Registry No. 1, 67660-23-5; 2 (R^1 = Ph; R^2 = R^3 = H), 1504-58-1; 2 (R^1 = Ph; R^2 = Ph; R^3 = H), 1817-49-8; 2 (R^1 = Ph; R^2 = Et; R^3 = H), 27975-78-6; 2 (R^1 = $PhSCH_2$; R^2 = Et; R^3 = H), 75031-46-8; 2 (R^1 = TMS; R^2 = Bu; R^3 = H), 75045-85-1; 2 (R^1 = Bu; R^2 = Ph; R^3 = Me), 18215-71-9; 2 (R^1 = Bu; R^2, R^3 = $-(CH_2)_5-$), 15332-33-9; 3 (R^1 = Ph; R^2 = R^3 = H; R^4 = Me), 22433-39-2; 3 (R^1 = Ph; R^2 = Ph; R^3 = H; R^4 = Me), 53544-89-1; 3 (R^1 = Ph; R^2 = Et; R^3 = H; R^4 = Me), 75031-47-9; 3 (R^1 = $PhSCH_2$; R^2 = Et; R^3 = H; R^4 = Bu), 75031-48-0; 3 (R^1 = TMS; R^2 = Bu; R^3 = H; R^4 = Me), 75031-49-1; 3 (R^1 = Bu; R^2 = Ph; R^3 = Me; R^4 = Me), 75031-50-4; 3 (R^1 = Bu; R^2, R^3 = $-(CH_2)_5-$; R^4 = Ph), 75031-51-5; **8a**, 67978-48-7; **8a** acetate, 75031-52-6; **8b**, 40964-63-4; (*E*)-**9a**, 56392-49-5; (*Z*)-**9a**, 56392-46-2; (*E*)-**9b**, 31552-03-1; (*Z*)-**9b**, 31552-04-2; **10a**, 59415-24-6; **10b**, 75031-53-7; CuI, 7681-65-4.

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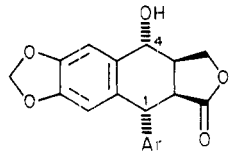
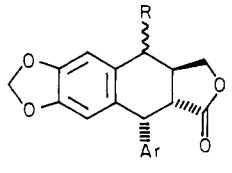
A Stereo- and Regiocontrolled Synthesis of Podophyllum Lignans

Summary: A Diels–Alder adduct of an isobenzofuran (generated in situ) and dimethyl acetylenedicarboxylate is converted by a series of controlled reductions and isomerizations to the lignans deoxy- and isodeoxypodophyllotoxin in seven stages.

Sir: The potent antimitotic activity of the *Podophyllum* lignans has been the subject of much chemical and biochemical study.[1] Structural and stereochemical parameters for the inhibition of tubulin polymerization by these compounds have been recently defined.[2] The pioneering synthetic efforts of Gensler et al. resulted[3] in a route to picropodophyllin (1) which was subsequently converted to its THP-enolate and kinetically reprotonated to podophyllotoxin (2). Subsequently, two other formal syntheses



1



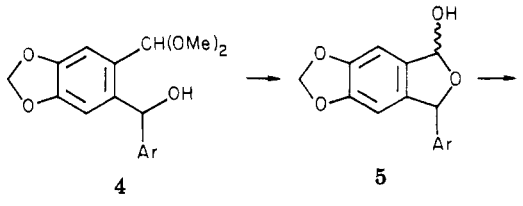
2, R = α-OH
3, R = H

Ar = 3,4,5-trimethoxyphenyl

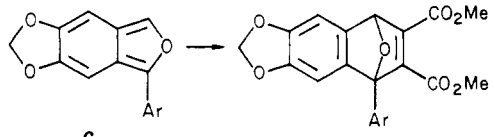
have been reported,[4] each relying ultimately on the enolate reprotonation as before. No other successful synthetic strategy has yet been demonstrated for the elaboration of the strained 1,2-*cis*,2,3-*trans* system of these compounds. This stereochemistry which is crucial to the antimitotic activity of these compounds is also the major obstacle in the way of a simple synthesis of these relatively simple molecules.

We now describe an eight-step solution to the problem and illustrate it herein with the total synthesis of the antimitotic lignan (±)-deoxypodophyllotoxin (3). In order to circumvent the problem of facile epimerization of the *cis*-1-phenyltetralin *trans*-2,3-lactones, we have selected a suitable bicyclo precursor, established the necessary 1,2,3 stereo- and regiochemistry and then generated the desired phenyltetralin system under nonbasic conditions.

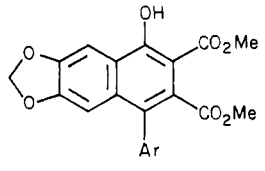
The dimethyl acetal of 6-bromopiperonal was lithiated and reacted with 3,4,5-trimethoxybenzaldehyde as before[5,6] to yield the crystalline alcohol 4. This compound upon brief treatment on a steam bath with excess dimethyl acetylenedicarboxylate and a catalytic quantity of glacial acetic acid was converted through intermediates 5 and 6 to the crystalline oxygen-bridged Diels–Alder adduct 7.[7]



4 5



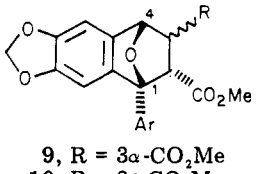
6 7



8

Ar = 3,4,5-trimethoxyphenyl

The mother liquors contained the hemiacetal 5 which was recycled without isolation in the same manner. The recycling procedure is essential, since any attempt to effect a complete conversion of 4 to 7 in one pass results in the production of substantial quantities of the isomeric naphthol 8. In this manner an overall yield of 67% was achieved. The realization of 7 in satisfactory yield was our first important goal. It provided in two steps the required carbon atoms and is our bicyclo substrate upon which a series of carefully chosen regio- and stereocontrolled transformations were carried out. Hydrogenation (H_2, Pd, ethyl acetate, 50 psi), resulted in the quantitative and exclusive formation of the endo ester 9. The stereochemical outcome of the hydrogenation was immediately



9, R = 3α-CO_2Me
10, R = 3β-CO_2Me
11, R = 3β-CH_2OH

Ar = 3,4,5-trimethoxyphenyl

(1) For reviews, see: Hartwell, J. L.; Schrecker, A. W. *Fortschr. Chem. Naturst.* **1958**, *15*, 83; Ayres, D. C. In "Chemistry of Lignans"; Rao, C. B. S., Ed.; Andhra University Press: India, 1978.
(2) Brewer, C. F.; Loike, J. D.; Horowitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215; *Cancer Res.* **1978**, *38*, 2688. Kelleher, J. K. *Cancer Treat. Rep.* **1978**, *62*, 1443.
(3) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004.
(4) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 6082. Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Chem. Commun.* **1980**, 262.
(5) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354.
(6) ^{1}H NMR spectra were determined in $CDCl_3$ at 60, 80, 220, and 360 MHz as required. Instruments operating in the FT mode were used at the last three frequencies. Melting points were determined on a Büchi SMP-20 unit and are uncorrected. Acceptable elemental analyses were obtained for all new compounds.
(7) 7: mp 159 °C; ^{1}H NMR δ 3.73 (s, 3 H), 3.77 (s, 3 H), 3.87 (s, 9 H), 5.90 (close q, 2 H), 5.95 (s, 1 H), 6.77 (s, 2 H), 6.90 (s, 2 H); IR ($CHCl_3$) $\nu_{C=O}$ 1720 cm^{-1}.

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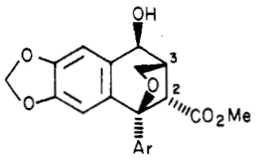
evident from the appearance of the bridgehead proton as a doublet at 5.47 ppm and from the relatively upfield position of the ester methoxyl signals at 3.53 ppm. The latter resonance confirms the shielded, endo disposition of both ester groups. Treatment of this product with sodium methoxide in methanol at room temperature for 3 h caused a smooth epimerization of the C-3 ester moiety alone, resulting in the desired, 1,2-*cis*,2,3-*trans* isomer **10**[8] in 90% yield. Again, the ^1H NMR spectrum was of diagnostic value in assigning the relative configuration. The appearance of the bridgehead proton at 5.62 ppm, now as a singlet, and the shift of one ester methoxy signal downfield to 3.77 ppm identify the site of epimerization (C-3) conclusively. The doublets at 4.07 and 3.20 ppm are assigned to protons at C-2 and C-3, respectively. We have investigated this remarkable selective epimerization by repeating the process in deuteriomethanol for varying durations. After 1 h, deuteration and epimerization at C-3 were complete, and very little deuteration at C-2 had taken place. Prolonging the reaction time for up to 8 h merely increases the extent of deuteration at C-2 but causes no other changes. The process was monitored by both ^1H NMR and mass spectrometry and a detailed account of these data will be published later. For now it will suffice to note that deuteration and epimerization at C-3 result in loss of the signal at 3.20 ppm and collapse of the doublet at 4.07 ppm to a singlet whose integrated intensity is a measure of deuteration at C-2. The all-cis 2,2,1-bicyclo system of **9** might be expected to seek relief from crowding by the formation of a thermodynamically favored all-trans epimer. The results indicate, however, that protonation of the C-2 enolate from the α face of the molecule does not take place in this system, probably because of hindrance from the trisubstituted aryl moiety at C-1.

The exo ester moiety was now selectively reduced with lithium triethylborohydride in dry tetrahydrofuran to the alcohol **11**[8] (74%). The ^1H NMR spectrum does not unambiguously define the stereochemistry at C-2. It is conceivable that the basic conditions of the reaction could have epimerized the product before workup. The configuration at C-2 was therefore established in the following manner. Brief exposure of **11** to acid produced inter alia the methyleneoxy bridged ester **12** [mp 188 °C; IR ($CHCl_3$) 3600–3400 (br), 1740 cm^{-1}]. The ^1H NMR spectrum of this compound had several broad signals associated in particular with the C_1-aryl substituent. These signals sharpened considerably at 65 °C, indicating a certain restriction in rotation about the C_1–$C_{1'}$ bond. All the other signals with the exception of the bridging methylene group were sufficiently sharp at room temperature and the following assignments (aided by a spectrum of the 3-deuterio analogue at 220 MHz and by decoupling) are pertinent: δ 5.09 (H-4, q, $J_{3,4}$ = 4.03, $J_{H,OH}$ = 6.55 Hz), 3.10 (H-3, br t when CH_2 is decoupled), 3.25 (H-2, unequal d, $J_{2,3}$ = 5.54 Hz), 2.63 (OH, d, $J_{H,OH}$ = 6.55 Hz). It follows that the molecule is correctly depicted as **12** for if the configuration at C-2 were inverted, H-2 would appear as a singlet ($\phi_{2,3} \approx 90°$). Thus the relative configuration of **11** is secure.

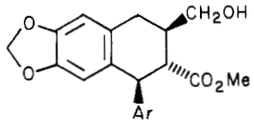
Selective hydrogenolysis of **11** achieved with Raney nickel (refluxing ethanol, 3 h, 57% yield) led to methyl epipodophyllate **13** (mp 217 °C; IR (Nujol) 3480, 3370, 1735 cm^{-1}) which was also prepared as the dideuterio hydroxymethyl analogue by using lithium triethylborodeuteride in the ester reduction. The four protons of the saturated ring B of the latter appeared at δ 4.45 (H-1, d), 3.55 (H-2, q), 2.39 (H-3, q), and 4.98 (H-4, d) (when D_2O was added). Coupling constants and assignments were confirmed by double irradiation ($J_{1,2}$ = 6.05, $J_{2,3}$ = 12.2, $J_{3,4}$ = 3.51 Hz). These values compare very favorably with the corresponding couplings for epipodophyllotoxin[2] (4.9, 13.8, and 3.0 Hz, respectively) and suggest a similar configuration and conformation for the two compounds. The Raney nickel hydrogenolysis is thus both regio- and stereoselective and proceeds with retention of configuration at C-1.



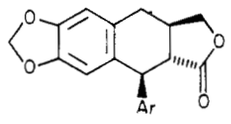
12

Ar = 3,4,5-trimethoxyphenyl

Removal of the benzylic hydroxyl group at C-4 was now accomplished by a second hydrogenolysis (Pd/acetic acid/70 psi/70% yield) and the product (**14**) was identified by the coincidence of its infrared spectrum with a published trace.[9] Lactonization of **14** to (±)-deoxypodophyllotoxin (**3**, mp 236 °C) was accomplished as previously described[9] and the C-3a dideuterio analogue was similar prepared. The infrared[9,10] and ^1H NMR spectra[2] of **3** were identical with published data for (−)-deoxypodophyllotoxin.



15



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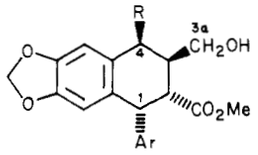

13, R = OH
14, R = H

Ar = 3,4,5-trimethoxyphenyl

Hydrogenolysis of **11** with palladium (10% Pd/C, ethyl acetate–acetic acid, 50 psi) instead of Raney nickel produced in 65% yield a 5:2 mixture of **15** and **14**. The presence of both isomers was clearly apparent in the ^1H NMR spectrum of the product at 220 MHz and H-1 of **15** was identified as a doublet at 4.20 ppm ($J_{1,2}$ = 11.5 Hz). This result is in accordance with the known[11] tendency of palladium to effect benzylic hydrogenolysis with inversion of configuration. This product was lactonized without separation of the C-1 epimers and (±)-isodeoxypodophyllotoxin (**16**) was separated by chromatography. We

(8) **10**: mp 164 °C; ^1H NMR δ 3.20 (d, 1 H, J = 4 Hz), 3.53 (s, 3 H), 3.77 (s, 3 H), 3.83 (s, 9 H), 4.07 (d, 1 H, J = 4 Hz), 5.62 (s, 1 H), 5.94 (br s, 2 H), 6.45 (s, 1 H), 6.82 (s, 1 H), 6.93 (s, 2 H); IR ($CHCl_3$) $\nu_{C=O}$ 1740 cm^{-1}. **11**: mp 160 °C; ^1H NMR δ 2.04 (t, 1 H, J = 5 Hz, removed with D_2O), 2.43 (t of d, 1 H, J = 7, 4 Hz), 3.20 (d, 1 H, J = 4 Hz), 3.55 (s, 3 H), 3.7–4.0 (2 H, obscured by ArOMe), 3.84 (s, 6 H), 3.86 (s, 3 H), 5.25 (s, 1 H), 5.7 (compact q, 2 H), 6.52 (s, 1 H), 6.80 (s, 1 H), 6.92 (s, 2 H); IR ($CHCl_3$) ν 3500 (br), 1740 cm^{-1}.

(9) Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1963**, *46*, 2127. **14**: mp 190 °C; ^1H NMR δ 6.63 (s, 1 H), 6.40 (s, 1 H), 6.14 (s, 2 H), 5.88 (s, 2 H), 4.38 (d, 1 H, $J_{1,2}$ = 5.66 Hz), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.60 (s, 3 H), 3.6–3.8 (2 H overlapped by ArOMe), 2.4–3.2 (comlex, 4 H), 1.95 (t, 1 H, J = 5.3 Hz, exchanges with D_2O).

(10) Schrecker, A. W.; Hartwell, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 5916.

(11) For a discussion of the stereochemistry of hydrogenolysis, see: Rylander, P. N. "Catalytic Hydrogenation in Organic Synthesis"; Academic Press: New York, 1979.

have observed that lactonization of the all-trans **15** is much faster than that of its C-1 epimer **14**. The melting point[12] (258 °C) and infrared spectrum[10] of **16** established its identity and the ^1H NMR spectrum at 360 MHz was identical with one previously described.[12]

The process described above is adaptable to the synthesis of (±)-deoxypodophyllotoxin deuterated (or tritiated) specifically at C-3, -3a, -5, and/or -2'(-6') as desired. 2-Deuteriopiperonal and 2(6)-deuteriotrimethoxybenzaldehyde are readily available by our acetal deprotonation procedure.[13] Such labeled analogues might be useful in metabolic studies.

The instability of podophyllic acid[14] is probably a major factor in the failure of our efforts to lactonize methyl epipodophyllate in satisfactory yield. Modifications of the synthesis designed to overcome this problem are currently being explored and will be reported later.[15]

(12) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. Brown, E.; Robin, J.-P.; Dhal, R. *J. Chem. Soc. Chem. Commun.* **1976**, 556. Decoupling experiments permitted the following additional assignments for **16**: 4.05 (d, H-1), 4.52 (q, H-3a equatorial), 3.90 (q, H-3a axial), $J_{1,2}$ = 10, $J_{3a(gem)}$ = 8, $J_{3,3a(ax\text{-}eq)}$ = 6, and $J_{3,3a(diax)}$ = 9 Hz.

(13) Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921.

(14) Renz, J.; Kuhn, M.; von Wartburg, A. *Justus Liebigs Ann. Chem.* **1965**, *681*, 207. The hydrolysis of the methyl ester moiety of **13** is unfortunately not a trivial problem. Epimerization at C-2 (base), extensive decomposition (acid), or aromatization (lithium iodide/DMF) were some of the consequences. The "unnecessary" removal of the C-4 hydroxyl group was therefore undertaken to confirm the stereochemical outcome and to gain one of the desired objectives of the synthesis, (±)-deoxypodophyllotoxin.

(15) Support of this work by the Natural Sciences and Engineering Research Council of Canada and Wilfrid Laurier University is gratefully acknowledged.

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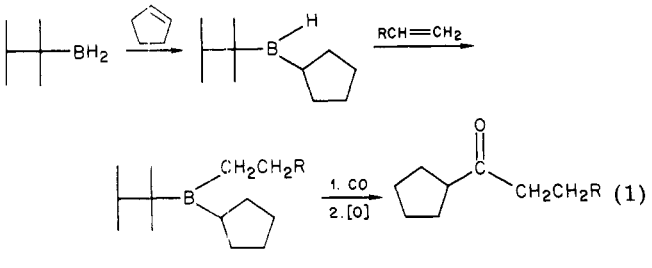
Thexylchloroborane-Methyl Sulfide. A Selective Monohydroborating Agent with Exceptional Regioselectivity

Summary: Thexylchloroborane, readily prepared from 2,3-dimethyl-2-butene and monochloroborane–methyl sulfide in dichloromethane solution, hydroborates representative alkenes with excellent regioselectivity to afford thexylalkylchloroboranes.

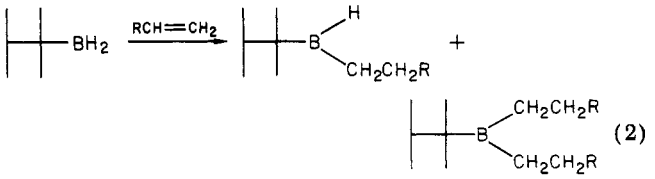
Sir: Thexylborane is an exceptionally valuable reagent which can be used to stitch two olefins together either by carbonylation or by cyanidation to form the corresponding ketone[1] (eq 1).



(1)

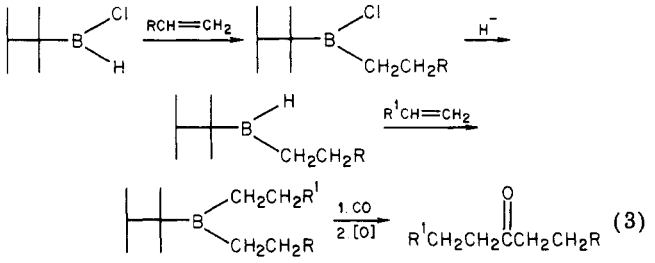
(1) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285. Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 129. For a review of application of thexylborane, see: Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77.

Unfortunately, the synthesis fails in attempting to stitch together two monosubstituted vinyl derivatives[2] (eq 2). It



(2)

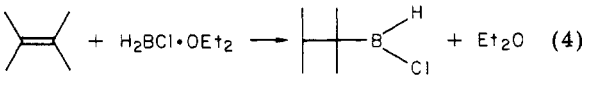
occurred to us that this problem might be solved by the use of thexylchloroborane (ThBHCl) (eq 3). However, we



(3)

encountered a number of difficulties in its synthesis and utilization. The reaction of monochloroborane–THF[3] with 2,3-dimethyl-2-butene in THF proceeds to form thexylchloroborane, stabilized as a THF adduct (ThBHCl·THF). However, the reaction of this derivative with olefins at 0 °C was sluggish and higher temperatures appeared undesirable,[4] both because of the known disproportionation in the hydroboration of olefins with monochloroborane in THF[5] and because of the facile cleavage of THF by chloroborane derivatives, such as boron trichloride[6] and dialkylchloroboranes.[7]

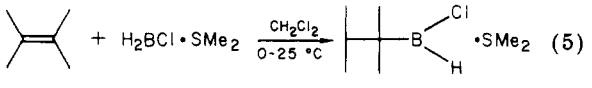
Accordingly, we undertook to synthesize thexylchloroborane in ethyl ether,[4] a solvent much more resistant to boron trichloride and dialkylchloroboranes.[5] In this solvent the initial hydroboration proceeds nicely (eq 4). However,



(4)

the subsequent hydroboration of 1-hexene with this reagent did not proceed cleanly, yielding mixtures of $ThBCl_2$, $ThBR_2$, and ThBRCl. Spectroscopic examination revealed that the reagent corresponds to a rapidly equilibrating mixture of $ThBH_2$, ThBHCl, and $ThBCl_2$.[4]

Accordingly, we shifted to the use of $H_2BCl{\cdot}SMe_2$ as the hydroborating agent.[8] Indeed, this solved the problem. The hydroboration in methylene chloride proceeded smoothly, forming 98% pure $ThBHCl{\cdot}SMe_2$ (eq 5). This



(5)

reagent is remarkably stable at room temperature and hydroborates representative olefins rapidly and cleanly to give pure thexylmonoalkylchloroborane (eq 6).

(2) Katz, J.-J. Ph.D. Thesis, Purdue University, 1974.

(3) (a) Brown, H. C.; Tierney, P. A. *J. Inorg. Nucl. Chem.* **1959**, *9*, 51. (b) Zweifel, G. *J. Organomet. Chem.* **1967**, *9*, 215. (c) Pasto, D. J.; Balasubramaniyan, P. *J. Am. Chem. Soc.* **1967**, *89*, 295.

(4) (a) Sikorski, J. A. M.S. Thesis, Purdue University, 1976. (b) However, by operating at a higher temperature, 25 °C, Zweifel and Pearson have successfully hydroborated olefins in THF with ThBHCl without concurrent attack on the solvent (*J. Am. Chem. Soc.* **1980**, *102*, 5919).

(5) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1785.

(6) Garrard, W.; Lappert, M. F. *Chem. Rev.* **1958**, *58*, 1081.

(7) Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221.

(8) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417.

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