1, J = 10 Hz), 5.68 (d, 1, J = 9 Hz), 6.41 (s, 1), 7.24–7.84 (m, 7), and 8.24 (m, 1); HRMS m/e (rel intensity) found 558.21118 (100) [calcd for $C_{30}H_{30}N_4O_7$, 558.21145 (M^+)].

Oxidation of Deoxytryptoquivaline (3). To a stirred solution of deoxytryptoquivaline (**3**, 16.7 mg, 0.032 mmol) in dichloromethane (5 ml) at room temperature was added m-chloroperbenzoic acid (m-CPBA, 6.3 mg, 0.037 mmol). The reaction mixture was diluted with dichloromethane (20 ml) after 15 min, and washed with dilute aqueous $NaHCO_3$. The organic layer was dried (anhydrous Na_2SO_4), evaporated in vacuo, and chromatographed (HPLC, 3% 2-propanol in hexane as solvent) to give tryptoquivaline (**1**, 12.6 mg, 73% yield), identical with authentic material.

Oxidation of Deoxytryptoquivalone (8). Deoxynortryptoquivalone (**8**, 19.6 mg, 0.042 mmol) was oxidized with m-CPBA (8.2 mg, 0.048 mmol) to give, after workup and chromatography (HPLC, 3% 2-propanol in hexane), nortryptoquivalone (**7**, 12.6 mg, 62% yield), identical with authentic material.

Oxidation of Deoxynortryptoquivaline (4). Deoxynortryptoquivaline (**4**, 38.4 mg, 0.074 mmol) was oxidized with m-CPBA (14.2 mg, 0.082 mmol) to give, after workup and chromatography (HPLC, 5% 2-propanol in hexane), nortryptoquivaline (**2**, 34.3 mg, 86.6% yield) identical with authentic material.

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Registry No.—**1**, 55387-45-6; **2**, 60676-56-4; **3**, 60676-57-5; **4**, 60676-58-6; **5**, 60676-59-7; **6**, 60676-60-0; **7**, 55387-46-7; **8**, 60676-61-1; **9**, 4464-33-9; **10**, 27909-08-6.

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Podophyllotoxin Derivatives. 3.[1] The Remaining Diastereomeric C-4 Alcohols and Ketone of the L Series[2]

V. Nambi Aiyar and Frederic C. Chang*†

Department of Biochemistry, University of Tennessee, Center for the Health Sciences, Memphis, Tennessee 38163

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The preparation of L-isopodophyllotoxin (**5**), L-isopicropodophyllin (**7**), and L-isopodophyllotoxone (**12**) is described. With these compounds the eight possible diastereomeric C-4 alcohols (toxins) and four possible C-4 ketones of the L series[2] are all known. Alcohol **5** instead of its epimer **6** was obtained by sodium borohydride reduction of **12** contrary to predictions based on previously reported reduction of DL-**12**.

In the L series, of the eight possible diastereomers of the podophyllotoxin structure (chiral centers at C-2, -3, and -4) and four of the podophyllotoxone structure (chiral centers at C-2 and -3), recent publications[1,3] left two of the alcohols and one ketone undescribed. This is a report of the preparation of these compounds, namely L-isopodophyllotoxin (**5**, 2β,3α,4β), L-isopicropodophyllin (**7**, 2α,3α,4β), and L-isopodophyllotoxone (**12**, 2β,3α) (Chart I).

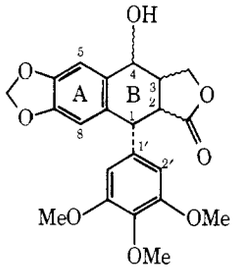
The Alcohols (Toxins). Compound **5** (2β,3α,4β), previously known only as an unresolved component of a DL mixture,[4] was obtained by inversion at C-4 on treatment of **6** (2β,3α,4α) with dilute acid. Alcohol **6** had been prepared starting with **8** (2α,3α,4α) by an indirect method involving simultaneous epimerization at C-2 and cleavage of the lactone group, and subsequent relactionization of the resulting hydroxy acid (Scheme I).

Additionally **5** was derived from L-isopodophyllotoxone (**12**, see below), by $NaBH_4$ reduction. Finding **5** as the predominant (72%) and sole alcoholic reduction product was unexpected, because it had previously been reported[4] that the DL form of **12** when reduced with $Zn(BH_4)_2$ afforded DL-**6**, the C-4 epimer of DL-**5**.[5] The identity of our reduction product was established by direct spectral (ir, NMR, mass) comparisons of both the alcohol and its acetate with authentic DL samples (prepared by a different route) provided by two laboratories.[6]

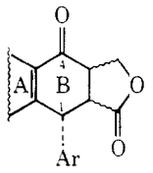
Moreover **5** can be reconverted to **6**. The interconversions between **5** and **6** are analogous to the known and fully discussed[7,8] interconversions between alcohols **1** (2α,3β,4α) and **2** (2α,3β,4β). The four compounds constitute the two pairs of half-chair structures made rigid by the 2,3-trans-lactone fusion,[1] with **5** and **6** in the 2β,3α and **1** and **2** in the 2α,3β configurations. Thus the 4-OH groups in both **2** (4β) and **6** (4α), having pseudoaxial conformations, are inverted on treatment with dilute HCl, whereas the corresponding hydroxy groups in **1** (4α) and **5** (4β), being pseudoequatorial, require a two-step process (via the 4-chloro derivative) to complete the inversion.

† Department of Biochemistry, University of South Alabama, Mobile, Ala. 36688.

Chart I



1	podophyllotoxin	(2α,3β,4α)
2	epipodophyllotoxin	(2α,3β,4β)
3	picropodophyllin	(2β,3β,4α)
4	epipicropodophyllin	(2β,3β,4β)
5	isopodophyllotoxin	(2β,3α,4β)
6	epiisopodophyllotoxin	(2β,3α,4α)
7	isopicropodophyllin	(2α,3α,4β)
8	epiisopicropodophyllin	(2α,3α,4α)



9	isopicropodophyllone	(2α,3α)
10	podophyllotoxone	(2α,3β)
11	picropodophyllone	(2β,3β)
12	isopodophyllotoxone	(2β,3α)

In this and subsequent charts partial formulas are used, and "Ar" at C-1 indicates the α-substituted 3,4,5-trimethoxyphenyl group.

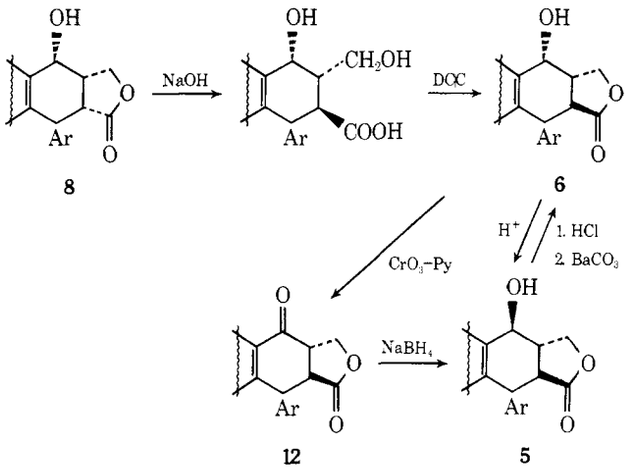
Previous tentative explanations for the supposed formation of **6** from ketone **12** have been admittedly speculative.[1,4] Now confirmation that **12** yields instead the equatorial alcohol **5** as the major reduction product provides a more consistent stereochemical picture of metal hydride reduction of the two rigid trans ketones **10** and **12.** Molecular models show that with both trans ketones, hydride attack from the less hindered side of the molecule (β side in **10,** α side in **12**) would result in the presumably more stable equatorial alcohol in each case, as is actually found experimentally.

Compound **7** (2α,3α,4β) was obtained in low yield (14%) by inversion of alcohol **8** (2α,3α,4α) in dilute acid. As with the 2β,3β-cis alcohols **3** and **4,** acid-catalyzed dehydration takes place readily,[10] but in this instance β-apopicropodophyllin (**16**) is the major product.[11] In stronger acid the proportion of elimination product increases. The structure of **7** was substantiated[12] by spectral and mass analyses, and conversion to **5.**

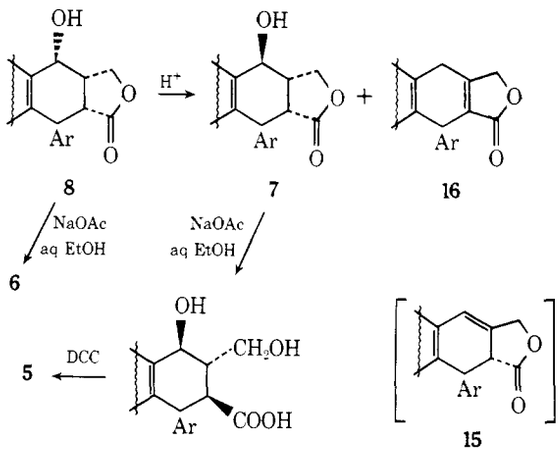
This conversion is a two-step process: inversion at C-2 with concomitant cleavage of the lactone ring by treatment with sodium acetate in aqueous alcohol, and subsequent relactonization of the resulting hydroxy acid (Scheme II). Cleavage of the lactone ring of **7** on being refluxed in NaOAc was expected, in analogy with a similar reaction of deoxyisopicropodophyllin reported by Schrecker and Hartwell.[13] However, unexpectedly, compound **8,** which has the same cis (2α,3α) configuration of **7,** under identical reaction conditions does not undergo cleavage of the lactone, but in a slow reaction is epimerized at C-2 to **6** (2β,3α,4α). The 2β,3α-deoxyisopodophyllotoxin also was cleaved to hydroxy acid according to Schrecker and Hartwell.[13]

In our earlier work[1] we found that **8** even at room temperature is cleaved by NaOH in aqueous ethanol to give the epimerized (at C-2) dihydroxy acid, and had deduced that the epimerization step precedes cleavage of the lactone. The present finding of the inverted product with lactone group

Scheme I



Scheme II



intact under milder alkaline conditions supports that sequence of reaction steps. The difference in stability of the lactone ring between the epimers **7** and **8** thus is related to the configuration of the hydroxy group at C-4. How a hydroxy group γ to the carbonyl affects the cleavage is intriguing.[14]

L-Isopodophyllotoxone (12). On the basis of the reported preparation[4] of the DL form of **12** from DL-**5** by oxidation with MnO_2, we had expected that the oxidation of optically active alcohol **6** to **12** would be straightforward. However, when the oxidation of **6** was attempted with freshly prepared MnO_2[15] following the procedure used for the DL compound,[4] the reaction proceeded sluggishly[16] and only a trace of ketonic material resulted. Changing reaction conditions to improve the yield was unproductive, and other oxidizing agents were explored. We found that the Sarett reagent (chromic anhydride–pyridine) was effective; ketone **12** was produced in 89% yield in a smooth reaction. Subsequently the diastereomeric ketones **10** and **11** were obtained from the corresponding alcohols with this reagent in yields as good as or superior to that reported with MnO_2.[4] The DL ketone (DL-**12**), prepared by the CrO_3–pyridine method from DL-**6** in 72% yield, was found to be much less soluble in organic solvents ($CHCl_3$, methanol, and acetone)[17] than the L compound.

Experimental Section[18]

L-Isopodophyllotoxin (5). 1. By Epimerization of 6. A solution of **6** (50 mg) in dioxane (10 ml) was refluxed with 2 N HCl (10 ml) for 3 h, diluted with water, and extracted with $CHCl_3$ (3 × 10 ml). Removal of solvent after washing with water and subsequent drying yielded a residue (44 mg) which was purified by preparative TLC (EtOAc–hexane, 65:35, twice). Two major components were isolated. One (R_f 0.40) was crystallized ($CHCl_3$–EtOH) and identified as

starting compound 6 (17 mg, 34%). The other product (R_f 0.46) crystallized from $CHCl_3$–EtOH as colorless needles (21 mg, 42%), mp 244–246 °C, and was characterized as L-isopodophyllotoxin: $[\alpha]_D$ −187° (c 0.70, pyridine); UV max (EtOH) 287 nm (ε 4.13) and 248 (3.72); IR (KBr) 2.95 (OH) and 5.62 μ (lactone C=O); NMR (Me_2SO) τ 6.36 (s, 3 H, -OMe), 6.30 (s, 6 H, -OMe), 4.13 (s, 2 H, $-OCH_2O-$), 3.88 (s, H, C-5) [four groups of signals remain:[19] 6.84 (perturbed t), 6.01–5.67 (perturbed multiplet), 5.48 (perturbed t), and 5.14 (d, J = 5.0 Hz)]; mass spectrum m/e 414 (rel intensity) (M^+, 100), 399 (30), 254 (26), 181 (24), 168 (72), and 153 (36).

Anal. Calcd for $C_{22}H_{22}O_8 \cdot \frac{1}{2}H_2O$: C, 62.41; H, 5.43. Found: C, 62.69; H, 5.43.

The product 5 was indistinguishable from DL-5[6] in direct comparisons by TLC, HPLC, and in their NMR, IR, and mass spectra.

2. By Reduction of Ketone 12. A. A solution of 12 (100 mg) in dioxane (20 ml) at 0 °C was treated with 80 mg of $NaBH_4$, allowed to stand for 1 h, diluted with water, and neutralized with a few drops of HOAc. The mixture was further diluted with water and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ extract was processed to yield a residue which on crystallization gave colorless needles (72 mg, 72%), which were found to be identical with 5 obtained in part 1 above (mixture melting point, TLC, HPLC, IR, NMR).

B. A similar experiment carried out on 10 mg of 12 in which $Zn(BH_4)_2$[20] was used as the reducing agent, after 50 h, was processed. The residue examined by TLC and HPLC contained 5 as a minor product, and unchanged 12 as the major product. No indication of alcohol 6[21] was seen.

Acetate of 5 was prepared with acetic anhydride in pyridine at 25 °C and crystallized from $CHCl_3$–EtOH as colorless plates: mp 232–234 °C; $[\alpha]_D$ +83.8° (c 0.8, $CHCl_3$); IR ($CHCl_3$) 5.62 (lactone C=O) and 5.77 μ (ester C=O); NMR[5] (pyridine) τ 7.83 (s, 3 H, -OCOMe), 6.32 (s, 6 H, -OMe), 6.15 (s, 3 H, -OMe), 4.08 (d, 2 H, J = 3.5 Hz, $-OCH_2O-$), 3.61 (d, H, J = 8.9 Hz, C-4), 3.40 (s, H, C-8), 3.16 (s, 2 H, C-15, -19), and 3.01 (s, H, C-5); mass spectrum m/e (rel intensity) 456 (M^+, 52) 396 (20), 168 (100) and 153 (72).

The acetates of 5 and DL-5[6] had identical IR, NMR, and mass spectra, and TLC properties.

Reconversion of 5 to 6.[7,8] Through a solution of 5 (50 mg) in Me_2SO (15 ml) HCl gas was passed for 2 h. The reaction product was diluted with water, extracted with $CHCl_3$ (3 × 15 ml), washed, dried, and evaporated (40 mg). TLC showed the complete disappearance of the starting compound. The residue was taken in acetone and refluxed with $BaCO_3$ (40 mg) for 4 h. The reaction product was filtered and the filtrate evaporated to dryness (32 mg). The residue, purified by preparative TLC (EtOAc–hexane, 65:35, twice), yielded two compounds[21] identified as 6 (13 mg, 36%) and unchanged 5 (8 mg, 16%) by TLC, IR, and NMR.

L-Isopicropodophyllin (7). Alcohol 8 (200 mg) in dioxane (20 ml) was refluxed in 20 ml of 0.002 N HCl for 12 h. When diluted with water, a solid (80 mg) precipitated. The filtrate was extracted with $CHCl_3$ (3 × 20 ml), washed with water, dried, and evaporated to yield 110 mg of residue. Purification by preparative TLC (EtOAc–hexane, 1:1) afforded three products. The first (R_f 0.30, 12 mg) crystallized from $CHCl_3$–MeOH, mp 261–263 °C, was identified as starting compound 8.

The second product (R_f 0.50, 28 mg, 21%[22]), which crystallized from $CHCl_3$–hexane, was characterized as L-isopicropodophyllin (7): mp 92–94 °C; $[\alpha]_D$ −133° ($CHCl_3$); IR (KBr) 2.90 (OH) and 5.70 μ (lactone C=O); UV max (EtOH) 287 nm (ε 3.79) and 248 (4.07); NMR (Me_2SO) τ 6.40 (s, 3 H, -OMe), 6.36 (s, 6 H, -OMe), 5.36 (d, H, J = 3.0 Hz, C-4), 4.06 (s, 2 H, $-OCH_2O-$), 3.63 (s, 2 H, C-15, -19), 3.17 (s, H, C-8), and 2.97 (s, H, C-5), several groups of multiplets between 7.30 and 5.25 remain unassigned;[19] mass spectrum m/e (rel intensity) 414 (M^+, 30), 396 (51), 246 (30), 202 (42), 181 (40), 168 (100), and 153 (58).

Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.67; H, 5.35.

The product 7 was found to be identical with a sample provided by Dr. von Wartburg[12] according to comparisons by IR and NMR.

The third product (R_f 0.60, 40 mg) crystallized from MeOH: mp 220–222 °C; $[\alpha]_D$ +92° (c 0.85, $CHCl_3$); IR ($CHCl_3$) 5.65 μ (lactone C=O); UV max (EtOH) 290 nm (ε 3.51) and 254 (1.79); mass spectrum m/e (rel intensity) 396 (M^+, 4), 168 (100), and 153 (60). It was identified as β-apopicropodophyllin (16) by direct comparison (mixture melting point, TLC, and IR) with an authentic sample prepared from picropodophyllin (3).[23]

Acetate of 7, prepared as for the acetate of 5, was crystallized from hexane: mp 86–88 °C; $[\alpha]_D$ −105.0° (c 0.84, $CHCl_3$); IR ($CHCl_3$) 5.68 (lactone C=O) and 5.75 μ (ester C=O); NMR (pyridine) τ 7.88 (s, 3 H, -OCOMe), 6.27 (s, 6 H, -OMe), 6.14 (s, 3 H, -OMe), 4.04 (d, 2 H, $-OCH_2O-$), 3.81 (d, H, J = 4.4 Hz, C-4), 3.10 (s, 2 H, C-15, -19); mass spectrum m/e (rel intensity) 456 (M^+, 10), 396 (75), 379 (24), 168 (100), and 153 (56).

Conversion of 7 to 5 (via Inversion at C-2, Cleavage, and Relactonization). A solution of 7 (30 mg) in 50% aqueous EtOH (25 ml), after being refluxed with NaOAc (50 mg) for 1 h, was diluted with water, extracted with $CHCl_3$ (3 × 10 ml), dried, and evaporated. To the residue (22 mg) dissolved in $CHCl_3$ was added DCC (20 mg). After 1 h the solvent was removed and the residue was purified by preparative TLC (EtOAc–hexane). The main product (R_f 0.42, 18 mg, 60%) was further purified by crystallization from EtOH, mp 240–242 °C. It was identified as 5 by direct comparison with an authentic sample (mixture melting point, TLC, HPLC, and IR).

Conversion of 8 to 6 (Inversion at C-2). Alcohol 8 (100 mg) and NaOAc (1 g) were refluxed in 50% aqueous EtOH for 40 h. The product was diluted with water, extracted with $CHCl_3$ (4 × 20 ml), washed with water, dried, and evaporated. The residue obtained (92 mg) was resolved by preparative TLC (EtOAc–hexane, 65:35, twice). Two compounds were obtained. The major one was the starting compound (68 mg) and the other (18 mg, 18%), crystallized from $CHCl_3$–MeOH as colorless needles, mp 242–244 °C, was identified as 6 by direct comparison with an authentic sample (mixture melting point, TLC, and IR).

L-Isopodophyllotoxone (12). Alcohol 6 (200 mg) dissolved in pyridine (2 ml) was mixed with CrO_3–pyridine complex[24] (prepared by adding 500 mg of CrO_3 to 5 ml of pyridine), and kept at 25 °C for 20 h. After dilution with water, extraction with $CHCl_3$, washing with water, and subsequent drying and removal of solvent from the extract, the resulting residue out of methanol afforded 160 mg of crystalline 12. The mother liquor by preparative TLC purification (EtOAc–hexane, 1:1) yielded an additional 18 mg of 12 (total yield 89%). The product was characterized as L-isopodophyllotoxone (12): mp 206–208 °C; $[\alpha]_D$ −63.8° (c 0.62, $CHCl_3$); IR ($CHCl_3$) 5.60 (lactone C=O) and 5.92 μ (ketone C=O); UV max (EtOH) 234 nm (ε 4.47), 273 (3.95), and 317 (3.91); NMR (Me_2SO) τ 6.28 (s, 3 H, OMe), 6.24 (s, 6 H, -OMe), 3.92 (s, 2 H, $-OCH_2O$), 3.70 (s, H, C-8), and 3.40 (s, 2 H, C-15, -19), 2.66 (s, H, C-5), the remaining unresolved signals (τ 6.20–5.28) are partly merged with the methoxy group signals; mass spectrum m/e 412 (M^+, 100), 397 (28), 367 (25), 337 (10), 297 (12), 168 (46), and 153 (38).

DL-Isopodophyllotoxone (DL-12). Both DL-iso- (DL-5) and DL-epiisopodophyllotoxin (DL-6) were oxidized and processed similarly to obtain DL-12 in yields of 68 and 72%, respectively. DL-12 was sparingly soluble in $CHCl_3$, methanol, and acetone, but could be crystallized from methanol. L-12 and DL-12 had identical IR, NMR, and mass spectra, and were indistinguishable by TLC and HPLC.

In an experiment in which DL-5 was treated with MnO_2 using the conditions reported[4] for its oxidation, the reaction proceeded very slowly. After 8 h at reflux, the product was processed. By preparative TLC 42% of the alcohol was recovered, and 6% of a component having the R_f (TLC) value of authentic DL ketone was obtained. The remainder of the product was a dark brown unidentified mixture.

The oxidation of DL-6 by use of MnO_2 was also attempted; results were similarly poor.

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Registry No.—5, 26540-82-9; 5 acetate, 60660-48-2; 6, 4375-05-7; 7, 60660-49-3; 7 acetate, 60660-50-6; 8, 55568-80-4; 12, 60660-51-7; 16, 477-52-1.

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(2) L configuration: ref 1, footnote 1.
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(4) W. J. Gensler and F. Johnson, *J. Am. Chem. Soc.*, **85**, 3670 (1963).
(5) E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963). Dr. Schreier, who reversed the assignment of configuration at C-4 of DL-iso- and epiisopodophyllotoxin on the basis of NMR studies on the epimeric acetates, had obtained the epimeric alcohols through reactions involving the synthetic DL-dihydroxy acids. He did not have access to the Gensler DL-epiisopodophyllotoxin obtained by reduction of the ketone for a direct comparison (private communication from Dr. E. Schreier).

We have repeated the $Zn(BH_4)_2$ reduction of DL-**12** and obtained in low yield a mixture of products (TLC) from which only compound DL-**5** was identifiable. (Dr. Gensler has kindly pointed out that the $Zn(BH_4)_2$ used in his work had been prepared from $NaBH_4$ while ours was derived from $LiBH_4$.) Apparently reduction of complex ketones by mixed metal hydrides is erratic.

$NaBH_4$ in methanol had been used successfully[1] to reduce ketone **9** (2α,3α) to alcohol **8** (2α,3α,4α). Subsequently we have found that ketones **10** and **11** by the same reagent yield alcohols **1** and **3**, respectively, the reported products by $Zn(BH_4)_2$ reduction.[9]

(6) We are indebted to Drs. W. J. Gensler and A. von Wartburg for these reference samples.
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(11) The olefin α-apopodophyllotoxin (**15**, 2α), which would be the primary product of dehydration of **7** (or **8**), is unknown. Apparently it is unstable and is promptly isomerized to the β isomer [W. J. Gensler, Q. A. Ahmed, Z. Muljiani, and C. D. Gatsonis, *J. Am. Chem. Soc.*, **93**, 2515 (1970)]. Following the reaction by TLC failed to show a second olefinic product.
(12) Further confirmation was forthcoming when a sample of **7** provided by Dr. von Wartburg proved to be identical with our product by direct comparisons (IR, NMR). The Sandoz compound (unpublished) had been prepared in 1970 by Mr. Max Kuhn (private communication from Dr. von Wartburg).
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(14) More detailed studies with this and the other diastereomers are in progress. The stability of the lactone ring of **8** is especially interesting in view of the previous observation[1] that it is the one stereoisomer which is cleaved to hydroxy acid under hydrogenolysis conditions (Pd/C).
(15) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. H. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(16) Drs. von Wartburg and E. Schreier in a private communication have confirmed that their manganese dioxide oxidations of DL-**6** to the ketone DL-**12** were "slow and incomplete".
(17) DL-Epiisopodophyllotoxin (DL-**6**) also dissolves poorly in these solvents; probably the poor yield in its oxidation can be attributed to the low solubility. DL-Isosikkomotoxin, which differs from DL-**12** only in having methoxy groups at C-6 and C-7 instead of the 6,7-methylenedioxy group, was oxidized to the corresponding ketone by MnO_2 in 60% yield.[5]
(18) Melting points were determined on an electrical hot stage and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Infracord 137; optical rotation measurements with a Carl Zeiss photoelectric precision polarimeter. Ultraviolet spectra were measured on a Beckman Acta T. M. III spectrometer. Mass spectra were obtained on a Finnegan 1015 GC–MS spectrometer. Nuclear magnetic resonance spectra were done on Varian A-60A, XL-100, or CFT-20 spectrometers, with tetramethylsilane as internal reference; chemical shifts are given on the τ scale.
(19) These signals are temporarily unassigned [see D. C. Ayres, J. A. Harris, P. N. Jenkins, and L. Phillips, *J. Chem. Soc.*, 1343 (1972)].
(20) E. Wiberg and W. Henle, *Z. Naturforsch.*, **76**, 579 (1952).
(21) Epimers **5** and **6** are well resolved by HPLC on a μ-Porasil (Waters Associates) column by methylene chloride–2-propanol (97:3) at a flow rate of 0.7 ml/min.
(22) Based on starting compound consumed.
(23) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **74**, 5676 (1952).
(24) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

A Reinvestigation of the Reaction of α-Pinene with Hypochlorous Acid

Joseph Wolinsky* and Martin K. Vogel[1]

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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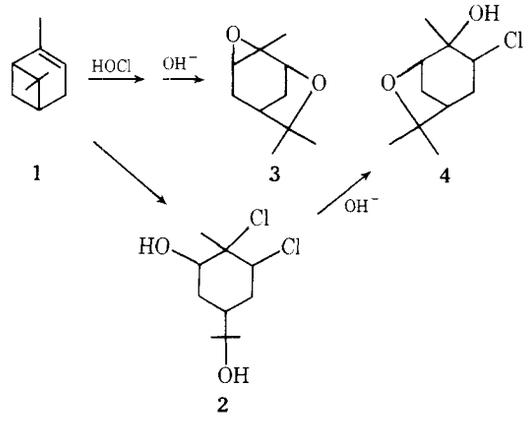
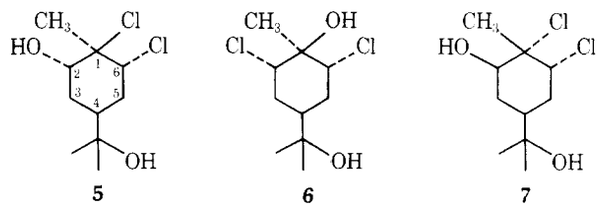
Treatment of α-pinene with hypochlorous acid yields three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively. The structure and stereochemistry of these isomers were established by spectral and chemical means. Treatment of dichlorohydrin **5** with 1 equiv of potassium hydroxide at ambient temperature affords an epoxychlorohydrin **13**. Further reaction of **13** with another equivalent of base at ambient temperature yields a 60:40 mixture of (−)-pinol oxide (**3**) and pinol chlorohydrin (**4**). Epoxide **13** is selectively converted to (−)-pinol oxide (**3**) by reaction with potassium hydroxide at 100 °C or to pinol chlorohydrin (**4**) by reaction with water containing a trace of acid. Zinc and ethanol slowly converts pinol chlorohydrin (**4**) into (+)-pinol (**14**) which is epoxidized to (+)-pinol oxide (**3**), the enantiomer of (−)-pinol oxide (**3**) obtained by the action of alkali on **5**.

α-Pinene (**1**) is known to react with 2 equiv of hypochlorous acid[2–4] to afford, among other products, an optically active dichlorohydrin **2**, mp 136–137 °C. The action of alkali on



dichlorohydrin **2** or on the crude mixture obtained from hypochlorous acid and α-pinene gave pinol oxide (**3**)[5] and optically active, mp 131–132 °C, and racemic, mp 104–105 °C, pinol chlorohydrin (**4**). Assignment of stereochemistry to these materials based on the evidence provided in the literature is not possible. Moreover, a number of the confusing observations made by Wagner[2] and Henderson[3] can be traced to their use of α-pinene which was of questionable optical purity[7] and contained β-pinene.

Our need for a sample of optically active pinol oxide (**3**) prompted us to reinvestigate the action of hypochlorous acid on (+)-α-pinene.[8] We observed that the procedure of Wagner[2] involving the addition of a sodium hypochlorite solution to acetic acid and α-pinene led to a complicated mixture of products. We then turned to the procedure of Henderson and Marsh[3] using a distilled solution of hypochlorous acid prepared from calcium hypochlorite and boric acid[10] and in this way obtained three isomeric *p*-menthane dichlorohydrins **5**, **6**, and **7** in a ratio of 90:5:1, respectively.



The major product **5** partially crystallized from the crude mixture. The remainder of the mixture was subjected to column chromatography affording additional quantities of pure **5** as well the two minor isomers **6** and **7**, both of which were still contaminated with **5**.