Registry No. pCDD(99-126) (oxidized), 89213-87-6; pCDD(83-126) (oxidized), 112509-58-7; pCDD(88) (oxidized), 116887-28-6; pCDD-(99-126) (reduced), 91917-63-4; pCDD(83-126) (reduced), 116887-25-3; pCDD(88) (reduced), 116887-29-7; BOC-Asp(OcHx)-OH, 73821-95-1; BOC-Pro-Pro-OH, 15401-08-8; BOC-Arg-OH, 13726-76-6; BOC-Phe-OH, 13734-34-4; BOC-Ser-OH, 3262-72-4; BOC-Asn-OH, 7536-55-2; BOC-Cys-OH, 20887-95-0; BOC-Gly-OH, 4530-20-5; BOC-Leu-OH, 13139-15-6; BOC-Gln-OH, 13726-85-7; BOC-Ala-OH, 15761-38-3; BOC-Ile-OH, 13139-16-7; BOC-Asp-OH, 13726-67-5; BOC-Met-OH, 2488-15-5; BOC-Lys-OH, 13734-28-6; BOC-Trp-OH, 13139-14-5; BOC-Val-OH, 13734-41-3; BOC-Glu-OH, 2419-94-5; BOC-Thr-OH, 2592-18-9; BOC-Pro-OH, 15761-39-4.

Supplementary Material Available: Figures 13-18 showing elution profiles of synthetic pCDD(99-126) on Sephadex G50 fine and in HPLC, the rabbit aorta relaxant activity of purified synthetic pCDD(99-126), the gel filtration profile of synthetic pCDD 88 on Sephadex G50 fine, the elution profiles of synthetic pCDD 88 after immunoaffinity purification in HPLC, and a standard curve for pCDD 88 in two-site ELISA (4 pages). Ordering information is given on any current masthead page.

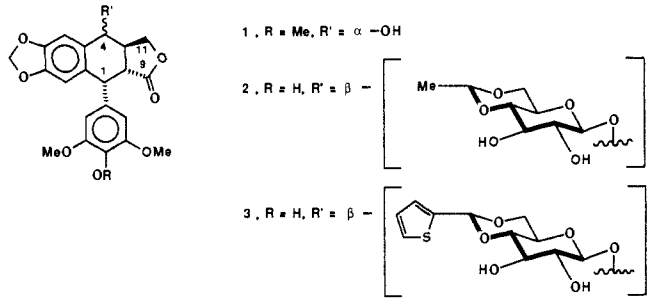
Asymmetric Total Synthesis of (-)-Podophyllotoxin†

Robert C. Andrews, Simon J. Teague, and A. I. Meyers*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received May 2, 1988. Revised Manuscript Received June 27, 1988*

Abstract: Using a diastereoselective addition of the appropriate aryllithium to a naphthalene-containing chiral oxazoline leads to advanced intermediate **11** in the podophyllotoxin series. The latter is obtained in a 92:8 de. Transformation of the oxazoline moiety to the requisite lactone **18** followed by invoking the Kende route to the target gave natural (-)-podophyllotoxin in 94% ee. The overall yield of the sequence, accomplished in 24 steps, was 5%.

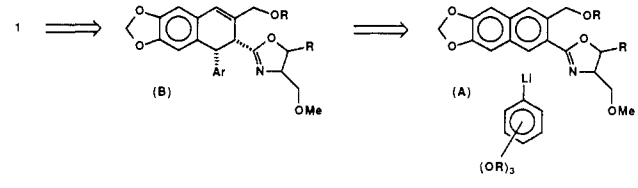
The aryltetralin lactone podophyllotoxin (**1**) occupies a unique and significant place among lignan natural products since its recognition as a potent antitumor agent when affixed to a glucopyranose moiety.[1] Thus, Etopside (**2**) and Teniposide (**3**) are



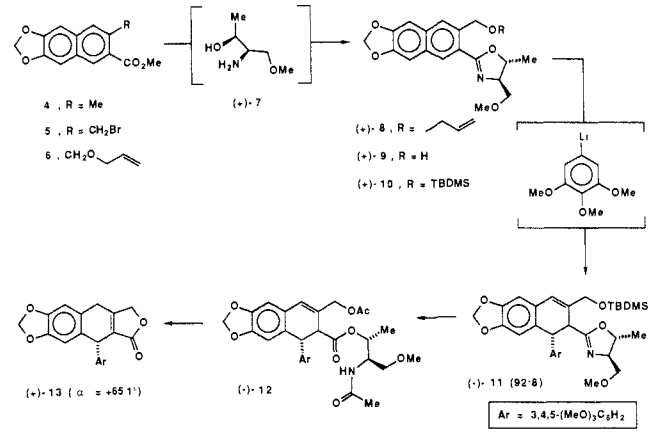
currently in the armory of antitumor drugs.[2] Although the natural podophyllin resin was used in folk medicine,[3] it was not until the 1940s that its antitumor activity was confirmed and this triggered intense studies toward synthetic routes led mainly by the late Professor Walter Gensler.[4] Gensler's contributions[4] in the 1950s and 1960s on synthetic, structural, and mechanistic aspects of podophyllotoxin provided much of the basis for the synthetic studies that followed.[5] All the reported synthetic routes to **1** produced racemic material or involved classical resolution techniques.[6] Our current studies on the asymmetric tandem addition to chiral naphthalenes[7] (Scheme I) appeared to provide a very attractive route to chiral lignans and, in particular, podophyllotoxin. Thus, diastereoselective addition of an aryllithium to an oxazoline-containing naphthalene (**A**) would, in principle, provide an adduct (**B**) that could be elaborated with the proper substituents. Removal of the chiral oxazoline in **B** would lead to (-)-podophyllotoxin (**1**).

The synthetic route originated (Scheme II) with the naphthoic ester **4**, prepared earlier in our laboratory.[8] Bromination using

Scheme I



Scheme II



NBS-AIBN (CCl_4, 70-74 °C) proceeded to give **5** (86%). The allyl ether **6** was prepared (92%, NaH, allyl alcohol) and then

† This paper is dedicated to the memory of Professor Walter J. Gensler (1917-1987).

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(2) (a) Stahelin, H. *Eur. J. Cancer* **1973**, *9*, 215. (b) Keller-juslen, C.; Kuhn, M.; von Wartburg, A.; Stahelin, H. *J. Med. Chem.* **1971**, *14*, 936.

(3) Hartwell, J. L.; Schrecker, A. W. *Fortschr. Chem. Org. Naturst.* **1958**, *15*, 83.

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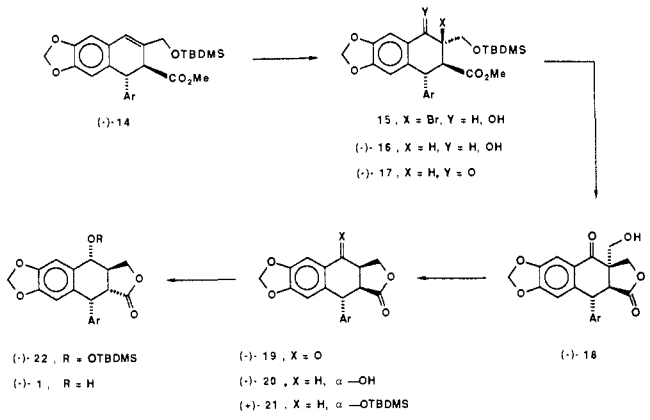
Scheme III



the ester saponified ($NaOH-H_2O$-THF). The resulting (allyloxy)naphthoic acid was treated with the methoxyamino alcohol (+)-7[9] in the presence of the $Ph_3P-CCl_4-Et_3N$ (Vorbruggen's conditions[10]), producing (+)-**8** in 80–85% yield. Removal of the allyl protecting group was accomplished by isomerization to the vinyl ether with Wilkinson's catalyst,[11] and subsequent cleavage with alkaline permanganate[12] furnished (+)-**9** (68% for both steps). The alcohol was protected[13] as its silyl ether (+)-**10** and was now in a position to be asymmetrically alkylated. The trimethoxyaryllithium (prepared from the bromide[14] by *t*-BuLi, THF, -78 °C, 25 min) was added to (+)-**10** (-40 °C, 72 h, THF) and quenched with 2-propanol, affording, after workup, (-)-**11** in 70–80% yield as a 92:8 mixture of diastereomers (HPLC and ^1H NMR). The oxazoline moiety was removed by a three-step sequence: (a) Treatment of (-)-**11** with a mixture of trifluoroacetic acid–$Na_2SO_4-H_2O$ gave an unstable ester ammonium salt.[15] (b) Acylation (Ac_2O, pyridine) produced the stable acetate–acetamide (-)-**12** in 88–90% yield. (c) Treatment with Ti(*i*-PrO)$_4$ in hot ethanol,[16] followed by oxalic acid, gave (+)-β-apopicropodophyllin (**13**) in 84% yield. Thus, two transesterifications followed by double-bond migration occurred smoothly, producing the known degradation product **13** from (-)-podophyllotoxin.[6,17] The route to (-)-**1** was continued by the sequence shown in Scheme III. Lactone **13** was smoothly transformed into ester **14** (NaOH, CH_2N_2, TBDMS-Cl, 88%) and then into the bromohydrin **15** (NBS, H_2O–THF–DMSO), which was immediately debrominated to (-)-**16** (79% AIBN, Bu_3SnH)[18] without any other products being formed. The stereochemistry at C-3 was found to be epimeric with C-3 in **1** (via spectral data), and **16** was therefore transformed into the ketone (-)-**17** (PDC, CH_2Cl_2, 87%). Unfortunately, the latter could not be successfully epimerized at C-3 to the desired stereochemistry. By the technique of Kende,[5e] formaldehyde was introduced, via an aldol reaction, and after the formaldehyde adduct was heated in ethanolic *p*-toluenesulfonic acid, lactone **18** was produced in 95% yield.[19] The asymmetric synthetic route to (-)-podophyllotoxin was completed by simply intercepting the Kende synthesis.[5f] Thermolytic extrusion of formaldehyde in **18** gave picropodophyllone (-)-**19**. Reduction with LiAl(*t*-BuO)$_3$H in THF gave picropodophyllin ((-)-**20**), which was protected as its silyl ether (+)-**21** (TBDMS-OTf, 2,6-lutidine).[21] When a solution of (+)-**21** was metalated with lithium hexamethyldisilazide in THF (-78 °C) and allowed to warm to 0 °C, recooled to -78 °C, and quenched with 4.3 M acetic acid, there was obtained a 1:1.7 mixture (70% total recovery) of (-)-**22** and (+)-**21**, respectively, each obtained pure by chromatography (silica gel, 25% ethyl acetate–hexane). Desilylation (Et_3NHF, CH_3CN)[22] of **22** gave (-)-podophyllotoxin (**1**) in 79% yield: mp 157–160 °C; $[\alpha]^{22}_D$ -85° (*c* 0.29, EtOH); 81% ee.[23] After recrystallization from CH_2Cl_2–hexane (1:5), the following data were obtained: mp 158–159.5 °C; $[\alpha]^{22}_D$ -97° (*c* 0.33, EtOH); 93–94% ee.

In summary, the first asymmetric synthesis of the lignan antitumor agent podophyllotoxin (**1**) has been achieved in 93% ee requiring 24 steps in an overall yield of 5%. This asymmetric addition to naphthalenes has been applied to other important natural products of different architecture and will be reported in due course.

Experimental Section

3-[(Allyloxy)methyl]-6,7-(methylenedioxy)-2-naphthoic Acid (6). A solution of 3.015 g (11.86 mmol) of ester **4**, 2.33 g (13.1 mmol) of *N*-bromosuccinimide, and 300 mg of azobis(isobutyronitrile) in 70 mL of carbon tetrachloride was heated under argon at 72 °C for 18.5 h. The yellow mixture was cooled to room temperature, filtered, and evaporated to give crude bromide **5**. Recrystallization of the crude product from methanol (25 mL) gave 3.381 g (85%) of bromide **5**: mp 136–137 °C; IR (KBr) ν 3010, 1718, 1450, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (s, 3 H), 5.09 (s, 2 H), 6.08 (s, 2 H), 7.08 (s, 1 H), 7.14 (s, 1 H), 7.68 (s, 1 H), 8.34 (s, 1 H).

A sample of 1.71 g (35.6 mmol) of 50% sodium hydride in oil was washed with hexane and resuspended in 100 mL of THF under argon. The mixture was chilled to 0 °C under argon as 4.03 mL (59.3 mmol) of allyl alcohol was added dropwise. After 30 min 3.35 g (10.05 mmol) of bromide **5** in 15 mL of THF was added. The mixture was stirred at room temperature for 25 h, and then 14.0 mL (70 mmol) of 5 N aqueous sodium hydroxide and 14.0 mL of water were added and the mixture was heated to reflux. After 2 h the mixture was cooled to room temperature, was diluted with 50 mL of water, and was acidified to pH 2 with 3 N hydrochloric acid. The mixture was extracted with five 100-mL portions of chloroform. Drying of the organic solutions over $MgSO_4$ and evaporation gave 2.457 g (96%) of acid **6** as a pale yellow solid: mp 124–128 °C. Further purification was not attempted: IR (KBr) ν 3300, 2900, 1680, 155, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (d, J = 6.1 Hz, 2 H), 5.00 (s, 2 H), 5.27 (d, J = 12.9 Hz, 1 H), 5.39 (d, J = 16.6 Hz, 1 H), 6.09 (br s, 3 H), 7.11 (s, 1 H, 7.17 (s, 1 H), 7.87 (s, 1 H), 8.47 (s, 1 H).

A sample of acid **6** was esterified with excess diazomethane in ether–ethyl acetate at 0 °C for 30 min. Evaporation and chromatography

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(7) (a) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592. (b) Meyers, A. I.; Barner, B.; Roth, G.; Hoyer, D.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611. A full account of the scope and limitations, complete experimental details, and mechanistic stereochemical aspects are discussed.

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(9) This was derived from *l*-threonine, through a sequence described in: Hoyer, D. Ph.D. Dissertation, Colorado State University, 1988.

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(11) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3224.

(12) Cunningham, J.; Gigg, R.; Warren, C. D. *Tetrahedron Lett.* **1964**, 1191.

(13) Silyl ethers were not useful protecting groups during the introduction of the oxazoline moiety: Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

(14) Kozak, I.; Kronrad, L.; Prochazka, M. *J. Labelled Compd. Radiopharm.* **1978**, *15*, 401.

(15) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.

(16) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.

(17) The degradation of natural (-)-**1** was carried out according to Gensler[6] and gave (+)-**13**, $[\alpha]_D$ 76.6°. When compared to synthetic (+)-**13** in this work, $[\alpha]_D$ +65.1°, the optical purity was 84–85%. This is in excellent agreement with the 84% ee obtained for **11**.

(18) Coblens, K. E.; Maralidharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041.

(19) The NMR spectrum of this material was identical with the spectrum supplied by Professor A. S. Kende. Furthermore, the Mosher ester[20] of **18** showed base-line-separated peaks for the C-11 methylene protons in the ratio of 9:1 (80% ee). The 3–4% loss in optical purity (84% ee in **13**) is presumed to have occurred in the base treatment in transforming **13** to **14**.

(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(21) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(22) Hunig, S.; Wehner, G. *Synthesis* **1975**, *1980*.

(23) Authentic podophyllotoxin recrystallized in the same manner showed the following data: mp 158.5–159.5 °C; $[\alpha]^{22}_D$ -104° (*c* 0.36, EtOH). Recycling of (+)-**22** to the mixture **21**–**22** is, of course, possible in order to maximize the yield of (-)-**1**.

on silica gel (elution with 30% ethyl acetate–hexane) gave the corresponding methyl ester: mp 76–78 °C; IR (KBr) ν 2900, 1715, 1615, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 4.16 (d, J = 5.4 Hz, 2 H), 4.97 (s, 2 H), 5.23 (dd, J = 10.2, 1.7 Hz, 1 H), 5.37 (dd, J = 17.2, 1.7 Hz, 1 H), 6.01 (s, 2 H), 6.04 (m, 1 H), 7.07 (s, 2 H), 7.84 (s, 1 H), 8.75 (s, 1 H).

(+)-2-[(4*R*,5*R*)-4-(Methoxymethyl)-5-methyl-2-oxazolinyl]-3-[(allyloxy)methyl]-6,7-(methylenedioxy)naphthalene (8). A solution of 233 mg (0.814 mmol) of acid **6** and 106 mg (0.889 mmol) of auxilliary (+)-**7** was stirred in 0.8 mL of pyridine and 0.8 mL of acetonitrile as 0.35 mL (2.49 mmol) of triethylamine and 0.25 mL (2.58 mmol) of carbon tetrachloride were added. The mixture was stirred rapidly under argon as 650 mg (2.48 mmol) of triphenylphosphine was added dropwise via syringe pump over 1.5 h as a solution in 0.8 mL of pyridine and 0.8 mL of acetonitrile. After 33 h at room temperature the volatiles were removed at 40 °C (25 Torr). The residue was dissolved in a minimum amount of chloroform and was passed through 10 g of silica gel (elution with 15% ethyl acetate–hexane followed by 30% ethyl acetate–hexane) to give 223 mg (74%) of oxazoline **8** as a viscous oil: $[\alpha]^{21}_D$ +22.7° (c 4.02, $CHCl_3$); IR (film) ν 2890, 1635, 1455, 1225 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.46 (d, J = 7.1 Hz, 3 H), 3.20 (br s, 4 H), 3.65 (dd, J = 9.6, 5.5 Hz, 1 H), 4.02 (m, 1 H), 4.13 (d, J = 6.5 Hz, 2 H), 5.21 (d, J = 8.9 Hz, 1 H), 5.34 (d, J = 17.1 Hz, 1 H), 6.02 (br s, 3 H), 7.09 (br s, 2 H), 7.82 (s, 1 H), 8.19 (s, 1 H).

(+)-2-[(4*R*,5*R*)-4-(Methoxymethyl)-5-methyl-2-oxazolinyl]-3-(hydroxymethyl)-6,7-(methylenedioxy)naphthalene (9). A solution of 1.551 g (4.198 mmol) of oxazoline **8** and 585 mg (5.21 mmol) of 1,4-diazabicyclo[2.2.2]octane in 13 mL of 1-propanol was treated with 25 mg (0.0270 mmol) of tris(triphenylphosphino)rhodium(I) chloride and was heated to reflux for 3.0 h. The mixture was evaporated to dryness under reduced pressure, and the residue was chromatographed on 25 g of silica gel (elution with 40% ethyl acetate–hexane) to give 1.507 g (97%) of the vinyl ethers (1:1 cis–trans mixture) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.45 (d, J = 6 Hz, 3 H), 1.71 and 1.58 (2 d, J = 5 Hz each, 3 H combined), 3.41 (m, 4 H), 3.70 (m, 1 H), 4.00 (m, 1 H), 4.50 (m, 1 H), 4.65 (m, 1 H), 4.90 (m, 1 H), 5.28 and 5.18 (2 s, 2 H combined), 6.04 (s, 2 H), 6.36 and 6.10 (2 d, J = 13 and 3 Hz, 1 H combined), 7.11 (s, 1 H), 7.12 (s, 1 H), 7.79 (s, 1 H), 8.21 (s, 1 H).

The vinyl ethers (1.50 g, 4.06 mmol) were stirred at room temperature in 84 mL of 5% methanolic sodium hydroxide as 90 mL of 4% aqueous potassium permanganate was added dropwise. Thin-layer chromatographic analysis (70% ethyl acetate–hexane/SiO_2) detected no starting material. The mixture was then filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 70 mL of chloroform and was washed with water, dried over $MgSO_4$ and evaporated. Chromatography of the residue on 20 g of silica gel (elution with 50% ethyl acetate–hexane) gave 910 mg (68%) of alcohol **9** as an oil: $[\alpha]^{21}_D$ +46.2° (c 3.45, $CHCl_3$); IR (film) ν 3280, 2905, 1632, 1455, 1210 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47 (d, J = 6.7 Hz, 3 H), 3.41 (s, 3 H), 3.48 (dd, J = 9.6, 6.8 Hz, 1 H), 3.68 (dd, J = 9.6, 4.8 Hz, 1 H), 4.06 (m, 1 H), 4.71 (m, 1 H), 4.77 (s, 2 H), 6.02 (s, 2 H), 6.82 (br s, 1 H), 7.04 (s, 1 H), 7.13 (s, 1 H), 7.60 (s, 1 H), 8.22 (s, 1 H).

(+)-2-[(4*R*,5*R*)-4-(Methoxymethyl)-5-methyl-2-oxazolinyl]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-6,7-(methylenedioxy)naphthalene (10). A solution of 626 mg (1.900 mmol) of alcohol **9** in 10 mL of dichloromethane was stirred at room temperature as 350 μL (2.51 mmol) of triethylamine, 85 mg of 4-(dimethylamino)pyridine, and 375 mg (2.49 mmol) of *tert*-butylchlorodimethylsilane were added. After 1 h at room temperature the mixture was diluted with 1 mL of saturated ammonium chloride and water and was extracted with two 30-mL portions of chloroform. Drying of the organic layers over $MgSO_4$ and evaporation afforded the crude silyl ether, which was chromatographed on 30 g of silica gel (elution with 30% ethyl acetate–hexane) to provide 793 mg (94%) of oxazoline **10** as an oil: $[\alpha]^{21}_D$ +16° (c 0.40, $CHCl_3$); IR (film) ν 2910, 1635, 1455 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 1.03 (s, 9 H), 1.45 (d, J = 6.8 Hz, 3 H), 3.40 (br s, 4 H), 3.65 (dd, J = 9.1, 5.3 Hz, 1 H), 4.01 (m, 1 H), 4.60 (m, 1 H), 5.16 (s, 2 H), 6.02 (s, 2 H), 7.11 (s, 2 H), 7.94 (s, 1 H), 8.10 (s, 1 H). Anal. Calcd for $C_{24}H_{33}O_5NSi$: C, 64.98, H, 7.50; N, 3.17. Found: C, 64.32; H, 7.52; N, 3.05.

(1*R*,2*S*)-1-(3,4,5-Trimethoxyphenyl)-2-[(4*R*,5*R*)-4-(methoxymethyl)-5-methyl-2-oxazolinyl]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-6,7-(methylenedioxy)-1,2-dihydronaphthalene (11). A solution of 720 mg (2.91 mmol) of 3,4,5-trimethoxy-1-bromobenzene was chilled to −78 °C in 9 mL of THF under argon. The mixture was stirred while alternately evacuating the vessel at 1 Torr and refilling with argon. After 10 such cycles 3.20 mL (5.85 mmol) of 1.83 M *tert*-butyllithium was added dropwise and the yellow mixture was stirred at −78 °C for 30 min.

A solution of 563 mg (1.27 mmol) of oxazoline **10** in 3.6 mL of THF was chilled to −78 °C and was evacuated/argon-filled in the above manner. The aryllithium reagent mixture was taken up while cold into a dry syringe and was added dropwise to the stirring oxazoline solution. After 10 min at −78 °C the greenish reaction mixture was carefully sealed, warmed to −40 °C, and stirred for 72 h.

The red mixture was quenched with 500 μL of 2-propanol, warmed to room temperature, and stirred for 6.0 h. Addition of 3 mL of saturated ammonium chloride and extraction with three 30-mL portions of chloroform were followed by drying of the organic layer over $MgSO_4$ and concentration in vacuo. Chromatography of the residue on 25 g of silica gel (elution with 40% ethyl acetate–hexane followed by 50% ethyl acetate–hexane) gave 549 mg (71%) of oxazoline **11** as an oil. Analysis by HPLC (50% ethyl acetate–hexane, 25 mm × 4.6 mm Rainin Microsorb) indicated a 92:8 diastereomer mixture that was supported by ^{1}H NMR analysis: $[\alpha]^{24}_D$ −26.2° (c 2.44, $CHCl_3$); IR (film) ν 2925, 1650, 1587, 1482, 1455 cm^{-1}; ^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.02 (2 s, 3 H each), 0.88 (s, 9 H), 1.17 (d, J = 5.8 Hz, 3 H), 3.02 (t, J = 7.8 Hz, 1 H), 3.25 (s, 3 H), 3.37 (dd, J = 7.8, 7.1 Hz, 1 H), 3.52 (d, J = 6.5 Hz, 1 H), 3.66 (m, 1 H), 3.77 (s, 6 H), 3.80 (s, 3 H), 4.21 (d, J = 14.3 Hz, 1 H), 4.32 (d, J = 14.3 Hz, 1 H), 4.38 (m, 2 H), 5.91 (s, 2 H), 6.38 (s, 2 H), 6.47 (s, 1 H), 6.54 (s, 1 H), 6.68 (s, 1 H). Anal. Calcd for $C_{33}H_{45}O_8NSi$: C, 64.78; H, 7.41; N, 2.30. Found: C, 64.32; H, 7.61; H, 2.2.

(1*R*,2*S*)-1-(3,4,5-Trimethoxyphenyl)-2-[(2*R*,3*R*)[[3-(acetylamino)-4-methoxybut-2-yl]oxy]carbonyl]-3-(acetoxymethyl)-6,7-(methylenedioxy)-1,2-dihydronaphthalene (12). A solution of 514 mg (0.840 mmol) of oxazoline **11** in 8 mL of THF was treated under argon with, in turn, 6.3 g of powdered sodium sulfate, 0.79 mL of water, and 0.32 mL (4.12 mmol) of trifluoroacetic acid. The mixture was stirred rapidly at room temperature for 5.5 h and then was treated with 1 g of anhydrous sodium sulfate. Filtration and concentration in vacuo at 30 °C gave the crude unstable salt, which without delay was diluted with 4 mL of dichloromethane and chilled to 0 °C as 0.78 mL (8.4 mmol) of acetic anhydride and 1.3 mL (16.8 mmol) of pyridine were added in turn. Stirring at 0 °C for 2 h and at room temperature for 1 h was followed by quenching with methanol, dilution with cold 1 N hydrochloric acid, and extraction with three 20-mL portions of dichloromethane. The organic phase was washed with saturated sodium bicarbonate and brine and was dried over $MgSO_4$. Concentration under reduced pressure and chromatography on 20 g of silica gel (elution with 10% 2-propanol in 50% ethyl acetate–hexane) gave 387 mg (87%) of ester **12** as an oil: $[\alpha]^{23}_D$ −145° (c 1.23, $CHCl_3$); IR (film) ν 3365, 3300, 2920, 1730, 1668, 1580, 1473, 1225 cm^{-1}; ^{1}H NMR, 270 MHz ($CDCl_3$) δ 1.13 (d, J = 6.3 Hz, 3 H), 1.91 (s, 3 H), 1.97 (s, 3 H), 3.12 (dd, J = 7.0, 12.8 Hz, 1 H), 3.26 (dd, J = 5.8, 7.0 Hz, 1 H), 3.27 (s, 3 H), 3.34 (d, J = 2.3 Hz, 1 H), 3.78 (s, 6 H), 3.79 (s, 3 H), 4.17 (m, 1 H), 4.40 (d, J = 2.3 Hz, 1 H), 5.14 (m, 1 H), 5.78 (d, J = 9.1 Hz, 1 H), 5.94 (s, 2 H), 6.32 (s, 2 H), 6.55 (s, 1 H), 6.62 (s, 1 H), 6.70 (s, 1 H).

(+)-β-Apopicropodophyllin (13). A solution of 384 mg (0.681 mmol) of ester acetate **12** was stirred under argon in 2.2 mL of absolute ethanol as 202 μL (0.682 mmol) of titanium tetraisopropoxide was added. The mixture was heated at 50 °C for 1 h and at 80 °C for 2.0 h, then was cooled to room temperature, and was treated with 2 mL of saturated aqueous oxalic acid. Extraction of the mixture with three 20-mL portions of chloroform and drying of the organic mixture over $MgSO_4$ gave a crude oil upon solvent removal. Chromatography on 20 g of silica gel (elution with 50% ethyl acetate–hexane) gave 228 mg (84%) of β-apopicropodophyllin (**13**) as a white solid, mp 208–213 °C. Further purification by recrystallization was not attempted: $[\alpha]^{23}_D$ +65.1° (c 2.72, $CHCl_3$); IR (KBr) ν 2935, 1760, 1687, 1585, 1615, 1500, 1320 cm^{-1}; ^{1}H NMR, 270 MHz ($CDCl_3$) δ 3.73 (dd, J = 21.0, 3.4 Hz, 1 H), 3.78 (s, 6 H), 3.77 (dd, J = 21.0, 7.3 Hz, 1 H), 4.82 (s, 1 H), 4.83 (d, J = 17.2 Hz, 1 H), 4.91 (d, J = 17.2 Hz, 1 H), 5.95 (s, 1 H), 5.96 (s, 1 H), 6.38 (s, 2 H), 6.64 (s, 1 H), 6.72 (s, 1 H).

(−)-(1*R*,2*S*)-1-(3,4,5-Trimethoxyphenyl)-2-(methoxycarbonyl)-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-6,7-(methylenedioxy)-1,2-dihydronaphthalene (14). A mixture of 228 mg (0.575 mmol) of synthetic β-apopicropodophyllin (**13**) in 3.8 mL of 50% aqueous methanol was treated under argon with 0.35 mL (1.75 mmol) of 5 N aqueous sodium hydroxide. The mixture was alternately evacuated at 20 Torr and the vessel refilled with argon. After 10 such cycles the mixture was heated at 60 °C for 8 h and then was cooled to 0 °C as 8 mL of 25% acetic acid was added. The mixture was extracted with three 30-mL portions of dichloromethane. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Toluene (10 mL) was added to the crude mixture, which was concentrated at reduced pressure. This was repeated two times further to free the crude product of acetic acid. The crude product was chromatographed on 15 g of silica gel (elution with 10% 2-propanol in 70% ethyl acetate–hexane) to give 229 mg (96%) of α-apopicropodophyllic acid: mp 165–169 °C; IR (KBr) ν 3380, 2960, 1710, 1585, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (d, J = 2.3 Hz), 3.75 (s, 6 H), 3.79 (s, 3 H), 4.21 (d, J = 12.6 Hz, 1 H) 4.33 (d, J = 12.6 Hz, 1 H), 4.63 (d,

J = 2.3 Hz, 1 H), 5.93 (d, J = 1.0 Hz, 1 H), 5.95 (d, J = 1.0 Hz, 1 H), 6.27 (s, 2 H), 6.55 (s, 1 H), 6.65 (s, 1 H), 6.69 (s, 1 H). This material was somewhat unstable and was used without delay in the next step.

Diazomethane was generated by addition of 1.1 mL of 50% potassium hydroxide to a stirring slurry of 300 mg of *N*-methyl-*N*-nitrosourea in 6 mL of 1:1 water–ether at 0 °C. After 20 min the ether layer was removed by pipet and added to an ice-cold solution of 219 mg (0.528 mmol) of the dihydronaphthoic acid in 3 mL of THF. After 10 min glacial acetic acid was added just until the yellow color was discharged. Toluene (20 mL) was added, and the mixture was concentrated in vacuo. The residue was stirred in 5 mL of dry dichloromethane at 0 °C as 30 mg of 4-(dimethylamino)pyridine, 173 mg (1.15 mmol) of *tert*-butyldimethylchlorosilane, and 0.32 mL (2.30 mmol) of trimethylamine were added. The mixture was stirred at 0 °C for 30 min and at room temperature for 10 min. Water and saturated ammonium chloride were added, and the mixture was extracted with three 20-mL portions of dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated to afford a crude oil that was chromatographed on 20 g of silica gel (elution with 20% ethyl acetate–hexane followed by 30% ethyl acetate–hexane) to afford 264 mg (92%) of silyl methyl ester **14** as an oil: $[\alpha]^{23}_D$ −73.8° (c 1.07, $CHCl_3$); IR (film) ν 2930, 1730, 1587, 1483, 1225, 1120 cm^{-1}; ^1H NMR, 270 MHz ($CDCl_3$) δ −0.04 (s, 3 H), 0.82 (s, 9 H), 3.40 (d, J = 3.4 Hz, 1 H), 3.62 (s, 3 H), 3.5 (s, 6 H), 3.98 (s, 3 H), 4.19 (d, J = 15.3 Hz, 1 H), 4.27 (d, J = 15.3 Hz, 1 H), 5.90, 5.91 (2 s, 1 H each), 6.29 (s, 2 H), 6.47 (s, 1 H), 6.56 (s, 1 H), 6.68 (s, 1 H). Anal. Calcd for $C_{29}H_{38}O_8Si$: C, 64.18; H, 7.06. Found: C, 64.52; H, 6.97.

(−)-(1*R*,2*S*,3*S*,4*R*)-1-(3,4,5-Trimethoxyphenyl)-2-(methoxycarbonyl)-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-hydroxy-6,7-(methylenedioxy)-1,2,3,4-tetrahydronaphthalene (16). A solution of 225 mg (0.414 mmol) of ester **14** in 0.4 mL of dry DMSO and 1.6 mL of THF was chilled to 0 °C under argon as 22 μL (1.22 mmol) of water was added followed by 220 mg (1.24 mmol) of *N*-bromosuccinimide. The mixture was stirred at 0 °C for 6.0 h, then was diluted with 1 mL of saturated sodium bicarbonate and water, and was extracted with two 20-mL portions of ethyl acetate. The organic phases were washed with water and brine and were dried over $MgSO_4$. Concentration in vacuo afforded 263 mg (100%) of crude bromohydrin **15**. Filtration through a short pad of silica gel (elution with 50% ethyl acetate–hexane) gave a sample suitable for spectral analysis. The product was not stable to storage and was used without delay in the ensuing step.

Bromohydrin **15** in 2.0 mL of toluene was treated with 20 mg of azobis(isobutyronitrile) and 335 μL (1.24 mmol) of tri-*n*-butyltin hydride. The mixture was alternately evacuated (20 Torr) and refilled with argon. After five such cycles the mixture was stirred and heated under argon at 120 °C (bath temperature) for 4 h. Cooling to room temperature was followed by concentration of the mixture to a volume of 0.5 mL. Chromatography of the mixture on 15 g of silica gel (elution with 20% ethyl acetate–hexane followed by 50% ethyl acetate–hexane) gave 183 mg (79%) of ester **16**, which solidified on standing: mp 61–63 °C; $[\alpha]^{23}_D$ −39.2° (c 2.6, $CHCl_3$); IR (KBr) ν 3490, 2940, 1738, 1590, 1500 cm^{-1}; ^1H NMR, 270 MHz ($CDCl_3$) δ 0.06 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 2.22 (m, 1 H), 3.30 (t, J = 11.4 Hz, 1 H), 3.50 (s, 3 H), 3.74 (m, 1 H), 3.78 (s, 6 H), 3.84 (s, 3 H), 3.86 (m, 1 H), 4.09 (d, J = 11.4 Hz, 1 H), 4.93 (s, 1 H), 5.87 (s, 1 H), 5.89 (s, 1 H), 6.29 (s, 1 H), 6.36 (s, 2 H), 6.82 (s, 1 H). Anal. Calcd for $C_{29}H_{40}O_9Si$: C, 62.12; H, 7.19. Found: C, 61.81; H, 7.14.

(−)-(1*R*,2*S*,3*R*)-1-(3,4,5-Trimethoxyphenyl)-2-(methoxycarbonyl)-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-6,7-(methylenedioxy)-2,3-dihydro-4(1*H*)-naphthalenone (17). A solution of 73 mg (0.309 mmol) of alcohol **16** was stirred in 3 mL of dichloromethane at room temperature as 600 mg of powdered 3-Å molecular sieves was added followed by 295 mg (0.284 mmol) of pyridinium dichromate. After 4 h at room temperature the mixture was diluted with an equal volume of ether and was filtered through a short pad of Celite and Florisil (elution with ether and dichloromethane). Concentration of the filtrate at reduced pressure was followed by chromatography on 10 g of silica gel (elution with 30% ethyl acetate–hexane followed by 50% ethyl acetate–hexane) to afford 151 mg (87%) of ketone **17** as an oil: $[\alpha]^{20}_D$ −3.6° (c 1.11, $CHCl_3$); IR (film) ν 2940, 1730, 1670, 1585, 1472, 1242 cm^{-1}; ^1H NMR, 270 MHz ($CDCl_3$) δ 0.04 (s, 6 H), 0.85 (s, 9 H), 2.92 (dt, J = 12.2, 3.6 Hz, 1 H), 3.42 (s, 3 H), 3.52 (dd, J = 12.2, 11.6 Hz, 1 H), 3.76 (dd, J = 9.9, 3.4 Hz, 1 H), 3.81 (s, 6 H), 3.83 (s, 3 H), 4.30 (d, J = 11.6 Hz, 1 H), 4.32 (dd, J = 9.9, 3.6 Hz, 1 H), 5.98 (s, 1 H), 5.99 (s, 1 H), 6.26 (s, 1 H), 6.38 (s, 2 H), 7.50 (s, 1 H). Anal. Calcd for $C_{29}H_{38}O_9Si$: C, 62.34; H, 6.86. Found: C, 62.36; H, 6.98.

(−)-3-(Hydroxymethyl)picropodophyllone (18). A solution of 88.7 mg (0.159 mmol) of keto ester **17** in 1.2 mL of THF was treated under argon with 1.2 mL of 37% aqueous formaldehyde followed by 64 μL (0.32 mmol) of 5 N aqueous sodium hydroxide. The mixture was stirred rapidly at room temperature for 26 h, at which time it was acidified with 2 mL of 1 N aqueous sodium bisulfate and was extracted with four 20-mL portions of dichloromethane. Drying of the organic phase over $MgSO_4$ and concentration gave an oil that was dissolved in 1.5 mL of 80% aqueous ethanol and was treated with 5 mg (0.026 mmol) of *p*-toluenesulfonic acid. The mixture was heated for 24 h at 60–65 °C, then was cooled to room temperature, and was treated with 0.5 mL of triethylamine. Evaporation at reduced pressure with azeotropic drying by toluene was followed by chromatography on 15 g of silica gel (elution with 50% ethyl acetate–hexane) to afford 67.1 mg (95%) of keto lactone **18**: mp 105–108 °C; $[\alpha]^{23}_D$ −23.7 (c 0.38, $CHCl_3$); IR (KBr) ν 3490, 2925, 1770, 1660, 1605, 1583, 1472 cm^{-1}; ^1H NMR, 270 MHz ($CDCl_3$) δ 3.27 (d, J = 12.4 Hz, 1 H), 3.36 (d, J = 2.3 Hz, 1 He, 3.64 (d, J = 12.4 Hz, 1 H), 3.73 (s, 6 H), 3.81 (s, 3 H), 4.34 (d, J = 10.4 Hz, 1 H), 4.59 (d, J = 10.4 Hz, 1 H), 4.59 (d, J = 10.4 Hz, 1 H), 4.78 (d, J = 2.3 Hz, 1 H), 6.07 (s, 1 H), 6.10 (s, 1 H), 6.15 (s, 2 H), 6.70 (s, 1 H), 7.47 (s, 1 H).

(−)-Picropodophyllone (19). A solution of 20.9 mg (0.0483 mmol) of (−)-3-(hydroxymethyl)picropodophyllin (**18**) in 4.8 mL of dry xylenes was placed in a base-washed, thick-walled glass tube. The tube was chilled to −78 °C, evacuated, sealed, and then heated at 210 °C for 36 h. The tube was cooled to −78 °C and opened, and the contents were concentrated at reduced pressure. Chromatography of the crude product on 5 g of silica gel (elution with 50% ethyl acetate–hexane) gave 14.3 mg (74%) of crystalline (−)-picropodophyllone (**19**): mp 153–158 °C: $[\alpha]^{22}_D$ −87.8° (c 1.22, $CHCl_3$); IR (KBr) ν 2910, 1772, 1664, 1473; ^1H NMR ($CDCl_3$) δ 3.30 (d, J = 1.5 Hz, 1 H), 3.31 (s, 1 H), 3.76 (s, 6 H), 3.80 (s, 3 H), 4.35 (ddd, J = 9.2, 4.7, 1.5 Hz, 1 H), 4.68 (s, 1 H), 4.75 (d, J = 9.2 Hz, 1 H), 6.03 (s, 1 H), 6.04 (s, 1 H), 6.23 (s, 2 H), 6.68 (s, 1 H), 7.49 (s, 1 H).

(−)-Picropodophyllin (20). A slurry of 28.0 mg (0.110 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 0.3 mL of THF was stirred at room temperature as 11.1 mg (0.0267 mmol) of (−)-picropodophyllone (**19**) in 2 mL of THF was added dropwise. After 3.5 h at room temperature the mixture was quenched by careful addition of 1 mL of saturated aqueous ammonium chloride and 1 mL of saturated aqueous oxalic acid. The mixture was extracted with three 20-mL portions of chloroform. Drying of the organic phases over $MgSO_4$ and concentration afforded the crude product, which was chromatographed on 5 g of silica gel (elution with 50% ethyl acetate–hexane followed by 10% 2-propanol in 50% ethyl acetate–hexane) to provide 10.5 mg (94%) of crystalline (−)-picropodophyllin (**20**): mp 216–219 °C; $[\alpha]^{22}_D$ −11° (c 0.27, $CHCl_3$); IR (KBr) ν 3340, 2920, 1745, 1583, 1242, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (m, 1 H), 3.23 (dd, J = 8.2, 5.5 Hz, 1 H), 3.81 (s, 6 H), 3.86 (s, 3 H), 4.09 (d, J = 5.1 Hz, 1 H), 4.46 (m, 3 H), 5.92 (d, J = 1.3 Hz, 1 H), 5.94 (d, J = 1.3 Hz, 1 H), 6.36 (s, 1 H), 6.45 (s, 2 H), 7.05 (s, 1 H).

(+)-4-*O*-(*tert*-Butyldimethylsilyl)picropodophyllin (21). A solution of 40.4 mg (0.100 mmol) of (−)-picropodophyllin (**20**) in 2.0 mL of dry CH_2Cl_2 was chilled to 0 °C under argon as 70 μL (0.60 mmol) of 2,6-lutidine and 92 μL (0.40 mmol) of *tert*-butyldimethylsilyl triflate were added dropwise. The mixture was stirred at 0 °C for 4 h, at which time 1 mL of water and 1 mL of saturated aqueous oxalic acid were added. The layers were separated, and the aqueous layer was extracted with four 10-mL portions of CH_2Cl_2. Drying of the organic layers over $MgSO_4$ and concentration under reduced pressure gave the crude silyl ether, which was chromatographed on 11 g of silica gel (elution with 30% ethyl acetate–hexane followed by 50% ethyl acetate–hexane) to provide 48.4 mg (93%) of crystalline silyl ether (+)-**21**: $[\alpha]^{23}_D$ +41.1° (c 0.73, $CHCl_3$); IR (KBr) ν 2930, 1770, 1583, 1470, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 3 H), 0.21 (s, 3 H), 1.01 (s, 9 H), 2.60 (m, 1 H), 3.21 (dd, J = 9.5, 7.7 Hz, 1 H), 3.84 (s, 6 H), 3.88 (s, 3 H), 3.93 (d, J = 9.5 Hz, 1 H), 4.36 (dd, J = 9.7, 3.7 Hz, 1 H), 4.45 (d, J = 9.6 Hz, 1 H), 4.52 (dd, J = 9.7, 1.6 Hz, 1 H), 5.92 (s, 1 H), 5.93 (s, 1 H), 6.23 (s, 1 H), 6.48 (s, 2 H), 6.98 (s, 1 H).

(−)-4-*O*-(*tert*-Butyldimethylsilyl)podophyllotoxin (22). A solution of 17.7 mg (0.0332 mmol) of silyl ether (+)-**21** in 0.65 mL of THF was chilled to −78 °C under argon as 71 μL (0.067 mmol) of 0.94 M lithium hexamethyldisilazide in THF was added dropwise. The mixture was brought to 0 °C over 40 min and then was rechilled to −78 °C as 0.31 mL (1.3 mmol) of 4.3 M acetic acid in THF was added rapidly. After 10 min at −78 °C the mixture was brought to room temperature, diluted with water, and extracted with four 10-mL portions of chloroform. Drying of the organic phases over $MgSO_4$ and concentration gave the crude product. Chromatography on 6 g of silica gel (elution with 25% ethyl acetate–hexane) first gave 4.5 mg of (−)-**22** as an oil followed by 7.6 mg of crystalline (+)-**21**: mp 156–160 °C (ratio 1:1.7, combined yield of 70%). Data for (−)-**22**: $[\alpha]^{22}_D$ −86° (c 0.14, $CHCl_3$); IR (KBr) ν 2910, 1770, 1580, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 3 H), 0.29 (s, 3 H), 0.94 (s, 9 H), 2.83 (m, 1 H), 2.84 (d, J = 1.5 Hz, 1 H), 3.72

(s, 6 H), 3.82 (s, 3 H), 3.93 (br d, J = 6.2 Hz, 1 H), 4.50 (d, J = 6.2 Hz, 1 H), 4.58 (br d, J = 1.5 Hz), 4.80 (d, J = 7.9 Hz, 1 H), 5.95 (s, 1 H), 5.97 (s, 1 H), 6.37 (s, 2 H), 6.48 (s, 1 H), 6.93 (s, 1 H).

(-)-Podophyllotoxin (1). A solution of 4.7 mg (0.009 06 mmol) of silyl ether (-)-**22** in 0.45 mL of acetonitrile was treated at room temperature under argon with 27 μL (0.054 mmol) of a 2.0 M solution of triethylammonium fluoride in acetonitrile. The mixture was stirred at room temperature for 3 days, at which time the mixture was concentrated under reduced pressure. Chromatography of the residue on 3 g of silica gel (elution with 30% ethyl acetate-hexane followed by 70% ethyl acetate-hexane) gave 2.9 mg (79%) of crystalline (-)-podophyllotoxin (**1**): mp 157-160 °C; $[\alpha]^{22}_D$ -85° (c 0.29, EtOH); IR (KBr) ν 3450, 2900, 1769, 1580, 1472, 1225, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 2 H), 3.76 (s, 6 H), 3.82 (s, 3 H), 4.10 (br t, J = 9.4 Hz, 1 H), 4.61 (m, 2 H), 4.79 (br d, J = 6.6 Hz, 1 H), 5.97 (d, J = 1.1 Hz, 1 H), 5.99 (d, J = 1.1 Hz, 1 H), 6.37 (s, 2 H), 6.52 (s, 1 H), 7.12 (s, 1 H).

Recrystallization of a sample of 5.2 mg of synthetic (-)-podophyllotoxin from 1:5 CH_2Cl_2-hexanes gave 4.4 mg of crystalline (-)-**1**: mp 158-159.5 °C; $[\alpha]^{21}_D$ -97° (c 0.33, EtOH).

A sample of authentic (-)-podophyllotoxin recrystallized in the same manner gave crystalline (-)-**1**: mp 158.5-159.5 °C; $[\alpha]^{22}_D$ -104° (c 0.36, EtOH).

Acknowledgment. We are grateful to the National Institutes of Health for their support of this study. An NIH (NRSA) Postdoctoral Fellowship (to R.C.A.) and an SERC Postdoctoral Fellowship (to S.J.T.) are also gratefully acknowledged. Finally, we are grateful to Professor Andrew S. Kende for providing spectra and details from his own studies and Drs. Terrance W. Doyle and T. Kaneko of Bristol-Myers for authentic samples of podophyllotoxin and other technical information.

Conformational Analysis of 14-Membered Macrolides Using X-ray Crystallography and Molecular Mechanics Calculations

Thomas H. Keller, Edward G. Neeland, Steven Rettig, James Trotter,* and Larry Weiler*

Contribution from the Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Y6. *Received February 29, 1988*

Abstract: The solid-state conformations of nine 14-membered-ring macrolides were determined by X-ray crystallography. In each conformation, the geometry of the lactone group was s-trans and the lactone C-O-C-H torsional angle was within a 0-40° arc. Geminally disubstituted atoms were found to occupy the corner positions. These trends greatly simplified the conformational analysis of the large-ring lactones. Two macrolides crystallized in a previously unreported low-energy conformation for 14-membered lactones. A modified nomenclature for the conformations of large rings is proposed which is based upon the number of bonds separating corner and pseudocorner atoms.

For the last 30 years chemists have shown that the conformational analysis of small ring compounds can be a powerful tool in understanding the physical and chemical properties of these systems. Simple pictorial representations, such as the cyclohexane chair, have demonstrated the potential of graphical representations of molecular conformation to rationalize known results and suggest new reactions.

Recently, Still and Galynker[1] described the profound effects of conformational control on the reactivity of medium and large rings. Following this pioneering work, several other research groups[2] have elegantly used conformational control to introduce new asymmetric centers on medium and large rings. Since the stereochemical outcome of a reaction in a large ring compound is usually not obvious, the planning of a synthesis of complex large rings must include a careful conformational analysis. Invariably researchers have relied on the use of computer calculations[2] to determine the important conformations controlling these reactions.

For some time we have been intrigued with the possibility of developing a simple pictorial model for the conformation of large rings with the hope that this model might be useful in understanding the chemistry of these systems. Some of these chemical findings have been published.[3] In this paper, we outline our efforts to determine the principles of conformational analysis governing the stereochemistry of reactions in 14-membered lactones. The macrolide antibiotics[4] are well represented by 14-membered lactones, and these compounds have been popular targets for synthetic chemists over the past decade.[5]

At first glance, the conformational analysis of 14-membered rings seems to be overwhelmingly complex. Although large rings can exist in a number of stable conformations, only a few of these are of low enough energy to be appreciably populated at room temperature. In his pioneering work, Dale[6] showed that conformations of 14-membered rings that are superimposable on a diamond lattice framework are of lower energy. He found that the minimum energy conformation was the [3434][7] conformation.[6] Later calculations on cyclotetradecane, however, revealed two low-energy conformations that were not superimposable on the diamond lattice.[8] These were the [3344] conformation, with a strain energy of 1.1 kcal/mol relative to the [3434] conformation, and the [3335] conformation, with a strain energy of 2.4 kcal/mol relative to the [3434] conformation. These two nondiamond lattice

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