechanics analysis of **4** predicted a high degree of structural commonality with **1** suggesting that the space filling properties of **4** and its derivatives would be inherently similar to those of **1**, **2**, or **3**. This report details a stereocontrolled synthesis of 2-azapodophyllotoxin (**4**), a stable analog of podophyllotoxin (**1**).



Reaction of 3-(4,5-methylenedioxyphenyl)propenol[5] (**5**) with aqueous pyridinium bromide perbromide in dioxane for 3 days gave an intermediate dibromodiol (>95% threo) which was converted to the corresponding ketal **6** on exposure to dimethoxypropane and ρ-toluenesulfonic acid in dichloromethane at 23° for 24 hr in 55% overall yield. The assignment of *trans-*



5 **6** **7**

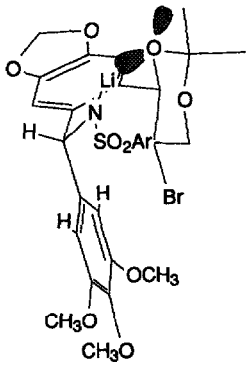
8 **9** **10**

11 **12**

stereochemistry in **6** is based on an observed J_H = 9.5 Hz for the vicinal methine protons (compared to a calculated[5] J_H = 10.0 Hz for the expected chair conformation of this structure).

Treatment of **6** with 1.0 equiv of n-butyllithium in THF at -75° for 10 min followed by the addition of 3,4,5-trimethoxyphenilidinbenzenesulfonimide[7] (**7**) afforded the sulfonamide **8** in 80% yield. Reaction of **8** with sodium hydride in DMF at 0° gave the tetrahydroisoquinoline derivative **9** as the major product of an 85:15 mixture of stereoisomers at C-1 in 78% yield. Alternatively, *in situ* treatment of the reaction product (**8**) with 2.0 equiv of HMPA followed by warming to 0° and reaction for 24 hr gave **9** directly in 71% overall yield. The relative stereochemistry of **9** was determined by pmr analysis (observation of a positive NOE between H-3 and H-2') and by X-ray diffraction analysis. This interesting reaction has been used to prepare simple 1-substituted

dihydroisoquinolines,[8] however this is the first example that produces a highly substituted ring system with control of relative stereochemistry. The stereochemical course of this tandem nucleophilic addition-cyclization strategy can be understood on the basis of aryllithium addition to the face of the sulfonylimine - as a consequence of the least congested transition state - followed by internal Sn2 displacement of bromide from the intermediate in which the lithiated sulfonimide is stabilizied by internal chelation with the dioxolane oxygen (**Figure**).



Figure

Consecutive removal of the benzene sulfonamide function in **9** and hydrolysis of the dimethylketal was accomplished by treatment with sodium napthalenide/dimethoxyethane[9] in THF at -75° for 10 min and hydrolysis with 2N HCl in aqueous dioxane at 23° for 3 hr respectively to give the amino-diol **10** in 61% overall yield. Conversion of **10** to 4-epi-2-azapodophyllotoxin (**11**) was accomplished by treatment of **8** with phosgene/pyridine in dichloromethane at 0° for 4 hr in 75% yield. Inversion of C-4 stereochemistry in **11** was accomplished in the following fashion: oxidation of **11** with pyridinium chlorochromate in dichloromethane at 23° for 4 hr gave 4-keto-2-azapodophyllotoxin (**12**), which on reaction with lithium tri-t-butyloxyaluminum hydride in THF at 23° for 10 min gave 2-azapodophyllotoxin (**4**) in 65% overall yield.

We have subsequently shown that **11** is a useful substrate for the synthesis of 4-epi-O-glycosidic-2-azapodophyllotoxins. The details of this chemistry and the biological activity of the azapodophyllotoxins and related derivatives will be reported in forthcoming articles.

Acknowledgements: The authors wish to thank Messrs. Tom Elsey and Jon Pascal for their assistance in nmr spectroscopy; Dr. Noel Jones and Mr. John Schwartzendruber for X-ray diffraction analysis; and Profs. D. A. Evans and P. L. Fuchs for many helpful discussions.

References and Notes

1. (a) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004-8. (b) Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826-8. (c) Van der Eycken J.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871-4. (d) Macdonald D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749-50. (e) Van der Eycken J.; De Clercq, P.; Vandewalle, M. *Tetrahedron.* **1986**, *42*, 4297-308. (f) Jung, M. E.; Lowen, G. T. *Tetrahedron Lett.* **1986**, *27*, 5319-22. (g) Kaneko T.; Wong H. *Tetrahedron Lett.* **1987**, *28*, 517-20.

2. Kelly, M. G.; Hartwell, J. L. *J. Natl. Cancer Inst.* **1954**, *14*, 967.

3. (a) Arnold A. M.; Whitehouse, J. M. A. *The Lancet* **1981**, 912-915. (b) Arnold, A. M. *Cancer Chemother. Pharmacol.* **1979**, *3*, 71-80. (c) O'Dwyer, P. J.; Alonso, M. T.; Leyland-Jones, B.; Marsoni, S. *Cancer Treatment Reports* **1984**, *68*, 1455-1466. (d) Macbeth, F. R. *Cancer Chemother. Pharmacol.* **1982**, *7*, 87-91.

4. Evans, W. E.; Sinkule, J. A.; Horvath, A.; Crom, W. R.; Dow, L. W.; Rivera, G. *Proc. Am. Assoc. Cancer Res.* **1981**, 690.

5. Freudenberg, K.; Heel, W. *Chem. Ber.* **1953**, *86*, 190-196.

6. Proton-proton coupling constants were calculated for structures generated by the molecular modeling program MacroModel (W. C. Still, Columbia University, New York, NY) using the algorithm developed by Altona (Haasnoot C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron*, **1980**, *36*, 2783-2791.

7. Reaction of 3,4,5-trimethoxybenzaldehyde dimethylketal with benzenesulfonamide at 170° for 30 min gave the sufonimine which was recrystallizied from toluene (m.p. 130-5°). See: Albrecht, R.; Kresze, G.; Mlakar, B. *Ber.* **1964**, *97*, 483-489.

8. (a) Jakiela, D. J.; Helquist, P.; Jones, L. D. *Org. Synth.* **1984**, *62*, 74-85. (b) Hergrueter, C. A.; Brewer, P. D.; Tagat, T.; Helquist, P. Tetrahedron Lett. **1977**, 4145-82.

9. (a) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311-5312. (b) Closson, W. D.; Ji, S.; Schulerberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650-657.

(Received in USA 14 September 1988)