$[\alpha]^{25}D$ +43.75° (*c* 3.440, benzene). A sample was crystallized once from *n*-heptane: mp 98–99°; $[\alpha]^{25}D$ +47.29° (*c* 3.478, benzene). In a similar manner from **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$), and **1b**, $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$), was obtained **2a**, $[\alpha]^{25}D$ +29.41° (*c* 3.478, benzene), and **2b**, mp 107–108°, $[\alpha]^{25}D$ −2.93° (*c* 3.478, benzene), respectively. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.68; H, 9.80; N, 6.13.

(*R*)-(+)-*N*,*N*-Dimethyl-3-phenyl-4,4-dimethylpentylamine (3).—A solution of 15.5 g (0.066 mol) of crude **2c** in 230 ml of anhydrous ether was slowly added to a stirred suspension of 5.87 g (0.154 mol) of $LiAlH_4$ in 130 ml of ether. The resulting mixture was stirred at the reflux temperature for 26 hr and then it was worked up by a standard procedure[1] to give 13.0 g (90%) of **3c**: bp 84° (1.4 mm); $n^{25}D$ 1.4934–1.4936; $\alpha^{25}D$ +19.08° (neat); $[\alpha]^{25}D$ +18.65° (*c* 2.198, benzene). Runs **a** and **b** were carried out under identical conditions to give amines **3a** [bp 95° (2.3 mm), $\alpha^{25}D$ +12.84° (neat)] and **3b** [bp 79° (1 mm); $n^{25}D$ 1.4930–1.4931; $\alpha^{25}D$ +1.28° (neat)]. *Anal.* Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.89; H, 11.45; N, 6.45.

(*R*)-(+)-3-Phenyl-4,4-dimethyl-1-pentene (5).—The amine **3c** (12.5 g, 0.057 mol) was converted to its oxide[19] which was heated under 1.5 mm of pressure at a temperature of 120° until the decomposition was complete, 25 min. The distillate was worked up by the usual manner[19] and the crude alkene was distilled to give 8.5 g (86%) of **5c** [99% pure by glpc analysis (on 2-m Apiezon L column at 160°)]: bp 94° (15 mm); $n^{25}D$ 1.5032; $\alpha^{25}D$ +84.29° (neat). In run **a** the olefin was purified by preparative glpc (on 5-m 10% BDS column at 140°) to give pure **5a** (>99%): bp 97° (16 mm); $n^{25}D$ 1.5028; d_4^{25} 0.8808; $\alpha^{25}D$ +56.66° (neat); $[\alpha]^{25}D$ +64.33° (neat). Its ir spectrum showed no bands at 1625 and 980–960 cm^{-1}.[1] On a later run from **3b** was obtained **5b**: $n^{25}D$ 1.5029–1.5030; $[\alpha]^{25}D$ −6.49° (neat). *Anal.* Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.87; H, 10.16.

(*R*)-(+)-2-Phenyl-3,3-dimethyl-1-butanol.—To 25.2 g (0.664 mol) of $LiAlH_4$ in 326 ml of ether was added dropwise 70.0 g (0.364 mol) of **7a**, $[\alpha]^{25}D$ −52.89° (*c* 5.294, $CHCl_3$),[6] in 270 ml of dry ether. The mixture was refluxed 20 hr and then worked up by a standard procedure[1,2] to give 63.5 g (98%) of crude (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol which was extracted continuously with pentane; from the resultant solution the carbinol (62.0 g), mp 96° [lit. mp of partially active material,[2] 75–90°], $[\alpha]^{25}D$ +2.00° (*c* 5.212, $CHCl_3$), was recovered. On a later run from **7e**, $[\alpha]^{25}D$ +60.68° (*c* 4.958, $CHCl_3$), was obtained (−)-carbinol: mp 97°; $[\alpha]^{25}D$ −2.31° (*c* 6.060, $CHCl_3$). In run **f** the acid **7**, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), was reduced to give a product with mp 97°, $[\alpha]^{25}D$ +2.38° (*c* 5.988, $CHCl_3$).

(*R*)-(+)-3-Phenyl-4,4-dimethylpentanoic Acid (1).—(*R*)-(+)-2-Phenyl-3,3-dimethyl-1-butanol, $[\alpha]^{25}D$ +2.00 ($CHCl_3$), was converted into **8a**, 88% pure (glpc).[2] The Grignard reagent from the above chloride was carbonated with Dry Ice. The reaction mixture was processed in the usual way[1] to give 9.5 g (57%) of crude **1a**, mp 108–110° (lit.[7] 114–116°). The acid was extracted continuously with pentane to yield 9.0 g of **1a**, $[\alpha]^{25}D$ +14.09° (*c* 2.344, $CHCl_3$); its methyl ester was shown to be 99% pure (glpc). On a later run from **8e** (98% pure), bp 79° (1.5 mm) [lit.[2] 79–82° (1 mm)], $n^{25}D$ 1.5153, $\alpha^{25}D$ −39.22° (neat) [obtained by reacting the tosylate of the carbinol, $[\alpha]^{25}D$ −2.31 ($CHCl_3$), with LiCl in dimethylformamide (62% yield)],[15] was prepared **1e**, mp 94–95°. This acid was converted, by diazomethane, to its methyl ester **4e**: bp 133° (13 mm); $n^{25}D$ 1.4953; $\alpha^{25}D$ −23.32° (neat).

(*S*)-(+)-2-Phenyl-3,3-dimethylbutanoic Acid Methyl Ester (6).—To a solution of 2.13 g (0.011 mol) of **7f**, mp 142°, $[\alpha]^{25}D$ −62.52° (*c* 4.958, $CHCl_3$), in 15 ml of ether at 0° was added slowly and with shaking an ether solution of diazomethane. The excess of diazomethane and ether was removed under reduced pressure and distillation gave 2.0 g (88%) of **6f**: bp 122° (15 mm); $n^{25}D$ 1.4938; $\alpha^{25}D$ −58.32° (neat). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.02; H, 8.67.

(*R*)-(+)-3-Phenyl-4,4-dimethylpentanoic Acid Methyl Ester (4).—By the method above described 2.04 g (0.0098 mol) of **1d**, mp 93–94°, $[\alpha]^{25}D$ +14.48° (*c* 2.624, $CHCl_3$), was converted to **4d** (82%): bp 139–140° (15 mm); $n^{25}D$ 1.4946; $\alpha^{25}D$ +15.57° (neat). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.12.

(19) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2137 (1952).

Arndt–Eistert Reaction on the (*S*)-2-Phenyl-3,3-dimethylbutanoic Acid (7).—The acid **7b** (73.0 g, 0.379 mol), $[\alpha]^{25}D$ +5.69° (*c* 5.443, $CHCl_3$), was converted to its chloride (**9b**) with the procedure above described for **1c**. A 3.5-g sample of distilled acid chloride was treated with absolute methanol.[13] Distillation gave 2.5 g (75%) of **6b**: $n^{25}D$ 1.4940; $\alpha^{25}D$ +4.44° (neat); $[\alpha]^{25}D$ +4.36° (*c* 5.150, MeOH). The residual chloride (75.0 g, 0.356 mol), bp 89° (2 mm), in 180 ml of ether was reacted with an ice-cold ether solution of diazomethane, prepared from 2.9 mol of *N*-nitrosomethylurea.[13] The crude diazo ketone, in 575 ml of purified dioxane, was subjected to the Wolff rearrangement in a solution of aqueous dioxane containing silver oxide and sodium thiosulfate.[13] The recovered acid was extracted continuously with pentane to give 53.1 g (72%) of **1b**: mp 116°; $[\alpha]^{25}D$ −1.42° (*c* 5.769, $CHCl_3$).

Oxidation of (*R*)-(+)-3-Phenyl-4,4-dimethyl-1-pentene (5).—The alkene **5a** (3.0 g, 0.017 mol), $[\alpha]^{25}D$ +64.33° (neat), was oxidized in 112 hr, by $KMnO_4$–$NaIO_4$ mixture in 60% aqueous *tert*-butyl alcohol, according to the procedure of Gil-Av and Shabtai.[9] The crude acid (83%) was esterified with diazomethane to give **6a**: $n^{25}D$ 1.4935; $\alpha^{25}D$ −38.46° (neat). In another experiment **5b**, $[\alpha]^{25}D$ −6.49° (neat), afforded **6b**: $n^{25}D$ 1.4940; $\alpha^{25}D$ +3.65° (neat).

Registry No.—**1**, 23406-59-9; **2**, 33124-15-1; **3**, 33124-16-2; **4**, 33124-17-3; **5**, 33124-18-4; **6**, 26164-17-0; **7**, 13490-71-6; (*R*)-(+)-2-phenyl-3,3-dimethyl-1-butanol, 33124-21-9.

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2-Carboxydeoxypicropodophyllin

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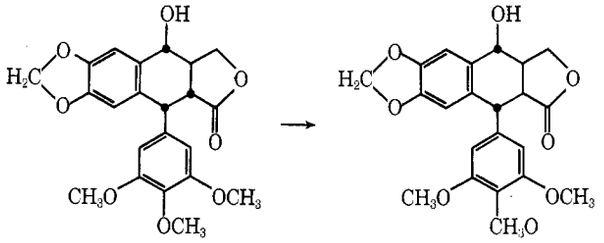
Podophyllotoxin (**1**) and also derivatives such as deoxypodophyllotoxin (**3**), which have the same con-



podophyllotoxin (**1**) → picropodophyllin (**2**)

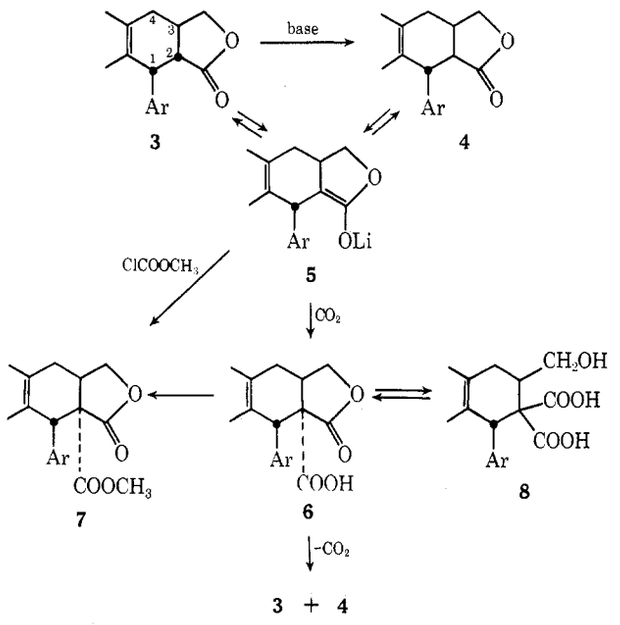
figurations at positions 1, 2, and 3,[1] are active cytotoxic agents and have been extensively investigated as cancer chemotherapeutic agents.[2] All of these podophyllo-

(1) J. L. Hartwell and A. N. Schrecker, *Progr. Chem. Org. Natur. Prod.*, **15**, 83 (1958).

(2) *Cf.* M. G. Kelly and J. L. Hartwell, *J. Nat. Cancer Inst.*, **14**, 967 (1954); H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim.-Forsch.*, **11**, 327, 459 (1961); E. Schreier, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966, Paper P-34. Two derivatives have actually received considerable clinical application, namely, *O*,*O*-benzylidenepodophyllotoxin-β-D-glucoside and podophyllic acid *N*-ethylhydrazide (*cf.* H. Lettré and S. Witte, "Experimentelle und Klinische Erfahrungen mit Podophyllinderivaten in der Tumortherapie," F. K. Schattauer-Verlag, Stuttgart, 1967).

toxin compounds epimerize easily by base-catalyzed removal of the proton at position 2.[1,3] The resulting products, now in the picropodophyllin (2) configuration, are virtually inert.[3] Since the cell probably utilizes this epimerization as a detoxication mechanism,[4] replacing the H at the 2 position with a group offering no opportunity for epimerization should block at least one mode of physiological deactivation and furnish a more persistent agent. With this in mind, we set out to prepare analogs substituted at position 2. The present paper reports the results of work aimed at attaching a carboxy group by carbonating the enolate from deoxypodophyllotoxin.

The starting material, 4-deoxypodophyllotoxin (**3**), although isolable from plant sources,[5,6] is more conveniently prepared by catalytic hydrogenolysis of podophyllotoxin (**1**).[7] Epimerization gave deoxypicropodophyllin (**4**).[6,7] Enolate **5**, prepared by the action of triphenylmethyllithium (butyllithium could also be used) on either deoxypodophyllotoxin (**3**) or deoxypicropodophyllin (**4**) was carboxylated with carbon dioxide to produce 2-carboxydeoxypicropodophyllin (**6**). The corresponding methyl ester **7** was obtained either from the acid or by allowing the enolate to react with methyl chloroformate. Confirmation that the carboxyl group is on the 2 position, as anticipated, came from the fact that thermal decarboxylation of acid **6** produced a mixture of deoxypodophyllotoxin (**3**) and deoxypicropodophyllin (**4**). Since, under the decarboxylation conditions employed, the two products **3** and **4** failed to interconvert, they must be derived from some common intermediate stage, and if the carboxy group is placed on the 2 position as in **6**, the enol[8] common to both products **3** and **4** serves in a straightforward way as this intermediate.



Assignment of the cis-fused (picropodophyllin) configuration to carboxylation product **6** rather than the trans-fused (podophyllotoxin) configuration rests on the observation that, when malonic acid **8** formed by saponifying the lactone ring of **6** is warmed, cyclization occurs to regenerate starting material **6**. The other lactone product, although *a priori* possible, is not observed. All information on the relative stability of the cis lactone system, as in **6**, *vs.* the corresponding trans lactone points to the former as energetically favored.[3] Since the transition state for lactonization of malonic acid **8** to a cis lactone would be expected to reflect this preference, the lactone product would be the cis-fused 2-carboxydeoxypicropodophyllin rather than the trans-fused 2-carboxydeoxypodophyllotoxin.

The lactone carbonyl infrared absorption offers no support for the cis assignment and, if anything, could be taken as favoring the opposite conclusion. Thus the lactone peak in carboxylation product **6** appears at 1770–1780 cm^{-1}, and the lactone absorption in the derived methyl ester **7** at 1787 cm^{-1}. These values fall closer to the 1780-cm^{-1} absorption peak for deoxypodophyllotoxin (**3**) than to the 1765-cm^{-1} peak for deoxypicropodophyllin (**4**). However, we tend to mistrust this kind of comparison. Local structural features not only can shift carbonyl absorption peaks but also, since several factors might be involved, do this in a way that is hard to predict.[9,10]

Questions remain on why carbonation furnishes none of the stereoisomeric 2-carboxydeoxypodophyllotoxin and on why the yield could not be brought over 40–50%. Factors that might operate to favor the cis picropodophyllin configuration over the trans podophyllotoxin configuration—a result contrary to what may be predicted on the basis of the planar enolate grouping[8]—have been discussed before.[11] Why the carbonation yields were not higher despite the elaborate precautions taken to exclude moisture and oxygen is a matter of speculation. Possibly carbonation on oxygen instead of carbon occurs to yield the enol half-ester of carbonic acid, which is stable enough to drain the supply of enolate **5** but not stable enough to isolate.

Experimental Section

General.—Melting points were taken in open capillary tubes and are uncorrected. Composition analyses were determined by Microanalytical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass., Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Scandinavian Microchemical Laboratory, Herlev, Denmark. Volatile solvents were generally removed in a rotary evaporator under water-pump vacuum at moderate temperatures. Nuclear magnetic resonance spectra were determined at 60 MHz. Thin layer chromatographic analyses were obtained with the help of commercial silica gel plates and films. Estimates indicate that, for samples in the

(3) See W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 3224 (1966).

(4) *Cf.* H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim.-Forsch.*, **11**, 327 (1961); J. J. Kocsis, E. J. Walaszek, and E. M. K. Geiling, *Arch. Int. Pharmacodyn. Ther.*, **111**, 134 (1957); M. G. Kelly, J. Leiter, A. R. Bourke, and P. K. Smith, *Cancer Res.*, **11**, 263 (1951).

(5) K. Noguchi and M. Kawanami, *J. Pharm. Soc. (Jap.)*, **60**, 629 (1940); *Chem. Abstr.*, **47**, 6386 (1953); H. Kofod and C. Jørgenson, *Acta Chem. Scand.*, **9**, 346 (1955); J. L. Hartwell and A. W. Schrecker, *J. Amer. Chem. Soc.*, **76**, 4034 (1954).

(6) J. L. Hartwell, A. W. Schrecker, and J. M. Johnson, *ibid.*, **75**, 2138 (1953).

(7) *Cf.* A. W Schrecker, M. M. Trail, and J. L. Hartwell, *J. Org. Chem.*, **21**, 292 (1956).

(8) *Cf.* J. Hine in "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 303.

(9) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958; "Advances in Infrared Group Frequencies," Methuen, London, 1968.

(10) Optical rotatory dispersion and circular dichroism curves were determined for the 2-carboxydeoxypicropodophyllin (**6**), but the results offered little help in deciding between the picropodophyllin and podophyllotoxin configurations: private communication from Professor W. Klyne, Westfield College, University of London.

(11) W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).

order of 0.5 μg, 1–2% of extraneous material could be detected.

Reactions involving organometals and enolates were performed in clean glassware, dried carefully in a 100° oven, and often flamed while passing an inert gas through the apparatus. Air was vigorously excluded generally by using an atmosphere of oxygen-free nitrogen that had been bubbled first through a tower of concentrated sulfuric acid and then through calcium sulfate. The tetrahydrofuran and ether solvents were prepared routinely by condensing the vapors from a boiling mixture of solvent and lithium aluminum hydride directly into the reaction vessel. Solution transfers were made without opening the system to air, sometimes with the help of syringes that had just been flushed with pure nitrogen.

Deoxypodophyllotoxin (3) by Hydrogenolysis of Podophyllotoxin (1).—A mixture of 6.0 g of 10% palladium/carbon (Columbia Organic Chemicals) with 150 ml of acetic acid was stirred under hydrogen until no further hydrogen was absorbed. Podophyllotoxin (8.0 g; 19.3 mmol), mp 181–184° (lit.[1] 183–184°), was added, and the mixture was stirred at 95° under 2 atm of hydrogen for 5 hr, at which point the calculated volume of hydrogen had been absorbed. Continued stirring led to no further absorption. After catalyst and solvent had been removed, the residue was percolated through a small column of neutral alumina (<200 mesh) with the help of about 200 ml of methylene chloride. Solvent was removed in a low-actinic flask, and the residue, homogeneous according to thin layer chromatography (ether–methylene chloride, 6:1), was crystallized twice from methanol to give 5.6 g (73%) of deoxypodophyllotoxin (**3**), mp 166–168°. An additional 0.8 g obtained by reprocessing the mother liquors brought the yield to 83%: $[\alpha]_D$ −117° (*c* 1, $CHCl_3$); $[\alpha]_D$ −77.5° (*c* 0.5, C_2H_5OH); ir ($CHCl_3$) 1780, no absorption at 3700–3125 cm^{-1} [lit.[7] mp 168.4–169.4°; $[\alpha]_D$ −116.4° ($CHCl_3$)].

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.33; H, 5.53. Found: C, 66.43; H, 5.37.

Hydrogenolysis of podophyllotoxin to deoxypodophyllotoxin could also be performed effectively simply by bubbling hydrogen slowly through the hot, stirred mixture.

Deoxypicropodophyllin (4) by Epimerizing Deoxypodophyllotoxin (3).—The reaction was performed by boiling a mixture of deoxypodophyllotoxin (2.2 g, 5.5 mmol), 6.0 g (73 mmol) of anhydrous sodium acetate, and 50 ml of absolute ethanol for 18 hr.[6,7] Crystallized deoxypicropodophyllin, homogeneous according to thin layer chromatography, was obtained in 78% yield. Using ether–methylene chloride on a Camag silica gel plate, deoxypicropophyllin traveled with R_f 0.54, deoxypodophyllotoxin with R_f 0.75.

Appreciable quantities of deoxypicropodophyllin could also be recovered from the mixtures obtained in the carbonation experiments described below.

2-Carboxydeoxypicropodophyllin (6).—Tetrahydrofuran (*ca.* 300 ml) was condensed directly onto 35.0 g (0.14 mol) of pure dry triphenylmethane in an amber reaction vessel. A hexane solution of butyllithium (1.6 *N*) was injected in 10-ml portions to the swirled tetrahydrofuran solution until a total of 100 ml had been introduced (0.16 mol). Standardization of the resulting red solution of triphenylmethyllithium by titration against pure dry benzoic acid to the appearance of a red end point indicated an organometal content of 0.32 *M*. Samples were withdrawn by syringe, with the bottle always upright and with nitrogen used liberally. Prepared, stored, and utilized in this way, the triphenyllithium solution appeared to keep well.

Tetrahydrofuran (*ca.* 60 ml) was condensed directly onto 0.34 g (0.85 mmol) of deoxypicropodophyllin (**4**). Red triphenyllithium solution was then added dropwise from a syringe to the vigorously stirred solution. The reaction mixture, originally colorless, gradually became yellow to yellow-orange. The addition was interrupted when the red color from each drop of reagent took longer than 5 min to fade to orange; at this point 140% of the calculated amount had been introduced. The solution was transferred by syringe to a flask containing a large excess of solid carbon dioxide, which had been condensed at liquid nitrogen temperatures from specially dried commercial gas. The flask was then allowed to come to room temperature, and, when all the solid carbon dioxide had evaporated, solvent was removed *in vacuo* at temperatures no higher than 30°. Water (20 ml) was added, and the mixture was extracted with several portions of methylene chloride to remove triphenylmethane, triphenylcarbinol, deoxypicropodophyllin, and deoxypodophyllotoxin. The aqueous layer (pH 11) was cooled to 0° and acidified to pH 2 with 4 *N* hydrochloric acid to precipitate the desired product, which was separated by centrifugation, stirred with a small volume of cold water, and collected again. Crystallization of the solid from methanol or from methylene chloride–hexane afforded shining plates of 2-carboxydeoxypicropodophyllin (**6**) weighing 0.17 g (44%) and showing a single spot on thin layer chromatographic analysis (benzene–methanol, 3:1): mp (slow decomposition) >150°, or with rapid heating at 190–200° with foaming; $[\alpha]_D$ +143° (*c* 0.5, pyridine); ir (mineral oil mull) 3140 (OH), 1770–1780 (lactone carbonyl), 1725–1730 cm^{-1} (carboxy carbonyl).

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01; $3CH_3O$, 21.04. Found: C, 62.24; H, 5.01; CH_3O, 21.10.

Many variations of this preparation were tried with little or no improvement in yield. Carbonation of the lithium enolate derived from deoxypodophyllotoxin (**3**) instead of deoxypicropodophyllin gave practically the same results. In one modification the enolate was prepared by adding butyllithium in hexane (1.3 *M* equiv) to a tetrahydrofuran solution of deoxypodophyllotoxin in the presence of a catalytic amount of triphenylmethane (0.1 *M* equiv) until the red color persisted; thereafter carbonation with a stream of dry carbon dioxide gas gave 2-carboxydeoxypicropodophyllin in about 28% yield. Even in the *absence* of triphenylmethane, butyllithium (1.2 molar equiv) produced the enolate, since subsequent carbonation with gaseous carbon dioxide led to the acid product in one experiment in 12% and in another in 22% yield. However, unidentified products were also detected here. A tetrahydrofuran solution of triphenylmethylsodium could be prepared (60–75% yield) by substituting tetrahydrofuran for ether in the published directions[12] for converting an ether solution of triphenylmethyl chloride with sodium amalgam to ethereal triphenylmethylsodium. The sodium enolate, obtained by titrating deoxypodophyllotoxin (**3**) with the dark red organometal solution (1.4 molar equiv) to a persistent red, was carbonated either with gaseous or solid carbon dioxide. 2-Carboxydeoxypicropodophyllin was obtained in 25–28% conversion.

In every run, thin layer chromatographic analysis of the products before fractionation revealed the presence not only of acid product **6** but also of triphenylmethane, triphenylmethyl alcohol, deoxypicropodophyllin, and deoxypodophyllotoxin.

Decarboxylation of 2-Carboxydeoxypicropodophyllin (6).—A 3-mg sample of the acid in a capillary tube was brought at 150° and maintained at this temperature for 6 min, after which time the sample melted with foaming. After another 2 min at 150°, the material in chloroform solution was spotted on a thin layer chromatography plate together with deoxypodophyllotoxin (**3**) and deoxypicropodophyllin (**4**). Development of the plate with carbon tetrachloride–ether (4:1) produced only two spots, one with R_f 0.50 corresponding to deoxypodophyllotoxin and one with R_f 0.32 corresponding to deoxypicropodophyllin.

In another similar decarboxylation, the infrared absorption curve of the product (KBr pellet) was found to correspond exactly with that observed for a pelleted mixture of deoxypodophyllotoxin and deoxypicropodophyllin, with the latter predominating. No carboxyl carbonyl absorption (1725 cm^{-1}) was evident.

Thin layer chromatographic analysis showed that heating samples of deoxypodophyllotoxin or of deoxypicropodophyllin for 0.5 hr, either alone or in the presence of a little hexanoic acid, failed to interconvert the epimers or to change them in any way.

Hydrolysis and Relactonization of 2-Carboxydeoxypicropodophyllin (6).—A solution of the acid (80 mg, 0.17 mmol) in 10 ml of 0.2 *N* sodium hydroxide solution was warmed at 50° for 1 hr. After the mixture was cooled to 0°, it was acidified to pH 2 with 1 *N* hydrochloric acid, and whatever solid formed was collected and dried over calcium sulfate *in vacuo*. This solid (31 mg), developed on a thin layer plate with benzene–methanol (3:1), developed a very faint spot (R_f 0.19) matching that obtained for 2-carboxydeoxypicropodophyllin and a dark spot (R_f 0.09) attributed to the desired dicarboxy acid **8**. The neutralization equivalent of the solid (240) compared reasonably well with that calculated (230) for the expected diacid **8**. The infrared absorption curve (mineral oil mull) showed a maximum at 3500 cm^{-1} (hydroxyl), which is absent in the curve for 2-carboxydeoxypicropodophyllin, and also showed only one carbonyl

(12) C. R. Renfrew and C. F. Hauser, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 607.

peak at 1720 cm^{-1} (COOH) as compared with the two peaks (1780 and 1725) for the starting lactone acid.

Relactonization was effected by boiling the heterogenous mixture of diacid **8** (10 mg) with 30 ml of benzene for 2 hr. The single spot (R_f 0.19) obtained when the relactonized material was developed on a plate showed that only 2-carboxydeoxypicropodophyllin had been formed. The infrared absorption spectrum (mineral oil mull) was identical with that of 2-carboxydeoxypicropodophyllin. Exposing the relactonized material dissolved in tetrahydrofuran to ethereal diazomethane produced 2-carbomethoxydeoxypicropodophyllin (see below), which ran side by side on a silica gel plate with authentic ester (R_f 0.42 using carbon tetrachloride–ether, 4:1). Removing all solvent left a solid residue, which when mixed with authentic ester (mp 190–191°) showed mp 187–190°. The infrared absorption curves of the two esters were identical.

Methyl Ester of 2-Carboxydeoxypicropodophyllin. a. From the Acid.—A solution of 2-carboxydeoxypicropodophyllin (0.20 g) in 15 ml of pure tetrahydrofuran was treated with excess ethereal diazomethane. After 15 min, volatiles were removed, and the residue (0.21 g; homogeneous according to thin layer chromatography) was crystallized from methylene chloride–hexane. The resulting 2-carbomethoxydeoxypicropodophyllin (**7**), mp 189.5–191°, weighed 0.17 g (84%): $[\alpha]_D$ 110° (*c* 0.4, pyridine) or $[\alpha]_D$ 83° (*c* 0.4, $CHCl_3$); ir (CCl_4) 1787 for lactone carbonyl and 1731 cm^{-1} for ester carbonyl; nmr ($CDCl_3$) resembles the curve for deoxypicropodophyllin with δ 6.80, 6.58, and 6.38 (aromatic H's), 5.88 (s, methylenedioxy H's), multiplets with close-lying chemical shifts (12, 4, CH_3O), multiplets for all other protons.

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30; $4CH_3O$, 26.76. Found: C, 62.72, H, 5.29; CH_3O, 26.69.

b. From Enolate 5 with Methyl Chloroformate.—A 1 *M* butyllithium solution in hexane (0.84 ml, *ca.* 0.8 mmol) was added dropwise from a small graduated syringe sticking through a serum cap septum to a vigorously stirred solution of dry deoxypodophyllotoxin (**3**) (0.43 g, 1.1 mmol) and 0.26 g of triphenylmethane (1.1 mmol) in 20 ml of tetrahydrofuran that had just been distilled from calcium hydride. The resulting orange mixture was stirred further for 0.5 hr before dropwise injection of a solution of pure methyl chloroformate (0.13 g, 1.1 mmol) in 2 ml of dry tetrahydrofuran. After 1 hr, water was added, and the mixture was brought to pH 5.5 with a few drops of hydrochloric acid. The lower aqueous layer was extracted with ether, and the combined ether and hexane solutions were washed with water, dried, and stripped of volatiles. The residue was chromatographed through a 1-ft column of 60–100 mesh silica gel, with 50 ml of benzene serving to remove triphenylmethane and 100 ml of benzene–acetone (4:1) serving to remove product. The crude product was crystallized twice from methanol to give 0.28 g (56%) of 2-carbomethoxydeoxypicropodophyllin (**7**), mp 187–190°. This material showed a single spot on a Gelman silica gel strip (chloroform–ether, 4:1) with the same R_f as that from the methyl ester derived from acid **6** and spotted on the same plate; ir ($CHCl_3$) was identical with curve from the methylation product; the melting point was not depressed when the two esters were mixed.

Activity.—2-Carboxydeoxypicropodophyllin (**6**) was submitted to Cancer Chemotherapy National Service Center for screening. When tested against cell cultures of human epidermoid carcinoma of the nasopharynx,[13] a solution of the compound (NSC No. 92321) in dimethylformamide showed a confirmed ED_{50} toxicity (dose causing 50% growth inhibition) at less than 1.9 μg/ml, possible in the 0.2–0.5-μg/ml range.

Registry No.—**3**, 19186-35-7; **6**, 33369-69-6; **7**, 33369-70-9; **8**, 33369-71-0.

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Enol Acetylation of Methyl 12-Oxopodocarp-13-en-19-oate and Methyl 12-Oxopodocarp-8(14)-en-19-oate

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The enol acetylation of alicyclic unsaturated ketones has been largely restricted to the steroid series[2] where interest has been focused on reagents which result in either thermodynamically or kinetically controlled[3,4] reaction products. In connection with a diterpenoid synthesis problem we wished to prepare a specific ring C acetoxy diene from methyl 12-oxopodocarp-13-en-19-oate[5,6] (**1**), and we report here the acetoxy dienes obtainable under both thermodynamically and kinetically controlled conditions.

Enol acetylation of **1** with isopropenyl acetate and toluenesulfonic acid[7] (kinetic control) gave only the 11,13-diene **2** and starting ketone. Acetic anhydride and *p*-toluenesulfonic acid enol acetylation gave 30% diene **2**, 50% 8(14),12-diene **3**, 5% nonconjugated diene **9**, and 5% methyl podocarpate **10**. To ensure that a true thermodynamic equilibrium was present, the 11,13-diene **2** was subjected to acetic anhydride–toluenesulfonic acid equilibration, and the same ratio of 3:5 for **2** to **3** was obtained. The product composition in all experiments was determined by integration of the vinylic signals at 5.40 and 5.87 ppm together with the C-20 methyl absorptions in the pmr spectra of the direct reaction mixtures (see Experimental Section).[8]

The thermodynamic ratio of 3:5 noted for **2** to **3** is unexpected on the basis of double bond stabilities[9] which should lead to an equilibrium ratio of 1:9. The discrepancy must arise from other factors, and previous authors[10] have pointed out the dominance of steric interactions in determining the enol acetate ratios observed for simple cyclic ketones. To probe

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