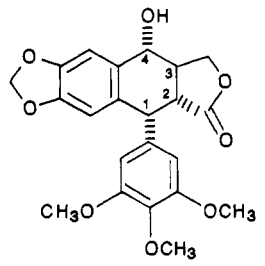
A Highly Stereoselective Diels-Alder Based Synthesis of (±)-Podophyllotoxin

Summary: A highly stereoselective synthesis of (±)-podophyllotoxin is described. The correct relative stereochemistry of the four chiral centers in podophyllotoxin is produced via an intramolecular Diels–Alder reaction involving an *o*-quinodimethane, generated by the opening of a *trans*-2-arylbenzocyclobutenol derivative.

Sir: Popdophyllotoxin (**1**) is the aglycone from which the clinically important anticancer drugs Etoposide (VP-16) and Teniposide (VM-26) are produced.[1] Several syntheses of **1** have been reported,[2-5] but only two[4,5] occur via a route that does not involve epimerization of thermodynamically more stable picropodophyllotoxin (**2**) to **1**, via kinetic protonation of ester enolates of **2**.[2,3] Rajapaska and Rodrigo prepared (±)-neopodophyllotoxin (**3**), which has the same relative stereochemistry as **1** via a very efficient sequence; **3** had previously been converted to **1**.[6]



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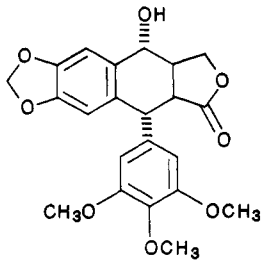

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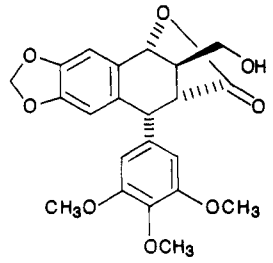

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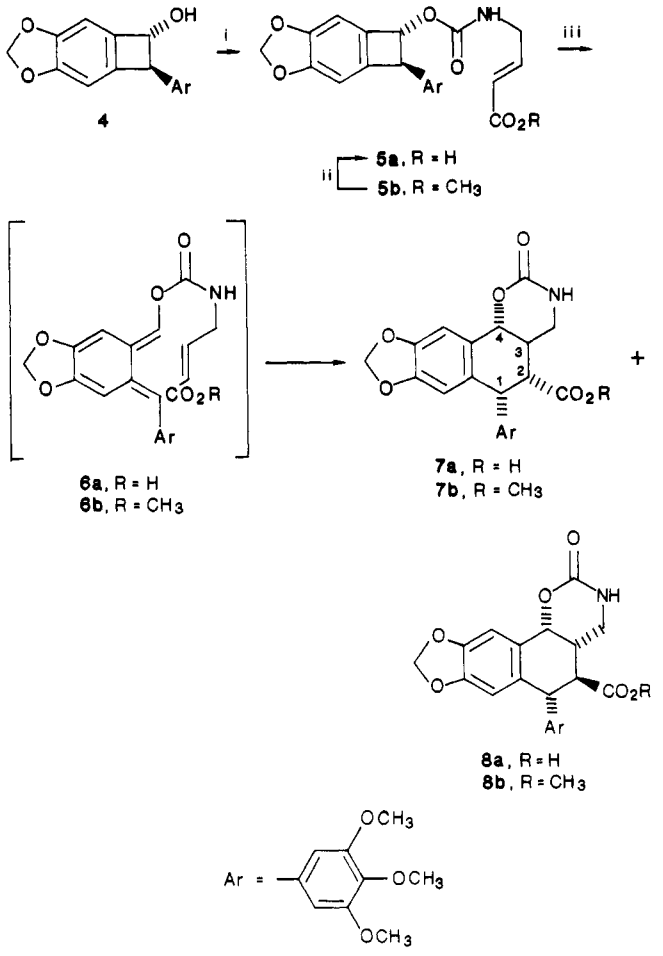
We have recently completed the first synthesis of several *trans*-2-arylbenzocyclobuten-1-ols, e.g., **4**[7] with the purpose of utilizing these compounds as intermediates in a stereocontrolled synthesis of **1** and derivatives according to Scheme I. The key feature of this approach[8] is that thermal conrotatory opening of the *trans*-2-aryl-benzocyclobutenol derivative **5** would generate the (*E,E*)-diene **6** which, upon intramolecular trapping, should furnish preferentially the trans-fused tricyclic compound **7**[9] in which all of the required relative stereochemistry of **1** has been established (Scheme I). We would like to report the successful completion of a synthesis of **1** based on this

Scheme I



[a] Reagents: (i) **9**, Ph_3SnOAc, CH_2Cl_2, 0–25 °C; (ii) LiOH/THF/H_2O; (iii) CH_3NO_2, 80–90 °C.

approach. The intramolecular approach is required since intermolecular trapping of suitably substituted *o*-quinodimethanes generates tetrahydronaphthalenes in which the substituents have the relative stereochemistry found in epiisopodophyllotoxin.[10]

The very labile character of **4**,[7] especially toward mildly basic conditions dictated that the connection between **4** and a crotonic ester to build **5** be made under essentially neutral conditions. It removed the possibility of using a carbonate (NH=O in **5a**) as the bridging group in **5a**[8] since the assembly of an unsymmetrical carbonate requires basic catalysis. In the event we decided to connect **4** with the required *trans*-crotyl ester moiety utilizing a urethane function. Thus the isocyanate **9**,[11] prepared by reacting methyl *trans*-4-aminocrotonate[12] with $COCl_2$ in refluxing toluene, was reacted with **4** in CH_2Cl_2 at 0–25 °C by using Ph_3SnOAc[13] as catalyst to afford the urethane **5b** in 47% yield from the acetate of **4**.[14]

The methyl ester **5b**[15] was hydrolyzed in 0.2 M aqueous LiOH/THF (1:4) at 25 °C for 4 h to give the acid **5a** in

(1) Jardine, I. *Anticancer Agents Based on Natural Product Models*; Academic: New York, 1980, pp 319–351.
(2) (a) Gensler, W. J.; Gatsonis, C. *J. Org. Chem.* **1966**, *31*, 4004. (b) Gensler, W. J.; Wang, S. Y. *J. Am. Chem. Soc.* **1954**, *76*, 5890. (c) Gensler, W. J.; Samour, S. M.; Wang, S. Y. *J. Am. Chem. Soc.* **1954**, *76*, 315.
(3) Kende, A. A.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082.
(4) Rajapaska, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208.
(5) Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871.
(6) Renz, J.; Kuhn, M.; von Wartburg, A. *Justus Liebigs Ann. Chem.* **1965**, *681*, 207.
(7) Macdonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235.
(8) This conceptual approach has previously been recognized. (a) Glinski, M. B. Ph.D. Thesis, University of Ottawa, 1982. (b) Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087.
(9) See footnote 14, ref 8b.
(10) Khan, Z.; Durst, T. *Can. J. Chem.*, in press.
(11) Compound **9**, bp 65 °C (0.075 mm) showed the expected M^+ = 141: IR 2257 (vs), 1725 (s) cm^{-1}; ^1H NMR δ 3.74 (s, 3 H), 4.13 (dd, *J* = 4.3, 2.1 Hz, 2 H), 6.10 (dt, J = 15.4, 2.1 Hz, 1 H), 6.88 (dt, *J* = 15.4, 4.3 Hz, 1 H).
(12) (a) Pinza, M.; Pifferi, G. *J. Pharm. Sci.* **1978**, *67*, 120. (b) Brehm, L.; Jacobsen, P.; Johansen, J. S.; Krogsgaard-Larson, P. *J. Chem. Soc., Perkin Trans 1* **1983**, 1459.
(13) Ozaki, J. *Chem. Rev.* **1972**, *72*, 457.
(14) The alcohol **4** was stored as its stable acetate and prepared immediately prior to use.[7] The formation of **5b** is accompanied by ring opening to 2-(3,4,5-trimethoxybenzyl)-4,5-(methylenedioxy)benzaldehyde.

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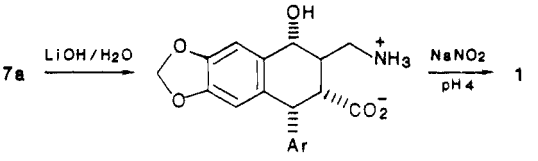
82% yield. Hydrolysis of **5b** to **5a** prior to thermolysis was necessary since methyl ester hydrolysis of the tricyclic ester **7b** was accompanied by up to 50% epimerization at C-2. The acid **5a**, when heated in nitromethane at 80–90 °C for 5 h underwent the expected cyclobutene ring opening followed by an intramolecular Diels–Alder reaction to afford a 5:1 mixture of tricyclic acids **7a** and **8a**. These intermediates were fully characterized as their methyl esters **7b**[16] and **8b**, obtained by treating the crude thermolysis mixture with CH_2N_2. The same esters were found in a 2:1 ratio upon heating **5b** in nitromethane. Thermolysis of **5a** followed by esterification of **7a** (CH_2N_2) gave **7b** in an isolated yield of 50% (twice recrystallized), indicating that the yield of the desired acid **7a** from **5a** was greater than 50%.

The stereochemical assignment of **7b** was based on several key vicinal coupling constants, a comparison with those in **8b**, and the eventual conversion of the precursor acid **7a** into podophyllotoxin. In particular, **7b** showed doublets at δ 5.05 (J = 9.9 Hz) and 4.44 (J = 6.0 Hz) due to H_4 and H_1, respectively consistent with trans-3,4 and cis-1,2 stereochemical relationships. In contrast, for **8b**, H_4 was found at δ 5.28 (J = 2.7 Hz) and H_1 at δ 4.14 (J = 11.5 Hz), indicating a cis arrangement for H_3,H_4 and a trans relationship for H_1,H_2.

Hydrolysis of the urethane **7a** with 0.1 M LiOH in H_2O at 100 °C for 0.5 h afforded the amino acid **10**, which was not characterized but diazotized with $NaNO_2$[17] at pH 4 ($H_2PO_4^-$/HCl) to give directly (±)-podophyllotoxin, mp 236–237 °C.[18]



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The conversion of methyl ester **5b** to podophyllotoxin was carried out more efficiently without isolation or purification of the various intermediates. Thus **5b** was initially hydrolyzed to **5a** as described. This acid, obtained after acidification of the reaction mixture and extraction with ethyl acetate was then dissolved in nitromethane and heated for 5 h at 80–90 °C; the solvent was removed under reduced pressure to give crude **7a** + **8a**. Further hydrolysis gave the amino acid **10**, which was diazotized to yield **1**.[19] The yield of **1** from **5b** after chromatography was 23%. Thus (±)-podophyllotoxin has been synthesized in six steps from *trans*-2-(3,4,5-trimethoxyphenyl)-4,5-(methylenedioxy)benzocyclobutyl acetate in 11%, nonoptimized, yield.

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Registry No. (±)-**1**, 77519-37-0; **4**, 104715-43-7; **5a**, 104715-45-9; **5b**, 104715-44-8; **7a**, 104715-46-0; **7b**, 104715-47-1; **8a**, 104759-82-2; **8b**, 104759-83-3; **9**, 104715-42-6; **10**, 104715-48-2; methyl *trans*-4-aminocrotonate, 99281-87-5.

(15) **5b**: ^{1}H NMR δ 3.72 (s, 3 H), 3.80 (s, 6 H), 3.81 (s, 3 H), 4.00 (m, 2 H), 4.36 (t, J = 0.6 Hz, 1 H), 4.90 (m, 1 H), 5.47 (d, J = 0.6 Hz, 1 H), 5.93 (d, J = 1.3 Hz, 1 H), 5.95 (d, J = 1.3 Hz, 1 H), 5.96 (dt, J = 15.9, 1.9 Hz, 1 H), 6.45 (s, 2 H), 6.70 (s, 1 H), 6.85 (s, 1 H), 6.92 (dt, J = 15.9, 4.6 Hz, 1 H).

(16) **7b**: ^{1}H NMR δ 2.64 (m, 1 H), 3.03 (m, 2 H), 3.56 (s, 3 H), 3.72 (s, 6 H), 3.78 (s, 3 H), 4.44 (d, J = 6.0 Hz, 1 H), 5.05 (d, J = 9.9 Hz, 1 H), 5.14 (m, 1 H), 5.92 (d, J = 1.3 Hz, 1 H), 5.94 (d, J = 1.3 Hz, 1 H), 6.12 (s, 2 H), 6.37 (s, 1 H), 7.15 (s, 1 H); exact mass calcd for $C_{24}H_{25}NO_9$ m/z 471.1527, found m/z 471.1527.

(17) We would like to thank Dr. T. Doyle, Bristol Laboratories, Syracuse, NY, for a discussion regarding this procedure. (Plieninger, H.; Ege, G.; Fischer, R.; Hoffman, W. *Chem. Ber.* **1961**, *94*, 2106.)

(18) The 300-MHz ^{1}H NMR and IR spectra of our preparation were identical with those of authentic podophyllotoxin. The mp of (±)-podophyllotoxin has not been reported.

(19) Epiisopodophyllotoxion (Glinski, M. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 573) the product expected from the hydrolysis and diazotization of **8a** was not detected in the crude product.

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